Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende pegvaliase til behandling af fenylketonuri

Vers. 2.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. pegvaliase, version 2.0
2. Forhandlingsnotat fra Amgros vedr. pegvaliase
3. Høringssvar fra ansøger, inkl. eventuel efterfølgende dialog vedr. den sundhedsøkonomiske afrapportering og lægemidlets værdi
4. Medicinrådets vurdering vedr. pegvaliase til behandling af patienter ≥ 16 år med fenylketonuri, version 1.0
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering vedr. pegvaliase til behandling af patienter ≥ 16 år med fenylketonuri, version 1.1

Medicinrådet

Medicinrådets sundhedsøkonomiske afrapportering

Pegvaliase

Fenylketonuri (PKU)

Version 2.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling, og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren.

Dokumentoplysninger	
Godkendelsesdato	26. maj 2021
Dokumentnummer	115935
Versionsnummer	2.0

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 26. maj 2021

Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
EPAR	*European Public Assessment Report*
ESP	Ekspeditionspris
LNAA	*Large neutral amino acids*
PAH	Fenylalanin hydroxylase
PKU	Fenylketonuri
SAIP	Sygehusapotekernes indkøbspris
SmPC	Produktresumé

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
På baggrund af kliniske data antages det, at den fulde effekt af pegvaliase opnås efter tre års behandling. Herefter antages effekten at være konstant. Der er usikkerhed om, hvor længe den gennemsnitlige patient vil være i behandling med pegvaliase. Det mest sandsynlige scenarie vurderer Medicinrådet er, at patienterne vil være i livslang behandling, hvilket i gennemsnit er 52 år. De inkrementelle omkostninger forbundet med pegvaliase i forhold til komparatorerne (restriktiv diæt eller semifri diæt i kombination med LNAA (herefter omtalt LNAA)) varierer de første tre år, hvorefter de årlige inkrementelle omkostninger er konstante. Omkostninger for fjerde år i behandling og frem er således baseret på de samme omkostninger, der blot diskonteres for hvert år.

Ved antagelsen om livslang behandling vil de inkrementelle omkostninger for pegvaliase være ca. [redacted] DKK pr. patient sammenlignet med restriktiv diæt. Det betyder, at de gennemsnitlige årlige inkrementelle omkostninger for pegvaliase pr. år vil være ca. [redacted] DKK pr. patient sammenlignet med restriktiv diæt. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. 10,3 mio. DKK pr. patient.

Ved antagelsen om livslang behandling vil de inkrementelle omkostninger for pegvaliase være ca. [redacted] DKK pr. patient sammenlignet med LNAA. Det betyder, at de gennemsnitlige årlige inkrementelle omkostninger for pegvaliase pr. år vil være ca. [redacted] DKK pr. patient sammenlignet med LNAA. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. 13,5 mio. DKK pr. patient.

Diskonteringen af de samlede omkostninger for behandling med pegvaliase, restriktiv diæt og LNAA gør, at de gennemsnitlige inkrementelle omkostninger pr. år afhænger af, hvor lang en behandlingslængde, der antages. De maksimale gennemsnitlige årlige inkrementelle omkostninger forventes at være ca. [redacted] DKK pr. år i sammenligningen med restriktiv diæt og ca. [redacted] DKK pr. år i sammenligningen med LNAA. Dette er estimeret ud fra de gennemsnitlige inkrementelle omkostninger pr. år ved tre års behandling. Jo længere patienterne er i behandling, jo lavere gennemsnitlige inkrementelle omkostninger pr. år vil der være.

De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningen for pegvaliase. Derfor har det stor betydning for analysens resultat, hvor mange daglige injektioner patienter på pegvaliase skal have. Derudover har det stor betydning, hvor stor en andel patienter der ophører behandling med pegvaliase. Estimaterne for disse parametre bygger på et usikkert datagrundlag, og de bidrager til stor usikkerhed i analysen.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af pegvaliase som mulig standardbehandling vil være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 18,1 mio. DKK i år 5.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af pegvaliase som mulig standardbehandling på danske hospitaler til patienter over 16 år med fenylketonuri (PKU).

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra BioMarin. Vi modtog ansøgningen den 15. januar 2021.

3.1 Patientpopulation

PKU er en medfødt stofskiftedefekt med autosomal recessiv arvegang. PKU skyldes mangel på funktionelt fenylalanin hydroxylase (PAH), som er et leverenzym involveret i omdannelsen af aminosyren fenylalanin til tyrosin. Fenylalanin indgår i alle kostens proteiner, og ved manglende omdannelse ophobes fenylalanin i blod og væv. Forhøjet fenylalaninkoncentration i blodbanen kan have skadelig effekt på hjernen. Behandlingen af PKU indbefatter en meget restriktiv diæt med det formål at holde fenylalaninkoncentrationen i blodet og hjernen nede. PKU inddeles i fire sværhedsgrader. Patienterne (voksne og børn samlet) opdeles i:

- Klassisk PKU (40 %)
- Moderat PKU (6 %)
- Mild PKU (25 %)
- Mild hyperfenylalaninæmi

PKU er en kronisk sygdom, som kræver livslang behandling for at fastholde et stabilt fenylalaninniveau i blodet. Dette gøres bl.a. ved diæt, hvor proteinindtaget fra naturlige kilder, der har et højt indhold af fenylalanin, reduceres. For at undgå proteinunderskud og mangel på vitaminer og mineraler modtager patienterne aminosyretilskud, som ikke indeholder fenylalanin [1]. Fagudvalget vurderer, at det i praksis vil være unge og voksne patienter med moderat og klassisk PKU, der har den største risiko for ikke at kunne nedbringe deres fenylalaninkoncentration i blodet til < 600 µmol/L ved diæt eller anden behandling. I alt udgør populationen af danske patienter over 16 år med moderat eller klassisk PKU 146 patienter [1]. Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport for pegvaliase.

3.1.1 Komparator

Medicinrådet har defineret restriktiv diæt og semifri diæt i kombination med LNAA som komparatorer til pegvaliase til patienter med moderat eller klassisk PKU. Medicinrådet har vurderet den kliniske værdi af pegvaliase på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har pegvaliase sammenlignet med enten en restriktiv diæt eller en semifri diæt i kombination med LNAA til behandling af PKU-patienter med ukontrollabelt niveau af fenylalanin i blodet?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for pegvaliase sammenlignet med restriktiv diæt, semifri diæt i kombination med LNAA og sapropterin. Fremover i denne rapport refererer LNAA til den samlede behandling med semifri diæt i kombination med LNAA. Nedenfor vurderer Medicinrådet den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for model

Ansøgers analyse sammenligner pegvaliase med restriktiv diæt og LNAA. Ansøger bygger sin analyse på data fra PRISM-1 og PRISM-2. PRISM-1 er et fase III, randomiseret studie, der sammenligner pegvaliase vedligeholdelsesdoser på 20 og 40 mg [2]. PRISM-2 er et fase III, randomiseret *discontinuation study*, som er et studiedesign, hvor alle patienter starter med at være i behandling, hvorefter de randomiseres til fortsat behandling eller placebo [3]. Patienter, der i PRISM-1 havde en reduktion på > 20 % i fenylalaninkoncentration, kunne gå videre til den randomiserede del af PRISM-2. PRISM-1 fungerede således som et såkaldt *feeder study* for PRISM-2. Yderligere beskrivelse af PRISM-studierne kan findes i Medicinrådets vurderingsrapport.

Udover data fra PRISM-studiet har ansøger inkluderet en følsomhedsanalyse, hvor data fra en indirekte komparativ analyse anvendes (Zori et al. 2019 [4]). Studiet præsenterer en indirekte sammenligning mellem pegvaliase og restriktiv diæt, hvor poolede fase III pegvaliase-data fra PRISM-1 og -2 sammenlignes med *propensity score*-matchede data fra PKUDOS-registret (*propensity score matching*: en statistisk metode, der bruges til at matche individer i to patientkohorter). Analysen rapporterer bl.a. sammenlignende data for naturligt proteinindtag.

Ansøger har valgt også at inkludere sapropterin som komparator, da ansøger argumenterer for, at det er det eneste andet lægemiddel, som har indikation til behandling af PKU og derfor anses for værende en relevant komparator.

Medicinrådets vurdering af ansøgers modelantagelser
Fagudvalget vurderer ikke, at sapropterin er en relevant komparator til pegvaliase, da lægemidlet oftest anvendes til behandling af patienter med mild PKU, og vil være afprøvet inden eventuel behandling med pegvaliase. Dermed er det ikke relevant for den

specifikke patientpopulation med moderat eller klassisk PKU, og Medicinrådet vælger derfor ikke at præsentere analysen med sapropterin som komparator.

Medicinrådet vælger ikke at præsentere analysen, hvor sapropterin er komparator.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en simpel omkostningsmodel til at estimere omkostningerne forbundet med behandlingen med pegvaliase, restriktiv diæt og LNAA. Modellen er ikke struktureret, så patienter kan være i forskellige sygdomsstadier. Effekten af behandlingerne er inkluderet i form af reduktion i behov for aminosyretilskud. Det antages, at ved behandling med pegvaliase vil det naturlige proteinindtag øges sammenlignet med restriktiv diæt. Ved at øge det naturlige proteinindtag reduceres patienternes behov for aminosyretilskud.

Behandling med pegvaliase

PRISM-studiet rapporterer, hvor meget aminosyretilskud patienterne fik i tillæg til pegvaliase. På baggrund af PRISM-studiet antager ansøger, at patienternes behov for aminosyretilskud vil falde, i takt med at behandlingens effekt sætter ind. For patienter, der modtager pegvaliase, antager ansøger, at det gennemsnitlige, daglige proteinindtag gennem aminosyretilskud vil være følgende:

- Efter 1 år i behandling med pegvaliase: 24,2 g
- Efter 2 år i behandling med pegvaliase: 20,3 g
- Efter ≥ 3 år i behandling med pegvaliase: 9,2 g

Ansøger antager, at en andel patienter ophører behandling med pegvaliase på grund af manglende respons eller bivirkninger. PRISM-studiet viste, at bivirkninger havde stor betydning for andelen der ophører behandling. Der blev derfor lavet en ændring under studiets forløb, så patienterne modtog antihistamin og antipyretika, og titreringsfasen blev forlænget. Ansøger antager, at 10,3 % ophører behandling med pegvaliase inden for et år efter opstart af behandling. Estimatet bygger på *real-world* data fra USA. Behandling med antihistamin og antipyretika er inkluderet i produktresuméet (SmPC'et) for pegvaliase. Ansøger antager, at ud af de 10,3 %, der ophører behandling med pegvaliase, vil 62 % af patienterne skifte til behandling med LNAA, og 38 % vil skifte til restriktiv diæt.

Behandling i form af restriktiv diæt

Ansøger anvender danske kliniske eksperters vurderinger af det naturlige proteinindtag til at estimere behovet for aminosyretilskud. De kliniske vurderinger blev præsenteret på et møde, hvor kliniske eksperter deltog i et *advisory board* for pegvaliase. Vurderingen er, at patienter, der er på restriktiv diæt, har et dagligt proteinindtag på 1,2 g/kg, hvoraf 80 % af proteinindtaget kommer fra aminosyretilskud. Ansøger anvender gennemsnitsvægten på 80,3 kg fra PRISM-studiet til at beregne det gennemsnitlige, daglige proteinindtag, der estimeres til ca. 96 g, hvoraf 77 g indtages gennem aminosyretilskud for patienter på restriktiv diæt.

Behandling med LNAA

Til estimering af behovet for aminosyretilskud anvender ansøger samme antagelser

vedrørende det daglige proteinbehov, som når patienterne er på restriktiv diæt, dvs. ca. 96 g. Ifølge de kliniske eksperter fra *advisory board* vil patienter på LNAA indtage 20 % af det daglige proteinbehov gennem aminosyretilskud. Patienter på LNAA skal derfor indtage ca. 19 g protein gennem aminosyretilskud for at nå det daglige proteinbehov. Ansøger antager dog, at proteinbehovet bliver dækket gennem indtagelsen af LNAA, og har derfor ikke inkluderet omkostninger til aminosyretilskud til patienter, der behandles med LNAA.

Ansøgers følsomhedsanalyse

I ansøgers følsomhedsanalyse, hvor data fra Zori et al.-studiet anvendes, rapporteres det naturlige proteinindtag for patienter på restriktiv diæt og patienter, der er i behandling med pegvaliase. For at estimere behovet for supplerende proteinindtag gennem aminosyretilskud trækker ansøger det naturlige proteinindtag fundet i studiet fra det gennemsnitlige proteinindtag ved baseline for pegvaliase-kohorten på 64 g protein. Derved antages et gennemsnitligt proteinbehov på 64 g pr. dag. På baggrund af Zori et al.-studiet antager ansøger et forbrug af aminosyretilskud, som kan ses i Tabel 1.

Tabel 1. Oversigt over antaget proteinindtag gennem aminosyretilskud i ansøgers følsomhedsanalyse

Behandling		Naturligt proteinindtag fra Zori et al.-studiet	Antaget proteinindtag gennem aminosyretilskud
Pegvaliase	Efter 1 år	47 g	17 g
	Efter 2 år	57 g	7 g
Restriktiv diæt	Efter 2 år	22 g	42 g

Medicinrådets vurdering af ansøgers modelantagelser

Fagudvalget vurderer, at ansøgers antagelse vedr. det daglige proteinbehov på ca. 96 g, for patienter på restriktiv diæt eller LNAA, er rimelig. Fagudvalget vurderer derudover, at ansøgers antagelser vedr. proteinindtag gennem aminosyretilskud for patienter, der behandles med pegvaliase, er rimelige.

Ansøger har anvendt Zori et al.-studiet i en følsomhedsanalyse til sammenligningen med restriktiv diæt. Fagudvalget vurderer, at Zori et al.-studiet udgør det bedste sammenligningsgrundlag mellem pegvaliase og restriktiv diæt. Medicinrådet vælger derfor at anvende data for Zori et al.-studiet som grundlag for behovet for aminosyretilskud på restriktiv diæt i Medicinrådets hovedanalyse. I ansøgers følsomhedsanalyse antages det, at patienterne skal opnå et proteinindtag på 64 g pr. dag. Dette ændrer Medicinrådet til ca. 96 g pr. dag, så det stemmer overens med fagudvalgets vurdering af det generelle proteinbehov for patienter på restriktiv diæt. Dermed skal det naturlige proteinindtag suppleres med aminosyretilskud, indtil patienten indtager omkring 96 g protein pr. dag. Estimaterne for proteinindtag gennem aminosyretilskud for patienter på restriktiv diæt kan ses i Tabel 2.

Ansøger antager, at patienter der modtager LNAA, vil få hele proteinbehovet dækket gennem LNAA. Ifølge fagudvalget vil en stor del af patienterne dog have behov for aminosyretilskud udover LNAA. Fagudvalget har adgang til en database fra Center for PKU, der viser, at ca. 53 % af patienterne, der modtager LNAA, får supplerende aminosyretilskud, og fagudvalget vurderer, at disse patienter i gennemsnit får 30 g protein gennem aminosyretilskud. Dette inkluderer Medicinrådet i sin hovedanalyse, jf. Tabel 2.

Tabel 2. Oversigt over antaget proteinindtag gennem aminosyretilskud ved behandling med pegvaliase, restriktiv diæt og LNAA i Medicinrådets hovedanalyse

Behandling		Naturligt proteinindtag	Antaget proteinindtag gennem aminosyretilskud	Datakilde
Pegvaliase	1 år	[redacted]	24,2 g	PRISM
	2 år	[redacted]	20,3 g	PRISM
	3 år	[redacted]	9,2 g	PRISM
Restriktiv diæt	Efter 2 år	22,0 g	74,3 g	Zori et al.
LNAA	-	-	15,9 g (30 g for 53 % af patienterne)	*Advisory board*/ fagudvalget

Der er usikkerhed forbundet med det reelle proteinindtag gennem aminosyretilskud for patienter, der behandles med pegvaliase. På baggrund af den kliniske data vurderer fagudvalget, at patienter, der behandles med pegvaliase, potentielt ikke vil have behov for aminosyretilskud efter tre års behandling med pegvaliase. Medicinrådet præsenterer derfor en følsomhedsanalyse, hvor det antages, at patienter ikke har behov for amino-syretilskud efter tre års behandling med pegvaliase.

Fagudvalget vurderer, at ca. 30-40 % af patienterne, der behandles med pegvaliase, vil ophøre behandling i løbet af det første år på grund af bivirkninger eller utilstrækkelig effekt. Fagudvalget understreger dog, at estimatet er usikkert. Den samlede andel af patienter, der udgik før tid fra PRISM-1 og -2, udgjorde ifølge *European Public Assessment Report* (EPAR'en) 100/261 (38,3 %), og fagudvalgets vurdering stemmer derfor overens med EPAR'en. Af de patienter, der ophører behandling med pegvaliase, vurderer fagudvalget, at 70 % af patienterne vil skifte til behandling med LNAA, og at 30 % vil skifte til restriktiv diæt. Medicinrådet ændrer derfor andelen af patienter, der ophører behandling med pegvaliase, til 35 % og ændrer andelen af patienter, der skifter til LNAA eller restriktiv diæt på baggrund af fagudvalgets vurderinger. Da fagudvalget vurderer, at estimatet for andelen, der ophører behandling med pegvaliase, er usikkert, præsenterer Medicinrådet en følsomhedsanalyse, hvor ansøgers estimat for andelen af patienter, der ophører behandling med pegvaliase (10,3 %), anvendes.

Medicinrådet anvender ansøgers følsomhedsanalyse som grundlag for behovet for aminosyretilskud ved restriktiv diæt, som bygger på data fra Zori et al.-studiet. Dog

ændres det antagede daglige proteinindtag, så det stemmer overens med fagudvalgets vurdering på ca. 96 g protein for patienter på restriktiv diæt. Medicinrådet tillægger på baggrund af databaseudtrækket fra Center for PKU omkostninger til 30 g protein fra aminosyretilskud til 53 % af patienterne, der modtager LNAA. Derudover ændrer Medicinrådet andelen af patienter, der ophører behandling med pegvaliase, til 35 % og ændrer andelen af patienter, der skifter til LNAA eller restriktiv diæt. Der præsenteres en følsomhedsanalyse, hvor det antages, at patienter ikke har behov for aminosyretilskud efter tre års behandling med pegvaliase. Derudover præsenteres en følsomhedsanalyse, hvor ansøgers estimat for andelen af patienter, der ophører behandling med pegvaliase (10,3 %), anvendes.

4.1.2 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 20 år. Ansøger argumenterer for, at tidshorisonten på 20 år er mest realistisk, på trods af at PKU er en kronisk sygdom og kræver livslang behandling. Dette begrunder ansøger med, at usikkerheden ved længere tidshorisonter bliver for stor, da der bl.a. kan introduceres nye behandlinger. Ansøger har inkluderet data for dødelighed for den generelle befolkning fra Danmarks Statistik i analysen.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 % pr. år. Modellen indebærer muligheden for at øge analysens tidshorisont. Omkostninger, der ligger efter år 35, bliver diskonteret med en rate på 3 % pr. år.

Medicinrådets vurdering af ansøgers analyseperspektiv
PKU er en kronisk sygdom, som kræver livslang behandling, og analysens tidshorisont skal være så lang, at alle væsentlige forskelle i behandlingsomkostninger mellem pegvaliase og restriktiv diæt eller LNAA opfanges. PKU er ikke forbundet med øget dødelighed, og ifølge Danmarks Statistisk er middellevetiden i Danmark ca. 81 år. Gennemsnitsalderen i PRISM-studiet var ca. 29 år. Medicinrådet ændrer derfor tidshorisonten til 52 år for at opnå en livslang tidshorisont, og justerer analysen, så dødeligheden svarer til aldersgennemsnittet i Medicinrådets hovedanalyse.

Patienter med PKU over 16 år kandiderer til behandling med pegvaliase. Den forventede, maksimale behandlingslængde er derfor 65 år for en patient, der opstarter behandling med pegvaliase, når vedkommende fylder 16 år. Medicinrådet præsenterer en følsomhedsanalyse, hvor den forventede, maksimale behandlingslængde på 65 år anvendes.

Ansøgers analyse indebærer, at effekten af behandlingerne antages at være konstant efter år 3. Medicinrådet præsenterer en følsomhedsanalyse, hvor tidshorisonten sættes til 3 år, da omkostningerne forbundet med de specifikke behandlinger (pegvaliase, restriktiv diæt og LNAA) antages at være konstante de resterende år, hvis der ses bort fra diskontering. I resultatafsnittet præsenterer Medicinrådet også de gennemsnitlige inkrementelle omkostninger pr. år patienterne er i behandling, når pegvaliase sammenlignes med restriktiv diæt og LNAA.

Siden ansøger har indsendt sin sundhedsøkonomiske analyse, har Finansministeriet ændret den samfundsøkonomiske diskonteringsrente. Medicinrådet ændrer derfor analysen, så omkostninger, der falder mellem år 1-35, diskonteres med en rate på 3,5 %, og omkostninger, der falder mellem år 36-70, diskonteres med 2,5 %.

Medicinrådet ændrer tidshorisonten til 52 år og ændrer diskonteringsrenterne jf. de nyeste samfundsøkonomiske diskonteringsrenter. Medicinrådet præsenterer følsomhedsanalyser, hvor tidshorisonten sættes til hhv. 65 år og 3 år.

4.2 Omkostninger

I det følgende er ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af pegvaliase sammenlignet med restriktiv diæt og LNAA præsenteret. Analysen inkluderer lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger, patientomkostninger, kommunale omkostninger og omkostninger relateret til komorbiditeter.

4.2.1 Lægemiddelomkostninger

Pegvaliase

Pegvaliase fås som injektion med 2,5 mg, 10 mg og 20 mg. Behandling med pegvaliase gives i tre faser: induktion, titrering og vedligeholdelse. Ansøger antager, at doseringen af pegvaliase øges fra en startdosis på 2,5 mg til 20 mg eller 40 mg som vedligeholdelsesdosis. Ifølge SmPC'et kan vedligeholdelsesdosis være op til 60 mg dagligt afhængigt af patientens behov. *Real-world* data for pegvaliase fra USA viser, at patienter i gennemsnit har en daglig vedligeholdelsesdosis på [redacted] mg. Ansøger antager derfor, at 75 % af patienterne vil modtage 20 mg pr. dag, og at 25 % vil modtage 40 mg pr. dag. Dermed antages det, at ingen patienter modtager 60 mg pegvaliase dagligt. Ansøger antager en langsommere overgang til højere dosis, end hvad der var gældende i PRISM-studiet. Dette antages for at imødekomme, at klinisk praksis kan afvige fra studiepraksis. Følgende dosistrin antages: 5 mg, 10 mg, 20 mg, 35 mg, 40 mg, 70 mg, 100 mg, 140 mg (20 mg pr. dag), 160 mg, 200 mg, 240 mg, 280 mg (40 mg pr. dag). Det antages, at patienterne er på hver dosis i to uger for at minimere immunresponset. Således antager ansøger, at induktionsfasen varer fra 4 uger, og at titreringsfasen varer 24 uger, hvorefter patienten overgår til vedligeholdelsesfasen efter uge 28. Ansøger antager, at når patienter er i vedligeholdelsesfasen, vil en patient i gennemsnit få [redacted] injektioner om dagen. Dette gennemsnit stammer fra data fra USA. Ansøger understreger, at hver plan for dosering i de tre faser er individuel og afhænger af patienternes immunrespons, hvorfor der kan være store variationer i doseringen mellem patienter.

Ansøger antager, at patienter, der behandles med pegvaliase, skal tage 1 tablet (10 mg) med antihistamin og 1 tablet (400 mg) med antipyretika dagligt som profylaktisk behandling. Derudover antager ansøger, at en patient årligt skal have én adrenalininjektion til akut behov.

LNAA

Til estimering af omkostninger forbundet med LNAA antager ansøger, at en patient skal

have 0,5 tabletter med LNAA pr. kg. Dette svarer til ca. 40 tabletter dagligt, når der antages en gennemsnitlig kropsvægt på 80,3 kg fra PRISM-studiet. Ansøger anvender omkostningen for LNAA-tabletterne PreKUnil. Prisen stammer fra det svenske online-apotek, apoteket.se, hvor en pakke med 550 tabletter af 500 mg aminosyrer koster 5.500 SEK. Ansøger omregner til DKK, og den anvendte pris pr. pakning er 3.905,55 DKK.

Aminosyretilskud

Ansøger har estimeret omkostningerne for aminosyretilskud ved at anvende prisen for Avonil-tabletter fra Prekulab. Ansøger anvender en svensk pris pr. pakke for 900 tabletter af 735 mg, som omregnes til danske kroner (DKK). Pr. 100 g tablet er der 55,8 g protein. Prisen pr. pakke er beregnet til 3.905,55 DKK. Dermed antager ansøger en pris på 10,6 DKK pr. gram protein.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger

Pegvaliase

Medicinrådet accepterer ansøgers antagelser vedrørende dosering af pegvaliase i induktions- og titreringsfasen, se Tabel 3.

Tabel 3. Ugentlig dosis af pegvaliase

Uge	Dosis pr. uge ved vedligeholdelsesdosis på 20 mg	Dosis pr. uge ved vedligeholdelsesdosis på 40 mg	Doseringsfase
1	2,5 mg	2,5 mg	Induktion
2	2,5 mg	2,5 mg	Induktion
3	2,5 mg	2,5 mg	Induktion
4	2,5 mg	2,5 mg	Induktion
5	5 mg	5 mg	Titrering
6	5 mg	5 mg	Titrering
7	10 mg	10 mg	Titrering
8	10 mg	10 mg	Titrering
9	20 mg	20 mg	Titrering
10	20 mg	20 mg	Titrering
11	35 mg	35 mg	Titrering
12	35 mg	35 mg	Titrering
13	40 mg	40 mg	Titrering
14	40 mg	40 mg	Titrering

Uge	Dosis pr. uge ved vedligeholdelsesdosis på 20 mg	Dosis pr. uge ved vedligeholdelsesdosis på 40 mg	Doseringsfase
15	70 mg	70 mg	Titrering
16	70 mg	70 mg	Titrering
17	100 mg	100 mg	Titrering
18	100 mg	100 mg	Titrering
19	140 mg	140 mg	Titrering
20	140 mg	140 mg	Titrering
21	140 mg	160 mg	Titrering
22	140 mg	160 mg	Titrering
23	140 mg	200 mg	Titrering
24	140 mg	200 mg	Titrering
25	140 mg	240 mg	Titrering
26	140 mg	240 mg	Titrering
27	140 mg	280 mg	Titrering
28	140 mg	280 mg	Titrering

Der er stor usikkerhed forbundet med det gennemsnitlige antal injektioner af pegvaliase i vedligeholdelsesfasen. Medicinrådet accepterer ansøgers antagelse om, at patienter i gennemsnit får [redacted] injektioner dagligt, men da fagudvalget vurderer, at estimatet er usikkert, præsenterer Medicinrådet en følsomhedsanalyse, hvor antallet af injektioner sættes til 1 injektion og 2 injektioner.

Ansøger har forhandlet priser på injektionerne med pegvaliase, der er betinget af, at Medicinrådet anbefaler pegvaliase som standardbehandling. De betingede priser er angivet i sygehusapotekets indkøbspris (SAIP), og kan ses i Tabel 4. Hvis Medicinrådet ikke anbefaler pegvaliase som standardbehandling, vil den gældende pris være [redacted] DKK pr. injektion uanset styrken.

Tabel 4. Anvendte lægemiddelpriser, SAIP (maj 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Pegvaliase	2,5 mg	1 stk.	[redacted]	Amgros
Pegvaliase	10 mg	1 stk.	[redacted]	Amgros

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Pegvaliase	20 mg	1 stk.	[redacted]	Amgros

Medicinrådet inkluderer omkostninger til profylaktisk behandling og adrenalininjektioner under patientomkostninger, da patienterne selv køber lægemidlerne på apoteket.

LNAA

Fagudvalget vurderer, at patienter, der modtager LNAA, får 45 tabletter om dagen. Medicinrådet ændrer derfor antallet af LNAA-tabletter fra 40 til 45 i Medicinrådets hovedanalyse. Det har lille betydning for analysens resultat. Medicinrådet anvender SAIP for PreKUnil i Medicinrådets hovedanalyse. Prisen er [redacted] DKK pr. pakke med 550 tabletter.

Aminosyretilskud

Ifølge fagudvalget kan patienter vælge mellem at få aminosyretilskud gennem tabletter, barer, pulver og færdigdrikke, og der er stor forskel på, hvilke produkter patienterne foretrækker. Hvis ét produkt ikke giver den ønskede virkning, skifter man til et andet produkt. På baggrund af et udtræk af de forskellige produkter med aminosyretilskud indsendt af fagudvalget har Medicinrådet beregnet en gennemsnitlig pris pr. gram protein for hver kategori: tabletter, barer, pulver og færdigdrikke. Disse gennemsnits-priser er herefter vægtet ud fra, hvor stor en andel af patienterne der modtager tabletter, barer, pulver og færdigdrikke. Disse andele stammer ligeledes fra et data-udtræk indsendt af fagudvalget. Den gennemsnitlige pris pr. gram protein estimeres til at være [redacted] DKK. Medicinrådet anvender denne pris i Medicinrådets hovedanalyse.

Medicinrådet accepterer ansøgers antagelser vedrørende lægemiddelomkostninger for pegvaliase, men præsenterer følsomhedsanalyser, hvor det gennemsnitlige antal daglige injektioner sættes til hhv. 1 og 2. Medicinrådet ændrer antallet af tabletter af LNAA fra 40 til 45 i Medicinrådets hovedanalyse. Derudover ændrer Medicinrådet omkostningen pr. gram protein i aminosyretilskud fra 10,6 DKK til [redacted] DKK.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Ansøger har ikke inkluderet omkostninger til administration af pegvaliase eller LNAA, men har inkluderet omkostninger til opstart af behandling for pegvaliase. Det antages, at patienten og en pårørende bliver oplært i at administrere pegvaliase med injektion og håndtere eventuelle bivirkninger, der måtte opstå i forbindelse med injektionen. Opstartsbesøget antages at vare en time, og ansøger anvender en timeomkostning for en overlæge på 1.316 DKK fra Medicinrådets værdisætning af enhedsomkostninger.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger og oplæring i administration af pegvaliase.

Monitoreringsomkostninger

Ansøger har ikke inkluderet omkostninger til monitorering, da ansøger argumenterer for, at der ikke vil være forskel på, hvordan patienterne monitoreres ved behandling med pegvaliase, LNAA eller restriktiv diæt.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger

Ifølge fagudvalget monitoreres patienter med PKU med en blodprøve én gang om måneden. Patientens fenylalaninniveau måles for at se, om patienten holder et stabilt fenylalaninniveau i blodet på eller < 600 µmol/L. Ved opstart af behandling med pegvaliase vil man dog lave hyppigere monitorering i løbet af det første år for at måle effekten af pegvaliase. Fagudvalget vurderer, at patienten skal tage en blodprøve hver anden uge de første 10 uger. Herefter tages daglige blodprøver i 14 dage for at vurdere effekten af pegvaliase ift. baseline. Gennemsnittet af de 14 blodprøver bør vise en reduktion i fenylalanin på minimum 20 %. I den efterfølgende tid tager patienten en blodprøve hver anden uge. Efter 6-9 måneder tages der en blodprøve hver uge i 12 uger for at se, om niveauet er kommet ned på eller < 600 µmol/L. Såfremt pegvaliase har tilstrækkelig effekt, fortsætter patienten i behandling og skal fremadrettet tage en blodprøve hver anden uge. I løbet af det første år tager patienter 44 blodprøver efter opstart af behandling med pegvaliase. Efter det første år monitoreres patienten normalt med én blodprøve om måneden. Medicinrådet tilføjer omkostningerne til de ekstra blodprøver.

Blodprøverne tages hjemme og sendes til hospitalet. Patienterne får svar på prøven ved en telefonkonsultation. Der antages en omkostning på 159 DKK pr. blodprøve, som dækker over materiale til blodprøven, porto til at indsende blodprøven, analyse og svar til patienten. Det antages, at materiale til blodprøve og porto udgør 30 DKK, mens analyse og telefonkonsultation er estimeret ud fra 2021 DRG-taksten på 129 DKK (65TE01: Telefon- og e-mail-konsultation, samt skriftlig kommunikation ved prøvesvar).

Medicinrådet inkluderer omkostninger til ekstra blodprøver ved opstart af behandling med pegvaliase.

Bivirkningsomkostninger

Ansøger har inkluderet bivirkningsomkostninger ved behandling med pegvaliase for bivirkninger af grad 3 eller mere med ≥ 3 %'s frekvens rapporteret i PRISM-studiet. Den eneste bivirkning inkluderet i ansøgers analyse er forstyrrelser i immunsystemet, hvilket dækker over hypersensitivitet og anafylaktiske reaktioner. Til estimeringen af omkostningerne forbundet med behandling af bivirkningerne anvender ansøger 2020 DRG-taksten 20.224 DKK (21MA04: Forgiftning og toksisk virkning af lægemiddel, pat. mindst 18 år, m. kompl. bidiag.). Der er ikke inkluderet bivirkninger i forbindelse med restriktiv diæt eller LNAA.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Medicinrådet accepterer ansøgers antagelser vedr. bivirkningsomkostninger, men ændrer DRG-taksten fra 2020 til den tilsvarende DRG-takst for 2021.

Omkostninger relateret til komorbiditet

Ansøger antager, at prævalensen af bestemte komorbiditeter er højere hos patienter med PKU end hos den generelle befolkning. Ansøger refererer til et studie af Burton et al. [5] og et tysk registerbaseret studie, som undersøger komorbiditeter hos voksne med PKU [6], og sammenligner komorbiditetsraterne for voksne med PKU med raterne for voksne uden PKU. Ansøger antager, at en normalisering af fenylalaninniveauet i blodet reducerer forekomsten af komorbiditeter hos patienter med PKU. Følgende komorbiditeter er inkluderet i ansøgers analyse:

- Osteoporose/osteopeni
- Nyreinsufficiens med eller uden hypertension
- Overvægt
- Depression
- Angst/fobier
- Underernæring
- Søvnforstyrrelser.

PRISM-studiet viste, at 51 % af patienterne, der behandles med pegvaliase, normaliserede deres fenylalaninniveau i blodet i år 2. Ansøger antager på den baggrund, at 51 % af patienter, der behandles med pegvaliase, vil have samme risiko for ovenstående komorbiditeter som den generelle befolkning. Ansøger argumenterer for, at der ikke ses normalisering af fenylalaninniveauet i blodet hos patienter, der er på restriktiv diæt eller modtager LNAA. For disse patienter antages samme prævalens for komorbiditeterne som for patienter med PKU.

Medicinrådets vurdering af ansøgers antagelser vedr. omkostninger relateret til komorbiditeter

Fagudvalget vurderer ikke, at der på nuværende tidspunkt er evidens for, at normalisering i fenylalaninniveauet i blodet vil medføre, at prævalensen for ovenstående komorbiditeter for patienter med PKU vil være den samme som for den generelle befolkning. Medicinrådet ekskluderer derfor omkostninger relateret til komorbiditeter i Medicinrådets hovedanalyse.

Medicinrådet accepterer ikke ansøgers antagelser vedr. omkostninger til komorbiditeter og ekskluderer derfor omkostningerne fra Medicinrådets hovedanalyse.

4.2.3 Patientomkostninger

Ansøgers analyse indeholder omkostninger for både patienterne og deres pårørende. Ansøger har inkluderet patientomkostninger til oplæring i administration af pegvaliase, hvor det antages, at en pårørende er med, og at oplæringen tager en time. På baggrund af den gennemsnitlige indtægt i Danmark i 2018 estimerer ansøger timeomkostningen for patienttid til 192 DKK. Ansøger har også inkluderet transportomkostninger i den forbindelse og antager transportomkostninger på 99 DKK. Der er ikke inkluderet patientomkostninger i forbindelse med administration af LNAA.

Ansøger antager, at en pårørende til en patient med PKU på restriktiv diæt ugentligt bruger 10 timer på at forberede mad. Denne antagelse baserer ansøger på vurderinger fra *advisory board*. Ansøger anvender en timeomkostning på 138 DKK dækkende for pårørendes fritid. For patienter, der behandles med pegvaliase eller LNAA, antager ansøger, at tiden brugt på forberedelse af mad er afhængig af reduktionen i protein-indtaget gennem aminosyretilskud. Det vil sige, at ved en reduktion i proteinindtaget gennem aminosyretilskud på 50 % antager ansøger, at der bruges 5 timer ugentligt på forberedelse af mad.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet skelner ikke mellem patienters tid og pårørendes tid. Medicinrådet anvender derfor en timeomkostning på 179 DKK for både patienter og pårørende, jf. Medicinrådets værdisætning af enhedsomkostninger. Ændringen har minimal betydning for analysens resultat.

Fagudvalget vurderer, at patienter, som er i stand til at reducere deres forbrug af aminosyretilskud ved behandling med pegvaliase eller LNAA, sandsynligvis vil bruge mindre tid på forberedelse af mad end patienter på restriktiv diæt. Dog vurderer fagudvalget, at der ikke nødvendigvis er tale om en direkte sammenhæng mellem tidsforbrug på forberedelse af mad og reduktion i aminosyretilskud. I mangel på et bedre estimat accepterer Medicinrådet ansøgers antagelser, men præsenterer følsomheds-analyser, hvor det antages, at patienterne har et tidsforbrug på 10 timer, uanset hvilken behandling de modtager. Estimatet af patienttid/pårørendes tid brugt til forberedelse af mad kan ses i Tabel 5.

Tabel 5. Estimat af effektiv patienttid til forberedelse af mad

		Proteinindtag gennem aminosyretilskud	Andel proteinindtag gennem aminosyretilskud sammenlignet med restriktiv diæt	Tidsforbrug på forberedelse af mad
Restriktiv diæt	-	74,3 g	-	10 timer
Pegvaliase	År 1	24,2 g	33 %	3,3 timer
	År 2	20,3 g	27 %	2,7 timer
	År 3	9,2 g	12 %	1,2 timer
LNAA	-	15,9 g (30 g for 53 % af patienterne)	21 %	2,1 timer

Medicinrådet sætter omkostninger til profylaktisk behandling og adrenalininjektioner under patientomkostninger, da patienterne selv køber lægemidlerne på apoteket. Ansøger antager, at patienter, der behandles med pegvaliase, skal tage 1 tablet (10 mg) med antihistamin (cetirizin) og 1 tablet (400 mg) med antipyretika (ibumetin) dagligt som profylaktisk behandling. Derudover antager ansøger, at en patient årligt skal have én adrenalininjektion (EpiPen) til akut behov. Fagudvalget vurderer, at patienter i

gennemsnit vil købe to adrenalininjektioner om året, men at ansøgers antagelser vedr. antihistamin og antipyretika er rimelige. Medicinrådet tilføjer derfor omkostninger til en ekstra adrenalininjektion, og de anvendte omkostninger til adrenalininjektioner og profylaktisk behandling kan ses i Tabel 6 angivet i ekspeditionens samlede pris (ESP).

Tabel 6. Anvendte lægemiddelpriser, ESP (februar 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
EpiPen	300 µg	1 stk.	361,50	Medicinpriser.dk
Cetirizin	10 mg	100 stk.	109,75	Webapoteket.dk
Ibumetin	400 mg	250 stk.	70,65	Medicinpriser.dk

Medicinrådet ændrer timeomkostningen for patienttid til 179 DKK og tilføjer omkostninger til en ekstra adrenalininjektion om året ved behandling med pegvaliase, men accepterer ansøgers tilgang vedr. patientomkostninger. Medicinrådet præsenterer en følsomhedsanalyse, hvor tidsforbruget på forberedelse af mad sættes til 10 timer, uanset om patienten er på restriktiv diæt eller i behandling med pegvaliase eller LNAA.

4.2.4 Kommunale omkostninger

For at vedligeholde et stabilt niveau af fenylalanin i blodet kan patienten spise bestemt mad, der har et lavt indhold af fenylalanin (herefter omtalt medicinsk mad). Da der er merudgifter forbundet med den medicinske mad sammenlignet med 'almindelig' mad, udbetaler kommunerne tilskud til patienter med PKU til dækning af disse merudgifter. Ansøger har inkluderet omkostninger til det kommunale tilskud. Center for PKU har i 2018 udarbejdet et skema for merudgifter til medicinsk mad, som ansøger anvender. Priserne er justeret ift. år 2020 ved brug af forbrugerprisindekset. Skemaet viser bl.a. merudgifterne for patienter, der er på restriktiv diæt, og patienter på LNAA. For pegvaliase antager ansøger, at der er direkte sammenhæng mellem merudgifterne for medicinsk mad og reduktionen af proteinindtag gennem aminosyretilskud ved behandling med pegvaliase. Det vil sige, at for hver procentvis reduktion af proteinindtag aminosyretilskud antager ansøger en tilsvarende procentvis reduktion i omkostninger til medicinsk mad.

Medicinrådets vurdering af ansøgers antagelser vedr. kommunale omkostninger
Medicinrådet accepterer ansøgers estimering af månedlige omkostninger til medicinsk mad, som kan ses i Tabel 7. Det er usikkert, hvor store omkostninger patienter på pegvaliase vil have til medicinsk mad, og Medicinrådet præsenterer derfor følsomhedsanalyser, hvor den månedlige omkostning til medicinsk mad for patienter på pegvaliase antages at være tilsvarende omkostningen for patienter på LNAA på 601 DKK.

Tabel 7. Estimerede omkostninger til medicinsk mad

		Proteinindtag gennem aminosyretilskud	Andel proteinindtag gennem aminosyretilskud sammenlignet med restriktiv diæt	Månedlig omkostning til medicinsk mad [DKK]
Restriktiv diæt	-	74,3 g	-	3.017
Pegvaliase	År 1	24,2 g	33 %	983
	År 2	20,3 g	27 %	824
	År 3	9,2 g	12 %	374
LNAA*	-	-	-	601

*Omkostninger til medicinsk mad til patienter på LNAA er angivet i merudgiftsskemaet fra Center for PKU og er derfor ikke beregnet på baggrund af reduktionen i forbruget af aminosyretilskud.

Medicinrådet accepterer ansøgers antagelser vedrørende medicinsk mad, men præsenterer følsomhedsanalyser, hvor det antages, at den månedlige omkostning til medicinsk mad for patienter på pegvaliase er tilsvarende omkostningen for patienter på LNAA.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges, se Tabel 8.

Tabel 8. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Sammenligning med restriktiv diæt	
Gennemsnitlig vedligeholdelsesdosis af pegvaliase	Varieres med ±10 %
Omkostninger til aminosyretilskud for pegvaliase	Varieres med ±10 %
Omkostninger til aminosyretilskud for restriktiv diæt	Varieres med ±10 %
Omkostninger til medicinsk mad for patienter, der modtager pegvaliase	Varieres med ±10 %
Omkostninger til medicinsk mad for patienter, der er på restriktiv diæt	Varieres med ±10 %
Pårørendes tid brugt på hjælp til patienter, der modtager pegvaliase	Varieres med ±10 %

Følsomhedsanalyse	Beskrivelse
Pårørendes tid brugt på patienter, der er på restriktiv diæt	Varieres med ±10 %
Tidshorisont	Sættes til 5 år og 10 år
Sammenligning med LNAA	
Gennemsnitlig vedligeholdelsesdosis af pegvaliase	Varieres med ±10 %
Gennemsnitligt antal tabletter LNAA	Varieres med ±10 %
Omkostninger til aminosyretilskud for pegvaliase	Varieres med ±10 %
Omkostninger til aminosyretilskud for LNAA	Varieres med ±10 %
Omkostninger til medicinsk mad for patienter, der modtager pegvaliase	Varieres med ±10 %
Omkostninger til medicinsk mad for patienter, der modtager LNAA	Varieres med ±10 %
Pårørendes tid brugt på hjælp til patienter, der modtager pegvaliase	Varieres med ±10 %
Pårørendes tid brugt på patienter, der modtager LNAA	Varieres med ±10 %
Tidshorisont	Sættes til 5 år og 10 år

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser, da Medicinrådet ønsker at præsentere resultaterne ved ændring af værdien af specifikke parametre i stedet for resultatet af en arbitrær procentvis reduktion/øgning af bestemte omkostninger.

Der er usikkerhed om patienters reelle proteinindtag gennem aminosyretilskud ved behandling med pegvaliase. Medicinrådet præsenterer en følsomhedsanalyse, hvor det antages, at patienter ikke har behov for aminosyretilskud efter tre års behandling med pegvaliase.

Fagudvalget vurderer, at ca. 35 % ophører behandling inden for ét år, mens ansøger antager, at andelen er 10,3 %, hvilket bygger på *real-world* data fra USA. Medicinrådet ønsker at undersøge betydningen af andelen af patienter, der ophører behandling med pegvaliase, og præsenterer derfor en følsomhedsanalyse, hvor ansøgers estimat anvendes.

PKU er en kronisk sygdom, og patienter med PKU har ikke en øget dødelighed sammenlignet med den generelle befolkning. Behandling med pegvaliase kan derfor være livslang, og dette skal tidshorisonten i analysen afspejle. I Medicinrådets hovedanalyse anvendes en tidshorisont på 52 år baseret på den gennemsnitlige alder i PRISM-studiet. Medicinrådet præsenterer en følsomhedsanalyse, hvor den forventede,

maksimale behandlingslængde på 65 år anvendes. Ansøgers analyse indebærer, at effekten af behandlingerne antages at være konstant efter år 3. Medicinrådet præsenterer derfor en følsomhedsanalyse, hvor tidshorisonten sættes til 3 år, da omkostningerne forbundet med de specifikke behandlinger (pegvaliase, restriktiv diæt og LNAA) antages at være konstante de resterende år, når der ses bort fra diskontering.

Gennemsnittet af daglige injektioner med pegvaliase antages i hovedanalysen at være [redacted] injektioner på baggrund af *real-world* data fra USA. Fagudvalget vurderer, at dette estimat er usikkert, og Medicinrådet præsenterer derfor følsomhedsanalyser, hvor det gennemsnitlige antal daglige injektioner sættes til hhv. 1 og 2.

Der er usikkerhed forbundet med, hvor meget tid patienter i gennemsnit bruger på forberedelse af mad, når de er i behandling med pegvaliase eller LNAA. Medicinrådet præsenterer en følsomhedsanalyse, hvor det antages, at patienter eller pårørende bruger 10 timer på forberedelse af mad, uanset om patienten er på restriktiv diæt eller i behandling med pegvaliase eller LNAA.

Medicinsk mad betales af kommunen, og Center for PKU har opgjort omkostningerne for patienter, der er på restriktiv diæt eller modtager LNAA. Det er usikkert, hvilke omkostninger der er til medicinsk mad for patienter, der modtager pegvaliase, og Medicinrådet præsenterer derfor en følsomhedsanalyse, hvor det antages, at omkostningerne til medicinsk mad er ens for patienter, uanset om de modtager LNAA eller pegvaliase.

Medicinrådet præsenterer kun egne følsomhedsanalyser. Der præsenteres følsomhedsanalyser, hvor patienter ikke har behov for aminosyretilskud efter tre års behandling med pegvaliase, hvor andelen af patienter, der ophører behandling med pegvaliase, sættes til 10,3 %, og hvor tidshorisonten sættes til hhv. 65 år og 3 år. Derudover præsenteres følsomhedsanalyser, hvor det gennemsnitlige antal injektioner med pegvaliase sættes til hhv. 1 og 2, og hvor antallet af timer, patienter eller pårørende bruger på forberedelse af mad, sættes til 10 timer, uanset hvilken behandling patienten modtager. Yderligere præsenteres en følsomhedsanalyse, hvor det antages, at omkostningerne til medicinsk mad er ens for patienter, uanset om de modtager LNAA eller pegvaliase.

4.4 Opsummering af basisantagelser

I Tabel 9 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 9. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Komparatorer	Restriktiv diæt LNAA Sapropterin	Restriktiv diæt LNAA

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	20 år	52 år
Diskonteringsrate	4 % fra år 1-35, 3 % fra år 36	3,5 % fra år 1-35, 2,5 % fra år 36
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Patientomkostninger Kommunale omkostninger Omkostninger relateret til komorbiditeter	Lægemiddelomkostninger Hospitalsomkostninger Patientomkostninger Kommunale omkostninger
Andel patienter, der ophører behandling med pegvaliase efter 1 års behandling	10,3 %	35 %
Gennemsnitlige, daglige antal injektioner med pegvaliase	[redacted]	[redacted]
Behov for proteinindtag gennem aminosyretilskud ved behandling med pegvaliase	Efter år 1: 24,2 g Efter år 2: 20,3 g Efter år 3: 9,2 g	Efter år 1: 24,2 g Efter år 2: 20,3 g Efter år 3: 9,2 g
Monitorering	Ingen forskel mellem pegvaliase, restriktiv diæt og LNAA	Inkludering af omkostninger til blodprøver i løbet af det første år ved behandling med pegvaliase

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af Tabel 9.

De inkrementelle omkostninger forbundet med pegvaliase i forhold til restriktiv diæt eller LNAA varierer de første tre år, hvorefter de årlige inkrementelle omkostninger er konstante. Omkostninger for fjerde år i behandling og frem er således baseret på de samme omkostninger, der blot diskonteres for hvert år.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i Medicinrådets hovedanalyse, hvor pegvaliase sammenlignes med restriktiv diæt under antagelsen om livslang behandling, hvilket i gennemsnit er 52 år.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 10,3 mio. DKK.

Når behandlingsvarigheden antages at være 52 år, vil de gennemsnitlige årlige inkrementelle omkostninger være ca. [redacted] DKK pr. patient.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 10.

Tabel 10. Resultatet af Medicinrådets hovedanalyse ved sammenligning med restriktiv diæt, DKK, diskonterede tal

	Pegvaliase	Restriktiv diæt	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	52.466	45.300	7.166
Patientomkostninger	556.136	2.209.931	-1.653.795
Kommunale omkostninger	208.122	859.704	-651.582
Totale omkostninger	[redacted]	[redacted]	[redacted]

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse, hvor pegvaliase sammenlignes med LNAA. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 13,5 mio. DKK.

Når behandlingsvarigheden antages at være 52 år, vil de gennemsnitlige inkrementelle omkostninger pr. år være ca. [redacted] DKK pr. patient.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 11.

Tabel 11. Resultatet af Medicinrådets hovedanalyse ved sammenligning med LNAA, DKK, diskonterede tal

	Pegvaliase	LNAA	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	52.466	45.300	7.166
Patientomkostninger	556.136	472.907	83.229
Kommunale omkostninger	208.122	171.252	36.870
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 12.

Tabel 12. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalyserne, DKK

Scenarie	Inkrementelle omkostninger
Sammenligning med restriktiv diæt	
Resultatet af hovedanalysen	[redacted]
Patienter har ikke behov for aminosyretilskud efter tre års behandling med pegvaliase	[redacted]
Andel af patienter, der ophører behandling med pegvaliase, sættes til 10,3 %	[redacted]
Tidshorisont: 3 år 65 år	[redacted]
Det gennemsnitlige antal injektioner med pegvaliase sættes til: 1 injektion 2 injektioner	[redacted]
Forberedelse af mad antages at tage 10 timer, uanset hvilken behandling patienten modtager	[redacted]
Omkostninger til medicinsk mad ved behandling med pegvaliase sættes til at være lig omkostningerne til medicinsk mad ved behandling med LNAA	[redacted]
Sammenligning med LNAA	
Resultatet af hovedanalysen	[redacted]
Patienter har ikke behov for aminosyretilskud efter tre års behandling med pegvaliase	[redacted]
Andel af patienter, der ophører behandling med pegvaliase, sættes til 10,3 %	[redacted]
Tidshorisont: 3 år 65 år	[redacted]
Det gennemsnitlige antal injektioner med pegvaliase sættes til:	[redacted]

Scenarie	Inkrementelle omkostninger
1 injektion 2 injektioner	
Forberedelse af mad antages at tage 10 timer, uanset hvilken behandling patienten modtager	[redacted]
Omkostninger til medicinsk mad ved behandling med pegvaliase sættes til at være lig omkostningerne til medicinsk mad ved behandling med LNAA	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at pegvaliase vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Pegvaliase bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Pegvaliase bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Ansøgers estimat af patientantal og markedsandel

Ansøger antager, at 146 patienter vil være kandidater til behandling med pegvaliase, og at der årligt vil være ca. 4 nye patienter med moderat eller klassisk PKU over 16 år. Ansøger antager, at hvis pegvaliase bliver anbefalet som standardbehandling, vil pegvaliase have et markedsoptag på ca. [redacted] % i år 1 stigende til ca. [redacted] % i det femte år efter en anbefaling. Markedsoptaget er antaget på baggrund af ansøgers forventning om, at patienter, der på nuværende tidspunkt er i behandling med LNAA, vil forblive på LNAA. Dermed antager ansøger, at pegvaliase kun vil blive tilbudt til ubehandlede patienter eller patienter på restriktiv diæt. Ansøger antager, at 10,3 % ophører behandling med pegvaliase det første år på grund af bivirkninger eller manglende effekt. For patienter, der ophører behandling med pegvaliase, antager ansøger, at 62 % af dem vil skifte til behandling med LNAA, og at de resterende 38 % vil skifte til restriktiv diæt.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget vurderer, at ansøgers antagelser vedrørende markedsoptag er rimelige, da man grundet begrænset kapacitet i Center for PKU kun kan opstarte behandling med pegvaliase for et begrænset antal patienter om året. Fagudvalget vurderer dog, at markedsoptaget fortsat vil være stigende efter år 5, da flere patienter forventes at vælge behandling med pegvaliase.

Fagudvalget anslår, at ca. 35 % af patienterne vil ophøre behandling med pegvaliase det første år af behandling. For patienter, der ophører behandling med pegvaliase, vurderer fagudvalget, at 70 % vil modtage LNAA, og at 30 % vil skifte til restriktiv diæt. Medicinrådet ændrer derfor egen hovedanalyse jf. fagudvalgets vurderinger. Estimater for patientantal pr. år ses Tabel 13.

Tabel 13. Medicinrådets estimat af antal patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Pegvaliase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Restriktiv diæt	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LNAA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Anbefales ikke		
Pegvaliase	0	0	0	0	0
Restriktiv diæt	58	61	64	66	69
LNAA	88	89	90	91	92

Da omkostninger til medicinsk mad betales af kommunen, ekskluderer Medicinrådet omkostningerne fra budgetkonsekvensanalysen.

Medicinrådet accepterer ansøgers antagelser vedr. patientantal, men ændrer andelen af patienter, der forventes at ophøre behandling til 35 %. Derudover antages det, at 70 % af disse patienter vil skifte til LNAA, og 30 % vil skifte til restriktiv diæt.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet har korrigeret følgende estimater i sin budgetkonsekvensanalyse i forhold til ansøgers budgetkonsekvensanalyse:

- 35 % antages at ophøre behandling med pegvaliase efter første år af behandlingen.
- 70 % af patienterne, der ophører behandling med pegvaliase, antages at skifte til LNAA, og 30 % antages at skifte til restriktiv diæt.
- Omkostninger til medicinsk mad ekskluderes fra budgetkonsekvensanalysen.

Medicinrådet estimerer, at anvendelse af pegvaliase vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 14.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 18,1 mio. DKK i år 5.

Tabel 14. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7. Diskussion

Behandling med pegvaliase er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med restriktiv diæt. Behandling med pegvaliase er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med LNAA. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkost-ningerne for pegvaliase. Der er usikkerhed forbundet med flere parametre i analysen, som har stor betydning for analysens resultat, herunder behandlingslængden, andelen af patienter, der ophører behandling med pegvaliase, og det gennemsnitlige antal daglige injektioner med pegvaliase.

Analysens tidshorisont afspejler den forventede behandlingsvarighed. Hovedanalysen indebærer en tidshorisont på 52 år, hvilket bygger på antagelsen om, at behandling med pegvaliase er livslang, og der tages udgangspunkt i gennemsnitsalderen i PRISM-studiet. Det er usikkert, hvor længe patienterne reelt vil være i behandling med pegvaliase. På baggrund af kliniske data antages det, at den fulde effekt af pegvaliase opnås efter tre års behandling. Herefter antages effekten at være konstant, og omkostningerne forbundet med pegvaliase, restriktiv diæt og LNAA er ligeledes konstante efter tre års behandling. Omkostningerne til behandling de efterfølgende år er således baseret på de samme tal, men diskonteringen gør, at de gennemsnitlige omkostninger pr. år falder for hvert år patienterne er i behandling.

Ved antagelsen om livslang behandling (52 år) vil de inkrementelle omkostninger for pegvaliase være ca. [redacted] DKK pr. patient sammenlignet med restriktiv diæt. Det betyder, at de gennemsnitlige årlige inkrementelle omkostninger for pegvaliase vil være ca. [redacted] DKK pr. patient pr. år sammenlignet med restriktiv diæt. Sættes tidshorisonten til 3 år eller 65 år, er de samlede inkrementelle omkostninger hhv. ca. [redacted] DKK og ca. [redacted]. DKK i sammenligningen med restriktiv diæt. De maksimale gennemsnitlige inkrementelle omkostninger pr. år forventes at være ca. [redacted] DKK i sammenligningen med restriktiv diæt. Dette er estimeret ud fra de gennemsnitlige årlige inkrementelle omkostninger ved tre års behandling. Jo længere patienterne er i behandling, jo lavere gennemsnitlige inkrementelle omkostninger pr. år vil der være.

Ved antagelsen om livslang behandling (52 år) vil de inkrementelle omkostninger for pegvaliase være ca. [redacted] DKK pr. patient sammenlignet med LNAA. Det betyder, at

de gennemsnitlige årlige inkrementelle omkostninger for pegvaliase vil være ca. [redacted] DKK pr. patient pr. år sammenlignet med LNAA. Sættes tidshorisonten til 3 år eller 65 år, er de samlede inkrementelle omkostninger hhv. ca. [redacted] DKK og ca. [redacted]. DKK i sammenligningen med LNAA. De maksimale gennemsnitlige årlige inkrementelle omkostninger forventes at være ca. [redacted] DKK pr. år i sammenligningen med LNAA. Dette er estimeret ud fra de gennemsnitlige inkrementelle omkostninger pr. år ved tre års behandling. Jo længere patienterne er i behandling, jo lavere gennemsnitlige inkrementelle omkostninger pr. år vil der være.

Andelen af patienter, der ophører behandling med pegvaliase, og det gennemsnitlige antal daglige injektioner med pegvaliase har ligeledes stor betydning for analysens resultat. Da estimaterne for disse parametre ikke bygger på et sikkert datagrundlag, vurderer Medicinrådet, at de bidrager til stor usikkerhed i analysen.

Fagudvalget vurderer, at ca. 35 % ophører behandling med pegvaliase. Sættes andelen til 10,3 %, som ansøger antager på baggrund af *real-world* data fra USA, øges de inkrementelle omkostninger fra ca. [redacted] DKK til ca. [redacted] DKK i sammenligningen med restriktiv diæt, mens de øges fra ca. [redacted] DKK til ca. [redacted] DKK i sammenligningen med LNAA.

Det gennemsnitlige antal daglige injektioner med pegvaliase på [redacted] er baseret på *real-world* data fra USA. Sættes antallet til 1 injektion dagligt, reduceres de inkrementelle omkostninger fra ca. [redacted] DKK til ca. [redacted] DKK i sammenligningen med restriktiv diæt. Sættes antallet til 2, øges de inkrementelle omkostninger til ca. [redacted] DKK.
Sættes antallet til 1 injektion dagligt, reduceres de inkrementelle omkostninger fra ca. [redacted] DKK til ca. [redacted] DKK i sammenligningen med LNAA. Sættes antallet til 2, øges de inkrementelle omkostninger til ca. [redacted] DKK.

I Medicinrådets hovedanalyse antages det, at patienter der behandles med pegvaliase, ugentligt bruger 3,3 timer, 2,7 timer og 1,2 timer i hhv. år 1, 2 og 3 (og de efterfølgende år) på forberedelse af mad. I sammenligningen med restriktiv diæt har det betydning, om det antages, at alle PKU-patienter bruger 10 timer om ugen på forberedelse af mad. De inkrementelle omkostninger stiger da fra ca. [redacted] DKK til ca. [redacted] DKK. Det har minimal betydning i sammenligningen med LNAA, da det i hovedanalysen antages, at der ikke er væsentlig forskel i tidsforbrug for patienter på pegvaliase og patienter på LNAA. Det har lille betydning for analysens resultat, om det antages, at patienter ikke har behov for aminosyretilskud efter tre års behandling med pegvaliase. Det har minimal betydning for analysens resultat, om omkostninger til medicinsk mad for patienter, der modtager pegvaliase, antages at være tilsvarende omkostningerne for patienter, der modtager LNAA.

Lægemiddelprisen for pegvaliase er betinget af, at pegvaliase anbefales som standardbehandling. Anbefales pegvaliase ikke, vil den gennemsnitlige inkrementelle omkostning pr. patient være ca. [redacted] DKK sammenlignet med restriktiv diæt og ca. [redacted] DKK sammenlignet med LNAA.

8. Referencer

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
2.0	26. maj 2021	Godkendt af Medicinrådet efter nyt pristilbud. Ingen yderligere ændringer.
1.0	28. april 2021	Godkendt af Medicinrådet.

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 20 år i sammenligning med restriktiv diæt. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 15.

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 20 år i sammenligning med restriktiv diæt. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 16.

Tabel 15. Resultatet af ansøgers hovedanalyse for sammenligningen med restriktiv diæt, DKK, diskonterede tal

	Pegvaliase	Restriktiv diæt	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	2.084	0	2.084
Patientomkostninger	177.165	1.055.330	-878.165
Omkostninger relateret til komorbiditet	79.758	92.928	-13.170
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 16. Resultatet af ansøgers hovedanalyse for sammenligningen med LNAA, DKK, diskonterede tal

	Pegvaliase	LNAA	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	2.084	0	2.084
Patientomkostninger	177.165	139.831	37.334
Omkostninger relateret til komorbiditet	79.758	92.928	-13.170
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af pegvaliase vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 17.

Tabel 17. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Forhandlingsnotat

Dato for behandling i Medicinrådet	26.05.2021
Leverandør	Biomarin
Lægemiddel	Pegvaliase (Palynziq)
Ansøgt indikation	Indiceret til behandling af patienter med fenylketonuri (PKU) i alderen 16 år og ældre, som har tilstrækkelig kontrol af fenylalanin i blodet (fenylalaninniveau i blodet på mere end 600 mikromol/l) på trods af forudgående anvendelse af tilgængelige behandlingsmuligheder.

Forhandlingsresultat

Amgros har som tidligere præsenteret en aftale om følgende priser på Pegvaliase:

Tabel 1: Nuværende priser på Pegvaliase

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Pegvaliase	2,5 mg	1 stk.	2.061,21	[redacted]	[redacted]
Pegvaliase	10 mg	1 stk.	2.061,21	[redacted]	[redacted]
Pegvaliase	20 mg	1 stk.	2.061,21	[redacted]	[redacted]

Aftalen er gældende til 31.12.2022 med mulighed for 12 måneders forlængelse.

Amgros har forhandlet et tilbud om en yderligere rabat på Pegvaliase. Denne pris er betinget af, at Medicinrådet anbefaler Pegvaliase, som standardbehandling. Prisen fremgår af tabellen nedenfor. Anbefaler Medicinrådet ikke Pegvaliase, som standardbehandling er priserne i tabel 1 gældende.

Tabel 2: Ny pris betinget af Medicinrådets anbefaling

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Pegvaliase	2,5 mg	1 stk.	2.061,21	[redacted]	[redacted]
Pegvaliase	10 mg	1 stk.	2.061,21	[redacted]	[redacted]
Pegvaliase	20 mg	1 stk.	2.061,21	[redacted]	[redacted]

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi på nuværende tidspunkt **har** opnået den bedste pris på pegvaliase. Denne vurdering baserer vi på følgende punkter:

[redacted]

Konklusion

Det er Amgros' vurdering, at vi har fået den bedste pris på pegvaliase, som leverandøren har mulighed for at tilbyde i Danmark på nuværende tidspunkt.

Status fra andre lande

Pegvaliase er på vej gennem processen i Norge. Der er offentliggjort en metodevurdering d. 12-03-2021[1]. En beslutning om anbefaling forventes snarest. Pegvaliase er også under behandling af TLV i Sverige og NICE.

[1] Pegvaliase (Palynziq) (nyemetoder.no)

Danish Medicines Council
Dampfærgevej 27-29, 3. th
2100 København Ø
Denmark

31st March 2021

Dear Sir or Madam,

Re: Evaluation of pegvaliase (Palynziq®)

Many thanks for undertaking an evaluation of pegvaliase for the treatment of patients over 16 years of age with phenylketonuria (PKU).

Following a review of the final drafts of the evaluation and the health economic reports of which BioMarin deems largely acceptable, BioMarin would like to comment on some points of the document for further clarification on the clinical and economic value of Pegvaliase in the management of PKU in Denmark:

Health Economic Report Point	**Responses**
p. 26, *"Table 13: The Danish Medicines Council's estimate of the number of patients per year"*	The Company disagrees with the rate of pegvaliase treatment uptake in Denmark that has been estimated by the expert committee. The numbers provided in the table are 44 patients in years 1 and 2, 55 in year 3, 66 in year 4 and 77 in year 5. However, this contrasts with the Danish experts' estimations and the Company's experience of treatment uptake in the US and Germany. Primarily, in Denmark there is only one center in Copenhagen that would initiate treatment. The clinical experts have no experience with the treatment as there have not been any clinical trial sites in Europe. In addition, the availability of nurses and physicians in the clinic is limited and therefore this will be a factor keeping low the numbers of pegvaliase patients. According to the Head of the PKU clinic, Copenhagen University Hospital, Rigshospitalet, Professor, Allan Lund regarding the initiation of pegvaliase treatment experts would need to clarify the PKU patients that would benefit more from initiating treatment and the need to assess the capacity of centre to initiate pegvaliase treatment. In his view, in the first year, the center would have capacity for a maximum of 5 patients reaching a maximum of 10 new patients per year, the following years. This argument is further supported by Kristen Ahring MSc, Clinical Dietitian at the PKU Center, Rigshospitalet, who argues that Denmark has patients of all ages and with all types of PKU (mild, moderate, classic),however, in her view the largest target audience will be younger adults with classic mutation, as they would benefit switching from Phe restricted diet. Older PKU patients treated with LNAAs for years would probably, be accustomed and comfortable with their treatment and probably not keen to start a new one. Furthermore, as she notes, it

should not be forgotten that it requires a large capacity to start each individual patient with pegvaliase treatment.

In addition, the low uptake has been confirmed by the real world experience in Germany where until March 2021 (date of issue of marketing authorisation valid throughout the European Union was 3rd May 2019) a total of 50 patients had started treatment, despite the G-BA initial estimation of 435 eligible PKU patients to pegvaliase treatment. The capacity of the German centres for the first year has been 14 sites treating PKU with a capacity of 5 patients per centres during induction/ titration and the total capacity for pegvaliase patients (assuming 1-2 induction/titration rounds) is estimated to be 70-140 patients.

Even in the US that the clinical trials had taken place, it is shown that market uptake takes time due to limited capacity and experience. There are currently, approximately 8,000 patients in clinic and the graph below shows the uptake.

The estimations of the Company for the number of patients per year, considering the opinions of the Danish experts and the experience from the US and Germany can be found in the table below and have been also presented in the virtual meeting with AMGROS on the 26th of March 2021.

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent		***3-5***	***8-15***	***18-30***	***28-45***
Incident	***3-5***	***5-10***	***10-15***	***10-15***	***10-15***
Total	**3-5**	**8-15**	**18-30**	**28-45**	**38-60**

	Discontinuation rate	10.3%	10.3%	10.3%	10.3%	10.3%
	Total	**2.7-4.5**	**7.5-14**	**16.5-27.4**	**25.4-40.9**	**34.4-54.3**
	DMC perspective	***44***	***44***	***55***	***66***	***77***

Therefore, the uptake of pegvaliase treatment will be very gradual and it is not expected that Denmark would reach 44 patients receiving pegvaliase treatment before the 5th year of launch.

Evaluation Report Point	**Responses**
p. 14 *"a significant proportion from the PRISM studies may have had mild PKU, which may affect the transferability of results to Danish patients, where only patients with moderate and classical PKU are assessed to be candidates"*	The genotype of the participants in PRISM trials had not been identified. However, the mean (SD) phenylalanine (Phe) concentration baseline of participants in PRISM 1 was 1232.7 µmol/L (386.36), indicating patients participating in the studies had difficulty maintaining their Phe levels at a low level prior to their introduction to pegvaliase treatment. The observed Phe levels decline had been sustained through 48 months of follow-up. Pegvaliase is the first and only therapy that directly addresses the underlying cause of PKU in all patients by substituting the missing or deficient Phe-metabolising enzyme activity, irrespective of residual PAH enzyme activity, therefore, there should not be any impact on the transferability of the results to the Danish PKU patients who have difficulty controlling their blood phe levels, irrespective of their genotype.
p. 18 *"In the protocol, quality of life is defined as a critical efficacy target that the expert committee wanted measured with the PKU-specific tool The Phenylketonuria impact and treatment Quality Of Life Questionnaire (PKU-QOL) or the generic tool The World Health Organization Quality of Life assessment-100 (WHOQOL-100). The applicant has not identified usable data for assessing the efficacy target for some of the desired comparisons"*	The Company had raised the issue of the outcomes tools' appropriateness while reviewing the initial draft DMC protocol. In the response to this document the Company raised some important reasons why the specific tools suggested by the expert committee were not used. More specifically: • Initial psychometric validation of the PKU-QoL shows poor content and construct validity. There has been further psychometric evaluation of this instrument and no clinically important difference (CID) estimates have been derived. • In the past, reducing blood Phe to the levels observed with pegvaliase was not possible and hence the tools were not designed to be sensitive enough to measure Phe at these levels. The Company is undertaking additional studies to investigate the utility of different patient centred outcome tools to understand the impact of PKU on a patient's QOL s and have initiated an outcomes study in Germany to explore this.

	• There is a poor correlation of PKU-QoL to the SF36. The Company is collecting data on both PKU-QoL and EQ-5D from the Outcomes Study in Germany which will help identify the correlation between EQ5D and PKU-QoL. • There is no Clinical Important Difference (CID) for the PKU-QoL total score. The tool is untested in its ability to distinguish between patients with differing levels of blood phenylalanine specifically blood phenylalanine levels within the normal range. The DMC has stated a 10-point change however there is an inherent lack of sensitivity of the tool, lack of longitudinal evidence and the PKU-QoL tool lacks psychometric properties. • The limited data on the use of the SF-36, BRIEF and WHO-QoL in PKU has shown the tools to be insensitive. The most common result of an insensitive instrument is to show 'ceiling effects' (i.e. patients answer 'no burden' to almost all questions) and is caused by poor content validity rather than low disease burden. Using instruments with ceiling effects to measure disease burden and benefit of treatment is inappropriate and ineffective. It is extremely difficult for a clinically meaningful change to be reported when baseline scores begin high due the presence of ceiling effects. • The Company has no experience of using WHO-QoL and no assessment of its clinical or psychometric properties. Furthermore, the Company has no knowledge of its sensitivity to Phe levels nor any view on its reliability to demonstrate QoL improvements in patients with Phe levels reaching those achieved with pegvaliase. As such its use cannot be supported. However as mentioned above the Company has experience with patient centred tools that have shown to be insensitive, such as SF-36, EQ-5D and [redacted]
p. 22, *"According to the EPAR, a large proportion surpassed from PRISM-1 (73%) directly to part 4 in PRISM-2, indicating that they did not tolerate the treatment or could not achieve the desired response from a fixed dose of resp. 20 mg and 40 mg a day."*	PKU patients' response to pegvaliase treatment is individual, it varies and is closely related to their immune response to the treatment In PRISM-1, pegvaliase-naïve participants with blood Phe>600 µmol/L were randomized 1:1 to a maintenance dose of 20 mg/day or 40 mg/ day of pegvaliase. Participants in PRISM-1 continued pegvaliase treatment in PRISM-2, a 4-part clinical trial that included an open-label, long-term extension study of pegvaliase doses of 5 mg/day to 60 mg/day (Part 4). Any participants unable to titrate or maintain a randomized 20 mg/day or 40 mg/day dose of pegvaliase in PRISM-1 enrolled directly into PRISM-2 Part 4, an open-label extension, where maintenance dose could be adjusted based on individual efficacy and tolerability. Furthermore, once recruitment for 165-302 (Part 2) was completed, 165-301 was closed early as the primary study objective of identifying subjects for the randomized discontinuation trial had been fulfilled. Thus, the percentage of patients moving directly into Part 4 of PRISM trial is not indicative of the effectiveness (or lack thereof) of pegvaliase but more so to allow for a bespoke titration program that caters to the individuality of immune response for each patient to pegvaliase. It should be noted that Part 4 has a dosing

	schedule akin to the real-world where patients are titrated according to their immune responses. Further, secondary data analysis shows that 75% of patients (Part 4) are controlled after 36months of treatment initiation according to the recommended European PKU treatment guidelines.
p.23, *"In addition, low blood levels of phenylalanine (hypophenylalaninemia) were observed in almost half of patients. The expert committee has no experience with this condition and, according to the EPAR, the clinical consequences of low blood levels of phenylalanine are unknown."*	Hypophenylalaninemia is not an adverse event but more an indicator of pegvaliase efficacy. Once the immune system is matured and is not fighting against pegvaliase anymore, patients experience a drop in Phe levels. Patients with less immune reaction to pegvaliase, can demonstrate more extensive drop. The company has compared the ratio of adverse events in patients with hypophenylalaninemia and those that have not experienced it and saw that patients with hypophenylalaninemia had less adverse events besides a temporary hair loss, which can also happen with diet when Phe levels drops very quickly and inadequate natural protein is consumed. Furthermore, there was a provision in the study protocol for patients experiencing hypophenylalaninemia to increase the natural protein intake in their diets to overcome the event.
p. 27, *"data for the relevant measurement times have been obtained from the EPAR for PRISM-2, Part 2. From this it appears, among other things, that there were no significant changes in attention symptoms measured with ADHD-RS-IV."*	As mentioned in the clinical dossier, in the 165-301 with pegvaliase treatment, 24-month follow-up data showed a mean decrease from Baseline (BL) in subscale scores of 6.4 points. In the subset of patients with BL ADHD RS-IV IA subscale score >9 (i.e. symptomatic in terms of inattention) patients showed the greatest improvement in inattention scores (mean decrease from BL in subscale scores of 9.6 points. Further, analysis of the change from BL in subscale score in relation to blood Phe showed that the 53 patients in the quartile with the largest blood Phe reduction also experienced the greatest reduction in subscale score, a mean (SD) decrease of 7.5 (5.6) points. Indeed, in the 8-week RDT in 165-302 the difference in least squares (LS) mean changes (RDT Entry to Week 8) with 95% confidence interval (CI) were reported for each PLA group compared to pooled pegvaliase data. In both the all patients analysis and in the subset with subscale score >9 before pegvaliase treatment these differences in LS mean changes were not significant over this short period of time, although the difference approached significance in the subset with subscale score >9 for PLA 20mg/day compared to pooled pegvaliase (LS mean diff 4.7 (95% CI -0.19, 9.5, p=0.06). However, the 8 weeks duration of the RDT was not enough time for neurocognitive changes to show as from the Company's experience in pegvaliase and sapropterin clinical programmes it takes time to observe neurocognitive changes.
p. 29, *"the expert committee estimates that treatment with pegvaliase will contribute positively to patients' quality of life*	The company considers that the percentage of discontinuation rate that has been adopted by the expert committee is very high and is not representing the experience from clinical studies, after inserting the mitigation measures and real word evidence of pegvaliase.

through fewer restrictions and estimates that pegvaliase treatment may be relevant to start up in approximately 100 patients corresponding to the majority of patients currently receiving LNAA and half of patients with classical PKU. Of these, 30-40% are expected to discontinue treatment due to side effects, lack of efficacy or challenges with treatment resistance."	As the primary reason for discontinuing pegvaliase has historically been experience of adverse events (AEs), the company would like to state again that, the introduction of risk mitigation measures including pre-medication and flexible dosing during Study 165-301 reduced the rate of discontinuation due to AEs in the first 6 months of treatment from 15.4% to 5.9% of patients. In total 5.6% of pegvaliase-treated patients experienced acute hypersensitivity reactions, 4.6% during the induction/titration compared to 1.7% during the maintenance phase. Hypersensitiviy reactions are consistent with a type III, IgM-related mechanism, which has allowed patients to be successfully re-challenged with pegvaliase. As shown in the Supplementary Table 2 (from Thomas et al. 2018) pegvaliase discontinuation during the first 6 months after the implementation of additional safety procedures was 13.6%. Most AEs occurred during the first 6 months of treatment, coinciding with the induction/titration phases, when the immune response against pegvaliase is the strongest. **Supplementary Table 2.** Pegvaliase Discontinuation in Early (First 6 Months) Treatment Before and After Implementation of Additional Safety Procedures (intent-to-treat population, N=261) Enrolled Before Implementation (N=143) / Enrolled After Implementation (N=118) Discontinued pegvaliase early, n (%): 34 (23.8%) / 16 (13.6%) Reason for pegvaliase discontinuation, n (%) Adverse event: 22 (15.4%) / 7 (5.9%) Lost to follow-up: 0 / 1 (0.8%) Other: 0 / 1 (0.8%) Physician decision: 3 (2.1%) / 1 (0.8%) Pregnancy: 1 (0.7%) / 0 Protocol deviation: 1 (0.7%) / 0 Withdrawal by participant: 7 (4.9%) / 6 (5.1%) Furthermore, evidence from real world in the US, shows a 10.8% discontinuation rate.

We hope we have clarified the points above and please do not hesitate to contact us for any further information with you.

Yours sincerely,

Mattias Janzen
Director, Country Manager Nordics

Fra:	Karen Kleberg Hansen
Til:	Soren Hansen; Katrine Jürs; Camilla Nybo Holmberg
Cc:	Annemette Anker Nielsen
Emne:	SV: BioMarins høringssvar angående Pegvaliase
Dato:	19. april 2021 14:02:00
Vedhæftede filer:	image001.png image002.jpg

Kære Søren

Tak for Biomarins høringssvar vedrørende Medicinrådets vurdering af lægemidlets værdi for pegvaliase og vedrørende den sundhedsøkonomiske afrapportering.

Vi har gennemgået jeres kommentarer til vurderingsrapporten og finder ikke anledning til at ændre den nuværende kategorisering.
På baggrund af jeres kommentarer til den sundhedsøkonomiske afrapportering, har sekretariatet ændret analysen af budgetkonsekvenserne, således at den er baseret på Biomarins antagelser vdr. markedsoptag.

Jeres høringssvar indgår i den videre behandling og bliver offentliggjort sammen med den endelige anbefaling.

Mvh
Karen

Karen Kleberg Hansen
Sundhedsvidenskabelig specialkonsulent
Cand.scient., ph.d.
kkh@medicinraadet.dk
+45 30 34 46 36

Medicinrådet
Dampfærgevej 27-29, 3. th.
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Fra: Soren Hansen <soren.hansen@bmrn.com>
Sendt: 31. marts 2021 12:36
Til: Karen Kleberg Hansen <kkh@medicinraadet.dk>; Katrine Jürs <KJU@medicinraadet.dk>; Camilla Nybo Holmberg <CNH@medicinraadet.dk>

Emne: BioMarins høringssvar angående Pegvaliase

Kære Karen, Katrine og Camilla

Hermed BioMarins høringssvar omkring evalueringen af Pegvaliase.

Med ønsket om en god påske.

Senior Territory Manager, Nordic
BioMarin Europe Limited
Mobile: +45 61199008
Email: soren.hansen@bmrn.com

Medicinrådet

Medicinrådets vurdering vedrørende pegvaliase til behandling af patienter over 16 år med fenylketonuri (PKU)

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
Godkendelsesdato	24. marts 2021
Dokumentnummer	109431
Versionsnummer	1.0

Indholdsfortegnelse

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 24. marts 2021

1. Medicinrådets konklusion

Medicinrådet finder, at den samlede værdi af pegvaliase sammenlignet med restriktiv diæt eller semifri diæt i kombination med LNAA ikke kan kategoriseres i henhold til Medicinrådets metoder. Rådet vurderer dog, at pegvaliase samlet set ser ud til at være et bedre behandlingsalternativ end de nuværende behandlingsmuligheder, fordi det hos nogle patienter kan sænke fenylalaninkoncentrationen i blodet til under 600 µmol/l. Det antages at bidrage positivt til patienternes livskvalitet gennem forbedrede eksekutive funktioner og færre kostrestriktioner på trods af væsentlige bivirkninger forbundet med behandling med pegvaliase.

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi, fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag. I de situationer konkluderer Medicinrådet, at samlet værdi kan ikke kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at tro, at det nye lægemiddel er dårligere end gældende standardbehandling eller ikke. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring.

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET) I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

ADHD-RS-IV:	*Investigator-rated Attention-Deficit Hyperactivity Disorder Rating Scale*
BH4:	Tetrahydrobiopterin
BRIEF-V:	*Behaviour Rating Inventory of Executive Function* – voksne
CANTAB:	*Cambridge Neuropsychological Test Automated Battery*
CI:	Konfidensinterval
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
mITT:	*Modified Intention To Treat*
LNAA:	*Large neutral amino acids*
PAH:	Fenylalanin hydroxylase
PKU:	Fenylketonuri
PKU-QOL:	*The Phenylketonuria impact and treatment Quality Of Life Questionnaire*
POMS:	*Profile of Mood States*
POMS-TMD:	*Profile of Mood States - Total Mood Disturbance*
TAP:	*Test of Attentional Performance*
WCST:	*Wisconsin Card Sorting Test*
WHOQOL-100:	*The World Health Organization Quality of Life assessment-100*

3. Introduktion

Formålet med Medicinrådets vurdering af pegvaliase til behandling af patienter over 16 år med fenylketonuri (PKU) er at vurdere den værdi, lægemidlet har, sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra BioMarin. Medicinrådet modtog ansøgningen den 11. januar 2021.

Det kliniske spørgsmål er: *Hvilken værdi har pegvaliase sammenlignet med enten en restriktiv diæt eller en semifri diæt i kombination med LNAA til behandling af PKU-patienter med ukontrollabelt niveau af fenylalanin i blodet?*

3.1 Fenylketonuri

Fenylketonuri (PKU) er en medfødt stofskiftedefekt med autosomal recessiv arvegang. PKU skyldes mangel på funktionelt fenylalanin hydroxylase (PAH), som er et leverenzym involveret i omdannelsen af aminosyren fenylalanin til tyrosin. Fenylalanin indgår i alle kostens proteiner, og ved manglende omdannelse ophobes fenylalanin i blod og væv. Fenylalanin transporteres aktivt over blodhjernebarrieren via et aminosyretransport-protein og ved forhøjet fenylalaninkoncentration i blodbanen øges transporten ind i hjernen, hvor forhøjede mængder fenylalanin har skadelig virkning. De skadelige virkninger omfatter:

- skader på de skeder, der beskytter nervebaner (myelinskader) i form af forsinket eller manglende myelinisering hos børn og tab af myelin hos voksne [1–3]
- påvirkning af neurotransmittersignalering i hjernen [4]
- påvirkning af hjernens glutaminerge system [5]
- påvirkning af proteinproduktionen i hjernen [3].

Udover den skadelige virkning af fenylalanin vil der dannes mindre tyrosin, som er et forstadie til neurotransmitterne dopamin og serotonin. Lavere niveauer af tyrosin i hjernen, hos både børn og voksne, fører blandt andet til svækket neurotransmittersignalering i hjernen, med konsekvenser på indlæring, humør og social funktionsevne.

Uden behandling fører PKU til irreversibel hjerneskade hos børn, som kan medføre underudviklet hjerne (mikrocefali), neurologiske symptomer, mental retardering og epilepsi. Børn er pga. deres umodne hjerne mere udsatte, men også voksne vil uden behandling udvikle neurologiske, psykiatriske og psykologiske symptomer [6]. PKU indgår i det neonatale screeningsprogram, og behandling kan derfor iværksættes hurtigt, inden hjerneskade opstår. Følges behandlingen, udvikler barnet sig normalt. Tidligt og kontinuerligt behandlede patienter med PKU har normal intelligenskvotient, men scoren ligger lidt lavere sammenlignet med raske søskende og forældre [7].

Behandlingen af PKU indbefatter en meget restriktiv diæt med det formål at holde fenylalanin-koncentrationen i blodet og hjernen nede. Patienten får ofte sværere ved at følge diæten med alderen. Hos voksne forventes symptomerne at være reversible, hvis diæten genoptages efter en rimelig tid. Ved forhøjede niveauer af fenylalanin vil patienterne opleve symptomer i form af neuropsykologiske komplikationer såsom hovedpine, angst, aggressivitet og depression, som indtræder hurtigt og aftager, når fenylalaninkoncentration falder igen. Endelig har flere studier beskrevet påvirkning af de eksekutive funktioner hos velbehandlede patienter med en i øvrigt normal mental udvikling [8,9]. Eksekutive funktioner indebærer f.eks. evnen til planlægning samt kontrol af adfærd og handlinger, dømmekraft, fleksibilitet i tankegang, evnen til at ændre strategier samt løbende at justere egen adfærd. Som konsekvens ses problemer med job, uddannelse, sociale relationer, søvn og en manglende evne til at interagere med samfundet [10–14]. Sværhedsgraden af symptomer korrelerer med koncentrationen af fenylalanin i blodet [7,15], men følsomheden overfor forhøjet fenylalanin varierer fra patient til patient. Følsomheden menes at falde med alderen for nogle patienter. PKU er forbundet med forringet livskvalitet [16–18], og sværhedsgraden af PKU er negativt associeret med patientens helbredsrelaterede livskvalitet [16]. Diætbehandlingen medfører, at PKU-patienter har øget risiko for nyresvigt, knogleskørhed, åreforkalkning, forhøjet blodtryk og blodprop i hjernen [19-21]. Prævalensen af PKU i Danmark er estimeret til ca. 1:10.000 [22], og der fødes årligt 6-10 børn med PKU i Danmark [23]. Alle danske patienter behandles ved Center for PKU under Rigshospitalet i København. Ifølge Den Neonatale Screenings Biobank (PKU-biobanken) er der 488 PKU-patienter i Danmark, hvoraf 357 er 16 år eller ældre. 46 af de voksne patienter er sendiagnosticeret.

PKU inddeles i fire sværhedsgrader. I Danmark baseres klassifikationen af PKU på, hvilke(n) mutationer patienterne har, idet nogle mutationer påvirker funktionen af PAH-enzymet mere end andre. Nogle patienter vil have nogen, omend betydeligt, nedsat enzymaktivitet, mens andre slet ingen enzymaktivitet har. Patienter med nogen bevaret PAH-aktivitet har mildere sygdom og lettere ved at holde fenylalaninniveauet nede. De kan også være kandidater til medicinsk behandling (se afsnittet Nuværende behandling), der øger PAH-aktiviteten. Patienterne, voksne og børn samlet, opdeles i:

- klassisk PKU (40 %)
- moderat PKU (6 %)
- mild PKU (25 %)
- mild hyperfenylalaninæmi (20 %).

Ni procent er enten uklassificerede, ikke undersøgte eller andet. Tallene inkluderer ikke sendiagnosticerede patienter. Tallene er baseret på data fra PKU-databasen.

I andre lande tager klassifikationen af PKU udgangspunkt i fenylalaninniveauet i blodplasma før påbegyndelse af diæt. Her kan klasserne defineres på følgende måde:

- klassisk PKU (> 1.200 µmol/L)
- moderat PKU (900-1.200 µmol/L)
- mild PKU (600-900 µmol/L)

- mild hyperfenylalaninæmi (< 600 µmol/L) [24].

Til sammenligning ligger koncentrationen hos baggrundsbefolkningen mellem cirka 40-60 µmol/L.

Fagudvalget vurderer, at det i praksis vil være unge og voksne patienter med moderat og klassisk PKU, der har den største risiko for ikke at kunne nedbringe deres fenylalaninkoncentration i blodet til under 600 µmol/L ved diæt eller anden behandling. Derved vil de have ukontrollerede blodniveauer af fenylalanin, som angivet i indikationen for pegvaliase.

Ved indførelsen af en ny behandlingsmulighed, der tillader en mere lempelig diæt, forventer fagudvalget, at flere patienter vil foretrække medicinsk behandling fremfor diæt alene.
I alt udgør populationen af danske patienter over 16 år med moderat eller klassisk PKU 146 patienter (PKU-databasen, 2020). Hovedparten forventes af have fenylalaninniveauer over 600 µmol/L ved diæt eller anden behandling. Alle patienter monitoreres livslangt ved at indsende en selvadministreret blodprøve til det behandlende center en gang om måneden.

3.2 Pegvaliase

Pegvaliase er indiceret til behandling af patienter med PKU i alderen 16 år og ældre, som har utilstrækkelig kontrol af fenylalanin i blodet (defineret ved et fenylalaninniveau i blodet på mere end 600 µmol/L påvist i over 50 % af indsendte månedlige blodprøver over en sammenhængende periode på minimum 6 måneder [20]) på trods af forudgående anvendelse af tilgængelige behandlingsmuligheder inklusive sapropterin og restriktiv diæt.

Pegvaliase er et rekombinant enzym, som omdanner fenylalanin til ammoniak og transkanelsyre, som udskilles i leveren. Herved sænkes patientens fenylalaninniveau i blodet uafhængigt af PAH-aktivitet, hvilket adskiller sig fra tilgængelige terapeutiske alternativer som sapropterin.
Pegvaliase administreres som en subkutan injektion, og den anbefalede startdosis er 2,5 mg administreret én gang ugentligt i 4 uger. Herefter titreres gradvist på basis af tolerabiliteten overfor pegvaliase, og vedligeholdelsesdosis fastlægges efterfølgende baseret på tolerabilitet og indtaget af proteiner i kosten, sådan at der opnås et fenylalaninniveau i blodet på 120 til 600 µmol/L. Under induktionen og titreringen anvendes også præmedicinering med H1-receptorantagonist, H2-receptorantagonist og et lægemiddel mod feber på grund af potentialet for en akut systemisk overfølsomhedsreaktion.

Målet med pegvaliasebehandling er at opretholde den anbefalede fenylalaninkoncentration i blodet, mens kosten normaliseres.

3.3 Nuværende behandling

Behandlingen af PKU er livslang og består af en meget restriktiv diæt, som begrænser proteinindtaget fra naturlige kilder, hvorved indtaget af fenylalanin også begrænses. Patienter med PKU, som følger diæten, skal helt undlade kød, fisk, mejeriprodukter, brød, ris, pasta og andre kornprodukter samt proteinholdige grøntsager som nødder og bælgfrugter i kosten. Andre grøntsager og fødevarer skal vejes og indtages i begrænset mængde. Da en sådan kost vil give alt for lidt protein og mangel på vitaminer og mineraler, suppleres med et diætpræparat som

proteinerstatning og vitamin- og mineraltilskud. Diætpræparaterne indeholder alle aminosyrer på nær fenylalanin og gives i form af et pulver eller evt. senere i livet op mod 250 kapsler eller tabletter dagligt. Pulveret blandes med vand og drikkes til måltiderne. Ud over pulver og tabletter findes aminosyretilskuddet også som flydende (”*ready to drink”*), barer og andre tabletter, man ikke skal tage så mange af. Mængden af aminosyretilskud bliver ordineret ud fra vægt, alder og aktivitetsniveau.

For hovedparten af patienterne, som helt mangler PAH-aktivitet, er den restriktive diæt i kombination med proteinerstatning den eneste nuværende behandlingsmulighed og opleves af mange voksne patienter som overordnet svær at følge.

Patienter med mild PKU, som har nogen bevaret PAH-aktivitet, kan i tillæg til diætkost blive behandlet med sapropterin (Kuvan). Sapropterin, en syntetisk form af co-faktor tetrahydrobiopterin (BH4), virker ved at øge metabolismen af fenylalanin til tyrosin, idet PAH-proteinstrukturen stabiliseres, og den tilbageværende aktivitet af PAH forøges.

Behandlingsmålet, hvad end patienten behandles med sapropterin i kombination med diætkost eller blot med en diætkost, følger europæiske PKU-guidelines, hvor der anbefales livslang kontrol med patientens fenylalaninniveau for at undgå de kliniske manifestationer af sygdommen. For børn og voksne > 12 år anbefales et fenylalaninniveau i blodet på 120-600 µmol/L [25,26]. Forholdet mellem blod- og hjerneniveauet af fenylalanin ligger omkring 4:1 til 3:1 [27–29]. Børn med PKU er generelt velbehandlede, idet forældre og andre omsorgspersoner er involveret i at sikre, at den restriktive diæt følges. For unge voksne ses, at det bliver stadig sværere at følge diæten på grund af påvirkning fra venner, de voksende krav i skolen samt at ansvaret for egen diæt i stadig større grad overlades til den unge selv. I voksenalderen ses, at mange patienter ikke når i mål i med at opnå kontrol med fenylalaninniveauet, som overstiger de anbefalede 600 µmol/L på trods af diætrestriktioner.

Voksne patienter med PKU, der ikke formår at følge den klassiske diætbehandling eller er sendiagnosticerede og/eller hidtil ubehandlede, kan tilbydes en mere lempelig diætbehandling (semifri diæt), hvis de samtidig indtager et kosttilskud med lange neutrale aminosyrer (*large neutral amino acids;* LNAA) uden fenylalanin. Et sådant kosttilskud kan øge konkurrencen mellem fenylalanin og de øvrige LNAA’er og nedsætte transporten af fenylalanin til hjernen [3,20]. Tilskud af LNAA sænker derfor ikke fenylalanin i blodbanen, som derfor anbefales at ligge mellem 900-1500 µmol/L. Overskrides den nedre grænse på 900 µmol/L kan proteinbehovet ikke dækkes fra kosten, medmindre man bliver suppleret med aminosyretilskud. Af de danske patienter over 16 år med moderat eller klassisk PKU får 62 % LNAA (PKU-databasen, 2020).

Semifri diæt tillader patienterne at spise frugt og grønt, ris, pasta og brød uden at veje det. Brugen af LNAA i behandlingen af PKU er hyppig i Danmark. Omend både dyrestudier [30-33] og kliniske studier [27,28,34-36] indikerer, at LNAA kan have en gavnlig effekt hos PKU-patienter, er der endnu ikke lavet et studie, der systematisk sammenligner effekten af LNAA med den klassiske diæt. Af samme grund begrænses LNAA til voksne patienter, hvis hjerne er mindre sårbar end et barns udviklende hjerne. Den kliniske erfaring i Danmark er, at voksne patienter ved at indtage LNAA-kosttilskud uden fenylalanin kan opnå en acceptabel sygdomskontrol, øget livskvalitet og en bedre adhærens til behandling [31,37]. Hvorvidt den gavnlige effekt af LNAA kan være

påvirket af øvrige omstændigheder er dog ikke belyst. Evt. skadelige effekter af det høje blodniveau af fenylalanin ved LNAA-behandling er ikke kendt.

Den overordnede behandling er rettet mod at undgå de kliniske manifestationer af sygdommen samt øge livskvaliteten hos patienter med PKU.

4. Metode

Medicinrådets protokol for vurdering vedrørende pegvaliase til behandling af patienter over 16 år med fenylketonuri (PKU) beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

Medicinrådets protokol angiver to komparatorer: restriktiv diæt og LNAA. Da standardbehandlingen i Danmark i høj grad inkluderer begge komparatorer uden en klar klinisk sondring af, hvilke patienter der bør behandles med restriktiv diæt alene eller med tillæg af LNAA, er der kun defineret et klinisk spørgsmål. Målet med behandling med pegvaliase er at reducere fenylalaninniveuaet i blodet, hvorved overførsel til hjernen reduceres. Målet med behandling med LNAA er derimod at øge konkurrencen med fenylalanin for transport over blodhjernebarrieren, hvorved fenylalaninniveuaet i hjernen reduceres. En effekt af behandling evalueres derfor hhv. ved en måling i blodet for pegvaliase og en måling i hjernen for LNAA. Af samme grund gennemgås den identificerede evidens for hver komparator separat nedenfor.

5.1.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøger har søgt litteratur med søgestrengen fra protokollen. Ansøger har ikke fundet kliniske studier, som muliggør en direkte sammenligning mellem pegvaliase og restriktiv diæt. To pivotale studier, PRISM-1 og -2 [38,39], er medtaget for at belyse effekterne af pegvaliase. Der er fundet en indirekte komparativ analyse, Zori et al. [40], som inddrager resultater fra PRISM-1 og -2 i en indirekte sammenligning med restriktiv diæt (*propensity score*-analyse). Herudover har ansøger fundet to supplerende studier til PRISM, som primært undersøger sikkerhedsaspekter ved pegvaliasebehandling.

Ansøger har ikke fundet kliniske studier som muliggør en direkte sammenligning mellem pegvaliase og LNAA. Der er fundet to studier, som belyser effekten af LNAA på relevante effektmål. For sammenligningen overfor LNAA er evidensen gennemgået narrativt.

En fuld oversigt over studier, der er relevante for vurderingen, er angivet i tabel 1.

Tabel 1. Oversigt over studier medtaget i vurderingen

Studie-ID	Publikation	N	Studiedesign
165-301; PRISM-1 NCT01819727 Thomas et al. 2018.	Pegvaliase for the treatment of phenylketonuria: Results of a long-term phase 3 clinical trial program (PRISM)	N = 261 (PKU, uklassificeret, ukontrolleret blodniveau), N = 203 overført til PRISM-2 Opfølgning: op til 36 uger	Ikke-randomiseret, dosis-respons- og sikkerhedsstudie **Intervention: Pegvaliase**
165-302; PRISM-2 NCT01889862 Thomas et al. 2018 Harding et al. 2018	Pegvaliase for the treatment of phenylketonuria: Results of a long-term phase 3 clinical trial program (PRISM). Pegvaliase for the treatment of phenylketonuria: A pivotal, double-blind randomized discontinuation Phase 3 clinical trial	N = 215 (patienter indgår fra 165-301, 165-205 og PAL-003) (PKU, uklassificeret, ukontrolleret blodniveau) Opfølgning: op til 212 uger	Delvist randomiseret, ublindet, dosis-repons, enkeltcrossover-studie **Intervention: Pegvaliase** **Kontrol: Placebo i randomiseret del**
165-205 NCT01560286 Zori et al. 2018	Induction, titration, and maintenance dosing regimen in a phase 2 study of pegvaliase for control of blood phenylalanine in adults with phenylketonuria	N = 24X Opfølgning: 48 uger	Fase II-studie, enkeltarm. **Intervention: Pegvaliase**
PAL-003 NCT00924703 Longo et al. 2018.	Long-term safety and efficacy of pegvaliase for the treatment of phenylketonuria in adults: combined phase 2 outcomes through PAL-003 extension study	N = 68 Opfølgning: op til 264 uger (mean 176,5 uger)	Fase II-studie, enkeltarm **Intervention: pegvaliase**
Zori et al. 2019	Long-term comparative effectiveness of pegvaliase versus standard of care comparators in adults with phenylketonuria	N = 250 Opfølgning: 24 mdr.	Kvalitativ analyse (*propensity score*) af PRISM-1 og -2 overfor PKUDOS-registret **Intervention: pegvaliase** **Kontrol: diæt**
Burlina et al. 2019	Large Neutral Amino Acid Therapy Increases Tyrosine Levels in Adult Patients with Phenylketonuria: A Long-Term Study	N = 12 Opfølgning: 12 mdr.	Ublindet, enkeltarmstudie **Intervention: LNAA**
Scala et al. 2020	Large Neutral Amino Acids (LNAAs) Supplementation Improves Neuropsychological Performances in Adult Patients with Phenylketonuria	N = 10 Opfølgning: 12 mdr.	Ublindet, enkeltarmstudie **Intervention: LNAA**
Schindeler et al. 2007	The effects of large neutral amino acid supplements in PKU: An MRS and neuropsychological study	N = 16 (klassisk PKU) Opfølgning: 20 uger	Dobbeltblindet randomiseret crossover-studie **Intervention: LNAA** **Kontrol: Placebo**

Studier med data for pegvaliase

PRISM-1

PRISM-1 [38,39] er et fase III-randomiseret studie, der sammenligner pegvaliase vedligeholdelsesdoser på 20 og 40 mg. Formålet med fase III-studiet PRISM-1 var at karakterisere sikkerhed og tolerabilitet af pegvaliase i pegvaliase-naive patienter, som selvadministrerer pegvaliase op til fastsatte doser på enten 20 eller 40 mg om dagen (induktion og titreringsfasen). Som det første indgik patienterne i en screeningsfase (dag -28 til dag 0), der evaluerede effekt og tolerabilitet. Patienter med behandlingsrespons, som tålte pegvaliase, fik herefter en fast startdosis på 2,5 mg/uge i 4 uger (induktionsfasen, hvor patienter desensibiliseres mod pegvaliase). Mellem uge 5 og op til uge 34 blev desensibiliserede patienter randomiseret 1:1 til at blive titreret op til en endelig dosis på hhv. 20 eller 40 mg om dagen i hver studiearm (titrereringsfasen). Indtil uge 36 (dvs. minimum 2 uger) blev behandling med den faste dosis opretholdt (vedligeholdelsesfasen). Patienter, der havde en reduktion på > 20 % i fenylalaninkoncentration, kunne gå videre til den randomiserede del af PRISM-2. PRISM-1 fungerede således som et såkaldt *feeder study* for PRISM-2.

I alt 261 PKU-patienter mellem 16-70 år indgik i studiet (et senere protokoltillæg ændrede dette inklusionskriterie til 18-70 år). Alle havde ukontrolleret blodniveau af fenylalanin defineret som phenylalanin-niveauerne > 600 µmol/L ved baseline og phenylalaninniveauet > 600 µmol/L i de 6 måneder, der gik forud for screeningen. Der blev ikke udført genotypning for at bestemme klassificeringer af PKU blandt studiepopulationen. Omkring 11 % (28/261) af patienterne var behandlingsnaive. Omkring 75 % (196/261) var tidligere behandlet med sapropterin, og 74 % (144/196) responderede ikke på tidligere sapropterinbehandling. 26 % (52/196) blev betragtet som sapropterinrespondere (*European Public Assessment Report,* EPAR).

PRISM-2

PRISM-2 [38,39] er et fase III, randomiseret *discontinuation study*, som er et studiedesign, hvor alle patienter starter med at være i behandling, hvorefter de randomiseres til fortsat behandling eller placebo. I PRISM-2 indgik 203 patienter fra PRISM-1. Derudover indgik 11 patienter fra PAL-003 og 1 fra 165-201, som begge er fase II-studier med fokus på bl.a. sikkerhed ved dosering og immunrespons.

I den første del af PRISM-2 fortsættes behandling med enten 20 eller 40 mg om dagen (part 1), hvorefter patienter med en minimum 20 % reduktion i fenylalaninkoncentration i blodet randomiseres til entenfortsat behandling eller placebo (dextran 40) i 8 uger (part 2). Herefter enten fortsætter eller genoptages behandlingen med enten 20 eller 40 mg (part 3). I studiets sidste del (part 4; vedligeholdelsesfasen), som er en *open-label extension* del kan behandlingen individualiseres ned til 5 mg eller op til 60 mg pegvaliase om dagen.

Patientpopulationen i PRISM-2's randomiserede del er således en selekteret patientpopulation af patienter, der har demonstreret respons på pegvaliase (minimum 20 % reduktion i fenylalaninkoncentration i blodet). Patienter, der ikke reducerede deres blodniveauer af fenylalanin tilstrækkeligt til at indgå i part 2, kunne fortsætte direkte til part 4.

Overførslen af patienter mellem PRISM-1 og -2, og mellem de forskellige faser af studierne, er betinget af respons og tolerabilitet af behandling. Overførslen er omfattende og bidrager til høj

kompleksitet i analysegrundlaget. På nær den randomiserede del af PRISM-2 (part 2, 8 uger), er de to studier at opfatte som ét en-armet studie med patienter, der har modtaget behandling med pegvaliase i en eller anden dosis. Data fra studiet udover den randomiserede del er derfor på linje med observationelle data. Der indgik 86 patienter i den randomiserede del, hvilket udgør studiets analysepopulation (*modified intention to treat-population; mITT*). Denne population er selekteret for respons på pegvaliase og derfor ikke repræsentativ for den danske patientpopulation. Evt. effektforskelle mellem placebo og pegvaliase kan i den randomiserede del forventes at være anderledes end i den danske patientpopulation. Baselinekarakteristika for mITT-populationen fremgår af tabel 2.

Zori et al 2019, *propensity score*-analyse

Zori et al. [40] præsenterer en indirekte sammenligning mellem pegvaliase og restriktiv diæt, hvor poolede fase 3-pegvaliase-data fra PRISM-1 og -2 sammenlignes med *propensity score*-matchede data fra PKUDOS-registret. Propensity score matching er en statistisk metode, der bruges til at matche individer i to patientkohorter. Af relevans for denne vurdering rapporterer analysen sammenlignende data for effektmålene fenylalaninkoncentration og naturligt proteinindtag. Fagudvalget vurderer, at denne analyse giver det bedste grundlag for en sammenligning med restriktiv diæt, om end den er begrænset af en lille, delvist selekteret population, og at kun to relevante effektmål indgår i analysen. For de effektmål vil analysens resultater vægtes over resultaterne for PRISM-2 (part 2). Baselinekarakteristika for de matchede populationer fra PRISM-2 og PKUDOS-registret i Zori et al. er angivet i tabel 2.

PAL-003 og 165-205

Disse to studier er fase-II-studier med fokus på sikkerhed. Populationerne fra de to studier udgør sammen med populationerne fra PRISM-1 og PRISM-2 den *safety* populationen for pegvaliase (N = 285), som også er vurderet i EPAR'en.

Studier med data for LNAA

Burlina et al. 2019

Burlina et al. [41] er et observationelt studie i 12 patienter, der blev selekteret på baggrund af deres dårlige adhærens til restriktiv diæt og kosttilskud. Patienterne responderede ikke på behandling med sapoprotein. Studiet havde en opfølgningstid på 12 måneder og målte koncentrationerne af fenylalanin og tyrosin i blodet.

Scala et al. 2020

Scala et al. [42] er et observationelt studie i 10 patienter med moderat og klassisk PKU vurderet på baggrund af genotype. Studiet havde en opfølgningstid på 12 måneder og inkluderede udover blodniveauer af fenylalanin og tyrosin og psykometriske effektmål, herunder livskvalitet (*psykological general well-being index*, PGWBI), eksekutive funktioner (*wisconsin card sorting test*, WCST), opmærksomhed (*test of attentional performance*, TAP) og øje-hånd koordination (*9-hole peg test,* HPG).

Schindeler et al. 2007

Schindeler et al. [34] er et prospektivt dobbeltblindet placebokontrolleret cross-over studie i 16 patienter. Studiets forløb i fire faser i randomiseret rækkefølge med en *wash-out* periode på 4

uger mellem hver fase. Alle patienter fuldførte alle faser. Fase 1: restriktiv diæt, aminosyretilskud og LNAA; Fase 2: restriktiv diæt, aminosyretilskud og placebo; Fase 3: restriktiv diæt og LNAA, og; Fase 4: restriktiv diæt og placebo. Studiet inkluderede koncentration af fenylalanin og andre aminosyrer i blod og hjerne samt neuropsykologiske test, herunder opmærksomhed (CPT) og eksekutive funktioner (CANTAB).

Øvrige studier

Ansøger har indsendt data vedr. seks øvrige studier for LNAA [27,35,36,43–45], som rapporterer for effektmålet behandlingsophør (gråmarkeret tabel 3b). Da studierne er forskellige ift. design og population og herudover meget små med en relativt kort opfølgningstid, har fagudvalget vurderet, at de ikke er relevante at inddrage i vurderingen.

Sammenlignelighed af populationer til sammenligning af pegvaliase og restriktiv diæt

Baselinekarakteristika for studiepopulationerne er angivet i tabel 2. Som det fremgår, er den tilgængelige baselinekarakteristik sparsom for andre studier end PRISM-2. Den angivne karakteristik er for den randomiserede del af studiet, hvor alle patienterne har været i behandling med pegvaliase. Derfor er deres baseline fenylalaninkoncentration i blodet lav. Fagudvalget vurderer, at der ikke er forskelle i baselinekarakteristik i PRISM-2, der giver anledning til at sætte spørgsmålstegn ved randomiseringen, eller som forventes at påvirke effektforskellene i studiets randomiserede del. Fagudvalget bemærker, at der ikke er oplysninger om patienternes klassificering af PKU, og det ikke er muligt at vurdere ud fra baseline fenylalaninniveauerne, da patienterne er behandlet med pegvaliase ved tidspunktet for baseline. Set ud fra antal patienter tidligere behandlet med sapropterin, som responderede på sapropterinbehandling (ca. 20 %), havde en betydelig andel fra PRISM-studierne muligvis mild PKU, hvilket kan påvirke overførbarheden af resultater til danske patienter, hvor det kun er patienter med moderat og klassisk PKU, der vurderes at være kandidater. Det er dog uklart, hvor stort et antal det reelt omhandler, og hvilken betydning det har for overførbarheden. Oplysninger om baselinekarakteristik i Zori et al. (*propensity score*-analysen) er så sparsomme, at det ikke er muligt at vurdere, om der er afvigelser, som evt. kunne påvirke effektforskellene mellem pegvaliase og restriktiv diæt. Baselineniveauerne af fenylalanin i blodet i Zori et al. er højere end ved start randomisering i PRISM-2, hvilket vidner om, at patienterne ved baseline i Zori et al. har haft et ukontrolleret niveau af fenylalanin.

Sammenlignelighed af studier til sammenligning af pegvaliase og LNAA

LNAA-studierne er små og indeholder meget lidt information om patienternes baselinekarakteristik, hvorfor det er vanskeligt at sammenligne populationerne. Datagrundlaget muliggør ikke en sammenligning mellem pegvaliase og LNAA.

Tabel 2. Baselinekarakteristika fra studier, hvor data anvendes i vurderingen

	PRISM-2 mITT placebo N = 28	PRISM-2 mITT Pegvaliase N = 58	Zori et al. diæt N = 125	Zori et al. Pegvaliase N = 125	Scala et al. LNAA N = 10	Burlina et al. LNAA N = 12	Schindeler et al. LNAA N = 16
Alder, mean (SD) [range]			31 (11)	30 (8)	23,6 [18-32]	[19-38]	24,9
Vægt, middel (SD)	85,7 (23.86)	80,1 (20,57)					
Højde, middel (SD)	168.7(9.47)	167.8 (8.43)					
BMI, middel (SD)	29.9 (6.98)	28.3 (6.59)					
< 25, n (%)	8 (28.6 %)	21 (36.2 %)					
≥ 25 < 30, n (%)	7 (25.0 %)	15 (25.9 %)					
≥ 30, n (%)	12(42.9 %)	22 (37.9 %)					
Fenylalaninkoncentration, µmol/l, middel (SD)	536.1 (432.54)	503.9 (520.28)	1089 (302)	1085 (294)	665-2480	752 (143)	
Naturligt proteinindtag, g/dag, middel (SD)	38.7 (24.18)	49.0 (23.84)	25 (19)[a]	34 (24)[b]			
Protein indtag fra kosttilskud, g, middel (SD)	24.5 (26.25)	13.2 (19.72)					
Protein fra restriktiv diæt, n (%)	4 (14.3 %)	1 (1.7 %)					
ADHD-RS IA	3.9 (4.05)	5.9 (5.54)					
POMS TMD selvrapporteret	15.7 (24.81)	19.9 (35.41)					
POMS TMD observatørrapportert	14.4 (22.41)	14.4 (24.71)					
PKU-klassificering	Uklassificeret, ukontrolleret fenylalanin	Uklassificeret, ukontrolleret fenylalanin	Uklassificeret, ukontrolleret fenylalanin	Uklassificeret, ukontrolleret fenylalanin	Uklassificeret, ukontrolleret fenylalanin	Klassisk PKU, ukontrolleret fenylalanin	Klassisk PKU
Sapropterin-behandling	Mixed non-respondenter/ respondenter	Mixed non-respondenter/ respondenter	Tidligere behandlet eller stoppet behandling undervejs i PKUDOS	Se PRISM-2		Tidligere behandlet, non-respondenter	

[a]N = 62, [b]N = 107

For sammenligningen overfor LNAA er der en række forhold, som udfordrer studiernes sammenlignelighed og anvendelighed. Dette diskuteres yderligere i afsnit 5.1.2.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Ansøger har indsendt et datagrundlag, som er i bedst mulig overensstemmelse med protokollen. Samlet set vurderer fagudvalget, at datagrundlaget er mangelfuldt, hvad angår sammenligning med begge komparatorer, og at der mangler data for mange af de efterspurgte effektmål. Herudover er en række af effektmålene opgjort anderledes end efterspurgt i protokollen. En oversigt over, hvilket data der er rapporteret for hvilke studier, fremgår af tabel 3a og 3b.

Tabel 3a. Oversigt over inkluderede LNAA-studier, som rapporterer for relevante effektmål

	PRISM-1 og -2	Zori et al.	PAL-003	165-205
Livskvalitet	-	-	-	-
Uønskede effekter	x$^{\alpha}$	x$^{\alpha}$	x$^{\alpha}$	x$^{\alpha}$
Fenylalanin i blodet	x$^{\beta}$	x$^{\beta}$	-	-
Proteinindtag	x$^{€}$	x$^{€}$	-	-
Psykiatriske effekter	x*	-	-	-
Eksekutive funktioner	x**	-	-	-

Orange markeringer angiver studie med (indirekte) komparative data for pegvaliase og restriktiv diæt. Øvrige studier rapporterer effektestimater for pegvaliase uden en kontrol.
$^{\alpha}$data er hentet fra EPAR'en, hvor sikkerhedsdata er rapporteret samlet.
$^{\beta}$effektmålet er også opgjort på anden vis end ønsket i protokollen; opgjort som gennemsnitligt øget fenylalaninniveau i blodet.
$^{€}$effektmålet er opgjort på anden vis end ønsket i protokollen; opgjort som gennemsnitligt øget proteinindtag.
*effektmål ikke opgjort ved relevant måletidspunkt. Data er hentet fra EPAR'en.
**data fra < 10 patienter.

Tabel 3b. Oversigt over inkluderede LNAA-studier, som rapporterer for relevante effektmål

	Burlina	Scala	Schindeler	Matalon[a]	Matalon[b]	Lou	Pietz	Yano[a]	Yano[b]
Livskvalitet	-	x[α] PGWBI /TAP	-	-	-	-	-	-	-
Behandlingsophør	x[β]	x[β]	x[β]	x	x	x	x	x	x
Phe i hjernen	-	-	(x[€])	-	-	-	-	-	-
Proteinindtag	x	-	x*	-	-	-	-	-	-
Psykiatriske effekter	-	-	(x**)	-	-	-	-	-	-
Eksekutiv funktioner	-	-	(x**)	-	-	-	-	-	-

Grå markeringer angiver studier, som ikke vurderes at bidrage med relevant information på trods af data for relevante effektmål. Øvrige studier er medtaget i vurderingen, og rapporterer ukontrollerede effektestimater for LNAA.
[α]fagudvalget vurderer, at værktøjet PGWBI kan anvendes til at vurdere livskvalitet og ikke psykiatriske effekter, som angivet i den endelige ansøgning.
[β]relativt kort opfølgningstid.
[€]effektmål undersøgt, men intet data rapporteret.
*effektmålet er opgjort på anden vis end ønsket i protokollen; opgjort som gennemsnitligt øget proteinindtag.
**målt, men uklart og utilstrækkeligt rapporteret.

Usikkerheder og begrænsninger i propensity score-analysen: Eftersom patienter i PRISM-studierne bliver matchet til patienter i PKUDOS-registret, dækker resultatet af analysen kun den delpopulation af PRISM, der kunne matches med patienter i registret, og herudover kun den delpopulation eller patienter for hvem, der er data for på måletidspunktet. Matchingen er kun foretaget på tre parametre: køn, alder og fenylalaninniveau ved baseline. Da usikkerheden i analysen øges med antallet af matching-variable, er andre vigtige prognostiske parametre udeladt af matchingen, hvilket potentielt kan introducere bias i resultaterne. Analyseresultatet skal derfor tolkes med stor forsigtighed.

Usikkerheder i definition af respondenter i PRISM-studierne: Non-respons til pegvaliase blev defineret som patienter, der var i stand til at tolerere pegvaliase i en vedligeholdelsesdosis på op til 60 mg/dag, men som stadig havde ukontrollerede fenylalaninniveauer efter 18 måneders behandling. En patient kunne dog stadig betragtes som respondent (vurderet af investigator), hvis patientens diæt var blevet mindre restriktiv, patienten havde et højere proteinindtag, og/eller patientens neurokognitive symptomer var forbedret. Denne andel udgjorde 8 % ved forsøgets afslutning (ref.: tillæg til den endelige ansøgning). Ifølge ansøger var tid til respons mellem 0,5 mdr. og 4,5 år og den gennemsnitlig tid for opnåelse af vedligeholdelsesniveau (stabile værdier under 600 µmol/L) [redacted] (upublicerede data, BioMarin Data on file). En tredjedel (33 %) var non-respondenter efter 18 måneders behandling (præspecificeret cut-off for respons), hvor nogle patienter med ukontrollerede niveauer af fenylalanin stadig blev betragtet som respondenter, hvis de opnåede det ønskede fenylalaninniveau inden for 4,5 år, eller hvis de havde gavnlige effekter af behandling målt ud fra andre parametre som mindre restriktiv diæt, øget naturligt proteinindtag og forbedring af kognitive symptomer [46].

Fagudvalget finder det problematisk, at patienter, der ikke opnår kontrolleret fenylalaninniveau, er medtaget i effektdata, da et kontrolleret fenylalaninniveau fremstilles som det primære mål for behandlingseffekt i studierne. Definitionen af non-respons øger misvisende antallet af respondenter.

Livskvalitet
I protokollen er livskvalitet defineret som et kritisk effektmål, som fagudvalget ønskede opgjort med det PKU-specifikke værktøj *The Phenylketonuria impact and treatment Quality Of Life Questionnaire* (PKU-QOL) eller det generiske værktøj *The World Health Organization Quality of Life assessment-100* (WHOQOL-100). Ansøger har ikke identificeret anvendeligt data for vurdering af effektmålet for nogle af de ønskede sammenligninger. For pegvaliase angiver ansøger, at der findes en webbaseret tilfredshedsundersøgelse vedrørende behandling med pegvaliase. Fagudvalget har ikke inddraget resultaterne af den undersøgelse i vurderingen. For LNAA rapporterer Scala et al. livskvalitet med værktøjerne PGWBI og TAP, som fagudvalget ikke er bekendt med.

Sikkerhed/uønskede hændelser
Uønskede hændelser er defineret som et kritisk effektmål i protokollen, og fagudvalget har ønsket at vurdere effektmålet kvalitativt ved en gennemgang af uønskede hændelser og årsager til behandlingsophør. Andelen, der ophører behandling, ønskedes også opgjort kvantitativt. Ansøger har inkluderet en opgørelse af behandlingsophør, som tillader en kvalitativ vurdering af effektmålet, men der er intet data, der tillader en sammenligning med restriktiv diæt. Vurderingen tager udgangspunkt i *safety* populationen for pegvaliase. Sikkerheden ved LNAA er pga. manglende data baseret på fagudvalgets kliniske erfaring.

Fenylalaninkoncentration
Effektmålet fenylalaninkoncentration er defineret som et vigtigt effektmål i protokollen og ønskes opgjort som andelen, der opnår en fenylalaninkoncentration i blodet på under 600 µmol/L og en forskel i fenylalaninkoncentrationen i hjernen. Ansøger har indsendt data for fenylalaninniveauet i blodet men ikke i hjernen. Der er komparative effektestimater mellem pegvaliase og restriktiv diæt fra *propensity score*-analysen og data for pegvaliase fra PRISM-1 og -2. Der er også data fra den gennemsnitlige fenylalaninkoncentration i blodet før og efter den randomiserede del af PRISM-2. Fagudvalget vurderer, at resultaterne fra den indirekte *propensity score*-analyse er mest pålidelige i forhold til at vurdere fenylalaninkoncentration i blodet, men anvender de ukontrollerede data fra PRISM-studierne understøttende.

Naturligt proteinindtag
Fagudvalget har defineret naturligt proteinindtag som et vigtigt effektmål og ønskede det opgjort som andelen, der kan øge proteinindtaget fra naturlige kilder til henholdsvis 40 og 70 g. Der er komparative effektestimater mellem pegvaliase og restriktiv diæt fra *propensity score*-analysen, men effektmålet er opgjort som en gennemsnitsværdi for proteinmængden fra naturlige kilder i gram ved baseline og efter 1 og 2 års behandling. Der er således ingen relative effektestimater for effektmålet. For pegvaliase er der data fra PRISM-1 og -2 efter 1 og 3 år. For LNAA er data for naturligt proteinindtag ikke målt i studierne men rapporteret i et studie, beregnet som differencen mellem det totale proteinindtag og indtag fra medicinsk proteintilskud.

Psykiatriske effekter
De psykiatriske effekter er et vigtigt effektmål i vurderingen og ønskes opgjort med værktøjerne ADHD-RS-IV og POMS. Ansøger har indsendt data fra PRISM-1 og 2, men ikke fra den randomiserede del (PRISM-2, part 2) og ikke i sammenligning med restriktiv diæt. Det er derfor ikke muligt at sammenligne effekterne med restriktiv diæt. Psykiatriske effekter efter pegvaliasebehandling alene er opgivet fra PRISM-2 i EPAR'en. Data for psykiatriske effekter af LNAA-behandling er ikke indsendt.

Eksekutive funktioner
Eksekutive funktioner er et vigtigt effektmål og ønskes opgjort med værktøjet BRIEF-V eller CANTAB. Ansøger inkluderer data fra PRISM-2, hvor der er data for CANTAB fra studiets randomiserede del (part 2). Sammenligningen gælder for de 8 uger, hvor en del af patienterne ikke behandles med pegvaliase. Der er ikke data for LNAA's effekt på eksekutive funktioner. Schindler et al. har givetvis målt eksekutive funktioner vha. CANTAB, men beskrivelserne er uklare og data ufuldstændigt rapporteret.

5.1.3 Evidensens kvalitet

Da vurderingen af pegvaliase er baseret på en narrativ sammenligning med hhv. restriktiv diæt og LNAA, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen. Sammenligningerne og det datagrundlag, der ligger til grund for sammenligningerne, er forbundet med væsentlige usikkerheder og begrænsninger, og Medicinrådet vurderer, at kvaliteten af den evidens, der ligger til grund for besvarelsen af det kliniske spørgsmål, er meget lav.

5.1.4 Effektestimater og kategorier

Effektestimater og -forskelle er i det følgende gennemgået for hvert effektmål. På baggrund af kvaliteten og karakteren af den samlede evidens, vil vurderingen basere sig på en kvalitativ gennemgang af datagrundlaget. Den kliniske værdi af pegvaliase vil af samme årsag ikke kunne kategoriseres jf. Medicinrådets metoder. Evidensgrundlaget er mangelfuldt i forhold til at vurdere pegvaliase ud fra de kriterier, som er fremsat i protokollen.

Livskvalitet
Som beskrevet i protokollen er effektmålet livskvalitet kritisk for vurderingen af lægemidlets værdi for patienterne, fordi hverdagen med PKU er mærket af de kostrestriktioner (og følgevirkningerne heraf), patienterne er underlagt som følge af deres sygdom. En lav livskvalitet kan også have afgørende betydning for, om patienterne finder gavn af og adhærerer til behandling. Manglende adhærens til behandling kan have alvorlige sociale, neurologiske og kognitive konsekvenser. Ansøger har ikke indsendt data vedr. livskvalitet, og den kliniske værdi af pegvaliase for effektmålet kan ikke evalueres.

Scala et al. rapporterer data for LNAA-behandling med værktøjet PGWBI og TAP. 10 patienter oplevede en stigning i deres livskvalitet efter behandling med LNAA i 12 måneder, men stigningen var ikke statistisk signifikant. Den største stigning sås for de patienter, der havde den laveste livskvalitet ved studiets start.

Uønskede hændelser

Effektmålet uønskede hændelser er kritisk for vurderingen af lægemidlets værdi for patienterne, fordi der er tale om en livslang behandling, hvor uønskede hændelser kan have væsentlig betydning for, om patienterne fortsætter behandling, eller om deres livskvalitet forringes i omfattende grad. Sikkerheden af behandling vurderes ifølge protokollen ud fra en kvalitativ gennemgang af uønskede hændelser og bivirkninger samt resultater for behandlingsophør (og årsager til ophør). Da der ikke findes sammenlignende data for sikkerhed, gennemgås evidensen for pegvaliase, restriktiv diæt og LNAA enkeltvis.

Sikkerhed ved behandling med pegvaliase

Sikkerheden af behandling med pegvaliase evalueres ud fra en *safety* population, som bestod af patienter fra PRISM-1 og -2, PAL-3 og 165-201 i induktions-, titrerings- og vedligeholdelsesfasen (I/T/M-populationen). *Safety* populationen inkluderede i alt 285 patienter, og alle informationer er gengivet fra EPAR'en.

Alle patienter (100 %) oplevede mindst en ikke-alvorlig bivirkning (*drug-related* AE), tabel 4. Hyppigheden af bivirkninger var relateret til, hvor meget pegvaliase en patient blev eksponeret for. Jo højere eksponering, des lavere rate. Bivirkninger er også beskrevet separat for placebogrupperne, men fagudvalget vurderer, at disse data ikke er retvisende af flere årsager: kontrolgruppen havde modtaget pegvaliase, inden hændelserne blev registreret efter forskellige behandlingslængder og opgjort i forskellige periodelængder, og placebo bestod af Dextran 40, som er en aktiv substans, der kan føre til overfølsomhedsreaktioner.

Overordnet set vurderer fagudvalget, at der var mange både alvorlige og ikke-alvorlige bivirkninger af pegvaliase, men at de hyppigst forekomne alvorlige bivirkninger potentielt kan forebygges eller minimeres vha. præmedicinering. De ikke-alvorlige bivirkningers betydning er usikker, da fagudvalget ikke er bekendt med, hvor mange patienter der ophører behandling som følge heraf. Fagudvalget fremhæver, at det anser alle tilfælde af angioødem og akut systemisk hypersensitivitet som bekymrende på grund af det nære slægtskab med anafylaksi. Herudover bemærkes det, at patienterne som udgangspunkt er immunsvækkede i nogen grad, og at immunrelaterede ændringer vil blive fulgt tæt i klinisk praksis.

Tabel 4. Antal patienter med alvorlige uønskede hændelser i *safety* population

(%) Antal patienter med events	I/T/M *safety* population (n = 285)
Enhver alvorlig uønsket hændelse	64 (22,4 %)
Anafylaktisk reaktion	14 (4,9 %)
Overfølsomhedsreaktion	9 (3,2 %)
Blod-kreatin-fosfokinase øget	5 (1,8 %)
Anafylactoid reaktion	3 (1,1 %)

(%) Antal patienter med events	I/T/M *safety* population (n = 285)
Angst	3 (1,1 %)
Angioødem	1 (0,4 %)
Blindtarmsbetændelse	2 (0,7 %)
Ledsmerter	1 (0,4 %)
Astma	1 (0,4 %)
Brystsmerter	2 (0,7 %)
Depression	1 (0,4 %)
Brystsmerter, ikke relateret til hjerte	2 (0,7 %)
Trafikuheld	2 (0,7 %)
Serumsyge	2 (0,7 %)
Hævet tunge	1 (0,4 %)
Pseudomonainfektion	1 (0,4 %)

Der blev rapporteret et dødsfald (trafikulykke), som ikke ansås relateret til behandling med pegvaliase. I alt 91 alvorlige uønskede hændelser (SAE'er) blev rapporteret for 64 patienter (tabel 4). 42 (46,2 %) SAE'er blev af efterforskerne vurderet relateret til pegvaliase (alvorlige bivirkninger), og 18 (19,8 %) SAE'er førte til behandlingsstop eller til videre undersøgelse.

Hovedparten af patienter (93,7 %) oplevede bivirkninger i form af overfølsomhedsreaktioner over for pegvaliase. Udvalgte bivirkninger af relevans for vurderingen er beskrevet i det følgende. Af særlig betydning optrådte akutte overfølsomhedsreaktioner i form af anafylaksi hos 16 patienter (6,1 %, 25 events). På grund af forekomsten af disse akutte overfølsomhedsreaktioner blev der indført en protokolændring, der krævede forbehandling med profylaktisk medicin før injektion med pegvaliase og tilstedeværelse af en observatør de første 16 uger af behandlingen. Herudover skulle en epi-pen bæres af patienten. Angioødem (allergisk reaktion, hævelser) grad 1 og 2 optrådte hos 21 patienter (7,4 %) og var typisk forbundet med hævelser i hoved- og halsregionen. Hypofenylalaninæmi (lavt niveau af fenylalanin i blodet, defineret som mindst to på

hinanden følgende fenylalaninniveauer i blodet < 30 µmol/L) forekom hos 125 (43,9 %) af patienterne. Medianvarigheden var 162 dage. Hos 80 % af patienterne, der oplevede hypofenylalaninæmi, faldt niveauet af fenylalanin i blodet til under 5 µmol/L. Ledsmerter optrådte 1876 gange hos i alt 241 (85 %) patienter. Ledsmerter var mest fremherskende under induktions- og titreringsfasen med typiske lokationer som ekstremiteter og ryg. De fleste tilfælde havde en varighed på under 14 dage, men en mindre andel (7 %) oplevede episoder med ledsmerter af en varighed på mindst 6 måneder. Der er registreret antistofudvikling mod pegvaliase, som er nærmere beskrevet under afsnit *6.3 Antistofudvikling mod pegvaliase*.

Behandlingsophør:
Behandlingsophør rapporteres for alle studier. Den samlede andel af patienter, der udgik før tid fra PRISM-1 og -2, udgjorde ifølge EPAR'en 100/261 (38,3 %), hvoraf 40/261 (15,5 %) udgik pga. uønskede hændelser. Frafald forekom typisk under initierings- og titreringsfasen. For LNAA-studierne er der ikke registreret behandlingsophør. Der var ikke behandlingsophør i studier med LNAA.

Årsager til behandlingsophør:
Årsager til behandlingsophør i PRISM-1 og -2 er angivet i tabel 5. De primære årsager var uønskede hændelser (især bivirkningerne anafylaksi og ledsmerter). Efter en række tiltag til at forbedre håndteringen af pegvaliase og nedsætte risikoen for uønskede hændelser, faldt det overordnede behandlingsophør over de første 6 måneder fra 23,8 % til 13,6 % og pga. uønskede hændelser fra 15,3 % til 5,9 % ([46] side 41). Behandlingsophøret faldt det første år af behandlingen fra 32,9 % til 18,6 % og pga. uønskede hændelser fra 16,8 % til 7,6 % ([46] side 56). Fagudvalget finder ikke opgørelsen af frafald opgjort transparent. Ifølge EPAR'en overgik en stor andel fra PRISM-1 (73 %) direkte til part 4 i PRISM-2, hvilket indikerer, at de ikke tålte behandlingen eller ikke kunne opnå det ønskede respons ud fra en fast dosis på hhv. 20 mg og 40 mg om dagen. 27 % af patienterne i PRISM-1 ophørte behandling inden overgang til part 4 pga. uønskede hændelser eller af andre årsager (f.eks. mistet opfølgning).

Tabel 5. Hyppigste årsager til behandlingsophør i PRISM-1 og -2

Årsager til behandlingsophør*	**PRISM-1 og -2** **N = 261**
Uønskede hændelser	40 (15,32 %)
Patients beslutning	29 (11,11 %)
Læges beslutning	10 (3,83 %)
Anden årsag***	21 (8,04 %)

** Non-respons på pegvaliase indgår ikke som årsag til at stoppe behandling. 33 % var non-respondenter efter 18 måneders behandling. **informationer hentet fra EPAR'en side 68. ****graviditet, protokolafvigelser, mistet til follow-up.

Sikkerhed ved behandling med restriktiv diæt

Bivirkninger og uønskede hændelser ved restriktiv diæt er i sin natur bundet op på fraværet af væsentlige byggesten i kosten og følgevirkninger heraf. Der er ikke indsendt data vedr. sikkerheden af behandling med restriktiv diæt, og andelen, der ophører behandling samt årsager hertil står endnu uklart.

Sikkerhed ved behandling med LNAA

Bivirkninger og uønskede hændelser ved behandling med LNAA er ikke dokumenterede, men studierne Schindeler et al. [34], Burlina et al. [41] og Scala et al. [42] rapporterede ikke patienter, som ophørte behandling med LNAA.

Samlede vurdering af sikkerhed

Fagudvalget finder ved gennemgangen af sikkerheden, at behandling med pegvaliase er bivirkningstung, men at bivirkningerne overordnet set er håndterbare. Alle patienter oplevede mindst en bivirkning, og ca. en femtedel oplevede en alvorlig bivirkning. De akutte overfølsomhedsreaktioner i form af anafylaksi anser fagudvalget for bekymrende, men hertil har ansøger indført sikkerhedsforanstaltninger med forebyggende konkomitant medicin, epi-pen og observatør. Herudover blev et lavt blodniveau af fenylalanin (hypofenylalaninæmi) observeret hos næsten halvdelen af patienterne. Fagudvalget har ikke erfaring med denne tilstand, og ifølge EPAR'en er de kliniske konsekvenser af et lavt blodniveau af fenylalanin ukendte. Fagudvalget bemærker, at en bemærkelsesværdigt stor andel patienter ophører behandling pga. bivirkninger eller på patientens eget initiativ. Dette kunne indikere lav tolerabilitet af pegvaliase og vækker bekymring, om hvorvidt patienterne vil adhærere til en livslang behandling. Hvad angår bivirkninger og uønskede hændelser ved restriktiv diæt og ved behandling med LNAA, er disse ikke undersøgt i studier. Den kliniske erfaring fra fagudvalget er, at der generelt er ingen eller meget få bivirkninger forbundet med de to eksisterende behandlingsformer. Den fenylalanin-begrænsede diæt medfører ingen kendte bivirkninger, men kan lede til mangeltilstande, herunder knogleskørhed. Dette forsøges modvirket ved at supplementere patienterne med vitaminer, mineraler, kalorier og fenylalaninfri proteintilskud, så de får deres døgnbehov dækket. I sjældne tilfælde er der beskrevet påvirket nyrefunktion hos patienter med restriktiv diæt, givetvis som følge af en øget proteinbelastning. Proteintilskuddet, der udgør et stort dagligt indtag af tabletter, pulver eller mixtur, kan medføre kvalme eller resultere i en nedsat adhærens til den restriktive diæt eller behandling med LNAA.

Fenylalaninkoncentration

Effektmålet fenylalaninkoncentration er vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi kontrol af fenylalaninniveauet er centralt for at undgå de kliniske manifestationer af sygdommen. Effektmålet evalueres ud fra andelen af patienter, der opnår en kontrolleret fenylalaninkoncentration i hhv. blodet og hjernen. Herudover har ansøger bidraget med data for den gennemsnitlige fenylalaninkoncentration i blodet.

Sammenligning med restriktiv diæt

Fagudvalget evaluerer effekten af pegvaliase på fenylkoncentrationen i blodet primært ud fra resultaterne af *propensity score*-analysen i Zori et al. [40]. Generelt var der et markant højere blodniveau af fenylalanin blandt patienter med restriktiv diæt efter 1 og 2 års behandling (1022 µmol/L og 965 µmol/L, tabel 6) sammenlignet med pegvaliase ved samme måletidspunkter (473 µmol/L og 302 µmol/L, tabel 6). Behandling med restriktiv diæt viste ingen bedring sammenlignet med niveauet fra baseline. Analysepopulationen i Zori et al. er markant indsnævret efter

matchingen for *propensity score* i forhold til studiepopulationen i PRIMS-1 og 2 [40]. Populationen indsnævres yderligere ved længere opfølgningstid, og de patienter, der indgår i analysen efter 2 år, er ikke de samme som efter 1 år. Dette betyder, at resultaterne skal tolkes med varsomhed, fordi data fra patienter, der ikke kan matches eller følges op, bortfalder. På baggrund af *propensity score*-analysen vurderer fagudvalget alligevel, at der er effekt af pegvaliase ift. at nedsætte koncentrationen af fenylalanin i blodet.

Tabel 6. Effektestimater for fenylalaninkoncentration i blodet, behandling med diæt vs. pegvaliase, *gennemsnitlig fenylalaninkoncentration*, Zori et al.

Gennemsnitlig fenylalaninkoncentration (µmol/L): diæt vs. pegvaliase			
	Zori et al diæt	Zori et al pegvaliase	Absolut forskel
År 1	1022 (SD 322)	473 (SD 451)	−567.8 (95 % CI −708.3; −427.4)
År 2	965 (SD 259)	302 (SD 392)	−670.9 (95 % CI −824.1; −517.7)
Baseline	1037 (SD 271)	1089 (SD 289)	-

Sammenholdes pegvaliase data fra Zori et al. med data fra publikationen for PRISM-2 [38,39] i forhold til ændring ift. baseline (tabel 7) er der en rimelig overensstemmelse, dog med en tendens til faldende fenylkoncentration over tid (op til 3 år). Effektestimaterne er behæftet med stor usikkerhed, og det er usikkert, hvor mange patienter der har effekt af behandling med pegvaliase.

Zori et al. angiver andelene af patienter, der opnår fenylalaninkoncentrationer under 600 µmol/L efter 1 og 2 år ved behandling med pegvaliase hhv. restriktiv diæt (tabel 8). Efter et år i behandling med pegvaliase har 60 % opnået et kontrolleret niveau sammenlignet med 6 % af patienterne på restriktiv diæt. Efter to år er det steget til 79 % hhv. 12 %. De absolutte forskelle mellem pegvaliase og restriktiv diæt skal tolkes med forsigtighed, da der ikke er data for alle matchede patienter (N er forskellig i de to grupper). Resultaterne indikerer, at der er en væsentlig andel af patienter i behandling med pegvaliase, der opnår et kontrolleret niveau af fenylalanin efter både 1 og 2 år. Data på gennemsnitlig fenylalaninkoncentration fra den randomiserede del af PRISM-2 [38], hvor udgangspunktet for de patienter, der stopper pegvaliasebehandling (der er to placebogrupper, som stopper behandling med hhv. 20 mg og 40 mg pegvaliase), ved randomiseringens start er 508 µmol/L og 654 µmol/L og stiger til 1164 µmol/L og 1509 µmol/L efter 8 uger. De patienter, der fortsætter behandling, har til sammenligning fortsat et stabilt niveau af fenylalanin under 600 µmol/L efter 8 uger [38].

Tabel 7. Effektestimater for fenylalaninkoncentration i blodet, behandling med pegvaliase, forskel fra baseline, *gennemsnitlig forskel i fenylalaninkoncentration,* PRISM-2 og Zori et al.

Gennemsnitlig forskel i fenylalaninkoncentration (µmol/L) fra baseline				
	PRISM- 2 pegvaliase	Forskel fra baseline	Zori et al. pegvaliase	Forskel fra baseline
6 mdr	782 (SD 527) N = 208	-452 (SD 531)	-	-
År 1	-	-	473 (SD 451) N = 87	-616
År 2	-	-	302 (SD 392) N = 80	-787
År 3	341 (SD 465) N = 48	-956 (SD 536)	-	-
Baseline	1233 (SD 386) N = 261	-	1089 (SD 289) N =1 25	

Tabel 8. Effektestimater for fenylalaninkoncentration i blodet, *andel der opnår kontrolleret fenylalaninkoncentration*, Zori et al 2019

Andel der opnår kontrolleret fenylalaninkoncentration, n (%): *: diæt vs. pegvaliase			
	Zori et al.	Zori et al.	Absolut forskel
År 1	3 (6 %)	52 (60 %)	+54 %-point
År 2	5 (12 %)	63 (79 %)	+67 %-point

**fenylalanin <600 µmol/L*

Sammenligning med LNAA

Fenylalaninkoncentrationen efter behandling med LNAA er kun relevant at vurdere i hjernen. Der er ikke indsendt yderligere data for at belyse dette.

Naturligt proteinindtag:

Effektmålet naturligt proteinindtag er vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi behandlingen er livslang og i dag består af en meget restriktiv diæt, som har stor betydning for patienternes livskvalitet. Da data for naturligt proteinindtag ikke er opgivet på den efterspurgte måde, er data analyseret kvalitativt med udgangspunkt i, hvor meget patienterne kan øge deres naturlige proteinindtag efter behandling.

Sammenligning med restriktiv diæt

Ifølge ansøger viser Zori et al., at naturligt proteinindtag kunne øges hos patienter behandlet med pegvaliase samtidigt med kontrol af fenylalanin i blodet [40]. Totalt proteinindtag ved pegvaliasebehandling i PRISM-2 var i gennemsnit (*upubl. data*):

[redacted]

Tabel 9 og 10 angiver det gennemsnitlige øgede proteinindtag fra naturlige kilder ved en indirekte sammenligning af behandling med hhv. restriktiv diæt og pegvaliase [40]. Disse data indikerer, at patienterne i gennemsnit var i stand til at normalisere deres naturlige proteinindtag inden for 1 år efter pegvaliasebehandling, og at effektforskellen fra restriktiv diæt var entydig og stigende over tid [46]. Data bør dog tolkes med forsigtighed, idet proteinbehov/-indtag angives i gram/kg legemsvægt, hvilket det gennemsnitlige øgede proteinindtag derfor også ifølge fagudvalget burde have været angivet i.

Tabel 9. Effektestimater for naturligt proteinindtag, PRISM-2 og Zori et al.

Gennemsnitligt naturligt øget proteinindtag (gram): diæt vs. pegvaliase			
	Zori et al. diæt	Zori et al. pegvaliase	Absolut forskel i gram
År 1	27 (SD 25)	47 (SD 22)	+20
År 2	22 (SD 16)	57 (SD 26)	+25

Tabel 10. Effektestimater for naturligt proteinindtag, PRISM-2 og Zori et al.

Gennemsnitligt øget naturligt proteinindtag (gram) fra baseline: diæt og pegvaliase						
	PRISM- 2 pegvaliase	Forskel i gram fra baseline	Zori et al. pegvaliase	Forskel i gram fra baseline	Zori et al. diæt	Forskel i gram fra baseline
Måned 12	47 (SD 29)	+8	-	-	-	-
År 1	-	-	47 (SD 22)	+13	27 (SD 25)	+2
År 2	-	-	57 (SD 26)	+23	22 (SD 16)	-3
År 3	72 (SD 27)	+33	-	-	-	-
Baseline	39 (SD 28)	-	34 (SD 24)		25 (SD 19)	

Der er ikke opgivet data for, hvor stor en andel der kan øge deres naturlige proteinindtag til hhv. 40 g og 70 g om dagen, som efterspurgt i protokollen. Desuden rapporteres et øget indtag af naturligt protein kun for patienter, der stadig er i behandling i den åbne fase, part 4, af studiet (der er dermed manglende data for patienter, der ikke længere er i behandling). Derfor skal data tolkes med forsigtighed.

Fagudvalget vurderer, at for patienter, der tolerer og fortsætter behandlingen, har pegvaliase potentiale til at normalisere patienternes proteinindtag fra naturlige kilder, samtidig med at fenylalaninkoncentrationen i blodet holdes under 600 µmol/l.

Sammenligning med LNAA

Ifølge ansøger viser Schindeler et al., at det gennemsnitlige naturlige proteinindtag hos 16

patienter med klassisk PKU var 28,1 g pr. dag efter to uger på LNAA-behandling [34]. Ansøger har rådført sig med kliniske eksperter, som udtrykker bred enighed om, at mængden af naturligt protein kan hæves til 80 % i kosten ved behandling med LNAA-tilskud (reduktion af kosttilskud fra 80 % til 20 %). Det vurderes, at patienter, der behandles med LNAA, stadig kræver en diæt for at opnå bedre behandlingsresultater i forhold til at opretholde et fenylalaninniveau under 1500 µmol/L (retningsgivende maksimale niveau) [46]. Studiet af Burlina et al. hos 10 patienter viser ingen forskel på naturligt proteinindtag før og efter behandling i 12 måneder med LNAA (21 g [range:13.5 - 28.5]. vs. 21 g [range:11.6 - 30.4]) [41]. Det er dog uklart, om dette kan forklares ved, at patienter, der tilbydes LNAA, i forvejen er non-kompliante, og at behandlingsmålet med LNAA ikke er at normalisere proteinindtaget fra naturlige kilder, men at mindske skaderne ved at patienten ikke følger den restriktive diæt og samtidigt give patienterne mulighed for at spise mere normalt end på restriktiv diæt.

Psykiatriske effekter
Effektmålet psykiatriske effekter er vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi forhøjede niveauer af fenylalanin medfører neuropsykologiske komplikationer, som ubehandlet kan have alvorlige fysiske og sociale konsekvenser. Ansøger har indsendt data for pegvaliase fra PRISM-1- og -2 til måletidspunkterne 1 år og 3 år [46]. Fagudvalget vurderer, at de psykiatriske effekter af behandling med pegvaliase, i lyset af manglende kontrolgruppe ved tidspunkterne 1 år og 3 år, mere retvisende kan måles fra baseline og efter randomisering til hhv. fortsat behandling eller seponering af pegvaliase i PRISM-2, part 2 (opfølgningstid 8 uger fra baseline), hvorfor ansøgers opgørelse ikke inddrages i vurderingen. Data for de relevante måletidspunkter er i stedet indhentet fra EPAR'en for PRISM-2, part 2. Herfra fremgår det bl.a., at der ikke var signifikante ændringer i opmærksomhedssymptomer målt med ADHD-RS-IV. Mean forskel fra baseline var 0,50 (95 % CI -2,07;3,06) og 1,64 (95 % CI -1,16;4,45) for hhv. 20 mg/dag og 40 mg/dag. Humør og adfærdsændringer blev selvrapporteret vha. PKU-POMS. Bl.a. med et delelement (*subscale confusion*) ud af seks (alle delelementer: angst, depression, vrede, aktivitet, træthed og forvirring) og for en PKU-POMS-version til måling af overordnede humørrelaterede ændringer (PKU-POMS TMD; *total mood disturbance*). PKU-POMS (*subscale confusion*) viste ingen signifikante ændringer og en mean forskel fra baseline på -0,82 (95 % CI -2,28;0,63) og 0,26 (95 % CI -1,57;7,75) for hhv. 20 mg/dag og 40 mg/dag. PKU-POMS-TMD viste ingen signifikante ændringer og en mean forskel fra baseline på -3,09 (95 % CI -10,31;4,13) og 0,08 (95 % CI -7,59;1,56) for hhv. 20 mg/dag og 40 mg/dag.

Overordnet set viste data for psykiatriske symptomer en forbedring i scoren, men bedringen var ikke statistisk signifikant og herudover for lille til at være klinisk relevant. Det sparsomme datagrundlag er overordnet set ikke tilstrækkeligt til at vurdere effektmålet psykiatriske effekter pålideligt.

Sammenligning med restriktiv diæt
Ansøger har ikke indsendt komparative data vedr. psykiatriske effekter.

Sammenligning med LNAA
Ansøger har ikke indsendt komparative data vedr. psykiatriske effekter.

Eksekutive funktioner
Effektmålet eksekutive funktioner er vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi forhøjede niveauer af fenylalanin påvirker de eksekutive funktioner som evnen til

planlægning samt kontrol af adfærd og handlinger, dømmekraft, fleksibilitet i tankegang, evnen til at ændre strategier samt løbende at justere egen adfærd. Som konsekvens ses problemer med job, uddannelse, sociale relationer, søvn og en manglende evne til at interagere med samfundet.

Ansøger har indsendt sparsomt data fra PRISM-2, part 2 (opfølgningstid 8 uger fra baseline) på hhv. 6 patienter (i behandling med pegvaliase) og 3 patienter (seponeret fra pegvaliasebehandling, også benævnt 'placebo'-gruppe). En ændring i eksekutive funktioner er i den endelige ansøgning opgivet for tre eksekutive delelementer fra den neuropsykologiske test *Cambridge Neuropsychological Test Automated Battery* (CANTAB). Fagudvalget vurderer, på trods af at CANTAB er et relevant værktøj, at de tre udvalgte delelementer fra testen (RVP, SST og SWM) ikke udgør et tilstrækkeligt grundlag for at vurdere effekt af behandling på de eksekutive funktioner. For vedvarende opmærksomhed målt med RVP er det valgte test-endepunkt i studiet *RVP Mean Response Latency (msec)* og ikke den konventionelle indikator for vedvarende opmærksomhed, som fagudvalget vurderer, er relevant at måle. Tilsvarende er der i studiet fra testen SST anvendt *SST Reaction Time (msec)* som test-endepunkt, som fagudvalget ikke kan vurdere relevansen af i forhold til at måle inhibitorisk kontrol, som testen er tiltænkt. Kun test-endepunktet fra SWM er fyldestgørende beskrevet.

Data viste en forbedring i scoren, men bedringen var ikke statistisk signifikant og herudover for lille til at være klinisk relevant. Det sparsomme datagrundlag og den selektive præsentation af data er overordnet set ikke tilstrækkeligt til at vurdere effektmålet eksekutive funktioner.

Sammenligning med restriktiv diæt

Ansøger har ikke indsendt komparative data vedr. eksekutive funktioner.

Sammenligning med LNAA

Ansøger har ikke indsendt komparative eller evaluerbare data vedr. eksekutive funktioner.

5.1.5 Fagudvalgets konklusion

Værdien af pegvaliase til behandling af patienter over 16 år med PKU kan ikke kategoriseres i henhold til Medicinrådets metoder. Datagrundlaget er sparsomt og af meget lav kvalitet. Vurderingen er derfor forbundet med væsentlig usikkerhed og baseret på en kvalitativ gennemgang af data og fagudvalgets kliniske erfaring med behandling af PKU-patienter.

Datagrundlaget indikerer, at pegvaliase hos patienter, der har et tilstrækkeligt respons og tåler behandling, kan sænke blodniveauet af fenylalanin til kontrollerede niveauer vha. én daglig administration (injektion). Patienter kan herudover måske øge deres proteinindtag fra naturlige kilder. Effekterne af pegvaliase på patienternes livskvalitet, psykiatriske effekter og kognitive funktioner er ikke belyst. Herudover anser fagudvalget pegvaliasebehandlingen som bivirkningstung med risiko for alvorlige potentielt livstruende bivirkninger (anafylaktiske reaktioner og angioødem i hoved-/halsregion) og mildere bivirkninger, samt for langtidsbivirkninger – hvoraf betydningen endnu er ukendt. Fagudvalget vurderer, at der er et stort behandlingsfrafald af patienter inden for de første år. Det er ud fra datagrundlaget ikke muligt at anslå, hvor stor en andel patienter der vil kunne fortsætte behandling med pegvaliase livslangt.

Effekterne af komparatoren restriktiv diæt er ikke tilstrækkeligt belyst i kliniske studier. Restriktiv diæt udgør i dag klinisk praksis ud fra rationalet om, at et mindre indtag af fenylalanin ultimativt begrænser hjernens indhold af fenylalanin. Restriktiv diæt nedbringer dog ofte livskvaliteten hos hovedparten af patienterne.

Effekterne af komparatoren LNAA er trods sin almindelige anvendelse til patienter med PKU i Danmark stort set ikke belyst i kliniske studier. Det er fagudvalgets erfaring, at LNAA kan have nogen gavn som supplement hos patienter, der ikke kan følge en restriktiv diæt, men at patienternes livskvalitet ikke væsentligt bedres med LNAA.

Samlet set vurderer fagudvalget, at pegvaliase ser ud til at være et bedre behandlingsalternativ end både restriktiv diæt og LNAA for voksne patienter med moderat eller klassisk PKU, som tåler pegvaliase, og som har vedvarende effekt af behandlingen.

Baggrunden er, at pegvaliase hos nogle patienter kan sænke fenylalaninkoncentrationen i blodet til værdier under 600 µmol/L, og på den måde antages at forbedre patienternes livskvalitet og eksekutive funktioner og muligheder for at gennemføre uddannelse og for at have tilknytning til arbejdsmarkedet. Det kan også muliggøre en tilnærmelsesvis normalisering af patienternes kost, så diæten bliver mindre restriktiv, og mere protein kan indtages fra naturlige kilder. Effekterne på livskvalitet, eksekutive funktioner og neuropsykiatriske mål er utilstrækkeligt belyst for både pegvaliase og komparatorer.
Fagudvalget vurderer baseret på klinisk erfaring, at behandling med pegvaliase vil bidrage positivt til patienternes livskvalitet gennem forbedrede eksekutive funktioner og færre restriktioner. Fagudvalget anslår, at pegvaliasebehandling kan være relevant at opstarte hos ca. 100 patienter svarende til hovedparten af patienter, der i dag får LNAA, og halvdelen af patienter med klassisk PKU. Af disse forventes 30-40 % at ophøre behandling pga. bivirkninger, manglende effekt eller udfordringer med behandlingsadhærens.

6. Andre overvejelser

6.1 Metode for måling af blodkoncentration af fenylalanin

I Danmark måles blodkoncentrationen af fenylalanin i blodplasma. Fagudvalget har efterspurgt oplysninger fra ansøger omkring referenceværdier for måling af fenylalanin i serum, plasma og/eller stabiliseret blod (EDTA, Citrat, Heparin, Heparin-Na-Fluorid og Citrat-Na-Fluorid) før og efter behandling med pegvaliase. Herudover en oversigt over, hvilke assays der er anvendt til måling af ovenstående og baggrunden for valget herfor.

Ansøger oplyser, at fenylalaninkoncentrationen udelukkende blev målt i blodplasma (venøst blod) i PRISM-studierne. Der er ikke indsendt referenceværdier eller oplysninger om anvendte assays som efterspurgt i protokollen, og fagudvalget kan derfor ikke vurdere, om målemetode og referenceværdier er sammenlignelige med danske forhold. Tidspunktet for måling af fenylalanin i blodet blev i studierne typisk foretaget om morgenen inden administration af pegvaliase.

6.2 Kostmæssige restriktioner i de pivotale studier

Fagudvalget ønskede information om de kostmæssige instruktioner, som patienter blev underlagt i studiet inkl. eventuelle kosttilskud.

Ifølge ansøger blev patienter vejledt til at opretholde en stabil kost (naturligt proteinindtag) inden for -/+10 % af baseline, medmindre fenylalaninniveauet blev for lavt. Patienterne blev behandlet med kosttilskuddet tyrosin, da tyrosin bliver en essential aminosyre, som kroppen ikke selv kan danne hos patienter på en fenylalaninfri kost, (500 mg tyrosintilskud 3 gange om dagen i hele studieperioden), men der var ingen yderligere kostmæssige instruktioner i de kliniske studier.

6.3 Administration af pegvaliase

Pegvaliase skal indledningsvist administreres ved ugentlige injektioner og herefter dagligt. Behandlingen forventes at være livslang. Fagudvalget ønskede en refleksion over eventuelle udfordringer ved administrationsvejen, f.eks. mulig indflydelse på adhærens til behandling.

Ifølge ansøger vil patienterne blive grundigt oplært i, hvordan pegvaliase skal administreres. Bl.a. skal en uddannet observatør være til stede de første 16 uger af behandlingen, og en epi-pen skal bæres af patienten som en sikkerhedsforanstaltning mod eventuelle anafylaktiske reaktioner.

6.4 Antistofudvikling mod pegvaliase

Antistofudvikling mod biologiske lægemidler kan manifestere sig som en aftagende (af ellers helt eller delvis opnået) effekt. Det kan betyde længere tid inden opnåelse af et gavnligt vedligeholdelsesniveau. Fagudvalget ønskede på denne baggrund oplysninger om eventuel antistofudvikling mod pegvaliase og den gennemsnitlige tid for opnåelse af vedligeholdelsesniveauet hos studiepopulationen.

Ifølge EPAR'en udviklede alle patienter i PRISM-studierne antistoffer (antidrug antibody; ADA) mod enten pegvaliase eller mod polyethylene glycol (PEG), som er indeholdt i lægemidlet. Effekten af ADA var forbigående og aftog inden for 2 uger, hvorefter der sås effekt af pegvaliase på niveau med patienter uden tilfælde af ADA-udvikling. Der var dermed ingen indikationer for at pegvaliase gradvist mistede virkning. Hos 70-80 % af patienterne blev der påvist neutraliserende antistoffer (Nab, der er i stand til at hæmme den enzymatiske aktivitet af pegvaliase). Generelt sås overfølsomhedsbivirkninger hyppigst hos patienter med de højeste antistofniveauer, men dette var ikke forudsigeligt for lægemidlets tolerabilitet. Ifølge EPAR'en er det ikke muligt at vurdere eventuelle langsigtede konsekvenser af antistofudvikling mod pegvaliase hos den enkelte patient.

6.5 Muligheder for normalisering af fenylalaninniveau i blodet

Fagudvalget ønskede informationer om, hvor stor en andel af patienterne, der nåede fenylalaninkoncentrationer mellem 120-360 µmol/L og lavere for at vurdere, om lægemidlet har potentiale til helt at normalisere fenylalaninkoncentrationerne, jf. referenceværdier.

På baggrund af data er det efter fagudvalgets vurdering muligt at nedbringe fenylalaninkoncentrationerne hos ca. halvdelen af patienter med behandlingsrespons til et niveau, hvor der ikke blot er tale om en normalisering, men også en mulig mangeltilstand af fenylalanin (hypofenylalaninæmi). Dette er nærmere beskrevet i afsnit *5.1.4 Effektestimater og kategorier, uønskede hændelser.*

6.6 Monitorering og seponering af pegvaliase

Monitorering

Den gennemsnitlige tid til et opnået vedligeholdelsesniveau (stabil dosering) af pegvaliase er ifølge ansøger ca. 8 måneder. Det er lang tid at administrere et lægemiddel inden at vurdere effekten, og for tidligere at kunne monitorere effekten af pegvaliase har fagudvalget opstillet følgende monitoreringsprocedure og seponeringskriterier, som lægger sig op ad praksis i det kliniske studie og proceduren ved vurdering af effekt for sapropterin.

Dosis af pegvaliase titreres langsomt op til 20 mg de første 24 uger, hvorefter dosis kan justeres op til 40 mg i løbet af de efterfølgende 16 uger.
Fagudvalget vurderer, at effekten skal monitoreres med gentagne fenylalaninmålinger over en længere periode. Derved får man et mere nuanceret grundlag at vurdere effekten på. Det er vigtigt, at patienten vejledes i at holde stabil kost (stabilt proteinindtag +/-10 % af baseline) og motionsvaner, i den periode effekten af pegvaliase vurderes – i praksis det første år af behandlingen.

Fagudvalget forventer, at behandling med pegvaliase forholdsvist hurtigt (hurtigere end efter 24 uger) vil påvirke fenylalaninniveauet i blodet, hvis patienten holder en stabil kost, og at effekten af pegvaliase derfor vil kunne vurderes tidligere i behandlingsforløbet. Halveringstiden af pegvaliase er 48 timer, og efter 10 dages dosering (5 halveringstider) vil pegvaliasekoncentrationen i princippet have nået steady-state. Dvs. at effekten af en op- eller nedtitrering i pegvaliase i forhold til fenylalaninkoncentrationen i blodet, under forudsætning af en stabil kost, først kan bedømmes tidligst 10 dage efter medicinjustering.

Fagudvalget vurderer, at følgende procedure vil være hensigtsmæssig for monitorering af effekt.

Det første år
Det første år måles patienternes fenylalanin hver anden uge. Efter ca. 10 uger måles fenylalaninkoncentrationen, og der indlægges et forløb på to uger, hvor fenylalaninkoncentrationen måles dagligt for at vurdere effekten af pegvaliase. Gennemsnittet af de 14 målinger skal vise en 20 % reduktion af fenylalanin i forhold til niveauet ved baseline.

Patienten følges herefter igen med blodprøver hver 14. dag. Efter 6-9 måneder (senest efter et år fra påbegyndt behandling) skal patienten have opnået et stabilt fenylalaninniveau under 600 µmol/l. Niveauet bestemmes efter 6-9 måneder ud fra 12 målinger (1 blodprøve om ugen i 12 uger), hvoraf mindst 8 målinger skal ligge under 600 µmol/l.

Efter første år
Efter det første år tages der blodprøver en gang om måneden livslangt, ligesom det er tilfældet ved diæt og behandling med LNAA. Ved ustabilt fenylalaninniveau over 600 µmol/l vurderes det,

om patienten skal følges mere tæt for at afveje behov for dosisjustering eller seponering pga. manglende effekt. Ved blodprøver, der viser subnormale niveauer af fenylalanin (under 30 µmol/l), vejledes patienterne i at regulere deres proteinindtag eller dosis af pegvaliase nedjusteres.

Seponering

Hvis der ikke er effekt (8 ud af 12 fenylalaninmålinger < 600 µmol/l) efter 40 uger i pegvaliasebehandling, og der er titreret op til max dosis på 40 mg eller ved intolerable bivirkninger, seponeres behandling.

Fagudvalget vurderer, at mellem 30-40 % af alle patienter, der opstarter behandling, vil skulle seponeres inden for det første år.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning udarbejdet af Medicinrådet på området.

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9. Sammensætning af fagudvalg

Medicinrådets fagudvalg vedrørende fenylketonuri

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Allan Bayat *Afdelingslæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Lars Bender *Overlæge*	Region Nordjylland
Kan ikke udpege kandidat, der opfylder Medicinrådets habilitetskrav	Region Midtjylland
Ulrike Dunkhase-Heinl *Overlæge*	Region Syddanmark
Har ikke specialet	Region Sjælland
Kan ikke udpege kandidat, der opfylder Medicinrådets habilitetskrav	Region Hovedstaden
Jette Lyngholm Nielsen *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Christina Gade *1. reservelæge*	Dansk Selskab for Klinisk Farmakologi
Bitten Aagaard *Overlæge*	Dansk Selskab for Klinisk Immunologi
Udpegning i gang	Dansk Sygepleje Selskab
Helle Merete Dissing *Patient/Patientrepræsentant*	Danske patienter
Laura Hoffenzits Kristensen *Patient/Patientrepræsentant*	Danske Patienter

Sammensætning af fagudvalg	
Christine Melsted Jørgensen *Klinisk diætist*	Inviteret af formanden
Lise Lykke Thomsen *Speciallæge i pædiatri*	Inviteret af formanden
Richardt Møllegaard Jepsen *Specialpsykolog i børne- og ungdomspsykiatri*	Inviteret af formanden

Medicinrådets sekretariat

Medicinrådet
Dampfærgevej 27-29, 3.th.
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk

10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	24. marts 2021	Godkendt af Medicinrådet

Medicinrådet

[1] Application for the reimbursement of pegvaliase for the treatment of patients with phenylketonuria (PKU) aged 16 years and older

Contents

General information

This application form should be submitted to the Danish Medicines Council (*Medicinrådet*) for the assessment of new medicines and new indications. The purpose of the form is to provide an overview of the basic information, literature search, study, and analysis results that will serve as the basis for the assessment. It indicates the minimum required information needed for the assessment.

The assessment of the pharmaceutical will be based on the outcomes defined in the protocol. Results for all critical and important outcomes (*kritiske og vigtige effektmål*) must be addressed in the application. The results of less important outcomes (*mindre vigtige effektmål*) do not need to be addressed. For all the data provided, a reference is mandatory.

During the completion of this form, elements should not be removed from the document. All sections should be filled in (if a section is not applicable, state "not applicable" and explain why). Table examples are provided in the form. Layout may deviate from the template to accommodate data; however, all requested information must be stated. We accept submission of appendices. Audits of literature searches and data analyses will occur.

In order to minimize translation errors between the application and the assessment report, submission in Danish is preferred.

If confidential data are submitted, highlight the data in yellow and write the expected publication date in a comment. If confidential data are submitted in an appendix, the document must in addition be watermarked as "confidential."

The application will be published simultaneously with the final assessment and recommendation report on the Danish Medicines Council's web page (www.medicinraadet.dk). Any data that will be considered in the assessment report will be published with the final application.

Checklist before submitting the application form:

- Are all relevant fields in the application form filled in?
- Are references indicated for all data?
- Is the application explicit and self-explanatory?

- Does the application meet the general requirements defined in the *Process and Methods Guide (version 2.0)* of the Danish Medicines Council for new medicines and new indications?
- Does the application meet the specific requirements in the protocol?
- Are deviation(s) from the protocol (if any) described?
- Are deviation(s) from the protocol (if any) justified?

1 Basic information

TABLE 1. CONTACT INFORMATION

Name	Mattias Janzén
Title	Director
Area of responsibility	Country Manager Nordics
Phone	+46 (0) 703 777970
E-mail	mattias.janzen@bmrn.com
Name	Søren Hansen
Title	Senior Territory Manager
Area of responsibility	Denmark and Iceland
Phone	+45 61199008
E-mail	soren.hansen@bmrn.com

TABLE 2. OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	Palynziq®
Generic name	Pegvaliase
Marketing authorization holder in Denmark	BioMarin International Limited 6th Floor, 2 Grand Canal Square, Dublin 2
ATC code	A16AB19
Pharmacotherapeutic group	Other alimentary tract and metabolism products
Active substance(s)	Pegvaliase
Pharmaceutical form(s)	Pegvaliase is an injection for subcutaneous use. It is a clear to slightly opalescent, colourless to pale yellow solution available as follows: 2.5 mg/0.5 mL, 10 mg/0.5 mL, and 20 mg/mL in a single-dose prefilled syringe
Mechanism of action	Pegvaliase is an enzyme substitution therapy that directly addresses the underlying cause of disease in PKU by substituting the missing or deficient Phe-metabolising enzyme activity
Dosage regimen	Pegvaliase is administered as a low dose induction followed by a slow upward titration to achieve stable maintenance dose and substantial blood Phe reductions, while minimising the onset and severity of hypersensitivity reactions. This dosing regimen is referred to as Induction, Titration, Maintenance (I/T/M), with maintenance being daily dosing of up to 20 - 60 mg, as required to reduce blood Phe to target level of 120 to ≤600 µmol/L.

<table>
<tr><td></td><td>The recommended dosing regimen is shown in the table below. The variability of immune response in individuals explains the difference in effective dose between patients. Dietary Phe intake should remain consistent until a maintenance dosage is established.
<table>
<tr><th></th><th>Dosage[1] administered subcutaneously</th><th>Minimum administration duration prior to next dosage increase[2]</th></tr>
<tr><td>Induction</td><td>2.5 mg once weekly</td><td>4 weeks</td></tr>
<tr><td rowspan="4">Titration</td><td>2.5 mg twice weekly</td><td>1 week</td></tr>
<tr><td>10 mg once weekly</td><td>1 week</td></tr>
<tr><td>10 mg twice weekly</td><td>1 week</td></tr>
<tr><td>10 mg four times a week</td><td>1 week</td></tr>
<tr><td rowspan="3">Maintenance[3]</td><td>10 mg daily</td><td>1 week</td></tr>
<tr><td>20 mg daily</td><td>12 - 24 weeks</td></tr>
<tr><td>40 mg daily
(2 consecutive injections of 20 mg prefilled syringe)</td><td>16 weeks</td></tr>
<tr><td>60 mg daily
(3 consecutive injections of 20 mg prefilled syringe)</td><td>Maximum recommended dosage</td></tr>
</table>

[1] The dosage may be reduced or the dietary phenylalanine intake may be modified if blood phenylalanine levels are 30 µmol/L or less.
[2] Additional time may be required prior to each dose escalation based on patient tolerability.
[3] Individualize treatment to the lowest effective and tolerated dosage. The dosage may be increased up to a maximum of 60 mg daily in patients who have not reached a response (≤ 600 µmol/L) after minimum administration duration specified.
</td></tr>
<tr><td>Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)</td><td>Pegvaliase is indicated for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood Phenylalanine (Phe) control (blood Phe levels greater than 600 µmol/L) despite prior management with available treatment options.</td></tr>
<tr><td>Other approved therapeutic indications</td><td>No</td></tr>
<tr><td>Will dispensing be restricted to hospitals?</td><td>Yes, initially.</td></tr>
</table>

Combination therapy and/or co-medication	Premedication prior to each dose (e.g., H1 antagonist, H2 antagonist, and antipyretic) is required during induction and titration due to the potential for an acute systemic hypersensitivity reaction. This may be continued during maintenance if needed. Prior to first dose of Palynziq, the patient should be trained on the signs and symptoms of an acute systemic hypersensitivity reaction and to seek immediate medical care if a reaction occurs, and how to properly administer adrenaline injection device (auto-injector or pre-filled syringe/pen).
Packaging – types, sizes/number of units, and concentrations	Solution available in 2.5 mg/0.5 mL, 10 mg/0.5 mL, and 20 mg/mL in a single-dose prefilled syringe. The 20 mg/mL syringes are also available in 10-pack. Injection for subcutaneous use.
Orphan drug designation	Yes

2 Abbreviations

ACMG	American College of Medical Genetic and Genomics
ADHD	Attention Deficit/Hyperactivity Disorder
ADHD RS-IV	Attention Deficit/Hyperactivity Disorder Rating Scale version IV
ADHD RS-IV IA	Attention Deficit/Hyperactivity Disorder Rating Scale version IV inattention subscale
AE	Adverse event
AS	Absolute shortfall
BH4	Tetrahydrobiopterin
CID	Clinically Important Difference
CSR	Clinical Study Report
CUA	Cost-utility analysis
DBS	Dried Blood Spot
DKK	Danish Kronor
DMC	Danish Medicines Council
EMA	European Medicines Agency
ESPKU	European Society for PKU and Allied Disorders Treated as PKU
FDA	United States Food and Drug Administration
HAE	Hypersensitivity acute event
HCRU	Healthcare resource use
HPA	Hyperphenylalanaemia
HRQoL	Health-related quality of life
HSUV	Health state utility values
IA	Inattention
ICER	Incremental cost-effectiveness ratio
IgE	Immunoglobulin E
I/T/M	Induction, Titration, Maintenance
ITT	Intention-to-treat
KOL	Key opinion leader
LS	Least squares
MAIC	Matching adjusted indirect comparison
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
MNT	Medical Nutritional Therapy
MRI	Magnetic Resonance Imaging
NBS	Newborn screening
OLE	Open label extension
PAH	Phenylalanine Ammonia Hydroxylase
PAL	Phenylalanine Ammonia Lyase

Phe	Phenylalanine
Pegvaliase	Polyethylene glycol
PKU	Phenylketonuria
PKUDOS	Phenylketonuria Demographic, Outcomes, and Safety Registry
PKU-POMS	Phenylketonuria-specific Profile of Mood States
POMS	Profile of Mood States
PPP	Pharmacy Purchasing Price
PRP	Pharmacy Retail Price
PSA	Probabilistic Sensitivity Analysis
QoL	Quality of life
RDT	Randomized discontinuation trial
RVP	Rapid visual processing
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SF-36	36-item Short Form Survey, SF-36
SmPC	Summary of Product characteristics
SMQ	Standardised MedDRA Query
SST	Stop signal task
STA	Single Technology Assessment
SWM	Spatial working memory
TMD	Total mood disturbance score
VAS	Visual analogue scale

3 Summary

Phenylketonuria (PKU) is a rare autosomal disease characterised by complete or partial deficiency of Phenylalanine hydroxylase (PAH) enzymatic activity, leading to elevated blood levels of the essential amino acid Phenylalanine (Phe) which is toxic to the brain. Elevated Phe causes detrimental effects on brain development and function, inhibits protein synthesis, and leads to white matter abnormalities that impact the speed of nervous transmission and impairs synthesis of the neurotransmitters dopamine, noradrenaline and serotonin [2-6].

Untreated PKU in children leads to severe disease characterised by microcephaly, irreversible intellectual disability, seizures, motor deficits, aberrant behaviour and psychiatric symptoms, although rarely seen nowadays due to the introduction of new-born screening in 1963. All PKU patients identified at new-born screening are recommended to be on a phe-restricted diet to manage the disease. However, it has been reported that with the onset of adolensence and further into adulthood, compliance to te recommended phe-restricted diet becomes more challenging posing a more significant disease burden on the patient. Adult patients with elevated blood Phe are at increased risk of serious neurocognitive and neuropsychiatric complications and other comorbid conditions compared to unaffected individuals. The neurocognitive and neuropsychiatric impairments correlate with elevated blood Phe levels and can be improved when blood Phe level is reduced [7], and even short-term high Phe levels have a significant direct negative effect on mood and neuropsychological performance in adult patients with PKU [8]. Overall, PKU has a negative impact on health-related quality of life (HRQoL) that is improved with better metabolic control [9].

The prevalence of PKU is approximately 1 in 10,000 newborns in Europe [10, 11]. In Denmark the birth prevalence was determined as 1 in 13,434 [12]. The prevalent population of patients with PKU aged ≥16 years in Denmark, according to estimations of the Danish advisors, is 311 of which 29 are treated with sapropterin, 100 with LNAAs (patients aged >18 years) and the remaining patients on the Phe-restricted diet.

Danish advisors follow the European PKU management guidelines [13] which recognise the necessity for life-long control of blood Phe levels. The recommendation in patients >12 years of age is for a blood Phe level between 120 and 600 µmol/L. [14, 15]. Blood Phe levels higher than the European recommendation are related with increased risk of serious neurocognitive and neuropsychiatric complications and other associated comorbid conditions.

The current PKU treatment landscape in Denmark consists of a Phe-restricted diet, Kuvan in those who are responders (i.e. those with residual PAH enzyme activity who can maintain blood Phe levels <600 µmol/L after 6 months of treatment and had a reduction of Phe during Kuvan testing at 30%) or supplementation with large neutral amino acids (LNAAs) if blood Phe levels are inadequately controlled (exceeding 600 µmol/L) with diet and/or Kuvan in adult PKU patients. PKU patients using LNAAs have their diet adjusted to consist of 80% natural protein intake and 20% LNAAs, allowing more freedom for the patient from a dietary perspective and targeting maintained blood Phe levels <1500 µmol/L [13].

With current treatment options (Sapropterin + Phe-restricted diet, Phe-restricted diet on its own, LNAAs in combination with semi-restrictive diet) it is very hard to achieve the blood Phe levels prescribed by the European PKU management guidelines[14, 15] and thus residual PKU disease burden persists with its associated complications of elevated blood Phe levels. Management by severe dietary phenylalanine

restriction is extremely limiting, can be socially isolating and is impossible to achieve for most adolescent and adult patients [16, 17].

Pegvaliase is a new treatment option for those unable to reach EU guideline recommended Phe levels with a robust evidence package from the clinical trial programme (placebo-controlled studies in the Phase 3 studies) including long term data from extension studies. With pegvaliase, it is now possible to achieve blood Phe levels reaching even normative levels that were unheard of previously. 69% achieve 600µmol/L at 24mths, 51% achieve <120µmol/L at 24mths [1]. This increases to 72% and 61% at 4 years for those reaching 600µmol/L and 120µmol/L respectively [18, 19].

Pegvaliase is the first and only therapy that directly addresses the underlying cause of PKU in all patients by substituting the missing or deficient Phe-metabolising enzyme activity, irrespective of residual PAH enzyme activity.

Following two recent modified Delphi meetings with PKU clinical advisors in Denmark, they aligned upon the key outcomes of relevance to PKU patients which would then enable a comparison to LNAAs (given there are no outcomes that correlate between those in the pegvaliase clinical trial programme and the limited evidence available supporting LNAAs). The outcomes identified by the KOLs are impulse control, reduced processing speed, attention, working memory, depression/anxiety and IQ.

There was consensus from the KOLs that these symptoms identified above are proportional to blood Phe levels. LNAAs have not been shown to consistently reduce blood Phe, as stated in the SLR report, Appendix A. It was accepted that pegvaliase would reduce these symptoms of relevance in PKU patients more effectively than LNAAs. The KOLs did state that some benefit is observed with LNAAs although recognising this is difficult to objectively measure, and the extent of improvement is based more on clinical observation than evidence based clinical trial data. Danish advisors confirmed that if pegvaliase was made available in Denmark, it would provide a better treatment option for PKU patients compared with existing therapies based on the existing evidence supporting its effectiveness in the management of PKU

Pegvaliase has the potential to reduce blood Phe levels to normative levels [1] and as such can reduce the associated PKU symptoms more effectively given the body of evidence that exists linking these outcomes to blood Phe levels.

In addition to blood Phe reduction, patient quality of life was also stated as a key outcome of relevance to PKU patients. Due to the present limitation of existing tools and their associated sensitivities in capturing the impact of PKU on patient's QoL, a Time-Trade Off (TTO) utility study was conducted in Sweden to elicit the correlation between PKU disease severity and patient disutility. The study also elicited the impact of restricted diet regimes on PKU patient's disutilities. The conclusion of the study illustrated that there was a direct relationship between disease severity and PKU patient disutilities as was also observed with restricted diet regimes. The applicability of this study to Danish PKU patients was validated by Danish advisors who also highlighted the suitability of diet normalisation as a proxy measure of QoL in PKU patients. Pegvaliase is the only licensed product that substantially lowers blood Phe levels (reduces disease severity) and improves the natural protein intake of PKU patients towards a normal diet. Diet normalisation is regarded by most PKU patients as reported by Danish advisors as a plausible proxy measure for QoL in PKU patients.

Pegvaliase is an effective treatment option for patients with PKU aged ≥16 years who have inadequate blood Phe control (>600 µmol/L) despite prior management with current therapies as it achieves a substantial

reduction in blood Phe, which is associated with clinically important improvements in neurocognitive and neuropsychiatric outcomes, and an increase in natural protein intake which allows patients to normalise their diet and potentially reduce the negative consequences of a Phe-restricted diet. These achievements with pegvaliase treatment are shown to be sustained over the long-term [18].

4 Literature search

A systematic literature review was undertaken, in accordance with the specified request in the evaluation protocol. The complete search strategy and the results are provided in Appendix A, attached to the application.

A PRISMA flow diagram showing the outcome of the search process is provided in Figure 1.

Inclusion criteria are detailed in Table 3 and exclusion criteria in Table 4. Citations excluded at first pass (after abstract/title review) were tagged ‘e1’. Citations excluded at second pass (after full-text review) were tagged ‘e2’.

A list of excluded references after full-text screening are given in table 26 of the SLR report (Appendix A).

FIGURE 1. PRISMA FLOW-CHART FOR STUDY IDENTIFICATION AND SELECTION OF CLINICAL EVIDENCE

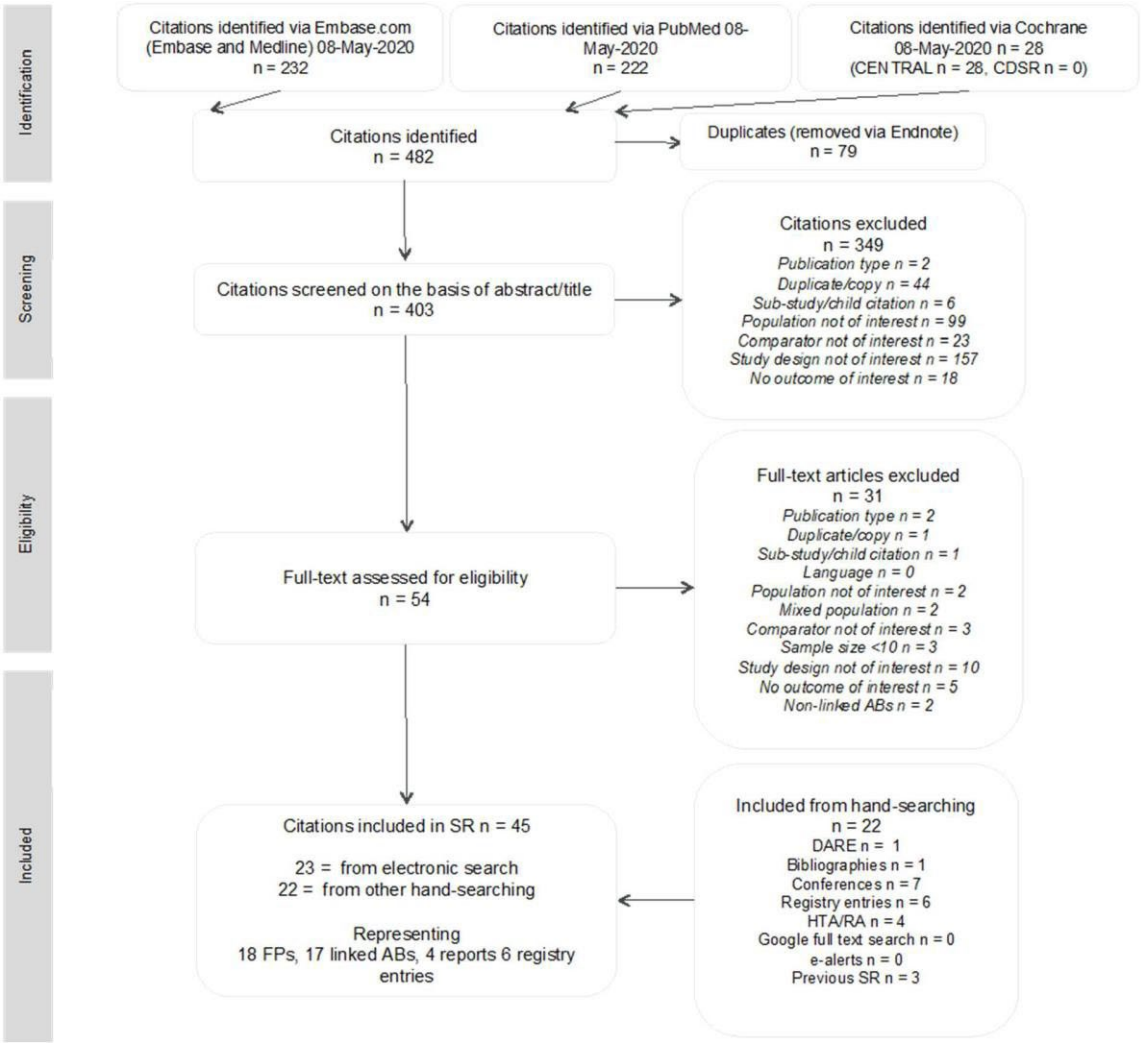


TABLE 3. PICOS INCLUSION CRITERIA FOR THE CLINICAL SR

Characteristic	Inclusion criteria
Population	Patients (16+ years) with PKU, uncontrolled (Phe>600 micromol/L) despite prior management with available treatment options
Mixed populations [+]	For mixed populations, at least 80% must be the population of interest *or* subgroup data for the population of interest must be reported separately Mixed data examples include: mixed PKU/BH4 deficiency; mixed adult/child populations; mixed level of control of blood Phe; mixed lines of treatment

Characteristic	Inclusion criteria
Interventions/ comparators	Pegvaliase +/- protein/Phe diet restriction in licensed setting Large neutral amino acids (LNAAs)
Outcomes	At least 1 prespecified outcome reported, as a 1ry or 2ry outcome, out of: • Phe concentration in blood • Change in neuropsychological function / psychiatric outcomes • Protein intake (natural protein intake, and protein supplements use) • Adverse effects of treatment / safety • Cognitive and mood symptoms / executive function • HRQoL (inc. utilities)
Study design	Prospective parallel design RCTs (phase 2-4[++]) with active or PLA controls ITCs or NMAs (with unique information) Other controlled clinical trials (interventional, prospective, non-RCT) Extension phases of trials (including single arm extensions) Prospective registry studies (analyses of prospectively collected data) / case series Case-control studies
Date limits	SRs/NMAs/ITCs of relevance from 2012 onwards. Individual studies are not limited
Country limits	No limits on clinical data
Child abstract	Child abstract (sub-study) with unique data
Publication type	Errata Original articles
Languages [§]	Any foreign language paper with an English abstract will be included at 1st pass if sufficient information is present in the English abstract to suspect that the eligibility criteria are met

- **Abbreviations:** AE, Adverse Event; HRQoL, Health-Related Quality of Life; ITC, indirect treatment comparison; NMA, network meta-analysis; PLA, placebo; RCT, Randomised Controlled Trial; SR, Systematic Review;
- + 80% was used as an initial standard, though arbitrary, cut-off, for mixed populations. During screening, dependent upon the data identified, the 80% cut-off may be revised, and the rationale documented.
- ++ The search strings will also capture phase 1/2 studies. These were included if the phase 2 data are reported, and the phase 2 data were extracted only. Phase 1 trials were excluded.

- § language capabilities included English, Czech, Danish, French, German, Hungarian, Italian, Polish, Portuguese and Spanish.

TABLE 4. EXCLUSION CRITERIA AND CODES FOR THE CLINICAL SR

Characteristic	Exclusion code & criterion	Explanatory notes
Publication type	e1 pub: Publication type not of interest	e.g. editorials, commentaries, letters, notes
Duplicate	e1 dup: Duplicate/copy	Exact duplicates or copy abstracts, for example where the content is almost identical. If there are discrepancies in the actual data reported, then both will be retained, and the discrepancy noted
Child abstract	e1/e2 child: Child abstract or sub-study with no unique data	To be determined at 1st or 2nd pass stage
Languages	e2 lang: Full text in language that can't be translated *	During screening, foreign language articles with insufficient information in the English abstract or without an abstract, or with an abstract in a language that can't be translated*, will have the full text obtained and added to the Endnote file. Those translatedwill be assessed in the usual way at 2nd pass. Those in languages that can't be translated will be excluded at 2nd pass, tagged and listed in the report for transparency as a paper for which the eligibility could not be established.
Population	e1/e2 pop: Not PKU (not PAH deficiency) HPA due to BH4 deficiency	BH4 deficiency will be excluded
	PKU in children or adolescents	Population of relevance for pegvaliase is adults
	Treatment-naïve PKU patients	Outside of EMA MAA scope
Mixed populations	e1/e2 mix:	<80% of the enrolled patients are the population of interest and subset results are

Characteristic	Exclusion code & criterion	Explanatory notes
	Mixed population enrolled	not reported separately for the population of interest
Interventions / comparators	e1/e2 comp: No comparator of interest e.g. trials of protein substitutes	Established clinical management without pegvaliase (e.g. diet therapy, sapropterin) will be excluded
Sample size	e2 size	<10 patients enrolled (>=10 is includable), except for maternal PKU where any size of study is includable
Study design	e1/e2 design: Not an RCT (phase 2, 3, 4), or a controlled non-RCT, or a registry, case-control, cross-sectional survey or case series study or chart/record review	
	Phase 1 only trials	Phase 1-2 studies reporting phase 2 data are eligible. Phase 1 only studies, or phase 1-2 studies reporting only the phase 1 data are excluded
	Retrospective studies	More prone to bias than prospectively conducted studies
	Case reports	Case series (n>10) may be relevant but not individual case reports
	PK/PD study only	No outcome of interest
	Cluster randomised trials	Individual subjects not randomised
	Non-systematic reviews	Any particularly interesting clinical-type reviews may be noted for discussing in the report. However, in general non-systematic reviews will be excluded.
	SRs/MAs/NMAs/ITCs	Relevant 2012+ SRs and MAs are kept in at 1st pass for cross-referencing purposes but will be excluded after 2nd pass, except if MA/ITC data not available elsewhere

Characteristic	Exclusion code & criterion	Explanatory notes
	Post-hoc pooled analyses	To avoid the same data being included twice. The original trials going into the pooled analysis, if relevant, will be included.
	Pilot studies <10 patients (except in maternal PKU where numbers may be small)	Not robust enough evidence for use
	Economic analyses or budget impact analyses	Clinical outcomes only
	In vitro studies or animal studies	Human in vivo only
	Screening/diagnostic studies	
	Protocol only articles	e.g. protocols of Cochrane reviews
Outcomes	e1/e2 out: No outcome of interest Very short-term outcomes (e.g. 24 hrs treatment only) Baseline only data	Paper does not report at least one outcome of interest, or does not report an outcome of interest sufficiently specified (wk of follow-up, ITT/mTT)
	Brain Phenylalanine level	
	RCTs not reporting an ITT or mITT analysis	Avoid biased outcome data entering dataset
Date limits	e1/e2 date: 2012 for SRs/MAs Unlimited for RCTs/trials	Most recent and relevant SRs since 2012 to be reference-checked
Standalone abstract	e2 ab	Abstracts or posters that are not linked to a full text publication reporting the design/methods and primary results will be excluded. Note: Abstracts reporting, for example, follow-up data for a study for which the methods have already been reported in a full paper, will be included.

- **Abbreviations:** 1st, first; 2nd, second; e1, excluded on abstract screening; e2, excluded on full paper screening; ITT, Intention-To-Treat; MA, meta-analysis; mITT, modified ITT; ITC, indirect treatment comparison; NMA,

network meta-analysis; PD, pharmacodynamics; PK, pharmacokinetic; RCT, Randomised Controlled Trial; SR, Systematic Review; wk, week

- * English, Czech, Danish, French, German, Hungarian, Italian, Polish, Portuguese and Spanish.

4.1 Relevant studies

A total of 45 citations were identified for inclusion in the systematic review according to the criteria above: representing 16 studies (Table 5) (16 citations + 25 linked citations) and 4 HTA/regulatory reports (Appendix A).

More information on the study selection process, excluded studies and reasons for exclusion is provided in Appendix A.

The 41 citations providing information on the 15 studies are given in Table 28 of Appendix A and represent 25 full papers, 6 registry entries at clinicaltrials.gov, and 10 conference abstracts. The four HTA/regulatory reports included the pegvaliase EPAR [20], and three GB-A reports [21-23]

One full paper reporting one of the pegvaliase phase 2 studies [24]and two additional recent conference abstracts presenting long-term data from the pooled pegvaliase phase 3 studies [18, 19] were added after the completion of the SLR, and are also included in this application.

One of the identified citations, Zori 2019 [25], is a full paper presenting an indirect treatment comparison between pegvaliase and comparators (dietary management; and sapropterin in conjunction with dietary management) where pooled phase 3 pegvaliase data were compared with matched data from the PKUDOS registry.

Additionally, study 165-304 has been excluded as not reporting so far any results and study Sri Bhashyam 2019 as patient preference study not reporting outcomes linked to clinical question.

To sum up, 15 studies has been included in this assessment as the ones identified via SLR and responding to the clinical question (Table 5).

TABLE 5. RELEVANT STUDIES INCLUDED IN THE ASSESSMENT

No	Name used in this application	Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
1	165-301	**Thomas, J., et al.,** Pegvaliase for the treatment of phenylketonuria: Results of a long-term phase 3 clinical trial program (PRISM). Mol Genet Metab,	165-301 (PRISM-1)	NCT01819727	2013-2015	1.2 1.3 1.4

No	Name used in this application	Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
		2018. [1] **Burton, B.K., et al**., Long-term safety of induction, titration, and maintenance dosing of pegvaliase treatment in adults with phenylketonuria. Journal of Inherited Metabolic Disease, 2018. 41: p. S104.[100]				
2	165-302	**Thomas, J., et al.,** Pegvaliase for the treatment of phenylketonuria: Results of a long-term phase 3 clinical trial program (PRISM). Mol Genet Metab, 2018.[1] **Harding C, Burton B, Thomas J, al.** e. Phase 3 PRISM-2 Long-term Extension Evaluating Efficacy and Safety of Pegvaliase for Treatment of Adults with Phenylketonuria. ACMG Annual Clinical Genetics Meeting 2017; Phoenix Arizona, USA2017. [25] **Harding CO**, W.H., Olbertz J, Gu K, Chandriani S, Adams D, Sanchez-Valle A, Update of efficacy and safety of pegvaliase for the treatment of adults with phenylketonuria, in ACMG Annual Clinical Genetics	165-302 (PRISM-2)	NCT01889862	2013-2019	1.2 1.3 1.4 1.5 1.6

No	Name used in this application	Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
		Meeting. 2020: San Antonio, Texas. [19] **Harding, C.O., et al.,** Pegvaliase for the treatment of phenylketonuria: A pivotal, double-blind randomized discontinuation Phase 3 clinical trial. Mol Genet Metab, 2018.[26] **Levy H, Harding C, Longo N, Bilder D, Burton B, Zori R, et** al. Phase 3 PRISM-2 long-term extension evaluating efficacy and safety of pegvaliase for treatment of adults with phenylketonuria. Journal of Inherited Metabolic Disease. 2016;39:S108. **[27]** **Vockley J**, Levy H, Amato S, Zori R, Thomas J, Burton B, et al. Phase 3 prism-2 long-term extension study evaluating efficacy and safety of pegvaliase for treatment of adults with phenylketonuria. Journal of Inborn Errors of Metabolism and Screening. 2017;5:128-9.[28] Rohr F, B.B., Longo N, Thomas JA, Harding CO, Rosen O, Gu Z , Olbertz J, Weng HH, Evaluating change in diet with pegvaliase treatment in adults with				

No	Name used in this application	Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
		phenylketonuria: Results from phase 2 and 3 clinical trials 2020. [18]				
3	165-205	Induction, titration, and maintenance dosing regimen in a phase 2 study of pegvaliase for control of blood phenylalanine in adults with phenylketonuria. **Zori R., et al.** Molecular Genetics and Metabolism. 2018 [24]	165-205	NCT01560286	2012-2015	1.2 1.3
4	PAL-003	Long-term safety and efficacy of pegvaliase for the treatment of phenylketonuria in adults: combined phase 2 outcomes through PAL-003 extension study. **Longo N, et al.** Orphanet J Rare Dis. 2018 [29]	PAL-003	NCT00924703	2009-2019	1.2 1.3
5	PAL-004	Registry records [30]	PAL-004	NCT01212744	2011-2015	1.2 1.3
6	Zori 2019	Long-term comparative effectiveness of pegvaliase versus standard of care comparators in adults with phenylketonuria. **Zori R, et al.** Molecular Genetics and Metabolism 2019 [31]	N/A	N/A	NR	1.2 1.3 1.4
[30]7	Burlina 2019	Large Neutral Amino Acid Therapy Increases	N/A	N/A	NR	1.2 1.3

No	Name used in this application	Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
		Tyrosine Levels in Adult Patients with Phenylketonuria: A Long-Term Study **Burlina AP, et al.** Nutrients 2019 [32]				1.4
8	Scala 2020	Large Neutral Amino Acids (LNAAs) Supplementation Improves Neuropsychological Performances in Adult Patients with Phenylketonuria **Scala I, et al.** Nutrients 2020 [33]	N/A	N/A	NR	1.2 1.3
9	Matalon 2006	Large neutral amino acids in the treatment of phenylketonuria (PKU) **Matalon R, et al.** J Inherit Metab Dis 2006 [34]	N/A	N/A	NR	1.2 1.3
10	Matalon 2007	Double blind placebo control trial of large neutral amino acids in treatment of PKU: Effect on blood phenylalanine **Matalon R, et al.** J Inherit Metab Dis 2007 [35]	N/A	N/A		1.2 1.3
11	Lou 1987	Increased Vigilance and Dopamine Synthesis by Large Doses of	N/A	N/A	NR	1.2 1.3

No	Name used in this application	Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
		Tyrosine or Phenylalanine Restriction in Phenylketonuria **Lou HC, et al.** Acta Paediatr Scand 1987[36]				
12	Pietz 1995	Effect of high-dose tyrosine supplementation on brain function adults with phenylketonuria **Pietz J, et al**. J Pediatr 1995 [37]	N/A	N/A	NR	1.2 1.3
13	Schindeler 2007	The effects of large neutral amino acid supplements in PKU: An MRS and neuropsychological study **Schindeler S, et al** Molecular Genetics and Metabolism 2007 [38]	N/A	N/A	NR	1.2 1.3 1.4
14	Yano 2013	Large Neutral Amino Acid Supplementation Increases Melatonin Synthesis in Phenylketonuria: A New Biomarker **Yano, et al**. J Pediatr 2013 [39]	N/A	N/A	NR	1.2 1.3
15	Yano 2014	Melatonin and Dopamine as Biomarkers to Optimize Treatment in Phenylketonuria: Effects of Tryptophan and Tyrosine Supplementation **Yano S, et al.** J Pediatr	N/A	N/A	NR	1.2 1.3

No	Name used in this application	Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
		2014 [40]				
		* The 1.1.- 1.6 numbers refer to the following outcomes measures: 1.1 Quality of life 1.2 Adverse events 1.3 Phenylalanine concentration 1.4 Natural protein intake 1.5 Neuropsychiatric symptoms 1.6 Executive function				

4.2 Main characteristics of included studies

The main characteristics of the included studies are presented in table format in the Appendix Tables [redacted]

The pegvaliase clinical trial programme is described in more detail in section 4.2.1 below.

4.2.1 Pegvaliase clinical trial programme - Pivotal Prospective Clinical Studies: 165-301 (PRISM-1) and 165-302 (PRISM-2)

The efficacy and safety of pegvaliase has been studied in an extensive clinical development programme including 355 patients of which 285 were part of an I/T/M dosing regimen, as recommended in the label.

The effects of pegvaliase in the treatment of PKU have been demonstrated in patients with PKU in Phase 2 and Phase 3 studies. The two Phase 3 studies of key relevance are: 165-301 (PRISM-1), an open label study to study safety and tolerability of initiating pegvaliase treatment using an I/T/M regimen, and 165-302 (PRISM-2), a follow- on study for efficacy assessment. In designing the phase 3 clinical programme for pegvaliase there were clear challenges to run a prolonged placebo- controlled study. Undertaking a randomised controlled trial would require the blinding of the study population over a prolonged period. This was not possible due to the treated patient recognizing active treatment due to the presence of hypersensitivity reactions before patients are able to reach the maintenance phase. In addition, it was deemed not ethically acceptable by study investigators to let placebo- controlled patients remain in a high Phe state in a placebo arm for a prolonged period of time. These perspectives have been important in designing the phase 3 program.

The study populations enrolled in the phase 3 clinical trials reflect the proposed indication for PKU patients aged 16 years and older with uncontrolled Phe (>600 µmol/L) on current management.

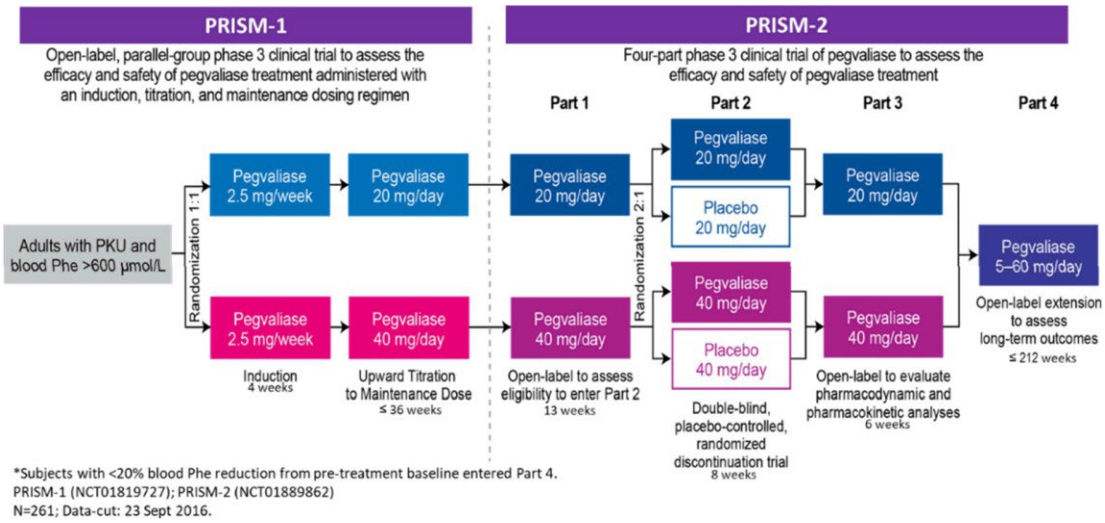
Study 165-301 was designed to further characterise the safety of pegvaliase during two I/T/M dose regimens. It was an open label randomised (1:1), multi-centre study of patients with PKU to assess the safety and tolerability of self-administered pegvaliase in two I/T/M dosage regimens.

Study 165-302 included a double blinded RDT over 8 weeks in the group of patients from 165-301 demonstrating an initial drop in Phe (Figure 2). A period of 8 weeks was chosen as the optimum period to demonstrate changes in blood Phe while not exposing patients to high Phe levels for an ethically unacceptable long time, as discussed above. All subjects entering 165-302, had uncontrolled blood Phe (>600 µmol/L) at pre-treatment baseline and the majority of the study participants were not following a Phe restricted diet which is typical of the current adult PKU populations. Finally, all patients who continued treatment moved into a long-term follow-up part (165-302 part 4) where they have been followed for up to 4 years. In this open label phase, dosage titration to a higher dose of 60 mg was possible (Figure 2).

The four parts of 165-302 were:

- Part 1: Open label, pegvaliase treatment administered at doses of 20 or 40 mg/day to determine eligible subjects for Part 2 (≥20% Phe reduction from baseline [treatment-naive] values that was used as an indication of initial pharmacological response), to be able to demonstrate efficacy within the eight-week phase of RDT in Part 2. Patients who did not meet these criteria (≥20% Phe reduction from baseline) went straight into Part 4.
- Part 2: Eight-week double-blind, placebo-controlled, RDT to evaluate pegvaliase (20 or 40 mg/day) versus matched placebo on blood Phe level (primary outcome), neuropsychiatric, and safety measures.
- Part 3: Six-week, open-label, one-way crossover study involving intense sampling for use in pharmacokinetic and pharmacodynamic analyses.
- Part 4: Long term, open label extension (OLE) trial to evaluate pegvaliase efficacy and safety with dose optimization allowed between 5 mg/day and 60 mg/day.

FIGURE 2. PEGVALIASE PHASE 3 CLINICAL TRIALS: 165-301 (PRISM-1) AND 165-302 (PRISM-2)



Since PKU is a congenital, life-long disease without a cure, long term data are essential for assessing treatment effects. BioMarin considers the long-term follow up data (i.e. the combined data-set of 165-301 and 165-302) as most relevant as this is most in-line with the indication, provides more realistic perspective

on the real world effectiveness of treatment with pegvaliase and allows for more realistic comparisons to well-developed long-term data on standard of care. In addition, only part 4 of 165-302 used the full maintenance range of 5 - 60 mg daily dose.

4.2.2 Relevant endpoints studied

The primary outcome measure in the trial was blood Phe level. Other outcome measures included the amount of natural protein intake, and neurocognitive and psychosocial functioning scores based on the ADHD RS-IV IA (Attention Deficit/Hyperactivity Disorder Rating Scale version IV inattention subscale) and the Profile of Mood States (POMS) instruments [1]

4.2.2.1 Blood Phe levels

An elevated blood Phe level is the direct result of PAH deficiency and remains the best surrogate measure of PKU treatment effectiveness. In addition, blood Phe is considered the most relevant primary efficacy outcome for clinical trials conducted in the field of PKU [41].

In this application, blood Phe is considered a critical endpoint for several reasons:

- Monitoring and maintaining blood Phe concentration within a given target treatment range is the objective of clinicians treating patients with PKU [14, 15, 42].
- According to European treatment guidelines, the primary goal of treatment is normal neurocognitive and psychosocial functioning with blood Phe being the best surrogate measure for this [15].
- Elevation of blood Phe is the direct result of the PAH deficiency in PKU patients and is seen as a biomarker for disease severity [43] and has a direct physiological relationship to white matter changes in the brain as well as impact of neurotransmitter imbalance [43]. The resulting blood Phe is, hence, correlated with CNS toxicity and related to PKU symptoms which in PKU patients aged 16 years and older are reversible when blood Phe levels are controlled [44], in line with other findings [7, 8, 45, 46].
- Precedence for therapeutic approval by both EMA and FDA. For example, the response to sapropterin is determined by a decrease in blood Phe levels [47].
- Blood Phe levels directly impacts cognitive outcomes of neurological function with more severe symptoms in patients with higher blood Phe levels [41].
- Studies demonstrate that lowering Phe improves neuropsychological symptoms including executive function and attention deficits, and reduces disease burden [7, 8, 48-51].
- In conclusion, blood Phe is directly relevant for patient care because Phe is a biomarker of disease severity, a compliance measure for PKU clinical treatment [43] as well as the most crucial factor in directing treatment [15] and direct links between Phe levels and neuropsychological symptoms including executive function and attention deficits have been described.

4.2.2.2 Natural protein intake

Patients with PKU require severe restriction of Phe intake to control blood Phe concentrations within guideline levels and are allotted very small amounts of natural protein per day, with the majority of protein coming from medical nutritional therapies. Such severe protein restriction has negative nutritional consequences. Phe-restricted diets have been associated with nutritional deficiencies, such as vitamin B12

and other B vitamins, vitamin D, folate, and calcium [52, 53]. Adherence to a Phe-restricted diet has been shown to be associated with factors known to contribute to obesity, osteoporosis, renal and cardiovascular disease:

- Reliance on nutritionally incomplete medical foods has been shown to increase the risk for obesity, bone pathology, and heart disease [54-56].
- Long-term restricted protein intake with amino acid substitution found in medical food preparations has been discussed as a potential contributor for chronic kidney disease [57].
- Folate deficiencies derived from a low-protein diet have been hypothesized to lead to elevated plasma homocysteine concentrations, exceeding the 97th age percentile in one-third of PKU subjects [56].
- Approximately 15% of PKU patients who had been on Phe-restricted nutritional therapy for a mean period of 22.6 years (range 7 to 39 years) were found to have an atherogenic profile that included significantly elevated triglycerides, elevated low-density lipoprotein (LDL), and decreased high-density lipoprotein (HDL) [55].

In addition, the diet imposes a considerable time burden and social limitation and is almost impossible for adolescents and adults to adhere to.

Following a Phe-restricted diet can lead to social isolation for patients with PKU, given the limited selection of natural foods that can be eaten, and the time burden (planning, accessing, calculating, and recording food intake) required for adherence to medical nutritional therapy [16].

The quality of life of the patient with PKU is greatly enhanced by the ability to eat more normal sources of protein [15, 42] providing a direct link between this outcome and patient HRQoL.

Against this background, natural protein intake is considered an important endpoint and this increase in natural protein intake, whilst maintaining blood Phe concentrations at a level within guidelines is therefore a positive outcome and therefore a key clinical endpoint.

4.2.2.3 Neurocognitive and psychosocial functioning

As mentioned above, European treatment guidelines state that the primary goal of treatment is normal neurocognitive and psychosocial functioning [15]. As such, neurocognitive and psychosocial functioning, assessed as ADHD RS-Inattention and POMS, is considered a critical endpoint for PKU patients.

4.2.2.3.1 ADHD RS-Inattention (IA)

One therapeutic goal with PKU treatments is to reduce inattention symptoms but currently there are real challenges in directly measuring the neurocognitive and neuropsychiatric complications caused by high blood Phe. The investigator-rated Attention-Deficit Hyperactivity Disorder (ADHD) Rating Scale IV (ADHD RS-IV) with adult prompts is a measure of attention-deficit and hyperactivity/impulsivity used in a number of studies of ADHD in adults [58] and could also be useful in PKU. The hyperactivity/impulsivity subscale is based on questions and items that has been shown to be less relevant to adults with PKU, while symptoms of inattention (IA) are more prevalent in this population [59]. Hence, the use of the IA subscale is supported in adults with PKU [60]. In addition, an investigator-reported tool such as the ADHD RS-IV has an advantage over self-reported ADHD rating scales as full self-awareness of inattention symptoms and effects of these

symptoms may be problematic in adults with PKU [60]. In the clinical trial results, improvements in inattention and correlations with Phe reduction were observed under long-term pegvaliase treatment and drops in inattention score correlated well with drops in blood Phe, i.e. the patients with the greatest reduction in Phe had the greatest reduction in IA.

Use of the ADHD RS-IV IA subscale has been validated in PKU through qualitative interviews with US clinicians (n=14) with experience of rating adults with PKU using the ADHD RS-IV [60]. However, the instrument is currently still used in clinical trials and not yet in main practice.

The clinically important difference (CID) for the inattention subscale has been estimated as 5.2 in ADHD patients [61]. This is likely to be an overestimation for PKU patients, as they generally have lower scores. Using data from pegvaliase trials and a distribution-based method, the CID was found to be 2.5 [62]. The CID indicated in the Summary of Product characteristics (SmPC) is conservatively considered as 5.2 [63].

4.2.2.3.2 Profile of Mood States (POMS and PKU-POMS)

The POMS questionnaire is designed to assess transient and variable mood states in adults [64] and has been used in numerous therapeutic areas. Self-rated and investigator-rated versions are available; both were administered in the pegvaliase clinical studies. While the POMS questionnaire is widely used, it has not been validated in patients with PKU.

The PKU-specific POMS (PKU-POMS) is a subset of the POMS instrument that was developed for the PRISM studies to assess mood states relevant to adult patients with PKU [65]. The 65-item POMS questionnaire was reduced to the 20-item PKU-POMS instrument covering items from each of the 6 domains included in the full-length questionnaire after three phases of qualitative and quantitative research with adults with PKU. The resulting 20-item PKU-POMS instrument with re-named domains (Activity, Anxiety, Confusion, Tiredness, Anger, Depression) was found to be clear, relevant and easy for patients with PKU to understand. Furthermore, the psychometric properties of the 20-item PKU-POMS supported the internal consistency of domains, convergent validity and responsiveness of the measure [65]. The PKU-POMS questionnaire is rated using the same 5-point scale as the original POMS tool.

In the pegvaliase PRISM trials, the total mood disturbance scores were reported over time for the POMS and PKU-POMS tools. The total mood disturbance (TMD) score comprises the sum of scores of the mood domains (anxiety, depression, anger, activity, tiredness). For both the full-length- and PKU-POMS, subjects were asked to respond based on how they felt during the past week. The PKU confusion subscale score (self-rated) from the PKU POMS is considered the most sensitive to changes in blood Phe levels, and thus the most clinically relevant measure in the PKU population. However, the instrument is currently still used in clinical trials and not yet in main practice.

A 2008 consensus meeting publication[66] reports that the available data suggest a change of 10 to 15 points on POMS TMD would be a reasonable benchmark for future studies to identify minimally important changes. Using data from pegvaliase trials and a distribution-based method, the CID was found to be 15.94 [67], and this conservative value has been considered in evaluating the results of pegvaliase clinical trials [68].

BioMarin CID estimates for PKU-POMS (6.63 points) and PKU-POMS confusion subscale (1.33 points) were estimated using data from the pegvaliase trials and a distribution-based method [67, 68]. The clinical relevance of the PKU-POMS TMD is supported by a significant correlation of the absolute change in PKU-

POMS TMD score with the absolute change in blood Phe (Spearman rank correlation coefficient = 0.29, p<0.05) demonstrated on pegvaliase during 165-301/302 [67, 68].

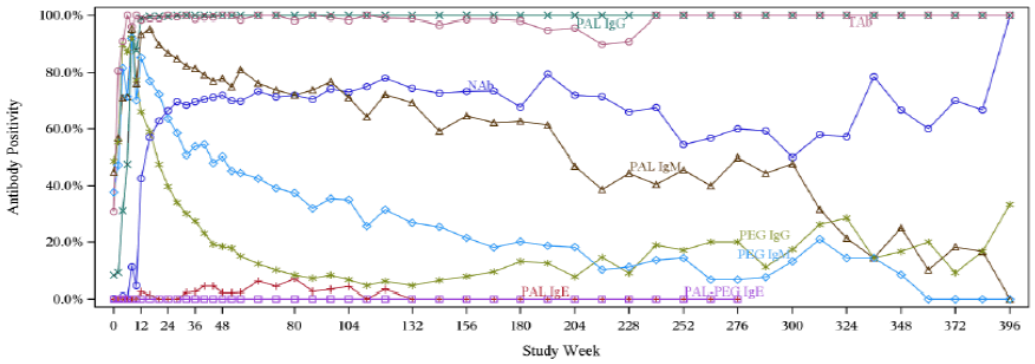
4.2.3 Safety

Pegvaliase has a manageable safety profile in most patients and its safety profile has been characterised with the long-term use. In general, the rate of AEs decreased with long-term treatment. Safety data is available for the I/T/M population of 285 patients. This is clinically relevant as it includes all patients who received pegvaliase using the I/T/M dosing regimen that is recommended in the SmPC as this approach achieves substantial blood Phe reduction in the majority of patients with a tolerable safety profile.

All patients receiving pegvaliase in trials using I/T/M dosing experienced AEs; however, most were mild or moderate and resolved without dose change or interruption [63]. Most AEs occurred during the first 6 months of treatment, coinciding with the induction/titration phases, when the immune-response against pegvaliase is the strongest [1]. AEs were most commonly mild to moderate (grade 1 [7.0%]) and grade 2 [68.4%]). Grade 3 and 4 AEs were reported by 22.1% and 2.1% respectively. One patient died by electrocution during the study which was assessed as being unrelated to the study drug.

All patients treated with pegvaliase developed anti-drug antibodies (ADA). Overall, the pattern of antibody development was generally similar across all studies in the pegvaliase clinical program, regardless of the dosing schedule during the induction/titration period. All patients developed sustained antibodies against the phenylalanine ammonia lyase (PAL) protein, and the majority of patients developed transient antibodies against polyethylene glycol (PEG) (Figure 3).

FIGURE 3. INCIDENCE OF ANTIBODY POSITIVITY OVER TIME IN PATIENTS IN THE MD POPULATION.



- Source: Palynziq® EPAR, 2019.

Data has demonstrated an association between antibody response and adverse events. Typically, hypersensitivity adverse events occurred most frequently during the first six months of treatment when the early immune response comprised of PEG IgM, PEG IgG and PAL IgM responses peaked, C3/C4 levels declined, and CIC levels were at their highest. The frequency of HAEs decreased over time in long term treatment as the incidence of these antibodies decreased [20].

The introduction of risk mitigation measures including pre-medication and flexible dosing during Study 165-301 reduced the rate of discontinuation due to AEs in the first 6 months of treatment from 15.4% to 5.9% of patients [redacted].

By all the results presented it is possible to conclude that the safety and tolerability profile of pegvaliase can be managed using an I/T/M dosing regimen, pre-medication and implementation of simple training and observation measures during the first 6 months of treatment. In this context, the safety and tolerability profile are considered acceptable.

5 Clinical questions

What value does pegvaliase have compared to either a restrictive diet or a semi-free diet in combination with LNAA for the treatment of PKU patients with uncontrollable blood phenylalanine levels?

In order to assess the relative benefit of pegvaliase over LNAAs, used in combination with the Phe-restricted diet, as per the DMC question, a meeting was held with Danish PKU advisors via two virtual advisory boards in June 2020 (22nd and 25th June 2020).

The objectives of the meetings were to firstly understand the clinical management of PKU patients in Denmark; secondly to understand the key outcomes of relevance to PKU patients to then allow a meaningful comparison of pegvaliase against LNAAs (in conjunction with Phe- restricted diet; and lastly to seek input to address the questions raised in the draft protocol.

The approach taken was more akin to a Delphi like methodology with multiple rounds to secure consensus by the advisors via surveys and discussion. The methodology, agenda and approach were all shared in advance with the DMC to enable input and contribution to the meeting. All stakeholders therefore had the opportunity to add their perspectives, raise queries and input into the agenda items [13].

The outputs of that meeting were then used to inform the relative benefit of pegvaliase over LNAAs (in conjunction with a Phe-restricted diet). To better understand this impact, the burden of PKU needs to be clearly articulated, the goals of therapy for PKU patients in Denmark highlighted and then the outcomes of relevance discussed in terms of the influence a novel treatment will have on them relative to current management. These are captured below.

Current management of PKU in Denmark

The current PKU treatment landscape in Denmark consists of:

1. A Phe-restricted diet consisting of severe restriction of Phe and protein supplements;
2. Sapropterin, in those who are responders, used in combination with the Phe-free diet; and
3. Large neutral amino acids (LNAAs) used in conjunction with a semi restrictive diet i.e. 60% increase in natural protein intake in comparison to a phe-restricted diet alone patient.

Treatment goals

European guidelines recommend lifelong management of blood phenylalanine (Phe) levels, with a target range of 120-600 µmol/L in patients aged ≥12 years, in order to achieve optimal clinical and neuropsychological outcomes [15]

The Danish advisors try to apply the blood Phe target levels suggested by the EU treatment guidelines however they agree that with the current treatment options available in Denmark, it is not possible to reach

these recommended blood Phe target levels. Adult PKU patients have difficulties in adhering to a Phe-restricted diet.

The advisors stated that if there was a treatment option that could lower blood Phe levels within the proposed target or to even reach normal levels or to lower CSF-PHE (with e.g. LNAA) to a similar degree, then the advisors were in consensus that they would use this option if it has an acceptable safety profile.

As diet has a high impact on QoL, pegvaliase also improves the QoL by allowing normalisation of diet. The advisors agreed that even when full diet normalisation is not possible, an increase from 30 to 60 g of natural protein per day will already make a big difference for the patients. The advisors agreed that diet normalisation would be a very significant treatment goal for Danish PKU patients.

In addition to normalisation of the Phe-restricted diet, the following patient-relevant outcomes are important treatment objectives for PKU patients: improvement in social functioning (loneliness, education/employment), improvement in executive functioning (attention, concentration, feeling of brain fog, processing speed), improvement in emotional functioning (mood swings, irritability/anger, anxiety), working memory, physical functioning (sleep problems, lack of energy) and lack or less impact on IQ.

Burden of PKU

- PKU in adult patients is characterised by a range of neurocognitive, neuropsychiatric and behavioural problems [69].
- Deficits in executive function in terms of attention, inhibitory control and cognitive flexibility have an adverse impact on daily functioning, including the ability to manage the Phe-restricted diet [17].
- Impairments of social and neurological performance and psychiatric symptom severity in patients with PKU aged ≥16 years are proportional to the elevation of blood Phe level and can be improved when Phe level is lowered [7]. This aligns with clinical opinion from the Danish advisors[13].
- PKU is associated with an increase in the prevalence of comorbidities across a range of other organ systems including osteoporosis, renal insufficiency and gastritis/oesophagitis[70, 71].
- Nutritional deficiencies associated with dietary management, which is the focus of current standard of care of PKU in Denmark, leads to an increase in the risk of bone disease, cardiovascular disease and obesity [54-56].
- PKU has a negative impact on health-related quality of life (HRQoL) that is improved with better metabolic control [9]
- Adult patients with PKU experience a range of difficulties that, although not immediately visible, impact key aspects of their lives such as independence, interpersonal relationships, educational and career goals [69].
- There is a high treatment burden associated with dietary management, including time required in planning, weighing and calculating the required protein intake for each meal. In addition, PKU patients suffer with social isolation as they are unable to socialise with family and friends when food is a large portion of the interaction thus adding to the overall burden of disease and diminished

quality of life [72, 73]. The PKU diet is extremely restrictive but restriction of dietary Phe intake is the cornerstone of PKU management. However, as a Phe-restricted diet imposes a great burden on the patient, treatment adherence critically declines from adolescence onwards, giving rise to large numbers of untreated or insufficiently treated adult patients [74]. Indeed, the advisors agreed that more than 25% of the adult PKU population discontinues their Phe-restricted diet. The main reasons are that they are tired of the restrictions and want a normal social life (dinners, school/work cafeteria, travel, etc.

- The advisors agreed that a Phe-restricted diet is very stringent and difficult to adhere to. Patients live with daily feelings of guilt as they cannot adhere to the diet and refuse to have blood Phe levels monitored because it is a reminder of their failure. This leads to a vicious cycle. Patients feel constantly guilty for not adhering to the Phe-restricted diet and are tired of feeling guilty and being told to go back onto the diet. Furthermore, travelling with a Phe-restricted diet is also very difficult as they have to foresee sufficient low Phe-foods and amino acid supplements (up to 250 tablets a day). One example reported by the clinical advisors related to a patient who was thought to be at risk of suicide due to the substantial number of tablets they were consuming as part of their PKU management
- If patients do not have to follow a Phe-restricted diet, they have more social freedom. They can go to a restaurant, attend parties, etc. without feeling different from their friends/family/colleagues.
- The advisors were in consensus that the diet does not need to be fully normalised to already being perceived as beneficial for the patient. Kuvan responders already report benefits from a less restricted diet.
- The advisors noted that the improvement in QoL is often observed by family/caregivers even at times when the patient may be unaware.
- Some of the advisors also mentioned that they and their patients on dietary or Kuvan treatment have severe concerns regarding the long-term effects of elevated blood Phe levels on brain health and ageing (e.g. risk of dementia, Parkinson's disease, etc.)

Outcomes of relevance

In order to understand how best to address this burden and to align to the treatment goals in Denmark, the advisors came together to find consensus on the outcomes of relevance to PKU patients. These outcomes would then allow a meaningful comparison of pegvaliase to LNAAs (taken in conjunction with a Phe-restricted diet).

The advisors found consensus on the outcomes below as the ones of most relevance to PKU patients via the modified Delphi approach previously mentioned.

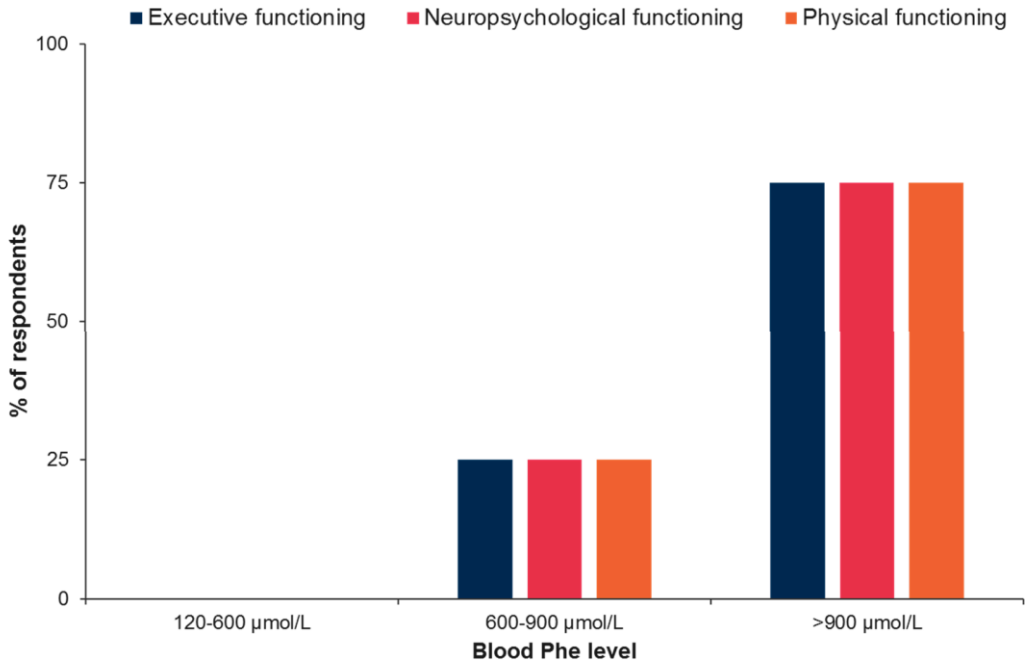
Patient-relevant outcome	
Social functioning	- Education/employment
Executive functioning	- Attention - Concentration - Feeling of brain fog - Processing speed - Working memory
Emotional functioning	- Mood swings - Irritability/anger - Anxiety
Physical functioning	- Sleep problems - Lack of energy

- The advisors were in consensus that there is a strong relationship between blood Phe levels and severity of these symptoms observed in adult PKU patients when treated with diet and/or Kuvan.

Impact of blood Phe on outcomes

- Consensus was reached regarding the role of blood Phe levels of >900 µmol/L and the negative impact these have on patient-relevant outcomes (outcomes as listed above)[13].
- Detailed below are the responses from the advisors relating to executive function, physical function and neuropsychological function in patients at various blood Phe levels. The results highlight the negative impact of blood Phe levels on these patient relevant outcomes
- The advisors also stated that lower blood Phe levels would allow a less restricted diet, which the advisors all agreed upon has a big impact on QoL of adult PKU patients. Given adult PKU patients often have poor dietary adherence and often feel guilty on a daily basis for not being able to stick to the dietary restrictions. They key outcome related to diet was not having to count, weigh, think, etc. about food and not feeling guilty at the end of the day when they were not able to adhere to the diet
- The advisors were in consensus that even a small amount of freedom from the diet makes a huge difference for the patient (e.g. from 30 to 60 g natural protein) as observed in Kuvan responders.
- The advisors agreed that more than 25% of the adult PKU population discontinues their Phe-restricted diet. The main reasons are that they are tired of the restrictions and want a normal social life (dinners, school/work cafeteria, travel, etc.

Figure 4: Negative impact of blood Phe levels on patient-relevant outcomes



Clinical evidence from the pegvaliase clinical trial programme

The results from the PRISM studies have been already been reported in section 4.

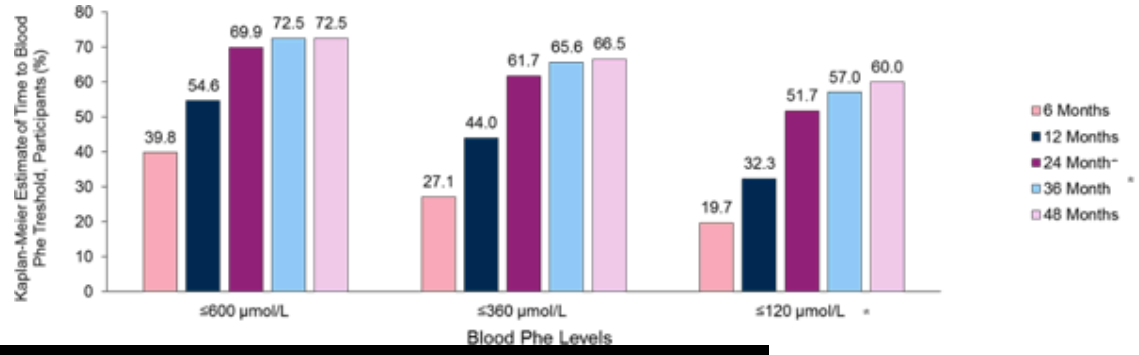
The primary outcome measure in the PRISM study for pegvaliase was blood Phe. Other outcome measures included the amount of natural protein intake, and neurocognitive and psychosocial functioning scores based on the ADHD RS-IV IA (Attention Deficit/Hyperactivity Disorder Rating Scale version IV inattention subscale) and the Profile of Mood States (POMS) instruments [1].

These outcome measures in the pegvaliase clinical trial programme align with the outcomes of relevance identified by the Danish advisors.

We observe from the clinical trial programme that pegvaliase achieves a substantial reduction in blood Phe that is associated with clinically important improvements in neurocognitive and neuropsychiatric outcomes and is sustained over the longer term.

- In patients aged ≥16 years with uncontrolled Phe despite prior treatment, pegvaliase brought Phe levels within guideline-recommended range (≤600 µmol/L) for the majority (72.5%) of patients and normalised Phe levels (≤120 µmol/L) for 60% of patients after 48 months of treatment [19]. (see Figure 5)

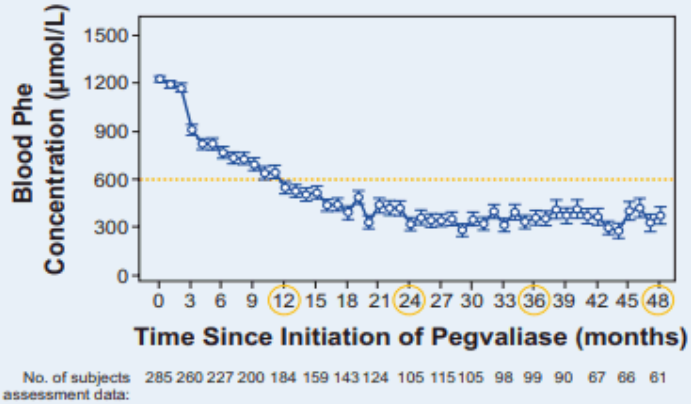
FIGURE 5. PROPORTION OF PATIENTS REACHING DIFFERENT TREATMENT TARGETS WITH LONG-TERM THERAPY (POOLED 165-301/302, ITT, N=261, ALL DOSES)



[redacted]Sources: Harding et al. 2020 [19 [redacted]

Pegvaliase has reduced blood Phe levels within the European guideline levels for the majority of patients and, importantly, was even able to normalise Phe levels (i.e. <120 µmol/L) for 60% of patients after 4 years of therapy. Throughout those 4 years the proportion reaching these levels of blood Phe increased over time highlighting the continued benefit of therapy and its sustainability over the longer term. Indeed, a poster presented at ACMG in 2020 (see Figure 6) shows the sustained treatment effect of pegvaliase in terms of blood Phe reduction after 48 months of follow up.

FIGURE 6. REDUCTIONS IN BLOOD PHE LEVELS OVER 48 MONTHS OF FOLLOW-UP (POOLED 165-301/302)



- Source: Rohr 2020 [18]

Impact of pegvaliase on protein intake

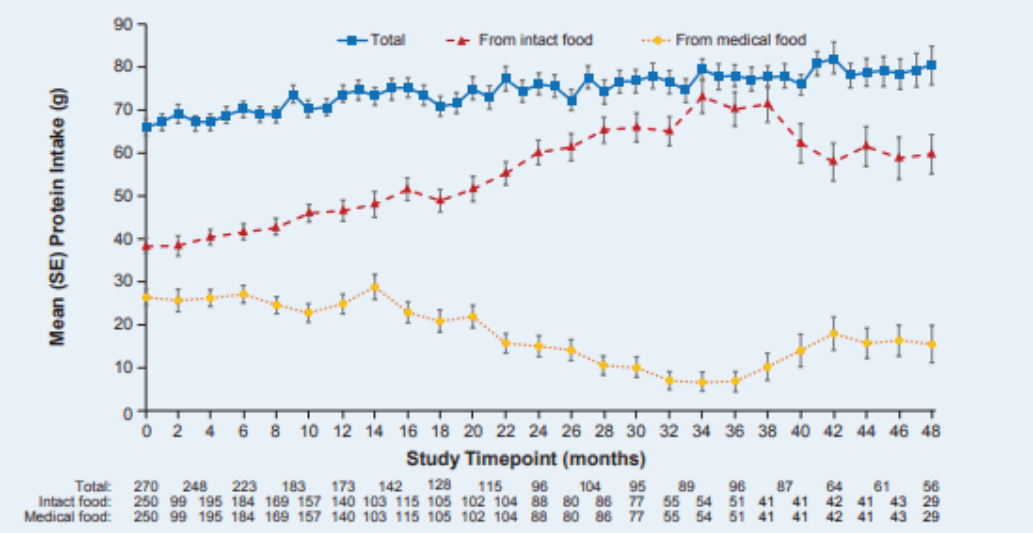
We also observe from the poster presented at ACMG in 2020 [18] that patients who have been on pegvaliase treatment for up to 4 years are receiving the majority of their protein intake from intact food and very little

from medical food. The mean (SD) total protein intake at baseline was 65.0 (32.0) g, and was relatively stable, with a change at Month 48 (n=49) of 7.1 (32.2)g (Figure 7). At Month 48, the mean (SD) change from baseline in protein intake from intact food increased by 18.2 (34.7) g, whereas intake from medical food decreased by 6.6 (23.5)g. Given the challenges with the Phe-restrcited diet, the ability to have the majority of natural protein from intact food will have a significant impact on the patient's quality of life, their feelings of guilt, feeling of social isolation and the ability to interact with friends and collegaues in a social environment. In addition the nutritional deficiences observed in PKU patients on the diet would be able to be reduced if patients protein intake was largely consumed from an intact diet rather the Phe-restricted diet.

For patients with severe PAH deficiency, restriction of Phe intake (in the Phe-restricted diet) may mean that they are allotted as little as 6-10g of natural protein per day. This is compared to about 50-60g for an average person based on 0.8g protein/kg body weight recommendation for the unaffected population.

Hence the protein intake below for patients on pegvaliase is close to 60g per day i.e. within the normal range for an unaffected individual.

FIGURE 7. PROTEIN INTAKE OVER 48 MONTHS OF FOLLOW-UP (POOLED 165-301/302)



- Source: Rohr 2020 [18]

In summary, the Danish advisors agreed that pegvaliase seems to be effective at lowering blood Phe levels in adult PKU patients to target levels proposed by the European guidelines. The clinical evidence from 4 years of data shows that 60% of patients at that time have reach normative levels i.e. <120 µmol/L and this proportion has increased year on year. Furthermore, 72.5% of patients at the 4-year stage have Phe levels below the EU recommended guidelines and this proportion has also increased year on year. According to the advisors, both the reduction of blood Phe and the normalisation of diet will positively impact the majority of the patient-relevant outcomes, including the QoL of the patient.

Role of LNAAs

The advisors [13] were in agreement that that there is no reduction in blood Phe level when using LNAAs and that the effectiveness of LNAAs cannot therefore be evaluated by assessing blood Phe levels. Furthermore, there was consensus on the fact that even if patients are on LNAAs, the blood Phe levels are not reduced and thus the need for these patients to commit to a Phe-restricted diet is necessary to reduce their blood Phe levels. It was stated by the advisors that LNAAs do not seem to work for all uncontrolled PKU patients, most probably for adherence reasons [13].

The clinical advisors offer LNAAs to patients who have failed on the Phe-restricted diet. As such, these patients are not adhering to the diet and thus will have elevated blood Phe levels which will not be reduced whilst on LNAAs especially if the Phe-restricted diet is somewhat reduced.

Hence a comparison with LNAAs in terms of blood Phe reduction and natural protein intake is almost diametrically opposed to the clinical evidence from the pegvaliase clinical trial programme and long- term data where we observe normalisation of blood Phe levels in 60% of patients and natural protein intake comparable to someone unaffected by PKU [19].

Clinical evidence underpinning LNAAs

Robust clinical evidence is lacking for LNAAs for the treatment of PKU, and hence it is not possible to perform a valid systematic or structured comparison of outcomes with pegvaliase.

This was based on a systematic review of the evidence which showed the limited studies available and the inconsistent results on the impact LNAAs have on blood Phe levels. There is no consistent evidence supporting a reduction in blood Phe levels.

From a neurocognitive perspective, the evidence base for LNAAs from the systematic review is inconsistent regarding executive and neuropsychological functioning in LNAA-supplemented PKU patients [33, 37, 38]. Some of the observations captured in the literature may be due to increased brain levels of tyrosine and tryptophan, the respective precursors of dopamine and serotonin however, no long-term data exists regarding the impact of LNAAs on executive and neuropsychological functioning.

Given there is no outcome that is comparable across the trial programmes, a plausible comparison with pegvaliase is not possible.

5.1 Outcomes Requested in the DMC's Protocol for the assessment of Pegvaliase

In order to further address question 5.1 in the DMC's assessment protocol for pegvaliase, the following results are requested to be presented:

1. ***Quality of life***, presented as the mean change in PKU-QOL score, alternatively in WHOQOL-100 score, from the start of treatment to a minimum of six months after treatment.
2. ***Adverse events***, presented as proportion of patients who discontinued treatment, a statement of reasons of discontinuation, and a qualitative review of all adverse events.

3. ***Phenylalanine concentration***, presented as the proportion of patients achieving controlled Phe levels in the blood and in the brain, based on the mean of 6 measurements per patient during 6 months from the timepoint where maintenance dose was achieved.
4. ***Natural protein intake***, presented as the proportion of patients that were able to increase the daily natural protein intake to at least 40 g and 70 g, respectively.
5. ***Neuropsychiatric symptoms***, presented as the change in mean ADHD-RS-IV inattention score and mean POMS score, from start of treatment to three and six months after treatment.
6. ***Executive function***, presented as BRIEF-V score, alternatively as CANTAB score, at the longest possible follow-up time.

Please find below BioMarin's responses for each endpoint:

1. Quality of Life

At present, no QoL tools have been successfully validated in PKU and blood phenylalanine levels observed with pegvaliase treatment have not been possible to reach previously. Therefore, there is no way of knowing which existing tools are able to capture the impact of treatment without longitudinal psychometric evaluation.

To date, no generic measure has been able to accurately capture burden of disease or impact of blood phenylalanine levels in PKU. Even within the more disease specific instruments, there is a lack of sensitivity, poor content and construct validity and the presence of ceiling effects. For this reason, we do not believe that any current tools will be able to adequately capture the burden of PKU or impact of pegvaliase treatment. In addition, it is not possible to use published Clinically Important Difference (CID) estimates for non-PKU specific instruments and apply them to data collected in a PKU population.

CID is defined as the magnitude of score change between two treatment groups that can be considered clinically important. It is also referred to as 'between patients' estimate and is measured against patients' mean score change from baseline. There are two accepted methods for deriving CID estimates. Distribution based methods base the estimate on the distribution of scores between patients at baseline, using the ½ standard deviation rule of baseline mean to determine an estimate the magnitude of score change is likely to represent a meaningful change. Anchor based estimates are derived by comparing the change in patient centred outcome (PCO) score to change in score of another outcome/instrument where there is already an established clinically meaningful score change threshold. By doing so, it is possible to generate a CID based on change vs. change analyses. When estimating CIDs in instruments that are not sensitive within a disease area, the magnitude of a clinically meaningful score change is likely to be far lower that it is in a disease area for which the tool is intended for use and is validated in. Lack of sensitivity in tools results in an inability to adequately capture change in health state and therefore the ability of the tool to pick up improvement or decline is very limited. Given this, it is not reasonable to expect a CID estimate produced for a tool in another disease area to be valid to PKU. The magnitude of score change that reflects a clinically relevant change to patients will be far higher in the intended disease area where the instrument is sensitive to change than in PKU.

The most common result of an insensitive instrument is to show 'ceiling effects' (i.e. patients answer 'no burden' to almost all questions). This can be seen in PKU on the SF-36 [75], BRIEF [76, 77] and WHO-QoL [78]

and is caused by poor content validity rather than low disease burden. Using instruments with ceiling effects to measure disease burden and benefit of treatment is inappropriate and ineffective. It is extremely difficult for a clinically meaningful change to be reported when baseline scores begin high due the presence of ceiling effects.

Because of the difficulties experienced when capturing outcomes in PKU, BioMarin has developed the PKU Symptom Severity and Impacts Scale (PKU SSIS). The PKU SSIS is a disease-specific instrument that consists of 22 items assessing various PKU related symptoms that may result from elevated blood phenylalanine levels over the past 7 days. The instrument was developed through extensive cognitive interviewing with patients and clinical experts [79]. The following domains are assessed in the instrument: Emotional; Cognitive, Behavioural, & Executive functioning; Physical, General Wellbeing; and Self-care. Initial content validation of the tool has shown strong content validity, sensitivity to phenylalanine and no floor or ceiling effects. The PKU SSIS is currently being implemented in a number of upcoming studies from which further validation work (including derivation of CID estimates) will be conducted. BioMarin recommends the use of the PKU SSIS as the primary tool for measuring outcomes in any data collection/studies going forward and suggests using distribution methods (i.e. ½ standard deviation of baseline mean) to estimate a clinically relevant score change in a study population until an anchor-based CID estimate is published. The PKU SSIS is currently undergoing full linguistic validation in a number of languages.

BioMarin believes that the PKU SSIS is the most relevant tool to capture the impact of PKU, and specifically elevated blood phenylalanine on patients' QoL, Cognitive and Executive Functioning, Mood and the Physical impacts of disease such as headaches and tremors. When considering other measures, it is important to understand their limitations and their subsequent ability to measure outcomes in PKU.

The PKU QoL is the only other existing tool that has been developed for and validated in patients with PKU [80]. Although the scale was developed for PKU specifically, the tool shows neither strong content nor construct validity. Convergent validity analyses showed only 8/65 items had Spearman's correlation coefficients >-0.5 when analysed against SF-36 domains. Further to this reliability analyses also showed only 8/65 items in the adult version of the scale had an acceptable Cronbach's alpha of >0.7. The majority of items with acceptable reliability relate to diet. The tool is also untested in its ability to distinguish between patients with differing levels of blood phenylalanine specifically blood phenylalanine levels within the normal range. Therefore, the discriminant validity of this tool in this population is untested. BioMarin is undertaking further studies to investigate the validity of the tool. Given the current limitations of the PKU QoL, data collection is recommended but focusing only on the impact of PKU on diet, as these are the only items with acceptable psychometric scores. There is no established CID estimate for the PKU-QoL. The DMC has stated a 10-point change however due to the lack of sensitivity of the tool, this cannot be used as a reliable measure for determining whether patients have experienced a clinically meaningful change in disease state. Given the lack of evidence of sensitivity of the PKU QoL to blood phenylalanine levels it is not appropriate to assign a CID estimate to this tool and any data outcomes should be descriptive only.

Although when tested in adult PKU patients the WHO-QOL was not able to distinguish between patients treated with BH4 and those on diet alone, all scores reported were in the normative range [78]. This demonstrates the presence of ceiling effects and lack of validity of this instrument in PKU. Even though the instrument has some capability to detect the QoL gain associated with diet liberalization, BioMarin believe that the PKU QoL is a more appropriate measure of this outcomes as it has been specifically validated for

patients with PKU and has published acceptable psychometric scores for the items relating to diet. In addition, it is believed that a 100-item questionnaire is too long to administer in a group of patients who suffer from cognitive impairment and inattention, especially when measured alongside other, more sensitive instruments.

The limited data on the use of the SF-36 in PKU has shown the tool to be insensitive with PKU patients reporting normative scores for both physical and mental components [75]. To the best of our knowledge, no published data exists on the use of the EQ-5D in PKU. BioMarin is currently conducting a utility study to derive EQ-5D values in PKU.

2. Adverse events

In the pegvaliase phase 3 trials, all 261 participants (pooled 165-301/302) reported at least 1 AE during the study that was assessed by the investigator to be related to study drug. Most AEs were mild or moderate (99%) and resolved without dose change or interruption (96%). The most commonly reported AEs by preferred term were arthralgia (70.5% of patients), ISR (62.1%), injection-site erythema (47.9%), and headache (47.1%), with exposure-adjusted rates of 2.6, 4.3, 1.7, and 1.6 events per person-year, respectively [1].

Treatment discontinuation data from phase 3 clinical trials were as below (pooled 165-301/302);

[redacted]

The most common adverse events leading to discontinuation were anaphylactic reaction (2.7% of participants; 4 of these 7 participants had a confirmed acute systemic hypersensitivity event), arthralgia (2.7%, n=7), injection site reaction (1.1%, n=3), and generalised rash (0.8%, n=2) [1].

To mitigate the discontinuation a protocol amendment (August 2014) has been made with additional risk mitigation strategies:

- At the initiation of 165-301 and 165-302, reduction or interruption of dosing was allowed for participants with AEs of at least moderate severity and premedication to reduce the severity of hypersensitivity adverse events (HAEs) was also allowed based on investigator discretion. Investigators were given greater flexibility to reduce or interrupt pegvaliase dosing due to mild AEs.
- Premedication to reduce the severity of HAEs, which was previously elective, was required prior to each pegvaliase dose during the induction and titration periods; the premedication regimen consisted of a histamine H1 receptor antagonist, an H2 receptor antagonist, and, if tolerated, an antipyretic.

- An observer was required to be present during pegvaliase administration for the first 16 weeks of treatment.
- Participants also received additional education on identifying and responding to HAE signs and symptoms and were given epinephrine injection pens for use in the event of an acute systemic hypersensitivity event, including potential events of anaphylaxis.

After implementation of these strategies, overall discontinuation rate decreased from 23.8% to 13.6% and discontinuation due to an adverse event decreased from 15.4% to 5.9%.

These mitigation strategies were recommended via label and as a result of these implementation, real world discontinuation rates are expected to be aligned with the numbers after implementation which are 13,6% overall discontinuation and 5.9% discontinuation due to adverse events.

Overall, AEs were reported more frequently in the early treatment phase (≤6 months) and AEs decreased in frequency with prolonged pegvaliase exposure. Sensitivity analyses evaluating adverse events before and after implementation of additional safety procedures demonstrate similar trends (Supplementary Table 5 [1]).

The event rate per person-year was 58.6 in the early treatment phase and declined to 19.4 in the late treatment phase.

There was no evidence captured on undesirable incidents and side effects with increased awareness of any immunological effects, effects of elevated levels of micronutrients due to unilateral diet, anaphylactic reactions, joint pain and allergic reactions. But since immunogenicity of pegvaliase has been known, Immune responses of the patients were assessed intensively.

Participants developed a sustained mean TAb titer response. Participants also developed a sustained anti-PAL antibody response and a transient anti-PEG antibody response. The data suggest that antibody responses impacted the safety profile of pegvaliase. HAEs occurred most frequently in early treatment (< 6 months) when the immune response comprised predominantly of PEG IgM, PEG IgG, and PAL IgM antibodies and mean C3 and C4 levels were decreasing. The frequency of HAEs decreased in late treatment (> 6 months) as mean PEG antibody titers decreased to baseline levels, PAL antibody titers remained stable, and C3/C4 levels increased [1].

Although temporally associated, no particular antibody analyte or titer level was predictive of an HAE or acute systemic hypersensitivity event for an individual participant. Despite the observed increase in antibody titers as described above, no events suggesting immune complex–mediated end-organ damage related to pegvaliase were observed. There was significant overlap of HAEs in patients from all TAb quartiles; thus, antibody titers were not predictive of development of HAEs [81].

3. Phenylalanine concentration

While normal neurocognitive and psychosocial functioning are the primary goals of treatment for PKU, they are not easy to measure directly. Elevated blood Phe concentration, being the direct result of PAH deficiency, is accepted as a highly relevant surrogate endpoint. Change in blood Phe concentration is a well-accepted measure of clinical benefit in interventional studies in PKU and was the primary efficacy endpoint across

pegvaliase and sapropterin clinical studies. European clinical guidelines also emphasise that reducing blood Phe concentration is the cornerstone of PKU management and endorse blood Phe as the primary marker for guiding treatment [14]. Recent European guidelines recommend lifelong treatment for any patient with PKU whose untreated blood Phe level is >600 µmol/L and the target range for patients aged ≥12 years is 120-600 µmol/L [14].

Blood Phe level reduction has been accepted by EU and US regulatory authorities as a clinical efficacy endpoint previously, since change in blood Phe concentration was the basis for the approval of sapropterin, the only approved pharmacological treatment for PKU before pegvaliase.

Patients with PKU also accept blood Phe as an important measure of disease control, as reflected by a recent study that found that a drop in blood Phe level was considered as an important potential benefit of a new treatment by 87.5% (405/463) of the PKU patients surveyed [43].

A paper published by Ahring et al, 2011 from Denmark highlighted the average blood Phe levels across 10 European centres. The mean adult blood Phe level was 777 µmol/L (604–855) [82]

In relation to the timeframe for measurement suggested by the DMC, 6 months is an insufficent time period against which to assess control. Furthermore, Phe concentration in the brain is not measured in Denmark and not routine practice across Europe due to the complexity of measurement (e.g. such as use of MRI spectroscopy) and lack of validation. Cerebrospinal fluid sampling is the gold standart for the assessment of brain Phe concentration, however this approach is very invasive and cannot be applied for routine clinical practice. Alternative methods like traditional magnetic resonance spectroscopy (MRS) yielded uncertain results of brain Phe and could not adequately measure brain Tyr and corraleted spectroscopy (COSY) has been performed in some proof of concept studies but it has not been validated, therefore there is no applicable methodology to assess brain Phe and Tyrosine in clinical practice.

For patients to achieve blood Phe control, in some patients, it can take 9 to 18 months to reach a stable maintenance dose and to be in line with the European guideline recommended Phe levels. We have also observed from the clinical trial that some patients take up to 16 months to reduce their Phe by 50% from a naïve baseline. As such, a time period of 6 months is insufficient to show this reduction [redacted]

A 6-month time period is therefore insufficient to show this scale of Phe reduction.

We are observing continued improvement in these patients over the longer term hence a better efficacy time point for psychiatric function would be 18 months.

According to Danish advisors considering the challenge of performing MRI spectroscopy in current clinical practice, blood Phe levels are an acceptable proxy for brain Phe levels [13].

4. Natural protein intake

In the clinical study, dietary instructions were in order to maintain the diet within -/+10% of baseline unless there is hypoPhe, quote from protocol; 'During this study, subjects will be instructed to maintain a stable diet.' There was no instruction in terms of which supplements shout be used or any additional refomented

supplements apart from Tyrosine which is not a recommendation in the label despite being a part of clinical study protocol [1].

Other diet related instructions in study protocol were:

- All subjects will be administered 500 mg of tyrosine supplement 3 times per day to take with food (including medical food) throughout the study.
- Subjects will be provided with a 3-day diet diary to complete, including medical food intake, for review with the dietitian and clinical study staff.
- If a subject's natural protein intake has changed ≥10% since the time of enrolment into the study, the subject will be counselled by the dietician to return to the protein intake they had at the time of enrolment into the study.
- If protein intake from medical food (Phe-free, amino acid supplements) has changed ≥25% since the time of enrolment into the study, the subject will be counselled by the dietician to return to the medical food intake they had at the time of enrolment into the study
- Modifications to subject diet may be performed if blood Phe levels are reduced to < 30 µmol/L, the dietician will instruct the subject to increase their dietary protein by 10% of Day 1 of Part 2 unless the subject is already consuming the appropriate DRI for age. Medical food may be discontinued once the dietician determines that the essential amino acids meet the DRI for age [1].

Results of phase 3 trials on dietary outcomes were as below:

Total daily protein intake remained relatively stable from a mean (SD) of 64.8 (32.2) g at baseline to 71.6 (24.3) g at 12 months and 77.4 (20.8) g at 24 months.

Protein intake from medical food decreased, from 26.3 (28.5) g at baseline to 24.2 (26.0) g at 12 months and 18.4 (25.2) g at 24 months. Dietary Phe intake increased, from a mean (SD) of 1700.2 (1194.4) mg at baseline to 2123.2 (1302.2) mg at 12 months and 2679.7 (1285.7) mg at 24 months. [1]

Mean (SD) total protein intake at baseline was 64.8 (32.2) g, and was relatively stable, with a change at Month 36 (n=44) of 12.7 (41.9) g. At Month 36, the mean (SD) change from baseline in protein intake from intact food increased by 27.3 (33.5) g, whereas intake from medical food decreased by 14.5 (31.6) g [18]Energy intake increased over time, with a mean (SD) change from baseline at Month 36 of 95.0 (874.0) kcal, which was associated with a mean (SD) increase in weight of 3.6 (6.8) kg.

Substantial and sustained reduction in blood Phe was observed even with increases in protein intake from intact food and decreases in medical food intake [18].

There was not restricted diet requirement in the inclusion criteria, 15% of the patients were on a restricted diet and baseline mean natural protein intake was g (SD); 38.5 (27.7)g [1]*, therefore 40 grams from natural protein sources, as a target with controlled Phe suggestion is not a result demonstrable with current available evidence due to inclusion criteria of the study not being limited patients with restricted diet and protocol not to alternate the diet on treatment more than +/-10%.*

5. Neuropsychiatric symptoms

CID estimates exist for both the ADHD-RS IV and Profile of Mood State (POMS). Psychometric analyses of both instruments showed the only valid domains/version in PKU were the inattention domain (IA) for the EQ-5D and the PKU POMS version of the POMS where a respective raw score change of 2.5 [7] and 6.6 [68] are considered clinically meaningful. Given the only way to derive a PKU POMS score is to measure the entire 65-item instrument, BioMarin does not believe it to be a suitable tool for measuring outcomes in a group of patients who suffer from cognitive impairment and inattention, especially when measured on alongside other, more sensitive instruments.

Overall, BioMarin believe the most reliable and holistic tool to capture the burden of disease and benefit of treatment in PKU is the PKU SSIS. This measured alongside the PKU QoL to measure the impact of diet and the ADHD-RS IA domain to measure inattention should capture the overall impact of PKU to patients.

In addition to this, given the difficulty in accurately assessing QoL in PKU patients, we are extracting key outcomes from clinical narratives from the US where pegvaliase has been available since mid-2018. This is in the process of publication but could be shared with the DMC prior to publication.

The German outcomes study will support greater understanding of QoL in patients achieving lower Phenylalanine levels than was considered feasible before.

6. Executive function

The BRIEF tool is not sensitive in PKU, does not show any correlation to blood phenylalanine and there is limited clinical experience of this tool. No CID has been determined for this [76, 77].

When measured in subjects treated with pegvaliase (n=9) the ADHD modules of the CANTAB did show some sensitivity to phenylalanine levels [1, 26]. However, as the sample size is so limited, no CID estimates can be derived. Additionally, since the CANTAB has migrated from a computer to an iPad-based assessment, the developer has not published any normative data. There is no way of reliably interpreting the relevance of scores or score changes until this is made available.

Systematic review

A systematic review has been undertaken, in accordance with the specified request in the evaluation protocol, and is detailed in the section 4 and attached to the application as Appendix A. However, many of the questions stated by the expert committee could not be answered from the literature review due to lack of studies reporting the requested data. There was a profound lack of data on the efficacy of LNAA treatment in PKU over longer treatment periods. Where no information was found in the available literature, BioMarin has collected advisors' opinion to support the application with insights from the clinical expertise [13].

In the sections below, BioMarin presents the best available information regarding the outcomes highlighted by the expert committee.

5.1 Presentation of relevant studies

The SLR identified 14 studies carrying relevant information on the outcomes targeted in the evaluation protocol, and one study undertaking a propensity score matched indirect treatment comparison (Table 5).

Seven of the 14 studies were randomised: randomised controlled trials (RCTs), randomised discontinuation trials (RDTs) and randomised crossover study data; while seven studies were single-arm and/or open-label (OL) follow-up/extension studies.

Five studies involved pegvaliase (the phase 2 dosing study 165-205, its open-label extension (OLE) PAL-003, the phase 2 PAL-004, the two phase 3 studies, 165-301 and 165-302 [1, 30, 83-86]. Pooled data from these pegvaliase studies was reported in 14 further citations[31, 81, 87-98], including the indirect treatment comparison (Zori 2019 [31]).

Nine studies investigated LNAA supplementation [32-40]. Two studies evaluated high dose tyrosine supplementation, one alongside Phe restricted diet (PRD) [36], the other after relaxation or termination of PRD[37]. Yano et al. 2014[40] studied tryptophan and tyrosine supplementation, Matalon et al. 2006 [34] and 2007 [35] studied an LNAA formulation called NeoPhe, Scala et al. 2020[33] studied an LNAA formulation called MovisCom and three further studies also reported LNAA experience [32, 38, 39], Burlina et al. 2019 with NeutrAfenil Micro R[32].

A comparison of relevant baseline characteristics is provided in Table 6.

Regarding characteristics of the participants at baseline (BL):

- The number of patients enrolled in LNAA studies was low in all nine studies (range 10-24 patients), considerably lower than in the pegvaliase trials.
- The LNAA study populations' mean ages were lower than in the pegvaliase studies.
- Mean age in randomised trials was between 21-44 years in studies reporting it. Two studies – Matalon et al. 2007 and Schindeler et al. 2007 – were included despite having mixed child/adult patients enrolled as it was considered likely that at least 70% of the population enrolled was 16+ years[35, 38].
- Percentage male patients was similar across most studies, excepting Yano et al. 2014[40] where it was higher at 80%.

- Mean BL blood Phe levels were similar in 165-301 [1, 84] and two[37, 40] of the three LNAA studies reporting it. In Matalon et al. 2017[35], the mean BL blood Phe level was lower (933 µmol/L) than in 165-301 (1233 µmol/L).
- Ethnicity was reported for pegvaliase PRISM studies but not for LNAA studies.
- Only Matalon et al. 2007 reported genotype: of 20 patients enrolled 6 were genotype ND, 6 R408W/R408W and other types reported in Figure 1 of their full paper[35].
- In most of the LNAA randomised trials, PRD/usual diet continued throughout the study[35, 38-40]. In Pietz et al. 1995[37], however, patients had relaxed or stopped strict dietary treatment for at least one year prior to study entry.

TABLE 6. BASELINE CHARACTERISTICS OF THE STUDIES INCLUDED IN THE APPLICATION

Study	Sample	N	Age			Gender	Blood Phe		
			Mean	SD	Range	% male	Mean	SD	Min, Max
165-301	PEG 20 mg	131	30.2	8.63	16 - 52	52.7	1241.0	389.70	285.0 , 2186.0
	PEG 40 mg	130	28.1	8.77	16 - 55	47.7	1224.4	384.28	483.0 , 2330.0
165-302	PEG (Pooled from 165-301)	261	29.2	8.8	16 -55	50.2	1232.7	386.4	285.0 , 2330.0
165-205	PEG	24	29.3	11.43		45.8	1168.8	290.98	713.0 , 2021.0
PAL-003	PEG	80	28.3	8.8		42.5	1302.4	351.5	249.0 , 2214.0
PAL-004	PEG	16	32.2	8.27	18-50	18.8	1482.1	363.46	968, 2214
Zori 2019	PEG (Matched vs Diet)	125	30	8	18-56	55.2	1085	294	601, 1764
	Diet	125	31	11	18-68	55.2	1089	302	605, 1872
	PEG (Matched vs Sapropterin+diet)	64	32	9	18-54	40.6	1172	329	601, 1942
	Sapropterin+diet	64	33	10	18-55	42.2	1176	383	624, 2258
Burlina 2019	LNAA	12	29.6	6.8	19-38	58.3	752	143	628, 1033
Scala 2020	LNAA	10	23.6	4.5	18-32	40.0	830.8	77.7	665, 937
Matalon 2006	LNAA 0.5 g/kg/day	8	20.5	NR	NR	36.4	957.4	NR	~400, ~1600
	LNAA 1 g/kg/day	3	16.5	NR	NR		1230	NR	~1200, ~1800
Matalon 2007	LNAA vs Placebo Crossover	20	NR	NR	11-32	40.0	932.9	NR	~400, ~1750
Lou 1987	Free diet+Tyr vs Placebo Crossover	9	18.4	3.1	15-24	66.7	NR	NR	NR
	Free diet+Tyr vs Free diet Crossover	14	18.1	2.9	15-24	64.3	NR	NR	NR
Pietz 1995	4-phase Crossover	24	20.8	NR	16-25	45.8	1273	280	847, 1798
Schindeler 2007	4-phase Crossover	16	24.8	NR	11-45	43.8	NR	NR	NR
Yano 2013	3-phase Crossover	10	29.1	9	20-49	66.7	NR	NR	NR
Yano 2014	LNAA vs LNAA+Tyr+Trp Crossover	10	29.4	9.4	21-51	80.0	1388.66	362.24	NR

5.2 Results per study

The results from each study, for relevant outcomes, are summarized in table format in Appendix Tables (Section 9, [redacted]

PLEASE NOTE THAT IDENTIFIED DATA WERE SELDOM, IF EVER, PRESENTED IN THE STUDIES IN LINE WITH THE FORMAT SUGGESTED IN THE DMC'S EXPERT COMMITTEE'S PROTOCOL, OR BASED ON STUDIES USING THE SUGGESTED INSTRUMENTS. DATA OF RELEVANCE TO THE DIFFERENT OUTCOMES WERE THEREFORE PRESENTED EVEN IF NOT MATCHING THE FORMAT SUGGESTED IN THE PROTOCOL. WHEN POSSIBLE, DATA HAVE BEEN EXTRACTED ATTEMPTING TO RESPOND ACCORDING TO THE QUESTION FORMULATION. IT WAS ALSO DIFFICULT TO DEFINE A UNIFORM ALTERNATIVE FORMAT TO PRESENT THE DATA THAT WOULD ALLOW A MORE DIRECT COMPARISON OF STUDIES, SO WE HAVE AT OUR BEST ABILITY TRIED TO PRESENT THE AVAILABLE DATA TO INFORM THE CLINICAL ASSESSMENT, IN TABLE 7, BELOW. TABLE 7. PICO TABLE

Outcome	Measurement	Studies included in the analysis	N	Timepoint / Time interval	Study result	Absolute difference in effect			Relative difference in effect			Methods used for quanti-tative synthesis
						Difference	CI	*P* value	Hazard/ Odds/Risk ratio	CI	*P* value	
1. QoL[1]	**Average change from baseline on PKU-QOL**	No data identified	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2. Adverse events	**Percentage of patients that ceases treatment**	**PEG** 165-301/302 165-205 PAL-003 PAL-004	**PEG** 261 24 68 16	**PEG** 4 years 48 weeks 144 weeks 13 weeks	**PEG** 15.3% 8.3% 5.9% 6.3%	NA	NA	NA	NA	NA	NA	NA
		LNAA Burlina 2019 Scala 2020 Matalon 2006 Matalon 2007 Lou 1987 Pietz 1995 Schindeler 2007 Yano 2013 Yano 2014	**LNAA** 12 10 11 20 14 24 16 10 10	**LNAA** 12 months 12 months 1 week 1 week 3 days 4 weeks 2 weeks 3 weeks 3 weeks	**LNAA** 0% 0% 0% 0% 0% 0% 0% 10% 20%							
3. Phenylalanine concentration	**Proportion of patients achieving blood Phe <600**	**PEG** 165-301 165-301/302 165-205 PAL-003	**PEG** 261 48 20 45	**PEG** 36 weeks 4 years 48 weeks 144 weeks	**PEG** 40.6% 72.5% 95% 64.4%	NA	NA	NA	NA	NA	NA	NA

		PAL-004	16	13 weeks	25%							
		LNAA Burlina 2019 Scala 2020 Matalon 2006 Matalon 2007	**LNAA** 12 10 11 20	**LNAA** 12 months 12 months 1 week 1 week	**LNAA** 0% 10% 63.6% 35%							
	Proportion of patients achieving brain Phe <600	No data identified	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Change in mean blood Phe concentration	**PEG** 165-301 (20 mg dose) 165-301 (40 mg dose) 165-301/302 165-301/302 165-205; group A [2] 165-205; group B [2] PAL-003 PAL-003 PAL-004	**PEG** 131 130 206 48 11 10 61 45 16	**PEG** From BL to 36 weeks From BL to 36 weeks From BL to 6 months From BL to 3 years From BL to 48 weeks From BL to 48 weeks From BL to 144 weeks From BL to 13 weeks	**PEG** - 373 µmol/L - 600 µmol/L - 452 µmol/L - 956 µmol/L - 899 µmol/L - 641 µmol/L - 796 µmol/L - 919 µmol/L - 410.8 µmol/L	NA	NA	NA	NA	NA	NA	NA

		LNAA Burlina 2019 Scala 2020 Matalon 2006; 0.5 mg Matalon 2006; 1.0 mg Matalon 2007 Lou 1987 Pietz 1995 Schindeler 2007; gr A[3] Schindeler 2007; gr B[3] Yano 2013 Yano 2014; gr A[4] Yano 2014; gr B[4]	**LNAA** 12 10 8 3 20 14 24 16 16 9 6 6	**LNAA** From BL to 12 months From BL to 12 months mean From BL to 1 week From BL to 1 week From BL to 1 week 3 days, vs placebo 4 weeks, vs placebo 2 weeks, vs placebo 2 weeks, vs placebo 3 weeks, vs placebo From BL to 3 weeks From BL to 3 weeks	**LNAA** + 142 µmol/L + 78 µmol/L - 499 µmol/L - 681 µmol/L - 364.5 µmol/L + 14 µmol/L + 36 µmol/L - 95 µmol/L - 222 µmol/L - 26 µmol/L - 117 µmol/L + 123 µmol/L								
4. Natural protein intake	**Proportion of patients achieving daily protein intake target levels**	No data identified	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

	Change in mean natural protein intake	**PEG** 165-301 165-301 165-301/302 165-301/302	**PEG** 160 49 160 46	**PEG** From BL to 12 months From BL to 24 months From BL to 6 months From BL to 3 years	**PEG** + 8.9 g/day + 20.5 g/day + 8.7 g/day + 27.3 g/day	NA	NA	NA	NA	NA	NA	NA
		LNAA Burlina 2019 Schindeler 2007; gr A[3] Schindeler 2007; gr B[3]	**LNAA** 12 16 16	**LNAA** From BL to 12 months 2 weeks, vs placebo 2 weeks, vs placebo	**LNAA** ± 0 g/day + 0.7 g/day - 8.6 g/day							
5. Neuro-psychiatric outcomes	**ADHD-RS-IV IA**	**PEG** 165-301/302 165-301/302	**PEG** 178 97	**PEG** From BL to 6 months From BL to 3 years	**PEG** - 4.7 - 6.7	NA	NA	NA	NA	NA	NA	NA
	POMS	**PEG** 165-301/302 165-301/302	**PEG** 181 100	**PEG** From BL to 6 months From BL to 3 years	**PEG** - 16.9 - 20.4	NA	NA	NA	NA	NA	NA	NA
	PKU-POMS	**PEG** 165-301/302 165-301/302	**PEG** 181 100	**PEG** From BL to 6 months From BL to 3 years	**PEG** - 8.2 - 9.5	NA	NA	NA	NA	NA	NA	NA
6. Executive function outcomes	**BRIEF V**	No data identified	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	CANTAB, Rapid visual processing	**PEG** 165-302, PEG vs PBO	**PEG** 6 vs 3	**PEG** From BL to 8 weeks	**PEG vs PBO** - 72.1	NA	NA	NA	NA	NA	NA	NA

	CANTAB, Spatial Working Memory	**PEG** 165-302, PEG vs PBO	**PEG** 6 vs 3	**PEG** From BL to 8 weeks	**PEG vs PBO** - 8.9	NA	NA	NA	NA	NA	NA	NA
	CANTAB, Rapid visual processing	**PEG** 165-302, PEG vs PBO	**PEG** 6 vs 3	**PEG** From BL to 8 weeks	**PEG vs PBO** - 64.3	NA	NA	NA	NA	NA	NA	NA

1 The SLR did not identify any studies that reported QoL outcomes

2 Group A: patients achieving maintenance dose within 24 weeks. Group B: patients achieving maintenance dose beyond 24 weeks.

3 Group A: LNAA vs placebo with concomitant medical treatment. Group B: LNAA vs placebo without concomitant medical treatment.

4 Group A: LNAA + TT supplementation. Group B: LNAA + Placebo. Both groups compared with washout (Baseline).

Comparative analyses

The evidence collected regarding the impact of pegvaliase and LNAA treatment (in conjunction with a Phe-restricted diet), respectively, on each of the relevant outcomes is discussed below. All the studies enrolled very small patients population (range:10-24), were single arm or with cross over design and follow up patients for a very limited time period (range:1-4 weeks) with exception of 12 months follow up period for studies Burlina 2019 [32] and Scala2020 [33].

Given the heterogeneity of study designs, patient profiles, assessed outcomes and limited sample sizes across both treatments, formal comparative analyses were not possible. Instead, we provide a narrative comparison and discussion on each relevant outcome. The data identified from the SLR have been complimented with insights provided by Danish clinical expertise in a recent modified Delphi meeting, discussed in section 5 [13].

In terms of other available indirect analysis, in the absence of long-term head-to-head comparative studies for pegvaliase, BioMarin has sought to apply the best available methodologies to existing data to compare the long-term effectiveness of pegvaliase to sapropterin + phenylalanine-restricted diet ('sapropterin + diet') and phenylalanine-restricted diet ('diet alone'), showing superior outcomes versus both these treatment modalities.

The traditional approach to indirect comparison using a meta-analysis of the trials of the different interventions with placebo as a common comparator was not possible due to the differences in trial designs and populations included in the trials. Pegvaliase has been studied specifically in patients with blood phenylalanine > 600 µmol/L and the mean baseline blood phenylalanine concentration was 1233 µmol/L for 165-301. In contrast, the threshold for sapropterin clinical studies was lower at > 450 µmol/L [99, 100] and the mean baseline blood phenylalanine concentration in the Phase 3 trial of sapropterin that included patients ≥16 years was 867 µmol/L [12].

The approach taken was to compare pegvaliase to standard of care comparators (sapropterin + diet and diet alone) in patients with uncontrolled blood phenylalanine (>600 µmol/L) using patient level data from the pegvaliase clinical trials that used an induction, titration and maintenance dosing regimen and matched cohorts based on baseline measures in a historical cohort derived from the PKUDOS registry (NCT00778206). PKUDOS is a voluntary, US multicentre, observational program for patients with PKU.

This indirect analysis showed that patients matched on age, gender and baseline blood phenylalanine were more likely to achieve blood phenylalanine levels within European guidelines (≤600 µmol/L) on pegvaliase than on sapropterin + diet or on diet alone (Table 32). Unlike pegvaliase, neither sapropterin nor diet alone were able to normalise blood phenylalanine levels in any patients. Patients on pegvaliase also showed higher natural protein intake than those on sapropterin + diet or diet alone [31].

5.2.1 Quality-of-life

Patient quality of life was also stated as a key outcome of relevance to PKU patients. However, no QoL tools have been successfully validated in PKU, and especially with the pegvaliase treatment that the blood phenylalanine levels of patients have never been at such low levels before, existing tools are not able to capture the impact of treatment without longitudinal psychometric evaluation. In addition, no generic measure has been able to accurately capture burden of disease or impact of blood phenylalanine levels in PKU. Because of the difficulties experienced when capturing outcomes in PKU, BioMarin has developed the PKU Symptom Severity and Impacts Scale (PKU SSIS), which is presented in section 5, and BioMarin believes that this is the most relevant tool to capture the impact of PKU, and specifically elevated blood phenylalanine on patients' QoL, Cognitive and Executive Functioning, Mood and the Physical impacts of disease such as headaches and tremors.

5.2.1.1.1 SLR findings

The SLR identified no studies reporting QoL measurements using either of the instruments proposed in the evaluation protocol: PKU-QOL or WHOQOL-100, or any other QoL measures reported in pegvaliase or LNAA studies.

The only literature information on QoL in relation to any of these treatments comes from Sri Bhashyam 2019[101] who reported on a patient preference web survey, that aimed to evaluate the minimum acceptable benefit (MAB) of pegvaliase (the minimum probability of achieving a blood Phe <360) that patients would require in order for patients to accept the risk of hypersensitivity reactions to pegvaliase. The MAB was 22.7% and 34.4% in the two different survey methods used (swing weighting and thresholding, respectively). These MAB values were lower than the expected benefit from pegvaliase in at least 69% of patients, meaning that most patients were willing to accept the risks of hypersensitivity reactions in order to achieve target blood Phe levels with pegvaliase. This study was excluded from the literature review as it did not report any of the outcomes listed in the research question.

5.2.1.1.2 Additional insights

The advisors noted that the improvement in QoL is often observed by family/caregivers even at times when the patient may be unaware. The advisors were in consensus that, in addition to normalisation of Phe-restricted diet, the patient-relevant outcomes, which are shown in Table 8, are additional key outcomes of relevance to PKU patients.

TABLE 8. PATIENT-RELEVANT OUTCOMES

Patient-relevant outcomes	
Social functioning	- Loneliness - Education/employment
Executive functioning	- Attention - Concentration - Feeling of brain fog - Processing speed

	- Working memory
Emotional/mental functioning	- Mood swings - Irritability/anger - Anxiety
Physical functioning	- Sleep problems - Lack of energy

The advisors were in consensus that it is difficult to find good all-round tools to measure the patient-relevant outcomes. It is clear that PKU patients are affected by these outcomes listed in Table 8 but it is more difficult to quantify.

The advisors mentioned that the PKU-QoL tool seems to lack sensitivity to detect blood Phe changes.

Some of the advisors had experience with the Short Form (SF)-36 survey in adult PKU patients. However, they mentioned that it is not a disease specific tool. Therefore, this survey does not fully reflect the disease burden and the changes observed in PKU patients upon blood Phe level reduction.

Due to the present limitation of existing tools in capturing the impact of PKU on patient's QoL, Time-Trade Off (TTO) utility study was conducted in Sweden to elicit the correlation between PKU disease severity and patient disutility. The study also elicited the impact of restricted diet regimes on PKU patient's disutilities. The conclusion of the study illustrated that there was a direct relationship between disease severity and PKU patient disutilities as was also observed with restricted diet regimes [102]. The applicability of this study to Danish PKU patients was validated by Danish advisors who also highlighted the suitability of diet normalisation as a proxy measure of QoL in PKU patients. Pegvaliase is the only licensed product that lowers blood Phe levels (reduces disease severity) and normalises diet in PKU patients and thus improves QoL in patients.

5.2.2 Adverse events

5.2.2.1.1 Treatment discontinuation, pegvaliase

As identified by the SLR (Appendix A), [redacted] [103] reported pooled ph2/3 data for pegvaliase. With a mean (SD) treatment duration of 24.4 (15.46) months, 7/285 pts (2.5%) withdrew due to AEs. Furthermore, incidence of AEs leading to drug discontinuation was reported by Harding 2018b [91] for pooled phase 2/3 pegvaliase studies by subgroup according to whether or not pts had experienced at least one HypoPhe event. AE incidence leading to drug discontinuation was lower (2%, 2/100) in patients with at least one HypoPhe event compared to pts who had not had a HypoPhe event (22%, 41/185).

A full summary of treatment discontinuation data reported from the pegvaliase clinical trial program, with primary reasons for early study drug discontinuation and early study withdrawal, given in Table 9.

In the MD Population (Pooled phase 2-3), a total of 35.5% of subjects (121/341) discontinued pegvaliase treatment prior to planned study completion; the most common reasons for early study drug discontinuation included adverse event (45 [13.2%] subjects), withdrawal by subject (40 [11.7%] subjects), physician decision

(13 [3.8%] subjects) and lost to follow-up (12 [3.5%] subjects). In the I/T/M Population (Pooled 165-205/301), 34.7% of subjects (99/285) discontinued pegvaliase treatment early, with the most common reasons being the same as those seen in the MD Population.

As of the data cutoff, 61.9% of subjects in the MD Population and 63.5% of subjects in the I/T/M Population were still continuing treatment with pegvaliase in one of the ongoing clinical studies (165-302 or PAL-003).

The majority of subjects, who discontinued the study treatment due to AEs, eventually also discontinued from the study; some subjects continued to be followed up without being re-dosed.

In addition, AEs leading to study drug discontinuation in 165-301 for 3 subjects, and an AE leading to study discontinuation for one subject were not captured as such in the clinical database and are not included in the incidence and event rates.

Implementation of premedication and safety minimization measures

After implementation of required premedication and other safety minimization measures, the overall study drug discontinuation rate in Phase 3 studies decreased from 23.8% to 13.6% in the first 6 months and from 32.9% to 18.6% in the first year. Additionally, to ensure the risk minimisation of acute systemic hypersensivity events, other measures were also introduced, flexibility to reduce or interrupt pegvaliase dosing due to mild AEs, implementation of an observer during pegvaliase administration during first 16 weeks and additional education on identifying and responding to HAEs signs and symtoms and reception of epinephrine injection pen for potential use in case of an acute systemic hypersensivity events. Similarly, the study drug discontinuation due to AEs dropped from 15.4% to 5.9% in the first 6 months and from 16.8% to 7.6% in the first year after implementation of required premedication and other safety minimization measures. The association of these additional safety measures with lower study drug discontinuation suggests patient tolerability may improve with the safety minimization measures, including the use of premedication during initiation of pegvaliase treatment.

SmPC recommendation of pre-medication

The SmPC states that "Patients should be instructed to pre-medicate with an H1-receptor antagonist, H2-receptor antagonist, and antipyretic. During maintenance, premedication may be reconsidered for subsequent injections based on patient tolerability to pegvaliase"

TABLE 9. SUBJECT DISPOSITION AND REASON FOR EARLY (STUDY DRUG OR STUDY) DISCONTINUATION BY PARENT STUDY

	Parent Study (Includes Data from All Subsequent Studies)						
	PAL-001 (n=25)	PAL-002 (n=40)	PAL-004 (n=16)	165-205 (n=24)	165-301 (n=261)	I/T/M[a] (n=285)	MD[b] (n=341)
Subject status of study drug completion[c], n (%)							

	Parent Study (Includes Data from All Subsequent Studies)						
	PAL-001 (n=25)	**PAL-002 (n=40)**	**PAL-004 (n=16)**	**165-205 (n=24)**	**165-301 (n=261)**	**I/T/M[a] (n=285)**	**MD[b] (n=341)**
Completed study drug in last enrolled study	25 (100.0%)	4 (10.0%)	0	1 (4.2%)	4 (1.5%)	5 (1.8%)	9 (2.6%)
Continuing study drug in ongoing studies[d]	0	19 (47.5%)	11 (68.8%)	16 (66.7%)	165 (63.2%)	181 (63.5%)	211 (61.9%)
Discontinued study drug early in last enrolled study	0	17 (42.5%)	5 (31.3%)	7 (29.2%)	92 (35.2%)	99 (34.7%)	121 (35.5%)
Reason for early study drug discontinuation, n (% of total discontinuations)[e]							
Adverse event	0	2 (5.0%)	0	4 (16.7%)	39 (14.9%)	43 (15.1%)	45 (13.2%)
Lost to follow-up	0	4 (10.0%)	0	0	8 (3.1%)	8 (2.8%)	12 (3.5%)
Physician decision	0	3 (7.5%)	1 (6.3%)	1 (4.2%)	8 (3.1%)	9 (3.2%)	13 (3.8%)
Pregnancy	0	0	0	0	2 (0.8%)	2 (0.7%)	2 (0.6%)
Protocol deviation	0	0	0	0	3 (1.1%)	3 (1.1%)	3 (0.9%)
Withdrawal by subject	0	7 (17.5%)	3 (18.8%)	2 (8.3%)	28 (10.7%)	30 (10.5%)	40 (11.7%)
Other	0	1 (2.5%)	1 (6.3%)	0	4 (1.5%)	4 (1.4%)	6 (1.8%)
Subject status of study completion[c], n (%)							
Completed last enrolled study	25 (100.0%)	4 (10.0%)	0	3 (12.5%)	10 (3.8%)	13 (4.6%)	17 (5.0%)
Continuing in ongoing studies[d]	0	19 (47.5%)	11 (68.8%)	16 (66.7%)	167 (64.0%)	183 (64.2%)	213 (62.5%)
Discontinued study early from last enrolled study	0	17 (42.5%)	5 (31.3%)	5 (20.8%)	84 (32.2%)	89 (31.2%)	111 (32.6%)
Reason for early study discontinuation n (% of total discontinuations)[e]							
Adverse event	0	2 (5.0%)	0	1 (4.2%)	25 (9.6%)	26 (9.1%)	28 (8.2%)
Death	0	0	0	0	1 (0.4%)	1 (0.4%)	1 (0.3%)
Lost to follow-up	0	4 (10.0%)	0	0	9 (3.4%)	9 (3.2%)	13 (3.8%)
Physician decision	0	3 (7.5%)	1 (6.3%)	1 (4.2%)	10 (3.8%)	11 (3.9%)	15 (4.4%)
Pregnancy	0	0	0	0	1 (0.4%)	1 (0.4%)	1 (0.3%)
Protocol deviation	0	0	0	0	3 (1.1%)	3 (1.1%)	3 (0.9%)
Study terminated by sponsor	0	0	0	0	1 (0.4%)	1 (0.4%)	1 (0.3%)

	Parent Study (Includes Data from All Subsequent Studies)						
	PAL-001 (n=25)	**PAL-002 (n=40)**	**PAL-004 (n=16)**	**165-205 (n=24)**	**165-301 (n=261)**	**I/T/M[a] (n=285)**	**MD[b] (n=341)**
Withdrawal by subject	0	7 (17.5%)	3 (18.80%)	3 (12.5%)	32 (12.3%)	35 (12.3%)	45 (13.2%)
Other	0	1 (2.5%)	1 (6.3%)	0	2 (0.8%)	2 (0.7%)	4 (1.2%)

- I/T/M, Induction, Titration, Maintenance (Population); MD, Multiple Dose (Population).
- The Safety Population included all enrolled subjects who received at least one dose of pegvaliase in any of the pegvaliase studies.
- The parent study was the first study in which a subject was enrolled. For subjects who continued pegvaliase in Study PAL-003 and/or Study 165-302, data from all enrolled studies were included.
- Adverse events leading to study drug discontinuation for subjects 0124-3210, 0312-3117, and 1308-3157 and AEs leading to study discontinuation for Subject 1308-3157, were not captured in the electronic case report form (eCRF) and are thus missing in the source table. For further information see the 165-301 Errata Memos (Module 5.3.5.3).
- [a] Subjects were from Study 165-205 or Study 165-301 where pegvaliase administration was initiated as an induction, titration, and maintenance dosing regimen.
- [b] Subjects who were only enrolled in the Phase 1, single-dose study, PAL-001, were excluded.
- [c] Based on the integrated data completion status reflected each subject's state in the last study in which the subject was enrolled.
- [d] Studies PAL-003 and 165-302 (Part 4) are ongoing.
- [e] Percentage was calculated based on the total number of subjects in each study or population.

5.2.2.1.2 Treatment discontinuation, LNAA

The LNAA studies included in the SLR (Appendix A) had small patient numbers and short follow-up times and it is therefore difficult to draw conclusions on the discontinuation rates on LNAA treatment when the studies are small and limited evidence. Only two studies, Burlina 2019 and Scala 2020 followed patients (n=10 and n=12, respectively) for 1 year, without any patients discontinuing.

The PKU advisors in the advisory board stated that less than 25% of the adult PKU population discontinue LNAA supplementation. Main discontinuation reasons are forgetting to take the supplements, number of tablets they need to take, and wanting to be more focused. The advisors' experience was that in busy or stressful periods with need to focus, high-functioning patients tend to go on a stricter diet to have more energy and focus. The implication is that LNAA supplementation is not effective in that outcome. If adult PKU patients discontinue LNAA supplementation, only 10% switch back to a Phe-restricted diet. It is assumed that the other 90% are lost to follow-up.

5.2.2.1.3 Qualitative review of adverse events, pegvaliase

The SLR reported adverse reactions to pegvaliase treatment including: Adverse events (AEs), adverse drug reactions (possibly treatment-related AEs, ADRs), serious AEs (SAEs), possibly related serious adverse drug reactions (SADRs), and hypersensitivity adverse events (HAEs).

In 165-301 and 165-302, the vast majority of patients experienced at least one AE, whether on pegvaliase (at either dose) or on placebo. Exposure-adjusted AE rates (events/person year) showed a higher event rate with pegvaliase compared with placebo [104]. AEs with at least 10% difference in incidence between pooled pegvaliase and placebo groups were headache and upper respiratory tract infection (URTI)[104].

AE rates (events/person year) appeared higher during initial treatment (58.30 events/person year in the phase 2 parent studies, mean treatment duration 16.4 weeks) compared to long-term follow up in PAL-003 (18.60 events/person year, mean treatment duration 176.5 weeks) [29]. All patients reported at least one AE, with the most common being injection-site reaction (72.5% of patients), injection-site erythema (67.5%), headache (67.5%) and arthralgia (65.0%)[29]. Most AEs were mild (12.5%) or moderate (76.3%) in severity; severe AEs were reported in 11.3% of patients only[29].

Zori et al. 2018[24] reported event rates in the first 24 weeks of study 165-205 and after 24 weeks during the PAL-003 extension study. They showed that during the first 24 weeks, the subset of patients achieving the MAIN dose (Phe ≤600µmol/L) by 24 weeks had much lower AE rate (35.63 events/person year) than did patients not achieving the MAIN dose by 24 weeks (68.78 events/person year). As patients continued, however, in PAL-003, the AE rates were similar between these subgroups (15.63 and 19.51 events/person year, respectively).

This pattern - of lower event rates with continued pegvaliase treatment - was also reflected in pooled phase 3 study data (Pooled 165-301/302) reported in Harding et al. 2019a[90]. AE rates were 17.6 events/person year with continued use beyond 6 mths, compared with 58.7 during the first 6 mths. Further pooled analyses at a mean 24.4 mths treatment duration reported event rates of 25.90 and 33.02 events/person year in ph2/3 pegvaliase treated patients with and without hypophenylalaninaemia (HypoPhe), respectively[91]. Lastly, event rates during induction/titration with pegvaliase appeared similar between young adults (16-<18 years) and in adults (18 years+)[97]. During maintenance dosing, event rates were lower than during induction/titration in both these age groups[98].

Burton 2018 [103] reported AE frequency from pooled ph2/3 pegvaliase studies, showing that mild AEs were experienced by 75% of patients and moderate AEs by a lower number of patients (25%). In almost all pegvaliase studies, most patients experienced at least one ADR. During the phase 2 165-205 study, rates of ADRs were higher in Group B (those not achieving the MAIN dose by Week 24) than in Group A (those achieving MAIN dose by Week 24), but this difference decreased with longer term treatment in PAL-003[24].

SAEs occurred in patients on pegvaliase at a frequency of 3% over the 8-week period with pooled pegvaliase data in the RDT [1], 5% in pooled phase 2 studies (PAL-003 extension study) with median treatment duration 16 weeks [29], and 5-15% over 71 weeks median treatment duration in 165-301(14). Exposure adjusted SAE rates were also available, showing that rates were higher initially (0.15[105] 0.16 [29] and 0.00-0.18 for early treatment to week 24 [24]), then lower during EXT phases (0.07 in PAL-003 [29]up to 176 weeks and 0.04 and 0.11 in Groups A and B, respectively (those achieving or not achieving target blood Phe by Week 24) in long-term follow-up to 204 weeks [24]. SAE frequency appeared higher (20%) in patients without vs with (7%) HypoPhe from pooled ph2/3 data [91], whereas frequency in young adults (16-<18 years) was similar to that in adults (≥18-65 years) (25% and 22%, respectively).

SADRs occurred rarely with pegvaliase in studies up to Week 24 (0-3%). With longer-term use and follow-up, SADRs were reported in 9-10% of patients followed for 2 years from pooled phase 3 data (Pooled 165-301/302) [31], and in up to 20% of patients in PAL-003 subgroup followed for up to 204 weeks who had not achieved the MAIN dose within the first 24 weeks of treatment [24]. It should be noted that the long-term subgroup data for PAL-003 had only 10 patients in each group, so frequencies may be uncertain. In the subgroup who had achieved the MAIN dose within the first 24 weeks, 0% of patients experienced a SADR.

In 165-301, HAEs occurred at a rate of 7.4 events/person year [105]. HAE frequency decreased in late treatment phase (> 6 mths, compared to in the first 6 mths) as mean pegvaliase antibody levels decreased, PAL antibody titers were stable and C3/C4 levels increased. In the phase 2 studies leading into PAL-003, HAE rate was 14.90 events/person year [29] for phase 2 study patients and lower at 4.30 events/person year for patients continuing in the EXT phase (in PAL-003) [29] . Acute systemic hypersensitivity events of anaphylaxis (ASHEA) and acute systemic hypersensitivity events as per Brown's severe criteria (ASHEB) were rare.

5.2.2.1.4 Qualitative review of adverse events, LNAA

The SLR did not identify any studies reporting adverse events from LNAA studies.

There is limited clinical evidence on LNAAs discontinuation rates for LNAAs. The advisors stated in the modified Delphi meetings that patients do stop taking LNAAs but this is variable and unclear. The advisors agreed that less than 25% of the adult PKU population discontinues LNAA supplementation. Main discontinuation reasons are forgetting to take the supplements, number of tablets they need to take and wanting to be more focussed. If adult PKU patients discontinue LNAA supplementation, only 10% switch back to a Phe-restricted diet. It is assumed that the other 90% are lost to follow-up. It was also noted by the Danish advisors that significant somatic comorbidities were frequently observed with PKU patients on LNAA treatments; some of these comorbidities include brain fog, fatigue, stress, slow perception, difficulty in concentrating and headaches. It is important to note this clinical presentation profile whilst considering the AE profile of LNAA treated patients as with the long-term impacts/comorbidities of a Phe-restricted diet including osteoporosis, renal insufficiency, overweight, depression, anxiety syndrome, nutritional deficiencies, and sleep disturbances [70, 106] .

5.2.2.1.5 Conclusions on adverse events, pegvaliase versus LNAA

Pegvaliase has a manageable safety profile in most patients and its safety profile has been characterised with the long-term use. Most AEs were mild or moderate and resolved without dose change or interruption . Most AEs occurred during the first 6 months of treatment, coinciding with the induction/titration phases, when the immune response against pegvaliase is the strongest [1].

The LNAAs adverse events are linked with their lack of efficacy in normalization of PHE level and thus all the burden for the patients of the uncontrolled Phe level. Moreover, 90% of patients who discontinue LNAA supplementation are lost to follow up and only 10% switch to Phe restricted diet.

5.2.3 Phenylalanine concentration

The studies identified in the SLR presented mean blood Phe levels at different time points, and in many cases also the proportion of patients achieving treatment goals. For pegvaliase, there is follow-up data from clinical trials (Pooled 165-301/302) for up to 4 years [19]. For LNAA, the longest follow-up data available was for 1 year of treatment [32, 33]. The SLR findings are discussed below.

The SLR was not able to identify any information on Phe levels in the brain. This was expected, given the methodological challenges associated with performing Phe measurements in brain tissue. There are no routine methods for measuring brain Phe in routine practice. Methods such as MRI scans and associated psectrometric methods are too expensive to implement in routine practice. As validated by the modified Delphi meetings [13] it is well established that blood Phe level is the most relevant surrogate marker of Phe

levels in the brain, with important PKU symptoms being proportional to blood Phe level and reversible upon sustained blood Phe reduction.

5.2.3.1.1 SLR findings, pegvaliase

The most relevant evidence on long-term achievements with pegvaliase treatment comes from the phase 3 extension study, 165-302 part 4 (Table 28). After 6 months with pegvaliase treatment at the maintenance dose, 38% of the patients had achieved controlled blood Phe (≤600 µmol/L). However, the clinical data has demonstrated that the treatment effect is sustained and further improved over longer treatment periods, and it may thus be even more relevant to consider longer follow-up periods when evaluating the efficacy on Phe reduction. After 3 and 4 years on treatment, 72.5% of the patients in 165-302 had achieved controlled blood Phe. In study 165-205 (Table 29Table 14), it was demonstrated that also patients who did not reach maintenance dose within 24 weeks responded to treatment, and achieved controlled blood Phe with longer follow-up (48 weeks).

When considering mean blood Phe observed, the phase 3 RCT showed that pegvaliase substantially reduced mean blood Phe over 36 weeks at 20 and 40 mg/day (165-301; Table 27). Long-term follow-up data to 3 years were available showing further reductions with continued treatment (mean blood Phe BL 1233 µmol/L, 3 years 341 µmol/L) [redacted]

In the phase 3 RDT (165-302), patients with controlled Phe levels <600 µmol/L who were randomised to discontinue pegvaliase (who received placebo) for 8 weeks showed increased blood Phe (from 536 µmol/L for pooled placebo arms at RDT entry, to 1385µmol/L by Week 8). By contrast, patients randomised to continue on pegvaliase maintained control of their blood Phe (from RDT entry for pooled pegvaliase arms 533 µmol/L, to 559 µmol/L by Week 8).

In the phase 2 OLE (PAL-003), patients showed sustained reductions in blood Phe over time up to 240 weeks (over 4.5 years). From BL 1302 µmol/L, blood Phe was reduced to 476 µmol/L in the 45 patients followed for 144 weeks [redacted] At later time points, mean blood Phe was 399 µmol/L at week 240 in 22 patients [94].

In the phase 2 study 165-205 [24], week 48 follow-up results were reported for subgroups defined by whether or not patients achieved a maintenance dose (i.e. blood Phe ≤600 µmol/L) by Week 24 (Table 29). They showed that those with blood Phe ≤600 µmol/L by Week 24 had further reductions by Week 48 (508 µmol/L at Week 24, 236 µmol/L by Week 48) and that those not achieving blood Phe ≤600 µmol/L by Week 24 had mean blood Phe below this target level with continued treatment to Week 48 (mean blood Phe 557 µmol/L by Week 48).

Further pooled data from the two phase 3 studies (Pooled 165-301/302) provided 1- and 2-year follow-up data showing that reductions in blood Phe were maintained long-term. Among these data, Burton et al. 2019a [88] reported specifically on a subgroup of patients who were stable on 60mg/day pegvaliase. The stable cohort was defined as those patients who had been on 60 mg/day for at least 4 weeks with at least 80% adherence. The EPAR reported a pooled analysis for the Induction, Titration, Maintenance (I/T/M) population (N=285) including data from 165-205 and its extension PAL-003, and 165-301 and its extension 165-302. Of these patients, 184 completed 12 months of pegvaliase treatment. Blood Phe after 12 months pegvaliase treatment were reduced by a mean (SD) of 674.9 (579.6) µmol/L (n=184) to a mean (SD) blood Phe of 546.6 (520.8) µmol/L. Furthermore, 67 patients reached 24 months of pegvaliase treatment. At 24

months, blood Phe were reduced by a mean (SD) of 913.6 (528.3) µmol/L (n=67) to a mean (SD) blood Phe of 294.3 (398.0) µmol/L.

5.2.3.1.2 SLR findings, LNAA

None of the LNAA studies reported the percentage of patients achieving a particular target level of blood Phe. However, the distribution of blood Phe levels was reported in a box plot by Schindeler 2007 [38], illustrating that the higher plasma Phe levels were found in the phases of the study with lowest LNAA intake. They also reported that on average plasma Phe was reduced by 24.9% in the active phase of the study.

Burlina 2019 [32] enrolled sub-optimally controlled (non-adherent to amino acid mixture), early-diagnosed adult patients with classical PKU in Padova, Italy. They investigated the effects of a microgranulated, slow-release LNAA product (NeutrAfenil® Micro R) taken 3x daily for 12 months, which provided 80% of total protein requirements and which did not taste unpleasant due to a methylcellulose film. Blood Phe was unchanged during the study overall, with blood Phe continuing to be poorly controlled. Adherence by patients to the LNNA product was very good. Adherence to amino acid supplements was problematic previously, due to the frequency of administration (4-5 times daily) and palatability issues. No other amino acids were given. The remaining 20% of total protein was supplied by natural foods. Patients indicated that they generally had either lunch or supper outside of the home with Phe intake 3-4 times the prescribed amount. Mean Phe (SD) was similar for most patients before (628 (148) -1033 (198) µmol/L) and after (range 736 (93) -1269 (265) µmol/L) LNAA treatment, whereas Tyr increased signficantly in 11 of the 12 patients (mean (SD) 59 (13) µmol/L in 12 mths prior to LNAA and 75 (16) µmol/L in 12 mths after LNAA treatment, p=00195). However, when examining the blood Phe at 6 mths and then 12 mths, mean Phe was found to significantly decrease (p=0.00458) in the first 6 mths, then significantly increase in the next 6 mths (p=0.0522). The authors suggest that this may have been due to patients keeping to a stricter diet in the first 6 mths and then relaxing dietary restrictions subsequently.

Further LNAA studies evaluated NeoPhe (Matalon 2006; Matalon 2007 [34, 35]), PheLNAA (Scala 2020 [33]), high dose tyrosine supplementation (Lou 1987; Pietz 1995 [36, 37]), PheBloc LNAA supplementation (Yano 2013 [39]), tyrosine and tryptophan supplementation with PheBloc LNAA (Yano 2014 [40]), and an LNAA powder mix (Schindeler 2007 [38]). The only LNAA formulation bringing blood Phe to below the target level (≤600 µmol/L) was NeoPhe [34, 35].

5.2.3.1.3 Conclusions on Phe concentration, pegvaliase versus LNAA

The advisors were in consensus that no reduction in blood Phe level is to be expected when using LNAAs and that the effectiveness of LNAAs cannot be evaluated by assessing blood Phe levels.
The advisors were in consensus that it is not possible to directly compare LNAA supplementation with pegvaliase as only limited data are available in the literature on executive and neuropsychological functioning, and because LNAA supplementation does not impact blood Phe levels (as studied as an endpoint in pegvaliase clinical trials and lowering blood-Phe is not an endpoint for LNAA). It was noted that a clinical trial comparing LNAA and pegvaliase systematically would be necessary to do this comparison. However, the advisors agreed (in the absence of real treatment experience & purely based on evidence/narratives shared) that pegvaliase may have a better treatment outcome profile compared to LNAAs.

Elevated blood Phe is the key driver of symptoms and effects of PKU: neuropsychiatric and neurocognitive symptoms, QoL aspects, social limitations, etc. There is consensus that reduction of blood Phe levels is the key treatment goal since the symptoms of elevated PKU are reversible with reduction of blood Phe. While pegvaliase treatment is shown to efficiently reduce blood Phe levels below 600 µmol/L (and even normalise the blood Phe <120 µmol/L for a majority of patients), and thus provide relief from the PKU symptoms; LNAA supplementation does not reduce the blood Phe levels and hence cannot address the issues with elevated Phe [7, 54].

Blood Phe is the best indicator of treatment improvement in PKU management and pegvaliase is the only treatment that reduces blood Phe in all PKU subgroups, a reduction that is achieved while allowing a diet normalisation which is associated with large QoL value for the patients. On both these two points, LNAA supplementation has poor effect compared with pegvaliase.

5.2.4 Natural protein intake

The SLR was unable to identify reported Phe intake and natural protein intake presented as proportion of patients achieving target amounts.

	Pegvaliase	LNAA
Natural protein intake	Data from Zori 2019 (Pooled 165-301/302) [31] show that natural intact protein intake could increase in patients treated with pegvaliase alongside maintaining control of blood Phe. Total protein intake upon pegvaliase treatment was on average in PRISM 2: [1] • 64,8 g per day at baseline [redacted] Patients on Pegvalise are able to increase their natural protein intake towards normalisation without any adverse efects on the blood Phe.	Mean natural protein intake was 28.1 g per day after 2 weeks on LNAA treatment (Schindeler 2007) No other literature data were found The advisors were in consensus that a benefit of LNAA supplementation is that the amount of natural protein can be elevated to 80% in the diet. This allows more freedom and lessens the burden of taking supplements (from 80% of diet consisting of supplements to 20%). This makes a huge difference for the patients. However, the advisors agreed that patients on LNAAs still require dietary compliance to achieve better treatment outcomes maintain blood-Phe level below 1500 µmol/L.

Advisors' input	The advisors were in consensus that from the patient's perspective the amount of natural protein is not the key outcome of diet normalisation. For the patients, the key outcome related to diet is not having to count, weigh, think, etc. about food and not feeling guilty at the end of the day when they were not able to adhere to recommended diet regimens. The advisors were in consensus that even any amount of freedom from diet makes a huge difference for the patient (e.g. from 30 to 60 g natural protein), as observed in sapropterin responders. The advisors agreed that diet normalisation is a very significant treatment outcome for Danish PKU patients.

5.2.4.1.1 SLR findings

The SLR were unable to identify reported Phe intake and natural protein intake presented as proportion of patients achieving target amounts. Instead, mean intake levels were reported (Table 7 and Table 8 of the SLR report; Appendix A). The data from Zori 2019 (Pooled 165-301/302) [31] show that natural intact protein intake could increase in patients treated with pegvaliase alongside maintaining control of blood Phe.

Total protein intake upon pegvaliase treatment was on average 68.2 g per day after 24 weeks (Study 165-205) [24] 47,4 g per day after 12 months [1], and 59 g per day after 24 months and 72,2g per day after 3 years (Study 165-301) [1, 94]. Patients on Pegvalise are able to increase their natural protein intake towards normalisation without any adverse efects on the blood Phe.

Natural protein intake upon LNAA treatment was reported by Schindeler 2007 [38], presented as mean intake per body weight at different time points. Assuming an average body weight of 72 kg, the mean natural protein intake was 28.1 g per day after 2 weeks on LNAA treatment.

The mean Phe intake reported upon pegvaliase treatment was 1,814 mg Phe per day after 24 weeks [24], 2,123 mg after 12 months [1] and 2,680 mg after 24 months [1]. Corresponding data upon LNAA treatment was presented in relation to patient body weight. Assuming an average body weight of 72 kg, the mean intake corresponded to 1,260 mg Phe per day after 2 weeks on LNAA treatment [38].

5.2.4.1.2 Additional insights

The advisors were in consensus that despite the lack of control of blood phe and the associated comorbidities, a benefit of LNAA supplementation is that the amount of natural protein can be elevated to 80% in the diet. This allows more freedom and lessens the burden of taking supplements (from 80% of diet consisting of supplements to 20%). However, the advisors agreed that patients on LNAAs still require dietary compliance to achieve better treatment outcomes and to maintain blood-Phe level below 1500 µmol/L.

The advisors were in consensus that in the patient's perspective the key outcome related to diet is not having to count, weigh, think, etc. about food and not feeling guilty at the end of the day when they were not able to adhere.

The advisors were in consensus that even a small amount of freedom from diet makes a huge difference for the patient (e.g. from 30 to 60 g natural protein), as observed in sapropterin responders.

The advisors agreed that diet normalisation is a very significant treatment outcome for Danish PKU patients.

5.2.5 Neuropsychiatric symptoms

	Pegvaliase	LNAAs
General comments	Clinical evidence available from 165-301/302 studies; summarized in this table and further discussed in text sections below.	None of the LNAA studies identified in the SLR used the same mood measures as the pegvaliase studies. Studies on mood or inattention identified in the SLR used other measures than POMS and ADHD-RS-IV. Lack of long-term studies.
ADHD-RS-IV IA	Phe levels correlate to inattention and confusion: the patients with the largest reductions in blood Phe during 165-301/302 studies experienced the greatest improvements in symptoms of inattention and confusion measured by the ADHD-RS IV IA subscale and the PKU-POMS Confusion subscale.	No evidence of benefit There is no data from the SLR regarding LNAA impact on ADHD-RS-IV
POMS	With pegvaliase treatment in 165-301, mean POMS scores halved from BL (35.7) to 24 mths (18.3). Mean PKU-POMS scores decreased from 15.9 at BL to 6.6 at 24 mths. The PKU-POMS confusion subscale scores also decreased, from 4.0 at BL to 2.4 at 12 mths and 2.0 at 24 mths. In 165-302, the LS mean change scores (for POMS, PKU-POMS and PKU-POMS confusion subscale score) from RDT Day	No evidence of benefit There is no data from the SLR regarding LNAA impact on POMS.

	1 to Week 8 for pooled pegvaliase vs PLA 20mg/day or 40 mg/day were not significantly different [data in DET].	
Long-term impact of pegvaliase on inattention and mood	Significant evidence from clinical trial programme captured in the text sections below and summarized here: • In the pegvaliase clinical trial programme, the primary ITT population (N=261) for long-term efficacy analyses of inattention and mood consists of patients who initiated pegvaliase treatment in 165-301 and includes all data collected in 165-301 and 165-302. • ADHD RS-IV IA subscale scores declined upon pegvaliase treatment indicating an improvement in inattention symptoms that was maintained with long-term treatment with pegvaliase. • The magnitude of the change from baseline in ADHD RS-IV IA scores was greater for patients considered symptomatic at baseline (score >9; n=116). • The median reduction from baseline inattention score was above the CID (defined as a reduction of at least 5.2) at 12, 24 and 36 months for patients with baseline symptoms of inattention score >9.	No evidence of consistent reduction in blood Phe No long-term studies of LNAA available

	• There was a temporal association of improvement in IA scores with reduction in blood Phe levels. • The mean POMS TMD and mean PKU-POMS TMD score both decreased (suggesting improvement) over time in parallel with reductions in blood Phe levels. • The mean and median change from baseline in the PKU-POMS Confusion subscale reached the CID (defined as a reduction of at least 1.33) from 12 months to 36 months after initiation of treatment	
Other instruments		Weak or negative evidence from small and short-term studies. Scala et al. 2020 [33]: • Improvement in distress and well-being, executive functions, sustained attention span and vigilance observed 3 months after starting LNAA and maintained through 12 months of treatment. • No difference in hand dexterity was noted, however. • All TAP vigilance and sustained attention scores improved significantly, at 3 and 12 months. Pietz et al. 1995[37]: • High dose tyrosine supplementation did not have any beneficial effect on brain function.

		• There were no differences on Dot Pattern Exercise (DPE) with high dose tyrosine vs placebo. • Nor did DPE improve with high dose tyrosine in a subgroup of 11 patients who performed below the median. Lou et al. 1987[36]: • evaluated the effect of high dose tyrosine on continuous reaction times (brain function measure) in 14 PKU patients on a Phe-free diet. • normal reaction times at BL were not affected • 12/14 patients had long reaction times at BL; for all of them tyrosine supplementation significantly reduced these reaction times (p<0.001). Schindeler et al. 2007 [38]: • assessed several related outcomes including overall intellectual functioning (Wechsler Abbreviated Scale of Intelligence). • Plasma Phe levels correlated with several attention measures. • Higher levels of anxiety symptoms were reported when patients were on LNAA treatment (F=5.2, p=0.039).

5.2.5.1.1 ADHD-RS-IV IA, pegvaliase

Change in attention and mood symptoms were measured in the phase 3 pegvaliase studies by the inattention subscale of the Attention Deficit Hyperactivity Disorder Rating Scale IV (ADHD RS-IV IA).

In 165-301 with pegvaliase treatment, 24 month follow-up data showed a mean decrease from BL in subscale scores of 6.4 points. In the subset of patients with BL ADHD RS-IV IA subscale score >9 (i.e. symptomatic in

terms of inattention) patients showed the greatest improvement in inattention scores (mean decrease from BL in subscale scores of 9.6 points.

Further, analysis of the change from BL in subscale score in relation to blood Phe showed that the 53 patients in the quartile with the largest blood Phe reduction also experienced the greatest reduction in subscale score, a mean (SD) decrease of 7.5 (5.6) points [1].

In the 8-week RDT in 165-302[104] the difference in least squares (LS) mean changes (RDT Entry to Week 8) with 95% confidence interval (CI) were reported for each PLA group compared to pooled pegvaliase data. In both the all patients analysis and in the subset with subscale score >9 before pegvaliase treatment these differences in LS mean changes were not significant over this short period of time, although the difference approached significance in the subset with subscale score >9 for PLA 20mg/day compared to pooled pegvaliase (LS mean diff 4.7 (95% CI -0.19, 9.5, p=0.06).

Berguig et al. 2019 [87] showed an inverse correlation between a change in 3-methoxy-4-hydroxyphenylglycol (MOPEG) and a change in ADHD RS-IV IA score in patients with a BL score ≥9 from pooled phase 3 pegvaliase data (r=-0.5434, p=0.0242) (Pooled 165-301/302). As MOPEG increased, ADHD RS-IV IA scores decreased, indicating improvement in attention. Their analyses showed that lower plasma Phe levels were associated with normalisation of neurotransmitter biosynthesis and improved inattention symptoms.

None of the LNAA studies identified in the SLR used the same inattention measures as the pegvaliase studies. Inattention measures used in LNAA studies are summarised in Table 11 of the SLR.

5.2.5.1.2 POMS, pegvaliase

With pegvaliase treatment in 165-301, mean POMS scores halved from BL (35.7) to 24 mths (18.3). Mean PKU-POMS scores decreased from 15.9 at BL to 6.6 at 24 mths. The PKU-POMS confusion subscale scores also decreased, from 4.0 at BL to 2.4 at 12 mths and 2.0 at 24 mths. In 165-302, the LS mean change scores (for POMS, PKU-POMS and PKU-POMS confusion subscale score) from RDT Day 1 to Week 8 for pooled pegvaliase vs PLA 20mg/day or 40 mg/day were not significantly different [data in DET].

None of the LNAA studies identified in the SLR used the same mood measures as the pegvaliase studies.

5.2.5.1.3 Long-term impact of pegvaliase on inattention and mood

In the pegvaliase clinical trial programme, the primary ITT population (N=261) for long-term efficacy analyses of inattention and mood consists of patients who initiated pegvaliase treatment in Study 165-301 and includes all data collected in 165-301 and 165-302.

TABLE 10 EFFICACY OF PEGVALIASE ON INATTENTION AND MOOD AT 12, 24 AND 36 MONTHS IN POOLED STUDY 165-301/302 (5TH FEBRUARY 2018 DATA CUT)

	Baseline [1]	12 months	24 months	36 months
Inattention subscale of ADHD RS-IV				
Mean (SD) n	9.8 (6.1) n = 253	5.0 (4.9) n = 178	4.2 (4.6) n = 167	3.7 (5.0) n = 97
Change from baseline, mean (SD) Change from baseline, median	-	-4.7 (5.6) -4.0	-5.9 (6.1) -5.0	-6.7 (6.4) -5.5

n[2]		n = 172	n = 160	n = 92
Inattention subscale of ADHD RS-IV, patients with score >9				
Mean (SD) n	15.3 (4.1) n = 116	7.6 (4.9) n = 80	5.9 (4.9) n = 76	5.1 (5.6) n = 45
Change from baseline, mean (SD) Change from baseline, median n[2]	-	-7.8 (5.5) -7.0 n = 80	-9.6 (5.9) -10.0 n = 76	-10.6 (6.4) -12.0 n = 45
POMS TMD				
Mean (SD) n	35.5 (31.9) n = 170	21.3 (31.2) n = 181	18.0 (29.7) n = 169	15.9 (31.5) n = 100
Change from baseline, mean (SD) Change from baseline, median n[2]	-	-16.9 (32.6) -16.5 n = 130	-20.1 (35.4) -17.0 n = 117	-20.4 (43.6) -18.0 n = 51
PKU-POMS TMD				
Mean (SD) n	15.9 (13.3) n = 170	8.5 (12.5) n = 181	6.6 (12.0) n = 169	6.1 (12.5) n = 100
Change from baseline, mean (SD) Change from baseline, median n[2]	-	-8.2 (13.7) -9.0 n = 130	-10.2 (14.7) -10.0 n = 117	-9.5 (17.9) -9.0 n = 51
Confusion subscale of PKU-POMS				
Mean (SD) n	4.0 (2.7) n = 170	2.4 (2.1) n = 181	2.0 (2.1) n = 169	1.8 (2.1) n = 100
Change from baseline, mean (SD) Change from baseline, median n[2]	-	-1.6 (2.5) -1.0 n = 130	-2.2 (2.7) -2.0 n = 117	-2.2 (3.1) -2.0 n = 51

[redacted]

- [1]Treatment naïve baseline in Study 165-301. Post-baseline values were mapped to the closest 3-month visit.
- [2]Change from baseline was based on subjects with available measurements at both time points. Not all patients had a baseline ADHD inattention score or POMS scores measured at the start of the study.

ADHD RS-IV IA subscale scores declined upon pegvaliase treatment indicating an improvement in inattention symptoms that was maintained with long-term treatment with pegvaliase, as shown inTable 10. The magnitude of the change from baseline in ADHD RS-IV IA scores was greater for patients considered symptomatic at baseline (score >9; n=116). The median reduction from baseline inattention score was above the CID (defined as a reduction of at least 5.2) at 12, 24 and 36 months for patients with baseline symptoms of inattention score >9, as shown in Figure 8. There was a temporal association of improvement in IA scores with reduction in blood Phe levels, as shown in Figure 9.

FIGURE 8. CHANGES IN OBSERVER RATED INATTENTION SCORE IN POOLED 165-301/302 (5TH FEBRUARY 2018 DATA CUT)

- Source: [redacted] [109]
- [1]Spencer et al, 2010 [61]

FIGURE 9. TEMPORAL ASSOCIATION OF INATTENTION SUBSCALE SCORE OF ADHD RS-IV AND BLOOD PHE LEVEL IN POOLED 165-301/302 IN PATIENTS WITH IA SCORE >9 AT BASELINE (5TH FEBRUARY 2018 DATA CUT)

- Source: [redacted]

Symptoms of mood were evaluated using the POMS tool that has been modified to be specific to PKU (PKU-POMS). The mean POMS TMD and mean PKU-POMS TMD score both decreased (suggesting improvement) over time (Table 10, Figure 10) in parallel with reductions in blood Phe levels. The PKU-POMS Confusion subscale is considered the domain most sensitive to changes in blood Phe levels based on results of Study 165-301. The mean and median change from baseline in the PKU-POMS Confusion subscale reached the CID (defined as a reduction of at least 1.33) from 12 months to 36 months after initiation of treatment (Figure 10).

FIGURE 10. CHANGE IN SELF-RATED SCALES MEASURING MOOD DURING POOLED STUDY 165-301/302 (5TH FEBRUARY 2018 DATA CUT)

- Source: [redacted][1] Quinn and Jain, 2019 [110]
- NB. The Palynziq SmPC ([109] discusses MCID for PKU-POMS Confusion subscale as 1

5.2.5.1.4 Correlation of Phe levels to inattention and confusion

Patients with the largest reductions in blood Phe during pooled study 165-301/302 experienced the greatest improvements in symptoms of inattention and confusion measured by the ADHD-RS IV IA subscale and the PKU-POMS Confusion subscale.

Significant correlations of change in ADHD RS-IV IA subscale score with changes in blood Phe (Spearman rank correlation coefficient = 0.19, $p<0.05$)[111], and of change in PKU-POMS Confusion score with change in blood Phe (Spearman rank correlation coefficient = 0.35, $p<0.01$) [110] were demonstrated during pooled study 165-301/302.

Patients in the quartile with the greatest reduction in blood Phe from baseline to last observation in Study 165-302 also experienced the greatest reduction in the ADHD RS-IV IA subscale score (Figure 11) and the PKU-POMS Confusion subscale (Figure 11) over the same period. For example, the 53 participants in the quartile with greatest blood Phe reduction (-2,143, -1,037.5) experienced the greatest reduction in ADHD RS-IV IA subscale score, a mean (SE) decrease of 8.5 (0.8) points. The reduction in ADHD RS-IV IA subscale scores was lower with successive quartiles of blood Phe reduction.

FIGURE 11. MEAN (SE) CHANGE FROM BASELINE IN INATTENTION SCORE BY CHANGE FROM BASELINE IN BLOOD PHE QUARTILES AT LAST OBSERVATION (5TH FEBRUARY 2018 DATA CUT).

- Source: [redacted] [107]

FIGURE 12. MEAN (SE) CHANGE FROM BASELINE IN PKU-POMS CONFUSION SCORE BY CHANGE FROM BASELINE IN BLOOD PHE QUARTILES AT LAST OBSERVATION (5TH FEBRUARY 2018 DATA CUT).

- Source: [redacted] [107]

5.2.5.1.5 Inattention in LNAA studies

Most of the LNAA studies indentifiied showed no outcome to address in attention whilts on LNAAs. The studies below were the only identified and are captured below, some of which had been published many years ago.

Scala 2020 [33] used the American Psychological General Well-Being Index (PGWBI), the Wisconsin Card Sorting Test (WCST), the Test of Attentional Performance (TAP), and the 9-Hole Peg Test (HPT) to assess neuropsychological function with the LNAA.

- Improvement in distress and well-being, executive functions, sustained attention span and vigilance were observed at 3 mths after starting LNAA and was maintained through the 12 mths of treatment. No difference in hand dexterity was noted, however.
- PGWBI score improved in all patients with LNAA supplementation (although not statistically significant) but was more apparent in patients with greater distress scores at BL.
- All TAP vigilance and sustained attention scores improved significantly, at 3 mths and at 12 mths.

As plasma Phe levels were above target levels in all patients during the study, in spite of the highest dose of LNAAs being used in clinical trials so far (0.8-1g/kg/day), the authors suggest that the improved psychological performance may have been due to increased brain levels of tyrosine and other LNAAs. They note that tyrosine is a precursor of dopamine and noradrenaline, which may be involved in mood, attention, motor function and anxiety, and that accumulation of Phe as seen in PKU competes with Tyr and tryptophan (a precusor of 5-HT) to cross the blood-brain barrier resulting in dopamine and 5-HT deficiency.

Pietz 1995 [37] demonstrated decreased sustained attention (Dot Pattern Exercise (DPE)) in adult PKU patients who had stopped or relaxed strict dietary treatment compared to (non-PKU) controls, particularly with regard to level of performance, stability of performance during the task, ability to sustain concentration during the task and accuracy.

- In these patients, high dose tyrosine supplementation did not have any beneficial effect on brain function.
- There were no differences on DPE for high dose tyrosine vs PLA patients.
- Nor did DPE improve with high dose tyrosine in a subgroup of 11 patients who performed below the median.

Lou 1987 [36] evaluated the effect of high dose tyrosine on continuous reaction times of PKU patients on a Phe-free diet. Reaction time and its variability ($90^{th} – 10^{th}$ percentile difference) is suggested to be indicative of brain function.

- In the double-blind crossover part of this study, a significant decrease in long reaction times (those 90^{th} percentile and above) was observed in 6 patients with tyrosine supplementation ($p<0.02$).
- Normal reaction times (those below the 90^{th} percentile) were not affected.
- Tyrosine is suggested by the authors to be facilitating attention or the initiation of motor activity.
- With a further 8 patients examined (making the total 14 patients), 12/14 had long reaction times (above the 90^{th} percentile of 14 normal controls) and in all these 12 patients tyrosine supplementation significantly reduced these reaction times ($p<0.001$).
- The authors conclude that large doses of tyrosine may be useful in PKU patients where strict dietary control is not possible.

In addition, Schindeler 2007 [38] assessed several related outcomes including overall intellectual functioning (Wechsler Abbreviated Scale of Intelligence).

- Plasma Phe levels correlated with:
    - semantic verbal fluency (VF-Category) (r=-0.525, p=0.018),
    - inattention (CPT-Errors) (r=-0.441, p=0.044),
    - spatial working memory (SWM) (r=-0.464, p=0.035),

- verbal generativity (VF-Letters) (r=-0.465, p=0.035),
- non-verbal self-monitoring (DF-reps) (r=-0.488, p=0.027).

- Patients had better performances on attention measures when subjects were on a standard medical product with or without concomitant LNAA treatment, in comparison to being off standard medical product with or without concomitant LNAA treatment (F=23.64, p=0.000).
- Higher levels of anxiety symptoms were reported when patients were on LNAA treatment (F=5.2, p=0.039).

5.2.6 Executive function

	Pegvaliase	**LNAA**
Executive function	Executive functioning tested using 3 tests in CANTAB in 9 patients in pegvaliase substudy 165-303 (subgroup of participants from study 165-302). The pooled pegvaliase group showed improvements in all 3 tests compared to pooled placebo subjects. Small sample size, though, so no statistical significance reached. Details in text section below.	SLR identified no studies reporting executive function measurements upon LNAA treatment.

5.2.6.1.1 SLR findings

The SLR identified no studies reporting executive function measurements using either of the instruments proposed in the evaluation protocol: BRIEF-V or CANTAB.

5.2.6.1.2 Executive function, pegvaliase

Executive functioning was tested in pegvaliase Sub-study 165-303, which included 9 patients who were participating in Study 165-302 Part 2. The primary endpoints for Sub-study 165-303 were 3 tests in CANTAB - a computerised, performance-based assessment of executive function: These were:

- RVP, a measure of sustained attention
- SWM, a visuospatial measure
- SST, a measure of inhibitory control and cognitive flexibility

For all these tests, a lower score indicates better performance, so a negative mean change is an improvement. Although the sample size was small and results were not all statistically significant, the pooled pegvaliase group showed improvements in all 3 tests compared to pooled placebo subjects, as shown in Table 11.

TABLE 11. RESULTS ON TESTS OF EXECUTIVE FUNCTION IN STUDY 165-302 PART 2 SUB-STUDY 165-303

	LS mean change (SE) from baseline to Week 8[1]		
	Pegvaliase (n=6)	**Placebo (n=3)**	**Difference p-value**
RVP Mean Response Latency (msec)	-34.2 (17.1)	37.9 (25.1)	-72.1 (31.7) p = 0.0719
SWM Between Errors 4-8 boxes (errors)	-4.8 (2.6)	4.2 (3.9)	-8.9 (5.1) p = 0.1377
SST Reaction Time (msec)	3.8 (13.3)	68.1 (19.6)	-64.3 (25.0) p = 0.0497

- Source: Harding et al. 2018 supplementary material [26]
- [1] Based on ANCOVA model, which includes treatment groups, blood Phe on entry to RDT and efficacy measure as factors.
- RVP: Rapid Visual Processing; SST: Stop Signal Task; SWM: Spatial Working Memory

6 Other considerations

6.1 Phenylalanine measurement

Protocol statement: *In Denmark, the blood concentration of phenylalanine is measured in blood plasma. The expert committee wants information from the applicant about reference values for measuring phenylalanine in serum, plasma and / or stabilized blood (EDTA, Citrate, Heparin, Heparin-Na-Fluoride and Citrate-Na-Fluoride) before and after treatment with pegvaliase, provided this information is available. In addition, an overview of which assays have been used to measure the above and the reason for choosing it. The expert committee points out that the blood level should be measured in the morning before any breakfast, and asks the applicant to indicate what guidelines have been set for measuring the blood level in the study population, incl. whether the blood level has been measured in capillary blood or vein blood. The purpose of this information is to be able to assess whether the biochemical data and reference values are comparable to Danish conditions, since the indication for pegvaliase is linked to the blood level of phenylalanine. The expert committee finds that biochemical data and the reference values are dependent on assay selection and the type of blood collection as well as daily variation of blood phenylalanine concentration.*

During clinical studies the recorded plasma Phe levels were taken from plasma (venous blood) however during post marketing management, experts who manage the treatment used both venous blood or capillary blood, (dried blood spot, DBS) to assess Phe levels. There have been studies focusing on this issue but the latest studies show that there is an overall agreement between plasma and DBS [112]. HypoPhe might me the only clinical situation where these assessments may vary but in this case the EMA label suggests to follow Phe lavels every two weeks and in this situation the experts suggest the use of a DBS-plasma correction factor for DBS measurement. Each laboratory should determine their own factor dependent on the filter card type, extraction and calibration protocols taking the plasma values as gold standard. Nonetheless the committee's decision of recording the method adopted is a sensible approach.

The timing of the sampling has been is an important topic, especially when plasma is used and there still can be active PAL in the blood. This can cause lower Phe levels than actual levels as a result since the enzyme will still work in withdrawn plasma. Although there has not been any evidence supporting that concern, general application is being done as morning fasting blood, before the daily injection, when active enzyme is at the lowest possible level in blood. [redacted]

6.2 Dietary instructions

The expert committee wants information about the dietary instructions that patients were subjected to in the study incl. any supplements. The reason for this is to assess whether there is agreement between the study population and Danish patients.

In the clinical study, dietary instructions were in order to maintain the diet within -/+10% of baseline unless there is hypoPhe. The protocol states: 'During this study, subjects will be instructed to maintain a stable diet.' There were no instruction in terms of which supplements should be used or any additional recommended

supplements apart from Tyrosine which is not a recommendation in the label despite being a part of the clinical study protocol [1].

Other diet related instructions in the study protocol were;

- All subjects will be administered 500 mg of tyrosine supplement 3 times per day to take with food (including medical food) throughout the study.
- Subjects will be provided with a 3-day diet diary to complete, including medical food intake, for review with the dietitian and clinical study staff.
- If a subject's natural protein intake has changed ≥10% since the time of enrollment into the study, the subject will be counseled by the dietician to return to the protein intake they had at the time of enrollment into the study.
- If protein intake from medical food (Phe-free, amino acid supplements) has changed ≥25% since the time of enrollment into the study, the subject will be counseled by the dietician to return to the medical food intake they had at the time of enrollment into the study
- Modifications to subject diet may be performed if blood Phe levels are reduced to < 30 µmol/L, the dietician will instruct the subject to increase their dietary protein by 10% of Day 1 of Part 2 unless the subject is already consuming the appropriate DRI for age. Medical food may be discontinued once the dietician determines that the essential amino acids meet the DRI for age [1].

The protocol was aiming to assess the efficacy of pegvaliase and minimize the effect of diet influencing the Phe levels. As a result, the clinical study protocol is not a true reflection of real world management. There is a European Dietary consensus report with pegvaliase treatment in development and will be submitted for publication before the end of 2021. Also, the 165-501 observational study (Europe +US) and 165-508 observational study (Germany) plans to cover efficacy, safety and dietary outcomes of the treatment.

6.3 Administration

The drug is administered by weekly injections and the treatment is expected to be lifelong. The expert committee wants a reflection on any challenges in the administration route, e.g. possible influence on adherence to treatment. In addition, a reflection on whether there are prospects for self-administration.

Administration is weekly for only induction period (first for weeks) after that it is daily. It is important to ensure the Committee is aware of the induction, titration and maintenance regimen.

Clinical studies have been conducted in patients who were willing to have the treatment so there were no patients with needle phobia, people who were concerned regarding the administration route, naturally were not included in the study. There were 24 patients who withdrew consent and left the study, but there was no information on consent being withdrawn 'due to administration issues'.

For detailed information on patient's preferences for pegvaliase treatment after being informed on treatment including the administration route; 'A benefit-risk analysis of pegvaliase for the treatment of phenylketonuria: A study of patients' preferences' by Sumitra Sri Bhashyam can provide insight on this

particular issue. In this study participants were asked to answer a free-text question about their thought process for selecting a treatment option. After responses were reviewed, motivations were coded as follows: 1) avoidance of hypersensitivity reactions; 2) improving blood Phe level; 3) concern about administration method — fear of injectables; and 4) desire to try a new treatment [101]. The study concludes that PKU patients value the clinical benefits provided by pegvaliase. In exchange for the chance to reduce blood Phe levels, participants were willing to accept the risk of hypersensitivity reactions and the delivery of pegvaliase via a subcutaneous injection [101].

6.4 Development of antibodies

The expert committee is aware that antibody development against biological drugs can occur and that this incident can manifest itself as a diminishing (of otherwise fully or partially achieved) effect. Though antibody development is best investigated in monoclonal antibody treatment, there are indications that patients can also develop antibodies to polyethylene glycol (pegvaliase), which are contained in pegvaliase [47]. It can mean a slower insertion effect and thus a longer time before obtaining a beneficial maintenance level. Against this background, the expert committee wishes to know whether a potential antibody development against pegvaliase has been investigated in the study. In addition, the average time to achieve the maintenance level of the study population.

Participants treated with pegvaliase developed antibodies against the PAL enzyme as well as against the PEG moiety conjugated to PAL. The sustained antibody response against PAL followed a predictable T cell – dependent antibody response, commonly mounted against foreign proteins, and the transient antibody response against PEG was typical of a T cell–independent type 2 antibody response. Hypersensitivity Adverse Events (HAEs) occurred more often in early treatment (< 6 months) when the immune response was still immature and was composed predominantly of peaking levels of PEG IgM, PEG IgG, and PAL IgM antibodies along with declining complement levels. The frequency of HAEs decreased in late treatment (> 6 months) as the immune response matured, the PEG antibody responses were lost, PAL IgG antibodies became most prevalent, and C3/C4 levels increased toward baseline. The antibody response in early treatment (< 6 months) was comprised predominantly of pentameric IgM (both PEG IgM and PAL IgM), which is more efficient at complement activation than the antibody response in late treatment (> 6 months), composed predominately of IgG (only PAL IgG). Furthermore, the primarily PAL IgG antibodies of the immune response in late treatment are likely less able to form complement-fixing immune complexes than the PEG antibodies of early treatment due to PAL epitope masking by the extensive PEGylation on the surface of the drug product. The observed decreases in C4 levels are consistent with immune complex-mediated activation of the complement pathway. The totality of the antibody data and the lack of IgE detection suggest that the predominant mechanism of hypersensitivity reactions is type III immune complex–mediated hypersensitivity. There were no IgE formation against both PEG and PAL during the clinical study and the assessment of baseline and on treatment antibody levels have no value on prediction of acute systemic hypersensitivty events, therefore no on treatment antibody level follow up were reccomended in the label. However real world data on on treatment antibody levels and their association of occurance and severity of HAEs will be assessed in 165-305 study on postmarketing usage on real world [1].

After assessment of the antibody levels and timing of achievement of efficacy, the label recommends that if a patient does not reach a clinically relevant blood phenylalanine reduction after 18 months of treatment, continuation should be reconsidered. The physician may decide, with the patient, to continue pegvaliase

treatment in those patients who show other beneficial effects (e.g. ability to increase protein intake from intact food or improvement of neurocognitive symptoms) [1].

6.5 Normalization of Phe levels

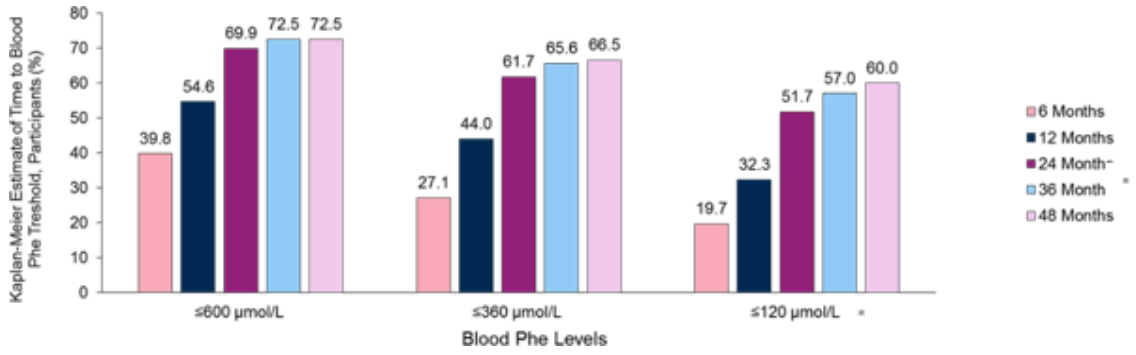
If possible, the expert committee wants information on the proportion of patients that attains phenylalanine concentrations between 120-360 micromol / l and lower to assess whether the drug has potential to completely normalize phenylalanine concentrations, cf. reference values.

Kaplan-Meier analyses of time to blood Phe thresholds (intent-to-treat population; N = 261). Percentages indicate cumulative estimate for achievement of blood Phe threshold during at least one assessment within the specified time period. Among participants who did not achieve the specified blood Phe threshold, time to reduction was censored at their last blood Phe assessment date, with the exception of those who discontinued pegvaliase and/or the study due to an adverse event, physician's decision, or withdrawal by participant, for whom the Phe reduction target was considered unachievable [1].

Blood Phe reduction to ≤360 µmol/L was achieved by 44.0% (95% CI: 38.2%, 50.4%) of participants by 12 months and 61.7% (95% CI: 54.4%, 67.1%) by 24 months, and 51.7% (95% CI, 44.8%, 58.0%) of participants achieved a blood Phe concentration of ≤120 µmol/L by 24 months [19].

The publication below by Harding et al captures this data in patients up to 48 months of treatment.

FIGURE 13. PROPORTION OF PATIENTS REACHING DIFFERENT TREATMENT TARGETS WITH LONG-TERM THERAPY (ITT, N=261, ALL DOSES)



[redacted] Sources: Harding et al. 2020 [19], [redacted]

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8 List of Appendices

Appendix A. Clinical systematic review to support the Danish HTA submission for pegvaliase (Palynziq™) as treatment for Phenylketonuria (PKU)

9 Appendix Tables

9.1 Main characteristics of included studies

9.1.1 Pegvaliase studies

TABLE 12. MAIN STUDY CHARACTERISTICS, 165-301 STUDY, PEGVALIASE

Trial name	165-301 (PRISM-1)
NCT number	NCT01819727
Objective	To study safety and tolerability of initiating self-administered pegvaliase treatment using an I/T/M regimen
Publications – title, author, journal, year	Thomas, J., et al., Pegvaliase for the treatment of phenylketonuria: Results of a long-term phase 3 clinical trial program (PRISM). Mol Genet Metab, 2018. 124(1): p. 27-38. [1] Harding, C.O., et al., Pegvaliase for the treatment of phenylketonuria: A pivotal, double-blind randomized discontinuation Phase 3 clinical trial. Mol Genet Metab, 2018. 124(1): p. 20-26. [26] Burton, B.K., et al., Long-term safety of induction, titration, and maintenance dosing of pegvaliaise treatment in adults with phenylketonuria. Journal of Inherited Metabolic Disease, 2018. 41: p. S104.[103]

	Levy H, Harding C, Longo N, Bilder D, Burton B, Zori R, et al. Phase 3 PRISM-2 long-term extension evaluating efficacy and safety of pegvaliase for treatment of adults with phenylketonuria. Journal of Inherited Metabolic Disease. 2016;39:S108.[27] Vockley J, Levy H, Amato S, Zori R, Thomas J, Burton B, et al. Phase 3 prism-2 long-term extension study evaluating efficacy and safety of pegvaliase for treatment of adults with phenylketonuria. Journal of Inborn Errors of Metabolism and Screening. 2017;5:128-9. [28]
Study type and design	Phase 3, induction, titration and maintenance dosing (I/T/M) randomised target dose trial. ('Feeder' study for Study 165-302) Patients were randomized 1:1 to titrate up to a maintenance dose of pegvaliase of 20 mg/day or 40 mg/day, which was maintained for 3 weeks before continuing into Study 165-302.
Follow-up time	4 weeks induction, ≤30 weeks titration, ≥3 weeks maintenance.

Population (inclusion and exclusion criteria)	Individuals eligible to participate in this study must meet all of the following criteria:
	• A current diagnosis of PKU with the following:
	  ○ Current blood Phe concentration >600 µmol/L at screening and
	  ○ Average blood Phe concentration of >600 µmol/L over the past 6 months (per available data)
	• Have no previous exposure to BMN 165
	• Are ≥18 and ≤70 years of age at the time of screening
	  ○ Subjects who are < 18 years of age but are already enrolled into the study may continue to participate
	• If taking sapropterin, have a treatment end date ≥14 days prior to Day 1 (ie, first dose of BMN 165)
	• Are willing and able to provide written, signed informed consent after the nature of the study has been explained and prior to any research-related procedures
	• Are willing and able to comply with all study procedures
	• Has identified a person who is ≥ 18 years of age who has the neurocognitive and linguistic capacities to comprehend and complete the POMS-Observer-rated scale
	• Has identified a competent person or persons who are ≥ 18 years of age who can observe the subject during study drug administration and for a minimum of 1 hour following administration until dose titration has completed and if needed upon return to dosing after an AE and per investigator determination.

	○ A home healthcare nurse may perform the study drug observations. • For females of childbearing potential, must have a negative pregnancy test at screening and be willing to have additional pregnancy tests during the study. (Females are considered not of childbearing potential if they have been in menopause for at least 2 years, have had a tubal ligation at least 1 year prior to screening, or have had a total hysterectomy.) • If sexually active, must be willing to use 2 acceptable methods of contraception while participating in the study and 4 weeks after the study. ○ Males post vasectomy 2 years with no known pregnancies for at least 2 years do not need to use any other forms of birth control during the study. ○ Females who have been in menopause for at least 2 years, have had a tubal ligation at least 1 year prior to screening, or have had a total hysterectomy do not need to use any other forms of contraception during the study. • Have received documented approval from a study dietician confirming that the subject is capable of maintaining their diet in accordance with dietary information presented in the protocol. • Have neurocognitive and linguistic capacities to comprehend and answer investigator's prompts for the ADHD RS-Investigator rated instrument and to complete the POMS-Subject rated scale. • If applicable, maintained stable dose of medication for attention deficit hyperactivity disorder (ADHD), depression, anxiety, or other psychiatric disorder for ≥8 weeks prior to enrollment and willing to maintain stable dose throughout study unless a change is medically indicated. • Are in generally good health, as evidenced by physical examination, clinical laboratory evaluations and ECG tests performed at screening EXCLUSION CRITERIA Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study: • Use of any investigational product or investigational medical device within 30 days prior to screening or requirement for any investigational agent prior to completion of all scheduled study assessments. • Use of any medication that is intended to treat PKU (except sapropterin), including the use of large neutral amino acids, within 2 days prior to administration of study drug Day 1 (first dose of BMN 165). Note: sapropterin treatment must be stopped ≥14 days before Day 1

<table>
<tr><td></td><td>

Use or planned use of any injectable drugs containing PEG (other than BMN 165), including medroxyprogesterone injection, within 3 months prior to screening and during study participation
Known hypersensitivity to any components of BMN 165
Current use of levodopa
A positive test for HIV antibody, hepatitis B surface antigen, or hepatitis C antibody
A history of organ transplantation or on chronic immunosuppressive therapy
A history of substance abuse (as defined by the Diagnostic and Statistical Manual of Mental Disorders [DSM IV]) in the past 12 months or current alcohol or drug abuse
Current participation in the sapropterin registry study (PKU Demographics, Outcomes and Safety [PKUDOS]). Patients may discontinue the PKUDOS registry trial to allow enrollment in this study
Pregnant or breastfeeding at screening or planning to become pregnant (self or partner) or breastfeed at any time during the study
Concurrent disease or condition that would interfere with study participation or safety (eg, history or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurological, oncologic, or psychiatric disease)
Major surgery planned during the study period
Any condition that, in the view of the investigator, places the subject at high risk of poor treatment compliance or terminating early from the study
Alanine aminotransferase (ALT) concentration ≥2 times the upper limit of normal
Creatinine >1.5 times the upper limit of normal.

</td></tr>
<tr><td>Intervention</td><td>261 patients were randomized 1:1 to titrate up to a maintenance dose of pegvaliase of 20 mg/day or 40 mg/day, which was maintained for 3 weeks before continuing into Study 165-302.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td>Subgroup</td><td>N</td><td>Age, mean (SD) range</td><td>Gender, % male</td><td>Blood Phe concentration, mean (SD)</td></tr>
<tr><td>20 mg pegvaliase</td><td>131</td><td>30.2 (8.63)</td><td>52.7</td><td>1241.0 (389.70)</td></tr>
<tr><td>40 mg pegvaliase</td><td>130</td><td>28.1 (8.77)</td><td>47.7</td><td>1224.4 (384.28)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Outcomes: Safety and tolerability during the I/T/M phase. Number of Participants with Hypersensitivity Adverse Reaction.</td></tr>
</table>

	Secondary/tertiary outcomes: Secondary endpoint include blood Phe level. Tertiary endpoints include ADHD RS total score, subscale scores of inattention and hyperactivity, POMS and PKU-POMS total scores and dietary protein intake from medical food and natural food.
Method of analysis	ITT Hypersensitivity AEs identified in two ways: Broad Algorithmic anaphylactic reaction Standardized MedDRA Queries (SMQ) Modified Hypersensitivity SMQ to include above additional preferred terms Safety was assessed through clinical laboratory tests performed monthly (Chemistry, Hematology, Urinalysis, Complements); Physical Exam every other month; Vital Signs and Injection-site Inspection weekly, Pregnancy Test, ECG and chest x-ray at baseline and at completion of the study. Patients was assessed for adverse events each time they were seen by clinical personnel
Subgroup analyses	N/A

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TABLE 13. MAIN STUDY CHARACTERISTICS, 165-302 STUDY, PEGVALIASE

Trial name	165-302 (PRISM-2)
NCT number	NCT01889862
Objective	To Evaluate the Efficacy and Safety of Subcutaneous Injections of BMN 165 Self-Administered by Adults with Phenylketonuria (PKU)
Publications – title, author, journal, year	Thomas, J., et al., Pegvaliase for the treatment of phenylketonuria: Results of a long-term phase 3 clinical trial program (PRISM). Mol Genet Metab, 2018. 124(1): p. 27-38.[1] Harding, C.O., et al., Pegvaliase for the treatment of phenylketonuria: A pivotal, double-blind randomized discontinuation Phase 3 clinical trial. Mol Genet Metab, 2018. 124(1): p. 20-26. [26]

	Burton, B.K., et al., Phase 3 PRISM Studies: Efficacy and safety of pegvaliase 60mg dose in adult patients with phenylketonuria. P-144., in Society for the Study of Inborn Errors of Metabolism (SSIEM), 57th annual symposium. 2019a: Rotterdam, NLD.[88]
Study type and design	A Four-Part, Phase 3, Randomized, Double-Blind, Placebo- Controlled, Discontinuation Trial (RDT). • PART 1: Open label, pegvaliase treatment administered at doses of 20 or 40 mg/day to determine eligible subjects for Part 2 (≥20% Phe reduction from baseline [treatment-naive] values that was used as an indication of initial pharmacological response), to be able to demonstrate efficacy within the eight-week phase of RDT in Part 2. Patients who did not meet this criterion (≥20% Phe reduction from baseline) went straight into Part 4. • PART 2: A Randomized, double-blind, placebo-controlled period of 8 weeks, evaluated pegvaliase (20 or 40 mg/day) versus matched placebo. • PART 3: PK (plasma BMN 165) and PD (plasma Phe) assessment. A Six-week, open-label, one-way crossover study involving intense sampling for use in pharmacokinetic and pharmacodynamic analyses. • PART4: A long-term, open-label extension (OLE) study to evaluate pegvaliase efficacy and safety with dose optimization allowed between 5 mg/day and 60 mg/day. The investigators, patients, and sponsor were masked to treatment assignment.
Follow-up time	At the time of the 5th February 2018 data cut, 157 patients from Study 165-301 were still ongoing in Study 165-302, all with exposure of at least 18 months and some with more than 54 months on treatment

Population (inclusion and exclusion criteria)	INCLUSION CRITERIA
	Individuals eligible to participate in this study must meet all of the following criteria:
	
	• Have completed a prior BMN 165 study (PAL-003 or 165-301) prior to screening
	• Have had a stable BMN 165 dose regimen for at least 14 days prior to screening
	• Are at least 18 y/o and no older than 70 y/o at screening
	  ○ Subjects who are < 18 y/o and are already enrolled into Study 165-301 under Amendment #1 (10JAN2014) may enroll into this study
	• Has identified a person who is > 18 y/o who has the neurocognitive and linguistic capacities to comprehend and complete the POMS-Observer rated scale
	• Has identified a competent person(s) > 18 y/o who can observe the subject during study drug administration at certain points in the study
	  ○ A home healthcare nurse may perform the study drug observations'

	• Are willing and able to provide written, signed informed consent after the nature of the study has been explained and prior to any research-related procedures; for minors, parent or guardian provides written consent and assent may be requested
	• Are willing and able to comply with all study procedures
	• For females of childbearing potential, must have a negative pregnancy test at screening and be willing to have additional pregnancy tests during the study. (Females are considered not of childbearing potential if they have been in menopause for at least 2 years, have had a tubal ligation at least 1 year prior to screening, or have had a total hysterectomy.)
	• If sexually active, must be willing to use 2 acceptable methods of contraception while participating in the study and 4 weeks after the study.
	  ○ Males post vasectomy 2 years with no known pregnancies for at least 2 years do not need to use any other forms of birth control during the study.
	  ○ Females who have been in menopause for at least 2 years, have had a tubal ligation at least 1 year prior to screening, or have had a total hysterectomy do not need to use any other forms of contraception during the study.
	• Have received documented approval from a study dietician confirming that the subject is capable of maintaining their diet in accordance with dietary information presented in the protocol.
	• Have neurocognitive and linguistic capacities to comprehend and answer investigator's prompts for the ADHD RS-Investigator rated instrument and to complete the POMS-Subject rated scale.
	• If applicable, maintained stable dose of medication for attention deficit hyperactivity disorder (ADHD), depression, anxiety, or other psychiatric disorder for ≥8 weeks prior to enrollment and willing to maintain stable dose throughout study unless a change is medically indicated.
	• Are in generally good health, as evidenced by physical examination, clinical laboratory evaluations and ECG tests performed at screening
	EXCLUSION CRITERIA
	Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:
	• Use of any investigational product or investigational medical device within 30 days prior to screening or requirement for any investigational agent prior to completion of all scheduled study assessments.

	• Use of any medication that is intended to treat PKU (except sapropterin), including the use of large neutral amino acids, within 2 days prior to administration of study drug Day 1 (first dose of BMN 165). Note: sapropterin treatment must be stopped ≥14 days before Day 1 • Use or planned use of any injectable drugs containing PEG (other than BMN 165), including medroxyprogesterone injection, within 3 months prior to screening and during study participation • Known hypersensitivity to any components of BMN 165 • Current use of levodopa • A positive test for HIV antibody, hepatitis B surface antigen, or hepatitis C antibody • A history of organ transplantation or on chronic immunosuppressive therapy • A history of substance abuse (as defined by the Diagnostic and Statistical Manual of Mental Disorders [DSM IV]) in the past 12 months or current alcohol or drug abuse • Current participation in the sapropterin registry study (PKU Demographics, Outcomes and Safety [PKUDOS]). Patients may discontinue the PKUDOS registry trial to allow enrollment in this study • Pregnant or breastfeeding at screening or planning to become pregnant (self or partner) or breastfeed at any time during the study • Concurrent disease or condition that would interfere with study participation or safety (e.g., history or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurological, oncologic, or psychiatric disease) • Major surgery planned during the study period • Any condition that, in the view of the investigator, places the subject at high risk of poor treatment compliance or terminating early from the study • Alanine aminotransferase (ALT) concentration ≥2 times the upper limit of normal • Creatinine >1.5 times the upper limit of normal.
Intervention	215 patients were enrolled. Open label pegvaliase treatment continued at maintenance dose from Study 165-301 (20 or 40 mg/day) for 3 to 13 weeks to determine eligible subjects for Part 2 (≥20% Phe reduction from treatment-naïve values, which was a signal of initial pharmacological response). In Part 2, an eight-week double-blind, placebo-controlled RDT, evaluated pegvaliase (20 or 40 mg/day) versus matched placebo. In an open label extension (OLE) part of the trial, pegvaliase ® dose optimisation was allowed between 5 mg/day and 60 mg/day.
Baseline characteristics	The study populations enrolled in the phase 3 clinical trials reflect the proposed indication for PKU patients aged 16 years and older with uncontrolled Phe (>600 µmol/L) on current management.

	<table><tr><th>N</th><th>Age, mean (SD) range</th><th>Gender, % male</th><th>Blood Phe concentration, mean (SD)</th></tr><tr><td>261</td><td>29.2 (8.8)</td><td>50.2</td><td>1232.7 (386.4)</td></tr></table>
Primary and secondary endpoints	The primary endpoint was Blood Phe level. Secondary endpoints included the amount of natural protein intake, and neurocognitive and psychosocial functioning scores based on the ADHD RS-IV IA (Attention Deficit/Hyperactivity Disorder Rating Scale version IV inattention subscale) and the Profile of Mood States (POMS) instruments
Method of analysis	Modified intent to treat (mITT) population (all subjects randomized in Part 2 with a mean blood Phe reduction of ≥20% (using the last two consecutive blood Phe assessments of Part 1) from baseline levels of Study 165-301 or the Phase 2 study in which they initiated BMN 165)
Subgroup analyses	N/A

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TABLE 14. MAIN STUDY CHARACTERISTICS, 165-205 STUDY, PEGVALIASE

Trial name	165-205
NCT number	NCT01560286
Objective	The primary objective of the study is to evaluate the effect of dosing regimens of multiple subcutaneous (SC) doses of rAvPAL-PEG to induce an early and sustained Phe reduction while decreasing the frequency and severity of hypersensitivity reactions in patients with PKU.
Publications – title, author, journal, year	Induction, titration, and maintenance dosing regimen in a phase 2 study of pegvaliase for control of blood phenylalanine in adults with phenylketonuria. Zori R, Thomas JA, Shur N, Rizzo WB, Decker C, Rosen O, et al. Molecular Genetics and Metabolism. 2018;125(3):217-27. [24]

Study type and design	24-week multicentre, Open Label, Phase 2 dose-finding study, May 2012 - Sept 2013, leading into PAL-003 OLE from Week 25
Follow-up time	48 weeks
Population (inclusion and exclusion criteria)	24 adults with PKU, naïve to PEG tx, prior SAP non-responders Inclusion Criteria: • A diagnosis of PKU • Evidence that the patient is a non-responder to sapropterin treatment • Between the ages of 16 and 70 years, inclusive • Maintained a stable diet with no significant modifications during the 4 weeks preceding the administration of study drug • In generally good health as evidenced by physical examination, clinical laboratory evaluations (hematology, chemistry, and urinalysis), and electrocardiogram (ECG) at Screening. Exclusion Criteria: • Use of any investigational product or investigational medical device within 30 days prior to Screening, or requirement for any investigational agent prior to completion of all scheduled study assessments. • Use of any medication that is intended to treat PKU, including use of large amino acids, within 2 days prior to the administration of study drug. • Use or planned use of any injectable drugs containing PEG (other than rAvPAL-PEG), within 3 months prior to Screening and during study participation. • A prior reaction that included systemic symptoms to a PEG containing product. • Concurrent disease or condition that would interfere with study participation or safety • Alanine aminotransferase (ALT) concentration > 2 times the upper limit of normal. • Creatinine > 1.5 times the upper limit of normal.
Intervention	IND: 2.5mg/wk PEG (for 4-8 weeks) TIT over at least 4 weeks: increased dose/frequency until [Phe] ≤600 µmol/L for at least 4 weeks without dose change

	MAIN: MAIN dose continued (up to a max of 75 mg/day PEG 5 days/wk (375mg/wk), or from June 2012 max frequency 7 days/wk
Baseline characteristics	Mean age 29.3 years (SD 11.4) Gender: 45.8% male Blood phe: mean 1168.8, SD 290.98
Primary and secondary endpoints	Primary endpoint: Blood Phenylalanine Concentration Secondary endpoints: • Number of Participants with Study Drug Related Adverse Events • Percentage of Participants with Positive Anti-PAL • Trough Concentration of BMN 165 • Percentage of Participants with Positive Anti-PEG IgG Antibody Positivity • Percentage of Participants with Positive PAL-IgM • Percentage of Participants with Positive Anti-PEG-IgM Antibody positivity • Percentage of Participants with Positive Neutralizing Antibodies [Nab] • Percentage of Participants with Positive Anti-PAL-IgE Antibodies Antibody • Percentage of Participants with Positive Anti-PAL-PEG IgE Antibodies
Method of analysis	The efficacy population will consist of all subjects who received any amount of study drug and have post-treatment blood Phe concentration measurements. The safety population will consist of all subjects who receive any amount of study drug throughout the study duration (secondary outcomes except [Trough Concentration of BMN 16]. The PK population will consist of all subjects who received any amount of study drug and have post-treatment plasma BMN 165 concentration measurements [Trough Concentration of BMN 165).
Subgroup analyses	N/A

TABLE 15. MAIN STUDY CHARACTERISTICS, PAL-003 STUDY, PEGVALIASE

Trial name	PAL-003
NCT number	NCT00924703
Objective	This study is an extension of previous rAvPAL-PEG studies. Administration of rAvPAL-PEG will be continued to assess whether long-term dosing of rAvPAL-PEG is safe and can maintain reduced blood Phe concentrations in PKU subjects.
Publications – title, author, journal, year	Long-term safety and efficacy of pegvaliase for the treatment of phenylketonuria in adults: combined phase 2 outcomes through PAL-003 extension study. Longo N, Zori R, Wasserstein MP, Vockley J, Burton BK, Decker C, et al. Orphanet J Rare Dis. 2018;13(1):108. [29]
Study type and design	OLE, multicentre, long-term phase 2 study
Follow-up time	Up to 264 weeks (mean treatment duration 176.5 weeks)
Population (inclusion and exclusion criteria)	68 adults with PKU who completed one of three prior dose-finding parent ph 2 studies (PAL-002, PAL-004, 165-205) and continued into EXT study.
Intervention	Continued PEG dosing regimen from the parent studies or started at a higher dose - Dose and/or frequency adjusted to achieve plasma Phe between 60 and 600 µmol/L: between 2.5 mg/week and 375 mg/week or between 0.001 mg/kg/week and 5 mg/kg/week, administered up to 7 days/week. Weight-based dosing allowed pts >75kg to receive dose >375mg/wk, but protocol amendment Oct 2014 made 375mg/wk the maximum. PRD adherence not required, but pts maintained total protein intake as per extension study entry. Protein intake could only be increased under supervision of investigator if pt had low Phe level. PEG dose could be altered or interrupted if pt had acute systemic HAE and could be withdrawn if HAE met Brown's severe criteria (hypoxia, hypotension, neurologic compromise)
Baseline characteristics	16-56 years (mean 28.3, SD 8.8) Age >= 18; 96,3% n=77 Gender, female 57.5% Mean (SD) plasma Phe 1302.4 (351.5)

	mean (SD) protein intake 69.4 (40)
Primary and secondary endpoints	[Blood Phe] Safety based on incidence of AEs and clinically significant changes in vital signs Antibody response Pharmacokinetics Safety based on clinically significant changes in laboratory test results
Method of analysis	Observational
Subgroup analyses	N/A

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TABLE 16. MAIN STUDY CHARACTERISTICS, PAL-004 STUDY, PEGVALIASE

Trial name	PAL-004
NCT number	NCT01212744
Objective	The purpose of this study is to evaluate the effect of daily administration of rAvPAL-PEG on the reduction of blood Phe concentrations in subjects with PKU.
Publications – title, author, journal, year	Yet unpublished. Results available from clinicaltrials.gov [30]
Study type and design	Open Label, multicenter, phase 2, single-arm. Interventional.
Follow-up time	Mean treatment duration 16.4 weeks
Population (inclusion and exclusion criteria)	16 PKU patients Inclusion Criteria: • Diagnosis of PKU • Evidence that the subject is a non-responder to Kuvan® treatment • Between the ages of 16 and 70 years, inclusive.

	• Maintained a stable diet with no significant modifications during the 4 weeks preceding the administration of study drug. • In generally good health Exclusion Criteria: • Prior use of rAvPAL-PEG. • Use of any investigational product or investigational medical device within 30 days prior to screening, or requirement for any investigational agent prior to completion of all scheduled study assessments. • Use of any medication that is intended to treat PKU within 14 days prior to the administration of study drug. • Use or planned use of any injectable drugs containing PEG (other than rAvPAL-PEG) within 3 months prior to screening and during study participation. • Concurrent disease or condition that would interfere with study participation or safety • Alanine aminotransferase (ALT) concentration > 2 times the upper limit of normal. • Creatinine > 1.5 times the upper limit of normal.
Intervention	PEG at various doses: 0.06, 0.1, 0.2, 0.4, 0.6, 0.8 mg/kg/day
Baseline characteristics	Age 16-70 years, mean (SD) 32.2 (8.27) Gender, 42.5% male Mean (SD) blood Phe: 1482.1 (363.46)
Primary and secondary endpoints	Primary outcome: • Blood Phenylalanine Concentration Secondary outcomes: • Study Drug Related Adverse Events • Percentage of Participants With PAL IgG Antibody Percentage of Participants • Plasma Concentrations of rAvPAL-PEG (BMN 165) • Percentage of Participants With PEG-IgG Antibody Positivity • Percentage of Participants With PAL-IgM Antibody Positivity • Percentage of Participants With PEG-IgM Antibody Positivity • Percentage of Participants With Neutralizing Antibody Positivity • Percentage of Participants With PAL-IgE Antibody Positivity • Percentage of Participants With PAL-PEG-IgE Antibody Positivity
Method of analysis	The efficacy population consisted of all subjects who received any amount of study drug and had post-treatment blood Phe concentration measurements. Safety was evaluated on the incidence of AEs and clinically significant changes in vital signs as well as clinical labs and ECG. The safety population consisted of all subjects who received any amount of study

	drug throughout the study duration and had post-treatment safety information (laboratory values, vital signs, adverse events, 12-lead electrocardiogram, chest x-ray, antibodies, and physical examinations).
Subgroup analyses	N/A

TABLE 17. MAIN STUDY CHARACTERISTICS, ZORI 2019, PEGVALIASE

Trial name	Zori 2019
NCT number	N/A
Objective	To provide insight into the relative effectiveness of treatment choices available for PKU based on long-term comparative evidence, applying best available methodologies to existing data.
Publications – title, author, journal, year	Zori, R., Ahring, K., Burton, B., Pastores, G.M., et al., *Long-term comparative effectiveness of pegvaliase versus standard of care comparators in adults with phenylketonuria.* Molecular Genetics and Metabolism, 2019. **128**(1-2): p. 92-101. [31]
Study type and design	The analyses compared pegvaliase with standard of care comparators in patients with baseline blood Phe>600 µmol/L (uncontrolled patients' analysis) using patient level data from the pegvaliase clinical trials, and matched cohorts based on baseline measures in a historical cohort derived from the PKUDOS registry.
Follow-up time	24 months
Population (inclusion and exclusion criteria)	The comparator population of sapropterin-treated patients (N=64) was selected from the PKUDOS registry. To best represent patients potentially eligible for entry into the pegvaliase clinical trials, the "sapropterin +diet" group was selected based on the following criteria: 1) intended to initiate sapropterin within 90 days of enrollment (i.e. new users of sapropterin); 2) ≥1 recorded sapropterin-naïve (i.e. pre-treatment) blood Phe value; 3) baseline blood Phe (last available measurement prior to initiating sapropterin)>600 µmol/L; 4) age≥18 years at initiation of sapropterin; and 5) available information on sapropterin dosing while enrolled.

<table>
<tr><td></td><td>The patients in this subgroup, regardless of sapropterin dose (range 5–20 mg/kg/day), were considered to be actively managed with diet in conjunction with sapropterin.

The comparator population of patients on a Phe-restricted diet alone (N=125) was also derived from the PKUDOS registry. Selection criteria for the “diet alone” group were
1) had previously received sapropterin before enrolling in PKUDOS or discontinued sapropterin while in the registry,
2) baseline blood Phe>600 µmol/L, and
3) ≥18 years of age at the time of baseline Phe measurement.
The patients in this subgroup were considered to only be potentially managed with diet alone.

The pegvaliase-treated patient group was selected from patients in the pegvaliase phase 2 165–205 trial and the phase 3 (165-301 and 165-302) trials treated with an induction, titration, maintenance (I/T/M) schedule. Both studies included adults with PKU with baseline blood Phe ≥600 µmol/L. The I/T/M schedule was followed by an active, open-label extension phase. Propensity score matching (based on baseline age, gender, and baseline blood Phe) was used to provide post-hoc comparable groups to explore the effectiveness of alternative treatment regimens in PKU. Two different cohorts were derived by propensity score matching, one with N=64 for the comparison with the ”sapropterin+diet” group, and one with N=125 for the comparison with the ”diet alone” group.</td></tr>
<tr><td>Intervention</td><td>Pegvaliase</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Subgroup</th><th>N</th><th>Age, mean (SD), range</th><th>Gender, % male</th><th>Blood Phe concentration, mean (SD), range</th></tr>
<tr><td>Sapropterin</td><td>64</td><td>33 (10), 18-55</td><td>42.2%</td><td>1176 (383), range 624-2258</td></tr>
<tr><td>Pegvaliase (matched vs sapropterin)</td><td>64</td><td>32 (9), 18-54</td><td>40.6%</td><td>1172 (329), range 601-1942</td></tr>
<tr><td>Phe-restricted diet</td><td>125</td><td>31 (11), 18-68</td><td>55.2%</td><td>1089 (302), range 605-1872</td></tr>
<tr><td>Pegvaliase (matched vs diet)</td><td>125</td><td>30 (8), 18-56</td><td>55.2%</td><td>1085 (294), range 601-1764</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Outcome measures included
• Blood Phe concentration at 1 and 2 years follow-up
• Change in blood Phe from baseline
• Percent of patients achieving blood Phe ≤600 µmol/L, ≤360 µmol/L, or ≤120 µmol/L (normative Phe concentration);
• Percent of patients achieving a ≥20%, ≥30% or ≥50% reduction from baseline Phe</td></tr>
</table>

	• Natural intact protein intake in g/day
Method of analysis	• Baseline blood Phe concentration was defined as the last available measurement prior to the first administration of pegvaliase in the 165–205 or PRISM-1 trials for the pegvaliase group. In the "sapropterin + diet" group, baseline blood Phe was the last available measurement prior to initiating sapropterin. For the 'diet alone' group, baseline blood Phe was defined as the measurement closest to the enrollment date within 90 days in case sapropterin was discontinued before enrollment. • If sapropterin was discontinued after enrollment, it was the value closest to the discontinuation date within 90 days of discontinuation. This implies that if patients in the "diet alone" group took sapropterin before enrollment in PKUDOS, assessments after enrollment were used for analysis; if patients took sapropterin after enrollment, assessments after the last sapropterin dose were used for analysis. • For the evaluation of blood Phe concentrations at 1-year and 2-year time points, only patients who had a Phe assessment recorded at 365 ± 45 days follow-up (for the 1-year analysis), or at 730 ± 90 days follow-up (for the 2-year analysis) were included. If a patient had more than one assessment during these time periods, the median of those assessments was used. • Natural intact protein intake was calculated as the total protein intake minus medical food protein intake for the "sapropterin + diet" and "diet alone" groups, and as average dietary protein intake from intact food for the pegvaliase group. • Safety data (adverse events [AEs], and study-drug related AEs and serious adverse events [SAEs]), based on the first 2 years after the first dose or enrollment, were compared for the comparator groups used in the uncontrolled patients primary analyses, i.e. pegvaliase versus "sapropterin + diet" and sapropterin versus "diet alone".
Subgroup analyses	N/A

9.1.2 LNAA studies

TABLE 18. MAIN STUDY CHARACTERISTICS, BURLINA 2019, LNAA

Trial name	Burlina 2019
NCT number	N/A
Objective	To determine the Phe, tyrosine (Tyr), and Phe/Tyr ratio in a cohort of sub-optimally controlled adult patients with classical PKU treated with a new LNAA formulation.
Publications – title, author, journal, year	Burlina AP, Cazzorla C, Massa P, Polo G, Loro C, Gueraldi D, et al. Large neutral amino acid therapy increases tyrosine levels in adult patients with phenylketonuria: A long-term study. Nutrients. 2019;11(10).[32]
Study type and design	Open label, single-arm
Follow-up time	12 months
Population (inclusion and exclusion criteria)	12 adults with PKU
Intervention	LNAA (NeutrAfenil Micro R) 3 times/day, 1g/kg body weight + LPD, for 12 mths
Baseline characteristics	Mean age 29.6 years (range 19-38) Male 58% (7/12) Mean blood [Phe] 752 µmol/L (SD 143), range 628-1033
Primary and secondary endpoints	Phe/Tyr ratio
Method of analysis	Observational, all patients
Subgroup analyses	N/A

TABLE 19. MAIN STUDY CHARACTERISTICS, SCALA 2020, LNAA

Trial name	Scala 2020
NCT number	N/A
Objective	To explore the effect of LNAAs supplementation on improving cognitive functions and well-being in patients with PKU with poor metabolic control.
Publications – title, author, journal, year	Scala I, Riccio MP, Marino M, Bravaccio C, Parenti G, Strisciuglio P. Large neutral amino acids (Lnaas) supplementation improves neuropsychological performances in adult patients with phenylketonuria. Nutrients. 2020;12(4). [33]
Study type and design	Observational single arm
Follow-up time	12 months
Population (inclusion and exclusion criteria)	10 adults with PKU
Intervention	LNAA (PheLNAA) 0.8-1g/kg/day for 12 months
Baseline characteristics	Mean age 23.6 years (range 4.5) Male 40% (4/10) Mean blood [Phe] 830.8 (SD 77.7) range 665-937 µmol/L
Primary and secondary endpoints	Neuropsychological assessment by using the American Psychological General Well-Being Index, the Wisconsin Card Sorting Test, the Test of Attentional Performance (TAP), and the 9-Hole Peg Test.
Method of analysis	All patients, observational.
Subgroup analyses	N/A

TABLE 20. MAIN STUDY CHARACTERISTICS, MATALON 2006, LNAA

Trial name	Matalon 2006
NCT number	NA
Objective	To study the effect on influx of phenylalanine (Phe) to the brain with a new formulation of LNAAs (NeoPhe).
Publications – title, author, journal, year	Large neutral amino acids in the treatment of phenylketonuria (PKU). Matalon R, Michals-Matalon K, Bhatia G, Grechanina E, Novikov P, McDonald JD, et al. Journal of Inherited Metabolic Disease. 2006;29(6):732-8. [34]
Study type and design	Open label single-arm (3 centres; RUS, UKR, USA)
Follow-up time	1 week
Population (inclusion and exclusion criteria)	11 PKU pts, mean age 16+ years
Intervention	LNAA (NeoPhe) 0.5g/kg/day (n=8) or 1g/kg/day (n=3)
Baseline characteristics	Mean age 20.5 years (n=8), 16.5 years (n=3) 36% male (4/11) Mean blood [Phe] (µmol/L): 957.4 (n=8); 1230 (n=3)
Primary and secondary endpoints	Change in blood phenylalanine concentration
Method of analysis	NA
Subgroup analyses	NA

TABLE 21. MAIN STUDY CHARACTERISTICS, MATALON 2007, LNAA

Trial name	Matalon 2007
NCT number	NA
Objective	Proof of principle study on the role of orally administered LNAA in lowering blood Phenylalanine concentrations in patients with PKU.
Publications – title, author, journal, year	Double blind placebo control trial of large neutral amino acids in treatment of PKU: effect on blood phenylalanine. Matalon R, Michals-Matalon K, Bhatia G, Burlina AB, Burlina AP, Braga C, et al. Journal of inherited metabolic disease. 2007;30(2):153-8. [35]
Study type and design	Double-blinded, randomised crossover, placebo-controlled, 1- week washout between treatments (6 centres: BRA, ITA, RUS, UKR, USA)
Follow-up time	1 week
Population (inclusion and exclusion criteria)	20 PKU patients (19 classical PKU)
Intervention	Intervention: LNAA (NeoPhe) 0.5g/kg/day (containing menthol to mask taste), in 3 divided doses with meals plus continue usual diet, for 1 week Comparator: PLA tablets (containing menthol) plus continue usual diet, for 1 week
Baseline characteristics	Age range 11-32 years 40 % males (8/20) Mean blood [Phe] (µmol/L): 932.9
Primary and secondary endpoints	Change in blood phenylalanine concentration
Method of analysis	N/A

Subgroup analyses	N/A

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TABLE22. MAIN STUDY CHARACTERISTICS, LOU 1987, LNAA

Trial name	Lou 1987
NCT number	N/A
Objective	Evaluate the effect of high dose tyrosine on continuous reaction times of PKU pts on a free diet.
Publications – title, author, journal, year	Lou HC, Lykkelund C, Gerdes AM, Udesen H, Bruhn P. Increased vigilance and dopamine synthesis by large doses of tyrosine or phenylalanine restriction in phenylketonuria. Acta paediatrica Scandinavica. 1987;76(4):560-5. [36]
Study type and design	Four different examinations, including two DB, randomised crossover
Follow-up time	N/A
Population (inclusion and exclusion criteria)	14 pts with PKU
Intervention	Free diet plus Tyr 160mg/kg or identical PLA for 3 days (6 pts) Free diet plus Tyr 160 mg/kg or free diet for 3 days (8 pts)
Baseline characteristics	Mean age 18.1 (SD 2.9) range 15-24 years Male sex 64.3% (9/14) Baseline blood Phe not reported
Primary and secondary endpoints	• continuous visual reaction times (msec) neurotransmitter synthesis, as judged by cerebrospinal fluid (CSF) homovanillic acid (HVA) and 5-hydroxyindole acetic acid (5-HIAA) levels
Method of analysis	N/A
Subgroup analyses	N/A

TABLE 23. MAIN STUDY CHARACTERISTICS, PIETZ 1995, LNAA

Trial name	Pietz 1995
NCT number	N/A
Objective	To characterize abnormalities of brain function in patients with phenylketonuria (PKU) who had relaxed or stopped the dietary regimen and to test whether oral high-dose tyrosine (Tyr) supplementation has a beneficial effect.
Publications – title, author, journal, year	Pietz J, Landwehr R, Kutscha A, Schmidt H, de Sonneville L, Trefz FK. Effect of high-dose tyrosine supplementation on brain function in adults with phenylketonuria. The Journal of pediatrics. 1995;127(6):936-43. [37]
Study type and design	Double-blind, placebo-controlled study, crossover treatment groups
Follow-up time	4 weeks
Population (inclusion and exclusion criteria)	24 early-treated PKU pts, age range 16-25 years (mean 20.8) who had relaxed or stopped strict diet for ≥ 1 year 24 health controls 15-25 years
Intervention	Oral tyrosine 100mg/kg bw/day (i.e. 25mg/kg bw 4x daily) or placebo for 4 weeks + relaxed diet or no strict diet
Baseline characteristics	Mean age 20.8 (range 16-25) Male 45.8% (11/24) Mean blood [Phe], µmol/L: 1273 (SD 280), range 847-1798
Primary and secondary endpoints	IQ (WAIS-R, WISC-R) Simple motor RT task, RT (msec) dominant (FMSE) Simple motor RT task, RT (msec) nondominant (FMSE) Sustained-attention task, series time (DPE)
Method of analysis	N/A
Subgroup analyses	N/A

TABLE 24. MAIN STUDY CHARACTERISTICS, SCHINDELER 2007, LNAA

Trial name	Schindeler 2007
NCT number	N/A
Objective	To determine the effects of large neutral amino acid (LNAA) supplements on brain and plasma phenylalanine (Phe) levels and other metabolites in early treated subjects with classical phenylketonuria (PKU), and to investigate the relationship between these metabolites and neuropsychological performance.
Publications – title, author, journal, year	Schindeler S, Ghosh-Jerath S, Thompson S, Rocca A, Joy P, Kemp A, et al. The effects of large neutral amino acid supplements in PKU: An MRS and neuropsychological study. Molecular Genetics and Metabolism. 2007;91(1):48-54. [38]
Study type and design	Double blind randomised crossover
Follow-up time	20 weeks
Population (inclusion and exclusion criteria)	16 classical PKU patients
Intervention	4 Phases, each of 14 days with 4 wk washout between phases: Phase 1: Usual medical product, usual PRD, LNAA tabs, 3 equal doses/day Phase 2: Usual medical product, usual PRD, PLA tabs, 3 equal doses/day Phase 3: No medical product, usual PRD, LNAA tabs, 3 equal doses/day Phase 4: No medical product, took usual PRD, PLA tabs, 3 equal doses/day
Baseline characteristics	Median age 24 years 9 mths (range 11 - 45 years) Male 44% (7/16) Baseline blood Phe concentration (µmol/L) not reported
Primary and secondary endpoints	Brain Phe and other metabolites were measured by proton magnetic resonance spectroscopy (MRS), and plasma amino acids quantified. A detailed neuropsychological assessment was performed on the same day as the MRS and plasma collection.

Method of analysis	N/A
Subgroup analyses	N/A

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TABLE 25. MAIN STUDY CHARACTERISTICS, YANO 2013, LNAA

Trial name	Yano 2013
NCT number	N/A
Objective	To determine whether levels of melatonin in blood and urine can serve as a peripheral biomarker to reflect brain serotonin synthesis in individuals with phenylketonuria (PKU).
Publications – title, author, journal, year	Yano S, Moseley K, Azen C. Large neutral amino acid supplementation increases melatonin synthesis in phenylketonuria: A new biomarker. Journal of Pediatrics. 2013;162(5):999-1003. [39]
Study type and design	Randomized double-blind placebo controlled crossover study consisting of three 3-week phases: phase 1 (washout), phase 2 (supplementation of large neutral amino acid [LNAA] tablets or placebo), and phase 3 (alternate supplementation).
Follow-up time	3x3 weeks
Population (inclusion and exclusion criteria)	10 adults with classical PKU
Intervention	Three 3-wk phases: phase 1 (washout), phase 2 (supplementation of LNAA (PheBloc) tablets), and phase 3 (crossover to PLA supplementation) Three 3-wk phases: phase 1 (washout), phase 2 (supplementation with PLA tabs), and phase 3 (crossover to LNAA supplementation)
Baseline characteristics	Mean age 29.1 years (SD 9), range 20-49 Male 67% (6 of those completing)

	Baseline blood Phe concentrations not reported
Primary and secondary endpoints	Blood melatonin, urine 6-sulfatoxymelatonin and dopamine in urine after each phase for subjects with PKU and once in 10 controls.
Method of analysis	N/A
Subgroup analyses	N/A

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TABLE 26. MAIN STUDY CHARACTERISTICS, YANO 2014, LNAA

Trial name	Yano 2014
NCT number	N/A
Objective	To determine whether additional supplementation of tryptophan (Trp) and tyrosine (Tyr) improve serotonin and dopamine metabolism in individuals with phenylketonuria treated with large neutral amino acid (LNAA) tablets.
Publications – title, author, journal, year	Yano S, Moseley K, Azen C. Melatonin and dopamine as biomarkers to optimize treatment in phenylketonuria: effects of tryptophan and tyrosine supplementation. Journal of pediatrics. 2014;165(1):184-9.e1. [40]
Study type and design	Double-blind, placebo-controlled cross-over study consisting of three 3-week phases: washout, treatment with LNAA tablets plus supplementation with either Trp and Tyr tablets or placebo, and LNAA tablets plus the alternate supplementation.
Follow-up time	9 weeks
Population (inclusion and exclusion criteria)	10 adults with PKU
Intervention	Three 3-wk phases: washout, treatment with LNAA tablets plus supplementation with either Tryptophan and Tyrosine tablets or PLA, and LNAA tablets plus the alternate supplementation.

Baseline characteristics	Mean age 29.4 years (SD 9.4), range 21-51 Male 80% (8/10) Mean blood [Phe], 1388.66µmol/L (SD 362.24)
Primary and secondary endpoints	Serum melatonin and urine 6-sulfatoxymelatonin and dopamine levels Plasma Trp:LNAA ratio Urine 6-sulfatoxymelatonin and plasma phenylalanine level
Method of analysis	All patients
Subgroup analyses	N/A

9.2 Results per study - Tables

9.2.1 Pegvaliase studies

9.2.1.1 Study 165-301 (PRISM-1)

- 261 adults with PKU and blood Phe ≥600 µmol/L for 6 mths prior to enrolment and no previous exposure to PEG
- Randomised to receive a target maintenance dose of pegvaliase of 20 mg/day or 40 mg/day after induction with a low dose and slow upwards titration.
- Titration duration ≤30 weeks.
- Blood Phe and protein intake evalauations were performed
- Feeder study to 165-302.
- The maintenance dose achieved in 165-301 was maintained for 3 weeks before continuing into Study 165-302.

TABLE 27. RESULTS OF STUDY: 165-301, PEGVALIASE

Trial name:	**165-301 (PRISM-1)**						
NCT number:	**NCT01819727**						
					Estimated absolute difference in effect		
Outcome	**Sample**	**Timepoint**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**
Discontinuation rate Source: [1]	Pegvaliase (pooled)	Longest follow-up	261	All: 20.7% (54/261) Due to AE: 11.1% (29/261)	N/A	N/A	N/A
Proportion of patients achieving blood Phe <600 Source: [1]	Pegvaliase, 20 mg	36 w	131	45 (34.4%)	N/A	N/A	N/A
	Pegvaliase, 40 mg	36 w	130	61 (49.6%)			
Mean blood Phe concentration Source: [1]	Pegvaliase, 20 mg	BL	131	1241 (1174 – 1308)	40 mg vs 20 mg: -112.8	-212.5, -13.1	p=0.0269
		36 w	131	868 (782 – 954)			

	Pegvaliase, 40 mg	BL	130	1224 (1158 – 1290)			
		36 w	130	624 (533 – 716)			
Mean natural protein intake* Source: [1]	Pegvaliase, pooled	BL	250	38.5 (33.2 – 43.8)	N/A	N/A	N/A
	Pegvaliase, pooled	12 m	160	47.4 (41.9 – 52.9)			
	Pegvaliase, pooled	24 m	49	59.0 (49.9 – 68.1)			

Outcomes not reported in study:

- QoL
- Proportion of patients achieving daily protein intake target levels
- Neuropsychiatric outcomes
- Executive function outcomes

Results of the long term follow up reported in Burton 2018:

- 285 subjects received pegvaliase treatment for up to 7.6 years, with a mean (SD) of 24.40 (15.46) months and total exposure of 579.6 person-years.
- Mean (SD) blood Phe decreased from pre-treatment baseline level of 1227 (379) mumol/L to 294 (398) mumol/L at month 24.
- Most adverse events (AEs) were mild (74.8%) or moderate (24.5%) in severity and resolved without dose interruption. The most common AEs were arthralgia (73%), injection-site reactions (65%), headache (51%), and injection-site erythema (50%). Exposure-adjusted rate of AEs (52.4 vs 19.0 event rate per person-year), serious AEs (0.24 vs 0.10), and hyper-sensitivity AEs (15.1 vs 4.0) were higher in the induction/titration period than in the maintenance period, respectively. Thirteen subjects had 21 externally adjudicated acute systemic hypersensitivity events: eight subjects continued pegvaliase after the event, four of which had subsequent events; 6 of the 8 subjects have remained on therapy. Drug-specific IgE was not detected near the time of the events and all 21 events resolved without sequelae. There is no evidence of immune complex related end organ damage.

- * Calculated from difference between reported total protein intake and MF protein intake

9.2.1.2 Study 165-302 (PRISM-2)

- Placebo-controlled double-blind RDT in patients with blood Phe levels already reduced by at least 20% on a maintenance dose of pegvaliase.
- 4 parts:
  - Part 1: Open label pegvaliase treatment continued at maintenance dose from Study 165-301 (20 or 40 mg/day) for 3 to 13 weeks to determine eligible subjects for Part 2 (≥20% Phe reduction from treatment-naïve values, which was a signal of initial pharmacological response).
  - Part 2: Eight-week double-blind, placebo-controlled RDT to evaluate pegvaliase (20 or 40 mg/day) versus matched placebo on efficacy and safety. Including patients who had shown a response to pegvaliase in Part 1 allowed for the effects of withdrawal to be more readily observed with a short duration of exposure to placebo.
  - Part 3: Six-week, open-label, one-way crossover study involving intense sampling for use in PK and pharmacodynamic (PD) analyses (results not discussed here).
  - Part 4: Long term, open label extension (OLE) trial to evaluate pegvaliase efficacy and safety with dose 116ptimization allowed between 5 mg/day and 60 mg/day.
- Results
- Executive functioning was tested in Sub-study 165-303, which included 9 patients who were participating in Study 165-302 Part 2.
  - 3 CANTAB tests were used:
  - RVP, a measure of sustained attention
  - SWM, a visuospatial measure
  - SST, a measure of inhibitory control and cognitive flexibility
- Discontinuation review (Feb 2018 data cut):
  - Considering Study 165-301 and 165-302 together, the disposition of the 261 patients is as follows:
    - Continuing study drug: 157; Completed study drug in 165-301: 4; Discontinued study drug early: 100.
    - The reasons for early discontinuation were: AEs (n = 40); Lost to follow-up (n = 9); Withdrawal by participant (n = 29); Physician decision (n = 10); Protocol deviation (n = 3); Pregnancy (n=2); Other (n=7)
  - Part 1:
    - Patients not meeting criteria for Part 2 or unable to complete Part 2 due to AEs were discontinued and transitioned to Part 4 with dose as tolerated (n=57)
    - 12 patients discontinued the study
  - Part 2:
    - 14 patients who did not have a blood Phe assessment within the window for Week 8 (Day 43 to 56) were excluded from analysis.

- 4 patients on pegvaliase did not complete because of AEs (1 discontinued and 3 transitioned to the OLE)
- 1 patient on placebo did not complete due to an AE and transitioned to the OLE.

TABLE 28. RESULTS OF STUDY: 165-302, PEGVALIASE

Trial name:	**165-302 (PRISM-2)**						
NCT number:	**NCT01889862**						
					Change from baseline		
Outcome	**Sample**	**Timepoint**	**N**	**Result (CI)**	**Difference**	**SD**	**P value**
Discontinuation rate Source: [1]	All patients (165-301 & 165-302)	Longest follow-up	261	All: 33.7% (88/261) Due to AE: 15.3% (40/261)	N/A	N/A	N/A
Proportion of patients achieving blood Phe <600 Source: [1] [19]	Pegvaliase	6 m	206	38.3% (32.6, 44.6)	N/A	N/A	N/A
		3 y	48	72.5% (NR)			
		4 y	48	72.5% (NR)			
Mean blood Phe concentration Source: [1] [19]	Pegvaliase	BL	261	1233 (SD 386)	N/A	N/A	N/A
		6 m	206	782 (SD 527)	-452	531	NR
		3y	48	341 (SD 465)	-956	536	NR
Mean natural protein intake Source: [1, 94]	Pegvaliase	BL	250	38.5 (SD 27.7)	N/A	N/A	N/A
		12 m	160	47.4 (SD 28.6)	+8.7	25.4	NR
		3 y	46	72.2 (SD 27.4)	+27.3	33.5	NR
Total dietary protein intake [Thomas supplementary tables]	Pegvaliase	BL	250	64.8 (32.2)	N/A	N/A	N/A
		12 m	160	71.6 (24.3)	+6,8		
		24 m	49	77.4 (20.8)	+5,8		
Neuropsychatric symptoms: ADHD-IV IA Source: [1, 22]	Pegvaliase	BL	253	9.8 (SD 6.1)	N/A	N/A	N/A
		12 m	178	5.0 (SD 4.9)	-4.7	5.6	NR

		3 y	97	3.7 (SD 5.0)	-6.7	6.4	NR
Neuropsychatric symptoms: POMS Source: [1, 22]	Pegvaliase	BL	170	35.5 (31.9)	N/A	N/A	N/A
		12 m	181	21.3 (31.2)	-16.9	32.6	NR
		3 y	100	15.9 (31.5)	-20.4	43.6	NR
Neuropsychatric symptoms: PKU-POMS Source: [1, 22]	Pegvaliase	BL	170	15.9 (13.3)	N/A	N/A	N/A
		12 m	181	8.5 (12.5)	-8.2	13.7	NR
		3 y	100	6.6 (12.0)	-9.5	17.9	NR
					Estimated absolute difference in effect		
Executive function: CANTAB, Rapid visual processing (Change from BL to w8) Source: [26]	Placebo	8 w	3	37.9 (SE 25.1)	-72.1	SE 31.7	p=0.0719
	Pegvaliase	8 w	6	-34.2 (SE 17.1)			
Executive function: CANTAB, Spatial Working Memory (Change from BL to w8) Source: [26]	Placebo	8 w	3	4.2 (SE 3.9)	-8.9	SE 5.1	p=0.1377
	Pegvaliase	8 w	6	-4.8 (SE 2.6)			
Executive function: CANTAB, Rapid visual processing (Change from BL to w8) Source: [26]	Placebo	8 w	3	68.1 (SE 19.6)	-64.3	SE 25.0	p=0.0497
	Pegvaliase	8 w	6	3.8 (SE 13.3)			
Outcomes not reported in study: • QoL • Proportion of patients achieving daily protein intake target levels							

Results from the RDT (165-302 part 2) reported in the Harding 2018 [26], demonstrating efficacy of pegvaliase versus placebo:

- The pooled pegvaliase group enrolled 66 participants and each placebo group enrolled 14 participants.

- The primary endpoint of change in blood Phe concentration from RDT entry to RDT Week 8 was met with clinically meaningful and statistically significant differences between the pegvaliase and placebo groups. Mean (SD) blood Phe at the beginning of the RDT when all participants were receiving pegvaliase was 563.9 µM (504.6) in the group assigned to the 20 mg/day placebo group (n=14), 508.2 µM (363.7) in those assigned to the 40 mg/day placebo group (n=14), and 503.9 µM (520.3) in those assigned to continue pegvaliase treatment (n=58).
- At Week 8 of the RDT, the least squares mean change (95% confidence interval) in blood Phe was 949.8 µM (760.4 to 1139.1) for the 20 mg/day placebo group and 664.8 µM (465.5 to 864.1) for the 40 mg/day placebo group in comparison to 26.5 µM (−68.3 to 121.3) for the pooled (20 mg/day and 40 mg/day) pegvaliase group (P < 0.0001 for pooled pegvaliase group vs each placebo group).
- Adverse events (AEs) were usually lower in the pooled placebo group when compared to the pooled pegvaliase group. The most common AEs for the pooled pegvaliase and pooled placebo groups were arthralgia (13.6% and 10.3%, respectively), headache (12.1% and 24.1%), anxiety (10.6% and 6.9%), fatigue (10.6% and 10.3%), and upper respiratory tract infection (1.5% and 17.2%).

Results reported in Burton 2019:

- As of Feb 5, 2018, the stable 60 mg/d cohort (n = 48) had a mean+/-SD 56.8+/-40.5 wks of dosing at 60 mg/d.
- On the 40 mg/d dose, mean blood Phe for this group was 1083.7 +/-370.53 mumol/L.
- After titration to 60 mg/d, mean Phe levels were reduced to 611.1+/-432.68 mumol/L at 16 wks and 504.9 +/-501.91 mumol/L at 32 wks and 77.1% of subjects achieved a Phe < 600 umol/L by 15 wks (range 1-32 wks) post-dose escalation.
- Among subjects who received pegvaliase 60 mg using the induction-titration-maintenance regimen (n = 98, 91.5 person-years of exposure), both incidence of adverse events (AEs) and exposure-adjusted AE rates (% of subjects) were comparable or lower after receiving a 60 mg/d (65.3%) than with lower doses - < 20 mg/d (99.3%); >=20-< 40 mg/d (86.8%); >=40-60 mg/d (96.9%).
- Exposure-adjusted event rates for serious AEs, hypersensitivity AEs (HAEs), injection-site reactions, and arthralgia were lower in subjects using 60 mg/d prior to the event than when receiving lower doses. Only 1 subject had 2 externally-adjudicated acute systemic HAEs on pegvaliase doses of 60 mg/d (2 additional events on lower doses) and discontinued treatment.

9.2.1.3 Study 165-205

- Open-label, dose-finding study, with long-term follow up
- Pegvaliase was administered using an induction, titration, and maintenance dosing regimen in 24 adults with PKU naïve to pegvaliase treatment
- Doses were gradually increased until blood Phe≤600 µmol/L was achieved and maintained for at least 4 weeks (maintenance dose achieved)
- Analyses were performed for participants who achieved (Group A, n=11) and did not achieve (Group B, n=13) maintenance dose during the first 24 weeks of study treatment.
- Followed up until 48 weeks, and from week 25 in OLE study PAL-003
- A total of 24 participants enrolled and completed the parent study, 165–205, including 2 participants who discontinued pegvaliase early but remained in the study for assessments.
- Discontinuation review:
    - The one Group B participant in the extension that did not achieve Phe≤600 µmol/L had discontinued pegvaliase treatment early due to recurrent acute systemic hypersensitivity events consistent with clinical NIAID/FAAN anaphylaxis criteria

TABLE 29. RESULTS OF STUDY: 165-205, PEGVALIASE

Trial name:	**165-205**						
NCT number:	**NCT01560286**						
					Change from baseline		
Outcome	**Sample**	**Timepoint**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**
Discontinuation rate Source: [24]	Pegvaliase, group A*	Longest follow-up	11	0 (0%)	N/A	N/A	N/A
	Pegvaliase, group B*	Longest follow-up	13	2 (15.4%)			
Proportion of patients achieving blood Phe <600 Source: [24]	Pegvaliase, group A*	24 w	11	11 (100%)	N/A	N/A	N/A
		48 w	10	10 (100%)	N/A	N/A	N/A
	Pegvaliase, group B*	24 w	13	3 (23%)	N/A	N/A	N/A
		48 w	10	9 (90%)	N/A	N/A	N/A
Mean blood Phe concentration	Pegvaliase group A*	BL	11	1135 (SD 348)	N/A	N/A	N/A
		48 w	11	236 (SD 308)	-899	NR	NR

Source: [24]	Pegvaliase group B*	BL	13	1198 (243)	N/A	N/A	N/A
		48 w	10	557 (SD 389)	-641	NR	NR
Outcomes not reported in study: • QoL • Proportion of patients achieving daily protein intake target levels • Neuropsychiatric outcomes • Executive function outcomes							

- *Group A: patients achieving maintenance dose within 24 weeks. Group B: patients achieving maintenance dose beyond 24 weeks.

9.2.1.122 Study PAL-

- OLE of phase 2 studies, including 165-205 and PAL-004
- 68 adults with PKU
- Participants continued the dose of pegvaliase from the parent study, with dose adjustments to achieve a plasma Phe concentration between 60 and 600 µmol/L

TABLE 30. RESULTS OF STUDY: PAL-003, PEGVALIASE

Trial name:	**PAL-003**						
NCT number:	**NCT00924703**						
					Change from baseline		
Outcome	**Sample**	**Timepoint**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**
Discontinuation rate Source: [29]	Pegvaliase	Longest follow-up	68	5.9% (4)	N/A	N/A	N/A
Proportion of patients achieving blood Phe <600 Source: [29]	Pegvaliase	48 w	61	57.4% (35/61)	N/A	N/A	N/A
		144 w	45	64.4% (29/45)	N/A	N/A	N/A
Mean blood Phe concentration Source: [29]	Pegvaliase	BL	68	1302 (SD 352)	N/A	N/A	N/A
		48 w	61	542 (SD 516)	-796	562	NR
		144 w	45	476 (SD 514)	-919	596	NR
Outcomes not reported in study: • QoL • Mean natural protein intake • Proportion of patients achieving daily protein intake target levels • Neuropsychiatric outcomes • Executive function outcomes							

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9.2.1.123 Study PAL-

- Phase 2, open-label dose-finding study
- 16 adults with a diagnosis of PKU with a blood Phe concentration of ≥600 µmol/L at the screening visit and an average blood Pheconcentration of ≥600 µmol/L for 6 months prior to enrollment.
- Participants (N= 16) in PAL-004 received pegvaliase as a subcutaneous injection in doses ranging from 0.001 to 0.4 mg/kg daily for 5 days per week for 13 weeks, followed by 3 additional weeks of follow-up assessments.
- 15 patients completed the study; 1 participant withdrew consent after experiencing moderate angioedema that was considered a severe AE.

TABLE 31. RESULTS OF STUDY: PAL-004, PEGVALIASE

Trial name:	**PAL-004**						
NCT number:	**NCT01212744**						
					Change from baseline		
Outcome	**Sample**	**Timepoint**	**N**	**Result (SD)**	**Difference**	**SD**	**P value**
Discontinuation rate Source:[113]	Pegvaliase	13 w	16	6.3% (1/16)	N/A	N/A	N/A
Proportion of patients achieving blood Phe <600 Source: [113]	Pegvaliase	13 w	16	25.0% (4/16)	N/A	N/A	N/A
Mean blood Phe concentration Source: [113]	Pegvaliase	BL	16	1482.1 (363.5)	N/A	N/A	N/A
		13 w	16	1045.31 (663.94)	-410.8	653.7	NR
Outcomes not reported in study: • QoL • Mean natural protein intake • Proportion of patients achieving daily protein intake target levels • Neuropsychiatric outcomes • Executive function outcomes							

9.2.1.6 Zori 2019

- The Zori 2019 study presents an indirect treatment comparison between pegvaliase and comparators (dietary management; and sapropterin in conjunction with dietary management) where pooled phase 3 pegvaliase data were compared with propensity score matched data of from the PKUDOS registry.
- The pegvaliase samples were generated from pooled phase 3 studies (165-301/302), hence a safety analysis was already provided above for these studies.
- For the comparator arms, the voluntary nature of the PKUDOS registry results in a less thorough documentation of adverse even ts, and the safety data were not considered to be reliable.

TABLE 32. RESULTS OF STUDY: ZORI 2019, PEGVALIASE

Trial name:	**N/A**						
NCT number:	**N/A**						
					Estimated absolute difference in effect		
Outcome	**Sample**	**Time-point**	**N**	**Result (SD)**	**Difference**	**95% CI**	**P value**
Proportion of patients achieving blood Phe <600 Source: [31]	Sapropterin	1 y	25	7 (28%)	1y: +28% 2y: +43%	N/A N/A	NR NR
		2 y	25	5 (25%)			
	Pegvaliase (matched vs sapropterin)	1 y	43	24 (56%)			
		2 y	40	27 (68%)			
	Phe-restricted diet	1 y	51	3 (6%)	1y: +54% 2y: +67%	N/A N/A	NR NR
		2 y	42	5 (12%)			
	Pegvaliase (matched vs diet)	1 y	87	52 (60%)			
		2 y	80	63 (79%)			
					Least squares mean difference in effect		
Mean blood Phe concentration Source: [31]	Sapropterin	BL	64	1075 (419)	1y: -339.4 2y: -647.6	1y: -660.2 to -138.7 2y: −910.0 to −385.3	1y: p=0.0032 2y: p<0.0001
		1 y	25	807 (389)			
		2 y	25	891 (381)			
	Pegvaliase	BL	64	1180 (317)			

	(matched vs sapropterin)	1 y	43	505 (509)			
		2 y	40	427 (527)			
	Phe-restricted diet	BL	125	1037 (271)			
		1 y	51	1022 (322)			
		2 y	42	965 (359)	1y: −567.8 2y: −670.9	1y: −708.3 to −427.4 2y: −824.1 to −517.7	1y: p<0.0001 2y: p<0.0001
	Pegvaliase (matched vs diet)	BL	125	1089 (289)			
		1 y	87	473 (451)			
		2 y	80	302 (392)			
					Change from baseline		
Mean natural protein intake Source: [31]	Sapropterin	BL	31	36 (31)	N/A	N/A	N/A
		1 y	4	23 (18)	-13	NR	NR
		2 y	7	28 (18)	-8	NR	NR
	Pegvaliase (matched vs sapropterin)	BL	56	33 (19)	N/A	N/A	N/A
		1 y	38	49 (28)	+16	NR	NR
		2 y	35	57 (29)	+24	NR	NR
	Phe-restricted diet	BL	62	25 (19)	N/A	N/A	N/A
		1 y	18	27 (25)	+2	NR	NR
		2 y	16	22 (16)	-3	NR	NR
	Pegvaliase (matched vs diet)	BL	107	34 (24)	N/A	N/A	N/A
		1 y	76	47 (22)	+13	NR	NR
		2 y	71	57 (26)	+23	NR	NR

Outcomes not reported in study:

- Adverse Events
- QoL
- Proportion of patients achieving daily protein intake target levels
- Neuropsychiatric outcomes
- Executive function outcomes

9.2.2 LNAA studies

9.2.2.1 Burlina 2019

- Single arm study
- 12 patients received a Phe-restricted diet plus a slow-release LNAA product taken three times per day, at a dose of 1 g/kg body weight (mean 0.8 ± 0.24 g/kg/day), over a 12-month period.
- Patients had fortnightly measurements of Phe and Tyr levels over a 12-month period after the introduction of LNAA.

TABLE 33. RESULTS OF STUDY: BURLINA 2019, LNAA

Trial name:	**N/A**						
NCT number:	**N/A**						
					Change from baseline		
Outcome	**Sample**	**Timepoint**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**
Discontinuation rate Source: [32]	LNAA	Longest follow-up	12	0 (0%)	N/A	N/A	N/A
Proportion of patients achieving blood Phe <600 Source: [32]	LNAA	BL	12	0 (0%)	N/A	N/A	N/A
		12 m	12	0 (0%)	N/A	N/A	N/A
Mean blood Phe concentration Source: [32]	LNAA	BL (mean over prior 12 m)	12	752 (671 - 833)	N/A	N/A	N/A
		12 m (mean over period)	12	894 (812 - 976)	+142	NR	0.0522
Mean natural protein intake * Source: [32]	LNAA	BL	12	21.0 (13.5 - 28.5)	N/A	N/A	N/A
		12 m	12	21.0 (11.6 - 30.4)	0	NR	NR

Outcomes not reported in study:

- QoL
- Proportion of patients achieving daily protein intake target levels
- Neuropsychiatric outcomes
- Executive function outcomes

- * Calculated from difference between reported total protein intake and MF protein intake

9.2.2.2 Scala 2020

- Single arm study
- 10 adult PKU patients with poor metabolic control were treated for 12 months with LNAAs (MovisCom, 0.8–1 g/kg/day)
- Patients underwent Phe and Tyrosine (Tyr) monitoring monthly.
- Neuropsychological assessment was performed at T0, T+3, and T+12 months by using the American Psychological General Well-Being Index, the Wisconsin Card Sorting Test, the Test of Attentional Performance, and the 9-Hole Peg Test.

TABLE 34. RESULTS OF STUDY: SCALA 2020, LNAA

Trial name:	**N/A**						
NCT number:	**N/A**						
					Change from baseline		
Outcome	**Sample**	**Timepoint**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**
Discontinuation rate Source: [33]	LNAA	Longest follow-up	10	0 (0%)	N/A	N/A	N/A
Proportion of patients achieving blood Phe <600 Source: [33]	LNAA	BL	10	0 (0%)	N/A	N/A	N/A
		12 m	10	1 (10%)			
Mean blood Phe concentration Source: [33]	LNAA	BL	10	831 (782 - 879)	N/A	N/A	N/A
		12 m (mean over period)	10	909 (777 - 1041)	+78	-37.9 - 193.9	N.S.
Neuropsychatric symptoms: PGWBI Source: [33]	LNAA	BL	10	78.0 (56.0 - 91.0)	N/A	N/A	N/A
		12 m	10	88.4 (79.7 - 97.1)	+10.4	NR	N.S.
Neuropsychatric symptoms: TAP vigilance, time to complete tasks Source: [33]	LNAA	BL	10	706 (655 - 757)	N/A	N/A	N/A
		12 m	10	609 (572 - 646)	-97	NR	<0.05
Neuropsychatric symptoms: TAP sustained attention, time to complete tasks Source: [33]	LNAA	BL	10	727 (636 - 818)	N/A	N/A	N/A
		12 m	10	589 (528 - 650)	-138	NR	<0.01

Neuropsychatric symptoms: TAP sustained attention, no of errors Source: [33]	LNAA	BL	10	6.0 (1.2 - 10.8)	N/A	N/A	N/A
		12 m	10	0.8 (0.5 - 1.1)	-5.2	NR	<0.01
Neuropsychatric symptoms: TAP sustained attention, no of omissions Source: [33]	LNAA	BL	10	9.0 (3.1 - 14.9)	N/A	N/A	N/A
		12 m	10	3.2 (1.8 - 4.6)	-5.8	NR	<0.05
Neuropsychatric symptoms: 9-hole peg test Source: [33]	LNAA	BL	10	23.0 (21.1 - 24.9)	N/A	N/A	N/A
		12 m	10	21.4 (20.2 - 22.6)	-1.6	NR	N.S.
Outcomes not reported in study: • QoL • Mean natural protein intake • Proportion of patients achieving daily protein intake target levels • Executive function outcomes							

9.2.2.3 Matalon 2006

- Open-label single arm study
- 11 PKU patients
- 1 week's LNAA treatment at 0.5 mg/kg/day (n=8) or 1.0 mg/kg/day (n=3)
- Baseline Phe was determined on four separate occasions and at zero time and post LNAA at one week. Blood Phe was also determined one week after LNAA treatment.

TABLE 35. RESULTS OF STUDY: MATALON 2006, LNAA

Trial name:	**N/A**						
NCT number:	**N/A**						
					Change from baseline		
Outcome	**Sample**	**Timepoint**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**
Discontinuation rate Source: [34]	LNAA 0.5 mg/kg/day	Longest follow-up	8	0 (0%)	N/A	N/A	N/A
	LNAA 1.0 mg/kg/day	Longest follow-up	3	0 (0%)			
Proportion of patients with blood Phe <600 Source: [34]	LNAA 0.5 mg/kg/day	BL	8	1 (13%)	N/A	N/A	N/A
		1 w	8	5 (63%)	N/A	N/A	N/A
	LNAA 1.0 mg/kg/day	BL	3	0 (0%)	N/A	N/A	N/A
		1 w	3	2 (66%)	N/A	N/A	N/A
Mean blood Phe concentration Source: [34]	LNAA 0.5 mg/kg/day	BL	8	957.4 (NR)	N/A	N/A	N/A
		1 w	8	458.4 (NR)	-499	NR	p=0.004
	LNAA 1.0 mg/kg/day	BL	3	1230 (NR)	N/A	N/A	N/A
		1 w	3	549.0 (NR)	-681	NR	NR
Outcomes not reported in study: • QoL • Mean natural protein intake • Proportion of patients achieving daily protein intake target levels • Neuropsychiatric outcomes • Executive function outcomes							

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9.2.2.4 Matalon 2007

- 20 PKU patients, whereof 19 with classical PKU
- 7 of the patients were Phe controlled on PKU medication throughout the study, with BL Phe of 532 µmol/L.
- Double blind, randomised crossover study, 1- week treatment periods, with 1-week washout period between the treatments
- Blood Phe was determined twice weekly.

TABLE 36. RESULTS OF STUDY: MATALON 2007, LNAA

Trial name:	**N/A**						
NCT number:	**N/A**						
					Estimated absolute difference in effect		
Outcome	**Sample**	**Timepoint**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**
Discontinuation rate Source: [34]	Placebo	1 w	20	0 (0%)	N/A	N/A	N/A
	LNAA	1 w	20	0 (0%)			
Proportion of patients with blood Phe <600 Source: [34]	Baseline	BL	20	5 (25%)	N/A	N/A	N/A
	Placebo	1 w	20	4 (20%)	+15%	NR	NR
	LNAA	1 w	20	7 (35%)			
Mean blood Phe concentration Source: [34]	Baseline	BL	20	932.9 (NR)	N/A	N/A	N/A
	Placebo	1 w	20	882.7 (NR)	-314.3	NR	NR
	LNAA	1 w	20	568.4 (NR)			
Outcomes not reported in study: • QoL • Mean natural protein intake • Proportion of patients achieving daily protein intake target levels • Neuropsychiatric outcomes • Executive function outcomes							

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9.2.2.5 Lou 1987

- 14 patients with classical PKU aged 15-24 years
- Double blind crossover study with free diet and free diet supplemented with tyrosine (160 mg/kg/day divided into three daily doses).
- The two regimens were administered for at least 3 days each in random order
- Plasma Phe levels were measured

TABLE 37. RESULTS OF STUDY: LOU 1987, LNAA

Trial name:	**N/A**						
NCT number:	**N/A**						
					Estimated absolute difference in effect		
Outcome	**Sample**	**Timepoint**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**
Discontinuation rate Source: [36]	Full cohort	3 days	14	0 (0%)	N/A	N/A	N/A
Mean blood Phe concentration Source: [36]	Placebo	3 days	14	1349 (1217 - 1481)	+14	-154 - 182	N.S.
	LNAA	3 days	14	1363 (1260 - 1466)			
Outcomes not reported in study: • QoL • Proportion of patients with blood Phe <600 µmol/L • Mean natural protein intake • Proportion of patients achieving daily protein intake target levels • Neuropsychiatric outcomes • Executive function outcomes •							

9.2.2.6 Pietz 1995

- 24 early-treated PKU patients in ages 16-25
- 24 healthy controls
- Double-blind, placebo-controlled crossover study
- Oral high-dose Tyr therapy (100 mg/kg body weight per day) or placebo, for 4 weeks.
- Six test times:
- Plasma concentrations of phenylalanine and Tyr were monitored
- Neuropsychologic tasks, visual evoked potentials, and spectral analysis of electroencephalographic activity were used to evaluate brain function.
- Discontinuation review:
    - All 24 patients enrolled in the study completed test sessions T1 to T6.
    - No significant adverse reactions or complaints were reported with respect to the intake of Tyr or placebo.
    - Standard laboratory investigations revealed no abnormalities.
- For the evaluation of Tyr treatment effects, three patients were excluded from statistical analysis according to the criteria for plasma Tyr increase during treatment.

TABLE 38. RESULTS OF STUDY: PIETZ 1995, LNAA

Trial name:	**N/A**						
NCT number:	**N/A**						
					Estimated absolute difference in effect		
Outcome	**Sample**	**Timepoint**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**
Discontinuation rate Source: [37]	Full cohort	Longest follow-up	24	0 (0%)	N/A	N/A	N/A
Mean blood Phe concentration Source: [37]	Placebo	4 w	24	1224 (1114 - 1334)	+36	-127 - 199	N.S.
	LNAA	4 w	24	1260 (1140 - 1380)			
Neuropsychatric symptoms: Simple motor RT task, RT (msec) dominant (FMSE) Source: [37]	Placebo	4 w	21	297 (277 - 317)	-17	-44 - 10	<0.05
	LNAA	4 w	21	280 (262 - 298)			
Neuropsychatric symptoms: Simple motor RT task, RT (msec) nondominant (FMSE) Source: [37]	Placebo	4 w	21	284 (266 - 302)	-3	-28 - 22	N.S.
	LNAA	4 w	21	281 (264 - 298)			
Neuropsychatric symptoms: Sustained-attention task, series time (DPE) Source: [37]	Placebo	4 w	21	7.8 (6.9 - 8.7)	0.0	-1.1 - 1.1	N.S.
	LNAA	4 w	21	7.8 (7.1 - 8.5)			
Outcomes not reported in study: • QoL • Proportion of patients with blood Phe <600 µmol/L • Mean natural protein intake • Proportion of patients achieving daily protein intake target levels • Executive function outcomes							

9.2.2.7 Schindeler 2007

- Double-blind randomized crossover study
- 16 classical PKU patients, all currently on diet and medical products for PKU
- 4 x 2-week phases, with a 4- week minimum washout period between phases: (1) medical product + LNAA; (2) medical product + placebo; (3) no medical product + LNAA; (4) no medical product + placebo.
- Discontinuation review:
  - Overall compliance for consumption of the prescribed amount of active LNAA tablets was very good.
  - In phase 1, the average number of prescribed tablets taken was 98%,
  - In phase 3 the average number of prescribed tablets taken was 94%.
  - Two of the subjects in phase 3 did not return their remaining tablets, hence compliance for these subjects was not assessed, and it was assumed that they had consumed all tablets prescribed.
- Dietary information, brain Phe levels, plasma Phe levels, and neuropsychological studies were assessed.
- Brain Phe levels were measured by magnetic resonance spectroscopy:
  - There was no significant difference in brain Phe between the phases (data not reported).
  - The range of brain Phe measurements was small (176–365 µmol/L).
  - There was no correlation between plasma and brain Phe when the plasma Phe was <1200 µmol/L,
  - For samples in phase 4 of the study where the plasma Phe was 1200 µmol/L or more there was a positive correlation (Spearman's ρ = 0.90, p = 0.04), although there were only five data points in the latter group.

TABLE 39. RESULTS OF STUDY: SCHINDELER 2007, LNAA

Trial name:	**N/A**						
NCT number:	**N/A**						
					Estimated absolute difference in effect		
Outcome	**Study arm**	**Timepoint**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**
Discontinuation rate Source: [38]	Full cohort	Longest follow-up	16	0 (0%)	N/A	N/A	N/A
Median blood Phe concentration Source: [38]	Medical + LNAA	2 w	16	639 (range 149-1044)	-95	NR	N.S.

	Medical + placebo	2 w	16	734 (range 19-1231)			
	No medical + LNAA	2 w	16	958 (range 553-1500)	-222	NR	p=0.001
	No medical + placebo	2 w	16	1180 (range 641-1744)			
Mean natural protein intake Source: [38]	Medical + LNAA	2 w	16	29.5 (range 9.4 - 46.1)	+0.7	NR	NR
	Medical + placebo	2 w	16	28.8 (range 10.1 - 67.7)			
	No medical + LNAA	2 w	16	28.1 (range 8.6 - 49.0)	-8.6	NR	NR
	No medical + placebo	2 w	16	36.7 (range 12.2 - 44.6)			
Outcomes not reported in study: • QoL • Proportion of patients with blood Phe <600 µmol/L • Proportion of patients achieving daily protein intake target levels • Neuropsychiatric outcomes • Executive function outcomes							

- * Reported as g/kg/day, converted to g/day assuming an average weight of 72 kg.

9.2.2.8 Yano 2013

- 10 adult individuals with PKU
- Randomized, double-blind, placebo controlled cross-over study
- 3 x 3-week phases: (1) washout; (2) supplementation of LNAA tablets or placebo; (3) alternate supplementation.
- Plasma amino acid measurements were conducted after each phase.
- Discontinuation review:
    - 1 subject with PKU (because of poor compliance) failed to complete the study.

- Nine subjects with PKU completed the study without experiencing any untoward effects.

- Repeated measures ANOVA showed no differences between placebo and washout phases on any outcome measures. Therefore, all within group comparisons were reported for LNAA supplementation versus placebo phases.

TABLE 40. RESULTS OF STUDY: YANO 2013, LNAA

Trial name:	**N/A**						
NCT number:	**N/A**						
					Estimated absolute difference in effect		
Outcome	**Sample**	**Timepoint**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**
Discontinuation rate Source: [39]	LNAA	3 w	10	1 (10%)	N/A	N/A	N/A
Mean blood Phe concentration Source: [39]	Placebo	3 w	9	1574 (1418 - 1730)	-26	-252 - 200	N.S.
	LNAA	3 w	9	1548 (1385 - 1711)			
Outcomes not reported in study: • QoL • Proportion of patients with blood Phe <600 µmol/L • Mean natural protein intake • Proportion of patients achieving daily protein intake target levels • Neuropsychiatric outcomes • Executive function outcomes							

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9.2.2.9 Yano 2014

- 10 adult individuals with PKU
- Randomized, double-blind, placebo controlled cross-over study
- 3 x 3-week phases: (1) washout; (2) treatment with LNAA tablets plus supplementation with either Trp and Tyr tablets or placebo; (3) LNAA tablets plus the alternate supplementation.
- Plasma amino acid measurements were conducted after each phase.
- Discontinuation review:

- 2 subjects failed to complete the LNAA + TT phase owing to discomfort, including dizziness and nausea, attributed to the Trp/Tyr tablets. For these subjects, Trp/Tyr supplementation was reduced to administer 65 mg/kg/day of Trp and 150 mg/kg/day of Tyr for the remainder of the LNAA + TT phase.
- 1 subject failed to complete the LNAA + TT phase because of poor compliance
- 1 subject accidentally took the study tablets just before a blood draw in the LNAA + TT phase, thereby invalidating plasma amino acid analysis. These data were removed from the statistical analysis.
- All subjects (n = 10) completed the washout and LNAA phases (LNAA and placebo supplement),
- 6 subjects completed the study following the protocol,
- 2 subjects completed the study with a reduced amount of Trp/Tyr supplementation in the LNAA + TT phase.

TABLE 41. RESULTS OF STUDY: YANO 2014, LNAA

Trial name:	**N/A**						
NCT number:	**N/A**						
					Change from baseline (washout)		
Outcome	**Sample**	**Timepoint**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**
Discontinuation rate Source: [40]	Washout (W)	3 w	10	0 (0%)	N/A	N/A	N/A
	LNAA + TT (T)	3 w	10	2 (20%)	N/A	N/A	N/A
	LNAA + placebo (L)	3 w	10	0 (0%)	N/A	N/A	N/A
Mean blood Phe concentration Source: [40]	Washout (W)	BL	6	1389 (1099 - 1679)	N/A	N/A	N/A
	LNAA + TT (T)	3 w	6	1149 (866 - 1432)	-117	-532 – 297	N.S.
	LNAA + placebo (L)	3 w	6	1272 (975 - 1568)	+123	-287 - 532	N.S.

Outcomes not reported in study:

- QoL
- Proportion of patients with blood Phe <600 µmol/L
- Mean natural protein intake
- Proportion of patients achieving daily protein intake target levels
- Neuropsychiatric outcomes
- Executive function outcomes

Pegvaliase (Palynziq®) Cost Consequence and Budget Impact Analysis

Technical Report

1 Introduction

This economic report supports BioMarin's HTA submission for pegvaliase (Palynziq®) to the Danish Medicines Council. It provides a cost consequence and budget impact analysis to evaluate the effect of recommending pegvaliase as a standard management of PKU in Denmark. All calculations are performed and detailed in the enclosed excel model.

2 Patient population

The patient population considered is the full indicated patient population, i.e. patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood Phenylalanine (Phe) control (blood Phe levels greater than 600 µmol/L) despite prior management with available treatment options.

As summarized in the DMC protocol, the prevalence of PKU in Denmark is estimated at approx. 1:10,000 [1], and 6-10 children are born with PKU annually in Denmark [2]. All Danish patients are treated at the Center for PKU under the Rigshospitalet in Copenhagen. According to the Neonatal Screening Biobank (PKU Biobank), there are 488 PKU patients in Denmark, of which 357 are 16 years or older. 46 of the adult patients are late diagnosed [1].

PKU can be divided into four levels of severity. In Denmark, the classification of PKU is based on which mutations the patients have, with some mutations affecting the function of the PAH enzyme more than others. Some patients will have some, albeit significantly, reduced enzyme activity, while others have no enzyme activity at all. Patients with any retained PAH activity have milder disease and are easier to manage by keeping the phenylalanine level down. They may also be candidates for medical treatment with sapropterin that increases PAH-activity [1].

The DMC specialist committee estimates that in practice it will be adult patients with moderate and classic PKU that have the greatest risk of not being able to reduce their phenylalanine concentration in the blood to below 600 µmol/L by diet or other treatment. Approximately 40% of patients have classical PKU, 6% moderate PKU. In total, the population of Danish patients over the age of 16 with moderate or classic PKU comprises of 146 patients (PKU-database, 2020). Most are expected to have phenylalanine levels above 600 µmol/L [1]. If 46% of the 6-10 new PKU patients per year have classical or moderate PKU, this predicts an annual growth of the target patient population with an average of 3.7 new patients ≥16 years with classical or moderate PKU.

3 The intervention

Basic information about the intervention is summarized in Table 1.

Table 1. Overview of the pharmaceutical

<table>
<tr><td>Proprietary name</td><td>Palynziq</td></tr>
<tr><td>Generic name</td><td>Pegvaliase</td></tr>
<tr><td>Marketing authorization holder in Denmark</td><td>BioMarin International Limited
6th Floor, 2 Grand Canal Square,
Dublin 2</td></tr>
<tr><td>ATC code</td><td>A16AB19</td></tr>
<tr><td>Pharmacotherapeutic group</td><td>Other alimentary tract and metabolism products</td></tr>
<tr><td>Active substance(s)</td><td>Pegvaliase</td></tr>
<tr><td>Pharmaceutical form(s)</td><td>Pegvaliase is an injection for subcutaneous use. It is a clear to slightly opalescent, colourless to pale yellow solution available as follows: 2.5 mg/0.5 mL, 10 mg/0.5 mL, and 20 mg/mL in a single-dose prefilled syringe</td></tr>
<tr><td>Mechanism of action</td><td>Pegvaliase is an enzyme substitution therapy that directly addresses the underlying cause of disease in PKU by substituting the missing or deficient Phe-metabolising enzyme activity</td></tr>
<tr><td>Dosage regimen</td><td>Pegvaliase is administered as a low dose induction followed by a slow upward titration to achieve stable maintenance dose and substantial blood Phe reductions, while minimizing the onset and severity of hypersensitivity reactions. This dosing regimen is referred to as Induction, Titration, Maintenance (I/T/M), with maintenance being daily dosing of up to 20 - 60 mg, as required to reduce blood Phe to target level of 120 to ≤600 µmol/L. The recommended dosing regimen from the pegvaliase SmPC [3] is shown in the table below. The variability of immune response in individuals explains the difference in effective dose between patients. Dietary Phe intake should remain consistent until a maintenance dosage is established.
<table>
<tr><th></th><th>Dosage[1] administered subcutaneously</th><th>Minimum administration duration prior to next dosage increase[2]</th></tr>
<tr><td>Induction</td><td>2.5 mg once weekly</td><td>4 weeks</td></tr>
<tr><td rowspan="2">Titration</td><td>2.5 mg twice weekly</td><td>1 week</td></tr>
<tr><td>10 mg once weekly</td><td>1 week</td></tr>
</table>
</td></tr>
</table>

	<table><tr><td></td><td>10 mg twice weekly</td><td>1 week</td></tr><tr><td></td><td>10 mg four times a week</td><td>1 week</td></tr><tr><td></td><td>10 mg daily</td><td>1 week</td></tr><tr><td>Maintenance[3]</td><td>20 mg daily</td><td>12 - 24 weeks</td></tr><tr><td></td><td>40 mg daily (2 consecutive injections of 20 mg prefilled syringe)</td><td>16 weeks</td></tr><tr><td></td><td>60 mg daily (3 consecutive injections of 20 mg prefilled syringe)</td><td>Maximum recommended dosage</td></tr></table> [1] The dosage may be reduced or the dietary phenylalanine intake may be modified if blood phenylalanine levels are 30 µmol/L or less. [2] Additional time may be required prior to each dose escalation based on patient tolerability. [3] Individualize treatment to the lowest effective and tolerated dosage. The dosage may be increased up to a maximum of 60 mg daily in patients who have not reached a response (≤ 600 µmol/L) after minimum administration duration specified.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Palynziq® is indicated for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood Phenylalanine (Phe) control (blood Phe levels greater than 600 µmol/L) despite prior management with available treatment options.
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Premedication prior to each dose (e.g., H1 antagonist, H2 antagonist, and antipyretic) is required during induction and titration due to the potential for an acute systemic hypersensitivity reaction. This may be continued during maintenance if needed.
Packaging – types, sizes/number of units, and concentrations	Solution available in 2.5 mg/0.5 mL, 10 mg/0.5 mL, and 20 mg/mL in a single-dose prefilled syringe. The 20 mg/mL syringes are also available in 10-pack. Injection for subcutaneous use.
Orphan drug designation	Yes

4 Comparator(s)

Pegvaliase is compared with LNAA treatment, as instructed by the DMC expert committee protocol.

A second comparator, sapropterin, is also included in the analyses. This is the only other pharmaceutical option licensed in PKU, and as such it is valuable to compare the cost of sapropterin treatment with the cost of pegvaliase treatment.

The remaining treatment option is restrictive diet, limiting the intake of Phe by excluding natural protein intake from the diet, supplemented with special amino acid supplementation.

5 Perspective of analysis

Base case: Reduced societal, in accordance with guidelines

6 Time horizon

The cost per patient analysis is in the base case performed over a time horizon of 20 years.

Shorter time horizons are also assessed in sensitivity analyses: 5 and 10 years.

Costs are discounted by 4.0% per year in the cost per patient analysis.

The treatment is life long, and longer time horizons can be assessed in the model. However, time horizons over 20 years are associated with uncertainties of the development over longer periods, e.g. introduction of new drugs and changes in treatment policies.

Danish background mortality rates from 2018-2019 (Statistics Denmark) have been applied in the model to account for the development of the patient population over the longer time horizons.

7 Cost per patient analysis

7.1 Method and assumptions

Important model settings and assumptions are summarized in Table 2.

Table 2. Model settings and assumptions

Model parameter	Base-case assumption
Model type	Cost consequence model
Time Horizon	20 years
Discount rate	4 %
Included costs	• Medicines costs • Diet costs • Hospital costs • Patient and caregiver costs • Comorbidity costs
Dose	Induction/Titration/Maintenance (I/T/M) dosing regimen Average dose during maintenance treatment: [redacted]
Treatment line	First line
Treatment duration	• Intervention: Life-long • LNAA: Life-long • Sapropterin: Life-long • Diet: Life-long
Subsequent treatment lines	No
Wastage included	Yes
Other important assumptions	• As observed in clinical trials, successful Palynziq treatment allows patients to revert to a normalized diet without Phe restrictions • Normalisation of blood Phe levels <120 µmol/L reduces comorbidity prevalence to background levels. • Patients that discontinue pegvaliase treatment are assumed to revert to either LNAA (62%) or diet alone (38%) treatment, with the split between treatments reflecting the current share of patients on LNAA treatment in Denmark.

7.2 Cost inputs

7.2.1 Medicines costs, pegvaliase

7.2.1.1 Resource use

Pegvaliase is administered as a low dose induction followed by a slow upward titration to achieve a stable maintenance dose and substantial blood Phe reductions, while minimizing the onset and

severity of hypersensitivity reactions [3]. The dosing regimen is referred to as Induction, Titration, Maintenance (I/T/M). Following a request from the DMC, the model will reflect the dosing regimen of the pivotal trial (study 165-301) where patients were induced for 4 weeks at 2.5 mg per week, and titrated for up to 30 weeks on 5 mg-280 mg/week followed by maintenance dose of 20 mg/day or 40 mg/day (Figure 1).

Figure 1. Induction, Titration & Maintenance Schedule (165-301)

Pegvaliase Dosing (Induction, Titration, and Maintenance), Vial and Syringe						
Study Period	**Duration**	**Total Weekly Fixed Dose (mg)**	**Total Weekly Volume (mL) [a]**	**Mg per Dose**	**Volume per Dose (±0.01 mL) [a]**	**Frequency of Administration per Week**
Induction	4 weeks	2.5 [b]	0.18	2.5	0.18	1
		2.5 [b]	0.18	2.5	0.18	1
		2.5	0.18	2.5	0.18	1
		2.5	0.18	2.5	0.18	1
Titration	Up to 30 weeks	5	0.36	2.5	0.18	2 [c]
		10	0.68	10	0.68	1
		20	1.36	10	0.68	2 [c]
		40	2.72	10	0.68	4
		70	4.76	10	0.68	7
		140 [d] (20 mg/day)	9.38	20	1.34	7
		280 [d] (40 mg/day)	18.76	40	2.68	7
Maintenance	At least 2 weeks	20 mg/day or 40 mg/day				

In detail, the model input for the induction and titration regimen is done in accordance with the 165-301 clinical study report which states that the ITM schedule allowed for up to a minimum of 6 weeks titration up from 2.5mg/week to 20mg/day assuming there is no AE induced dose interruption, and then up to a maximum of 30 weeks assuming dose interruption. The dosing schedule in the clinical study report assumed this 6/7 week non-interruption up to the 6 week period, i.e. in steps of 5 mg, 10 mg, 20 mg, 40 mg, 70 mg, 140 mg (20 mg/day) and 280 mg (40 mg/day). Further, participation in the clinical trial requires compliance to the dosing schedule and protocols. In the real world setting, there will be dose interruption based on the individuality of the immune response, and to account for a slower ramping up for these patients the model pragmatically assumes the following weekly dose steps: 5 mg, 10 mg, 20 mg, 35 mg, 40 mg, 70 mg, 100 mg, 140 mg (20mg/day), 160 mg, 200 mg, 240 mg, 280 mg (40mg/day), with an additional assumption that patients stay on each dose for 2 weeks to minimize the immune response to also account for the variability of the individual immune response. These assumptions thus allow for 4 weeks of induction and a maximum of 24 weeks titration, as summarized in Table 3 which also provides the weighted average number of syringes consumed by week during induction and titration, between patients requiring a maintenance dose of 20 mg/day and those requiring a maintenance dose of 40 mg/day. Real-life data from the US demonstrate that a majority of treated PKU patients are on [redacted], we thus assume accordingly that 75% are maintained on 20 mg per day and the other 25% on 40 mg per day.

Table 3. Induction and titration dosing regimen applied in the model

Week no	Weekly dose, patients with 20 mg maint. dose	Weekly dose, patients with 40 mg maint. dose	syringe size (2.5/10/20)	syringes per week, patients with 20 mg maint. dose	syringes per week, patients with 40 mg maint. dose	syringes per week, weighted average	ITM
1	2,5	2,5	2,5	1	1	1,00	I
2	2,5	2,5	2,5	1	1	1,00	I
3	2,5	2,5	2,5	1	1	1,00	I
4	2,5	2,5	2,5	1	1	1,00	I
5	5	5	2,5	2	2	2,00	T
6	5	5	2,5	2	2	2,00	T
7	10	10	10	1	1	1,00	T
8	10	10	10	1	1	1,00	T
9	20	20	10	2	2	2,00	T
10	20	20	10	2	2	2,00	T
11	35	35	10 & 2.5	5	5	5,00	T
12	35	35	10 & 2.5	5	5	5,00	T
13	40	40	10	4	4	4,00	T
14	40	40	10	4	4	4,00	T
15	70	70	10	7	7	7,00	T
16	70	70	10	7	7	7,00	T
17	100	100	20	5	5	5,00	T
18	100	100	20	5	5	5,00	T
19	140	140	20	7	7	7,00	T
20	140	140	20	7	7	7,00	T
21	140	160	20	7	8	7,25	T
22	140	160	20	7	8	7,25	T
23	140	200	20	7	10	7,75	T
24	140	200	20	7	10	7,75	T
25	140	240	20	7	12	8,25	T
26	140	240	20	7	12	8,25	T
27	140	280	20	7	14	8,75	T
28	140	280	20	7	14	8,75	T

It should be noted that the dosing schedule of each patient is unique and based largely on the immune response of the patient to pegvaliase treatment and as such, there are patients in the real

world setting who are on non-standard maintenance dosing regiments such as 5 mg/day and 10 mg/day.

After the initial I/T phases, an average maintenance dose of [redacted] is applied from week 29 in the model. This dose is based on [redacted] Pegvaliase was approved by the FDA in May 2018. As such, the largest amount of real-world evidence regarding the use of pegvaliase is therefore available from the US. It should be noted (and as observed in the figure) that patients prefer fewer injections/day as illustrated in the figure below in addition to the dose down-adjustments based on increased tolerability of pegvaliase. Further, it has been reported that patients experience injection fatigue to which treating physicians increase the dose but with fewer injections. These average daily injections range are based on a maximum of 60mg/day dosing according to the expanded label indication in the US. The label indication in Europe for Pegvaliase is up to 60mg/day. [redacted]

Also, since the different syringe sizes all have the same price, the number of syringes used is of higher relevance for the economic analysis than the average dose used.

[redacted]

The assumptions above result in the average pegvaliase syringe consumption presented in Table 4.

Table 4. Drug consumption, pegvaliase

Time period	No of syringes used
Year 1, week 1-28	[redacted]
Year 1, week 29-52	[redacted]
Year 2+, annual use	[redacted]

A discontinuation rate of 10.3% is applied in the model. This assumption is based on real world discontinuation rates on the use of pegvaliase in the US and Germany. The last evaluation showed 10.3% in the US and 8% in Germany. The published discontinuation rates in the PRISM trials is 18.6% [4], but it should be noted that amendments were made in the trial to add antihistamines and antipyretics as well as slow down the titration rates to reduce discontinuations due to adverse events. These have now been implemented in the SmPC with a real-world use of pegvaliase relating to the lower real-world discontinuation rate of 10.3%.

It is assumed in the model that all discontinuation happens during the first year of treatment, because the majority of discontinuations are based on hypersensitivity acute events (HAEs) which are minimized by dose adjustments to mitigate the adverse immune responses.

For patients who discontinue pegvaliase treatment, two alternative optional scenarios are built into the model: either that these patients are lost-to-follow up, or that these patients are assumed to switch to other treatment options (either LNAA or diet alone) for the remainder of the analysis. The latter option is applied as the base case analysis. The base case assumes that 62% of discontinuing patients switch to LNAA treatment, and 38% to diet alone treatment, reflecting data from the PKU-database that 62% of Danish patients over 16 years of age with moderate or classic PKU are currently receiving LNAA [1]. The treatment switch is implemented in the model so that for each year, the pegvaliase arm carries the weighted average costs for pegvaliase, LNAA, and diet alone treatment, based on the percentages presented in Table 5. This is done for all cost categories.

Table 5. Treatment distribution by model year, for the pegvaliase arm if patients switch treatment upon discontinuation

Year	Discontinuation share	Share of pegvaliase starting population, by current treatment		
		Pegvaliase	LNAA	Diet alone
1	0%	100%	0%	0%
2	10.3%	89.7%	6.4%	3.9%
3	10.3%	89.7%	6.4%	3.9%
4	10.3%	89.7%	6.4%	3.9%
5+	10.3%	89.7%	6.4%	3.9%

7.2.1.2 Wastage

There is no wastage per se associated with pegvaliase. The average consumption of syringes during maintenance ([redacted]) represents the actual number of syringes

consumed on average i.e. some patients will inject one syringe and some two syringes per day etc. hence landing at an average of [redacted].

7.2.1.3 Unit cost

Pegvaliase is formulated as a self-administered subcutaneous injection. Accordingly, costs were calculated by vial size (Table 6), with no drug administration costs included.

Table 6. Drug cost, pegvaliase vials

Pegvaliase syringe	AIP, Pharmacy Purchasing Price (PPP)	AUP, Pharmacy Retail Price (PRP), incl VAT	Reference
Vial 2.5 mg (per prefilled syringe)	DKK 1,977	DKK 2,683.30	BioMarin
Vial 10 mg (per prefilled syringe)	DKK 1,977	DKK 2,683.30	BioMarin
Vial 20 mg (per prefilled syringe)	DKK 1,977	DKK 2,683.30	BioMarin

7.2.1.4 Resulting cost

The estimated cost per patient on Palynziq® resulting from the assumptions above can be seen in Table 14, for the first year of treatment and subsequent years, respectively.

Table 7. Estimated treatment cost per patient for Palynziq®

Treatment period	Treatment cost per patient (AIP)
Cost year 1, week 1-28	[redacted]
Cost year 1, week 29-52	[redacted]
Cost subsequent years: maintenance cost per year (365.25 days)	[redacted]

7.2.2 Medicines costs, LNAA

7.2.2.1 Resource use

The LNAA product considered in the cost consequence analysis is PreKUnil PKU LNAA tablets from Prekulab. The recommended daily dose is 0.5 tablets per kg bodyweight [5]. This corresponds to 40 tablets per day, based on an average body weight of 80.3 kg (from the PRISM trial population [6]). Each tablet is 750 mg whereof 500 mg amino acids.

7.2.2.2 Unit cost

PreKUnil is provided in packs of 550 tablets × 500 mg AA. It can be acquired from Swedish apoteket.se for a cost of SEK 5,500 per pack, equivalent to DKK 3,905.55 per pack (exchange rate 2020-06-30; DKK 71.01 = SEK 100; [7]), and DKK 7.10 per tablet.

7.2.2.3 Resulting cost

Table 8. Estimated cost per patient for LNAA treatment

Cost per tablet	Average daily dose	Cost per day	Cost per year
DKK 7.10	40 tablets	DKK 285	DKK 104,072

7.2.3 Medicines costs, sapropterin

7.2.3.1 Resource use

Sapropterin is an oral therapy and therefore has no drug administration costs associated with its administration [8]. The average daily consumption of sapropterin 100 mg tablets is specified in Table 9.

Table 9. Drug consumption, sapropterin

	Cost/quantity	**Source**
Strength per tablet	100 mg	Sapropterin SPC [8]
Average daily dose	20 mg/kg	KOL input [9]
Average PKU patient weight	80.3 kg	PRISM trial population [6]
Average daily consumption	16.1 tablets per day	Calculated

7.2.3.2 Unit cost

Sapropterin is provided in packs of 120 tablets × 100 mg. The PPP cost per pack is DKK 27,395.80 (medicinpriser.dk 2020-06-30). This corresponds to a cost of DKK 228.30 per tablet.

7.2.3.3 Resulting cost

The resulting annual cost of sapropterin per patient per year was DKK 1,200,758 (Table 10), applied as the cost per cycle for sapropterin treatment.

Table 10. Drug costs, sapropterin

Cost per tablet	Average daily dose	Cost per day	Cost per year
DKK 228.30	16.1 tablets	DKK 3,664	DKK 1,338,372

7.2.4 Medicines cost, pegvaliase premedication

7.2.4.1 Resource use

In the PRISM trials, HAEs were minimised by utilising pre-medications prior to each pegvaliase dose during the induction and titration periods. The pre-medication regimen consisted of a histamine H1 receptor antagonist, an H2 receptor antagonist, and, if tolerated, an antipyretic.

Premedication prior to each dose (e.g., H1 antagonist, H2 antagonist, and antipyretic) is therefore required during induction and titration due to the potential for an acute systemic hypersensitivity

reaction [3]. This may be continued during maintenance if needed. The cost of prophylaxis treatment was thus included in the model.

Only patients receiving Palynziq® were assumed to require prophylaxis treatment, antihistamines and antipyretics, as they may experience anaphylaxis. Generic treatment (Ibuprofen) was used as a proxy for antipyretics cost.

It was assumed that patients on Palynziq® treatment would consume:

- 1 autoinjectable adrenaline pen per year, on average
- 1 antihistamine tablet per day, i.e. one per Palynziq® dose
- 1 antipyretic tablet per day, i.e. one per Palynziq® dose

The model assumes daily use of antihistamines and antipyretics for the daily injections as well as an annual cost for an adrenaline injection pen for use in the event of an acute systemic hypersensitivity event.

7.2.4.2 Unit cost

Cost inputs, together with assumed consumption, are presented in Table 12.

Table 11. Prophylaxis unit costs

	Pack size	Cost, AIP	Cost per unit	Source
Autoinjectable adrenaline	1 pen × 300 µg	DKK 510.00	DKK 510.00	EpiPen, Orifarm (adrenaline), medicinpriser.dk 2020-06-30
Antihistamines (tablets)	100 × 10 mg	DKK 70.40	DKK 0.70	Cetirizin, Teva (cetirizine), apopro.dk 2020-06-30, excl VAT
Antipyretics	250 × 400 mg	DKK 86.10	DKK 0.34	Ibumetin, Takeda Pharma (ibuprofen), medicinpriser.dk 2020-06-30

7.2.4.3 Resulting cost

The resulting costs of premedication are presented in Table 12, summing up to a total cost of DKK 829 per year.

Table 12. Prophylaxis cost per year for Palynziq.

	Usage per year	Unit cost	Annual cost
Autoinjectable adrenaline	1 pen × 300 µg	DKK 510	DKK 510
Antihistamines (tablets)	365 × 10 mg	DKK 0.70	DKK 257
Antipyretics	365 × 400 mg	DKK 0.34	DKK 126

7.2.5 Diet costs

The cost of a Phe-restricted diet was applied in all treatment arms. The costs for a full Phe-restricted diet consist out of costs for amino acid supplements and costs for Phe free foods.

In all treatment arms, successful treatment allows the patient to maintain a less restricted diet. The degree of diet relaxation differs between the treatment arms.

7.2.5.1 Resource use

Amino acid supplements

Danish clinical expertise (modified Delphi meeting [9]) reported that patients on a full Phe-restricted diet have a daily protein intake of 1.2 g per kg body weight with 80% coming from amino acid supplements. This corresponds to 77.3 g protein from amino acid supplementation based on an average body weight of 80.3 kg.

Patients on LNAA treatment were reported to consume 20% of this amount, *i.e.* on average 19.3 g per day (modified Delphi meeting [9]). As these amino acids are provided as a part of the LNAA supplementation tablets, no extra costs were applied for amino acid supplementation for the LNAA arm in the model beyond those associated with LNAA treatment as described above.

Daily protein intake was measured in the pegvaliase clinical trial program. Long-term data show that patients treated with pegvaliase were able to increase their protein intake from natural food from initially 39 g/day to 47 g/day after 12 months, 54 g/day after 24 months and 72 g/day after 36 months [10]. This corresponds to a change for this population (36 months) of 27 g/day ($p<0.0001$, 95% CI 17.08, 37.45). It is important to note that the increase was possible while the Phe values were reduced at the same time. Correspondingly, the protein intake from medical food decreased over this time; the average daily protein intake from amino acid supplements was 24.2 g after 12 months; 20.3 g after 24 months; and 9.2 g/day after 36 months [10].

For patients on sapropterin treatment, a 48% reduction in protein supplement intake compared with patients on Phe-restricted diet alone have been reported [11]. This reduction was applied in the model generating an average intake of 37.0 g per day of amino acid supplements.

Low-protein food

The Center for PKU has issued a standard scheme for added monthly expenditure due to keeping a Phe-restricted diet [12]. The scheme presents costs associated with a full Phe-restricted diet, and costs associated with a semi-restricted diet during LNAA treatment.

Pegvaliase treatment will also allow patients to maintain a less restricted diet, with an estimated caloric intake from Phe-free foods at approximately 31% of a fully restricted diet during year 1, 26% of a fully restricted diet during year 2, and 12% of a fully restricted diet during subsequent years. These percentages were estimated to align with the gradual reduction in amino acid supplementation described.

Similarly, for sapropterin, it is estimated that patients can maintain a diet corresponding to 48% of a fully restricted diet [11].

7.2.5.2 Unit cost

Amino acid supplements

Amino acid supplement tablets (Avonil, Prekulab) can be acquired from Swedish apoteket.se for a cost of SEK 5,500 per pack of 900 tablets (735 mg per tablet; 55.8 g protein equivalents per 100 g

[13]), corresponding to DKK 3,906 per pack (exchange rate 2020-06-30; DKK 71.01 = SEK 100; [7]), and DKK 10.58 per gram of protein.

Low-protein food

The suggested added expenditure according to the standard scheme for a full Phe-restricted diet in adult patients is DKK 3,017 per month; while the added expenditure for a semi-restricted diet in adult patients on LNAA treatment is DKK 601 per month [12]. These costs were adjusted to DKK of 2020.

7.2.5.3 Resulting cost

The resulting dietary costs are presented in Table 13.

Table 13. Annual costs for diet

Treatment	Caloric intake from phe-free food, % of fully restricted diet	Added expenditure per month	Annual cost, low-protein food	Annual cost, amino acid supplements
Semi-restricted diet, on LNAA treatment	N/A	DKK 601 [1]	DKK 7,213	-
Phe-restricted diet	100%	DKK 3,017 [1]	DKK 36,210	DKK 297,534
On pegvaliase treatment, year 1	31% [2]	DKK 948	DKK 11,374	DKK 93,460
On pegvaliase treatment, year 2	26% [2]	DKK 795	DKK 9,541	DKK 78,398
On pegvaliase treatment, subsequent years	12% [2]	DKK 360	DKK 4,324	DKK 35,530
On sapropterin treatment	48% [3]	DKK 1,448	DKK 17,381	DKK 142,816

Source: [1] [12], [2] Alignment with reduction in amino acid supplement intake [10], [3] [11]

7.2.6 Hospital costs

No major differences in healthcare resource use for treatment administration or monitoring between the treatment arms have been identified, with the exception of an initial visit for the initiation of treatment (monitoring/administrative) which differentiates pegvaliase from the comparator treatments. The self-administration of pegvaliase by the patient in the presence of an observer is an intricate part of the treatment of PKU. At the initiation of treatment, the patient and the observer (which could be a family member) are trained and equipped with the right medical tools by a certified physician to manage any injection site reactions and immune system mediated responses. This approach minimizes the burden on the health care system whilst ensuring that the patient has the best possible support in their PKU treatment. The cost associated with the physician administrative time (up to 60mins) is included in the model.

In addition, all costs due to management of adverse events in pegvaliase treatment have however been considered.

7.2.6.1 Resource use

60 minutes of physician time is spent during the initiation of treatment.

The AE rates included in the model is based on the highest incidence of adverse events reported in the PRISM-2 trial with a >/= Grade 3 AE rating & >/=3% incidence rate. Based on data from the pegvaliase phase 3 trial 165-302, immune system disorders was the only AE included in the model, at 3.8% (Table 14). Immune system disorders included hypersensitivity and anaphylactic reaction.

In cases of acute systemic hypersensitivity reactions in the pegvaliase clinical trials, the reactions generally (88% of episodes) occurred within the first hour after injection, but have occurred up to 24 hours after dosing. Reactions were managed by adrenaline, corticosteroids, antihistamines and/or oxygen under emergency medical care.

Table 14. Adverse Events (grades 3-4) reported in study 165-302 (N=215)

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: 165-302 CSR [14]

7.2.6.2 Unit cost

For physician's time spent during the initiation of treatment visit, a 1,316 DKK cost per hour for a senior physician is applied in the model [15].

The cost associated with DRG 21MA04 (Poisioning and toxic effect of pharmaceutical, ≥18 years, complicating bidiagnosis) was applied in the model as the unit cost per event of an acute systemic hypersensitivity reaction: DKK 20,224 [16].

7.2.6.3 Resulting cost

The estimated cost for the visit at the initiation of pegvaliase treatment is 1,316 DKK.

The estimated annual AE cost per average patient was thus DKK 667 for patients treated with pegvaliase based on the 3.3% of patients experiencing this AE. No AE cost was applied for patients treated with LNAA or with sapropterin. Costs associated with AEs were considered in the model within the first cycle, as the AEs are experienced only during the induction and/or titration phases.

7.2.7 Non-hospital cost

No differences in non-hospital health care consumption between the treatment arms were identified.

Non-hospital costs associated with PKU comorbidities are presented in sections below.

7.2.8 Patient and caregiver time costs

7.2.8.1 Resource use

No major patient costs for treatment administration or monitoring between the treatment arms have been identified, with the exception of the initial 60 minutes visit for the initiation of treatment (monitoring/administrative) which differentiates pegvaliase from the comparator treatments. It is assumed that both patient and caregiver are present at this visit, since it involves observer training. The visit is thus associated with 2 x 60 minutes of productivity loss, plus transportation costs for an average of 2 x 14 km in line with DMC instructions [15].

Besides costs associated with this initial visit, no patient costs are assumed in the model. The PKU treatments are self-administrated and thus not assumed to incur any treatment related patient costs. Ordinary regular follow-up visits for management of the disease are assumed to be unaffected by the choice of treatment.

On the other hand, caregiver costs are included as follows.

The clinical expertise (modified Delphi meeting [9]) reported that caregivers of PKU patients with LNAA and dietary treatment are allocated reimbursement for 10 hours per week for time associated with diet preparation and intake. This represents time spent to administrate treatment.

Indirect costs associated with PKU comorbidities and treatment effects are presented in section below.

For pegvaliase, LNAA, and sapropterin treated patients, a reduction in caregiver costs was assumed that aligned with the percentage reduction of medical food intake applied in the diet cost calculations.

With regards to pegvaliase, patients in the PRISM study [4] were consuming a mean of 64.8g of protein at baseline (SD 32.2g), 71.6g at 12months (SD 24.3g) and 77.4g of protein at 24mths (SD 20.8g) on average. An unaffected individual would consume approximately 0.8g per kg of protein such that an 80kg patient would therefore require 64g of protein. Given the pegvaliase patients in the study are consuming protein in excess of the amount an unaffected individual would consume,

the need for time spent for preparation of medical food is considerably reduced as their protein requirements are being met from intact food.

Furthermore, the PRISM study data demonstrates a strong correlation between the reduction of blood Phe and improvement in neurocognitive & executive functioning thus limiting any carer necessity for support given their improvement in cognitive function. The Thomas paper [4] also highlights the proportion of Pegvaliase patients that can normalize their dietary intake which is a significant improvement on the patient's QoL and the associated care-giver burden for alternative treatments.

However, as a conservative approach and for consistency purposes we have aligned the assumptions on dietary consumption and on caregiver time, so that the % reduction in protein supplementation is applied also as % reduction of caregiver support needed.

In summary patients on pegvaliase are unlikely to require additional caregiver time/support for food preparation and treatment, however substantial caregiver time is needed to sustain management by diet/MNT with or without sapropterin.

7.2.8.2 Unit cost

The unit costs used to estimate the value of lost productivity is given in Table 15. For transportation, a cost of DKK 3.52 per km is applied in the model [15].

Table 15. Productivity unit costs

Average annual income before tax, 2018	DKK 326,048
Average annual income after tax, 2018	DKK 235,312
Working hours per year	1,702
Working hours per day	7.4
Productivity cost per day	DKK 1,418
Productivity cost per hour	DKK 192
Leisure time cost per hour	DKK 138

Source: Statistics Denmark [17]

7.2.8.3 Resulting cost

Hospital visit for the initiation of pegvaliase treatment

The initial visit represents a patient and caregiver cost of DKK 482, including DKK 383 for 2 lost hours of productivity and DKK 99 for transportation costs. This cost is only applied to the pegvaliase arm.

Time spent on dietary management

The value of lost leisure time is applied for the caregiver time spent on supporting the preparation and intake of medical food and LNAA supplements.

The 520 lost caregiver hours per year thus represents an indirect cost of DKK 71,893 which is applied for diet treatment in the cost analysis.

Caregiver costs were also applied on the sapropterin arm by 48% (DKK 34,509), on the LNAA arm by 25% (DKK 17,973), and on the pegvaliase arm by 31% (DKK 22,583) in year 1, 26%

(DKK 18,943) in year 2, and 12% (DKK 8,585) in subsequent years, for consistency with the dietary assumptions.

7.2.9 Comorbidity costs

PKU disease has negative effects on patients' health which go beyond the neuropsychiatric and neurocognitive symptoms. In a US register-based study published in 2018 [18], Burton and colleagues evaluated PKU comorbidities across various organ systems, to explore the disease burden in adult patients. PKU patients aged ≥20 years were compared to matched non-PKU controls in a dataset providing up to 16 years' follow-up (1998-2014). Prevalence rates were expressed as event rates per 100 person years (PY). The results demonstrated that the comorbidity burden in adult PKU patients is higher than that observed in the general population with similar demographic and clinical characteristics. This was demonstrated by higher prevalence of comorbid conditions in the PKU group compared with the controls and also through an increase in overall disease burden among PKU patients.

Further insights in PKU comorbidities was given by a German register based study ([19]), who analyzed outcomes of selected comorbidities in a 1-year time frame (Jan-Dec 2015) in PKU patients aged ≥18 years, and in matched controls from the general population.

The economic burden of the higher comorbidity prevalence was included in the economic model, based on the evidence from the 165-302 trial that a majority of Palynziq treated patients achieve normalized blood Phe levels (<120 µmol/L). It is here assumed that normalization of blood Phe levels restore the comorbidity prevalence rates to that of the general population. The cumulative probability of reaching normal levels with Palynziq is 51% by year 2 [6], and we thus assume that the event rate of half of Palynziq group (those with blood Phe >120 µmol/L) will persist at the prevalence among PKU patients, while the rate among the other half (those with blood Phe <120 µmol/L) will equal the rate of the general population.

This approach is conservative in the sense that improvement of comorbidities is only applied in patients with normalized blood Phe, while probable improvement on patients who are controlled (<600 µmol/L) but not normalized are overlooked. We also excluded comorbidities that were considered less reversible with blood Phe reduction.

7.2.9.1 Resource use

Prevalence in PKU (untreated cohort) of relevant comorbidities were sourced from the Rutsch [19] and Burton [18] studies. The literature data and the estimated improvement from Palynziq treatment, based on the assumptions discussed above, are presented in Table 16.

Table 16. Prevalence of selected comorbidities in PKU and in the general population

Disorder	Prevalence in PKU	Background prevalence	Source	Calculated prevalence in Palynziq treated patients (50% normalization)
Osteoporosis/Osteopenia	1.24%	0.79%	Burton 2018 [18]	1.02%
Renal insufficiency with or without hypertension	4.06%	1.93%	Burton 2018 [18]	3.00%
Overweight	5.35%	2.25%	Burton 2018 [18]	3.8%
Depression	19.6%	14.8%	Rutsch 2018[19]	17.2%
Anxiety/Phobias	10.6%	5.8%	Rutsch 2018 [19]	8.2%
Malnutrition/ Nutritional deficiencies	4.5%	3.8%	Rutsch 2018 [19]	4.15%
Sleep disturbances	8.8%	8.3%	Rutsch 2018 [19]	8.55%

Normalization of blood Phe levels (<120 µmol/L) is not observed upon treatment with sapropterin, LNAA or restrictive diet, thus the comorbidity prevalence in these treatment arms will reflect the PKU prevalence.

7.2.9.2 Unit cost

Relevant annual cost per patient, by disorder, were derived from the literature. Cost of brain disorders except the one for depression were derived from a publication describing costs of disorders of the brain in Europe in 2010 ([20]). In this publication, the estimated annual cost of the disorders specified above were presented per country, including costs specific to Denmark. With regards to the annual cost of depression in Denmark, no Danish publications could be identified. Instead, a Swedish publication describing the societal cost of depression in 10,000 patients in 2008 was utilized ([21]). The annual cost per patient with overweight in Denmark was sourced from a 2017 publication by Kjellberg and collegues who explored this cost with a register-based approach ([22]). The annual cost of renal dysfunction for Danish patients was sourced from a 2017 publication estimating the annual direct and indirect costs of patients with autosomal dominant polycystic kidney disease [23]. The annual cost per patient with osteoporosis in Denmark was estimated based on the cost of osteoporosis per capita and the prevalence in the total population, reported by Hernlund et al 2013 ([24]).

All costs were converted to DKK [25] and inflated to May 2020 mean price level (latest available) using the consumer price index [26].

The calculated annual unit costs for each comorbidity is presented in Table 17 below:

Table 17. Comorbidity annual cost per patient, converted to DKK 2020

Disorder	Total cost (DKK)	Direct healthcare costs (DKK)	Direct non-medical costs (DKK)	Indirect costs (DKK)
Renal dysfunction	82,257	28,978	NR	53,280
Osteoporosis	30,606	30,606	NR	0
Anxiety disorder	10,903	6,869	NR	4,034
Sleep disorder	8,019	4,411	NR	3,609
Eating disorder	5,521	3,920	497	1,104
Epilepsi	48,584	23,320	5,344	19,919
Depression	147,094	17,651	NR	129,443
Overweight (Obesity class I)	12,687	3,340	NR	9,347

7.2.9.3 Resulting cost

The calculated annual costs by treatment arm are presented in Table 18 and Table 19.

It should be noted that the indirect costs were not applied in the cost calculations of the model, they were only included initially to withdraw these costs from the total costs to generate the direct costs.

Table 18. Annual cost associated with PKU comorbidities in pegvaliase treated patients

Disorder	Pegvaliase			
	Total cost (DKK)	Direct medical costs (DKK)	Direct health care costs (DKK)	Indirect costs (DKK)
Renal dysfunction	2 464	868	0	1 596
Osteoporosis	3 290	3 290	0	0
Anxiety disorder	894	563	0	331
Sleep disorder	686	377	0	309
Eating disorder	229	163	21	46
Epilepsi	1 117	536	123	458
Depression	25 300	3 036	0	22 264
Total	33 980	8 833	144	25 003

Table 19. Annual cost associated with PKU comorbidities in LNAA, diet or sapropterin treated patients

Disorder	LNAA, diet or sapropterin			
	Total cost (DKK)	Direct medical costs (DKK)	Direct health care costs (DKK)	Indirect costs (DKK)
Renal dysfunction	3 340	1 176	0	2 163
Osteoporosis	3 979	3 979	0	0
Anxiety disorder	1 156	728	0	428
Sleep disorder	706	388	0	318
Eating disorder	248	176	22	50
Epilepsy	1 555	746	171	637
Depression	28 830	3 460	0	25 371
Total	39 813	10 654	193	28 966

7.3 Results

Table 20. Results – per patient costs, 20 years' time horizon, 4.0 % annual discounting

Cost components	Pegvaliase (DKK)	Comparator (DKK)			Difference (DKK)		
		LNAA	Sapropterin	Diet	vs. LNAA	vs. Sapropterin	vs. Diet
Direct costs	12,701,684	1,659,075	21,227,985	4,797,057	11,042,609	-8,526,301	7,904,627
- medicine costs	11,830,891	1,468,030	18,878,961	0	10,362,861	-7,048,071	11,830,891
- diet costs	792,069	101,746	2,259,724	4,707,758	690,323	-1,467,655	-3,915,689
- hospital costs	2,085	0	0	0	2,085	2,085	2,085
- non-hospital costs	0	0	0	0	0	0	0
- Comorbidity costs, direct costs	76,640	89,299	89,299	89,299	-12,660	-12,660	-12,660
Indirect costs	184,847	253,530	486,777	1,014,120	-68,683	-301,930	-829,273
- Cost of patient and caregiver time lost due to treatment	184,847	253,530	486,777	1,014,120	-68,683	-301,930	-829,273
Total costs per patient (base case)	12,886,531	1,912,605	21,714,762	5,811,177	10,973,926	-8,828,231	7,075,354

7.3.1 Base case results

7.3.1.1 Pegvaliase compared to LNAA

As can be seen in Table 20, treatment with pegvaliase is expected to be more costly when compared with LNAA (pegvaliase is 11.0 MDKK more costly over a time horizon of 20 years). The higher costs are almost exclusively incurred by the pegvaliase medicinal cost (10.4 MDKK higher), while savings in caregiver time and comorbidity costs are expected for patients treated with pegvaliase over a time horizon of 20 years.

7.3.1.2 Pegvaliase compared to sapropterin

Treatment with pegvaliase is expected to be less costly when compared with sapropterin (pegvaliase is 8.8 MDKK less costly over a time horizon of 20 years; Table 20). The cost savings are primarily due to reduced medicinal costs (total medicinal cost savings for pegvaliase is estimated to 7.0 MDKK compared with sapropterin) and from reduced costs for diet and caregiver costs.

7.3.1.3 Pegvaliase compared to restrictive diet

Treatment with pegvaliase is expected to be more costly when compared with restrictive diet alone (+7.1 MDKK per patient over 20 years; Table 20). The higher costs are incurred by the pegvaliase medicinal cost, which is to some extent countered with savings in dietary costs and reduced caregiver time.

7.4 Sensitivity analyses

7.4.1 Deterministic sensitivity analyses

Deterministic sensitivity analyses were performed for the base case, in which model parameters were varied by ±10%. Shorter time horizons were also assessed. The incremental results are presented in Table 21.

As shown, the results of the cost per patient analysis was the most sensitive to the average dose of pegvaliase and comparators, respectively. This reflects the findings from the base case analyses where the medicines costs were the major cost driver in all treatment alternatives except restrictive diet.

Table 21. Incremental results from deterministic sensitivity analyses

Analysis	Change from base case	Incremental cost (DKK)		
		Versus LNAA	Versus sapropterin	Versus diet
Base case		**10,973,926**	**-8,828,231**	**7,075,354**
Pegvaliase average maintenance dose (syringes per day)	±10%	9,827,178	-9,974,979	5,928,606
		12,120,675	-7,681,483	8,222,102
Comparator average dose per day	±10%	11,112,019	-6,940,335	7,075,354
		10,835,834	-10,716,127	7,075,354
Protein supplement cost, pegvaliase	±10%	10,919,114	-8,883,044	7,020,541
		11,028,739	-8,773,418	7,130,167
Protein supplement cost, comparator	±10%	10,958,664	-8,642,038	7,479,790
		10,989,189	-9,014,424	6,670,918
Low-protein food cost, pegvaliase	±10%	10,967,256	-8,834,902	7,068,683
		10,980,597	-8,821,560	7,082,025
Low-protein food cost, comparator	±10%	10,974,969	-8,790,780	7,117,300
		10,972,884	-8,870,585	7,033,409
Caregiver time, pegvaliase	±10%	10,960,682	-8,841,475	7,062,110
		10,987,171	-8,814,987	7,088,598
Caregiver time, comparator	±10%	10,994,087	-8,779,553	7,171,574
		10,953,765	-8,876,909	6,979,134
Time horizon	10 years	6,543,879	-5,288,016	4,214,461
Time horizon	5 years	3,578,803	-2,918,514	2,299,636

7.4.2 Scenario analysis

On request from DMC, a scenario analysis has been introduced where the pegvaliase dietary input data are based on the subgroup of the PRISM population that was matched against historic diet and sapropterin cohorts from the PKUDOS registry in a matched adjusted indirect comparison analysis [27]. This study reported adjusted natural protein intake during year 1 and year 2 of pegvaliase treatment, sapropterin treatment and diet alone treatment.

In the current cost analysis for the DMC submission, the cost associated with medical protein intake (i.e. the amount of protein intake from amino acid supplementation) is assessed, while Zori et al [27] reported natural protein intake. In order to apply the Zori data in the current analysis, the natural protein intake was used to estimate the average medical protein intake by subtracting the

average natural protein intake from the baseline average total protein intake of 64 g in the pegvaliase cohort reported in the Zori et al supplementary material [27]. The resulting input data applied in the scenario analysis are presented in Table 22. As a reference, the corresponding base case inputs were 24.2 g and 20.3 g for year 1 and year 2 on pegvaliase treatment, 37.0 g on sapropterin, and 77.0 g on diet alone treatment. The medical protein intake derived from Zori et al were thus lower than in the model base case, especially for diet alone treatment.

Table 22. Derivation of dietary input data derived from Zori et al 2019.

	Natural protein intake (reported in Zori 2019) [27]	Medical protein intake (calculated from Zori 2019)	Comment
Pegvaliase, year 1	49 g	15 g	
Pegvaliase, year 2	57 g	7 g	Year 2 data extended for rest of model horizon
Sapropterin, year 2	28 g	36 g	Year 2 data applied for entire model horizon[1]
Diet alone, year 2	22 g	42 g	Year 2 data applied for entire model horizon[1]

[1] One input value should be selected for the model, and the year 2 values were assumed to be more representative of the long-term dietary intake than the year 1 value. For reference, the reported natural protein intake at year 1 were similar those at year 2: 23 g and 27 g for sapropterin and diet alone, respectively [27].

The scenario analysis was modelled so that these alternative assumptions on medical protein intake also affected the assumptions on % of Phe-restricted diet maintained, which in turn had down-stream effects on the assumptions on consumption of Phe-free food and amount of caregiver time spent on supporting the dietary management.

The results of this scenario analysis are presented in Table 23. As compared with the base case analysis, this scenario resulted in a slightly smaller added cost versus LNAA treatment, a larger cost saving versus sapropterin treatment, and a larger added cost versus diet alone treatment.

Table 23. Incremental results from scenario analysis

Analysis	Incremental cost (DKK)		
	Versus LNAA	Versus sapropterin	Versus diet
Base case	10,973,926	-8,828,231	7,075,354
Scenario: dietary input from Zori et al 2019	10,597,285	-9,515,065	8,819,194

8 Budget impact analysis

8.1 Market forecast

As discussed earlier in section 2, the population of Danish patients over the age of 16 with moderate or classic PKU comprises 146 patients (PKU-database, 2020), and 6-10 children are born with PKU annually in Denmark. Approximately 40% of patients have classical PKU, and 6%

moderate PKU. Of the Danish patients over 16 years of age with moderate or classic PKU, 62% receive LNAA (PKU-database, 2020) [1].

These numbers translate into:

- 91 patients currently on LNAA treatment (146 patients × 62%), and
- 55 currently untreated patients;
- an adult patient population growth of on average 8 patients per year (average of 6-10 patients), of which
- ~3.7 new patients would have classical or moderate PKU (8 patients × 46%), and
- ~2.3 new patients would start LNAA treatment (3.7 patients × 62%) - in the absence of pegvaliase as a recommended treatment option.

Regarding sapropterin, according to Danish KOL input (April 2019 adboard), ~10% of adult patients are sapropterin responders, with 29 adult patients on sapropterin treatment at the time. Ten percent of 6-10 new patients per year would mean on average 0.8 new sapropterin patients per year. The sapropterin patients are assumed to belong to the mild PKU group.

Pegvaliase

BioMarin's prediction of patient numbers on pegvaliase treatment, if recommended in Denmark, are as follows, given that it's one treatment center in Denmark, and the limiting factor is the number of simultaneous patients in the induction/titration phases (I/T), which generally takes 6 months:

- During the first year, [redacted] are expected to start treatment and reach the maintenance dose, and [redacted] to enter the I/T phase.
- During the following year, [redacted] are expected to start treatment and reach the maintenance dose, and [redacted] new patients to enter the I/T phase.
- During the years 3-5; [redacted] per year are expected to start treatment and reach the maintenance dose, and [redacted] patients per year to enter the I/T phase.

If no patients discontinue treatment, this would sum up to [redacted] on Palynziq treatment by the end of year 5. However, clinical experience from US indicate that 10.3% of patients discontinue treatment during the first year. In the forecast, this was implemented from year 2-5, rendering a total number of [redacted] by the end of year 5.

LNAA

It is assumed that patients currently on LNAA treatment will continue on LNAA treatment, so that Palynziq treated patients will be found among currently untreated patients or patients on dietary restriction alone. Upon recommendation of Palynziq as standard treatment, new patients are expected to receive Palynziq treatment rather than LNAA treatment.

It is further assumed that 62% of patients that discontinue pegvaliase treatment will start LNAA treatment in the following year. The percentage is based on the current share of LNAA treated patients among Danish patients over 16 years of age with moderate or classic PKU [1].

Sapropterin

It is further assumed that the sapropterin patient number predictions will be independent of Palynziq recommendation.

The data and assumptions above can be summarized into the following 5-year predictions of patient numbers, with and without recommendation of Palynziq as standard treatment, as presented below (Table 24;Table 25).

In the excel model, more detailed tables are provided that specifies the number of patients per year by their year of treatment. This separation of patients by their year of treatment allows the analysis to consider which year the patients start treatment.

Table 24. Number of patients per year if pegvaliase is recommended as standard treatment

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Palynziq	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LNAA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sapropterin [1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dietary/No treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	175	179	184	188	193

[1] The sapropterin patients are assumed to be in the mild PKU population

Table 25. Number of patients per year if pegvaliase is not recommended as standard treatment

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Palynziq	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LNAA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sapropterin [1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dietary/No treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	175	179	184	188	193

[1] The sapropterin patients are assumed to be in the mild PKU population

8.2 Calculations and Results

The total annual cost per treatment regimen is presented in the tables below (Table 26; Table 27). The total costs were derived by multiplying the number of patients for each treatment and treatment year, with the annual direct medical cost per patient for each treatment and treatment year. Undiscounted costs were applied in the budget impact calculations. For sapropterin, the drug costs were reduced by 37.7% to account for patient co-payment.

Results are presented separately for the scenario where pegvaliase is recommended as standard treatment (Table 26) and for the scenario when pegvaliase is *not* recommended as standard treatment (Table 27).

Table 26. Total costs per year if pegvaliase is recommended as standard treatment

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Palynziq	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sapropterin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LNAA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	60,765,597	67,262,937	74,896,619	82,675,880	90,368,876

Table 27. Total costs per year if pegvaliase is *not* recommended as standard treatment

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Palynziq	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sapropterin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LNAA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	58,416,745	59,960,923	61,505,100	63,049,278	64,593,455

If pegvaliase is recommended as standard treatment, the total costs are estimated to range from approximately 61 MDKK year 1 following introduction to 90 MDKK year 5. If pegvaliase is not recommended as standard treatment the total costs are estimated to range from approximately 58 MDKK year 1 following introduction to 65 MDKK year 5.

The total budget impact was derived by deducting the “pegvaliase is not recommended as standard treatment” total costs from the total costs of “pegvaliase is recommended as standard treatment”. The budget impact is presented in Table 28 below:

Table 28. Budget impact of recommending pegvaliase as standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
= (Costs of recommendation for standard treatment) – (costs without recommendation for standard treatment)	2,348,852	7,302,014	13,391,519	19,626,602	25,775,421

The total budget impact of recommending pegvaliase as standard treatment is estimated to approximately 2.3 MDKK year 1 and increases to 25.8 MDKK year 5 after introduction.

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Medicinrådet

Medicinrådets protokol for vurdering af pegvaliase til behandling af patienter over 16 år med fenylketonuri (PKU)

Versionsnr.: 1.1

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om protokollen

Protokollen er grundlaget for Medicinrådets vurdering af et nyt lægemiddel. Den indeholder et eller flere kliniske spørgsmål, som ansøger skal besvare i den endelige ansøgning, og som Medicinrådet skal basere sin vurdering på.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	09.03.2020
Ikrafttrædelsesdato	10.03.2020
Dokumentnummer	74518
Versionsnummer	1.1

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 10. marts 2020

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Palynziq
Generisk navn	Pegvaliase
Firma	BioMarin
ATC-kode	A16AB19
Virkningsmekanisme	Pegvaliase er et rekombinant enzym, som omdanner fenylalanin til ammoniak og *trans*-kanelsyre, som elimineres primært via leveren.
Administration/dosis	Pegvaliase findes i 2,5, 10 og 20 mg opløsning til subkutan injektion. Den anbefalede induktionsdosis er 2,5 mg administreret én gang om ugen i fire uger. Herefter titreres dosis gradvist op baseret på tolerabilitet, til der opnås fenylalanin-koncentration i blodet (serum) på 120 til 600 mikromol/l. Vedligeholdelsesdosis er individuelt tilpasset sådan, at patienten opnår kontrol med fenylalanin-koncentrationen, indregnet patientens indtag af protein via kosten og tolerabiliteten overfor pegvaliase. Den anbefalede maksimale dosis er 60 mg dagligt.
EMA-indikation	Pegvaliase er indiceret til behandling af patienter med fenylketonuri (PKU) i alderen 16 år og ældre, som har utilstrækkelig kontrol af fenylalanin i blodet (fenylalaninniveau i blodet på mere end 600 mikromol/l) på trods af forudgående anvendelse af tilgængelige behandlingsmuligheder. Pegvaliase modtog markedsføringstilladelse i maj 2019.
Accelerated assessment	Nej
Orphan drug	Ja
Conditional approval	Nej
Øvrige indikationer	Ingen

2 Forkortelser

ADHD-RS-IV: *Investigator-rated Attention-Deficit Hyperactivity Disorder Rating Scale*

BH4:	Tetrahydrobiopterin
BRIEF-V:	*Behaviour Rating Inventory of Executive Function* – voksne
CANTAB:	*Cambridge Neuropsychological Test Automated Battery*
CI:	Konfidensinterval
EMA:	*European Medicines Agency*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
LNAA:	*Large neutral amino acids*
OR:	*Odds ratio*
PAH:	Fenylalanin hydroxylase
PKU:	Fenylketonuri
POMS:	*Profile of Mood States*
RR:	Relativ risiko
WHOQOL:	*World Health Organization Quality of Life*

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af pegvaliase som mulig standardbehandling af patienter med fenylketonuri (PKU). I protokollen angives en definition af population(er), komparator(er) og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende pegvaliase modtaget den 30. april 2019.

Protokollen danner grundlag for den endelige ansøgning for vurdering af pegvaliase sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem pegvaliase og komparatorer af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

4 Baggrund

Fenylketonuri (PKU) er en medfødt stofskiftedefekt med autosomal recessiv arvegang. PKU skyldes mangel på funktionelt fenylalanin hydroxylase (PAH), som er et leverenzym involveret i omdannelsen af aminosyren fenylalanin til tyrosin. Fenylalanin indgår i alle kostens proteiner, og ved manglende omdannelse ophobes fenylalanin i blod og væv. Fenylalanin transporteres aktivt over blodhjernebarrieren via et aminosyretransport-protein og ved forhøjet fenylalaninkoncentration i blodbanen øges transporten ind i hjernen, hvor forhøjede mængder fenylalanin har skadelig virkning. De skadelige virkninger omfatter:

- Skader på de skeder der beskytter nervebaner (myelinskader) i form af forsinket eller manglende myelinisering hos børn og tab af myelin hos voksne [1–3]
- påvirkning af neurotransmittersignalering i hjernen [4]
- påvirkning af hjernens glutaminerge system [5]
- påvirkning af proteinproduktionen i hjernen [3].

Udover den skadelige virkning af fenylalanin vil der dannes mindre tyrosin, som er et forstadie til neurotransmitterne dopamin og serotonin. Lavere niveauer af tyrosin i hjernen, hos både børn og voksne, fører blandt andet til svækket neurotransmittersignalering i hjernen, med konsekvenser på indlæring, humør og social funktionsevne.

Uden behandling fører PKU til irreversibel hjerneskade hos børn, som kan medføre underudviklet hjerne (microcefali), neurologiske symptomer, mental retardering og epilepsi. Børn er pga. deres umodne hjerne mere udsatte, men også voksne vil uden behandling udvikle neurologiske, psykiatriske og psykologiske symptomer [6]. PKU indgår i det neonatale screeningsprogram, og behandling kan derfor iværksættes hurtigt, inden hjerneskade opstår. Følges behandlingen, udvikler barnet sig normalt. Tidligt og kontinuerligt behandlede patienter med PKU har normal intelligenskvotient, men scoren ligger lidt lavere sammenlignet med raske søskende og forældre [7].

Behandlingen af PKU indbefatter en meget restriktiv diæt med det formål at holde fenylalanin-koncentrationen i blodet og hjernen nede. Patienten får ofte sværere ved at følge diæten med alderen. Hos voksne forventes symptomerne at være reversible, hvis diæten genoptages efter en rimelig tid. Ved forhøjede niveauer af fenylalanin vil patienterne opleve symptomer i form af neuropsykologiske komplikationer såsom hovedpine, angst, aggressivitet og depression, som indtræder hurtigt og aftager, når fenylalaninkoncentration falder igen. Endelig har flere studier beskrevet påvirkning af de eksekutive funktioner hos velbehandlede patienter med en i øvrigt normal mental udvikling [8,9]. Eksekutive funktioner indebærer f.eks. evnen til planlægning samt kontrol af adfærd og handlinger, dømmekraft, fleksibilitet i tankegang, evnen til at ændre strategier samt løbende at justere egen adfærd. Som konsekvens ses problemer med job, uddannelse, sociale

relationer, søvn og en manglende evne til at interagere med samfundet [10–14]. Sværhedsgraden af symptomer korrelerer med koncentrationen af fenylalanin i blodet [7,15], men følsomheden overfor forhøjet fenylalanin varierer fra patient til patient. Følsomheden menes at falde med alderen for nogle patienter. PKU er forbundet med forringet livskvalitet [16–18], og sværhedsgraden af PKU er negativt associeret med patientens helbredsrelaterede livskvalitet [16]. Diætbehandlingen medfører, at PKU-patienter har øget risiko for nyresvigt, knogleskørhed, åreforkalkning, forhøjet blodtryk og blodprop i hjernen [19–21].

Prævalensen af PKU i Danmark er estimeret til ca. 1:10.000 [22], og der fødes årligt 6-10 børn med PKU i Danmark [23]. Alle danske patienter behandles ved Center for PKU under Rigshospitalet i København. Ifølge Den Neonatale Screenings Biobank (PKU-biobanken) er der 488 PKU-patienter i Danmark, hvoraf 357 er 16 år eller ældre. 46 af de voksne patienter er sendiagnosticeret.

PKU inddeles i fire sværhedsgrader. I Danmark baseres klassifikationen af PKU på, hvilke(n) mutationer patienterne har, idet nogle mutationer påvirker funktionen af PAH-enzymet mere end andre. Nogle patienter vil have nogen, omend betydeligt, nedsat enzymaktivitet, mens andre slet ingen enzymaktivitet har. Patienter med nogen bevaret PAH-aktivitet har mildere sygdom og lettere ved at holde fenylalaninniveauet nede. De kan også være kandidater til medicinsk behandling (se afsnittet nuværende behandling), der øger PAH-aktiviteten. Patienterne, voksne og børn samlet, opdeles i:

- Klassisk PKU (40 %)
- moderat PKU (6 %)
- mild PKU (25 %)
- mild hyperfenylalaninæmi (20 %).

Ni procent er enten uklassificerede, ikke undersøgte eller andet. Tallene inkluderer ikke sendiagnosticerede patienter. Tallene er baseret på data fra PKU-databasen.

I andre lande tager klassifikationen af PKU udgangspunkt i fenylalaninniveauet i blodplasma før påbegyndelse af diæt. Her kan klasserne defineres på følgende måde:

- Klassisk PKU (> 1.200 mikromol/l)
- moderat PKU (900-1.200 mikromol/l)
- mild PKU (600-900 mikromol/l)
- mild hyperfenylalaninæmi (< 600 mikromol/l) [24].

Til sammenligning ligger koncentrationen hos baggrundsbefolkningen mellem cirka 40-60 mikromol/L.

Fagudvalget vurderer, at det i praksis vil være voksne patienter med moderat og klassisk PKU, der har den største risiko for ikke at kunne nedbringe deres fenylalaninkoncentration i blodet til under 600 mikromol/l ved diæt eller anden behandling. Derved vil de have ukontrollerede blodniveauer af fenylalanin, som angivet i indikationen for pegvaliase.

Ved indførelsen af en ny behandlingsmulighed, der tillader en mere lempelig diæt, forventer fagudvalget, at flere patienter vil foretrække medicinsk behandling fremfor diæt.

I alt udgør populationen af danske patienter over 16 år med moderat eller klassisk PKU 146 patienter (PKU-databasen, 2020). Hovedparten forventes af have fenylalaninniveauer over 600 mikromol/l. Alle patienter monitoreres livslangt ved at indsende en selvadministreret blodprøve til det behandlende center med posten. Patienter tilbydes en neuropsykologisk vurdering med test af eksekutive funktioner én gang årligt.

4.1 Nuværende behandling

Behandlingen af PKU er livslang og består af en meget restriktiv diæt, som begrænser proteinindtaget fra naturlige kilder, hvorved indtaget af fenylalanin også begrænses. Patienter med PKU, som følger diæten skal helt undlade kød, fisk, mejeriprodukter, brød, ris, pasta og andre kornprodukter samt proteinholdige grøntsager som nødder og bælgfrugter i kosten. Andre grøntsager og fødevarer skal vejes og indtages i begrænset mængde. Da en sådan kost vil give alt for lidt protein og mangel på vitaminer og mineraler, suppleres med et diætpræparat som proteinerstatning og vitamin- og mineraltilskud. Diætpræparaterne indeholder alle aminosyrer på nær fenylalanin og gives i form af et pulver eller evt. senere i livet op mod 250 kapsler eller tabletter dagligt. Pulveret blandes med vand og drikkes til måltiderne. Ud over pulver og tabletter findes aminosyretilskuddet også som flydende (”*ready to drink”*), barer og andre tabletter, man ikke skal tage så mange af. Mængden af aminosyretilskud bliver ordineret ud fra vægt, alder og aktivitetsniveau.

For hovedparten af patienterne, som helt mangler PAH-aktivitet, er den restriktive diæt i kombination med proteinerstatning den eneste nuværende behandlingsmulighed og opleves af mange voksne patienter som overordnet svær at følge.

Patienter med mild PKU, som har nogen bevaret PAH-aktivitet, kan i tillæg til diætkost blive behandlet med sapropterin (Kuvan). Sapropterin, en syntetisk form af co-faktor tetrahydrobiopterin (BH4), virker ved at øge metabolismen af fenylalanin til tyrosin, idet PAH-proteinstrukturen stabiliseres, og den tilbageværende aktivitet af PAH forøges.

Behandlingsmålet, hvad end patienten behandles med sapropterin i kombination med diætkost eller blot med en diætkost, følger europæiske PKU-guidelines, hvor der anbefales livslang kontrol med patientens fenylalaninniveau for at undgå de kliniske manifestationer af sygdommen. For børn og voksne > 12 år anbefales et fenylalaninniveau i blodet på 120-600 mikromol/L [25,26]. Forholdet mellem blod- og hjerneniveauet af fenylalanin ligger omkring 4:1 til 3:1 [27–29].

Børn med PKU er generelt velbehandlede, idet forældre og andre omsorgspersoner er involveret i at sikre, at den restriktive diæt følges. For unge voksne ses, at det bliver stadig sværere at følge diæten på grund af påvirkning fra venner, de voksende krav i skolen samt at ansvaret for egen diæt i stadig større grad overlades til den unge selv. I voksenalderen ses, at mange patienter ikke når i mål i med at opnå kontrol med fenylalaninniveauet, som overstiger de anbefalede 600 mikromol/l på trods af diætrestriktioner.

Voksne patienter med PKU, der ikke formår at følge den klassiske diætbehandling eller er sendiagnosticerede og/eller hidtil ubehandlede, kan tilbydes en mere lempelig diætbehandling (semifri diæt), hvis de samtidig indtager et kosttilskud med lange neutrale aminosyrer (*large neutral amino acids;* LNAA) uden fenylalanin. Et sådant kosttilskud kan øge konkurrencen mellem fenylalanin og de øvrige LNAA’er og nedsætte transporten af fenylalanin til hjernen [3,20]. Tilskud af LNAA sænker derfor ikke fenylalanin i blodbanen, som derfor anbefales at ligge mellem 900-1500 mikromol/l. Overskrides den nedre grænse på 900 mikromol/l kan proteinbehovet ikke dækkes fra kosten, medmindre man bliver suppleret med aminosyretilskud. Af de danske patienter over 16 år med moderat eller klassisk PKU får 62 % LNAA (PKU-databasen, 2020).

Semifri diæt tillader patienterne at spise frugt og grønt, ris og pasta og brød uden at veje det. Brugen af LNAA i behandlingen af PKU er især hyppig i Danmark. Omend både dyrestudier [30–33] og kliniske studier [27,28,34–36] indikerer, at LNAA kan have en gavnlig effekt hos PKU-patienter, er der ikke endnu lavet et studie, der systematisk sammenligner effekten af LNAA med den klassiske diæt. Af samme grund begrænses LNAA til voksne patienter, hvis hjerne er mindre sårbar end et barns udviklende hjerne. Den kliniske erfaring i Danmark er, at voksne patienter ved at indtage LNAA-kosttilskud uden fenylalanin opnår en acceptabel sygdomskontrol, øget livskvalitet, forbedret niveau af neurotransmittere i hjernen og en bedre

adhærens til behandling [31,37]. Evt. skadelige effekter af det høje blodniveau af fenylalanin ved LNAA-behandling er ikke kendt.

Den overordnede behandling er rettet mod at undgå de kliniske manifestationer af sygdommen samt øge livskvaliteten hos patienter med PKU.

4.2 Pegvaliase

Pegvaliase er indiceret til behandling af patienter med PKU i alderen 16 år og ældre, som har utilstrækkelig kontrol af fenylalanin i blodet (defineret ved et fenylalaninniveau i blodet på mere end 600 mikromol/l påvist i over 50 % af indsendte månedlige blodprøver over en sammenhængende periode på minimum 6 måneder [20]) på trods af forudgående anvendelse af tilgængelige behandlingsmuligheder inklusive sapropterin og restriktiv diæt.

Pegvaliase er et rekombinant enzym, som omdanner fenylalanin til ammoniak og transkanelsyre, som udskilles i leveren. Herved sænkes patientens fenylalaninniveau i blodet uafhængigt af PAH-aktivitet, hvilket adskiller sig fra tilgængelige terapeutiske alternativer som sapropterin.

Pegvaliase administreres som en subkutan injektion, og den anbefalede startdosis er 2,5 mg administreret én gang ugentligt i 4 uger. Herefter titreres gradvist på basis af tolerabiliteten overfor pegvaliase, og vedligeholdelsesdosis fastlægges efterfølgende baseret på tolerabilitet og indtaget af proteiner i kosten, sådan at der opnås et fenylalaninniveau i blodet på 120 til 600 mikromol/l. Under induktionen og titreringen anvendes også præmedicinering med H1-receptorantagonist, H2-receptorantagonist og et lægemiddel mod feber på grund af potentialet for en akut systemisk overfølsomhedsreaktion.

Målet med pegvaliasebehandling er at opretholde den anbefalede fenylalaninkoncentration i blodet, mens kosten normaliseres.

5 Kliniske spørgsmål

5.1 Klinisk spørgsmål

Hvilken værdi har pegvaliase sammenlignet med enten en restriktiv diæt eller en semifri diæt i kombination med LNAA til behandling af PKU-patienter med ukontrollabelt niveau af fenylalanin i blodet?

Population
Patienter med moderat eller klassisk PKU i alderen 16 år og ældre med ukontrollabelt niveau af fenylalanin i blodet.

Intervention
Pegvaliase.

Komparator

- Restriktiv diæt
- Semifri diæt i kombination med LNAA.

Effektmål
Effektmålene fremgår af tabel 1 og er beskrevet i afsnit 5.3.

5.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, den mindste klinisk relevante forskel, som, fagudvalget vurderer, er klinisk relevant, og de valgte effektmåls kategori.

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. De relative effektestimater skal angives i relativ risiko (RR) eller hazard ratio (HR). Hvis studierne resulterer i en odds ratio (OR), skal denne transformeres til relativ risiko, jf. appendiks 2 i Medicinrådets håndbog. Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel samt indplacering i de tre effektmålsgrupper (”dødelighed” ”livskvalitet, alvorlige symptomer og bivirkninger” og ”ikkealvorlige symptomer og bivirkninger”).

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
Livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring fra baseline på PKU-QOL for hvert delelement (kvalitativ gennemgang pr. delelement)	10 point for hvert delelement
Uønskede hændelser	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel, der ophører behandling	10 %-point
			Kvalitativ gennemgang af uønskede hændelser inkl. bivirkninger	*Ikke relevant*
Fenylalaninkoncentration	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel, der opnår et kontrolleret niveau i blodet over 6 måneder fra start af vedligeholdelsesdosis	15 %-point
			Andel, der opnår et kontrolleret niveau i hjernen over 6 måneder fra start af vedligeholdelsesdosis	15 %-point
Naturligt proteinindtag	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel der kan øge deres naturlige proteinindtag til 40 g.	10 %-point
			Andel der kan øge deres naturlige proteinindtag til 70 g.	10 %-point
Psykiatriske effekter	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	ADHD-RS-IV, *inattention* (investigator-rated version)	Ansøger bedes redegøre for den mindste klinisk relevante forskel
			POMS	
Eksekutive funktioner	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	BRIEF-V	Ansøger bedes redegøre for den mindste klinisk relevante forskel

Hvor ikke andet er opgivet under beskrivelsen af de enkelte effektmål, ønskes længst mulig opfølgningstid.

5.2.1 Kritiske effektmål

Livskvalitet

Livskvaliteten for patienter med PKU er påvirket af kostrestriktionerne (og følgevirkningerne heraf), som sjældent er detaljeret beskrevet i generiske værktøjer til måling af livskvalitet. Livskvaliteten for PKU-patienter målt med generiske værktøjer kan ligge misvisende tæt på baggrundsbefolkningens [38]. Derfor ønsker fagudvalget, at livskvaliteten for voksne patienter med PKU (≥ 16 år) opgøres ved hjælp af et sygdomsspecifikt instrument til måling af livskvalitet, PKU-QOL [39]. Dette værktøj er selvrapporteret og er inddelt i fire domæner med spørgsmål, der afdækker patientens symptomer (12 spørgsmål), patientens diæt og kosttilskud (23 spørgsmål), patientens dagligdag med PKU (12 spørgsmål) og patientens følelser i relation til PKU (18 spørgsmål). Hvert svar giver fra 0-4 point, og scoren fra hvert domæne transformeres, så den ligger på 0-100, hvor en mediane score på 25 indikerer en lille påvirkning (*mild impact*) [39]. Jo højere score, jo lavere livskvalitet. Der er ikke beskrevet nogen mindste klinisk relevant forskel i litteraturen. Fagudvalget vurderer, at den mindste klinisk relevante forskel er 10 point mellem den gennemsnitlige score for hver gruppe opgjort pr. delelement [38]. På grund af usikkerheden om den mindste klinisk relevante forskel vil vurderingen også basere sig på en kvalitativ gennemgang af forskellene for hvert delelement.

I det tilfælde, at data ikke kan leveres for PKU-QOL, og til trods for at fagudvalget finder generiske værktøjer til måling af livskvaliteten hos patienter med PKU suboptimal, vil fagudvalget acceptere livskvalitet opgjort efter WHO's generiske livskvalitetsinstrument WHOQOL-100 [40]. Til sammenligning med andre generiske instrumenter til måling af livskvalitet, som EQ-5D og SF-36, kan WHOQOL-100, udover at inkludere fysisk og social funktion, psykisk og alment helbred i sin måling, også afdække kognitiv funktion af psykosocial karakter. Værktøjet består af seks domæner og 100 spørgsmål (pointscore 1-5 pr. spørgsmål), hvor der opnås en samlet score pr. domæne, og en score, der relaterer sig til den overordnede livskvalitet og helbredstilstand på tværs af domæner. Højere score angiver bedre livskvalitet. Fagudvalget finder, at især det psykosociale element af WHOQOL-100 er passende for populationen. WHOQOL-100 er tidligere anvendt til at teste livskvaliteten hos voksne patienter med PKU [41] og patienter med andre arvelige metaboliske sygdomme [42], men fagudvalget finder ikke, at det gennem disse studier er muligt at fastsætte en brugbar mindste klinisk relevant forskel. Angives data for WHOQOL-100 ønsker fagudvalget resultaterne opgjort specifikt for domænet, der måler psykosocial funktion ledsaget af en fyldestgørende argumentation fra ansøger for en mindste klinisk relevant forskel.

For livskvalitet gælder, at livskvalitet ønskes opgjort som ændring fra behandlingsstart til minimum seks måneder efter behandling.

Uønskede hændelser

Fagudvalget ønsker, at data for sikkerhed opgøres som behandlingsophør i kombination med en kvalitativ gennemgang af uønskede hændelser og bivirkninger. Der synes at være store individuelle forskelle i præferencer til behandling, og hvor godt patienter adhærerer til behandling, som ikke nødvendigvis afspejles af sygdomsgrad og symptomer. Derfor ønsker fagudvalget også en opgørelse af årsager til behandlingsophør.

Fagudvalget ønsker at foretage en kvalitativ gennemgang af alle uønskede hændelser og bivirkninger med øget opmærksomhed på eventuelle immunologiske effekter, effekter af forhøjede niveauer af mikronæringsstoffer pga. ensidig diæt, anafylaksiske reaktioner, smerter i leddene og allergiske reaktioner Fagudvalget vurderer, at en forskel på 10 %-point i behandlingsophør mellem grupperne er klinisk relevant.

5.2.2 Vigtige effektmål

Fenylalaninkoncentration

For høj koncentration af fenylalanin og for lav koncentration af andre neutrale aminosyrer i hjernen antages at påvirke hjernens vækst og funktion. I klinikken monitoreres PKU ved at bestemme blodniveau af fenylalanin. Fagudvalget fremhæver, at fenylalaninkoncentrationen i blodet er et surrogatmål for fenylalaninkoncentrationen målt i cerebrospinalvæsken, som dog kun kan undersøges med rygmarvspunktur eller ved MR-spektroskopi af hjernen, og som ikke anvendes i klinisk praksis til monitorering af PKU-patienter. Fagudvalget vurderer, at effektmålet *fenylalaninkoncentration* er vigtigt i forhold til at kunne belyse effekten af pegvaliase og ønsker effektmålet opgjort både ved målinger af fenylalanin i blodet og i hjernen. Fagudvalget fremhæver, at det anbefalede maksimale niveau i blodet på 600 mikromol/l er bestemt ud fra et estimat, som beskrives i de europæiske guidelines fra 2017 [20], men at der kun er sparsom evidens til at belyse et sådan klinisk relevant blodniveau. Koncentrationen af fenylalanin i hjernen er vigtig i forbindelse med sammenligningen med LNAA-behandling, da blodniveauet af fenylalanin her ikke vil være retvisende.

Fagudvalget bemærker, at niveauerne af fenylalanin i blodet fluktuerer over tid, og at kontrol af blodniveau ret beset bør vurderes på mere end én måling. Fagudvalget ønsker derfor data for det gennemsnitlige niveau for hver patient målt seks gange over seks måneder fra tiden, hvor et vedligeholdelsesniveau er opnået og herefter data for gennemsnittet af gennemsnittet (*mean of means*) mellem grupperne. Ca. 35 % af populationen med moderat eller klassisk PKU vurderes med nuværende behandling at opnå niveauer under 600 mikromol/l. Fagudvalget fastsætter den mindste klinisk relevante forskel til 15 %-point, hvilket svarer til, at ca. 20 flere patienter opnår kontrol med deres fenylalaninniveau.

Naturligt proteinindtag

Fagudvalget vurderer, at der er store udfordringer ved at følge den krævede restriktive diæt, og deres erfaring er, at der ofte er et proportionelt forhold mellem patienternes livskvalitet og graden af diætrestriktion. Patienternes naturlige proteinindtag kan måles ved kostregistreringer eller kostanamnese. Voksne med PKU indtager ca. 10 gram naturligt protein om dagen ved en restriktiv diæt. Til sammenligning indtager voksne uden PKU ifølge DTU fødevareinstituttet i gennemsnit 88 gram protein (mænd 101 gram versus kvinder 76 gram). Fagudvalget finder det klinisk relevant, at patienterne kan spise en semifri diæt, uden at fenylalaninniveauet overstiger 600 mikromol/l. Det svarer til et indtag på ca. 40-50 gram protein om dagen fra naturlige kilder. Derfor ønsker fagudvalget effektmålet opgjort som andel af patienterne, der øger deres proteinindtag til 40 gram fra naturlige kilder, som mål for en lempeligere diæt og færre restriktioner i patienternes hverdag. Med den restriktive diæt opfylder ingen af patienterne dette. For patienter, der behandles med LNAA, forventes hovedparten at opfylde dette. Fagudvalget vurderer, at den mindste klinisk relevante forskel er 10 %-point.

Fagudvalget ønsker også, at ansøger belyser potentialet for, at patienterne lever helt fri af diætrestriktioner og proteintilskud. For at undgå proteintilskud skal patienterne indtage ca. 70 gram protein om dagen. Derfor ønsker fagudvalget også andelen af patienter, der kan øge deres proteinindtag fra naturlige kilder til 70 gram om dagen. Den mindste klinisk relevante forskel er 10 %-point.

Psykiatriske effekter
Psykiatriske komplikationer er i udgangspunktet reversible hos voksne og inkluderer depression, fobier og angst. Fagudvalget ønsker psykiatriske effekter opgjort som ADHD-symptomer og humørrelaterede symptomer som angst, depression og vrede.

Investigator-rated Attention-Deficit Hyperactivity Disorder Rating Scale (ADHD RS-IV) er et værktøj til måling af uopmærksomhed og hyperaktivitet/impulsivitet hos voksne med ADHD. Underskalaen uopmærksomhed (*inattention*) er undersøgt i en *post hoc*-analyse af voksne med PKU og vurderes relevant for patienter med PKU [43]. ADHD RS-IV har den fordel, at symptomer og virkningen af symptomer rapporteres af forsøgslederen fremfor patienten selv, idet fuld selvbevidsthed om symptomer og virkninger af disse symptomer kan være problematisk hos voksne med PKU. Der er ikke beskrevet en mindste klinisk relevant forskel for patienter med PKU, men den mindste klinisk relevante forskel mellem to behandlinger er undersøgt i patienter med ADHD og er for ADHD-RS total score på 6,6 [44]. På grund af usikkerheden om den mindste klinisk relevante forskel for PKU-patienter på subskalaen *inattention* ønsker fagudvalget resultaterne opgjort specifikt for subskalaen, ledsaget af en fyldestgørende argumentation for en mindste klinisk relevant forskel i gennemsnitlig ændring i score fra baseline mellem grupperne samt en angivelse af niveauet for en normal opmærksomhedsfunktion.

Patienters humør inklusive angst og aggressiv adfærd kan evalueres ved brug af et standardiseret spørgeskema kaldet *Profile of Mood States* (POMS) [45,46] som foreslået af ansøger. Spørgeskemaet belyser humør inden for følgende fem kategorier: Angst (*tension*), depression, aggressiv adfærd (*anger*), vigør og træthed (*fatigue*). Fagudvalget er ikke bekendt med POMS, men har vurderet, at det kan anvendes, såfremt ansøger kan redegøre for, om kategorierne *tension* og *anger* er ækvivalent med angst og aggressiv adfærd. Høj POMS-score afspejler dårligere humør-relaterede effekter sammenlignet med en lav score. Spørgeskemaet er ofte anvendt, hurtigt administreret og kan udfyldes af andre end patienten selv, f.eks. af en pårørende. Fagudvalget vurderer, at en bedring af sygdomskontrol som resultat af et blodfenylalaninniveau under 600 mikromol /l også bør resultere i, at patienten eller pårørende/omgivelser oplever bedring i patientens humør inklusive omfanget af angst og aggressiv adfærd. Ansøger bedes redegøre for den mindste klinisk relevante forskel.

Fagudvalget ønsker disse effektmål opgjort som ændring fra behandlingsstart til tre måneder og seks måneder efter behandling.

Eksekutive funktioner

Eksekutive funktioner involverer evnen til at generere effektive måder at håndtere nye opgaver og situationer på. Eksekutive funktioner kan måles med spørgeskemaer og dels med neuropsykologiske tests. Fordelen ved sidstnævnte er objektiviteten, mens fordelen ved spørgeskemaet er generaliserbarhed til eksekutive funktioner i dagligdagslivet, som fagudvalget finder relevant for populationen.

Fagudvalget ønsker eksekutive funktioner hos voksne opgjort ved hjælpe af spørgeskemaet *Behaviour Rating Inventory of Executive Function* – Voksne (BRIEF-V). BRIEF-V er et velafprøvet og pålideligt spørgeskema, der omfatter en total score samt to underordnede indekser og en række subskalaer. Herved er det er muligt at generere en relativ detaljeret profil over behandlingseffekt på eksekutive funktioner som f.eks. impulshæmning, monitorering, arbejdshukommelse, emotionel kontrol, planlægning/organisering, initiering osv.

Nogle patienter kan have reduceret indsigt i egne eksekutive funktioner, og BRIEF-V findes derfor i to versioner, der udfyldes parallelt: en version til selvrapportering og en ekstern bedømmerversion. For at kunne vurdere effekten ønsker fagudvalget at se data for, hvor mange patienter der opnår det samme niveau som baggrundsbefolkningen for intervention og komparatorer. Fagudvalget ønsker, at ansøger redegør for niveauerne med nuværende behandling.

Såfremt data ikke kan leveres opgjort med BRIEF-V, ønsker fagudvalget eksekutive funktioner opgjort ved hjælp af en test af arbejdshukommelse og planlægningsevne. Fagudvalget vurderer, at eksekutive delelementer fra den neuropsykologiske test *Cambridge Neuropsychological Test Automated Battery* (CANTAB) er bedst til formålet. CANTAB er et valideret instrument, der er velbeskrevet i litteraturen (https://www.cambridgecognition.com/). Eftersom behandlingen med lægemidlet er indiceret til en

population med et bredt aldersspænd (≥ 16 år), finder fagudvalget, at CANTAB har den fordel, at testen er sensitiv over for alderens indvirkning på de eksekutive funktioner. Der kan i øvrigt forventes en re-test-effekt (læringseffekt) ved gentagen testning, som fagudvalget ønsker, der tages højde for i afrapporteringen.

5.3 Litteratursøgning

Vurderingen af klinisk merværdi baseres som udgangspunkt på data fra peer-reviewed publicerede fuldtekstartikler og data fra EMAs EPAR – public assessment report(s). Data skal derudover stemme overens med protokollens beskrivelser.

Sekretariatet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere peer-reviewede publicerede fuldtekstartikler, hvor pegvaliase er sammenlignet direkte med komparatorerne.

Sekretariatet fandt følgende artikel, som er relevant, og som kan anvendes til direkte sammenligningen med den ene komparator for flere af de definerede effektmål:

- Thomas et al. 2018. Pegvaliase for the treatment of phenylketonuria: Results of a long-term phase 3 clinical trial program (PRISM). Mol Genet Metab. 124(1):27-38.
- Harding et al. 2018. Pegvaliase for the treatment of phenylketonuria: A pivotal, double-blind randomized discontinuation Phase 3 clinical trial. Mol Genet Metab. 2018 May;124(1):20-26.

Virksomheden skal derfor søge efter yderligere studier, der kan belyse sammenligningen med den anden komparator (LNAA) og de effektmål der ikke belyses i de ovennævnte artikler. Til det formål har sekretariatet udarbejdet søgestrenge, som skal anvendes i MEDLINE (via PubMed) og CENTRAL (via Cochrane Library). Søgestrengene kan findes i bilag 1. Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparatorer.

Kriterier for udvælgelse af litteratur
Virksomheden skal først ekskludere artikler på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Inklusions- og eksklusionskriterier: Artiklerne skal være i overensstemmelse med det kliniske spørgsmål. Studier med andre populationer og studier der ikke rapporterer mindst ét af de kritiske effektmål ekskluderes.

6 Databehandling og analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention to treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser, specielt i forhold til præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængelig for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (ORR, SAE, behandlingsstop pga. bivirkninger og ikkealvorlige bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risikoreduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end ét sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

7 Andre overvejelser

I Danmark måles blodkoncentrationen af fenylalanin i blodplasma. Fagudvalget ønsker oplysninger fra ansøger omkring referenceværdier for måling af phenylalanin i serum, plasma og/eller stabiliseret blod (EDTA, Citrat, Heparin, Heparin-Na-Fluorid og Citrat-Na-Fluorid) før og efter behandling med pegvaliase, såfremt disse oplysninger findes. Herudover en oversigt over, hvilke assays der er anvendt til måling af ovenstående og baggrunden for valget herfor. Fagudvalget påpeger, at blodniveauet bør måles om morgenen inden eventuel morgenmad, og beder ansøger angive, hvilke retningslinjer der har været udstukket for måling af blodniveauet i studiepopulationen, inkl. om blodniveauet har været målt i kapillærblod eller veneblod. Formålet med disse oplysninger er at kunne vurdere, om de biokemiske data og referenceværdier er sammenlignelige med danske forhold, idet indikationen for pegvaliase er bundet op på blodniveauet af fenylalanin. Fagudvalget finder, at biokemiske data og referenceværdierne er afhængige af valg af assay og typen af blodopsamling samt døgnvariation af fenylalaninkoncentration i blodet.

Fagudvalget ønsker information om de kostmæssige instruktioner, som patienter blev underlagt i studiet inkl. eventuelle kosttilskud. Baggrunden herfor er at vurdere, om der er overensstemmelse mellem studiepopulationen og danske patienter.

Lægemidlet administreres ved ugentlige injektioner, og behandlingen forventes at være livslang. Fagudvalget ønsker en refleksion over eventuelle udfordringer ved administrationsvejen, f.eks. mulig indflydelse på adhærens til behandling. Herudover refleksion over om der er udsigter til selvadministration.

Fagudvalget er bekendt med, at antistofudvikling mod biologiske lægemidler kan forekomme, og at denne hændelse kan manifestere sig som en aftagende (af ellers helt eller delvis opnået) effekt. Selvom antistofudvikling er bedst undersøgt ved behandling med monoklonale antistoffer, er der indikationer på, at patienter også kan udvikle antistoffer mod polyethylene glycol (PEG), som er indeholdt i pegvaliase [47]. Det kan betyde en langsommere indsættende effekt og dermed længere tid inden opnåelse af et gavnligt vedligeholdelsesniveau. Fagudvalget ønsker på denne baggrund oplyst, om en potentiel antistofudvikling mod pegvaliase har været undersøgt i studiet. Herudover den gennemsnitlige tid for opnåelse af vedligeholdelsesniveauet hos studiepopulationen.

Fagudvalget ønsker om muligt informationer om, hvor stor en andel af patienterne, der opnår fenylalaninkoncentrationer mellem 120-360 mikromol/l og lavere for at vurdere, om lægemidlet har potentiale til helt at normalisere fenylalaninkoncentrationerne, jf. referenceværdier.

I det tilfælde, at ansøger leverer sparsom evidens på de i protokollen efterspurgte data, vil fagudvalget gennemgå evidensen narrativt.

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9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende fenylketonuri

Formand	**Indstillet af**
Allan Bayat Afdelingslæge	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Lars Bender Overlæge	Region Nordjylland
Kan ikke udpege en kandidat, der opfylder Medicinrådets habilitetskrav	Region Midtjylland
Ulrike Dunkhase-Heinl Overlæge	Region Syddanmark
Kan ikke udpege en kandidat, da regionen ikke har specialet	Region Sjælland
Kan ikke udpege en kandidat, der opfylder Medicinrådets habilitetskrav	Region Hovedstaden
Jette Lyngholm Nielsen Klinisk farmaceut	Dansk Selskab for Sygehusapoteksledelse
Christina Gade 1. reservelæge	Dansk Selskab for Klinisk Farmakologi
Bitten Aagaard Overlæge	Dansk Selskab for Klinisk Immunologi
Christine Melsted Jørgensen Klinisk diætist	Inviteret af formanden
Lise Lykke Thomsen Speciallæge i pædiatri	Inviteret af formanden
Helle Merete Dissing Patient/patientrepræsentant	Danske Patienter
Laura Hoffenzits Kristensen Patient/patientrepræsentant	Danske Patienter
Eksterne personer, som har bidraget til arbejdet	
Richardt Møllegaard Jepsen Seniorforsker, Ph.D., Specialpsykolog i børne- og ungdomspsykiatri	Udpeget af formanden

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. th. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Snezana Djurisic (projekt- og metodeansvarlig) Karen Kleberg Hansen (projektdeltager) Anette Pultera Nielsen (fagudvalgskoordinator) Jan Odgaard-Jensen (biostatistiker) Jesper Skov Neergaard/Bettina Fabricius Christensen (informationsspecialist) Annemette Anker Nielsen (teamleder)

10 Versionslog

Version	Dato	Ændring
1.1	4. juni 2020	Opdatering af fagudvalgets sammensætning med bidrag af ekstern ekspertise
1.0	09.03.2020	Godkendt af Medicinrådet.

11 Bilag 1. Søgestrenge

PubMed, https://www.ncbi.nlm.nih.gov/pubmed

Sæt	Søgetermer	Kommentarer
1	Phenylketonurias[mh]	Population
2	Phenylalanine hydroxylase/df[mh]	
3	phenylketonuria*[tiab] OR PKU[tiab]	
4	((phenylalanine hydroxylase[tiab] OR PAH[tiab]) AND deficiency[tiab])	
5	#1 OR #2 OR #3 OR #4	
6	pegvaliase[nm]	Lægemiddel
7	pegvaliase[tiab] OR Palynziq* [tiab]	
8	#5 AND (#6 OR #7)	Population + lægemiddel
9	Amino Acids, Neutral[mh]	(Diæt m.) LNAA
10	large neutral amino acid*[tiab] OR LNAA*[tiab]	
11	#5 AND (#9 OR #10)	Population + LNAA
12	#8 OR #11	Samlet søgning

CENTRAL, Cochrane Library https://www.cochranelibrary.com/advanced-search/search-manager

Sæt	Søgetermer	Kommentarer
1	[mh Phenylketonurias]	Population
2	(phenylketonuria* OR PKU):ti,ab,kw	
3	((phenylalanine hydroxylase OR PAH) NEAR/5 deficiency):ti,ab,kw	
4	#1 OR #2 OR #3	
5	(pegvaliase OR Palynziq*):ti,ab,kw	Lægemiddel
6	#4 AND #5	Population + lægemiddel
7	[mh "Amino Acids, Neutral"]	(Diæt m.) LNAA
8	("large neutral amino acid" OR "large neutral amino acids" OR LNAA*):ti,ab	
9	#4 AND (#7 OR #8)	Population + LNAA
10	#6 OR #9 in Trials	Samlet søgning