Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende ropeginterferon-alfa-2b til behandling af polycytæmia vera

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. ropeginterferon-alfa-2b, version 1.0
2. Forhandlingsnotat fra Amgros vedr. ropeginterferon-alfa-2b
3. Høringssvar fra ansøger
4. Medicinrådets vurdering vedr. ropeginterferonalfa-2b til behandling af polycytæmia vera, version 1.0
5. Ansøgers endelige ansøgning
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7. Medicinrådets protokol for vurdering vedr. ropeginterferon-alfa-2b til behandling af polycytæmia vera, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Ropeginterferon-alfa-2b

Polycytæmia vera

Version 1.0

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*.

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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
PV	Polycytæmia vera
SAIP	Sygehusapotekernes indkøbspris

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for ropeginterferon-alfa-2b, ca. [redacted] DKK pr. patient sammenlignet med hydroxyurea og [redacted] DKK pr. patient sammenlignet med pegyleret interferon-alfa-2a. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning hhv. ca. 3,0 mio. DKK og 3,4 mio. DKK pr. patient.

De inkrementelle omkostninger er primært drevet af lægemiddelomkostninger, og det er derfor behandlingsvarigheden, der har størst betydning for analysernes resultater. Yderligere er der usikkerhed omkring titreringsperiodens længde, men denne er ikke af væsentlig betydning for resultatet.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af ropeginterferon-alfa-2b som mulig standardbehandling vil være ca. [redacted] DKK mod hydroxyurea og ca. [redacted] DKK mod pegyleret interferon-alfa-2a i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne i år 5 ca. 24,7 mio. DKK mod hydroxyurea og 49,0 mio. DKK mod pegyleret interferon-alfa-2a.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af ropeginterferon-alfa-2b (Besremi) som mulig standardbehandling på danske hospitaler til polycytæmia vera.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra AOP Pharma. Medicinrådet modtog ansøgningen den 29. marts 2022.

3.1 Patientpopulation

Polycytæmia vera (PV) er en kronisk myeloproliferativ sygdom, hvor der sker en overproduktion af hovedsageligt røde blodlegemer (erythrocytter), men eventuelt også hvide blodlegemer (leukocytter) og blodplader (trombocytter). I Danmark diagnosticeres ca. 170 patienter årligt med PV. Ca. halvdelen diagnosticeres i 64-79-årsalderen, men en fjerdedel er yngre, og en fjerdedel er ældre [1]. 5-årsoverlevelsen i Danmark er ca. 80 % [1], og den samlede medianoverlevelse er opgjort til omkring 19 år [2]. PV betragtes dermed som en kronisk sygdom, dog med en vis overdødelighed [2].

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af ropeginterferon-alfa-2b på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har ropeginterferon-alfa-2b sammenlignet med hydroxyurea for patienter over 60 år med polycytæmia vera?

Klinisk spørgsmål 2:

Hvilken værdi har ropeginterferon-alfa-2b sammenlignet med pegyleret interferon-alfa-2a for voksne patienter under 60 år med polycytæmia vera?

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 ropeginterferon-alfa-2b sammenlignet med hydroxyurea eller pegyleret interferon-alfa-2a. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

Sammenligningen med hydroxyurea er lavet på baggrund af data fra CONTINUATION-PV [3] og Peginvera [4]. Continuation-PV er et ekstenderet fase 3 head-to-head-studie mod hydroxyurea, mens Peginvera er et fase 2-studie.

Sammenligningen med pegyleret interferon-alfa-2a er narrativ og baseret udelukkende på CONTINUATION-PV og MPN-RC 112 [5], sidstnævnte er et fase 3-studie, der sammenligner pegyleret interferon-alfa-2a med hydroxyurea.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en omkostningsanalyse til at estimere omkostningerne forbundet med behandlingen med ropeginterferon-alfa-2b. Denne tilgang er valgt, da ansøger ikke vurderer, at der er dokumenteret signifikant forskel mellem hverken hydroxyurea eller pegyleret interferon-alfa-2a.

Ansøger har indsendt en simpel kohortemodel uden effektmål. Modellen har en cykluslængde på fire uger, hvilket ansøger argumenterer er passende, da de subkutane behandlinger administreres hver fjerde uge.

Ansøger antager, at behandlingsvarigheden svarer til analysens tidshorisont for alle lægemidler, med et lille frafald baseret på andelen af behandlingsophør fra CONTINUATION-PV og MPN-RC-112. Dette er efterfølgende omregnet til en fire ugers sandsynlighed præsenteret i Tabel 1. Ansøger antager, at sandsynlighederne er konstante, dvs. at patienterne ved hver cyklus har samme sandsynlighed for at ophøre behandling gennem hele deres behandlingsforløb.

Tabel 1. Behandlingsophør i den sundhedsøkonomiske model

	Ropeginterferon alfa-2b[3]	**Hydroxyurea**[3]	**Pegyleret interferon-alfa-2a**[5]
Antal patienter, der ophører behandling	[redacted]	[redacted]	25/50 (50 %)
Sandsynlighed for behandlingsophør per cyklus	[redacted]	[redacted]	3,21 %

Medicinrådets vurdering af ansøgers modelantagelser

Medicinrådet er enigt i ansøgers valg af omkostningsminimeringsanalyse, da Medicinrådet vurderer, at modellering af effekt på baggrund af den kliniske evidens kan udelades, da der ikke er dokumenteret effektforskelle mellem behandlingerne.

Medicinrådet accepterer ansøgers antagelse om, at behandlingsvarighed svarer til analysernes tidshorisont. Dette skyldes, at behandling typisk varer til død eller intolerance, hvilket er repræsenteret ved det modellerede konstante frafald. Medicinrådet vurderer dog, at frafaldet ved pegyleret interferon-alfa-2a er meget højt og ændrer derved antallet af patienter, der ophører behandling til 40 %, hvilket sænker den fire ugers sandsynlighed for frafald til [redacted] % fra [redacted] %. Denne ændring vurderes at have minimal betydning for analysens resultat gennem en lille stigning i omkostninger for pegyleret interferon-alfa-2a.

Medicinrådet accepterer overordnet ansøgers tilgang vedr. modelantagelser med undtagelse af antallet af patienter, der ophører behandling af pegyleret interferon-alfa-2a.

4.1.2 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 5 år, hvilket ansøger begrunder med, at dette kan understøttes af det kliniske studie CONTINUATION-PV's opfølgningslængde.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 % pr. år.

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet vurderer, at ansøgers valgte tidshorisont ikke er tilstrækkelig til at opfange alle væsentlige forskelle i omkostningerne. PV er en kronisk sygdom, hvor behandlingen er livsvarig. Medicinrådet anslår, at patienter over 60 år behandles i ca. 14 år (klinisk spørgsmål 1), mens patienter under 60 år anslås at modtage behandling i ca. 30 år (klinisk spørgsmål 2). Medicinrådet ændrer derfor tidshorisonterne i analyserne til hhv. 14 år og 30 år.

Denne ændring vurderes at have stor betydning for analysens resultat, da omkostninger akkumuleres over længere tid.

Medicinrådet accepterer ansøgers valg vedr. diskontering, men ændrer tidshorisonten i begge analyser.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af ropeginterferon-alfa-2b sammenlignet med hydroxyurea og pegyleret interferon-alfa-2a. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger og patientomkostninger. Ansøger har ikke inkluderet bivirkningsrelaterede omkostninger, da ansøger antager, at sikkerhedsprofilerne er ens for alle lægemidlerne.

Omkostningerne er cyklusbestemt, hvilket betyder, at omkostningerne påregnes for hver cyklus.

4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP).

Ansøger baserer lægemiddeldoser på Medicinrådets protokol.

Ropeginterferon-alfa-2b
Ansøger har i den sundhedsøkonomiske analyse, på baggrund af Peginvera-studiet, estimeret, at en patient i gennemsnit modtager [redacted] mcg ropeginterferon-alfa-2b per uge svarende til [redacted] mcg hver fjerde uge. Yderligere antager ansøger, at der ikke forekommer spild, da injektionspennen for ropeginterferon-alfa-2b kan anvendes flere gange, hvorfor der årligt estimeres et forbrug på [redacted] injektionspenne eller [redacted] hver fjerde uge. Ansøger antager, at titreringsperioden samt et skift i administrationsintervallet er inkluderet i den udregnede gennemsnitlige dosis.

Tabel 2. Ropeginterferon-alfa-2b posologi

Gns. antal doser	Gns. behandlingslængde	Gns. dosis	Mcg per uge	Injektionspenne per år
[redacted]				

Hydroxyurea

Ansøger antager på baggrund af protokollen, at hydroxyurea administreres dagligt med en dosis på 15 mg/kg. Der antages en gennemsnitlig vægt på 76,11 kg [3], hvilket giver en daglig dosis på 1.141,56 mg rundet op til 1.500 mg, så det passer med et helt antal piller.

Pegyleret interferon-alfa-2a

Ansøger antager, at en hel injektionspen på 135 mcg pegyleret interferon-alfa-2a bruges per administration, da penne ikke kan gemmes.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger

Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 3.

Tabel 3. Anvendte lægemiddelpriser, SAIP (april 2022)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Ropeginterferon alfa-2b	250 mcg	1 stk.	[redacted]	Amgros
Hydroxyurea	500 mg	100 stk.	[redacted]	Amgros
Pegyleret interferon-alfa-2a	135 mcg	4 stk.	[redacted]	Amgros

Medicinrådet bemærker, at ansøger benytter en gennemsnitsdosis for ropeginterferon-alfa-2b igennem hele modellens løbetid. Medicinrådet vurderer, at dette ikke i tilstrækkelig grad fanger de reelle omkostninger ved optitrering. Dosis ændres derved til at repræsentere titreringsperioden, hvor dosis gradvist øges indtil en maksimal dosis på 310 mcg (svarende til ansøgers estimat af gennemsnitlig dosis). Jf. produktresuméet for ropeginterferon-alfa-2b, kan patienter overgå til behandling hver fjerde uge i stedet for hver anden uge. Dette bør tidligst ske 1,5 år efter opstart af behandlingen. Medicinrådet vurderer, at der vil gå ca. tre år, inden administrationsintervallet kan øges fra to uger til fire for den gennemsnitlige patient. Man vil sikre, at patienten har stabilt og vedvarende

respons, inden man øger administrationsintervallet. Dette vurderes at have en effekt på analysens resultat.

Medicinrådet vurderer, at ansøgers antagelser vedr. dosis med hydroxyurea er overestimeret. Medicinrådet vurderer, at der ikke vil være medicinspild ved behandling med hydroxyurea, da man øger/reducerer antallet af dage mellem administrationer, således at patienten får den optimale dosis. Den gennemsnitlige dosis anslås at være 750 mg. Medicinrådet ændrer derfor dosis til 750 mg dagligt. Denne ændring vurderes at have en minimal betydning for analysens resultat.

Medicinrådet accepterer ansøgers antagelser vedr. pegyleret interferon-alfa-2a.

Medicinrådet accepterer overordnet ansøgers valg vedr. lægemiddelomkostninger, men ændrer doseringsfrekvens for ropeginterferon alfa-2b samt fjerner medicinspild for hydroxyurea.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Ansøger har inkluderet administrationsomkostninger i form af oplæring til selvadministration for ropeginterferon-alfa-2b og pegyleret interferon-alfa-2a. Ansøger anvender DRG-takster for 2022 til estimering af omkostningerne.

Ansøger vurderer, at der ikke er administrationsomkostninger forbundet med behandling med hydroxyurea, da det indtages peroralt.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Medicinrådet accepterer ansøgers tilgang til estimering af administrationsomkostninger, men inkluderer en omkostning for en kommunal sygeplejerske, der forventes at hjælpe ca. 20 % af patienterne med subkutane injektioner. Anvendte enhedsomkostninger kan ses i Tabel 4.

Tabel 4. Omkostninger til lægemiddeladministration

	Enhedsomkostning [DKK]	Kilde
Oplæring i subkutan selvadministration	3.225	DRG 2022, 17MA98: MDC17 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD459 Polycythaemia vera, Procedure: BWAA31: Medicingivning ved subkutan injektion
Kommunal sygeplejerske	329	Medicinrådets værdisætning af enhedsomkostninger v1.6

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger.

Monitoreringsomkostninger

Ansøger antager, at alle patienter uanset behandling har to årlige monitoreringsbesøg i form af lægekonsultationer.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger

Medicinrådet vurderer, at ansøgers estimat om to årlige monitoreringsbesøg for alle behandlinger er rimelig, dog gælder dette først efter en evt. titreringsperiode (ropeginterferon-alfa-2b og pegyleret interferon-alfa-2a). Medicinrådet vurderer, at der under titrering vil være seks monitoreringsbesøg det første år og tre til fire de efterfølgende år.

Denne ændring vurderes at have lille betydning for analysens resultat.

Tabel 5. Omkostninger til monitorering

	Enhedsomkostning [DKK]	Kilde
Monitoreringsbesøg	3.225	DRG 2022, 17MA98: MDC17 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD459 Polycythaemia vera.

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger, men tilføjer et monitoreringsforløb for interferonbehandlingerne.

Bivirkningsomkostninger

Ansøger har ikke inkluderet omkostninger forbundet med bivirkninger, da de vurderer, at der ikke er væsentlige forskelle i sikkerhedsprofilen imellem behandlingerne.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Medicinrådet vurderer, at der på baggrund af de kliniske studier (PROUD-/CONTINUATION-PV og MPN-RC-112) ikke er dokumenteret væsentlige forskelle i bivirkningsprofilerne, og accepterer derfor ansøgers antagelse. Dog vurderes antagelsen at være usikker, da nogle af de kendte bivirkninger ved hydroxyurea, som eksempelvis non-melanom-hudcancer, først viser sig efter et længere behandlingsforløb, og de er derfor svære at opfange i studier.

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger.

4.2.3 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrations- og monitoreringsbesøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid. Ansøger inkluderer derudover omkostninger til hjemmeadministration af ropeginterferon-alfa-2b.

Ansøger anvender en enhedsomkostning for patienttid på 181 DKK pr. time og transportomkostninger på 140 DKK pr. besøg, jf. Medicinrådets værdisætning af enhedsomkostninger.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet accepterer ansøgers estimerede patienttid, som kan ses i Tabel 6.

Tabel 6. Estimat af effektiv patienttid

	Patienttid [minutter]
Monitoreringsbesøg	60
Hjemmeadministration ved subkutan injektion	10

Medicinrådet accepterer ansøgers tilgang til estimering af patientomkostninger. I Tabel 7 er estimater for patienternes gennemsnitlige årlige omkostninger vist.

Tabel 7. Estimerede patientomkostninger pr. år

	Ropeginterferon-alfa-2b [DKK]	Hydroxyurea [DKK]	Pegyleret interferon-alfa-2a [DKK]
Årlige omkostninger år 1	[redacted]	[redacted]	[redacted]
Årlige omkostninger år 2-3	[redacted]	[redacted]	[redacted]
Årlige omkostninger år 3+	[redacted]	[redacted]	[redacted]

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostninger.

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 blot udarbejdet to følsomhedsanalyser, hvor effekten af variation i tidshorisonten undersøges. Følgende følsomhedsanalyser er udført:

Tabel 8. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Følsomhedsanalyse 1 – 10-årig tidshorisont	Tidshorisonten svarer i denne analyse til den gennemsnitlige behandlingsvarighed. Behandlingsvarigheden vil sandsynligvis være kortere for nogle patienter.
Følsomhedsanalyse 2 – 40-årig tidshorisont	Tidshorisonten svarer i denne analyse til den gennemsnitlige behandlingsvarighed. Behandlingsvarigheden vil sandsynligvis være længere for nogle patienter, da nogle bliver diagnosticeret allerede i 40'erne.

Følsomhedsanalyse	Beskrivelse
Følsomhedsanalyse 3 – 18-måneders titreringsforløb	Det er meget usikkert, hvornår man vil forlænge administrationsintervallet fra hver 2. uge til hver 4. uge ved behandling med ropeginterferon-alfa-2b.
Følsomhedsanalyse 4 – 4-årig titreringsforløb	Det er meget usikkert, hvornår man vil forlænge administrationsintervallet fra hver 2. uge til hver 4. uge ved behandling med ropeginterferon-alfa-2b,
Følsomhedsanalyse 5 – Inkluder medicinspild for ropeginterferon-alfa-2b	Da patienter ikke modtager en fast dosis, kan der grundet pennens størrelse opstå medicinspild. Klinikere vil dog forsøge at ramme doseringer, der gør det muligt at nedbringe medicinspild.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Da ansøger kun har udført følsomhedsanalyser på tidshorisonten, og disse er væsentligt kortere end de af Medicinrådet valgte tidshorisonter, vælger Medicinrådet ikke at præsentere disse. Det skal dog nævnes, at det eneste parameter, der har større indflydelse på resultaterne, er den pris, ropeginterferon-alfa-2b indkøbes til.

Medicinrådet vælger at udføre følsomhedsanalyser på parametrene tidshorisont, titreringsperiode og medicinspild. Da prisen er den primære forskel mellem interventionen og de to komparatorer, vælger Medicinrådet at udføre følsomhedsanalyser på de førnævnte parametre, da de har direkte indflydelse på lægemiddelforbruget og derved de inkrementelle omkostninger.

Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser.

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
Tidshorisont	5 år	Klinisk spørgsmål 1: 14 år (sammenligning med hydroxyurea) Klinisk spørgsmål 2: 30 år (sammenligning med pegyleret interferon-alfa-2a)
Diskonteringsrate	3,5 %	3,5 %

Basisantagelser	Ansøger	Medicinrådet
Inkluderede omkostninger	Lægemiddel Administration Monitorering Patient og transport	Lægemiddel Administration Monitorering Patient og transport
Dosering:		
Ropeginterferon-alfa-2b	310 mcg hver 4. uge	310 mcg hver 2. uge (år 0-3) 310 mcg hver 4. uge (år 3+)
Hydroxyurea	1500 mg dagligt	750 mg dagligt 135 mcg ugentligt
Pegyleret interferon-alfa-2a	135 mcg ugentligt	
Inkludering af spild	Ja (Hydroxyurea og pegyleret interferon-alfa-2a)	Ja (pegyleret interferon-alfa-2a)

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.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK mod Hydroxyurea og ca. [redacted] DKK mod pegyleret interferon-alfa-2a i Medicinrådets hovedanalyse. Omkostningerne for ropeginterferon-alfa-2b falder dog væsentligt efter år tre, da administrationsintervallet herefter øges til hver 4 uge.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 3,0 mio. DKK mod hydroxyurea og ca. 3,4 mio. DKK mod pegyleret interferon-alfa-2a.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 10 og Tabel 11.

Tabel 10. Resultatet af Medicinrådets hovedanalyse ved sammenligning med hydroxyurea, klinisk spørgsmål 1, DKK, diskonterede tal

	Ropeginterferon-alfa-2b	Hydroxyurea	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	104.823	68.955	35.868
Patientomkostninger	13.119	7.085	6.034
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 11. Resultatet af Medicinrådets hovedanalyse ved sammenligning med pegyleret interferon-alfa-2a, klinisk spørgsmål 2, DKK, diskonterede tal

	Ropeginterferon-alfa-2b	Pegyleret interferon-alfa-2a	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	141.453	135.374	6.079
Patientomkostninger	18.465	19.164	-699
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 hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger vs. Hydroxyurea	Inkrementelle omkostninger vs. pegyleret interferon-alfa-2a
Resultatet af hovedanalysen	[redacted]	[redacted]
Følsomhedsanalyse 1 – 1-årig tidshorisont	[redacted]	[redacted]
Følsomhedsanalyse 2 – 10-årig tidshorisont	[redacted]	[redacted]
Følsomhedsanalyse 3 – 40-årig tidshorisont	Ikke relevant	[redacted]

Scenarie	Inkrementelle omkostninger vs. Hydroxyurea	Inkrementelle omkostninger vs. pegyleret interferon-alfa-2a
Følsomhedsanalyse 4 – 18-måneders titreringsforløb	[redacted]	[redacted]
Følsomhedsanalyse 5 – 4-årig titreringsforløb	[redacted]	[redacted]
Følsomhedsanalyse 6 – Inkluder komplet medicinspil for ropeginterferon-alfa-2b	[redacted]	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at ropeginterferon-alfa-2b vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Ropeginterferon-alfa-2b bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Ropeginterferon-alfa-2b bliver ikke anbefalet som mulig standardbehandling.

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

6.1 Estimat af patientantal og markedsandel

Ansøger har på baggrund af Medicinrådets protokol antaget, at der vil være hhv. 125 og 30 patienter om året, der ved anbefaling vil være kandidater til behandling med ropeginterferon-alfa-2b i de to populationer. I populationen over 60 år antager ansøger, at 10 % af incidente patienter vil blive behandlet med ropeginterferon-alfa-2b, mens der for populationen under 60 år vil være et højere initialt markedsoptag, der gradvist vil stige. Her vil 50 % blive behandlet med ropeginterferon-alfa-2b i år 1 og 90 % i år 5. Markedsoptaget i populationen under 60 er ifølge ansøger baseret på erfaring fra andre lande samt højere tolerabilitet.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er blevet konsulteret i forhold til patientantal, hvis ropeginterferon-alfa-2b anbefales som mulig standardbehandling, og hvis ikke ropeginterferon-alfa-2b anbefales. Fagudvalget estimerer, at ansøgers estimerede patientantal til den pågældende indikation er rimelige og har valgt ikke at ændre disse, se Tabel 13 og Tabel 14.

Tabel 13. Medicinrådets estimat af antal nye patienter over 60 år pr. år, klinisk spørgsmål 1

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Ropeginterferon-alfa-2b	13	25	38	50	63
Hydroxyurea	112	225	337	450	562
			Anbefales ikke		
Ropeginterferon-alfa-2b	0	0	0	0	0
Hydroxyurea	125	250	375	500	625

Tabel 14. Medicinrådets estimat af antal nye patienter under 60 år pr. år, klinisk spørgsmål 2

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Ropeginterferon-alfa-2b	15	36	63	96	135
Pegyleret interferon-alfa-2a	15	24	27	24	15
			Anbefales ikke		
Ropeginterferon-alfa-2b	0	0	0	0	0
Pegyleret interferon-alfa-2a	30	60	90	120	150

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet har accepteret ansøgers estimater i forhold til budgetkonsekvensanalysens patientantal.

Medicinrådet estimerer, at anvendelse af ropeginterferon-alfa-2b vil resultere i budgetkonsekvenser på ca. [redacted] DKK mod hydroxyurea og ca. [redacted] DKK mod pegyleret interferon-alfa-2a i det femte år efter en anbefaling. Resultaterne er præsenteret i Tabel 15 og Tabel 16.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 24,7 mio. DKK mod hydroxyurea og ca. 49 mio. DKK mod pegyleret interferon-alfa-2a i år 5.

Tabel 15. Medicinrådets analyse af totale budgetkonsekvenser mod hydroxyurea, klinisk spørgsmål 1, 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]

Tabel 16. Medicinrådets analyse af totale budgetkonsekvenser mod pegyleret interferon-alfa-2a, klinisk spørgsmål 2, 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 ropeginterferon-alfa-2b er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med hydroxyurea og ca. [redacted] DKK sammenlignet med behandling med pegyleret interferon-alfa-2a. De inkrementelle omkostninger er næsten udelukkende drevet af prisen for ropeginterferon-alfa-2b.

Analysen har visse usikkerheder omkring dosering af ropeginterferon-alfa-2b i form af behandlingslængden, titreringsperioden, og hvorvidt medicinspild kan minimeres. Disse usikkerheder påvirker lægemiddelforbruget, og da de inkrementelle omkostninger er drevet af prisen på ropeginterferon-alfa-2b, er usikkerheden omkring disse parametre væsentlig.

Hvis titreringsperioden forkortes til 18 måneder i analysen, bliver de inkrementelle omkostninger reduceret fra [redacted] DKK sammenlignet med hydroxyurea og [redacted] DKK sammenlignet med pegyleret interferon-alfa-2a til hhv. [redacted] DKK og [redacted] DKK. Hvis det antages, at der er medicinspild med ropeginterferon-alfa-2b, det vil sige patienter, der modtager ropeginterferon-alfa-2b, og som ikke gemmer rester fra injektionspenne til næste injektion, så øges de inkrementelle omkostninger fra [redacted] DKK sammenlignet med hydroxyurea og [redacted] DKK sammenlignet med pegyleret interferon-alfa-2a til hhv. [redacted] DKK og [redacted] DKK.

8. Referencer

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5. Yacoub A, Mascarenhas J, Kosiorek H, Prchal JT, Berenzon D, Baer MR, et al. Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. Blood. 2019;134(18):1498–509.

9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	31. august 2022	Godkendt af Medicinrådet.

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK mod hydroxyurea og [redacted] DKK mod pegyleret interferon-alfa-2a over en tidshorisont på 5 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 17 og Tabel 18.

Tabel 17. Resultatet af ansøgers hovedanalyse mod hydroxyurea, klinisk spørgsmål 1, DKK, diskonterede tal

	ropeginterferon-alfa-2b	hydroxyurea	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	[redacted]	[redacted]	[redacted]
Patientomkostninger	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 18. Resultatet af ansøgers hovedanalyse mod pegyleret interferon-alfa-2a, klinisk spørgsmål 2, DKK, diskonterede tal

	ropeginterferon-alfa-2b	Pegyleret interferon-alfa-2a	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	[redacted]	[redacted]	[redacted]
Patientomkostninger	[redacted]	[redacted]	[redacted]
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. Ansøger har estimeret patientantal og markedsandele præsenteret i Tabel 19 og Tabel 20.

Tabel 19. Medicinrådets estimat af antal nye patienter over 60 år pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Ropeginterferon-alfa-2b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxyurea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Anbefales ikke		
Ropeginterferon-alfa-2b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxyurea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 20. Medicinrådets estimat af antal nye patienter under 60 år pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Ropeginterferon-alfa-2b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegyleret interferon-alfa-2a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Anbefales ikke		
Ropeginterferon-alfa-2b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegyleret interferon-alfa-2a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af ropeginterferon-alfa-2b vil resultere i budgetkonsekvenser i år 5 på ca. [redacted]. DKK mod hydroxyurea og ca. [redacted] DKK mod pegyleret interferon-alfa-2a. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 21 og Tabel 22.

Tabel 21. Ansøgers hovedanalyse for totale budgetkonsekvenser mod hydroxyurea, 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]

Tabel 22. Ansøgers hovedanalyse for totale budgetkonsekvenser mod pegyleret interferon-alfa-2a, 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]

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16.08.2022
MGK, ECH

Forhandlingsnotat

Dato for behandling i Medicinrådet	31.08.2022
Leverandør	AOP Orphan Pharmaceuticals Sweden AB
Lægemiddel	Besremi (ropeginterferon-alfa-2b)
Ansøgt indikation	Polycytæmi vera

Forhandlingsresultat

Amgros har opnået følgende pris på Besremi (ropeginterferon-alfa-2b):

Tabel 1: Priser på Besremi (ropeginterferon-alfa-2b)

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Ny SAIP fra [redacted] (DKK)	Rabatprocent ift. AIP
Besremi (ropeginterferon-alfa-2b)	Injektionsvæske, opl. i pen 250 mcg/0,5 ml	1 stk.	17.502,29	[redacted]	[redacted]	[redacted]

Amgros har indgået en aftale med leverandøren, som er gældende fra [redacted].
[redacted]

Informationer fra forhandlingen

Amgros har ikke forhandlet med leverandøren, da Besremi (ropeginterferon-alfa-2b) har været i udbud.

Konkurrencesituationen

Nedenfor ses en sammenligning af årlige lægemiddelpriser, for lægemidler, som indgår i Medicinrådets vurdering.

Tabel 2: Sammenligning af lægemiddelpriser

Lægemiddel	Styrke/dosis	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddelomkostning SAIP pr. år (DKK)
Besremi (ropeginterferon-alfa-2b)	250 mcg/ 0,5ml/ 310 mcg hver 2. uge*	1 stk.	[redacted]	32	[redacted]
Besremi (ropeginterferon-alfa-2b)	250 mcg/ 0,5ml/ 310 mcg hver 4. uge**	1 stk.	[redacted]	16	[redacted]
Hydroxyurea	500 mg/ 750 mg dagligt	100 stk.	[redacted]	11	[redacted]
Pegasys (Peginterferon alfa-2a)	135 mcg/ 135 mcg ugentligt	4 stk.	[redacted]	13	[redacted]

*Administrationsinterval gældende for år 0-3 af behandlingen
**Administrationsinterval gældende efter år 3 af behandlingen

Status fra andre lande

Norge: Under vurdering[1]
Sverige: [redacted]
England: Under vurdering[2]

Konklusion

Amgros vurderer, at vi har opnået den bedst mulige pris, nuværende konkurrencesituation taget i betragtning.

[1] https://nyemetoder.no/metoder/ropeginterferon-alfa-2b-besremi
[2] https://www.nice.org.uk/guidance/indevelopment/gid-ta10497

Stockholm 2022-05-14

AOP comments on the DMC Value report and Health Economic report for BESREMi (ropeginterferon-alpha-2b).

Dear DMC,

Thank you for sharing your assessment of the clinical added benefit and health economic reporting for our AOP product BESREMi (ropeginterferon-alpha-2b).

We will in this document share our feedback on your reports.

Value Report

In general, AOP accepts that the value of BESREMi cannot be categorized within the DMC's framework.

As available data are limited and some of the values of BESREMi are not (yet) appropriately captured, we would also like to thank the DMC for acknowledging that there may be a potential (survival) gain for PV patients from optimizing treatment.

Clinical Questions #1

What added clinical value do ropeginterferon-alfa-2b bring in comparison with hydroxyurea for PV patients >60 years

- The DMC state that the safety is likely to be different for treatment over several years, where especially the increased risk of non-melanoma skin cancer when treated with hydroxyurea is in our belief of high importance since PV is a lifelong disease.
- Even more importantly, BESREMi is considered a disease modifying, non-leukemogenic substance resulting in additional, difficult to measure, value for patients suffering from PV
- The clinical evidence suggest that patients achieve a reduction in the JAK2 mutation burden in the long term with ropeginterferon-alpha-2b treatment, which is not the case for treatment with hydroxyurea, is not weighted in the DMC evaluation. AOP accept this but want to stress that many leading medical experts across Europe find this clinically relevant and important.

Clinical Question #2

What added clinical value do BESREMi (ropeginterferon-alfa-2b) bring in comparison with pegylated interferon-alfa2a for adult PV patients below 60 years

- The recognition of the fact that overall, ropeginterferon-alpha-2b may have a milder adverse reaction profile than pegylated interferon-alpha-2a is in our belief of high importance especially since PV is a lifelong disease.
- BESREMi is the only interferon-alfa with an approved label for PV, i.e., a proven benefit/risk ratio in PV patients which consequently provides a lowering of uncertainties for patients and physicians.
- BESREMi is supported by the largest clinical trial program within PV with a proven benefit/risk profile.

Budget Impact Model

DMC assessment on the BESREMi Budget Impact Model is also very well done and we at AOP accept all proposed changes but find it challenging to understand the proposed changes and underlying assumptions of the time horizons (see below).

- While understanding and accepting the rationale for increasing the time horizon to 14 or 30 years, we would like to stress that a simple prolongation of the time horizon would be a gross oversimplification of the treatment pathway.
  Rather one would be required to also include follow-on therapies of patients coming off HU/IFN into the equation (mainly Jakavi for patients treated with HU (in the absence of BESREMi), or HU/Jakavi for those patients treated with BESREMi /Pegasys 1L). Ideally, disease transformation would be considered in a 30-year horizon as well.
- Our reason for choosing 5-year time horizon was to have the comparisons between BESREMi vs hydroxyurea and BESREMi vs pegylated interferon-alfa-2a as clean as possible.
- We also want to clarify, as shared in the process, that we will be open to discuss the BESREMi pricing in Denmark and will hopefully come to an agreement with AMGROS in our meeting on 10th of June.

We look forward to your response and a continued dialogue.

Warm regards / Christian Feinberg on behalf of AOP Orphan Pharmaceuticals

Managing Director AOP Orphan Pharmaceuticals Sweden AB

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Medicinrådet

Medicinrådets vurdering vedrørende ropeginterferon-alfa-2b til behandling af polycytæmia vera

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	18. maj 2022
Dokumentnummer	141372
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet har vurderet effekten og sikkerheden af ropeginterferon-alfa-2b til behandling af patienter med blodkræftsygdommen polycytæmia vera, der har behov for cytoreduktiv behandling (behandling, der nedsætter antallet af blodceller). Patienterne behandles i dag med enten hydroxyurea (som udgangspunkt patienter, der er 60 år eller ældre ved starten af behandlingen) eller pegyleret interferon-alfa-2a (som udgangspunkt patienter, der er yngre end 60 år ved starten af behandlingen).

Det indsendte data tyder ikke på, at effekten af behandling med ropeginterferon-alfa-2b er væsentlig anderledes end effekten af de nuværende behandlinger. Værdien af ropeginterferon-alfa-2b i forhold til hydroxyurea og pegyleret interferon-alfa-2a kan dog ikke kategoriseres efter Medicinrådets metoder, fordi datagrundlaget er for usikkert.

I forhold til hydroxyurea vurderer Medicinrådet, at ropeginterferon-alfa-2b kan være et mere sikkert alternativ, hvis patienten skal behandles i mange år. Det skyldes, at der er en kendt sammenhæng mellem langtidsbehandling med hydroxyurea og udvikling af non-melanom hudkræft.

I forhold til pegyleret interferon-alfa-2a vurderer Medicinrådet, at ropeginterferon-alfa-2b muligvis medfører færre og mildere bivirkninger. Dette er dog usikkert, da lægemidlerne ikke er sammenlignet direkte med hinanden i et randomiseret klinisk studie.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 19. maj 2022

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. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

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

AML: Akut myeloid leukæmi

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*)

HR: *Hazard ratio*

IQR: *Interquartile range*

ITT: *Intention to treat*

JAK: Janus kinase

MKRF: Mindste klinisk relevante forskel

MPN-SAF: *Myeloproliferative neoplasms-symptom assessment form*

OR: *Odds ratio*

PICO: Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*

PV: Polycytæmia vera

PP: *Per Protocol*

RCT: Randomiseret kontrolleret studie *(Randomised Controlled Trial)*

RR: Relativ risiko

SMD *Standardized Mean Difference*

3. Introduktion

Formålet med Medicinrådets vurdering af ropeginterferon-alfa-2b (Besremi) til polycytæmia vera er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling. Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra AOP Pharma. Medicinrådet modtog ansøgningen den 29. marts 2022.

De kliniske spørgsmål er:

1. Hvilken værdi har ropeginterferon-alfa-2b sammenlignet med hydroxyurea for patienter over 60 år med polycytæmia vera?
2. Hvilken værdi har ropeginterferon-alfa-2b sammenlignet med pegyleret interferon-alfa-2a for voksne patienter under 60 år med polycytæmia vera?

3.1 Polycytæmia vera

Polycytæmia vera (PV) er en kronisk myeloproliferativ sygdom, hvor der sker en overproduktion af hovedsageligt røde blodlegemer (erythrocytter), men eventuelt også hvide blodlegemer (leukocytter) og blodplader (trombocytter). Stort set alle patienter med PV har en underliggende mutation i enzymet, Janus kinase-2 (JAK2), hvoraf langt størstedelen har en specifik mutation, JAK2 V617F [1,2]. JAK2-mutationen medfører en øget signalering fra receptorer, der kontrollerer dannelsen af røde blodlegemer, hvide blodlegemer og blodplader, og mutationen anses for at være den overordnede driver for udviklingen af PV [3].

I Danmark diagnosticeres ca. 170 patienter årligt med PV. Ca. halvdelen diagnosticeres i 64-79-års alderen, men en fjerdedel er yngre og en fjerdedel er ældre [4]. 5-års overlevelsen i Danmark er ca. 80 % [4], og den samlede medianoverlevelse er opgjort til omkring 19 år [5]. PV betragtes dermed som en kronisk sygdom, dog med en vis overdødelighed [5]. Sygdommen opdages oftest under udredning af andre symptomer, herunder cirkulationsproblemer eller blodpropper, som kan forekomme i alle dele af kredsløbet, men hos en del patienter opdages sygdommen pga. blodprøveresultater taget i anden sammenhæng.

PV indledes med en stabil fase af mange års varighed. I den stabile fase har patienterne en betydelig højere risiko for tromboemboliske hændelser med dertilhørende komorbiditet, sammenlignet med raske jævnaldrende, men patienterne kan også have en øget blødningstendens. Samlet set udvikler ca. 25 % tromboemboliske hændelser i sygdomsforløbet, men almindelige risikofaktorer for blodpropper har stor betydning for den enkelte patients samlede risiko [2]. Udviklingen af tromboemboliske- og andre kardiovaskulære hændelser er sandsynligvis en væsentlig faktor for overdødeligheden ved PV [5]. Patienternes sygdomssymptomer varierer meget i den stabile fase. De fleste patienter har ingen symptomer på diagnosetidspunktet, mens nogle oplever sygdomsrelateret hovedpine, svimmelhed, synsforstyrrelse, træthed, hudkløe, føleforstyrrelse i hænder eller fødder, hurtig mathed eller komplikationer i form af

blodprop eller blødning. De symptomer vil fortsætte med at påvirke patientens livskvalitet afhængig af behandlingsrespons.

Efter den stabile fase kan nogle patienter udvikle myelofibrose (6-10 %), som er en bindevævsdannelse i knoglemarven med fortrængning af blodproduktionen, eller akut myeloid leukæmi (AML) (3-5 %). Disse er alvorlige sygdomme med høj dødelighed og kan bidrage til en generel forringet overlevelse for patienter med PV [5,6].

3.2 Ropeginterferon-alfa-2b

Ropeginterferon-alfa-2b markedsføres under handelsnavnet Besremi® og har indikation som monoterapi til behandling af PV uden symptomatisk splenomegali (forstørret milt) hos voksne patienter. Lægemidlet fik markedsføringstilladelse i EMA i februar 2019. Fagudvalget vurderer, at symptomatisk splenomegali forekommer meget sjældent i patienter med PV, og at der ikke findes et klinisk ræsonnement for denne opdeling af patienter. Derfor fører dette kriterium i praksis ikke til en indskrænkning af den mulige patientpopulation.

Ropeginterferon-alfa-2b er et pegyleret interferon. Behandling med lægemidlet medfører både sænkede blodværdier og en reduktion af patientens JAK2V617F-mutationsbyrde (det molekylære mål for sygdomsmængden) [7,8]. Den bagvedliggende virkningsmekanisme er ikke fuldt klarlagt. Ved lægemidlets binding til cellemembranen initierer interferon en kompleks intracellulær kaskade, der bl.a. hæmmer cellevækst og differentiering og øger immunrespons. Virkningen synes altså at kunne tilskrives dels en effekt på celledeling, og dels en mulig effekt på kroppens immunrespons over for de sygdomsramte celler [9].

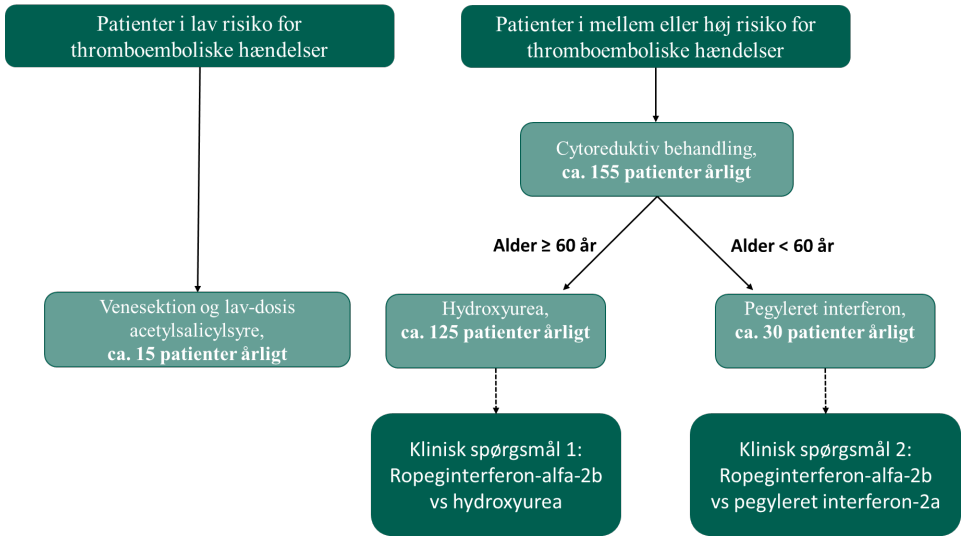
Ropeginterferon-alfa-2b er formuleret som en injektionsvæske (opløsning) i penne og administreres subkutant hver anden uge.

Startdosis er 100 µg og øges gradvist hver anden uge med 50 µg indtil stabilisering af hæmatologiske parametre (hæmatokrit < 45 %, blodplader < $400 \cdot 10^9$/l og hvide blodlegemer < $10 \cdot 10^9$/l). Doseringsintervallet kan forøges til hver 4. uge. Den maksimale enkeltdosis er 500 µg administreret hver 2. uge.

3.3 Nuværende behandling

Behandlingen af PV foregår typisk ambulant på hæmatologiske afdelinger. Behandlingen i den stabile fase er afhængig af risikofaktorer (alder > 60 år, tidligere tromboemboliske hændelser, blodpladetal, andre risikofaktorer for tromboser og antallet af hvide blodlegemer) [10]. Generelt fokuserer den på at reducere risikoen for at udvikle tromboemboliske hændelser ved at sænke hæmatokritværdien (volumenfraktionen af røde blodlegemer) til 45 % eller derunder [11]. For patienter i lav-risikogruppen (patienter uden nogen af de ovennævnte risikofaktorer) kan dette ofte håndteres ved venesektioner (blodtapninger) samt lav-dosis acetylsalicylsyre (se Figur 1 nedenfor) [10]. Fagudvalget vurderer, at dette gælder knap 10 % af patienterne.

Såkaldt cytoreduktiv behandling med lægemidler, der kan normalisere eller nærnormalisere blodværdierne, tilbydes i dag flere patienter end tidligere (omkring 90 % af patienterne), dels for at sænke de forhøjede blodværdier, og dels med henblik på at reducere behovet for venesektion. Cytoreduktiv behandling foregår normalt enten med lægemidlerne hydroxyurea eller pegyleret interferon-alfa-2a [11]. Lægemidlerne har forskellig virkningsmekanisme, administrationsform og bivirkningsprofil. Standardbehandlingen er pegyleret interferon, hvis patienten er under 60 år (knap 20 % af patienterne), mens hydroxyurea kan anvendes, hvis patienten er over 60 år (omkring 70-75 % af patienterne) (se Figur 1 nedenfor for behandlingsalgoritme og forventede patientantal) [10]. Opdelingen efter alder skyldes, at hydroxyurea er mistænkt for at kunne øge risikoen for sekundære neoplasier, og derfor ønsker man som udgangspunkt ikke at behandle yngre patienter med dette. Hydroxyurea har en dokumenteret effekt på patienternes risiko for kardiovaskulære events herunder arterielle tromboser ift. venesektion alene [12,13]. Pegyleret interferon-alfa-2a er ikke indiceret af EMA til behandling af PV, men anvendes som standard i klinisk praksis både i Danmark og internationalt inklusive de andre nordiske lande, da det giver sammenlignelig kontrol over blodværdierne med hydroxyurea og ikke mistænkes for at forårsage sekundære neoplasier [2,10,11].



Figur 1: Oversigt over behandlingsalgoritmen for patienter med polycytæmia vera og de deraf afledte kliniske spørgsmål.

Ved cytoreduktiv behandling kan der opnås en normalisering af blodværdierne (hæmatologisk remission/komplet hæmatologisk respons). Dette kan dog ikke sidestilles med helbredelse, idet den underlæggende JAK2-mutation, og derved sygdomsdriver, er uforandret. Behandling med pegylerede interferoner kan dog reducere antallet af celler, der bærer forandringen [14–16]. Det er uvist, hvad dette betyder for langtidsoverlevelse og livskvaliteten [2], men studier, der vil kunne dokumentere en eventuel effekt på overlevelsen, vil kræve meget lang observationstid og byde på udfordringer med hensyn til at holde populationerne separerede.

4. Metode

Medicinrådets protokol for vurdering vedrørende ropeginterferon-alfa-2b til behandling af polycytæmia vera 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

Klinisk spørgsmål 1 er:

Hvilken værdi har ropeginterferon-alfa-2b sammenlignet med hydroxyurea for patienter over 60 år med polycytæmia vera?

5.1.1 Litteratur

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

Ansøgningen baserer sig på den artikel, der er angivet i protokollen, samt én yderligere artikel, som ansøger har tilføjet (PEGINVERA-studiet).

Tabel 1. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, intervention og komparator
Gisslinger et al. 2020 [17] EPAR [9]	PROUD-PV og CONTINUATION-PV	NCT01949805 og NCT02218047	Voksne (≥ 18 år) med polycytæmia vera med JAK2-Val617Phe-mutation, som enten ikke tidligere har modtaget cytoreduktiv behandling, eller som maksimalt har været behandlet med hydroxyurea i 3 år. CONTINUATION var et opfølgningsstudie, hvor patienter, der havde gennemgået PROUD, blev behandlet i yderligere 24 måneder. For at blive inkluderet i opfølgningsstudiet skulle patienterne have: - Normaliseret niveau eller minimum 35 % reduktion fra	Fase III, open-label randomiseret klinisk studie. PROUD: Ropeginterferon-alfa-2b (n = 127) overfor hydroxyurea (n = 127) CONTINUATION: Ropeginterferon-alfa-2b (n = 95) overfor

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, intervention og komparator
			baseline af mindst 2 ud af 3 blodcelletal (hæmatokrit, blodplader, hvide blodlegemer), eller - Normaliseret miltstørrelse, eller - Klinisk bekræftet gavn af behandlingen med ropeginterferon-alfa-2b.	hydroxyurea (n = 76)
Gisslinger et al. 2015 [18]	PEGINVERA	NCT01193699	Voksne (≥ 18 år) med polycytæmia vera med JAK2-mutation, som enten ikke tidligere har modtaget cytoreduktiv behandling, eller som blev/havde været behandlet med hydroxyurea, men som ikke havde opnået kontrol med hematokritværdien eller oplevede andre sygdomssymptomer.	Fase-I/II, open-label ikke-kontrolleret klinisk studie. Ropeginterferon-alfa-2b (n = 51)

Ansøger har indsendt upublicerede data fra studierapporten fra PROUD-PV/CONTINUATION-PV for de effektmål, hvor data ikke er publiceret i Gisslinger et al. 2020 (andel af patienter, der oplever minimum én tromboembolisk hændelse samt kvantitative opgørelser af uønskede hændelser). Derudover har ansøger suppleret data fra Gisslinger et al. 2020 med data fra studierapporten for effektmålet, komplet hæmatologisk respons, da studierapporten indeholder data med længere opfølgningstid fra CONTINUATION-PV. Disse data besvarer effektmål i protokollens kliniske spørgsmål og lever op til Medicinrådets principper for anvendelse af upublicerede data, jf. Princippapir for anvendelse af upublicerede data i vurderinger af nye lægemidler og indikationsudvidelser. Desuden anvendes EMAs EPAR, der indeholder data for livskvalitet målt ved EQ-5D ved flere opfølgningstidspunkter [9]. Studierne PROUD-PV og CONTINUATION-PV er beskrevet yderligere nedenfor.

Ansøger har indsendt data fra det ikke-kontrollerede kliniske studie, PEGINVERA, som er en del af det samlede udviklingsprogram for ropeginterferon-alfa-2b [19]. Medicinrådet anvender ikke disse data til vurderingen af klinisk spørgsmål 1, da de stammer fra et ikke-kontrolleret studie, og der i forvejen er tilgængelige data til at foretage en direkte sammenligning af interventionen og komparatoren fra PROUD-PV/CONTINUATION-PV. Medicinrådet foretager således vurderingen af klinisk spørgsmål 1 alene ud fra studiedata fra PROUD-PV/CONTINUATION-PV baseret på én fuldtekstartikel (Gisslinger et al. 2020), EPAR og den kliniske studierapport.

PROUD-PV og CONTINUATION-PV

PROUD-PV var et fase III, multicenter (48 europæiske klinikker i Østrig, Bulgarien, Tjekkiet, Frankrig, Tyskland, Ungarn, Italien, Polen, Rumænien, Rusland, Slovakiet, Spanien og Ukraine), open-label, randomiseret klinisk studie, der undersøgte effekten og sikkerheden ved behandling med ropeginterferon-alfa-2b overfor hydroxyurea til voksne (≥ 18 år) med polycytæmia vera med kendt JAK2-Val617Phe-mutation. Patienterne var enten tidligere behandlet med hydroxyurea i maksimalt tre år eller nydiagnosticerede med et dokumenteret behov for cytoreduktiv behandling defineret som minimum én af følgende:

- Alder > 60 år
- Tidligere kardiovaskulært eller tromboembolisk event
- Manglende normalisering af hæmatokritværdien (< 45 %) ved gentagne venesektioner eller intolerance over for venesektioner
- Progressiv splenomegali
- Øgede blodpladetal (> 1000 · 10^9 blodplader/l) eller hvide blodlegemer (> 10 · 10^9 blodlegemer/l).

Patienterne, der tidligere var behandlet eller var i nuværende behandling med hydroxyurea, måtte ikke være i komplet respons defineret som hæmatokrit < 45 %, blodplader < 400·10^9/l, hvide blodlegemer < 10·10^9/l samt miltstørrelse ≤ 12 cm for kvinder og ≤ 13 cm for mænd. Samtidig måtte patienterne ikke have dokumenteret resistens eller intolerance over for hydroxyurea defineret som:

- Behov for venesektioner til at opretholde hæmatokrit < 45 % efter 3 måneders behandling med hydroxyurea (minimum 2 g/dag eller maksimalt tolereret dosis), eller
- Blodpladetal > 400·10^9/l og hvide blodlegemer > 10·10^9/l efter 3 måneders behandling med hydroxyurea (minimum 2 g/dag eller maksimalt tolereret dosis), eller
- Ingen afhjælpning af splenomegali eller sygdomsrelaterede symptomer efter 3 måneders behandling med hydroxyurea (minimum 2 g/dag eller maksimalt tolereret dosis), eller
- Nedsat hæmoglobin (< 10 g/dl), blodpladetal (< 100·10^9/l) eller neutrofiltal (< 1·10^9/l) ved den laveste dosis hydroxyurea, der samtidig giver hæmatologisk respons, eller
- Forekomst af bensår eller anden uacceptabel ikke-hæmatologisk toksicitet ved hydroxyurea.

Patienterne måtte ikke tidligere have modtaget pegyleret interferon. Randomiseringen var stratificereret i forhold til alder (ældre eller yngre end 60 år), forekomst af minimum én tidligere tromboembolisk hændelse og tidligere behandling med hydroxyurea.

Patienterne i interventionsarmen, der ikke var i behandling med hydroxyurea ved studiestart, startede behandlingen på 100 µg ropeginterferon-alfa-2b hver 2. uge. I de

første 12-ugers behandling blev dosis titreret op i trin på 50 µg per dosering (maksimalt 500 µg hver 2. uge), indtil patienten opnåede komplet hæmatologisk respons defineret som sænkning af blodværdierne til hæmatokrit < 45 %, blodplader < $400 \cdot 10^9$ blodplader/l og hvide blodlegemer < $10 \cdot 10^9$ blodlegemer/l. Ved komplet hæmatologisk respons forblev patienten på den dosis, hvor responset blev opnået. Patienter, der var i behandling med hydroxyurea ved randomiseringen, startede dosistitreringen med ropeginterferon-alfa-2b på 50 µg hver 2. uge og fik gradvist reduceret dosis af hydroxyurea over den første 12-ugers periode. Patienter i komparatorarmen blev ligeledes titreret op i dosis indtil komplet hæmatologisk respons. Overkrydsning mellem behandlingerne var ikke tilladt.

Studiets primære endepunkt var andelen af patienter med komplet hæmatologisk respons og samtidig normal miltstørrelse (længdediameter ≤ 12 cm for kvinder og ≤ 13 cm for mænd) efter 12-måneders behandling. Studiet var oprindeligt designet til at påvise en øget effekt af ropeginterferon-alfa-2b ift. hydroxyurea på det primære endemål, men den statistiske analyseplan blev ændret til at undersøge ikke-inferioritet, hvor grænsen for inferioritet var 10,5 % af responsraten for hydroxyurea. Studiets sekundære endepunkter inkluderede livskvalitet målt ved EQ-5D-3L, sikkerhed, komplet hæmatologisk respons og uden tilhørende krav om miltstørrelsen, tid til respons, responsvarighed og respons på JAK2-allelbyrden (molekylært respons).

Patienter, der gennemgik interventions- eller komparatorarmen i PROUD-PV, kunne indgå i opfølgningsstudiet CONTINUATION-PV, hvis de havde hæmatologisk respons på mindst 2 af blodcelletallene eller anden form for klinisk gavn af behandlingen. Komparatorarmen i CONTINUATION-PV bestod af patienter behandlet med hydroxyurea i PROUD-PV. I CONTINUATION-PV blev komparatorarmen ændret til '*best available treatment*', defineret som investigators valg blandt cytoreduktive behandlinger inklusive hydroxyurea, JAK2-hæmmer, konventionel eller pegyleret interferon-alfa (andet end ropeginterferon-alfa-2b), anagrelid, phosfor-32 eller busulfan. Størstedelen (97 % af patienterne) blev behandlet med hydroxyurea. Ca. 75 % af patienterne randomiseret til behandling med ropeginterferon-alfa-2b og 60 % af patienterne randomiseret til behandling med hydroxyurea ved starten af PROUD-PV fortsatte i CONTINUATION-PV. Det primære endepunkt bestod af to co-endepunkter, som indbefattede komplet hæmatologisk respons samt hhv. normal miltstørrelse og klinisk forbedring af polycytæmia vera-relaterede symptomer. De sekundære endepunkter var de samme som i PROUD-PV.

Tabel 2. Baselinekarakteristika ved indgangen til PROUD-PV

	PROUD-PV		CONTINUATION-PV*	
	Ropeginterferon-alfa-2b (n = 127)	**Hydroxyurea (n = 127)**	**Ropeginterferon-alfa-2b (n = 95)**	**Hydroxyurea (n = 76)**
Alder, median (range)	60 år (30-85)	60 år (21-81)	58 år (30-85)	59 år (32-79)
Køn (mand)	46 %	47 %	49 %	47 %
Tidligere behandlet med hydroxyurea	35 %	29 %	32 %	26 %
Varighed af tidligere behandling med hydroxyurea, median (IQR)	10,2 måneder (2,1-21,3)	7,9 måneder (2,7-19,2)	9,5 måneder (2,8-25,1)	8,2 måneder (2,6-23,0)
Tid fra diagnose, median (IQR)	1,9 måneder (0,7-11,2)	3,6 måneder (0,7-20,0)	1,8 måneder (0,6-6,8)	1,6 måneder (0,7-15,1)
Andel med tidligere tromboembolisk hændelse	20 %	18 %	22 %	18 %
JAK2-allelbyrde, gennemsnit (standardafvigelse)	41,9 % (24)	42,8 % (24)	42,8 % (23)	42,9 % (23)
Hæmatokritværdi, median (IQR)	47,1 % (44,2-51,3)	48,0 % (45,0-52,2)	47,7 % (44,4-52,0)	49,9 % (46,2-53,1)
Blodpladetal · 10^9/l, median (IQR)	485 (350-671)	452 (329-666)	488 (350-701)	451 (329-679)
Hvide blodlegemer · 10^9/l, median (IQR)	10,6 (8,0-13,4)	10,5 (7,9-14,5)	10,9 (8,0-14,6)	11,3 (8,7-15,1)
Miltstørrelse, median (IQR)	13,1 cm (11,0-15,0)	13,0 cm (11,5-15,2)	13,5 cm (11,5-15,0)	12,8 (11,3-15,5)
Andel med splenomegali	9 %	12 %	7 %	11 %

*: Baselinekarakteristika for CONTINUATION-PV viser karakteristika ved starten af PROUD-PV for de patienter, der efterfølgende indgik i CONTINUATION-PV. IQR = '*interquartile range*' = 25 % kvartilen til 75 % kvartilen.

Ved overgangen fra PROUD-PV til CONTINUATION-PV blev randomiseringen brudt, pga. selektionen af patienter ift. om de havde klinisk gavn af behandlingen (se ovenfor). Den brudte randomisering har dog ikke medført nogen bemærkelsesværdige ændringer i baselinekarakteristika, og fagudvalget vurderer, at baselinekarakteristika for interventions- og komparatorarmen er balancerede både i PROUD-PV og i CONTINUATION-PV. Fagudvalget bemærker desuden, at frafaldet af patienter mellem PROUD-PV og CONTINUATION-PV er størst i kontrolarmen. En eventuel skævhed vil medføre, at effekten af ropeginterferon sandsynligvis vil underestimeres ift. hydroxyurea, da patienterne uden respons ved behandling med hydroxyurea er frasorteret.

Ca. en tredjedel af patienterne har været i behandling med hydroxyurea inden studiestart med en median behandlingslængde på 8-10 måneder (maksimalt 3 år). Patienter, der tidligere havde vist resistens eller intolerance over for hydroxyurea, var dog ekskluderede (se ovenfor), og derfor forventer fagudvalget ikke, at det medfører en dårligere effekt af hydroxyurea i komparatorgruppen.

Patienterne i PROUD-PV og CONTINUATION-PV er yngre end patienterne i dansk klinisk praksis, hvis man sammenligner med den mediane debutalder for den samlede danske patientpopulation (ca. 60 år over for ca. 70 år medianalder). Fagudvalget bemærker dog, at man i dansk klinisk praksis normalt ikke behandler ældre patienter med interferoner, og gennemsnitsalderen i studiet stemmer derfor overens med de patienter, der i Danmark bliver tilbudt interferonbehandling. Miltstørrelse og blodbilledet er som forventet ved opstart af cytoreduktiv behandling.

Fagudvalget vurderer samlet set, at populationerne i PROUD-PV og CONTINUATION-PV er repræsentative for den forventede population i dansk klinisk praksis.

5.1.2 Databehandling og analyse

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

Ansøger har udført en direkte sammenligning af ropeginterferon-alfa-2b med hydroxyurea via data fra PROUD-PV og CONTINUATION-PV for alle effektmål defineret i protokollen. Ansøger anvender både data fra 12-måneders opfølgning i PROUD-PV og fra længst mulig opfølgning i CONTINUATION-PV (op til 60 måneder i alt).

Medicinrådet vurderer, at PROUD-PV og CONTINUATION-PV kan anvendes til en direkte sammenligning. Medicinrådet anvender data med længst mulig opfølgning til den direkte sammenligning og lægger dermed hovedsageligt vægt på data fra CONTINUATION-PV. Dette skyldes, at PV er en kronisk sygdom, hvor langtidsbehandling er forventet. Desuden er det almindeligt, at der går længere tid, inden hæmatologisk respons indtræder, og resultaterne indenfor de første 12 måneder er derfor ikke af afgørende betydning ift. behandlingsresultaterne på længere sigt. Medicinrådet bemærker dog, at data i CONTINUATION-PV kan være behæftet med større usikkerhed end data fra PROUD-PV, pga. den førnævnte selektion mellem studierne. Størstedelen af patienterne randomiseret i PROUD-PV indgik dog i CONTINUATION-PV (hhv. 75 % og 60 % for

ropeginterferon-alfa-2b og hydroxyurea), og baselinekarakteristika (Tabel 2) fra patienterne, der indgik i CONTINUATION-PV, indikerer, at populationerne stadig er sammenlignelige på trods af den brudte randomisering og stratificering. Medicinrådet bemærker, at ændringen i komparatorarmen fra hydroxyurea i PROUD-PV til *'best available treatment'* i CONTINUATION-PV ikke har nogen betydning, da 97 % af de patienter, der overgik til komparatorarmen i CONTINUATION-PV, fortsatte i behandling med hydroxyurea.

5.1.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor er en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (Afsnit 11, Tabel 10).

Evidensens kvalitet er nedgraderet ét trin pga. risiko for bias (se nedenfor), ét trin pga. mulig inkonsistens, da der kun indgår et studie i sammenligningen, og ét trin pga. unøjagtighed, da konfidensintervallerne omkring punktestimaterne er så brede, at de rummer både klinisk relevante forskelle og ingen forskelle.

Evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at der er høj risiko for bias forbundet med PROUD-PV og CONTINUATION, hovedsageligt pga. at studiet var ublindet. Dette kan have haft betydning for vurderingen af effektmålene og for frafaldet af patienter mellem PROUD-PV og CONTINUATION-PV.

Vurdering af risikoen for bias fremgår af bilag 1 (Tabel 8).

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 3. Resultater for sammenligningen af ropeginterferon-alfa-2b med hydroxyurea.

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal (ropeginterferon-alfa-2a vs. hydroxyurea)		Forskel i relative tal (ropeginterferon-alfa-2a vs. hydroxyurea)		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Tromboemboliske hændelser	Andel af patienterne, der oplever minimum en tromboembolisk hændelse (MKRF: 5 %-point)	Kritisk	[redacted]	Kan ikke kategoriseres	[redacted]	Kan ikke kategoriseres	Kan ikke kategoriseres
	Kvalitativ gennemgang af hændelserne		-	-	-	-	
Livskvalitet	MPN-SAF: Gennemsnitlig ændring fra baseline i *'total symptom score'* samt en kvalitativ gennemgang af domænescorer (MKRF: 10 point på *'total symptom score'*) eller EQ-5D: Gennemsnitlig ændring fra baseline (MKRF: 0,1 point ved EQ-5D utility-værdi eller 10 point ved EQ-5D-VAS)	Kritisk	Ikke angivet	Kan ikke kategoriseres	Ikke angivet	Kan ikke kategoriseres	Kan ikke kategoriseres

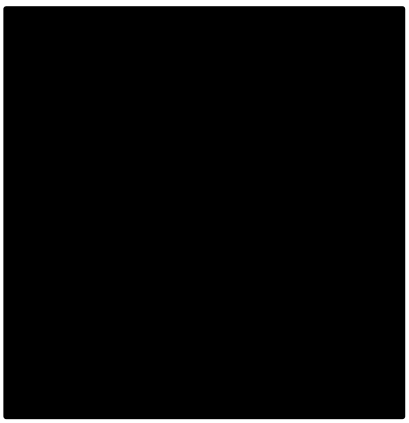
Bivirkninger	Andelen af patienter, der oplever minimum én uønsket hændelse af grad 3-4, (MKRF: 5 %-point)	Kritisk	[redacted]	Kan ikke kategoriseres	Ikke angivet	Kan ikke kategoriseres	Kan ikke kategoriseres
	Andelen af patienter, der oplever minimum én bivirkning af grad 3-4 (MKRF: 5 %-point)		[redacted]	Kan ikke kategoriseres	Ikke angivet	Kan ikke kategoriseres	
	Kvalitativ gennemgang af bivirkningsprofilen		-	-	-	-	
Komplet hæmatologisk respons	Andel af patienter, der oplever komplet hæmatologisk respons (MKRF: 15 %-point)	Vigtig	[redacted]	Ingen dokumenteret merværdi	[redacted]	Ingen dokumenteret merværdi	Ingen dokumenteret merværdi

Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget vurderer, at data ikke indikerer nogen forskelle af klinisk betydning ift. de prædefinerede effektmål.
Kvalitet af den samlede evidens	Meget lav.

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko

Tromboemboliske hændelser
Som beskrevet i protokollen er effektmålet tromboemboliske hændelser kritisk for vurderingen af lægemidlets værdi for patienterne, fordi tromboemboliske hændelser er en væsentlig årsag til øget sygdomsbyrde og overdødelighed for patienter med PV. Tromboemboliske hændelser dækker over både alvorlige hændelser, der kan medføre svær morbiditet eller død (eksempelvis lungeemboli og slagtilfælde), og milde hændelser (eksempelvis tromboflebit). Den forskellige alvorlighed af tromboemboliske hændelser betyder, at en samlet kvantitativ vurdering alene ikke nødvendigvis er retvisende. Derfor vurderer fagudvalget effektmålet ud fra en samlet vurdering af andelen af patienter, der oplever minimum én tromboembolisk hændelse (kvantitativ gennemgang), og hvilke specifikke hændelser der opstår (kvalitativ gennemgang).

Kvantitativ opgørelse af tromboemboliske hændelser
Ved 60-måneders opfølgningstid var andelen af patienter, der havde oplevet minimum én tromboembolisk hændelse hhv. [redacted] i interventions- og komparatorarmen. Andelen af patienter, der fortsatte behandlingen i CONTINUATION-PV, var større for ropeginterferon-alfa-2b end for hydroxyurea, og tromboemboliske hændelser er således opsamlet over i alt 499 patientår for ropeginterferon-alfa-2b over for 401 patientår for hydroxyurea. Den absolutte forskel er vist i Figur 2 nedenfor.



Figur 2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for tromboemboliske hændelser. De optrukne linjer indikerer den mindste klinisk relevante forskel (MKRF). De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor kan den foreløbige værdi af ropeginterferon-alfa-2b vedr. tromboemboliske hændelser ikke kategoriseres efter Medicinrådets metoder.

Den relative risiko var [redacted], hvorved den relative effektforskel ikke kan kategoriseres.

Kvalitativ gennemgang af tromboemboliske hændelser
Ansøger har indsendt en opgørelse over de tromboemboliske hændelser, der er opstået i løbet af studiet (Tabel 4).

Tabel 4: Oversigt over type og antal tromboemboliske hændelser registreret i løbet af PROUD-PV og CONTINUATION-PV. Bemærk, at tallene viser totale antal hændelser, og den samme patient kan opleve flere hændelser.

Tromboembolisk hændelse	Antal hændelser ved behandling med Ropeginterferon-alfa-2b	Antal hændelser ved behandling med hydroxyurea
Type og antal hændelser registreret i PROUD-PV		
Iskæmisk slagtilfælde kompliceret med hæmoragisk transformation	1	0
Iskæmisk slagtilfælde	1	0
Milttrombose / truncus coeliacus trombose*	1	0
Intrakardial trombe	1	0
Embolisme	0	1
Femoral arterieokklusion	0	1
Type og antal hændelser registreret i CONTINUATION-PV		
Iskæmisk slagtilfælde	1	0
Overfladisk tromboflebit	0	1
Dyb venøs trombose i ekstremitet	0	1
Cerebrovaskulær katastrofe	0	1

* Milttrombose / truncus coeliacus trombose opstod samtidig i én patient og skal betragtes som én hændelse.

Forekomsten af tromboemboliske hændelser er overordnet set lav i begge grupper. Der er ingen klare tendenser ift. alvorligheden af de tromboemboliske hændelser, og der er således ikke noget i den kvalitative gennemgang, der adskiller de to behandlinger.

Samlet vurdering af tromboemboliske hændelser
Den samlede værdi for ropeginterferon over for hydroxyurea kan ikke kategoriseres for effektmålet tromboemboliske hændelser, da usikkerhederne om estimaterne er for store. Fagudvalget vurderer, at der ikke er klinisk relevante forskelle mellem lægemidlerne for dette effektmål, hverken ud fra antallet eller alvorligheden af hændelser.

Livskvalitet
Som beskrevet i protokollen er effektmålet livskvalitet kritisk for vurderingen af lægemidlets værdi for patienterne, fordi sygdommen betragtes som kronisk, og patienterne kan have meget lange behandlingsforløb. Livskvaliteten kan fungere som et patientrelevant effektmål, som kan afveje, hvordan lægemidlernes fordele og ulemper samlet set påvirker patienten.

Livskvaliteten er opgjort vha. EQ-5D-3L som en samlet EQ-5D-score relativt til patienternes baselinemålinger. Efter 60-måneders opfølgning var de absolutte forandringer i den samlede score

Ansøger har ikke udført en statistisk sammenligning af effekterne mellem behandlingsarmene. Derfor kan værdien af ropeginterferon-alfa-2b ikke kategoriseres vedr. livskvalitet. Fagudvalget vurderer dog, at intet i data indikerer, at patienternes samlede livskvalitet påvirkes af hverken ropeginterferon-alfa-2b eller hydroxyurea.

Bivirkninger
Som beskrevet i protokollen er effektmålet bivirkninger kritisk for vurderingen af lægemidlets værdi for patienterne, fordi uønskede hændelser (*treatment emergent adverse events*) og bivirkninger (*treatment related adverse events*) af grad 3-4 er et udtryk for alvorlig toksicitet af lægemidlet, som kan påvirke patienternes livskvalitet.

Fagudvalget vurderer bivirkningerne samlet set ud fra kvantitative opgørelser af både uønskede hændelser og bivirkninger, da fagudvalget finder det relevant at vurdere, om der er forskelle i lægemidlernes toksicitet (afspejles i bivirkninger), men samtidig ønsker at vurdere, hvorledes dette kommer til udtryk i den samlede forekomst af uønskede hændelser, der også omfatter hændelser relateret til PV. Desuden foretager fagudvalget en kvalitativ gennemgang af bivirkningsprofilerne for ropeginterferon-alfa-2b og hydroxyurea.

Andelen af patienter, der oplevede minimum én hhv. uønsket hændelse og bivirkning af grad 3-4 er opgjort ved afslutningen af PROUD-PV (12 måneder) og ved 60 måneders opfølgning i CONTINUATION-PV. Fagudvalget lægger i vurderingen vægt på data med længst mulig opfølgning. Dette skyldes, at bivirkninger ved behandling med interferoner ofte er længere tid om at udvikle sig, hvorved forekomsten af bivirkninger muligvis underestimeres, hvis opfølgningstiden ikke er tilstrækkelig. Fagudvalget er bevidst om, at de kliniske data efter 60 måneder dækker over forskellige opfølgningsperioder mellem

intervention og komparator (499 patientår over for 401 patientår), hvilket kan føre til en lavere bivirkningsforekomst i komparatorgruppen.

Kvantitativ opgørelse af uønskede hændelser af grad 3-4
Over 60-måneders behandling oplevede [redacted]) minimum én uønsket hændelse af grad 3-4 i interventionsarmen, mens det tilsvarende var tilfældet for [redacted] i komparatorarmen. Ansøger har ikke udregnet et konfidensinterval omkring den absolutte forskel og har heller ikke udregnet en relativ forskel. Fagudvalget kan derfor ikke kategorisere den kliniske værdi, men bemærker, at punktestimatet for den absolutte forskel på 7,1 %-point overstiger den mindste klinisk relevante forskel på 5 %-point ift. en negativ værdi.

Kvantitativ opgørelse af bivirkninger af grad 3-4
Efter 60-måneders behandling oplevede [redacted]) minimum én bivirkning af grad 3-4 i interventionsarmen, mens det tilsvarende var tilfældet for [redacted] i komparatorarmen. Ansøger har ikke udregnet et konfidensinterval omkring den absolutte forskel og har heller ikke udregnet en relativ forskel. Fagudvalget kan derfor ikke kategorisere den kliniske værdi, men bemærker, at punktestimatet ikke indikerer nogen forskel mellem ropeginterferon-alfa-2b og hydroxyurea.

Kvalitativ gennemgang af bivirkningsprofilerne
Fagudvalget har ved gennemgangen af bivirkningsprofilerne taget udgangspunkt i de samlede opgørelser over uønskede hændelser publiceret i Gisslinger et al. 2020, tabel 4 [17]. Den mediane opfølgningstid i de to behandlingsarme var ved denne opgørelse hhv. 182 uger og 165 uger for ropeginterferon-alfa-2b og hydroxyurea.

Ropeginterferon-alfa-2b er overordnet set veltolereret, hvilket kan ses på de generelt lave forekomster af uønskede hændelser og særligt hændelser af grad 3-4. De hyppigst forekommende uønskede hændelser af grad 1-2 var trombocytopeni, leukocytopeni, anæmi, træthed og svimmelhed (11-21 %). Disse er direkte koblet til den farmakologiske effekt af lægemidlet og er dermed forventede. Desuden optrådte de sjældent i en grad, hvor de var behandlingskrævende. De uønskede hændelser kan dog alligevel medføre forringelse af patienternes livskvalitet. Fagudvalget bemærker, at en del patienter i studiet oplevede forhøjet alanin-aminotransferase, hovedsageligt i mildere grad (13 %), men også i grad 3 (4 %). Dette kan på sigt medføre, at en del patienter må ophøre med behandlingen.

De eneste grad 3-4 uønskede hændelser, der optrådte i mere end 5 % af patienterne, var en øgning i ϒ-glutamyl transferase (7 %). Uønskede hændelser medførte behandlingsophør for 11 patienter (8,7 %) i løbet af de første 12 måneder og yderligere 6 patienter (6,3 %) i løbet af opfølgningsstudiet. Én patient oplevede en uønsket hændelse, der førte til død (0,8 %). Hændelsen (glioblastom) var ikke relateret til ropeginterferon-alfa-2b.

Der blev rapporteret 19 uønskede hændelser, som der er særlig opmærksomhed på ved behandling med interferoner (*adverse events of special interest*). Dette var hypothyroidisme (2,1 %), iskæmisk slagtilfælde kompliceret med hæmoragisk

transformation, iskæmisk slagtilfælde, angst, depression, irritabilitet, humørsvingninger, nervøsitet, miltinfarkt, truncus coeliacus trombose, retinal skade, Sjøgrens syndrom, sløret syn, dermatitis acneiform, psoriasis og sarkoidose (alle 1,1 %). Isoleret set var alle disse hændelser sjældne, og de fleste var af grad 1-2. Fagudvalget bemærker dog, at de samlet set udgør en bred gruppe af hændelser, som der skal være opmærksomhed omkring ved behandling med interferoner, og at flere af disse hændelser kan påvirke patienternes livskvalitet negativt.

Sikkerhedsprofilen for hydroxyurea er overordnet set sammenlignelig med ropeginterferon-alfa-2b. De hyppigst forekommende uønskede hændelser er nedsatte blodcelletal, og uønskede hændelser af grad 3-4 er sjældne. Uønskede hændelser medførte behandlingsophør for 3 patienter (2,4 %) i løbet af de første 12 måneder og yderligere 2 patienter (2,6 %) i opfølgningsstudiet. Der var ingen uønskede hændelser, der førte til død. Fagudvalget bemærker, at det er velkendt, at behandling med hydroxyurea over en længere årrække medfører en øget risiko for non-melanom-hudcancer [20]. I PROUD-/CONTINUATION-PV er der observeret ét tilfælde af basalcellecarcinom, og fagudvalget forventer, at hyppigheden af dette vil stige ved længere tids behandling. Samtidig bemærker fagudvalget, at ca. 1-10 % af patienterne i behandling med hydroxyurea udvikler hudsår, som medfører behandlingsophør.

Samlet vurdering af bivirkninger
Den samlede værdi af ropeginterferon-alfa-2b over for hydroxyurea kan ikke kategoriseres efter Medicinrådets metoder. Både de kvantitative og kvalitative sammenligninger indikerer dog, at lægemidlerne er sammenlignelige mht. sikkerhed, i hvert fald når der tages udgangspunkt i behandling over 1-5 år. Fagudvalget understreger dog, at sikkerheden sandsynligvis er anderledes ved behandling over en længere årrække, hvor særligt den øgede risiko for non-melanom-hudcancer ved behandling med hydroxyurea betyder, at fagudvalget betragter ropeginterferon-alfa-2b som et mere sikkert alternativ til behandling over mange år.

Komplet hæmatologisk respons
Komplet hæmatologisk respons anvendes ofte som det primære effektmål ved kliniske studier omhandlende PV [14–16,21], og det anses som et direkte behandlingsmål for alle behandlinger for PV [2,11]. Definitionen af komplet hæmatologisk respons kan variere mellem studier, men som oftest defineres det som sænkning af blodværdierne til hæmatokrit < 45 %, blodplader < $400 \cdot 10^9$/l og hvide blodlegemer < $10 \cdot 10^9$/l, og nogle gange ledsages dette af fravær af forstørret milt og/eller fravær af øget sygdomsbyrde. Fagudvalget betragter sænkningen af hæmatokritværdien som den vigtigste af disse parametre, da patienter med hæmatokrit > 45 % har en øget risiko for kardiovaskulære dødsfald [22]. Derfor betragtes effektmålet også som vigtigt for vurderingen af lægemidlets værdi for patienterne.

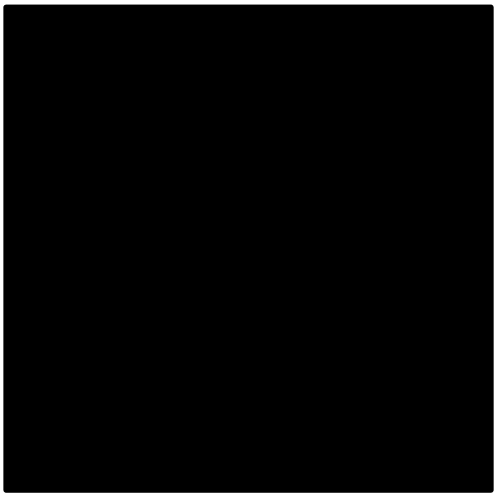
Komplet hæmatologisk responsrate er rapporteret i CONTINUATION-PV efter 12- (ved start af CONTINUATION-PV), 24-, 36-, 48- og 60-måneders behandling. Fagudvalget vægter respons med længst mulig opfølgningstid i kategoriseringen af effekten, men vurderer også det samlede forløb for responsraterne under behandlingen.

Det samlede forløb for responsraten ved behandling med ropeginterferon-alfa-2b og hydroxyurea er vist i figuren nedenfor.

Figur 3: Andel af patienter, der opnår komplet hæmatologisk respons som funktion af opfølgningstiden i de to behandlingsarme i CONTINUATION-PV. Komplet hæmatologisk respons er defineret som sænkning af blodværdierne til hæmatokrit < 45 %, blodplader < 400·10^9/l og hvide blodlegemer < 10·10^9/l. RR angiver den relative risiko for respons ved ropeginterferon over for hydroxyurea ved de forskellige opfølgningstidspunkter, og * markerer, at den relative risiko er signifikant højere end 1, hvilket viser en signifikant højere sandsynlighed for komplet hæmatologisk respons for patienter behandlet med ropeginterferon-alfa-2b.

Ved indgangen til CONTINUATION-PV havde hhv. 62 % og 75 % af patienterne opnået komplet hæmatologisk respons ved behandling med ropeginterferon og hydroxyurea (RR = 0,88 (95 % CI:[0,7; 1,05])). Responsraten var relativt stabilt ved ropeginterferon-alfa-2b, mens andelen af respondere faldt ved hydroxyurea. Der var således statistisk signifikant højere responsrate ved ropeginterferon-alfa-2b efter 24, 36 og 48 måneder [redacted]. Fagudvalget vurderer, at disse data samlet set indikerer, at et komplet hæmatologisk respons kan opretholdes over længere tid med ropeginterferon-alfa-2b end med hydroxyurea, men at det er meget usikkert, hvor stabilt responset er udover 60 måneder også for ropeginterferon-alfa-2b.

Til kategoriseringen af effekten tager fagudvalget udgangspunkt i komplet hæmatologisk responsrate ved 60-måneders opfølgning. Figuren nedenfor viser den absolutte forskel.



Figur 4: Punktestimat og 95% konfidensinterval for den absolutte forskel for komplet hæmatologisk respons. De optrukne linjer indikerer den mindste klinisk relevante forskel (MKRF). De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet ligger tættere på 0 (ingen effektforskel) end på en negativ klinisk relevant forskel. Derfor er den foreløbige værdi af ropeginterferon-alfa-2b vedr. komplet hæmatologisk respons ingen dokumenteret merværdi.

Den relative risiko var [redacted], hvorved den relative effektforskel viser ingen dokumenteret merværdi. Samlet set er værdien af ropeginterferon-alfa-2b over for hydroxyurea ingen dokumenteret merværdi for effektmålet komplet hæmatologisk respons. Fagudvalget vurderer dog, at ropeginteron-alfa-2b sandsynligvis medfører, at flere patienter opnår komplet hæmatologisk respons over en længere tidshorisont, men den eventuelle forskel overstiger ikke den fastsatte mindste klinisk relevante forskel.

5.1.5 Fagudvalgets konklusion

Samlet set kan værdien af ropeginterferon-alfa-2b til behandling af patienter med polycytæmia vera ikke kategoriseres sammenlignet med hydroxyurea. Dette skyldes, at der ikke foreligger data for flere af de kritiske effektmål, der tillader en kategorisering, og at konfidensintervallerne omkring de tilgængelige punktestimater er meget brede. Fagudvalget vurderer, at data samlet set ikke indikerer, at ropeginterferon er mere effektivt eller sikkert end hydroxyurea. Omvendt er der heller ikke noget, der tyder på, at det er dårligere. Endelig bemærker fagudvalget, at der er klinisk dokumentation for, at patienterne på længere sigt opnår en reduktion i JAK2-mutationsbyrden ved behandling med ropeginterferon-alfa-2b, hvilket ikke er tilfældet ved behandling med hydroxyurea (se 'andre overvejelser' i afsnit 6). Betydningen af dette er stadig uklar, og derfor har det ikke vægtet i kategoriseringen af lægemidlet.

5.2 Klinisk spørgsmål 2

Klinisk spørgsmål 2 er:

Hvilken værdi har ropeginterferon-alfa-2b sammenlignet med pegyleret interferon-alfa-2a for voksne patienter under 60 år med polycytæmia vera?

5.2.1 Litteratur

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

Ansøger har anvendt søgestrengen fra Medicinrådets protokol for vurdering vedrørende ropeginterferon-alfa-2b til behandling af polycytæmia vera og har identificeret 13 fuldtekstartikler, der rapporterer data fra 10 kliniske studier. Ingen af studierne undersøger effekten af ropeginterferon-alfa-2b over for en anden pegyleret interferon.

Tabel 5. Oversigt over studier, der undersøger effekt og sikkerhed af ropeginterferon-alfa-2b eller interferon-alfa-2a/-2b.

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, intervention og komparator
Gisslinger et al. 2020 [17] EPAR [9]	PROUD-PV og CONTINUATION-PV	NCT01949805 og NCT02218047	Voksne (≥ 18 år) med polycytæmia vera med JAK2-Val617Phe-mutation, som enten ikke tidligere har modtaget cytoreduktiv behandling, eller som maksimalt har været behandlet med hydroxyurea i 3 år. CONTINUATION var et opfølgningsstudie, hvor patienter, der havde gennemgået PROUD, blev behandlet i yderligere 24 måneder. For at blive inkluderet i opfølgningsstudiet skulle patienterne have: - Normaliseret niveau eller minimum 35 % reduktion fra baseline af mindst 2 ud af 3 blodcelletal (hæmatokrit, blodplader, hvide blodlegemer), eller - Normaliseret miltstørrelse, eller - Klinisk bekræftet gavn af behandlingen med ropeginterferon-alfa-2b.	Fase III, open-label randomiseret kliniske studie. PROUD: Ropeginterferon-alfa-2b (n = 127) overfor hydroxyurea (n = 127) CONTINUATION: Ropeginterferon-alfa-2b (n = 95) overfor hydroxyurea (n = 76)

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, intervention og komparator
Gisslinger et al. 2015 [18]	PEGINVERA	NCT01193699	Voksne (≥ 18 år) med polycytæmia vera med JAK2-mutation, som enten ikke tidligere har modtaget cytoreduktiv behandling, eller som blev/havde været behandlet med hydroxyurea, men som ikke havde opnået kontrol med hmatokritværdien eller oplevede andre sygdomssymptomer.	Fase-I/II, open-label ikke-kontrolleret klinisk studie. Ropeginterferon-alfa-2b (n = 51)
Quitas-Cardama et al. 2009 [16] Quitas-Cardama et al. 2013 [23] Masarova et al. 2017 [24]	-	-	Voksne (≥ 18 år) med PV eller essentiel trombocytose. Patienter kunne være nydiagnosticerede eller tidligere have modtaget cytoreduktiv behandling.	Fase II, ikke-kontrolleret klinisk studie. Pegyleret interferon-alfa-2a (n = 43 med PV)
Crisa et al. 2017 [25]	-	-	Patienter (< 65 år) med PV. Patienter kunne tidligere have modtaget cytoreduktiv behandling.	Observationelt klinisk studie, hvor to kohorter sammenlignes. Pegyleret interferon (n = 30) over for hydroxyurea (n = 35)
Huang et al. 2014 [14]	-	-	Patienter (18-65 år) med PV med JAK2-V617F-mutation eller essentiel trombocytose. Patienter kunne være nydiagnosticerede eller tidligere have modtaget cytoreduktiv behandling.	Open-label, kontrolleret klinisk studie. Interferon-alfa-2a (n = 64 med PV) over for hydroxyurea (n = 72 med PV)
Stauffer Larsen et al. 2013 [26]	-	-	Patienter med JAK2-V617F-muteret PV, essentiel trombocytose eller myelofibrose behandlet på danske centre. Ca. halvdelen af patienterne havde tidligere	Observationelt studie, ikke-kontrolleret studie.

Publikationer	Klinisk forsøg	NCT-nummer	Population	Studietype, intervention og komparator
			modtaget cytoreduktiv behandling.	Pegyleret interferon-alfa-2a eller -2b (n = 75 med PV)
Kiladjian et al. 2008 [15]	PVN1	NCT00241241	Patienter (18-65 år) med PV, som enten ikke tidligere er behandlet, eller som maksimalt har modtaget cytoreduktiv behandling I 2 år.	Fase II, ikke kontrolleret studie. Pegyleret interferon-alfa-2a (n = 37)
Samuelsson et al. 2006 [27]	-	-	Patienter med PV eller essentiel trombocytose, der ikke var i nuværende cytoreduktiv behandling, og som havde forhøjede blodpladetal ved inklusion (> $400 \cdot 10^9$).	Fase II, ikke-kontrolleret klinisk studie. Pegyleret interferon-alfa-2b (n = 21 med PV)
Yacoub et al 2019 [21] Mazza et al. 2022 [28] Mascarenhas et al. 2022 [29]	MPN-RC-112	NCT01259856	Patienter (> 18 år) med PV eller essentiel trombocytose med højrisiko-sygdom, ellersom havde behov for cytoreduktiv behandling grundet stor symptombyrde, og som ikke tidligere havde modtaget cytoreduktiv behandling eller maksimalt 3 måneders behandling med hydroxyurea.	Fase III, open-label, randomiseret klinisk studie. Pegyleret interferon-alfa-2a (n = 43 patienter med PV) over for hydroxyurea (n = 44 patienter med PV)

Datagrundlaget for effekten og sikkerheden af ropeginterferon-alfa-2b er det samme som beskrevet ved klinisk spørgsmål 1 (PROUD-PV og CONTINUATION-PV, se afsnit 5.1.1).

Effekten og sikkerheden af en anden form pegyleret interferon-alfa-2a eller -2b er undersøgt i seks studier, mens ét studie (Huang et al. 2014) undersøger effekten af ikke-pegyleret interferon. Kun ét af studierne (MPN-RC-112) er et randomiseret, prospektivt klinisk studie med en relevant komparator, og derfor anvender fagudvalget dette til at vurdere effekten af pegyleret interferon-2a til patienter med PV. Fagudvalget vil desuden udføre en deskriptiv vurdering af effekten af pegyleret interferon-alfa-2a i MPN-RC-112 over for effekten i studiet af Stauffer Larsen et al. for at belyse, om effekten er sammenlignelig med danske forhold.

MPN-RC-112

MPN-RC-112 var et randomiseret, open-label fase III-studie, hvor effekten og sikkerheden af pegyleret interferon-alfa-2a blev sammenlignet med hydroxyurea (randomiseret 1:1) til behandling af patienter med PV eller essentiel trombocytose. Patienterne med PV skulle være diagnosticeret inden for de seneste 5 år, have bekræftet JAK2-V617F-mutation og ikke tidligere have modtaget cytoreduktiv behandling (eller maksimalt 3 måneders behandling med hydroxyurea). Desuden skulle patienterne have højrisiko-sygdom, defineret som:

- Alder ≥ 60 år
- Tidligere tromboemboliske hændelser, erythromelalgia eller migræne
- Forstørret milt, som enten var symptomgivende eller > 5 cm under nederste ribben ('*costal margin*')
- Blodpladetal > 1000 · 10^9 blodplader/l
- Diabetes eller hypertension, der kræver farmakologisk behandling.

Startdosis af pegyleret interferon-alfa-2a var 45 µg/uge, som blev titreret op hver måned i trin á 45 µg/uge indtil opnået komplet hæmatologisk respons eller en maksimumsdosis på 180 µg/uge. Startdosis af hydroxyurea var 500 mg to gange dagligt.

Studiets primære endepunkt var andelen af patienter med komplet hæmatologisk respons og samtidig normal miltstørrelse (længdediameter ≤ 13 cm) og reduktion af sygdomsrelaterede symptomer efter 12 måneders behandling. Patienter med partielt respons kunne fortsætte i studiet indtil 6-års opfølgning med prædefinerede responsevalueringer ved 24 og 36 måneder. Studiets sekundære endepunkter var bl.a. andelen af patienter med uønskede hændelser af grad 3-4, forandring i patienternes '*total symptom score*' ved MPN-SAF, JAK2-allelbyrde, andel af patienter med progressiv sygdom og andelen af patienter med alvorlige kardiovaskulære hændelser.

Studiet af Stauffer Larsen et al. 2013 var et open-label observationelt studie, hvor der blev opsamlet data for patienter behandlet med pegyleret interferon-alfa-2a eller 2-b fra 8 danske behandlingscentre i perioden 2008 til 2011. Patienterne havde alle JAK2-V617F-mutation og modtog behandling med interferoner i minimum 12 måneder. Studiet inkluderede både patienter med PV, essentiel trombocytose og primær myelofibrose og rapporterer data for komplet hæmatologisk respons og reduktion i JAK2-mutationsbyrde opdelt efter sygdom.

Baselinekarakteristika for patienterne i MPN-RC-112 over for patienterne i PROUD-PV/CONTINUATION-PV ses i Tabel 6.

Tabel 6: Baselinekarakteristika for patienterne i CONTINUATION-PV sammenlignet med patienterne i MPN-RC-112.

	CONTINUATION-PV*		MPN-RC-112**	
	Ropeginterferon-alfa-2b (n = 95)	**Hydroxyurea (n = 76)**	**Pegyleret interferon-alfa-2a (n = 43/82**)**	**Hydroxyurea (n = 44/84**)**
Alder, median (range)	58 år (30-85)	59 år (32-79)	60 år (46-68) **	64 år (57-70) **
Køn (mand)	49 %	47 %	60 % **	58 % **
Tidligere behandlet med hydroxyurea	32 %	26 %	IR	IR
Varighed af tidligere behandling med hydroxyurea, median (IQR)	9,5 måneder (2,8-25,1)	8,2 måneder (2,6-23,0)	0-3 måneder	0-3 måneder
Tid fra diagnose, median (IQR)	1,8 måneder (0,6-6,8)	1,6 måneder (0,7-15,1)	2,6 måneder (1,6-6,4)	2,5 måneder (0,7-9,9)
Andel med tidligere tromboembolisk hændelse	22 %	18 %	30 %	27 %
JAK2-allelbyrde, gennemsnit (standardafvigelse)	42,8 % (23)	42,9 % (23)	IR	IR
Hæmatokritværdi, median (IQR)	47,7 % (44,4-52,0)	49,9 % (46,2-53,1)	43,8 % (38,2-47,1) **	43,3 % (38,8-47,4) **
Blodpladetal · 10^9/l, median (IQR)	488 (350-701)	451 (329-679)	602 (433-785) **	612 (460-785) **
Hvide blodlegemer · 10^9/l, median (IQR)	10,9 (8,0-14,6)	11,3 (8,7-15,1)	8,6 (7,2-12,5) **	9,0 (7,1-11,8) **
Miltstørrelse, median (IQR)	13,5 cm (11,5-15,0)	12,8 (11,3-15,5)	12,5 cm (11,0-15,0) **	12,5 cm (10,6-15,2) **

*: Baselinekarakteristika for CONTINUATION-PV viser karakteristika ved starten af PROUD-PV for de patienter, der efterfølgende indgik i CONTINUATION-PV. **: Baselinekarakteristik angivet for den samlede population af patienter med polycytæmia vera eller essentiel trombocytose, da statistikken ikke er angivet for populationen med polycytæmia vera alene. IQR = '*interquartile range*' = 25 % kvartilen til 75 % kvartilen.

Fagudvalget vurderer, at populationerne overordnet set er sammenlignelige med undtagelse af hæmatokrit og trombocyttal. Disse forskelle skyldes sandsynligvis, at MPN-RC-112 indeholder både patienter med PV og essentiel trombocytose. Patienterne med essentiel trombocytose formodes at have lavere hæmatokritværdi og højere trombocyttal, hvilket kan forklare forskellen.

5.2.2 Databehandling og analyse

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

Ansøger har udført en deskriptiv sammenligning af ropeginterferon-alfa-2b med pegyleret interferon-alfa-2a eller -2b vha. data fra PROUD-PV/CONTINUATION-PV og data fra alle studierne i Tabel 4. Ansøger anvender de samme data fra interventionsarmen i PROUD/CONTINUATION-PV som beskrevet i afsnit 5.1.2., både data fra 12 måneders opfølgning i PROUD-PV og fra længst mulig opfølgning i CONTINUATION-PV (op til 60 måneder i alt). Ansøger ekstraherer data fra alle publikationer i Tabel 5 for alle tilgængelige effektmål. De fleste af studierne rapporterer dog kun data for komplet hæmatologisk respons samt beskrivelser af sikkerheden, der kan anvendes i en kvalitativ analyse. Ansøger har desuden foretaget en statistisk indirekte sammenligning af komplet hæmatologisk respons ud fra 12 måneders responsrater i PROUD-PV og MPN-RC-112 ved hjælp af Buchers metode efter opfordring fra Medicinrådet. Ansøger argumenterer selv for, at populationerne er for forskellige til at udføre en statistisk indirekte sammenligning.

Fagudvalget vurderer, at PROUD-PV og CONTINUATION-PV kan anvendes til at vurdere effekten af ropeginterferon-alfa-2b. Studierne af pegyleret interferon-alfa-2a/2b er af varierende design og kvalitet, og fagudvalget lægger derfor hovedsageligt vægt på data fra MPN-RC-112, der er det eneste randomiserede kontrollerede studie. Fagudvalget inkluderer desuden studiet af Stauffer Larsen et al. til at perspektivere de observerede effekter i MPN-RC-112 ift. en dansk kontekst.

Fagudvalget anvender data efter 12 måneders opfølgning, da data rapporteres for dette tidspunkt for både PROUD-PV og MPN-RC-112. Fagudvalget bemærker, at effekten på længere sigt dermed ikke kan vurderes, og at den initiale dosistitreringsperiode kan medføre usikkerheder i vurderingen, da patienterne kan have forskellig tid i optimal behandling. Fagudvalget anvender både en deskriptiv sammenligning af data for komplet hæmatologisk respons og ansøgers indirekte sammenligning.

5.2.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Da evidensen er baseret på en delvist deskriptiv sammenligning og delvist indirekte sammenligning mellem interventionsarmene i PROUD-PV og MPN-RC-112, er der ikke foretaget en selvstændig GRADE-profil for klinisk spørgsmål 2. Ved den indirekte sammenligning tages der udgangspunkt i GRADE-profilen for PROUD-PV/CONTINUATION-PV, hvor evidensens kvalitet er meget lav (se afsnit 5.1.3).

Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at der er høj risiko for bias forbundet med PROUD-PV og CONTINUATION, hovedsageligt pga. at studiet var ublindet. Dette kan have haft betydning for vurderingen af effektmålene og for frafaldet af patienter mellem PROUD-PV og CONTINUATION-PV. Ligeledes er der høj risiko for bias ved MPN-RC-112 pga. det ublindede design, der kan have påvirket bedømmelsen af effektmålene.

Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 1 (Tabel 8 og Tabel 9).

5.2.4 Effektestimater og kategorier

I tabellen herunder fremgår effektestimaterne fra PROUD/CONTINUATION-PV og MPN-RC-112 til vurdering af klinisk spørgsmål 2. Datagrundlaget egner sig ikke til, at værdien af ropeginterferon-alfa-2b kan kategoriseres efter Medicinrådets metoder.

Tabel 7: Resultater for sammenligningen af ropeginterferon-alfs-2b med pegyleret inferon-alfa-2a.

Effektmål	Målenhed (MKRF)	Vigtighed	PROUD/CONTINUATION-PV			MPN-RC-112			Værdi for effektmålet
			Ropeginter-feron-alfa-2b	Hydro-xyurea/ BAT	Forskel	Pegyleret interferon-alfa-2a	Hydro-xyurea	Forskel	
Tromboemboliske hændelser	Andel af patienterne, der oplever minimum en tromboembolisk hændelse (MKRF: 5 %-point)	Kritisk	[redacted]	[redacted]	[redacted]	2 % (0,3; 13 %)	2 % (0,3; 15 %)	0 %-point	Kan ikke kategoriseres
	Kvalitativ gennemgang af hændelserne		-	-		-	-		
Livskvalitet	MPN-SAF: Gennemsnitlig ændring fra baseline i *'total symptom score'* samt en kvalitativ gennemgang af domænescorer (MKRF: 10 point på *'total symptom score'*) eller EQ-5D: Gennemsnitlig ændring fra baseline (MKRF: 0,1 point ved EQ-5D utilityværdi eller 10 point ved EQ-5D-VAS)	Kritisk	Ikke angivet	Ikke angivet	Ikke angivet	Ikke angivet	Ikke angivet	Ikke angivet	Kan ikke kategoriseres

Effektmål	Målenhed (MKRF)	Vigtighed	PROUD/CONTINUATION-PV			MPN-RC-112			Værdi for effektmålet
			Ropeginter-feron-alfa-2b	Hydro-xyurea/ BAT	Forskel	Pegyleret interferon-alfa-2a	Hydro-xyurea	Forskel	
Bivirkninger	Andelen af patienter, der oplever minimum én uønsket hændelse af grad 3-4, (MKRF: 5 %-point)	Kritisk	[redacted]	[redacted]	[redacted]	46 %	28 %	18 %-point	Kan ikke kategoriseres
	Andelen af patienter, der oplever minimum én bivirkning af grad 3-4 (MKRF: 5 %-point)		[redacted]	[redacted]	[redacted]	Ikke angivet	Ikke angivet	Ikke angivet	
	Kvalitativ gennemgang af bivirkningsprofilen		-	-	-	-	-	-	
Komplet hæmatologisk respons	Andel af patienter, der oplever komplet hæmatologisk respons (MKRF: 15 %-point)	Vigtig	43,1 %	45,6 %	-2,5 %-point (-9,85; 14,87)	48 %	42 %	6 %-point (-9; 21)	Kan ikke kategoriseres
Konklusion									

Effektmål	Målenhed (MKRF)	Vigtighed	PROUD/CONTINUATION-PV			MPN-RC-112			Værdi for effektmålet
			Ropeginterferon-alfa-2b	Hydroxyurea/ BAT	Forskel	Pegyleret interferon-alfa-2a	Hydroxyurea	Forskel	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget vurderer, at effekten af ropeginterferon-alfa-2b sandsynligvis er sammenlignelig med effekten af pegyleret interferon-alfa-2a. De to varianter kan have forskellig bivirkningsprofil, men vurderingen er usikker.								
Kvalitet af den samlede evidens	Meget lav.								

Tromboemboliske hændelser

Kvantitativ opgørelse af tromboemboliske hændelser
Andelen af patienter, der har oplevet minimum én tromboembolisk hændelse er ikke opgjort ved samme opfølgningstidspunkter i studierne. I PROUD/CONTINUATION oplevede
[redacted]af patienterne behandlet med hydroxyurea efter 12 måneders opfølgningstid. I MPN-RC-112 oplevede 2 % i begge behandlingsarme en trombose ved to års opfølgning. Dette er opgivet samlet for populationen med enten PV eller essentiel trombocytose, og det er ikke beskrevet, om patienterne oplevede andre lignende hændelser [29]. Dette medfører en usikkerhed i sammenligningen, men samlet set indikerer data ikke nogen effektforskelle mellem ropeginterferon-alfa-2b og pegyleret inferferon-alfa-2a for dette effektmål.

Kvalitativ gennemgang af tromboemboliske hændelser
Den kvalitative gennemgang af tromboemboliske hændelser ved behandling med ropeginterferon-alfa-2b er beskrevet i afsnit 5.1.4. I MPN-RC-112 er der ikke yderligere beskrivelser af de observerede tromboemboliske hændelser.

Samlet vurdering af tromboemboliske hændelser
Der er begrænsede studiedata til rådighed for dette effektmål, og værdien kan derfor ikke kategoriseres efter Medicinrådets metoder. Fagudvalget kan heller ikke vurdere, om der kan være forskelle mellem effekten af ropeginterferon-alfa-2b og pegyleret interferon-alfa-2a ift. at forebygge tromboemboliske hændelser. Dette skyldes, at hændelsesraterne i studierne overordnet set er lave, og studiepopulationerne små.

Livskvalitet
Livskvaliteten for patienterne er undersøgt ved forskellige metoder i de tilgængelige studier. I PROUD/CONTINUATION-PV er livskvaliteten undersøgt vha. EQ-5D-3L, mens livskvaliteten i MPN-RC-112 er undersøgt i en samlet population af patienter med PV eller essentiel trombocytose ved MPN-SAF [28]. Derfor kan fagudvalget ikke sammenligne resultaterne for ropeginterferon-alfa-2b med resultaterne for interferon-alfa-2a. Data fra de enkelte studier indikerer dog, at hverken ropeginterferon-alfa-2b eller interferon-alfa-2a påvirker patienternes livskvalitet anderledes end behandling med hydroxyurea.

Værdien af ropeginterferon kan ikke kategoriseres efter Medicinrådets metoder. Fagudvalget kan ikke vurdere, om ropeginterferon-alfa-2b kan påvirke patienternes livskvalitet anderledes end interferon-alfa-2a, men intet i de tilgængelige data indikerer, at dette kan være tilfældet.

Bivirkninger
Ved de kvantitative opgørelser af uønskede hændelser og bivirkninger tager fagudvalget udgangspunkt i data rapporteret ved udgangen af PROUD-PV (12 måneder) for ropeginterferon for at opnå en mere sammenlignelig opsamlingsperiode med MPN-RC-

112. Derfor er de kvantitative opgørelser anderledes her end ved klinisk spørgsmål 1, hvor der blev taget udgangspunkt i data efter 60 måneder.

Kvantitativ opgørelse af uønskede hændelser af grad 3-4
Efter 12 måneders behandling oplevede [redacted]) af patienterne behandlet med ropeginterferon-alfa-2b minimum én uønsket hændelse af grad 3-4 i interventionsarmen, mens det tilsvarende var tilfældet for [redacted] af patienterne behandlet med hydroxyurea.

I MPN-RC-112 er andelen af patienter, der oplevede minimum én uønsket hændelse af grad 3-4 opgivet for den samlede studiepopulation, hvoraf ca. halvdelen af patienterne havde PV, og den anden halvdel havde essentiel trombocytose. Fagudvalget vurderer, at de uønskede hændelser vil være sammenlignelige, og anvender derfor den samlede opgørelse. Efter en median behandlingstid på 81 uger havde 48 % (38 ud af 82 patienter) af patienterne behandlet med pegyleret interferon-alfa-2a oplevet minimum én uønsket hændelse af grad 3-4, mens det samme var tilfældet for 28 % (22 ud af 84 patienter) af patienterne behandlet med hydroxyurea [29]. De kvantitative opgørelser er vanskelige at sammenligne grundet de forskellige behandlingslængder. Data indikerer dog, at ropeginterferon-alfa-2b ikke medfører flere uønskede hændelser af grad 3-4 end hydroxyurea over 12 måneder, mens det modsatte kan være tilfældet for pegyleret interferon-alfa-2a over ca. 20 måneder.

Kvantitativ opgørelse af bivirkninger af grad 3-4
Efter 12 måneders behandling oplevede [redacted]) af patienterne behandlet med ropeginterferon-alfa-2b minimum én bivirkning af grad 3-4, mens det tilsvarende var tilfældet for [redacted] af patienterne behandlet med hydroxyurea. Effektmålet er ikke opgjort i MPN-RC-112.

Kvalitativ gennemgang af bivirkningsprofilerne
Bivirkningsprofilen for ropeginterferon-alfa-2a er gennemgået i klinisk spørgsmål 1 (se afsnit 5.1.4).

For pegyleret interferon-alfa-2a er der rapporteret få uønskede hændelser af grad 3-4, og de hyppigste af disse er træthed (7 %), hypertension (7 %) og hovedpine (4 %). De hyppigst forekommende uønskede hændelser af grad 1-2 var træthed (49 %), leukocytopeni (27 %) og hovedpine (22 %). Derudover oplevede en del patienter grad 1-2 uønskede hændelser, der typisk er relateret til pegyleret interferon-alfa-2a: influenzalignende symptomer (22 %), lokal reaktion på injektionsstedet (22 %), perifer sensorisk neuropati (20 %) og depression (15 %). Disse var alle væsentligt hyppigere forekommende i patienterne behandlet med pegyleret interferon-alfa-2a end i patienterne behandlet med hydroxyurea. Uønskede hændelser medførte behandlingsophør for 12 patienter (15 %), mens ingen patienter oplevede en uønsket hændelse, der førte til død. Fagudvalget vurderer, at den samlede bivirkningsprofil er forenelig med fagudvalgets kliniske erfaring med lægemidlet.

Samlet vurdering af bivirkninger

Den samlede værdi kan ikke kategoriseres. Fagudvalget vurderer, at de tilgængelige data

tyder på, at ropeginterferon-alfa-2b samlet set kan have en mildere bivirkningsprofil end pegyleret interferon-alfa-2a. Fagudvalget baserer dette både på de samlede kvantitative opgørelser over uønskede hændelser af grad 3-4 og på de rapporterede forekomster af bivirkninger, der er almindelig forekommende ved behandling med pegyleret interferon (depression, influenzalignende symptomer, træthed). Fagudvalget bemærker dog, at der kan være væsentlig forskel mellem rapporteringen af uønskede hændelser i de institutioner, der har foretaget de kliniske studier, hvilket gør vurderingen usikker.

Komplet hæmatologisk respons
For at kunne sammenligne estimaterne mellem PROUD/CONTINUATION-PV og MPN-RC-112 anvender fagudvalget komplet hæmatologisk responsrate uden tilhørende normalisering af miltstørrelse efter 12 måneders behandling. Fagudvalget er bevidste om, at responsraten for ropeginterferon-alfa-2b er stigende ved længere tids behandling (se afsnit 5.1.4), og at effekten af ropeginterferon-alfa-2b derved muligvis underestimeres. Der er dog samme tendens til større forskel mellem interferon og hydroxyurea i MPN-RC-112, hvilket reducerer fejlkilden.

Ved 12 måneder opnåede 43,1 % af patienterne behandlet med ropeginterferon-alfa-2b komplet hæmatologisk respons over for 45,6 % af patienterne behandlet med hydroxyurea. Dette resulterer i en forskel på -2,5 %-point (95 % CI: -9,85; 14,87), der ikke var statistisk signifikant.

I MPN-RC-112 opnåede 48 % af patienterne behandlet med interferon-alfa-2a komplet hæmatologisk respons efter 12 måneder over for 42 % af patienterne behandlet med hydroxyurea. Dette resulterer i en forskel på 6 %-point (95 % CI: -6; 21), der ikke var statistisk signifikant. I studiet af Stauffer Larsen et al. 2013, hvor pegyleret interferon-alfa-2a er undersøgt i et observationelt studie i 8 danske behandlingscentre, var der ca. 68 % af patienterne, der opnåede komplet hæmatologisk respons ved en median opfølgningstid på 42 måneder.

Ved indirekte sammenligning vha. Buchers metode ses en RR på 0,83 (95 % CI: [0,53; 1,30]) for komplet hæmatologisk respons ved behandling med ropeginterferon-alfa-2b overfor behandling med pegyleret interferon-alfa-2a. Den absolutte forskel mellem behandlingerne er -8 %-point (95 % CI: [-22,2; 14,1 %-point]). Den indirekte sammenligning viser altså, at der ikke er statistisk signifikant forskel mellem andelen, der opnår komplet hæmatologisk respons ved de to behandlinger.

Værdien af ropeginterferon-alfa-2a over for pegyleret interferon-alfa-2a kan ikke kategoriseres ved Medicinrådets metoder. Fagudvalget vurderer, at der sandsynligvis ikke er forskel mellem de to behandlinger i andelen af patienter, der opnår komplet hæmatologisk respons. Ingen af behandlingerne viste en signifikant forskellig responsrate fra hydroxyurea i direkte sammenlignende kliniske studier, og fagudvalget anser det derfor for usandsynligt, at der er klinisk relevant forskel (15 %-point) mellem behandlingerne.

5.2.5 Fagudvalgets konklusion

Samlet set kan værdien af ropeginterferon-alfa-2b til behandling af patienter med polycytæmia vera ikke kategoriseres sammenlignet med pegyleret interferon-alfa-2a. Dette skyldes, at der ikke foreligger data til at foretage en statistisk direkte eller indirekte sammenligning for nogen af de kritiske effektmål. Fagudvalget vurderer, at alle data tyder på, at effekten af ropeginterferon-alfa-2b er sammenlignelig med effekten for pegyleret interferon-alfa-2b. Fagudvalget vurderer, at ropeginterferon-alfa-2b muligvis medfører færre og mildere bivirkninger end pegyleret interferon-alfa-2a, men grundlaget for at vurdere dette er usikkert.

6. Andre overvejelser

Fagudvalget efterspurgte i protokollen data for reduktion af JAK2-mutationsbyrden samt data for hyppigheden af transformation til akut myeloid leukæmi eller myelofibrose for både interventionen og komparatoren.

Reduktion af JAK2-mutationsbyrden
Patienter med JAK2-V617F-mutation kan have forskellige grader af mutationsbyrde, dvs. forskellige andele af knoglemarvsstamceller, der bærer mutationen. Cytoreduktiv behandling kan reducere mutationsbyrden, hvilket antages at kunne forsinke sygdomsudviklingen og reducere risikoen for komplikationer [1]. Der findes ikke en klar dokumenteret sammenhæng mellem JAK2-mutationsbyrde og risiko for sygdomsprogression eller komplikationer, hvilket er årsagen til, at fagudvalget ikke inkluderede JAK2-mutationsbyrden som effektmål i protokollen. Det er dog en teoretisk plausibel mulighed, at en reduceret JAK2-mutationsbyrde kan forsinke sygdomsudviklingen, og et retrospektivt studie har indikeret en korrelation mellem høj JAK2-mutationsbyrde og øget risiko for at udvikle myelofibrose for patienter med PV [30].

JAK2-mutationsbyrden indgik som effektmål i PROUD/CONTINUATION-PV, og ansøger har således udført en direkte sammenligning af effekten af ropeginterferon-alfa-2b over for hydroxyurea på den gennemsnitlige mutationsbyrde ved forskellige behandlingstidspunkter.

Ved afslutningen af PROUD-PV (12 måneders behandling) var der ikke statistisk signifikant forskel på reduktionen i gennemsnitlig mutationsbyrde mellem behandlingerne. Patienterne behandlet med ropeginterferon-alfa-2b havde en gennemsnitlig mutationsbyrde på 41,9 % (standardafvigelse på 23,5 %) ved baseline, som var reduceret til 30,7 % (standardafvigelse på 22,7 %) efter 12 måneder, og patienterne behandlet med hydroxyurea havde en gennemsnitlig mutationsbyrde på 42,8 % (standardafvigelse på 24,1 %) ved baseline, som var reduceret til 25,9 % (standardafvigelse på 21,5 %) efter 12 måneder.

Ved længere tids behandling i CONTINUATION-PV udviklede mutationsbyrden sig forskelligt. Patienterne behandlet med ropeginterferon-alfa-2b opnåede fastholdelse eller yderligere reduktion af mutationsbyrden til 19,7 % (standardafvigelse på 21,3 %) efter 36 måneder og [redacted] efter 60 måneder. Patienterne behandlet med hydroxyurea oplevede modsat, at mutationsbyrden steg efter det initiale fald til hhv. 39,3 % (standardafvigelse på 25,9 %) og [redacted] ved 36 og 60 måneder. Mutationsbyrden var statistisk signifikant lavere for patienter behandlet med ropeginterferon-alfa-2b end for patienter behandlet med hydroxyurea efter både 36 og 60 måneder. Der er dermed klinisk dokumentation for, at patienterne opnår en reduktion i mutationsbyrden ved længere tids behandling med ropeginterferon-alfa-2b, hvilket ikke er tilfældet ved behandling med hydroxyurea.

Pegyleret interferon-alfa-2a kan ligeledes sænke JAK2-mutationsbyrden. I MPN-RC-112 opnåede patienterne sammenlignelig reduktion i JAK2-mutationsbyrden fra baseline efter 12 måneders behandling i begge behandlingsarme. Mutationsbyrden faldt yderligere efter 24 måneder i gruppen behandlet med pegyleret interferon-alfa-2a, mens mutationsbyrden var øget til baselineniveau i gruppen behandlet med hydroxyurea, hvilket var samme tendens som observeret i PROUD-PV og CONTINUATION-PV.

Der foreligger endnu ikke studier, der dokumenterer en overlevelsesfordel enten med hensyn til *overall survival* eller transformationsfri overlevelse for patienter, der opnår reduceret mutationsbyrde. Sådanne studier er metodemæssigt og ressourcemæssigt meget krævende på grund af den lange mediane overlevelse ved PV. Da PV-patienter som population dog har let nedsat overlevelse og væsentlig nedsat livskvalitet ved transformation, er der potentielt en gevinst ved optimering af behandlingen, som også er indikeret af ovennævnte observationelle studie [30].

Transformation til akut myeloid leukæmi eller myelofibrose

Ansøger har indsendt et retrospektivt studie (Abu-Zeinah et al. 2021 [31]), hvori risikoen for transition til myelofibrose og samlet overlevelse for alle patienter diagnosticeret med PV på et amerikansk center i perioden 1974-2019 blev opgjort. Patienterne blev inddelt i grupper, ift. hvilken behandling de havde modtaget (pegyleret interferon-alfa, hydroxyurea eller udelukkende venesektion), og derudover blev de inddelt efter, om de var høj- eller lav-risikogruppe. Lav risiko blev defineret som patienter, der var under 60 år og ikke havde haft tromboemboliske hændelser ved diagnosen, hvorimod alle, som var ældre end 60 år ved diagnosen, eller som havde oplevet en tromboembolisk hændelse, tilhørte højrisikogruppen. Medianalderen ved diagnosen var 54 år, og den mediane opfølgningstid var 10 år. Ud af de i alt 470 patienter var den primære behandling pegyleret interferon-alfa for 93 patienter, hydroxyurea for 189 patienter og venesektion for 133 patienter, mens de resterende patienter modtog 'anden cytoreduktiv behandling'. Den største forskel mellem patientgrupperne var, at patienterne primært behandlet med pegyleret interferon-alfa var yngre end de andre patientgrupper (medianalder på 50 år over for 58 år ved hydroxyurea og 54 år ved venesektion). Dette betød, at en væsentlig større andel af patienterne behandlet med pegyleret interferon-alfa tilhørte lav-risikogruppen i forhold til de andre grupper. Øvrige baselinekarakteristika var sammenlignelige mellem grupperne (se Tabel 11 i Bilag 3, afsnit 11).

Data stratificeret efter risikogruppe og primær behandling indikerer, at pegyleret interferon-alfa medførte længere samlet overlevelse og længere tid til transformation til myelofibrose hos patienter i både høj- og lavrisikogruppe. Samlet overlevelse ved 20 år i lavrisikogruppen var hhv. 100 % (pegyleret interferon-alfa), 85 % (hydroxyurea) og 80 % (venesektion), mens de tilsvarende overlevelsesrater i højrisikogruppen var 66 % (pegyleret interferon-alfa), 40 % (hydroxyurea) og 14 % (venesektion). Samme mønster er gældende for risikoen for transformation til myelofibrose, hvor den myelofibrosefri-overlevelse i lavrisikogruppen var hhv. 84 %, 65 % og 55 %, og i højrisikogruppen hhv. 89 %, 41 % og 36 %.

Studiet skal tolkes med forsigtighed, da det ikke er et kontrolleret, randomiseret prospektivt studie, men fagudvalget vurderer, at studiets resultater indikerer, at der kan være en værdi i form af en reduceret risiko for på længere sigt at udvikle myelofibrose ved behandling med pegyleret interferon ift. til venesektion og hydroxyurea. Dette understøtter rationalet for at behandle yngre patienter med pegyleret interferon-alfa, da disse patienter forventes at skulle være i behandling i mange år.

7. Relation til behandlingsvejledning

Medicinrådet har publiceret en Behandlingsvejledning vedrørende cytoreduktiv behandling af Essentiel Trombocytose og Polycytæmia Vera. Behandlingsvejledningen er imidlertid ikke godkendt af Medicinrådet, da den omhandler anvendelse af lægemidler uden for den godkendte indikation. Medicinrådet kunne på daværende tidspunkt ikke udfærdige en generel anbefaling om, at der til en bestemt patientgruppe skal anvendes et bestemt lægemiddel, som ikke er godkendt til den pågældende indikation, medmindre der ikke findes godkendte lægemidler. Behandlingsvejledningen har derfor ikke dannet grundlag for et udbud eller en lægemiddelrekommandation, og derfor vil fagudvalget ikke foretage en indplacering af ropegingerferon-alfa-2b i forbindelse med den nuværende vurdering.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kroniske myeloproliferative sygdomme (inkl. kronisk myeloid leukæmi)

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Jesper Stentoft *Professor, overlæge*	Indstillet som formand af Dansk Hæmatologisk Selskab og Region Midtjylland samt udpeget som medlem af Region Midtjylland
Medlemmer	**Udpeget af**
Gitte Thomsen *Afdelingslæge*	Region Nordjylland
Andreja Dimitrijevic *Overlæge*	Region Syddanmark
Lene Udby *Overlæge*	Region Sjælland
Bo Kok Mortensen *Afdelingslæge*	Region Hovedstaden
Sidsel Marcussen *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Andreas Brønden *1. reservelæge*	Dansk Selskab for Klinisk Farmakologi
Mette Munk *Sygeplejerske*	Dansk Sygepleje Selskab
Michael Olsen *Patient/patientrepræsentant*	Danske Patienter
Annette Johansen *Patient/patientrepræsentant*	Danske Patienter

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	18. maj 2022	Godkendt af Medicinrådet.

11. Bilag

Bilag 1: Cochrane – risiko for bias

Vurdering af risiko for bias ved Cochrane risk of bias tool 2.0.

Tabel 8. Vurdering af risiko for bias i Gisslinger et al. 2020, PROUD-PV og CONTINUATION-PV, NCT01949805 og NCT02218047

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Randomiseringen ved indgangen til PROUD-PV blev foretaget centralt vha. en randomiseringsliste genereret i Statistical Analysis System (SaS) version 9.3.
Effekt af tildeling til intervention	**Høj**	Studiet var open-label. Både patienter og investigatorer vidste derfor, om de modtog ropeginterferon-alfa-2b eller hydroxyurea. Det kan have haft betydning for indrapportering af uønskede hændelser og patientrapporteret livskvalitet. Samtidig kan det have haft betydning for fortsættelsen i CONTINUATION-PV, hvor væsentlig flere patienter valgte ikke at fortsætte i hydroxyurea-armen.
Manglende data for effektmål	**Lav**	Effektanalyserne er baseret på alle patienter med målinger ved de pågældende opfølgningstidspunkter. Patienter, der havde ophørt med behandlingen uanset årsag, blev medtaget i analyserne som ikke-respondere.
Risiko for bias ved indsamlingen af data	**Forbehold**	Studiet var open-label. Der blev foretaget flere foranstaltninger for at minimere bias. Blodprøveværdier blev målt på et centralt laboratorium, der ikke vidste hvilken behandling, patienterne havde modtaget, og miltstørrelsen blev målt ved CT/MRI, hvor den resulterende miltstørrelse er uafhængig af operatøren.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der er data tilgængelige for alle effektmål, og data er analyseret i henhold til analyseplanen.
Overordnet risiko for bias	**Høj**	Der er høj risiko for bias, ifm. at patienterne vidste, om de modtog ropeginterferon-alfa-2b eller hydroxyurea, hvilket kan have påvirket de selvrapporterede effektmål, hovedsageligt uønskede hændelser og livskvalitet.

Tabel 9. Vurdering af risiko for bias i Mascarenhas et al. 2022, MPN-RC-112, NCT01259856

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Patienterne blev randomiseret 1:1 vha. et centraliseret management website.
Effekt af tildeling til intervention	**Høj**	Studiet var open-label. Både patienter og investigatorer vidste derfor, om de modtog pegyleret interferon-alfa-2a eller hydroxyurea. Det kan have haft betydning for indrapportering af uønskede hændelser og patientrapporteret livskvalitet.
Manglende data for effektmål	**Lav**	Effektanalyserne er baseret ITT-populationerne.
Risiko for bias ved indsamlingen af data	**Forbehold**	Studiet var open-label. Respons blev bedømt af en central komité, der ikke vidste hvilken behandling, patienterne havde modtaget.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Forbehold**	Der er data tilgængelige for alle effektmål. For mange af effektmålene er data rapporteret samlet for PV og essentiel trombocytose. Derfor er der nogen risiko for, at resultater fra patienter med essentiel trombocytose systematisk kan have påvirket de samlede resultater.
Overordnet risiko for bias	**Høj**	Der er høj risiko for bias, ifm. at patienterne vidste, om de modtog pegyleret interferon-alfa-2a eller hydroxyurea, hvilket kan have påvirket de selvrapporterede effektmål, hovedsageligt uønskede hændelser og livskvalitet.

Bilag 2: GRADE

Klinisk spørgsmål 1 – ropeginterferon-alfa-2b sammenlignet med hydroxyurea til behandling af polycytæmia vera

Tabel 10. GRADE-evidensprofil for klinisk spørgsmål 1

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Ropeginterferon -alfa-2b	Hydroxyurea	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Tromboemboliske hændelser, 60 måneders opfølgning												
1	RCT	Alvorligt[a]	Alvorligt[b]	Ingen	Alvorligt[c]	Ingen	127	127	[redacted]	[redacted]	⨁◯◯◯ MEGET LAV	KRITISK
Livskvalitet												
Data for effektmålet er ikke opgjort i henhold til protokollen											Ikke relevant	KRITISK
Bivirkninger, 60 måneders opfølgning												
1	RCT	Alvorligt[a]	Alvorligt[b]	Ingen	Meget alvorligt[d]	Ingen	127	127	[redacted]	[redacted]	⨁◯◯◯ MEGET LAV	KRITISK
Komplet hæmatologisk respons, 60 måneders opfølgning												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Ropeginterferon -alfa-2b	Hydroxyurea	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
1	RCT	Alvorligt[a]	Alvorligt[b]	Ingen	Alvorligt[c]	Ingen	95	75	[redacted]	[redacted]	⨁◯◯◯ MEGET LAV	VIGTIG

Kvalitet af den samlede evidens MEGET LAV[e]

[a] Der er nedgraderet ét niveau, da der var nogle forbehold i vurderingen af risiko for bias.

[b] Der er nedgraderet ét niveau, da der kun var ét studie.

[c] Der er nedgraderet ét niveau, da konfidensintervallet indeholder én beslutningsgrænse.

[d] Der er nedgraderet to niveauer, da der ikke er udregnet konfidensintervaller for estimaterne, og de potentielt kan være meget brede og indeholde både positive og negative konklusioner.

[e] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Bilag 3: Baselinekarakteristika for patientgrupperne i Abu-Zeinah et al. 2021

Tabel 11: Baselinekarakteristika for patientgruppen i Abu Zeinah et al. 2021

	Samlet population (n = 470)	Venesektion (n = 133)	Interferon-alfa (n = 93)	Hydroxyurea (n = 189)	Anden behandling (n = 55)
Alder, median (range)	54 år (20-94)	54 år (20-94)	50 år (26-82)	58 år (22-84)	52 år (20-91)
Køn, kvinde	49 %	41 %	46 %	54 %	53 %
Etnicitet					
Kaukasisk	86 %	88 %	93 %	82 %	83 %
Asiatisk, afrikansk eller latinamerikansk	10 %	10 %	5 %	14 %	8 %
Anden	4 %	3 %	2 %	4 %	8 %
Kardiovaskulære risikofaktorer	21 %	10 %	27 %	26 %	24 %
Tidligere tromboser	14 %	11 %	12 %	16 %	15 %
Høj risiko iflg. ELN-kriterier	44 %	42 %	24 %	56 %	45 %
JAK2-V617F positive	98 %	96 %	99 %	99 %	100 %
Diagnoseår, median (range)	2005 (1966-2019)	2008 (1986-2019)	2005 (1982-2019)	2004 (1966-2018)	2004 (1986-2018)
Opfølgningstid, median (range)	10 år (0-45)	5 år (0-32)	13 år (1-35)	11 år (0-45)	9 år (1-32)
Tid fra diagnose til opstart af cytoreduktiv behandling, median (range)	1 år (0-30)	Ikke relevant	1 år (0-15)	1 år (0-26)	1 år (0-30)
Behandlingsvarighed, median (range)	4 år (0-28)	4 år (0-28)	5 år (1-26)	5 år (0-26)	3 år (1-15)

ELN = European LeukemiaNet

Application for the assessment of Besremi (ropeginterferon alfa-2b) for monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly

Contents

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1. Basic Information

Contact information	
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Overview of the pharmaceutical	
Proprietary name	Besremi
Generic name	ropeginterferon alfa-2b
Marketing authorization holder in Denmark	AOP Orphan Pharmaceuticals GmbH
ATC code	L03AB15
Pharmacotherapeutic group	Immunostimulants, interferons
Active substance(s)	Ropeginterferon alfa-2b
Pharmaceutical form(s)	Solution for injection in pre-filled pen (injection)

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Overview of the pharmaceutical	
Mechanism of action	Interferon alfa belongs to the class of type I interferons which exhibit their cellular effects by binding to a transmembrane receptor termed interferon alfa receptor (IFNAR). Binding to IFNAR initiates a downstream signalling cascade through the activation of kinases, particularly Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) and signal transducer and activator of transcription (STAT) proteins. Nuclear translocation of STAT proteins controls distinct gene-expression programs and exhibits various cellular effects. Interferon alfa was shown to have an inhibitory effect on the proliferation of hematopoietic and bone marrow fibroblast progenitor cells and antagonised the action of growth factors and other cytokines that have a role in the development of myelofibrosis. These actions may be involved in the therapeutic effects of interferon alfa in polycythaemia vera. Further, it was demonstrated that interferon alfa, and also ropeginterferon alfa-2b, is able to decrease the mutated JAK2V617F allele burden in patients with polycythaemia vera (a V617F point mutation in the JAK2 kinase is a hallmark of polycythaemia vera and is present in approximately 95% of patients). Ropeginterferon alfa-2b has been specifically developed for treating polycythemia vera and is administered through a dose adjustable pen, suitable for home administration.(1) It is a covalent conjugate of the protein interferon alfa-2b, produced in Escherichia coli cells by recombinant DNA technology, with a methoxypolyethylene glycol (mPEG) moiety. Ropeginterferon alfa-2b consists of a single positional isomer resulting in an extended elimination half-life compared to conventional interferons. This enables less frequent dosing (every other week, or monthly during maintenance therapy) and improved tolerability, supporting long-term patient compliance. It has therefore been classified as a new active substance.
Dosage regimen	Titration phase The dose is titrated individually with a recommended starting dose of 100 micrograms (or 50 micrograms in patients under another cytoreductive therapy). The dose should be gradually increased by 50 micrograms every two weeks (in parallel, other cytoreductive therapy should be decreased gradually, as appropriate) until stabilisation of the haematological parameters is achieved (haematocrit <45%, platelets <400 x 10^9/L and leukocytes <10 x 10^9/L). The maximum recommended single dose is 500 micrograms injected every two weeks. Phlebotomy as rescue treatment to normalize blood hyperviscosity may be necessary Maintenance phase The dose at which stabilisation of the haematological parameters is achieved should be maintained in a two-week administration interval for at least 1.5 years. After that, the dose may be adapted and/or the administration interval prolonged up to every four weeks, as appropriate for the patient.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Besremi is indicated as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly
Other approved therapeutic indications	NA
Will dispensing be restricted to hospitals?	Yes

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Overview of the pharmaceutical	
Combination therapy and/or co-medication	NA
Packaging – types, sizes/number of units, and concentrations	Besremi 250 micrograms/0.5 mL solution for injection in pre-filled pen Each pre-filled pen of 0.5 mL solution contains 250 micrograms of ropeginterferon alfa-2b as measured on a protein basis, corresponding to 500 micrograms/mL.
Orphan drug designation	NA

2. Abbreviations

Abbreviation	Definition
JAK1	Janus kinase 1
TYK2	tyrosine kinase 2
IFNAR	interferon alfa receptor
STAT	signal transducer and activator of transcription
mPEG	methoxypolyethylene glycol
EMA	European Medicines Agency
ropegIFN alfa-2b	Ropeginterferon alfa-2b
IFN	interferon
PV	Polycythaemia Vera
MPN	myeloproliferative neoplasm
HU	hydroxyurea
MPN-RC	Myeloproliferative Neoplasms - Research Consortium
ET	Essential Thrombocythemia
MTD	maximum tolerated dose
QoL	quality of life
CSR	clinical study report
BAT	best available treatment
EQ-5D-3L	EuroQol-5 Domain- 3 Level

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CI	Confidence interval
FAS	Full Analysis Set
SD	Standard deviations
Hct	heamatocrit
RR	Rate ratio
LOCF	Last Observation Carried Forward
OR	odds ratio
EOT	End of trial
VAS	visual analogic score
TEAE	treatment emergent adverse effect
SAE	Serious adverse events
AESI	adverse events of special interest
CHR	Complete haematological response
IQR	Interquartile range
MPNu	MPN unclassified
PVSG	Polycythemia Vera Study Group
WBC	white blood cell
PR	Partial hematologic response
MR	Molecular response
WHO	World Health Organization
EORTC	European Organization for Research and Treatment of Cancer
ANC	absolute neutrophil count
ITC	Indirect treatment comparison

3. Summary

Ropeginterferon alfa-2b (Besremi) [ropegIFN alfa-2b] is an innovative medicine which differs from previous interferon preparations; ropegIFN is a recombinant interferon produced by innovative pegylation technology. The World Health

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Organization recognized this by giving ropegIFN alfa-2b (Besremi) a unique ATC code (L03AB15). The EMA has also defined ropegIFN alfa-2b as a new active substance. RopegIFN alfa-2b is the first interferon which has been clinically studied and who's efficacy and safety profile is proven in the field of haematology.

Polycythaemia Vera (PV) (ICD-10 code: D45) is a rare type of acquired chronic myeloproliferative neoplasm (MPN). Orphanet estimated the prevalence of PV to be 3 per 10,000 in Europe. PV is a long-term debilitating and life-threatening condition. PV is associated with an increased risk of thrombosis, haemorrhage and progression to myelofibrosis and secondary acute myeloid leukaemia. Complications of PV can end in death. Thrombosis, the most common complication of PV, leads to serious morbidity and death in 37% of cases.

The clinical efficacy of ropegIFN alfa-2b in treatment of PV has been studied in phase 3 randomized controlled trial PROUD-PV and its extension study CONTINUATION-PV in comparison to hydroxyurea. The studies showed that although hydroxyurea was more effective in the short term (<1 year of treatment), ropegIFN alfa-2b was significantly more effective in the long term (≥1 year of treatment) in achieving and maintaining a haematological and molecular treatment response.
RopegIFN alfa-2b was well tolerated and showed a different safety profile compared to hydroxyurea at Months 12 and 36. The overall safety profile was consistent with class effects of other interferons used.

For the comparison of ropegIFN alfa-2b compared to pegylated interferon alfa-2a (Pegasys) for adult patients under the age of 60 the available evidence for IFN-alfa-2a/b is limited for the treatment of PV patients. Given that in the past, usage of interferons was considered off-label as no interferon had any approved haematological indication.

There is significant heterogeneity in study design, reported end points and patient populations included in the identified studies, which makes it difficult to do formal comparative statistics for the comparison of ropegIFN alfa-2b and IFN alfa-2a/b. Hence, the comparative analyses included in this application were mainly narrative.
The haematological responses across the included studies showed the varying estimates across type of interferon alfa, dosing, populations and time of assessment, ranging from 22% to 95%. The results from PROUD-PV and CONTINUATION-PV indicates that ropegIFN alfa-2b is within the range found in other interferon studies. Based on the development over time from the PROUD-PV to the CONTINUATION-PV the proportion of patients with hematological response increases, which aligns with the molecular structure and pharmacodynamics of ropegIFN alfa-2b as well as its proposed targeted activity on the JAK2 mutated clone.

Adverse events were heterogeneous reported across the included studies. Based on the rates of discontinuation due to adverse events reported in PROUD-PV (5.5%) and CONTINUATION-PV (8% at 36 months) for ropegIFN alfa-2b has lower rates of discontinuation compared to other pegIFN studies.

The present documentation has certain limitations. These include that the clinical questions only take into account comparison to HU and off-label pegIFN (Pegasys). Clinical practice and current Nordic MPN study group guidelines also include ruxolitinib (Jakavi) as a possible 3rd line option. Further, for clinical question 2, limited data are available and no head-to- head studies have been performed. vs. pegylated (or non-pegylated) interferon (which would have been considered an investigational medical product in clinical studies, requiring an additional treatment arm, and further increasing complexity of the study design).
Although there has not been any previously approved interferon available for PV, the need for the clinical benefit of interferons as cytoreductive therapy has made off-label interferons an important treatment option. However conventional interferons developed for other diseases and used off-label for PV do have limitations with respect to dosing interval and tolerability when used long-term for a chronic disease. Interferon is theoretically superior to other

therapies for treating PV as long-standing molecular remissions can be achieved.(2-4) Interferon does not increase the risk of leukemia(5). Further, it follows from Abu-Zeinah et al. 2021(6) that interferon-alpha is the only disease-modifying treatment for PV, also preventing the developing of myelofibrosis and has the potential of prolonging survival. Accordingly, interferons serve as an obvious treatment option for PV.
RopegIFN alfa-2b (Besremi) has been specifically developed and approved for PV in order to meet the need of an interferon with improved tolerability to be able to maintain effective long-term therapy. Structural innovations of RopegIFN alfa-2b (Besremi) with a single positional isomer and larger PEG molecule results in an extended elimination half-life compared to conventional interferons. This enables less frequent dosing (every other week, or monthly during maintenance therapy) and improved tolerability, supporting long-term patient compliance. RopegIFN alfa-2b (Besremi) is administered via a dose adjustable pen, suitable for home administration.

RopegIFN alfa-2b (Besremi) was approved in EU February 2019 and has since launch been introduced in several European countries with Austria and Germany being the most mature markets. Recently ropegIFN alfa-2b (Besremi) has also received approval by FDA. Reports from the clinical experience concludes that ropegIFN alfa-2b (Besremi) is a valuable addition to the treatment of patients with PV. Treatment with ropegIFN alfa-2b (Besremi) results in high and sustained haematological response rates and disease-modifying effects. This is corroborated by the fact that the allele burden of the JAK2 mutation, known as the driver mutation in PV, is significantly decreased in most patients treated with ropegIFN alfa-2b (Besremi) and in some patients is no longer detectable. From clinical practice it is reported that patients suffering from tolerability issues with Pegasys has been successfully switched to ropegIFN alfa-2b (Besremi) with better tolerability and compliance as outcome.(7)

As discussed in the DMC protocol PV is a chronic blood cancer that frequently leads to thrombosis and may transform into MF or AML. Consequently, it is crucial for these patients to have access to available and adequate treatment options. RopegIFN alfa-2b (Besremi) represents a therapeutic option developed specifically for treating PV, and provides improvement compared to conventional cytoreductive therapies performed either with hydroxyurea or off-label conventional interferons. Hence ropegIFN alfa-2b (Besremi) serves an important addition to the treatment options in PV

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4. Literature search

The following electronic databases were searched 03.01.2022: MEDLINE via PubMed and CENTRAL via Cochrane Library. The search strategy was carried out as defined in the protocol and no date limit was applied to the electronic searches.
Primary screening was performed by two reviewers who independently reviewed each reference (title and abstract) identified by the literature search, applied study selection criteria, and decided on whether to include or exclude the reference at that stage. Secondary screening included obtaining the full-text articles for potentially relevant studies identified by primary screening of titles and abstracts. These were independently reviewed by two reviewers against each eligibility criterion.

The systematic database searches identified 144 records. A de-duplication step was performed to remove studies that overlapped across the databases; 7 of the studies were identified as duplicates and excluded. The remaining 137 studies were screened based on the information reported in their titles and/or abstracts. Of these, 117 records were excluded, and 20 records were included. The 20 records were further assessed for eligibility for this review by full-text screening, which resulted in exclusion of 8 publications and inclusion of 12 publications. One additional record was identified through other sources. Thus, a total of 13 articles were included in this review.
Figure 1 presents the PRISMA flow diagram of studies identified for clinical review.

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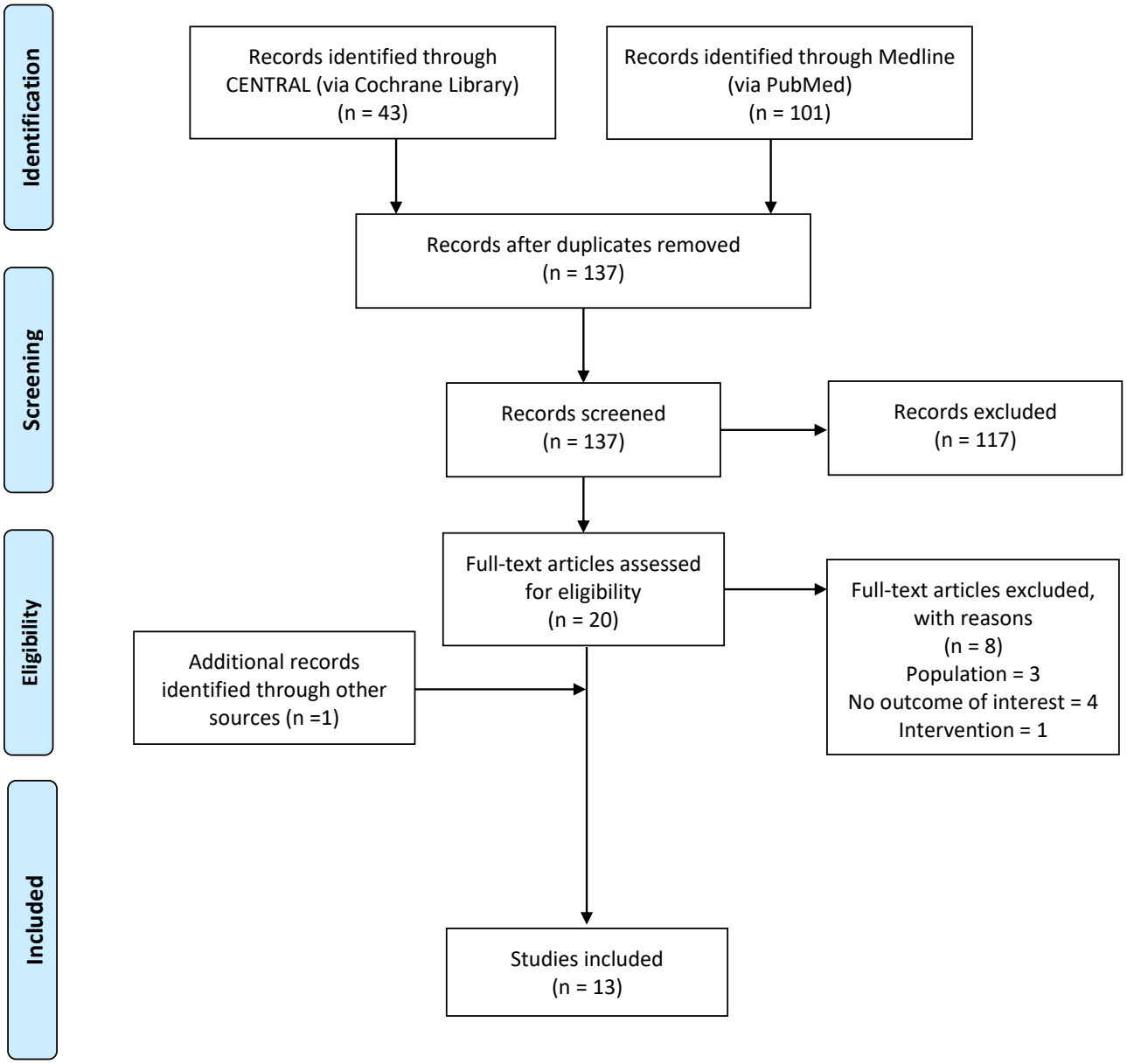
Figure 1 PRISMA flow diagram



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4.1 Relevant studies

Table 1 Relevant studies included in the assessment.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question 1 or 2
Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-Inferiority, phase 3 trial and its extension study, Gisslinger et al., Lancet Haematol, 2020	PROUD-PV/ CONTINUATION-PV	NCT01949805/ NCT02218047	Start date: September 2013 Completion date: July 2016 / Start date: November 2014 Completion date: April 2021	1 and 2
Ropeginterferon alfa-2b, a novel IFNa-2b, induces high response rates with low toxicity in patients with polycythemia vera, Gisslinger et al., Blood, 2015	PEGINVERA	NCT01193699	Start date: August 2010 Completion date: January 25, 2018	1 and 2
Pegylated interferon alfa-2a in patients with essential thrombocythaemia or polycythaemia vera: a post-hoc, median 83 month follow-up of an open-label, phase 2 trial, Masarova et al., Lancet Haematol., 2017	NA	NA	Not reported, but estimated 2009-2016 (latest publication with 7 years follow-up)	2
Molecular analysis of patients with polycythemia vera or essential thrombocythemia receiving pegylated interferon alfa-2a, Quintas-Cardama et al., Blood, 2013				

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question 1 or 2
Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera, Quintas-Cardama et al., J Clin Oncol, 2009				
Can pegylated interferon improve the outcome of polycythemia vera patients?, Crisa et al., J Hematol Oncol., 2017	NA	NA	Not reported	2
Interferon alfa-2b gains high sustained response therapy for advanced essential thrombocythemia and polycythemia vera with JAK2V617F positive mutation, Huang et al., Leuk Res., 2014	NA	NA	Start date: February 2009 Completion date: March 2014	2
Long term molecular responses in a cohort of Danish patients with essential thrombocythemia, polycythemia vera and myelofibrosis treated with recombinant interferon alfa, Stauffer Larsen et al., Leuk Res., 2013	NA	NA	1996-2011	2
Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera, Kiladjian et al., Blood, 2008	NA	NCT00241241	Start date: 2004 Completion date: January 2008	2

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question 1 or 2
A phase II trial of pegylated interferon alfa-2b therapy for polycythemia vera and essential thrombocythemia: feasibility, clinical and biologic effects, and impact on quality of life, Samuelsson et al., Cancer, 2006	NA	NA	Start date: 2001 Completion date: 2005	2
Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea, Yacoub et al., Blood, 2019	MPN-RC 111	NCT01259817	Start date: September 2011 Completion date: December, 2016	2
A Randomized, Phase 3, Trial of Interferon-α versus Hydroxyurea in Polycythemia Vera and Essential Thrombocythemia, Mascarenhas et al., Blood, 2022	MPN-RC 112	NCT01259856	Start date: September 2011 Completion date: June 30, 2017	2
Symptom burden and quality of life in patients with high-risk essential thrombocythaemia and polycythaemia vera receiving hydroxyurea or pegylated interferon alfa-2a: a post-3hoc analysis of the MPN-RC 111 and 112 trials, Mazza et al., Lancet Haematol., 2022				

4.2 Main characteristics of included studies

The systematic literature review identified 13 publications from 11 studies which have used various interferon alfa (IFN a2) compounds as the main intervention, including the pivotal trials for ropeginterferon alfa-2b, PROUD-PV,

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CONTINUATION-PV and PEGINVERA. Of these publications, 11 included (pegylated) interferon alfa-2a or alfa-2b as the main intervention aligning with the comparator for clinical question 2, as stated in the DMC protocol.
The PROUD-PV and CONTINUATION-PV trials were conducted in 48 clinics across Europe. Of the interferon alfa-2a or alfa-2b studies, five were conducted in Europe, one in Denmark, one in China and one in the USA. The year of publication ranged from 2006 to 2022. Eight studies were published as peer-reviewed articles and only one as a letter to the editor(8). All studies were open-label. The design of these studies varied considerably (see Table 1 for details).

Table 1 Main characteristics of included studies

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))
PROUD-PV	Assessing the efficacy and safety of RopegIFN alfa-2b vs. Hydroxyurea in patients with Polycythemia Vera	Open-label, randomized, multicentre, controlled, parallel-arm, phase III study	18 years or older with early-stage polycythaemia vera (no history of cytoreductive treatment or less than 3 years of previous hydroxyurea treatment)	RopegIFN alfa-2b (n=127) Hydroxyurea (n=127)
CONTINUATION-PV	Assessing the efficacy and safety of RopegIFN alfa-2b vs. Hydroxyurea in patients with Polycythemia Vera	Open-label extension study of PROUD-PV	18 years or older with early-stage polycythaemia vera (no history of cytoreductive treatment or less than 3 years of previous hydroxyurea treatment)	RopegIFN alfa-2b (n=95) Hydroxyurea (n=76)
PEGINVERA	Identification of the maximum tolerated dose (MTD) of RopegIFN alfa-2b. Moreover, the safety and tolerability will be assessed, and efficacy explored.	Open-label, Prospective, Multicentre, Phase I/II Dose Escalation Study	Patients 18 years or older with a diagnosis of ET or PV, either newly diagnosed or previously treated	RopegIFN alfa-2b (n=51)
NCT00452023	Assessing if Pegasys (IFN-alfa-2a) can help to control the disease in patients with ET, PV, AMM/MF, and Ph-negative CML	Prospective, open-label, single-center, phase II	Patients 18 years or older with a diagnosis of ET or PV, either newly diagnosed or previously treated	Pegylated IFN-alfa (PV n=43; ET n= 39)
Crisa et al. 2017	Not reported	Observational study	PV patients below 65 years	Pegylated IFN-alfa -2a (n=30)
Huang et al. 2014	To evaluate treatment response, efficacy therapy and safety to IFN-alfa-2b for the essential thrombocythemia (ET)	Open-label, observational, multicenter	Essential thrombocythemia and polycythemia vera with JAK2V617F positive mutation patients (ages 18–65 years old)	IFN-alfa-2b (n = 64) Hydroxyurea (n=72)

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))
	and polycythemia vera (PV) with JAK2V617F positive mutation			
Stauffer Larsen et al. 2013	To report on clinical and molecular data in the largest cohort of JAK2 V617F mutant MPN Danish patients being treated long-term with rIFN-alfa2 (rIFN-alfa2a and rIFN-alfa2b in a non-clinical trial setting	Open-label, retrospective, observational single center	JAK2V6177F mutated ET, PV or primary myelofibrosis. 18 years or older	IFN-alfa-2a/b (n = 102 [19 ET; 75 PV])
PVN1 (Kiladjian et al. 2008)	Evaluation of efficacy, safety, and monitoring of residual disease using JAK2V617F quantification (%V617F) of pegylated IFN-alfa-2a in 40 PV patients	Prospective, open-label, single-arm, phase II	PV diagnosis according to Polycythemia Vera Study Group (PVSG) criteria, age 18 to 65 years, and no previous treatment or only phlebotomies or cytoreductive treatment for less than 2 years	IFN-alfa-2a n = 37
Samuelsson et al. 2006	Investigate the feasibility of PEG-IFN therapy, its biologic effects, and its impact on quality of life (QoL) in patients with PV and ET	Prospective, open label, Phase II clinical	Diagnosis of PV or ET patients age 18 years and older	Pegylated IFN-alfa-2b (ET=21; PV = 21)
MPN-RC 111	Evaluate the ability of Pegylated Interferon Alfa-2a to achieve Complete Response or Partial Response in patients with (1) high risk polycythemia vera or (2) high risk essential thrombocythemia or (3) splanchic vein thrombosis	Prospective, open-label, single-arm, phase II	Diagnosis of PV or ET patients age 18 years and older	Pegylated IFN-alfa-2a (n=82) PV = 50 ET = 65
MPN-RC 112	Assess the effectiveness of giving participants who have been diagnosed with ET or PV either Pegylated Interferon Alfa-2a	Randomized, open label, phase 3	Diagnosis of PV or ET patients age 18 years and older	Hydroxyurea (n=86) Pegylated IFN-alfa-2a (n=82)

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))
	(PEGASYS) or Hydroxyurea			

The number of participants varied from 30(8) to 254(1) with varying inclusion of across PV and ET. PROUD-PV only included PV patients. Five studies were a single-arm design(2-4, 9, 10). Four studies used HU as comparator(1, 8, 11, 12).

All papers aimed to assess the efficacy and safety of the pharmacological agent used. All papers (reported results for efficacy (haematological response) and safety. Data regarding the proportion of patients experiencing at least one certain event (thromboembolic or adverse event) was not reported in any of the identified publications. For PROUD-PV and CONTINUATION-PV these data were obtained through the CSRs. A full overview of which publications reports the outcomes defined by the DMC protocol can be found in Table 2.

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Table 2 Reported outcomes in the included studies

	PROUD-PV	CONTINUATION-PV	PEGINVERA	NCT00452023	Crisa 2017	Huang et al. 2014	Stauffer Larsen 2013	PVN1 (Kiladjian 2008)	Samuelsson 2006	MPN-RC 112
Proportion of patients experiencing at least one thromboembolic event	Yes	Yes	NR	NR	Yes	NR	Yes	NR	Yes	Yes
Proportion experiencing complete hematological response	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
MPN-SAF mean change from baseline in total symptom score	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
EQ-5D Mean change from baseline	Yes (CSR)	Yes CSR	NR	NR	NR	NR	NR	NR	NR	NR
Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4	Yes CSR	Yes CSR	NR	Yes (combined for PV and ET)	NR	NR	NR	Yes	NR	Yes
Proportion experiencing at least one treatment related adverse events of grade 3-4	Yes CSR	Yes CSR	NR	NR	NR	NR	NR	NR	NR	NR

5. Clinical questions

5.1 Ropeginterferon alfa-2b (Besremi) compared to hydroxyurea (HU) for patients over 60 years of age with polycythaemia vera

5.1.1 Presentation of relevant studies

5.1.1.1 PROUD-PV and CONTINUATION-PV

The publication by Gisslinger et al. 2020 of the PROUD-PV and CONTINUATION-PV studies comparing ropegIFN alfa-2b to hydroxyurea has been assessed as sufficient evidence for answering clinical question 1.(1)

The clinical development program for comparing ropegIFN alfa-2b in PV includes the following Phase III program comprised by:

- PROUD-PV Study, a randomized, open-label, controlled parallel-arm, non-Inferiority study of ropeginterferon IFN alfa-2b versus HU in 254 patients with PV,
- CONTINUATION-PV Study, an open-label, Phase IIIb extension study assessing the long-term efficacy and safety of ropeginterferon alfa-2b in PV patients who completed the ropeginterferon alfa-2b arm of the PROUD-PV Study in comparison to patients who completed the HU arm of PROUD-PV Study and are managed according to standard of care/best available treatment (BAT)

PROUD-PV and its extension study, CONTINUATION-PV, were phase 3, randomised, controlled, open-label, trials done in 48 clinics in Europe. Patients were eligible if 18 years or older with early stage polycythaemia vera (no history of cytoreductive treatment or less than 3 years of previous hydroxyurea treatment) diagnosed by WHO's 2008 criteria. Patients were randomly assigned 1:1 to ropegIFN alfa-2b (subcutaneously every 2 weeks, starting at 100 µg, or 50 µg if the patient was transitioning from hydroxyurea) or hydroxyurea (orally starting at 500 mg/day).

After 1 year, patients could opt to enter the extension part of the trial, CONTINUATION-PV. The primary endpoint in PROUD-PV was disease response rate at Month 12 defined as haematocrit <45% without phlebotomy (at least 3 months since last phlebotomy), platelets $<400x10^9$/L, leukocytes $<10x10^9$/L (these 3 variables defining the complete haematological response) and normal spleen size (defined as longitudinal diameter ≤12 cm for females and ≤13 cm for males).
A patient was classified as “responder” (i.e. treatment success) only if all of the disease response criteria were met. If at least one criterion was not met, the patient was classified as “non-responder” (treatment failure) regardless of whether data for evaluation of other criteria were available or not. Patient withdrawn, for any reason, were defined as treatment failures as well.

The main secondary endpoints were:

- Efficacy: disease response rate over time, time to first disease response, disease response duration, number of phlebotomies performed, molecular response and haematological parameters (haematocrit, leukocytes, platelets, erythrocytes) and spleen size change from baseline to last patient visit.
- Safety.
- Quality of life (assessed on EQ-5D-3L questionnaire) and change of JAK2 V617F allelic burden over time were also analysed.

Analysis of the primary endpoint (disease response defined as complete haematological response with spleen size normality) was performed in the FAS population via a non-inferiority unilateral test (α = 2.5%) using the Cochran-Mantel-Haenszel method for estimation, with:

- H0: ropegIFN alfa-2b inferior to HU: pT ≤pR - 0,1050 (95% CI upper limit of the response rate difference between both arms ≤-10,5%), where pT was the response rate in ropegIFN alfa-2b arm et pR the response rate in hydroxyurea arm.
- H1: non-inferiority of ropegIFN alfa-2b versus HU: pT >pR - 0,1050 (95% CI lower limit of the response rate difference >-10,5%).

The chosen non-inferiority margin was based on an assumed overall response rate of 25% after 12 months of study treatment and allowing a random fluctuation of response rates of 4%.

A post-hoc non-inferiority analysis of the disease response rate defined as the complete haematological response (without spleen size normality) was performed with a non-inferiority margin of -20.0%. The reason for changing the primary endpoint was that significant splenomegaly was only present in a few patients at baseline and spleen size fluctuations observed during the trial were small in the range of that observed also in a healthy population.
The changes in non-Inferiority margin were based on the change of assumed overall response rate for the respective disease response definition. Secondary efficacy endpoints analysis was performed for exploratory purposes using descriptive analysis and standard statistical tests.

A total of 257 patients were enrolled at 48 sites in 13 countries: Austria (6 sites), Bulgaria (4 sites), Czech Republic (4 sites), France (3 sites), Hungary (5 sites), Italy (1 site), Poland (5 sites), Romania (4 sites), Russia (5 sites), Slovakia (2 sites), Spain (1 site), Ukraine (5 sites).

Two hundred fifty-four (254) patients received at least one dose and were included in the safety analysis set and included in the Full Analysis Set (FAS): 127 patients were enrolled into each arm.

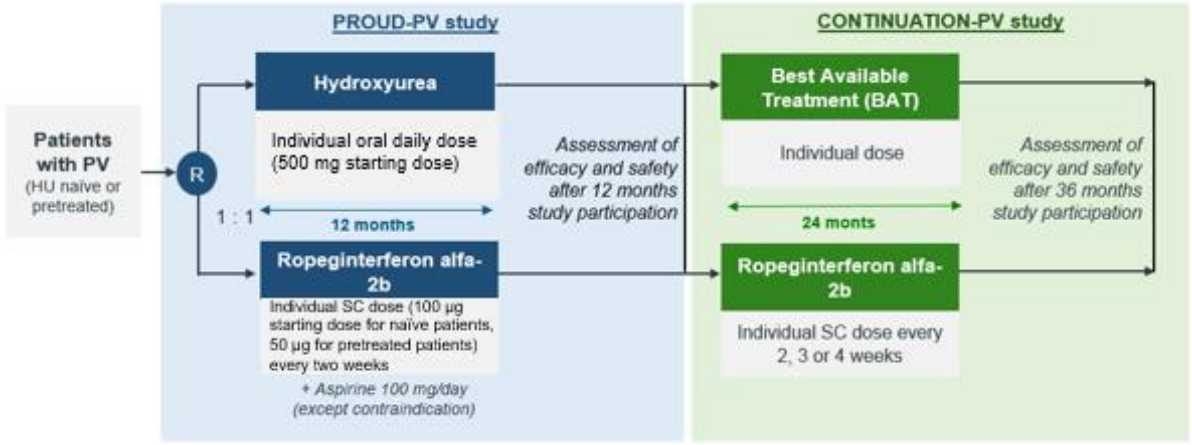
Demographic and clinical characteristics of patients randomized in PROUD-PV were comparable between both arms. The mean age at inclusion was 58.2 years with a median of 60 years [range 21; 85]. 46.9% were male and 100 % of patients were Caucasian.
The median duration of PV was 1.9 months in the ropegIFN alfa-2b arm and 3.6 months in the HU arm indicating that patients were diagnosed at an early stage of the disease. Out of 94 HU pre-treated patients, 82 patients had records of HU-treatment at study entry, with a median duration of 8.7 months. HU intolerant and HU resistant patients were excluded from study participation.

Table 3 PROUD-PV demographic and baseline characteristics

Variable	RopegIFN alfa-2b N = 127	HU N = 127	All patients N = 254
Mean age (SD)	58.5 (±10.81)	57.9 (±13.10)	58.2 (±11.99)
Gender: Female (%) **Male (%)**	68 (53.5%) 59 (46.5%)	67 (52.8%) 60 (47.2%)	135 (53.1%) 119 (46.9%)
Caucasian ethnicity	123 (96.9%)	120 (94.5)	243 (95.7%)
Duration of PV (months) Md(range)	1.9 (0-146)	3.6 (0-126)	2.3 (0-146)
HU pre-treated (%)	47 (37.0%)	47 (37.0%)	94 (37.0%)
Duration of previous treatment with HU (months) Md(range)	10.2 (1-34)	7.9 (1-36)	8.7 (1-36)
JAK 2 V617F allelic burden (%)	41.9% (±23.49)	42.8 (±24.14)	42.4 (±23.77)

Haematological parameters were comparable between the two treatment arms with the following mean values: haematocrit 49.7%, leukocytes 12.4x10^9/L and platelets 542.4x10^9/L. Spleen size was comparable between the two treatment arms with 49.7% of patients having a normal spleen size.
Among patients, 98.9% were JAK2 V617F positive, with a median JAK2 V617F allelic burden of 37.4%.
[redacted]

CONTINUATION-PV
A total of 171 patients, all previously enrolled into PROUD-PV Study at 41 sites in 12 countries, were included in the safety set for the CONTINUATION-PV Study. The roll-over rate from PROUD-PV Study into its extension study CONTINUATION-PV Study was 78.8% (171/217); 89.6% (95/106) for ropegIFN alfa-2b-treated and 68.5% (76/111) for (in PROUD-PV Study) HU- treated patients. No selection bias was detected, i.e. patients completing PROUD-PV Study and enrolling in CONTINUATION-PV Study (in both treatment arms) were comparable regarding baseline characteristics (start of treatment in PROUD-PV Study, Month 0) as well as regarding complete haematological responder rates at end of PROUD-PV Study (Month 12).



R: Randomization
Source: CONTINUATION-PV Study CSR.

The primary endpoint was a co-primary efficacy evaluation criterion assessing the disease response rate:

- Complete hematologic response (Hct <45% without phlebotomy [at least 3 months since the last phlebotomy], PLTs <400x10^9/L, WBCs <10x10^9/L), and normal spleen size.
- Complete hematologic response (Hct <45% without phlebotomy [at least 3 months since the last phlebotomy], PLTs <400x10^9/L, WBCs <10x10^9/L), resolution and/or clinically improvement of disease-related signs (clinical significant splenomegaly) and disease-related symptoms (microvascular disturbances, pruritus, headache).

The main secondary endpoints were:

- The change in haematological parameters and spleen size over time, maintenance rate of disease response, duration of response maintenance/further improvement in response, time to disease response, progression-

free time, phlebotomy needs, disease related signs and disease-related symptoms, quality of life (EQ-5D-3L) and JAK2 V617F allelic burden.

- Safety.

Regarding the analyses of the primary endpoint, comparison of treatment arms was performed using Log-Binomial regression model with repeated measures adjusted for stratification group. Outcome of this model, responders' rate ratio (RR) between treatment arms (ropegIFN alfa-2b/control) at assessment visits and its 95% confidence intervals, was presented. Analyses of responses, where missing response (including missing response due to discontinuation) was imputed using Last Observation Carried Forward (LOCF) method, were performed as exploratory sensitivity analyses.
The analyses of other efficacy endpoints included analyses of longitudinal data performed using regression models with repeated measures. Time-to-event data were analysed using Kaplan-Meier method and treatment arms compared using Cox hazards model. The level of significance (alfa) was 5%. All CI and tests were two-sided.

In CONTINUATION-PV, the following endpoints were analysed using the same methodology as for the co-primary endpoint CHR and normal spleen size: (1) CHR without the spleen size, (2) CHR with splenomegaly defined as spleen size > 17 cm. These are considered sensitivity analyses for the primary endpoint. The LOCF analyses for the co-primary endpoints, CHR without the spleen criterion, and CHR with splenomegaly defined as spleen size > 17 cm are also considered sensitivity analyses.

Regarding the analytical methods for the secondary endpoints, changes from baseline in haematological parameters, spleen size, quality of life (EQ-5D-3L) and JAK2 allelic burden were analysed descriptively and using a model with repeated measures (as described for the primary endpoint), and the outcome presented using LS Means and their 95% CIs, difference of LS Means (ropeginterferon-control) and its 95% CI, SE, and two-side p-value. Molecular response was dichotomised to any response (partial or complete) vs no response, and response rates were analysed using the same statistical model as the primary endpoint. Maintenance of disease response at assessment visits was compared between the treatment arms using log-binomial regression model. Outcome of the log-binomial model was presented using RR and its 95% CIs and p-value. Duration of response maintenance an time to disease response were compared between the treatment arms using a log-rank test and using Cox proportional hazards model. Outcome of the Cox proportional hazards model was presented using Hazard ratio (HR) for ropeginterferon/control and its 95% CIs and p-value. For progression free-time (cumulative number of days in response), comparison was performed by a log-negative binomial model comparing incidence rate of responses at assessment visits. Outcome of the model was presented using ratio in incidence rate for ropeginterferon/Control and its 95% CIs and p-value. Phlebotomy need (binary outcome) was analysed using a log-binomial model. Relative risk (risk ratio, RR) of "Phlebotomy need" between treatment arms (ropeginterferon/Control) and its 95% confidence intervals was calculated from estimates of regression coefficients (RR = exp(estimate of regression coefficient); RR and its 95% CIs and p-values were presented. Further, count of phlebotomies in period since the last assessment visit was calculated and incidence count of phlebotomies per patient-visit was calculated. Comparison treatment arm in incidence rate of phlebotomies per patient-visit is planned to be performed using negative binomial regression model with repeated measures. Incidence rate ratios (IRR) between treatment arms (AOP2014/Control and its 95% confidence intervals will be calculated from estimates of regression coefficients (IRR = exp(estimate of regression coefficient). Comparison of percentage of phlebotomy-free patients per each treatment year (12 months periods since the first study drug administration) will be done by likelihood ratio test in 2x2 contingency table, for each treatment year separately, using the patient-years. For resolution and/or clinical improvement of disease related sings and resolution and/or clinical improvement of disease related symptoms (achieved, not achieved), the same statistical methods of analysis as for primary endpoint

was used. Further, occurrence of disease related signs and symptoms was analyzed descriptively. All safety parameters were analysed descriptively.

At treatment start (i.e. PROUD inclusion), the mean age was 57.5 years with a median of 59.0 years (range: 30.0; 85.0). Out of the 171 patients enrolled, 48.5% patients were male. All patients were Caucasian.
The mean duration of PV since diagnosis was 11.2 months with a median of 1.7 months (range: 0.0; 145.5) indicating that patients were diagnosed at an early stage. [redacted]
At screening, 98.2% were JAK-2V617F positive with a mean JAK-2V617F allelic burden of 42.9%.
The mean values of haematological parameters were comparable between treatment arms: haematocrit, 49.0% (±5.44); platelets, 531.1 (±264.74) 10^9/L and leukocytes, 12.0 (±4.70) 10^9/L.
Normal spleen size (≤12 cm for females and ≤13 cm for males) was recorded in 43.9% of patients (with a median spleen size (longitudinal diameter in cm) of 12.6 in females and 14.5 in males. In addition, 8.8% of patients showed a splenomegaly with a median spleen size of 15.5 cm. Disease related symptoms were reported for 18.7% of patients.

5.1.1.2 PEGINVERA

The PEGINVERA-PV Study is an open-label, prospective, multicentre, phase I/II dose escalation study, conducted in Austria to determine the maximum tolerable dose (MTD) of ropegIFN alfa-2b (stage 1), and to determine the standard safety and tolerability of ropegIFN alfa-2b in patients with Polycythaemia Vera, including analysis of PK parameters (stage 2).

Stage I: determination of the maximum tolerated dose (MTD)
In Stage I of the study (short-term exposure), MTD was defined as the highest dose at which there is at most one patient with a dose limiting toxicity. It is the result of the standard 3+3 dose escalation process out of 6 patients (3 patients per cohort).

Stage II: efficacy and safety evaluation
In Stage II of the study (long-term exposure), additional patients were recruited in order to further investigate the drug efficacy and safety in Polycythaemia Vera. Their doses were escalated dependent on the patient's response and tolerability (from 100 – 450 µg). Patients were treated with the study medication as long as they derive a clinical benefit from the treatment with acceptable tolerability.

After inclusion, all patients were to be phlebotomized until haematocrit reached ≤ 45 % prior to the first administration of ropegIFN alfa-2b.

A total of 51 patients were enrolled into 6 centres in Austria (Safety Set). Twenty-five (25) patients were enrolled for stage 1 of the study and continued in stage 2, and an additional 26 patients were directly enrolled into stage 2.
All 51 patients enrolled in the study were treated. A total of 25 patients completed the study; of the 26 patients who discontinued, most (15/26) did so during the first year of treatment. The majority (27/51; 52.9%) of patients completed 5 years of treatment and 16 (31.4%) completed 6 years of treatment.
Of the 51 patients included in the safety set, 46 patients (90.2%) were eligible for the FAS and 5 were excluded due to major protocol deviations.

Among the 51 patients enrolled and treated, 60.8% of patients were male and 98.0% were Caucasian. The mean age at inclusion was 58.7 years. The proportion of all patients entering the study for whom their disease history was already known was 84.3%. The remaining 15.7% patients were newly diagnosed with PV. At the time of screening, 33.3% patients were undergoing treatment with HU. The median number of phlebotomies performed in the last 3 months prior to screening was 1.0. The median JAK2 V617F allele burden was 42.0% (range 0.0 to 99.0). Haematological response measurements were available for all patients at screening. Spleen size was measured and recorded for 47/51 of patients: 51.6% of male patients and 60.0% female patients had enlarged spleens.

5.1.2 Results per study

5.1.2.1 PROUD-PV and CONTINUATION-PV

5.1.2.1.1 Thromboembolic events

5.1.2.1.1.1 Proportion of patients experiencing at least one thromboembolic event

The DMC protocol requests information on the proportion of patients experiencing at least one thromboembolic event. This an endpoint that has not been defined as an outcome in the clinical trial, hence the information has been sourced from safety tables in the PROUD-PV and CONTINUATION-PV clinical study reports (CSRs) related to all treatment-emergent adverse events by MedDRA preferred term within the entire treatment period (Data on file).

Both arms included 127 patients in PROUD-PV, of which [redacted] in the ropegIFN alfa-2b arm had experienced at least one thromboembolic event ([redacted]) compared to 2 patients in the hydroxyurea arm ([redacted]), resulting in an absolute difference of xxxx. Given the limited number of events no formal statistical tests has been performed.(13) The CONTINUATION-PV provides additional data at 60 months. The proportion of events for ropegIFN alfa-2b arm remained the same as described for PROUD-PV ([redacted]) but the proportion of patients experiencing at least one thromboembolic event in the HU-arm increase [redacted] over [redacted] patient-years.(14)

Table 4 Proportion of patients experiencing at least one thromboembolic event PROUD-PV and CONTINUATION-PV

Timepoint	Study arm	N	Result (CI)	References
PROUD-PV (12 months)	Ropeginterferon alfa-2b	127	[redacted]	[redacted]
	Hydroxyurea	127	[redacted]	
CONTINUATION-PV at 60 months	Ropeginterferon alfa-2b	127	[redacted]	[redacted]
	Hydroxyurea	127	[redacted]	

*[redacted]

5.1.2.1.1.2 Proportion of patients experiencing complete hematological response

In PROUD-PV, the primary efficacy endpoint was disease response rate at Month 12. This was defined as the proportion of patients with a complete haematological response (haematocrit <45% without phlebotomy [at least 3 months since last phlebotomy], platelets <400x10^9/L and leukocytes <10x10^9/L) and a spleen normality (spleen length

≤12 cm for females and ≤13 cm for males). At Month 12, the disease response rate was 21.3% in the ropegIFN alfa-2b arm versus 27.6% in the HU arm with a response rate difference of -6.57 (95% CI: -17.23;4.09; p=0.2233). The non-Inferiority of ropegIFN alfa-2b vs HU at Month 12 was not demonstrated.

The criteria "spleen normality" has been assessed as non-relevant as minimal changes were observed, as also stated by the clinical expert committee in the DMC protocol. The proportion of patients experiencing complete hematological response without the spleen criterion were similar between the treatment groups with 53 of 123 patient (43.09%) in the ropegIFN alfa-2b arm and 57 of 125 patients (45.6%) in the HU arm. In both arms data were missing for 4 patients. Discontinued patients were considered non-responders. The estimates result in an absolute difference of -3.02% (95% CI: -15.55; 9.52) demonstrating non-inferiority of ropegIFN alfa-2b vs HU at Month 12.

During PROUD-PV, there was a significant difference between the two treatments regarding the duration of (individual) titration phase to achieve optimal haematological response. The median individual titration phase was [redacted] for ropegIFN alfa-2b and [redacted] for HU. This difference in reaching the individual titration phase end can explain the delay in efficacy of ropegIFN alfa-2b, compared to HU

The CONTINUATION-PV provides additional data; analyses were performed at 24, 36 and 60 months. The proportion of patients treated with ropegIFN alfa-2b that experienced a complete hematological response at 60 months were [redacted] and [redacted] in the HU arm.(14) The estimates result in an absolute difference of [redacted]

5.1.2.1.1.3 Qualitative review of events

RopegIFN alfa-2b is not indicated in patients with symptomatic splenomegaly; the patients enrolled in the PROUD-PV study represent an early PV population and only a small subgroup of patients had clinically significant splenomegaly at baseline. Efficacy parameters including spleen size were prospectively planned in the PROUD-PV and CONTINUATION-PV studies, but the impact of treatment on spleen size remains difficult to interpret in this early-stage PV population, as reflected by the endpoints included in the DMC protocol. For complete haematological response without the spleen criterion at 12 months, responses were similar between the treatment groups (53 [43%] of 123 patients for ropegIFN alfa-2b versus 57 [46%] of 125 patients in the hydroxyurea group (95% CI: -15.55, 9.52 [p=0.63]). Hydroxyurea pretreatment had no significant effect on complete haematological response at 12 months. In ropegIFN alfa-2b group at 12 months, 18 (39%) of 46 patients who had been pretreated with hydroxurea and 35 (46%) of 77 patients previously untreated with hydroxyurea had a complete haematological response (OR: 0.57 [95% CI: 0.20-1.42] p=0.24); in the hydroxyurea group, 15 (32%) of 47 previously treated patients and 42 (54%) of 78 patients previously untreated were responders (OR: 0.43 [95% CI: 0.17-1.02], p=0.066).

Table 5). CHR rates in the CONTINUATION-PV study had decreased slightly in both treatment arms at 60 months, which in part reflects patient attrition in this long-term study, since patients who prematurely discontinued the study (44/171 [25.7%] overall as of Month 60) were prospectively defined as non-responders.

Table 5 Haematologic response (without spleen size criterion) at assessment visits in CONTINUATION-PV – FAS

Study Month	Responder/N	Responder %	Responder/N	Responder %	RR [95% CI]

		Ropeg IFN (N=95)		Control (N=76)	P-value	
MONTH 12 (EOT in PR)	59/95	62.1	57/76	75.0	0.1303	0.85 [0.70-1.05]
MONTH 24	67/95	70.5	33/67	49.3	0.0129	1.41 [1.07-1.84]
MONTH 36	67/95	70.5	38/74	51.4	0.0104	1.39 [1.08-1.78]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CONTINUATION-PV Clinical Study Report, Table 14.2.2.2.1-1 Haematologic response (without spleen size criterion) at assessment visits – FAS (data on file*)*

Response kinetics for the composite endpoint complete haematological response and improved disease burden showed a similar pattern to the results for complete haematological response alone: proportion of patients with a response in the ropegIFN alfa-2b group increased gradually up to 24 months and remained high at 36 months, whereas in the hydroxyurea group, the response was highest at 12 months and reduced thereafter. The difference in response between the treatment groups was significant at 36 months.

Molecular responses in PROUD-PV were not significantly different between the treatment groups at 12 months (42 [34%] of 123 in the ropegIFN alfa-2b groups vs 52 [42%] of 123 in the hydroxyurea group; p=0.19). In both groups, a reduction in mean JAK2 Val617Phe allele burden compared with baseline was evident at 12 months (from 41.9% [SD 23.49] to 30.7% [SD 22.66] in the ropegIFN alfa-2b group and from 42.8% [SD 24.14] to 25.9% [SD 21.49] in the hydroxyurea group). At 24 months and 36 months of treatment, assessed in the CONTINUATION-PV study, the numbers of patients with a molecular response were significantly higher in the ropegIFN alfa-2b group than in the hydroxyurea group. Patients treated with ropegIFN alfa-2b showed a steady decrease in the mean absolute JAK2 Val617Phe allele burden to less than half the baseline level by month 36 (from 42.8% [SD 23.4] to 19.7% [SD 21.3]) whereas in the hydroxyurea group the reduction was transient and was lost by month 36 (42.9% [SD 23.0] at baseline and 39.3% [SD 25.91] at month 36). At months 24 and 36, mean JAK2 Val617Phe allele burden was significantly lower among patients treated with ropegIFN alfa-2b compared with the hydroxyurea group (at month 24, 20.9% [SD 20.8] and 32.1% [SD 23.4], respectively, p<0.0001; at month 36, 19.7% [SD 21.3] and 39.3% [SD 25.9], respectively; p<0.0001).(1) [redacted]

The major disease-related cardiovascular and thromboembolic events event rates in PROUD-PV were 8.7% (11/127) of patients in the ropegIFN alfa-2b arm and 5.5% (7/127) of patients in the HU treatment arm. The most frequently observed major cardiovascular PV-related adverse events in the ropegIFN alfa-2b arm were atrial fibrillation (3 events in 2.4% of patients), while in HU patients most events were caused also by atrial fibrillation (2.4%) but also due to cardiac failure (3.2%).(15)

Table 6 Thromboembolic events occurring during the titration and maintenance phases in PROUD-PV Study

Thromboembolic events	ropegIFN alfa-2b (N=127)	HU (N=127)

Titration phase	N	%	N	%
[redacted]				
[redacted]				
Maintenance period				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

*[redacted]

Table 7 Thromboembolic events occurring during the PROUD-PV and CONTINUATION-PV studies

Thromboembolic events	ropegIFN alfa-2b	HU
PROUD-PV	N	N
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
CONTINUATION-PV		
[redacted]		
[redacted]		
[redacted]		
[redacted]		

*[redacted]

Phlebotomy need during the individual titration phase (i.e. visits with haematocrit > 45%) ranged between 0-27 visits (median 3.0 [Q1-Q3: 1-6]) and 0-6 visits (median 1.0 [Q1-Q3: 0- 2]), respectively in the ropegIFN alfa-2b and HU treatment arm. Patients with thromboembolic events during the individual titration phase (i.e. in ropegIFN alfa-2b arm only), did not differ significantly with 0 and 2 visits (for the two identified patients).(15)

5.1.2.1.2 Quality of life

5.1.2.1.2.1 MPN-SAF mean change from baseline in total symptom score

MPN-SAF was not assessed in PROUD-PV or CONTINUATION-PV.

5.1.2.1.2.2 EQ-5D Mean change from baseline

The change from baseline for the visual analogic score (VAS) and total score of EQ-5D-3L was comparable between the ropegIFN alfa-2b and HU treatment arm at Month 12: respectively for VAS: 1.3 (±12.56) and 1.8 (±13.09); for total score: 0.2 (±1.08) and 0.1 (±1.17).(1)

5.1.2.1.3 Adverse events

5.1.2.1.3.1 Proportion of patients experiencing at least one treatment emergent adverse event of grade 3-4

In the PROUD-PV study [redacted] in the ropegIFN alfa-2b arm had experienced at least one treatment emergent adverse events of grade 3-4 [redacted] compared to [redacted] patients in the hydroxyurea arm [redacted], resulting in an absolute difference of [redacted] At 60 months the proportion of treatment emergent adverse events of grade 3-5 were [redacted], respectively(14).

5.1.2.1.3.2 Proportion experiencing at least one treatment related adverse event of grade 3-4

In the PROUD-PV study [redacted] in the ropegIFN alfa-2b arm had experienced at least one treatment related adverse events of grade 3-4 [redacted] compared to xx xxxx xxx xxx patients in the hydroxyurea arm [redacted], resulting in an absolute difference of [redacted] At 60 months the proportion of treatment related adverse events of grade 3-5 [redacted] ropegIFN alfa-2b and BAT arm, respectively(14).

5.1.2.1.3.3 Qualitative review of adverse reaction profile

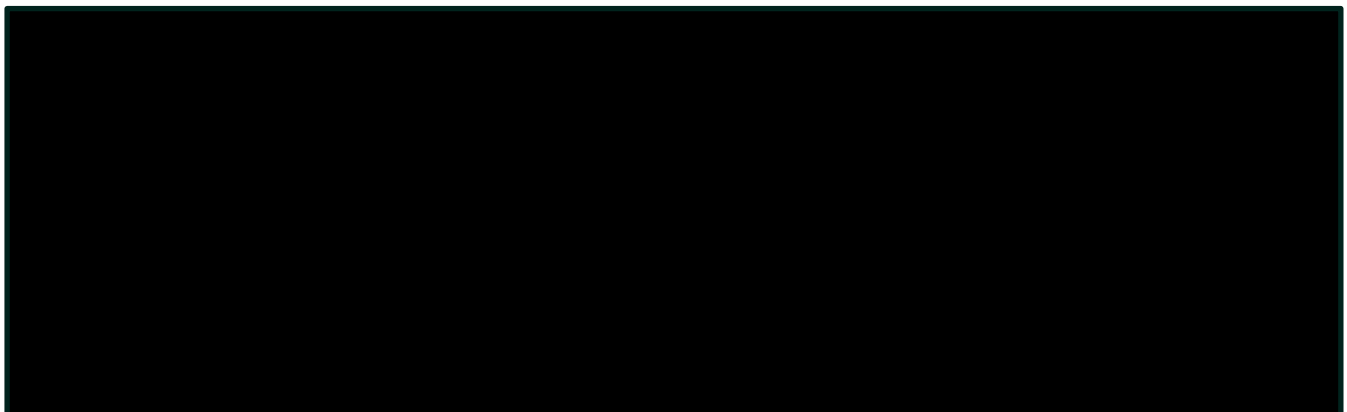
Overall treatment exposure

[redacted]

All 95 patients in the ropegIFN alfa-2b arm received study drug while all patients in the control arm received standard first line treatment. Both medicinal products were dosed individually, following their pre-specified dosing schemes to achieve an optimal disease response. The duration of treatment exposure is equal to the extent of exposure.

[redacted]

Figure 3 Summary of ropegIFN alfa-2b and HU dose administered by assessment visit (FAS patients enrolled in CONTINUATION-PV study)



[redacted]

RopegIFN alfa-2b was well tolerated and safe, and showed a different safety profile compared to HU.
A summary of adverse events in PROUD-PV and CONTINUATION-PV (36 months) are provided in the following tables.

Table 8 Overview of adverse events – PROUD-PV Study (Safety Set)

[redacted]

AE: Adverse Event, TEAE: Treatment Emergent Adverse Events
Source: PROUD-PV Study CSR)

Table 9 Overview of adverse events – CONTINUATION-PV Study (Safety Set 36 months)

[redacted]

TEAE: Treatment-emergent Adverse Event
Source: CONTINUATION-PV Study CSR, 36-month treatment analysis

The most frequently reported treatment emergent adverse effect (TEAE) (frequency >10%) in PROUD-PV were:

- RopegIFN alfa-2b arm: thrombocytopenia (15.0%), gamma-glutamyl-transferase increased (14.2%) and fatigue (12.6%).
- HU arm: thrombocytopenia (28.3%), anaemia (24.4%), leukopenia (21.3%) and fatigue (11.8%).

In CONTINUATION-PV the most frequently reported TEAE (frequency >10%) at Month 36 were:

- [redacted]

- [redacted]

Treatment-related adverse events

[redacted]

Grade 3-4 adverse events

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Adverse events leading to study discontinuation

[redacted]

Deaths

[redacted]

Adverse events of special interest

[redacted]

In CONTINUATION-PV no new safety and tolerability signals were detected in the fifth year. Treatment related adverse events were reported in 25.6% and 24.2% of patients in the ropegIFN alfa-2b and control arms, respectively, and one patient in each arm withdrew due to drug-related toxicity. Three patients (3.8%) in the ropegIFN alfa-2b arm reported grade ≥3 treatment-related adverse events in the fifth year; over the entire treatment period, the rate of grade ≥3 drug-related adverse events was the same in each study arm (16.5%).(16)

5.1.2.2 PEGINVERA

5.1.2.2.1 Thromboembolic events

5.1.2.2.1.1 Proportion of patients experiencing at least one thromboembolic event
Not reported

5.1.2.2.1.2 Proportion of patients experiencing complete hematological response
[redacted]

5.1.2.2.1.3 Qualitative review of events
See above

5.1.2.2.2 Quality of life

5.1.2.2.2.1 MPN-SAF mean change from baseline in total symptom score
Not reported

5.1.2.2.2.2 EQ-5D Mean change from baseline
Not reported

5.1.2.2.3 Adverse events

5.1.2.2.3.1 Proportion of patients experiencing at least one treatment emergent adverse event of grade 3-4
Not reported

5.1.2.2.3.2 Proportion experiencing at least one treatment related adverse event of grade 3-4
Not reported

5.1.2.2.3.3 Qualitative review of adverse reaction profile
[redacted]

[redacted]

[redacted]

[redacted]

5.1.3 Comparative analyses

The clinical benefit for ropegIFN alfa-2b is supported by the phase III program (pivotal PROUD-PV and CONTINUATION-PV Study):

1. Complete haematological response (CHR)
    - RopegIFN alfa-2b has shown to be effective in stabilizing haematological parameters from Week 12 onwards following treatment start.
    - Results of PROUD-PV Study show that short-term efficacy (hematologic response) of ropegIFN alfa-2b is non-inferior to HU treatment.
    - Within the first 36 months of treatment with ropegIFN alfa-2b CHR (without spleen size criterion) consistently increased (62.1% at Month 12, 70.5% at Month 24 and 36), whereas the response rates in the control arm (Best available treatment arm, majority of patients still receiving HU) decreased after 12 months of treatment (75.0% at Month 12, 49.3% at Month 24, 51.4% at 36 Month). Stabilisation of response rates was achieved within the 3rd year of treatment (up to 36 months of treatment) with significant higher response rates observed in the ropegIFN alfa-2b arm (RR: 1.38 [95% CI: 1.07 to 1.79], p=0.0122). The response rate decreased from the 3rd year to the 5th year in both arms (70.5% to 55.8% for ropegIFN alfa-2b and 51.4% to 44.0% for BAT).

2. Safety
    - RopegIFN alfa-2b was well tolerated and showed a different safety profile compared to hydroxyurea at Months 12 and 36. The overall safety profile was consistent with class effects of other interferons used.
    - The slow titration of ropegIFN alfa-2b (individual titration duration of 16.2 weeks and 11.4 weeks, respectively in the ropegIFN alfa-2b and HU treatment arm) resulted in a better safety than reported for other interferons.

- In addition, as for other IFNs, no teratogenicity and leukemogenicity potential is expected for ropegIFN alfa-2b.
- During the phase 3 development program, two cases of acute leukaemia were observed in HU treated patients. None were observed in ropegIFN alfa-2b arm

The comparative analysis is based on the results from the PROUD-PV and CONTINUATION-PV studies which have been presented in section 5.1.2.1 and 9.3.

5.2 Ropeginterferon-alfa-2b (Besremi) compared to pegylated interferon-alfa-2a (Pegasys) for adult patients under the age of 60 with polycythaemia vera

5.2.1 Presentation of relevant studies

The main characteristics of the included studies have been presented previously in Table 1 within section 4.2.
There is significant heterogeneity in study design, reported end points and patient populations (PV and/or ET) included in the identified studies. PROUD-PV and CONTINUATION-PV provided evidence for ropegIFN alfa-2b in a PV-specific population supporting the regulatory approved indication for treatment of PV patients.
Pegylated interferon alfa-2a (Pegasys) do not have an EMA-approved label for PV and is used off-label when used for treating PV patients.

5.2.1.1 PROUD-PV and CONTINUATION-PV

The clinical development program for comparing ropegIFN alfa-2b in PV includes the following Phase III program comprised by:

- PROUD-PV Study, a randomized, open-label, controlled parallel-arm, non-Inferiority study of ropegIFN IFN alfa-2b versus HU in 254 patients with PV,
- CONTINUATION-PV Study, an open-label, Phase IIIb extension study assessing the long-term efficacy and safety of ropegIFN alfa-2b in PV patients who completed the ropegIFN alfa-2b arm of the PROUD-PV Study in comparison to patients who completed the HU arm of PROUD-PV Study and are managed according to standard of care/best available treatment.

PROUD-PV and its extension study, CONTINUATION-PV, were phase 3, randomised, controlled, open-label, trials done in 48 clinics in Europe. Patients were eligible if 18 years or older with early stage polycythaemia vera (no history of cytoreductive treatment or less than 3 years of previous hydroxyurea treatment) diagnosed by WHO's 2008 criteria. Patients were randomly assigned 1:1 to ropegIFN alfa-2b (subcutaneously every 2 weeks, starting at 100 µg) or hydroxyurea (orally starting at 500 mg/day).(1)

After 1 year, patients could opt to enter the extension part of the trial, CONTINUATION-PV. The primary endpoint in PROUD-PV was disease response rate at Month 12 defined as haematocrit <45% without phlebotomy (at least 3 months since last phlebotomy), platelets <400x10^9/L, leukocytes <10x10^9/L (these 3 variables defining the complete haematological response) and normal spleen size (defined as longitudinal diameter ≤12 cm for females and ≤13 cm for males).
A patient was classified as “responder” (i.e. treatment success) only if all of the disease response criteria were met. If at least one criterion was not met, the patient was classified as “non-responder” (treatment failure) regardless of whether data for evaluation of other criteria were available or not. Patient withdrawn, for any reason, were defined as treatment failures as well.(1)

The main secondary endpoints were:

- Efficacy: disease response rate over time, time to first disease response, disease response duration, number of phlebotomies performed, molecular response and haematological parameters (haematocrit, leukocytes, platelets, erythrocytes) and spleen size change from baseline to last patient visit.
- Safety.
- Quality of life (assessed on EQ-5D-3L questionnaire) and change of JAK2 V617F allelic burden over time were also analysed.

Analysis of the primary endpoint (disease response defined as complete haematological response with spleen size normality) was performed in the FAS population via a non-inferiority unilateral test (α = 2.5%) using the Cochran-Mantel-Haenszel method for estimation, with:

- H0: ropegIFN alfa-2b inferior to HU: pT ≤pR - 0,1050 (95% CI upper limit of the response rate difference between both arms ≤-10,5%), where pT was the response rate in ropegIFN alfa-2b arm et pR the response rate in hydroxyurea arm.
- H1: non-Inferiority of ropegIFN alfa-2b versus HU: pT >pR - 0,1050 (95% CI lower limit of the response rate difference >-10,5%).

The chosen non-inferiority margin was based on an assumed overall response rate of 25% after 12 months of study treatment and allowing a random fluctuation of response rates of 4%.

A post-hoc non-Inferiority analysis of the disease response rate defined as the complete haematological response (without spleen size normality) was performed with a non-Inferiority margin of -20.0%. The reason for changing the primary endpoint was that significant splenomegaly was only present in a few patients at baseline and spleen size fluctuations observed during the trial were small in the range of that observed also in a healthy population.
The changes in non-Inferiority margin were based on the change of assumed overall response rate for the respective disease response definition. Secondary efficacy endpoints analysis was performed for exploratory purposes using descriptive analysis and standard statistical tests.

A total of 257 patients were enrolled at 48 sites in 13 countries: Austria (6 sites), Bulgaria (4 sites), Czech Republic (4 sites), France (3 sites), Hungary (5 sites), Italy (1 site), Poland (5 sites), Romania (4 sites), Russia (5 sites), Slovakia (2 sites), Spain (1 site), Ukraine (5 sites).

Two hundred fifty-four (254) patients received at least one dose and were included in the safety analysis set and included in the Full Analysis Set (FAS): 127 patients were enrolled into each arm.

Demographic and clinical characteristics of patients randomized in PROUD-PV were comparable between both arms. The mean age at inclusion was 58.2 years with a median of 60 years [range 21; 85]. 46.9% were male and 100 % of patients were Caucasian.
The median duration of PV was 1.9 months in the ropegIFN alfa-2b arm and 3.6 months in the HU arm indicating that patients were diagnosed at an early stage of the disease. Out of 94 HU pre-treated patients, 82 patients had records of HU-treatment at study entry, with a median duration of 8.7 months. HU intolerant and HU resistant patients were excluded from study participation.

Table 10 PROUD-PV demographic and baseline characteristics

Variable	RopegIFN alfa-2b N = 127	HU N = 127	All patients N = 254
Mean age (SD)	58.5 (±10.81)	57.9 (±13.10)	58.2 (±11.99)

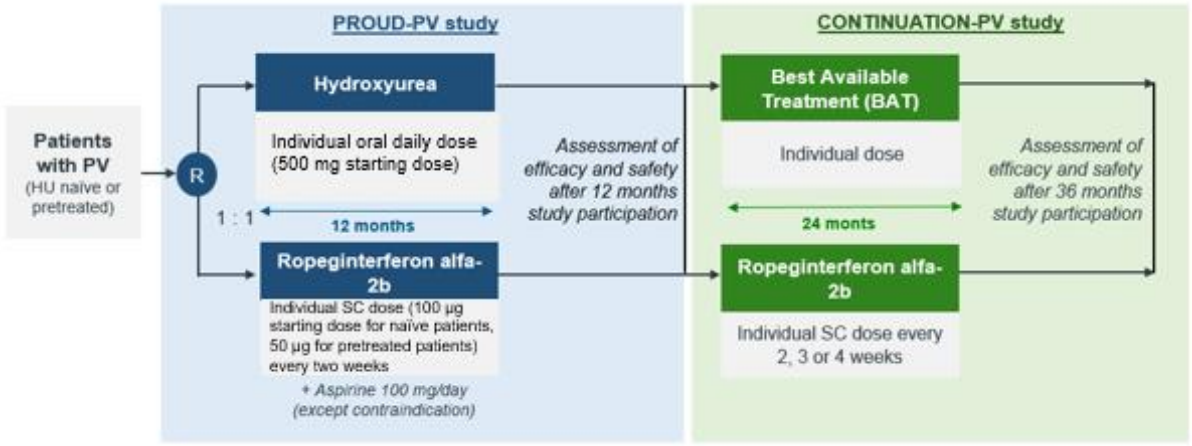
Variable	RopegIFN alfa-2b N = 127	HU N = 127	All patients N = 254
Gender: Female (%) **Male (%)**	68 (53.5%) 59 (46.5%)	67 (52.8%) 60 (47.2%)	135 (53.1%) 119 (46.9%)
Caucasian ethnicity	123 (96.9%)	120 (94.5)	243 (95.7%)
Duration of PV (months) Md(range)	1.9 (0-146)	3.6 (0-126)	2.3 (0-146)
HU pre-treated (%)	47 (37.0%)	47 (37.0%)	94 (37.0%)
Duration of previous treatment with HU (months) Md(range)	10.2 (1-34)	7.9 (1-36)	8.7 (1-36)
JAK 2 V617F allelic burden (%)	41.9% (±23.49)	42.8 (±24.14)	42.4 (±23.77)

Haematological parameters were comparable between the two treatment arms with the following mean values: haematocrit 49.7%, leukocytes 12.4x10^9/L and platelets 542.4x10^9/L. Spleen size was comparable between the two treatment arms with 49.7% of patients having a normal spleen size.
Among patients, 98.9% were JAK2 V617F positive, with a median JAK2 V617F allelic burden of 37.4%.
For patients with medical history available, hypertension was the most common condition (55.9%), followed by phlebotomy (40.2%).

CONTINUATION-PV

A total of 171 patients, all previously enrolled into PROUD-PV Study at 41 sites in 12 countries, were included in the safety set for the CONTINUATION-PV Study. The roll-over rate from PROUD-PV Study into its extension study CONTINUATION-PV Study was 78.8% (171/217); 89.6% (95/106) for ropegIFN alfa-2b-treated and 68.5% (76/111) for (in PROUD-PV Study) HU- treated patients. No selection bias was detected, i.e. patients completing PROUD-PV Study and enrolling in CONTINUATION-PV Study (in both treatment arms) were comparable regarding baseline characteristics (start of treatment in PROUD-PV Study, Month 0) as well as regarding complete haematological responder rates at end of PROUD-PV Study (Month 12).

Figure 5 CONTINUATION-PV study overview



R: Randomization
Source: CONTINUATION-PV Study CSR.

The primary endpoint was a co-primary efficacy evaluation criterion assessing the disease response rate:

- Complete hematologic response (Hct <45% without phlebotomy [at least 3 months since the last phlebotomy], PLTs <400x10^9/L, WBCs <10x10^9/L), and normal spleen size.

- Complete hematologic response (Hct <45% without phlebotomy [at least 3 months since the last phlebotomy], PLTs <400x10^9/L, WBCs <10x10^9/L), resolution and/or clinically improvement of disease-related signs (clinical significant splenomegaly) and disease-related symptoms (microvascular disturbances, pruritus, headache).

The main secondary endpoints were:

- The change in haematological parameters and spleen size over time, maintenance rate of disease response, duration of response maintenance/further improvement in response, time to disease response, progression-free time, phlebotomy needs, disease related signs and disease-related symptoms, quality of life (EQ-5D-3L) and JAK2 V617F allelic burden.
- Safety.

Regarding the analyses of the primary endpoint, comparison of treatment arms was performed using Log-Binomial regression model with repeated measures adjusted for stratification group. Outcome of this model, responders' rate ratio (RR) between treatment arms (ropegIFN alfa-2b/control) at assessment visits and its 95% confidence intervals, was presented. Analyses of responses, where missing response (including missing response due to discontinuation) was imputed using Last Observation Carried Forward method, were performed as exploratory sensitivity analyses. The analyses of other efficacy endpoints included analyses of longitudinal data performed using regression models with repeated measures. Time-to-event data were analysed using Kaplan-Meier method and treatment arms compared using Cox hazards model. The level of significance (alfa) was 5%. All CI and tests were two-sided.

At treatment start (i.e. PROUD inclusion), the mean age was 57.5 years with a median of 59.0 years (range: 30.0; 85.0). Out of the 171 patients enrolled, 48.5% patients were male. All patients were Caucasian.
The mean duration of PV since diagnosis was 11.2 months with a median of 1.7 months (range: 0.0; 145.5) indicating that patients were diagnosed at an early stage. [redacted]
At screening, 98.2% were JAK-2V617F positive with a mean JAK-2V617F allelic burden of 42.9%.
The mean values of haematological parameters were comparable between treatment arms: haematocrit, 49.0% (±5.44); platelets, 531.1 (±264.74) 10^9/L and leukocytes, 12.0 (±4.70) 10^9/L.
Normal spleen size (≤12 cm for females and ≤13 cm for males) was recorded in 43.9% of patients (with a median spleen size (longitudinal diameter in cm) of 12.6 in females and 14.5 in males. In addition, 8.8% of patients showed a splenomegaly with a median spleen size of 15.5 cm. Disease related symptoms were reported for 18.7% of patients.

5.2.1.2 PEGINVERA

The PEGINVERA-PV Study is an open-label, prospective, multicentre, phase I/II dose escalation study, conducted in Austria to determine the maximum tolerable dose (MTD) of ropegIFN alfa-2b (stage 1), and to determine the standard safety and tolerability of ropegIFN alfa-2b in patients with Polycythaemia Vera, including analysis of PK parameters (stage 2).

Stage I: determination of the maximum tolerated dose (MTD)
In Stage I of the study (short-term exposure), MTD was defined as the highest dose at which there is at most one patient with a dose limiting toxicity. It is the result of the standard 3+3 dose escalation process out of 6 patients (3 patients per cohort).

Stage II: efficacy and safety evaluation
In Stage II of the study (long-term exposure), additional patients were recruited in order to further investigate the drug efficacy and safety in Polycythaemia Vera. Their doses were escalated dependent on the patient's response and tolerability (from 100 – 450 µg). Patients were treated with the study medication as long as they derive a clinical benefit from the treatment with acceptable tolerability.

After inclusion, all patients were to be phlebotomized until haematocrit reached ≤ 45 % prior to the first administration of ropegIFN alfa-2b.

A total of 51 patients were enrolled into 6 centres in Austria (Safety Set). Twenty-five (25) patients were enrolled for stage 1 of the study and continued in stage 2, and an additional 26 patients were directly enrolled into stage 2.
All 51 patients enrolled in the study were treated. A total of 25 patients completed the study; of the 26 patients who discontinued, most (15/26) did so during the first year of treatment. The majority (27/51; 52.9%) of patients completed 5 years of treatment and 16 (31.4%) completed 6 years of treatment.
Of the 51 patients included in the safety set, 46 patients (90.2%) were eligible for the FAS and 5 were excluded due to major protocol deviations.

Among the 51 patients enrolled and treated, 60.8% of patients were male and 98.0% were Caucasian. The mean age at inclusion was 58.7 years. The proportion of all patients entering the study for whom their disease history was already known was 84.3%. The remaining 15.7% patients were newly diagnosed with PV. At the time of screening, 33.3% patients were undergoing treatment with HU. The median number of phlebotomies performed in the last 3 months prior to screening was 1.0. The median JAK2 V617F allele burden was 42.0% (range 0.0 to 99.0).
Haematological response measurements were available for all patients at screening. Spleen size was measured and recorded for 47/51 of patients: 51.6% of male patients and 60.0% female patients had enlarged spleens.

5.2.1.3 NCT00452023 (Masarova et al. 2017; Quintas-Cardama et al. 2013; Quintas-Cardama et al. 2009)

Forty-three patients with polycythemia vera and 40 with essential thrombocythemia were enrolled in this phase 2 trial of PEG-IFN-α-2a between May 31, 2005 and October 13, 2009, and 32 (39%) patients were still on study (polycythemia vera n=14, essential thrombocythemia n=18) at the time of 84 months (IQR: 69–94 months) follow-up.
Twenty-six (31%) patients were older than 60 years. Sixty-three percent of patients had received some form of therapy (in addition to aspirin) prior to enrollment, including standard IFN-α (n=14) and PEG-IFN-α-2a (n=1).
Patients older than 18 years with either newly diagnosed or previously treated essential thrombocythemia or polycythemia vera according to the 2005 Polycythemia Vera Study Group criteria were eligible to enroll.(3, 18, 19)

PEG-IFN-α-2a was administered subcutaneously once weekly. The initial starting dose was 450 µg/week but was decreased in a stepwise manner due to toxicity to a final starting dose of 90 µg/week: 3 patients were started at a dose of 450 µg/week, 3 at 360 µg/week, 19 at 270 µg/week, 26 at 180 µg/week, and 32 at 90 µg/week. Treatment was continued as long as the patients derived clinical benefit. During the study, the dose was modified based on toxicity or lack of efficacy. Any grade 3 or 4 event required therapy interruption. If the event resolved to grade 0 or 1 therapy could be resumed at a lower dose level.
The primary endpoint was hematologic response rate, as defined by European LeukemiaNet criteria 13. CHR was defined as normalization of blood counts (essential thrombocythemia: platelets 440 x 10^9/L; PV: hemoglobin < 15.0 g/L without phlebotomy) with complete resolution of palpable splenomegaly/symptoms in the absence of a thrombotic event. Secondary endpoints were to evaluate the toxicities in these patients as well as the bone marrow morphologic and molecular disease characteristics before and during therapy.(3, 18, 19)

The efficacy analysis was based on an intention to treat population. Responses and clinical data were analyzed using descriptive statistics. Fisher's exact test was used to compare responses in different groups for categorical variable. The Mann-Whitney U or Kruskal-Wallis tests were used to compare continuous variables, as indicated.(3, 18, 19)

Table 11 Baseline characteristics

Variable	PV (n=43)
Median age, (IQR)	54 (44–63)
Gender: Female (%)	26 (60)
Male (%)	17 (40)
High risk disease, n (%)	14(33)
Time from diagnosis to study entry, months (IQR)	50 (13–89)
History of major thrombosis, n (%)	2 (4.6)
No. JAK2 V617F-positive patients (%)	41 (95%)
Abnormal karyotype, n (%)	2 (5)
Median white blood cell count, 10^9/L (IQR)	11.2 (8–16)
Median hemoglobin, g/dL (IQR)	14.2 (13–15)
Median platelet count, 109/L (IQR)	496 (338–786)
Significant splenomegaly, n (% of known)	7/42 (16)
Median spleen size BCM in cm (IQR)	11 (4–14)
Disease-related symptoms, n (%)	19 (44)
Phlebotomy, n (%)	32 (74%)
HU pre-treated (%)	18 (45)
Duration of previous treatment with HU (months) Md(range)	10.2 (1-34)
JAK 2 V617F allelic burden, median (IQR)	65 (34–78)

5.2.1.4 Crisa et al. 2017

Crisa et al. presented data from an observational study on 65 PV patients aged 65 years or younger, who received either peg-IFN (30) or HU (35) according to the physician choice. Median follow-up was 75 months. The two cohorts were comparable for patient and disease characteristics.
Patients diagnosed with PV according to WHO 2008 classification, aged 65 years or younger, with normal cardiac, renal, and liver function, and without history of autoimmune disease were eligible for this study. According to the physician choice, newly diagnosed patients requiring cytoreductive treatment could receive either peg-IFNalfa-2a (Pegasys, Roche) or HU and patients previously treated with HU could be switched to peg-IFN regardless of the response achieved.(8)

Data were prospectively collected in the Registry of Myeloproliferative Neoplasms of Università degli Studi di Torino, CR was defined according to European LeukemiaNet 2009 criteria. Treatment with peg-IFN was started subcutaneously at 90 µg weekly and increased to 135 µg weekly if tolerated. The dose was decreased in case of intolerance or cytopenia. HU dose could range from 500 up to 2000 mg orally per day and was modulated according to hematological response. Two different populations were compared: patients who received peg-IFN vs the control group receiving HU only.(8)

In the peg-IFN group, 19 patients (63%) had previously received HU for a median time of 50 months (range: 2–120 months) and were in hematological response. There was not any significant difference in terms of age, gender, and disease characteristics between patients treated front line with peg-IFN and those who previously received HU.(8)

5.2.1.5 Huang et al. 2014

This open-label, prospective, observational study enrolled participants with ET and PV with JAK2V617F positive mutation from February 2009 to March 2014. All adult patients (ages 18–65 years old) were diagnosed according to

the WHO 2008 classification. A total of 123 ET patients received IFN-alfa-2b therapy with JAK2V617F positive or negative mutation; and 136 PV patients with JAK2V617F+ received IFN-alfa-2b or HU therapy according to random number assignment.
In the PV arm, 41/66 (62.1%) patients with JAK2V617F+ accomplished full course IFN treatment, and 35/57 (61.4%) patients with JAK2V617F− finished IFN treatment until the termination of the study. A total of 17/136 patients with PV did not persist on a full-course treatment. (12)

5.2.1.6 Stauffer Larsen et al. 2013

This open-label, retrospective, observational single center study reported clinical and molecular data in the largest cohort of JAK2 V617F mutant MPN Danish patients (n = 102) being treated long-term with rIFN-alfa2 (rIFN-alfa2a and rIFN-alfa2b in a non-clinical trial setting. In total 102 patients with JAK2V617F mutated MPN patients were evaluable and included in the study encompassing 19 patients with ET, 75 patients with PV, 4 patients with proliferative myelofibrosis of whom 2 had PMF and 2 had post-polycythemic MF, and 4 patients with MPN unclassified (MPNu). Patients fulfilled the WHO criteria.
There was an equal gender distribution (49 males and 53 females), with a male:female ratio according to diagnosis: ET 1:1.5; PV 1:1; PMF 3:1 and MPNu 3:1.
The median age was 52 years (range: 17–75 years). Patients who initiated therapy IFN within 6 months from diagnosis was defined as newly diagnosed patients. Fifty-one patients met this criterion (11 with ET, 38 with PV,1 with PMF and one with MPNu). The median follow-uptime was 42months (range12–146months), and the intervals median disease duration was 51 months (95% CI: 44–65).(2)
Treatment with rIFN-alfa2 was initiated in the first patient August 1996 and in the last patient 2011. The majority of patients were treated with peg-IFN-2a (n=70) or 2b (n=19), whereas 13 patients were treated with at least two different types of interferon. Dosing schedules varied considerably, both in respect to the administered dose and the dosing intervals. The median weekly dose of peg-IFN-alfa2a was 74 µg/week (range: 26-157) and the median pegIFN-alfa2b dose was 38 µg/week (range: 30–100).(2)

5.2.1.7 PVN1 (Kiladjian et al. 2008)

This prospective, open-label, single-arm, phase II evaluated the efficacy, safety, and monitoring of residual disease using JAK2V617F quantification (%V617F) of pegylated IFN-alfa-2a in 40 PV patients. Objectives included evaluation of efficacy, safety, and monitoring of residual disease using JAK2V617F quantification (%V617F). Median follow-up was 31.4 months. Inclusion criteria were as follows: PV diagnosis according to Polycythemia Vera Study Group (PVSG) criteria, age 18 to 65 years, and no previous treatment or only phlebotomies or cytoreductive treatment for less than 2 years. Exclusion criteria included usual contraindications to peg-IFN-alfa-2a.(4)

The primary end point was hematologic response at 12 months. Complete hematologic response was defined by a Hct level lower than 45% in males and 42% in females without phlebotomy, absence of splenomegaly, and normal white blood cell (WBC) ($<10x10^9$/L) and platelet counts ($<400x10^9$/L). Partial hematologic response (PR) was defined by Hct less than 45% in males and 42% in females, but with persistent splenomegaly or elevated ($>400x\ 10^9$/L) platelet count, or reduction of phlebotomy requirements by at least 50%.
Secondary end points included cumulative toxicity during the first 12 months of the study and evolution of %V617F. Toxicity, also assessed beyond the first year of treatment, was evaluated using the International Common Toxicity Criteria (version 2.0). Molecular response (MR) was defined as “complete” when JAK2V617F became undetectable.(4)

Peg-IFN-alfa-2a was started subcutaneously at 90 µg weekly for 2 weeks, with a dose escalation (every 2 weeks, and in the absence of toxicity) to 135 µg/week and to 180 µg/week in the absence of hematologic response.(4)

Median age was 49 years (Q1-Q3: 42-53 years), and 16 (43%) patients were males. Thirteen patients (35%) had splenomegaly (including 7 with palpable splenomegaly and 6 detected on ultrasound). Mean spleen size on ultrasound was 14 cm (range: 11-18 cm), and mean spleen enlargement below costal margin in patients with clinical splenomegaly was 2 cm (range: 1-4 cm). Five patients (14%) had a history of major thrombotic events. Treatment before inclusion included phlebotomies alone in 20 (54%) patients, with a median number of phlebotomies during the 3 months before study entry of 3 (range: 2-11; Q1-Q3: 3-5), HU in 12 (32%) patients, and no treatment in the remaining 5 (14%) patients, all recently diagnosed. Thirty-one (86%) patients were already on low-dose aspirin at study entry. Median time between PV diagnosis and inclusion was 5 months (Q1-Q3: 1-11 months).(4)

5.2.1.8 Samuelsson et al. 2006

This prospective, open label, Phase II clinical of 42 patients, including 21 patients with PV and 21 patients with ET trial investigate the feasibility of PEG-IFN therapy, its biologic effects, and its impact on QoL in patients with PV and ET. Patients were included between January 2001 and May 2003, and all patients were followed for 24 months. Inclusion criteria were a diagnosis of PV or ET and a platelet count >400 x 10^9/L in patients who had a previous thromboembolic episode or ongoing microcirculatory symptoms, a platelet count >1000 x 10^9/L in asymptomatic patients aged 18 years and older, and signed informed consent. Exclusion criteria were previous IFN therapy; ongoing therapy with another myelosuppressive agent; previous severe autoimmune disease; previous endogenous depression requiring medical therapy; pregnancy; cardiac failure (New York Heart Association Grades III and IV); serum creatinine or alanine aminotransferase levels >1.5 and >3 times the upper normal reference value, respectively; or another concurrent malignancy. The median age was 54 years (mean: 53 years; range: 29-77 years), and the median disease duration was 0.80 years (mean: 3.1 years; range: 0.01-30.2 years).(9)

The primary objective of this study was to evaluate the feasibility of PEG-IFN therapy in patients with PV and ET with regard to reaching pre-set objectives of platelet reductions, which were defined as achieving a platelet count <400 x 10^9/L in patients who had a previous thromboembolic episode or ongoing microcirculatory symptoms or achieving a platelet count <600 x 10^9/L in asymptomatic patients who were without previous thromboembolic complications. Having achieved this objective for at least 4 weeks was defined as a complete platelet response, and all other patient outcomes were defined as failures. Secondary objectives were to evaluate efficacy with regard to thromboembolic events, cessation of phlebotomy requirement in patients with PV, overall survival, spleen size, polycythemia rubra vera-1 (PRV-1) expression, and bone marrow cytogenetics. Another secondary objective was to delineate the impact of PEG-IFN treatment on QoL.
All patients were treated with self-administered subcutaneous PEG-IFN once weekly at a starting dose of 0.5 µg/kg. In patients who failed to achieve a platelet count <400 x 10^9/L (symptomatic patients) or <600 x 10^9/L (asymptomatic patients) after 12 weeks at the initial dose level, the dose was increased to 1.0 µg/kg once weekly. When the pre-set objective for platelet reduction was reached (i.e., CR), the dose of PEG-IFN was reduced gradually to the lowest dose that maintained the CR. Patients were taken off study if they had not reached CR after 6 months or at any time if they did not tolerate side effects.(9)

Patients underwent clinical examination in the outpatient clinic before the start of therapy and monthly during the first 3 months. Thereafter, patients were seen every third month or more frequently if clinically indicated. All adverse reactions were documented and graded according to the World Health Organization (WHO) standard toxicity scale. QoL evaluations were performed before the start of treatment and after 3 months, 6 months, 12 months, and 24 months. To obtain a standardized point of measurement, the patients were asked to complete the questionnaires before their medical examination. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 core questionnaire (version 3.0) was used.(9)

5.2.1.9 MPN-RC 112

This study was a randomized, open label, phase 3 clinical trial comparing HU and PEG in pts with high risk ET/PV. Pts were treated for up to 12 months to achieve PR or CR (ELN/IWG-MRT response criteria). Pts who achieved a PR/CR continued therapy for up to a maximum of 6 years. Minimum follow up was 1 year from the time the last patient was randomized. The primary objective was to compare the CR rate following HU vs. PEG at 12 months with 3 month confirmation. Secondary objectives included a comparison of toxicity and tolerability; PR rates; incidence of specific pre-defined toxicities and tolerance to therapy; impact of therapy on key biomarkers; survival and incidence of myelodysplastic syndrome, myelofibrosis, or leukemic transformation; and incidence of major cardiovascular events. Bone marrow pathologic responses were evaluated by central blinded expert review at baseline, 12, 24 months and end of study.
A total of 169 patients enrolled in the study; 86 were randomized to HU and 82 to PEG. Baseline characteristics were well balanced between the treatment arms except for median age which was higher in the HU arm. Median duration of follow-up was 89.9 weeks (range: 0 to 292.3) and the median treatment duration was 86.0 weeks (range: 0 to 287.3)(20)

5.2.1.10 MPN-RC 111

This study was a single-arm, open-label, phase 2, multicentre trial at 17 hospitals and cancer centres in Italy and the USA, evaluating the clinical–haematological response to pegylated interferon alfa-2a in patients who were resistant or intolerant to hydroxyurea. The diagnosis of ET or PV was established using criteria outlined by the World Health Organization (WHO) 2008. Patients were excluded if they had received previous therapy for ET and PV with an agent other than HU, had had prior therapy with IFN, or had contraindications to IFN therapy, such as an uncontrolled autoimmune disorder, uncontrolled depression, or severe retinal disease. The study was designed to accrue 84 patients each with ET or PV for a total of 168 patients, but because of lack of study drug availability, the study was closed to accrual in December 2016 after 115 patients were enrolled from February 2012 through December 2015. An intention-to-treat (ITT) response evaluation was performed every 12 months. Patients who achieved at least a partial response (PR) remained on treatment and were observed for a maximum of 4 years. All enrolled patients were included in response assessments. The primary end point consisted of complete response (CR) and PR (overall response rate, ORR) at 12 months, as determined by European LeukemiaNet (ELN) criteria, which define CR as correction of the platelet count to <400x 10^9/L, HCT to <45% without phlebotomy (for PV patients only), and WBC to <10 x 10^9/L; resolution of splenomegaly; and resolution of disease-related symptoms (defined as microvascular disturbances, headache, and pruritus). Responses were assessed by a blinded central review committee. Secondary end points included the evaluation of toxicity, safety, and tolerability of PEG; the impact of PEG on key disease biomarkers; the incidence of disease transformation; the evaluation of changes in bone marrow (BM) histopathology, quality of life (QoL), and patient-reported symptoms; and the assessment of major cardiovascular events.
The drug was administered subcutaneously at a starting dose of 45 µg weekly and titrated monthly in 45 µg increments for response up to a maximum of 180 µg weekly.

A total of 115 patients (ET, 65; PV, 50) participated in the study. The median patient age was 64.0 years. The median time from diagnosis was 37.3 months for ET and 54.8 months for PV. Seventy-seven (67.5%) patients were classified as HU-intolerant, and 37 (32.5%) were HU-resistant. Prior thrombosis was present in 32.3% of ET patients and in 22% of PV patients. Seven (ET, 4; PV, 3) of 32 patients had an event during the year prior to enrolment (transient ischemic attack, 2; deep venous thrombosis, 1, other, 4).

5.2.2 Results per study

5.2.2.1 PROUD-PV and CONTINUATION-PV

5.2.2.1.1 Thromboembolic events

5.2.2.1.1.1 Proportion of patients experiencing at least one thromboembolic event

The DMC protocol requests information on the proportion of patients experiencing at least one thromboembolic event. This an endpoint that has not been defined as an outcome in the clinical trial, hence the information has been sourced from safety tables in the PROUD-PV and CONTINUATION-PV clinical study reports (CSRs) related to all treatment-emergent adverse events by MedDRA preferred term within the entire treatment period (Data on file).

Both arms included 127 patients in PROUD-PV, of which [redacted] in the ropegIFN alfa-2b arm had experienced at least one thromboembolic event [redacted] compared to 2 patients in the hydroxyurea arm [redacted] resulting in an absolute difference of [redacted]. Given the limited number of events no formal statistical tests has been performed.(13) The CONTINUATION-PV provides additional data at 60 months. The proportion of events for ropegIFN alfa-2b arm remained the same as described for PROUD-PV [redacted] but the proportion of patients experiencing at least one thromboembolic event in the HU-arm increase [redacted] over 401 patient-years.(14)

Table 12 Proportion of patients experiencing at least one thromboembolic event PROUD-PV and CONTINUATION-PV

Timepoint	Study arm	N	Result (CI)	References
PROUD-PV (12 months)	Ropeginterferon alfa-2b	[redacted]	[redacted]	[redacted]
	Hydroxyurea	[redacted]	[redacted]	
CONTINUATION-PV at 60 months	Ropeginterferon alfa-2b	[redacted]	[redacted]	[redacted]
	Hydroxyurea	[redacted]	[redacted]	

[redacted]

5.2.2.1.1.2 Proportion of patients experiencing complete hematological response

In PROUD-PV, the primary efficacy endpoint was disease response rate at Month 12. This was defined as the proportion of patients with a complete haematological response (haematocrit <45% without phlebotomy [at least 3 months since last phlebotomy], platelets <400x10^9/L and leukocytes <10x10^9/L) and a spleen normality (spleen length ≤12 cm for females and ≤13 cm for males). At Month 12, the disease response rate was [redacted] in the ropegIFN alfa-2b arm versus [redacted] in the HU arm with a response rate difference of [redacted]

The criteria “spleen normality” has been assessed as non-relevant as minimal changes were observed, as also stated by the clinical expert committee in the DMC protocol. The proportion of patients experiencing complete hematological response without the spleen criterion were [redacted] between the treatment groups with [redacted] in the ropegIFN alfa-2b arm and [redacted] in the HU arm. In both arms data were

missing for x patients. Discontinued patients were considered non-responders. The estimates result in an absolute difference of xxxxxx (xxxxxxxxxxxxxxx) demonstrating xxxxxxxxxxxxxx of ropegIFN alfa-2b vs HU at Month 12.

During PROUD-PV, there was a significant difference between the two treatments regarding the duration of (individual) titration phase to achieve optimal haematological response. The median individual titration phase was 16.0 weeks (range: 4-64 weeks) for ropegIFN alfa-2b and 10.4 weeks (range: 2-38 weeks) for HU. This difference in reaching the individual titration phase end can explain the delay in efficacy of ropegIFN alfa-2b, compared to HU

The CONTINUATION-PV provides additional data; analyses were performed at 24, 36 and 60 months. The proportion of patients treated with ropegIFN alfa-2b that experienced a complete hematological response at 60 months were xx xxx xx xxxxxxx (xxxxxx) and xx xx xx xxxxxxxx (xxxxxx) in the HU arm.(xx) The estimates result in an absolute difference of xx.xxx.

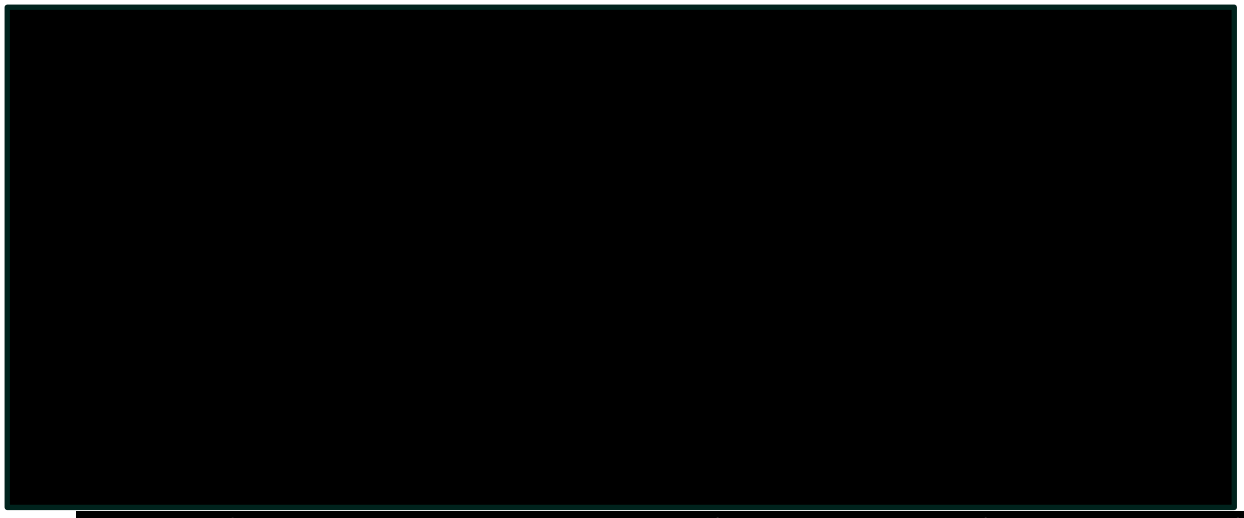
5.2.2.1.1.3 Qualitative review of events

RopegIFN alfa-2b is not indicated in patients with symptomatic splenomegaly; the patients enrolled in the PROUD-PV study represent an early PV population and only a small subgroup of patients had clinically significant splenomegaly at baseline. Efficacy parameters including spleen size were prospectively planned in the PROUD-PV and CONTINUATION-PV studies, but the impact of treatment on spleen size remains difficult to interpret in this early-stage PV population, as reflected by the endpoints included in the DMC protocol. For complete haematological response without the spleen criterion at 12 months, responses were similar between the treatment groups [xxxxxxx] xx xxx xxxxxxxx for ropegIFN alfa-2b versus xxx[xxx] xx xxxx xxxxxxxxx in the hydroxyurea group (xxxxxxxxxxxxx, xxxxx [xxxxxx]). xxxxxxxxxxx xxxxxxxxxx xxx xxx xxxxxxxxx xxxxxxx xx xxxxxxxx xxxxxxxxxx xxxxxxx xx xxxxxxxxxx. In ropegIFN alfa-2b group at 12 months, xxxx(xxxxx) xx xx xxxxxxxxx who had been pretreated with hydroxurea and xx (xxxx) xx xx xxxxxxx previously untreated with hydroxyurea had a complete haematological response (xxxxxxxxxxxxxxxxxx xxxxxxx;) in the hydroxyurea group, xxx (xxx) xx xx previously treated patients and xx xxxxxx xx xx patients previously untreated were responders (xxxxxxxx xxxxx xxxxxxxxxx], xxxxxxxx).

In the extension study CONTINUATION-PV, the proportion of patients with a complete haematological response without spleen size criterion was xxxxxxxxx higher in the ropegIFN alfa-2b group than in the hydroxyurea group at 36 and 48 months of treatment (see

Table 13). CHR rates in the CONTINUATION-PV study had decreased slightly in both treatment arms at 60 months, which in part reflects patient attrition in this long-term study, since patients who prematurely discontinued the study (xxxxxxx [xxxxxx] overall as of Month 60) were prospectively defined as non-responders.

Table 13 Haematologic response (without spleen size criterion) at assessment visits in CONTINUATION-PV – FAS



Source: xxxxxxxxxx xxxxxxlxxxxxxx xxxxxx, xxxxx xxxxxxxxxxxx xxxxxxxxx xxxxxxxxx (xxxxxxx xxxxxxx xxxxx xxxxxxxx) xx xxxxxxxxxx xxxxxx – xxxx (xxxxx xx xxxx)

Response kinetics for the composite endpoint complete haematological response and improved disease burden showed a similar pattern to the results for complete haematological response alone: proportion of patients with a response in the ropegIFN alfa-2b group increased gradually up to 24 months and remained high at 36 months, whereas in the hydroxyurea group, the response was highest at 12 months and reduced thereafter. The difference in response between the treatment groups was significant at 36 months.

Molecular responses in PROUD-PV were not significantly different between the treatment groups at 12 months (42 [34%] of 123 in the ropegIFN alfa-2b groups vs 52 [42%] of 123 in the hydroxyurea group; p=0.19). In both groups, a reduction in mean JAK2 Val617Phe allele burden compared with baseline was evident at 12 months (from 41.9% [SD 23.49] to 30.7% [SD 22.66] in the ropegIFN alfa-2b group and from 42.8% [SD 24.14] to 25.9% [SD 21.49] in the hydroxyurea group). At 24 months and 36 months of treatment, assessed in the CONTINUATION-PV study, the numbers of patients with a molecular response were significantly higher in the ropegIFN alfa-2b group than in the hydroxyurea group. Patients treated with ropegIFN alfa-2b showed a steady decrease in the mean absolute JAK2 Val617Phe allele burden to less than half the baseline level by month 36 (from 42.8% [SD 23.4] to 19.7% [SD 21.3]) whereas in the hydroxyurea group the reduction was transient and was lost by month 36 (42.9% [SD 23.0] at baseline and 39.3% [SD 25.91] at month 36). At months 24 and 36, mean JAK2 Val617Phe allele burden was significantly lower among patients treated with ropegIFN alfa-2b compared with the hydroxyurea group (at month 24, 20.9% [SD 20.8] and 32.1% [SD 23.4], respectively, p<0.0001; at month 36, 19.7% [SD 21.3] and 39.3% [SD 25.9], respectively; p<0.0001).(1) xxxx xxxx xxxxxxxxx xxxxx xxxxxxxx xxxxxxxx; xxx xxxx xxxxx xxxxxxxx xxxxx xxxxx xx xx xxxxxx xxx xxxxx xxx xxxx xxxxxxxx xxxxxxx xxx xxxxxxx xxxx xxxxx xxx xxxx xxxxxxx xxx (xxxxxxxxx).(xx)

The major disease-related cardiovascular and thromboembolic events event rates in PROUD-PV were 8.7% (11/127) of patients in the ropegIFN alfa-2b arm and 5.5% (7/127) of patients in the HU treatment arm. The most frequently observed major cardiovascular PV-related adverse events in the ropegIFN alfa-2b arm were atrial fibrillation (3 events in 2.4% of patients), while in HU patients most events were caused also by atrial fibrillation (2.4%) but also due to cardiac failure (3.2%).(15)

Table 14 Thromboembolic events occurring during the titration and maintenance phases in PROUD-PV Study

[redacted]

Phlebotomy need during the individual titration phase (i.e. visits with haematocrit > 45%) ranged between 0-27 visits (median 3.0 [Q1-Q3: 1-6]) and 0-6 visits (median 1.0 [Q1-Q3: 0- 2]), respectively in the ropegIFN alfa-2b and HU treatment arm. Patients with thromboembolic events during the individual titration phase (i.e. in ropegIFN alfa-2b arm only), did not differ significantly with 0 and 2 visits (for the two identified patients).(15)

5.2.2.1.2 Quality of life

5.2.2.1.2.1 MPN-SAF mean change from baseline in total symptom score

MPN-SAF was not assessed in PROUD-PV or CONTINUATION-PV.

5.2.2.1.2.2 EQ-5D Mean change from baseline

The change from baseline for the visual analogic score (VAS) and total score of EQ-5D-3L was comparable between the ropegIFN alfa-2b and HU treatment arm at Month 12: respectively for VAS: 1.3 (±12.56) and 1.8 (±13.09); for total score: 0.2 (±1.08) and 0.1 (±1.17).(1)

5.2.2.1.3 Adverse events

5.2.2.1.3.1 Proportion of patients experiencing at least one treatment emergent adverse event of grade 3-4

In the PROUD-PV study [redacted] in the ropegIFN alfa-2b arm had experienced at least one treatment emergent adverse events of grade 3-4 [redacted] compared to [redacted] patients in the hydroxyurea arm [redacted], resulting in an absolute difference of [redacted] At 60 months the proportion of treatment emergent adverse events of grade 3-5 were [redacted].

5.2.2.1.3.2 Proportion experiencing at least one treatment related adverse event of grade 3-4

In the PROUD-PV study [redacted] in the ropegIFN alfa-2b arm had experienced at least one treatment related adverse events of grade 3-4 [redacted] compared to [redacted] patients in the hydroxyurea arm [redacted], resulting in an absolute difference of 6.30% (95% CI: -1.12% to 13.71%) and an estimated relative difference risk ratio [redacted] At 60 months the proportion of treatment related adverse events of grade 3-5 were [redacted] ropegIFN alfa-2b and BAT arm, respectively(14).

5.2.2.1.3.3 Qualitative review of adverse reaction profile

Overall treatment exposure

[redacted]

Figure 6 Summary of ropegIFN alfa-2b and HU dose administered by assessment visit (FAS patients enrolled in CONTINUATION-PV study)

[redacted]

Data collected for the 36-month treatment analysis represent [redacted] patient-years in the ropegIFN alfa-2b arm and [redacted] patient-years in the control arm.

RopegIFN alfa-2b was well tolerated and safe, and showed a different safety profile compared to HU.
A summary of adverse events in PROUD-PV and CONTINUATION-PV (36 months) are provided in the following tables.

Table 15 Overview of adverse events – PROUD-PV Study (Safety Set)

Type of events, n (%)	RopegIFN alfa-2b [redacted]	Hydroxyurea [redacted]	All patients [redacted]
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

Type of events, n (%)	RopegIFN alfa-2b [redacted]	Hydroxyurea [redacted]	All patients [redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

AE: Adverse Event, TEAE: Treatment Emergent Adverse Events

Source: PROUD-PV Study CSR

Table 16 Overview of adverse events – CONTINUATION-PV Study (Safety Set 36 months)

Type of events	RopegIFN alfa-2b [redacted]	BAT [redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

TEAE: Treatment-emergent Adverse Event

Source: CONTINUATION-PV Study CSR, 36-month treatment analysis

The most frequently reported treatment emergent adverse effect (TEAE) (frequency >10%) in PROUD-PV were:

- RopegIFN alfa-2b arm: thrombocytopenia (15.0%), gamma-glutamyl-transferase increased (14.2%) and fatigue (12.6%).
- HU arm: thrombocytopenia (28.3%), anaemia (24.4%), leukopenia (21.3%) and fatigue (11.8%).

In CONTINUATION-PV the most frequently reported TEAE (frequency >10%) at Month 36 were:

- [redacted]

- [redacted]

Treatment-related adverse events

Of the 1278 TEAEs reported in the ropegIFN alfa-2b arm at 36 months, 613 TEAEs in 76.8% of patients were classified as having a reasonable causal relationship with the study drug). The most frequently observed TEAEs related to ropegIFN alfa-2b (frequency > 10%) were: thrombocytopenia (25.3%), leukopenia (22.1%), gamma-glutamyltransferase increased (11.6%), anaemia (10.5%), alanine aminotransferase increased (10.5%) and myalgia (10.5%).
In the BAT arm, 288/733 TEAEs in 84.2% of patients had at least one related TEAE during the 36-month treatment period. The most frequently observed TEAEs related to BAT (frequency > 10%) were: thrombocytopenia (32.9%), leukopenia (30.3%), anaemia (28.9%) and platelet count decreased (10.5%).

Grade 3-4 adverse events
Most TEAEs were mild (66.0%) in the ropegIFN alfa-2b arm and 66.7% in the BAT arm) and moderate (ropegIFN alfa-2b arm: 28.9%; BAT arm: 26.6%) in intensity at 36 months.

In the ropegIFN alfa-2b arm, 61 severe TEAEs (grade 3) were reported in 34.7% of patients, including 24 severe TEAE related to treatment reported in 14.7% of patients. The most frequently observed grade 3 TEAEs related to ropegIFN alfa-2b (frequency >3%) were: gamma-glutamyltransferase increased (5.3%), alanine aminotransferase increased (4.2%) and thrombocytopenia (3.2%). Four TEAEs in 2.1% of patients in the ropegIFN alfa-2b arm were classified as life-threatening (grade 4), 1 of which was related to treatment (increased gamma-glutamyltransferase).
A total of 45 severe TEAEs were reported in 32.9% of patients in the BAT arm. The most frequently observed grade 3 TEAEs related to BAT (frequency >3%) were: thrombocytopenia (6.6%) and leukopenia (5.3%). No life-threatening TEAEs (grade 4) were documented in this arm.

Serious adverse events (SAE)
Twenty-eight (28) serious TEAEs in 17/95 (17.9%) patients in the ropegIFN alfa-2b arm and 25 serious TEAEs in 17/76 (22.4%) patients in the BAT arm were reported at 36 months.
Serious Aes related to treatment were anaemia (1.1%) and microcytic anaemia (1.1%) in ropegIFN alfa-2b arm and acute leukaemia (1.3%), malignant melanoma (1.3%), anaemia (1.3%), granulocytopenia (1.3%) and leukopenia (1.3%) in the BAT arm.

Adverse events leading to study discontinuation
A total of 10 TEAEs leading to study discontinuation were reported in 7.4% of patients in the ropegIFN alfa-2b arm at 36 months. All recorded TEAEs occurred only once and included anaemia, thrombocytopenia, microcytic anaemia, bile duct cancer, tuberculosis, alanine aminotransferase increased, aspartate aminotransferase increased, Sjogren's syndrome, depression and nervousness. The TEAEs tuberculosis, bile duct cancer and nervousness were classified as unrelated to study drug and the remainder were considered related to treatment.
Six TEAEs led to discontinuation in 5 patients in the BAT arm: one event each of anaemia, thrombocytopenia, acute leukaemia, myelofibrosis, pyrexia and skin ulcer.

Deaths
Five SAEs in 3 patients had a fatal outcome in the CONTINUATION-PV Study: 1 patient (1.1%) in the ropegIFN alfa-2b arm and 2 patients in the BAT arm at 36 months. No deaths occurred that were considered by the investigator to be related to treatment with ropegIFN alfa-2b.

Adverse events of special interest
Nineteen (19) adverse events of special interest (AESI) were recorded in ropegIFN alfa-2b arm in 11.6% of patients (hypothyroidism [2.1%], hyperthyroidism, haemorrhagic transformation stroke, ischaemic stroke, anxiety, depression,

irritability, mood altered, nervousness, splenic infarction, truncus coeliacus thrombosis, retinal injury, Sjogren's syndrome, vision blurred, dermatitis acneiform, psoriasis and sarcoidosis [all 1.1%]). Most of these AESI related to interferon were not found in the BAT arm.
6 TEAEs of special interest in 7.9% of patients in the BAT arm were reported in the study (depression [2.6%], autoimmune thyroiditis, pericardial effusion, subcutaneous haematoma and thrombophlebitis superficial [all 1.3%]).

Eleven major cardiovascular PV-related TEAEs were reported in 8.4% of patients in the ropegIFN alfa-2b arm. Sixteen major cardiovascular PV-related TEAEs were reported in 5.3% of patients in the BAT arm.
The major cardiovascular PV-related TEAEs as per sponsor's definition in the ropegIFN alfa-2b were atrial fibrillation (3.2% of patients), peripheral arterial occlusive disease (1.1%), phlebitis (1.1%), haematemesis (1.1%), truncus coeliacus thrombosis (1.1%), splenic infarction (1.1%), haemorrhagic transformation stroke (1.1%) and ischaemic stroke (1.1%). These events related to interferon were not found in the BAT arm.
In the BAT arm the recorded major cardiovascular PV-related TEAEs as per sponsor's definition were atrial fibrillation (1.3%), pericardial effusion (1.3%), peripheral circulatory failure (1.3%), thrombophlebitis superficial (1.3%) and venous thrombosis limb (1.3%).
In CONTINUATION-PV no new safety and tolerability signals were detected in the fifth year. Treatment related adverse events were reported in 25.6% and 24.2% of patients in the ropegIFN alfa-2b and control arms, respectively, and one patient in each arm withdrew due to drug-related toxicity. Three patients (3.8%) in the ropegIFN alfa-2b arm reported grade ≥3 treatment-related adverse events in the fifth year; over the entire treatment period, the rate of grade ≥3 drug-related adverse events were the same in each study arm (16.5%).(16)

5.2.2.2 PEGINVERA

5.2.2.2.1 Thromboembolic events

5.2.2.2.1.1 Proportion of patients experiencing at least one thromboembolic event
Not reported

5.2.2.2.1.2 Proportion of patients experiencing complete hematological response
The best observed individual haematological response for patients in the FAS population was a complete response for 64.3% of patients (27/42) and a partial response for 33.3% of patients (14/42); no haematological response was observed for 1 patient (2.4%).
Among patients in the FAS who achieved a complete haematological response, the median time to response was approximately 7.8 months of treatment with ropegIFN alfa-2b. The median time on treatment required to achieve any haematological response was 10 weeks.(10)

5.2.2.2.1.3 Qualitative review of events
See above

5.2.2.2.2 Quality of life

5.2.2.2.2.1 MPN-SAF mean change from baseline in total symptom score
Not reported

5.2.2.2.2.2 EQ-5D Mean change from baseline
Not reported

5.2.2.2.3 Adverse events

5.2.2.2.3.1 Proportion of patients experiencing at least one treatment emergent adverse event of grade 3-4

Not reported

5.2.2.2.3.2 Proportion experiencing at least one treatment related adverse event of grade 3-4

Not reported

5.2.2.2.3.3 Qualitative review of adverse reaction profile

The majority (52.9%) of the patients completed 5 years of treatment and 16 (31.4%) completed 6 years of treatment during this study. The median duration of exposure to ropegIFN alfa-2b was approximately 5.1 years (0 to 87 months). In the FAS, the mean number of doses administered was 61.4, the mean dose received by any patient was 236.6 µg, and the mean cumulative dose was 15 094 µg (300 to 54 240 µg).

A total of 1176 treatment-emergent AEs (TEAEs) were recorded for 51/51 (100%) patients. The most frequently reported TEAEs with a frequency >20% were: arthralgia and fatigue (each in 47.1% of patients [24/51]), pruritus (in 45.1% of patients [23/51]), nasopharyngitis (in 41.2% of patients [21/51]), diarrhoea (in 33.3% of patients [17/51]), headache (in 29.4% of patients [15/51]), nausea and influenza like illness (each in 27.5% of patients [14/51]), pyrexia, (in 23.5% of patients [12/51]), back pain (in 25.5% of patients [13/51]) and dizziness (in 21.6% of patients [11/51]). Most of the 1176 TEAEs were mild (834 AEs in 49/51 [96.1%] patients) or moderate (296 AEs in 44/51 [86.3%] patients) in intensity. Most TEAEs resolved (1018/1176 [86.6%]); however, the majority of patients (35/51, 68.6%) had one or more ongoing TEAEs.

A total of 409 (34.8%) TEAEs reported in 94.1% (48/51) of patients were classified as having a reasonable causal relationship with the product. However, the majority of the related TEAEs (296/409 in 44 [86.3%] patients) were of mild intensity; 102 (in 34 [66.7%] patients) were moderate and 11 (in 10 [19.6%] patients) were severe.

The most frequent related TEAE symptoms (with a frequency > 20%) were (by PT): arthralgia (27 events for 16/51 [31.4%] patients), influenza like illness (26 events in 11/51 [21.6%] patients) and fatigue (16 events in 12/51 [23.5%] patients).
A total of 65 SAEs were reported for 28/51 (54.9%) patients. The majority of SAEs were of moderate intensity (28 SAEs in 27.5% of patients [14/51]) or severe intensity (24 SAEs in 33.3% of patients [17/51]).
Twelve SAEs reported by 8/51 patients (15.7%) were related to the product. The SAEs related to the product comprised (by PT): depression (2 events in 3.9% of patients [2/51]), anti-thyroid antibody positive (2 events in 1 patient); and reported single cases of the following; acute stress disorder, antinuclear antibody increased, arthralgia, atrial fibrillation, fatigue, influenza-like illness, pyrexia, and transaminases increased.
A total of 285 TEAEs (24.2%) reported for 46/51 (90.2%) patients led to additional treatment, 81 TEAEs (6.9%) reported for 31/51 (60.8%) patients led to dose reduction, 82 TEAEs (7.0%) reported for 33/51 (64.7%) patients led to dose interruption. A total of 21/51 (41.2%) patients discontinued due to a TEAE, the majority (13/21) of whom discontinued during the first year of treatment.
Six TEAEs were associated with an outcome of death in 3 patients; none of these events were related to the product.

5.2.2.3 NCT00452023 (Masarova et al. 2017; Quintas-Cardama et al. 2013; Quintas-Cardama et al. 2009)

5.2.2.3.1 Thromboembolic events

5.2.2.3.1.1 Proportion of patients experiencing at least one thromboembolic event

The DMC protocol requests information on the proportion of patients experiencing at least one thromboembolic event. Thromboembolic events were observed in six out of the 43 enrolled PV patients (13.9%), as presented in supplementary table 4 of the Masarova 2017 publication.(18)

5.2.2.3.1.2 Proportion of patients experiencing complete hematological response

All 43 enrolled PV patients were evaluable for a hematologic response with 33 patients experiencing CHR (77%) as an initial response of which 13 patients had CHR at last follow-up. The median duration of hematological response was 65 months (IQR: 43–87). Neither achievement of a HR nor time to response was associated with age, gender, baseline clinical characteristics, splenomegaly, molecular status or JAK2V617F allele burden.(18)

5.2.2.3.1.3 Qualitative review of events

Overall, 40 patients lost their response. Nineteen after dose reductions or drug holds due to intolerance or toxicity; one when he developed concurrent diffuse large B-cell lymphoma; and 20 due to progressive disease, despite being treated with the highest tolerable dose of PEG-IFN-α-2a. The median response duration among patients who lost their response was 46 months (IQR, 17–68). Among patients who were treated for at least 46 months, the median dose of PEG-IFN-α-2a was similar regardless of whether or not they lost their response (135 mcg/week vs 90 mcg/week, respectively, p=0.44). Remarkably, 7 patients (28%, 4 essential thrombocythemia, 3 polycythemia vera) have sustained their HR after discontinuation of PEG-IFN-α-2a (median time on therapy, 77 months [IQR, 56–98 months]; median response duration off study, 6 months [IQR, 4–34 months]).(18)

Thromboembolic events were observed in six patients with two mesenteric arterial thrombosis, one hepatic arterial thrombosis, one femoral artery DVT, one pulmonary embolism and one cerebrovascular accident, as outlined in

Table 17 Characteristics of patients with venous thrombotic event while on therapy

Age/Sex	Diagnosis	TT-VTE (months)	VTE type	Provoking event	HX VTE	FU on study, months
45F	PV	49	mesenteric art Thr	--	--	65.8
49F	PV	38	mesenteric art Thr	--	PE, PV Thr	40.4
32F	PV	60	hepatic art Thr	--	--	60.1
58M	PV	3	femoral artery DVT	heart cath	--	96.2
53F	PV	15	PE	elective surgery	--	44.7
43F	PV	4	CVA	angiogram	--	3.9

TT-VTE = time to venous thrombotic event from date of study enrollment; PE = pulmonary embolism; PV thrombosis = portal vein thrombosis; CVA = cerebrovascular accident; Thr = thrombosis; art = arterial; FU = follow-up

5.2.2.3.2 Quality of life

5.2.2.3.2.1 MPN-SAF mean change from baseline in total symptom score

MPN-SAF was not assessed in the study.

5.2.2.3.2.2 EQ-5D Mean change from baseline

EQ-5D was not assessed in the study.

5.2.2.3.3 Adverse events

5.2.2.3.3.1 Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4

The publications do not report the proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4. Please see section 0 Qualitative review of adverse reaction profile for information available.

5.2.2.3.3.2 Proportion experiencing at least one treatment related adverse events of grade 3-4

The publications do not report the proportion experiencing at least one treatment related adverse events of grade 3-4. Please see section 0 Qualitative review of adverse reaction profile for information available.

5.2.2.3.3.3 Qualitative review of adverse reaction profile

Among all patients, fatigue (75%), muscle pain (52%), nausea/vomiting and diarrhea (44%), and depression (32%) were the most common AEs. Severe hematologic AEs (Grade 3/4 or recurrent events despite dose reductions) occurred in 89% (n=22/25) of patients with polycythemia vera. The AE rate decreased with time on therapy, yet did not completely disappear. New grade 3-4 toxicities unrelated to dose occurred 24 months from start of therapy in 10–17% of patients annually. The most common late AEs were fatigue (prevalent in all years), anemia and neutropenia (highest in the 3rd & 6th year), and depression (highest in 4th–6th year). Four patients (3 essential thrombocythemia, 1 polycythemia vera) developed autoimmune toxicities after a median time on therapy of 47.5 months (range: 26 – 78 months). All cases were biopsy proven and included hepatitis, central nervous system vasculitis, lupus nephritis and other presentations (Sjogren syndrome, dermatitis and vasculitis). Screening for autoantibodies was only performed in patients with a clinical presentation suspicious for autoimmune disease (e.g., significant musculoskeletal or skin symptoms or any other atypical presentation). Thyroid function tests were done for all patients. None of the patients had a history of autoimmune disease, which was an exclusion criterion. Autoimmune thyroiditis, the most frequently reported autoimmune side effect of IFN-α 17, was observed in 15 patients (18%), but only 2 were severe (grade 3) enough to warrant treatment discontinuation.

Overall, the dose had to be adjusted over the course of treatment, either for toxicity or lack of efficacy, in all but 2 patients. Eighteen patients (22%) discontinued therapy due to drug related toxicities, grade 1–2 in 8 (10%) or grade 3–4 in 10 (12%) (Figure 1). Discontinuation rates were not correlated with PEG-IFN-α-2a dosage. The median time on therapy for these patients was 11 months (range: 2–60), although 4 patients requested discontinuation after < 6 months. Half of these patients had more than 1 type of toxicity, with the most common being neuropsychiatric (n=5 patients), gastrointestinal (n=4), and hematologic (n=3).

An additional 12 patients had therapy held for >6 months due to toxicity, with a median time on hold of 29 months (range, 7–79). The most common toxicities leading to significant treatment interruptions were grade 3 neutropenia and multiple grade 2 toxicities, such as anemia, fatigue, musculoskeletal pain, diarrhea, neuropathy, and depression. Ten of 12 patients were rechallenged at a lower dose of PEG-IFN-a-2a, but because of persistent and recurrent toxicities (mostly grade 3 hematologic) they remained off therapy. The other two are being treated with a very low dose (45 mcg every 4–6 weeks), despite similar, though less severe, (only grade 1 non-hematologic) side effects (musculoskeletal, gastrointestinal, rash), which they have deemed tolerable. Other reasons for discontinuation included motor vehicle accident (n=1); loss to follow-up (n=3); death (n=3); other malignancy (n=2); and financial (n=7). Three patients died while on study, but none were thought to be related to the study drug. One patient died of central pontine myelinolysis due to rapid correction of grade 3 hyponatremia, one due to complications from severe aortic stenosis and pulmonary hypertension, and one as a consequence of a motor vehicle accident.

5.2.2.4 Crisa et al. 2017

5.2.2.4.1 Thromboembolic events

5.2.2.4.1.1 Proportion of patients experiencing at least one thromboembolic event
No thrombotic events were observed during peg-IFN treatment.(8)

5.2.2.4.1.2 Proportion of patients experiencing complete hematological response
The reported proportion of patients experiencing complete response was 70% (27/30) of the cohort treated with peg-IFN.(8)

5.2.2.4.1.3 Qualitative review of events
Of the patients treated with peg-IFN 87% (26/30) responded, with a complete response rate of 70% (21/30). Median time to CR was 6 months and median peg-IFN dose at CR was 90 µg weekly. The four patients who did not respond had to early discontinue treatment due to intolerance.(8)

5.2.2.4.2 Quality of life

5.2.2.4.2.1 MPN-SAF mean change from baseline in total symptom score
MPN-SAF was not assessed in the study.

5.2.2.4.2.2 EQ-5D Mean change from baseline
EQ-5D was not assessed in the study.

5.2.2.4.3 Adverse events

5.2.2.4.3.1 Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4
The publication does not report the proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4. Please see section 0 Qualitative review of adverse reaction profile for information. available.

5.2.2.4.3.2 Proportion experiencing at least one treatment related adverse events of grade 3-4
The publication does not report the proportion experiencing at least one treatment related adverse events of grade 3-4. Please see section 0 Qualitative review of adverse reaction profile for information available.

5.2.2.4.3.3 Qualitative review of adverse reaction profile
Most patients (87%) experienced some adverse events: hematologic toxicity (43%, grade 3–4 7%), flu-like symptoms (30%), and liver test elevation (23%, grade 3–47%). Overall discontinuation rate was 20%. JAK2 allele burden reduction was observed in 88% of the patients (21/24 evaluable ones). Median JAK2 allele burden at diagnosis was 40.5% (range 1.5–91%), and it decreased to 17% (range: 0.3–81%) and 15.8% (range: 0–77%) at 12 and 24 months after treatment start, respectively.(8)

5.2.2.5 Huang et al. 2014

5.2.2.5.1 Thromboembolic events

5.2.2.5.1.1 Proportion of patients experiencing at least one thromboembolic event
Thrombotic events are not reported as an effect measure in the publication.(12)

5.2.2.5.1.2 Proportion of patients experiencing complete hematological response

The reported proportion of patients experiencing complete hematological response was 29.7% (19/64) of the cohort treated with IFN-alfa-2b. The overall hematologic response rate was 70.3% for receiving IFN-alfa-2b. CHR was defined as normalization of hematocrit (<45% in males and <42% in females), WBC and platelet counts, and spleen size, without the absence of thromboembolic events.(12)

5.2.2.5.1.3 Qualitative review of events

Of the patients treated with peg-IFN 87% (26/30) responded, with a complete response rate of 70% (21/30). Median time to CR was 6 months and median peg-IFN dose at CR was 90 µg weekly. The four patients who did not respond had to early discontinue treatment due to intolerance.(8)

5.2.2.5.2 Quality of life

5.2.2.5.2.1 MPN-SAF mean change from baseline in total symptom score

MPN-SAF was not assessed in the study.

5.2.2.5.2.2 EQ-5D Mean change from baseline

EQ-5D was not assessed in the study.

5.2.2.5.3 Adverse events

5.2.2.5.3.1 Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4

The publication does not report the proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4. Please see section 0 Qualitative review of adverse reaction profile for information available.

5.2.2.5.3.2 Proportion experiencing at least one treatment related adverse events of grade 3-4

The publication does not report the proportion experiencing at least one treatment related adverse events of grade 3-4. Please see section 0 Qualitative review of adverse reaction profile for information available.

5.2.2.5.3.3 Qualitative review of adverse reaction profile

The total deaths of 5/136 (3.7%) patients with PV were recorded during follow up. Among them, seven patients received IFN. 78/136 of PV patients developed some toxicity, but this was only generally grade 1-2. The main mild adverse event was fever (>38 ◦C), which was tolerated by most patients. Furthermore, for PV patients with JAK2V617F+ mutation, no neutropenia, infection, thrombocytopenia or renal failure were observed in the IFN-alfa-2b therapy group. Only one patient receiving IFN-alfa-2b had an allergic reaction (Grade 3-4, 1.6%).(12)

5.2.2.6 Stauffer Larsen et al. 2013

5.2.2.6.1 Thromboembolic events

5.2.2.6.1.1 Proportion of patients experiencing at least one thromboembolic event

The publication by Stauffer Larsen et al. 2013 reports one patient experiencing a thrombosis during the follow-up period while receiving IFN.(2)

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5.2.2.6.1.2 Proportion of patients experiencing complete hematological response

The reported proportion of patients experiencing complete hematological response was 29.7% (51/75) of patients with PV with normalization of platelet and white cell counts, hematocrit <0.45 and no need of phlebotomy 3 months prior to follow-up.(2)

5.2.2.6.1.3 Qualitative review of events

Not reported in the publication.(2)

5.2.2.6.2 Quality of life

5.2.2.6.2.1 MPN-SAF mean change from baseline in total symptom score

MPN-SAF was not assessed in the study.

5.2.2.6.2.2 EQ-5D Mean change from baseline

EQ-5D was not assessed in the study.

5.2.2.6.3 Adverse events

5.2.2.6.3.1 Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4

The publication does not report the proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4.

5.2.2.6.3.2 Proportion experiencing at least one treatment related adverse events of grade 3-4

The publication does not report the proportion experiencing at least one treatment related adverse events of grade 3-4.

5.2.2.6.3.3 Qualitative review of adverse reaction profile

The publication does not report on adverse reactions.

5.2.2.7 PVN1 (Kiladjian et al. 2008

5.2.2.7.1 Thromboembolic events

5.2.2.7.1.1 Proportion of patients experiencing at least one thromboembolic event

No patient experienced signs or symptoms of thrombosis or hemorrhage during the whole study period. Hence, no thrombosis was observed in this cohort after more than 30 months of median follow-up.

5.2.2.7.1.2 Proportion of patients experiencing complete hematological response

The reported proportion of patients experiencing complete hematological response was 94.6% (35/37) of the cohort treated with IFN-alfa-2a at the 12-month evaluation.(4)

5.2.2.7.1.3 Qualitative review of events

All the 37 patients had responded to peg-IFN-alfa-2a at the 12-month evaluation (primary study end point), including 35 hematologic CRs (94.6%), and 2 PRs (5.4%). Cumulative incidences of hematologic CRs and PRs are represented in Figure 1A, showing that 100% of responses were achieved within 12 months. Thirty-six patients became phlebotomy-free after 3 months, the last patient after 6 months, and 36 (97.3%) patients remained phlebotomy-free during all the

follow-up period. Time to response was not influenced by age, gender, baseline values of hemoglobin, Hct, platelet count, absolute neutrophil count (ANC), presence of splenomegaly, presence of JAK2 mutation, %V617F, presence of 9p LOH, and cumulative dose of peg-IFN-alfa-2a. Median cumulative dose of peg-IFN-alfa-2a received during the first 12 months was 109 µg/week (Q1-Q3: 90-135 µg/week). Hematologic responses were sustained beyond the first year. At the reference date of analysis (January 2008; median follow-up of 31.4 months), 29 of the 37 patients (78.4%) had received only peg-IFN-alfa-2a since inclusion, whereas 8 had switched to another treatment, including HU (n=7), or a phlebotomy regimen (n=1). Reasons for switching to another treatment were toxicity of peg-IFN-alfa-2a in 6 and achievement of only hematologic PR with peg-IFN-alfa-2a in 2. The 29 patients treated with peg-IFN-alfa-2a alone were in hematologic CR, still on treatment (n=24) or off peg-IFN-alfa-2a therapy (n=5) Those last 5 patients had stopped peg-IFN-alfa-2a after 12 to 24 months of treatment because of sustained CR with very low doses (n=3) or to toxicity (n=2), and were still in hematologic CR 3, 3, 6, 10, and 18 months, respectively, after peg-IFN-alfa-2a discontinuation, without requirement for any additional cytoreductive treatment. The 8 patients who required treatments other than peg-IFN-alfa-2a were still in CR (n=6, after switch to HU) or PR (n=2, after HU in 1, and phlebotomies only in 1). Overall, after 31.4 months of median follow-up, all patients were still in hematologic response, including 35 (94.6%) CRs and 2 PRs. No patient experienced signs or symptoms of thrombosis or hemorrhage during the whole study period.(4)

5.2.2.7.2 Quality of life

5.2.2.7.2.1 MPN-SAF mean change from baseline in total symptom score

MPN-SAF was not assessed in the study.

5.2.2.7.2.2 EQ-5D Mean change from baseline

EQ-5D was not assessed in the study.

5.2.2.7.3 Adverse events

5.2.2.7.3.1 Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4

Kiljadan et al. reports one grade 3 skin toxicity at 6 months resulting in 1 out of 37 patients experienced an adverse event of grade 3-4 throughout the trial (2.7%).(4)

5.2.2.7.3.2 Proportion experiencing at least one treatment related adverse events of grade 3-4

The publication does not report the proportion experiencing at least one treatment related adverse events of grade 3-4. Please see section 5.2.2.7.3.3 Qualitative review of adverse reaction profile for information available.

5.2.2.7.3.3 Qualitative review of adverse reaction profile

Adverse events were reported in 33 (89%) patients during the first 12 months of the study, whereas the other 4 (11%) patients remained free of AEs. A total of 239 AEs were reported (median number per patient: 4 AEs; Q1-Q3: 2-10 AEs). All reported AEs were of grade 1 or 2, except one grade 3 skin toxicity. The percentage of patients having AEs slightly decreased over time, from 65% during the first month to 50% at 12 months. Most common toxicities during the first month included musculoskeletal pain in 13 patients, skin toxicity in 6, asthenia in 6, and gastrointestinal symptoms in 4. At 12 months, those symptoms were still present in 7, 5, 7, and 2 patients, respectively. The Eastern Cooperative Oncology Group score at baseline and at 12 months was 0 in 90.3% and 83.3% patients, and 1 in 9.7% and 16.7% patients, respectively. During the whole study period, treatment was stopped in 13 patients, including 9 (24.3%) for toxicity (3%-8.1% during the first year). Causes of treatment discontinuation for toxicity during the first year (n=3) were: the only observed case of recurring grade 2 neutropenia that impeded weekly peg-IFN-alfa-2a administration resulting in non-satisfactory control of Hct in this JAK2 unmutated patient, grade 3 skin toxicity after 6 months (n=1),

and grade 2 fatigue and headaches after 9 months (n=1). After the first year, toxicity led to treatment discontinuation in 6 additional patients, including liver toxicity (n=1), occurrence of biologic markers of autoimmunity (n=1), muscular pain (n=2), peripheral neurologic toxicity (n=1), and fatigue (n=1). Discontinuation in the 4 remaining patients was the result of investigator's decision because of sustained hematologic CR (n=2), end of the predefined treatment period (n=1), and discovery of colon cancer (n=1).(4)

5.2.2.8 Samuelsson et al. 2006

5.2.2.8.1 Thromboembolic events

5.2.2.8.1.1 Proportion of patients experiencing at least one thromboembolic event

No thromboembolic or hemorrhagic complications were observed after 2 years of follow-up.(9)

5.2.2.8.1.2 Proportion of patients experiencing complete hematological response

At 6 months, 29 of 42 patients (69%) had achieved a complete response and were still on therapy. The median time to CR was 83 days.(9)

5.2.2.8.1.3 Qualitative review of events

The failure rate was 31% (13 of 42 patients). Of those 13 patients, 4 patients went off study early because of side effects, another 2 patients also were taken off study at 6 months because of side effects, and 7 patients had not reached a platelet CR at 6 months despite a maximal PEG-IFN dose of 1.0 µg/kg once weekly.
At 12 months, another 9 of 29 patients who achieved a CR at 6 months had discontinued therapy because of adverse events; all of those patients were in CR when therapy was stopped. There was no difference in the median age of patients who continued therapy after 12 months (median age: 54 years) and patients who stopped therapy before 12 months (median age: 53 years). One additional patient went off therapy at 15 months, whereas the remaining 19 patients (12 patients with PV and 7 patients with ET) continued therapy for the planned 24 months and achieved a CR rate of 45% (19 of 42 patients) and a failure rate of 55% (23 of 42 patients) at 2 years.(9)

5.2.2.8.2 Quality of life

5.2.2.8.2.1 MPN-SAF mean change from baseline in total symptom score

MPN-SAF was not assessed in the study.

5.2.2.8.2.2 EQ-5D Mean change from baseline

EQ-5D was not assessed in the study.

5.2.2.8.3 Adverse events

5.2.2.8.3.1 Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4

The publication does not report the proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4. Please see section 5.2.2.8.3.3 Qualitative review of adverse reaction profile for information. available.

5.2.2.8.3.2 Proportion experiencing at least one treatment related adverse events of grade 3-4

The publication does not report the proportion experiencing at least one treatment related adverse events of grade 3-4. Please see section 5.2.2.8.3.3 Qualitative review of adverse reaction profile for information available.

5.2.2.8.3.3 Qualitative review of adverse reaction profile

Adverse events were reported by all patients at some time during the study. The majority of adverse events were grade 1 or 2, although some patients had grade 3 adverse events, most notably fatigue and flu-like symptoms. There was no significant difference in the frequency or severity of adverse events between patients with ET and patients with PV. Only 8 of 19 patients who completed 24 months of therapy reported any adverse event at the end of study. Adverse events were the cause for discontinuation of therapy in 16 of 23 patients, and the dominating problem was fatigue in 6 patients, muscle pain in 3 patients, headache in 2 patients, flu-like symptoms in 1 patient, depression in 1 patient, erythema in 1 patient, hair loss in 1 patient, and tachycardia in 1 patient. In 14 of 16 patients, the treating physician and the patient concurred that PEG-IFN therapy should be stopped; in 2 patients, PEG-IFN was discontinued solely at the request of the patient.(9)

Mild elevations were noted in serum alanine aminotransferase levels in 19 patients, creatinine levels in 3 patients, and thyroid-stimulating hormone levels in 3 patients. One patient developed clinical and laboratory signs of hyperthyroidism after 24 months of therapy that may have been treatment related, because withdrawal of PEG-IFN led to a full recovery within 5 months without any further intervention. Other clinically significant events that occurred during the trial included was 1 each of the following; atrial fibrillation, pneumonia, hypertension, endocarditis after a foot injury with large skin abrasion, basal cell carcinoma, and multiple sclerosis. It was considered unlikely that these events were associated with PEG-IFN therapy.(9)

5.2.2.9 MPN-RC 112

5.2.2.9.1 Thromboembolic events

5.2.2.9.1.1 Proportion of patients experiencing at least one thromboembolic event

DMC protocol requests information on the proportion of patients experiencing at least one thromboembolic event. This endpoint is not directly reported as an outcome in the clinical trial or publication but Mascarenas et al. 2022 reports five events (HU: 3, IFN-alfa-2a: 2) occurred during the trial for the outcome overall complication-free survival, which is defined as free of major thrombotic event, major hemorrhagic complications, progression to myelofibrosis, progression to acute leukemia or death.

5.2.2.9.1.2 Proportion of patients experiencing complete hematological response

The reported proportion of patients experiencing complete hematological response without spleen normalization at 12 months were seen in 42% (36/86) of HU patients and 48% (40/82) of IFN-alfa-2a patients (difference of -6% [95% CI -9 to 21]) in the ITT population (PV and ET). 43% (19/44) and 65% (28/43) of PV patients receiving HU and IFN-alfa-2a achieved hematocrit control (without phlebotomy) at 12 months.(21) The reported proportion of patients experiencing complete hematological response with spleen normalization criteria was 28% (12/43) of the PV cohort treated with IFN-alfa-2a and 30% (13/43) for HU at the 12-month evaluation.(21)

At 36 months CR with spleen normalization was seen in 29% (5/17) of the PV cohort treated with IFN-alfa-2a and 17% (3/18) treated with HU.(21)

5.2.2.9.1.3 Qualitative review of events

Five events (HU: 3, IFN-alfa-2a: 2) occurred during the trial with a HR=0.60 (95% CI 0.10-3.62]. One IFN-alfa-2a treated patient had a bleeding event consisting of macroscopic hematuria requiring red cell transfusions. A second IFN-alfa-2a treated patient had a cerebral vascular accident. One HU treated patient developed bilateral vertebral artery blockage noted on imaging but without clinical consequences. One HU treated patient progressed to MF after 46 months. One

HU treated patient died from lung cancer at 9 months. Cumulative incidence of thrombosis was 2% (95% CI 0.3-13) for HU and 2% (0.3-15) for IFN-alfa-2a at 24 months.(21)

5.2.2.9.2 Quality of life

5.2.2.9.2.1 MPN-SAF mean change from baseline in total symptom score
MPN-SAF was not assessed in the study.

5.2.2.9.2.2 EQ-5D Mean change from baseline
EQ-5D was not assessed in the study.

5.2.2.9.3 Adverse events

5.2.2.9.3.1 Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4
Grade 3 or higher (any attribution) AEs occurred in 60 (37%) patients, HU: 22 (28%) and PEG: 38 (46%) in the ITT population. The outcome is not reported specifically for the PV cohort.(21)

5.2.2.9.3.2 Proportion experiencing at least one treatment related adverse events of grade 3-4
The publication does not report the proportion experiencing at least one treatment related adverse events of grade 3-4. Please see section 5.2.2.7.3.3 Qualitative review of adverse reaction profile for information available.

5.2.2.9.3.3 Qualitative review of adverse reaction profile
Mascarenhas et al. 2022 reports the following AEs: IFN-alfa-2a related AEs were common (flu-like symptoms, injection site reaction, peripheral sensory neuropathy, blurred vision). Grade 1-2 depression was seen in 15% of IFN-alfa-2a patients as compared to 3% of HU patients. Mucositis and anorexia were significantly more common in the HU arm, while leukopenia, flu-like symptoms, injection site reactions, AST elevations and depression occurred more frequently in the IFN-alfa-2a arm. In addition, hypertension, fatigue and lymphopenia were higher in the IFN-alfa-2a arm.

5.2.2.10 MPN-RC 111

5.2.2.10.1 Thromboembolic events

5.2.2.10.1.1 Proportion of patients experiencing at least one thromboembolic event
The proportion of patients experiencing at least one thromboembolic event is not reported in the study, but the cumulative incidence of major vascular events at 1 year was 2% (95% CI: 1%-8%) and at 2 years was 5% (95% CI: 2%-15%) and consisted of a grade 3 venous thromboembolic event, grade 3 cardiovascular disease, and 2 coronary artery occlusions: 1 grade 2 and 1 grade 3 myocardial infarction.(20)

5.2.2.10.1.2 Proportion of patients experiencing complete hematological response
In PV patients, 11 (22%) attained a CR and 19 (38%) at 12 months with a median follow-up time of 19.6 months (range: 0.6-56.6). At 12 months, 23 of 50 (46%) PV patients had achieved ≤45% HCT.(20)

5.2.2.10.1.3 Qualitative review of events
Please see information above.

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5.2.2.10.2 Quality of life

5.2.2.10.2.1 MPN-SAF mean change from baseline in total symptom score

QoL questionnaires were completed by 104 (90.4%) patients (ET, 57; PV, 47) at 3 months, 92 (80%) patients (ET, 52; PV, 40) at 6 months, 81 (70.4%) patients (ET, 47; PV, 34) at 9 months, and 74 (64.3%) patients (ET, 45; PV, 29) at 12 months. In a mixed model, patients experienced statistically significant improvements in MPN-related symptoms including TSS, fatigue, dizziness, numbness and tingling, and weight loss (all P, 0.05). However, PEG-related side effects, such as flulike symptoms, injection site irritation, blurry vision, and vision changes, also developed. GHS/QoL stayed relatively stable over time in those patients who tolerated treatment. Patients with a CR had significantly improved TSS, GHS/QoL score, fatigue, early satiety, and itching, compared with those with a PR/NR at 12 months (all P, 0.05).(20)

5.2.2.10.2.2 EQ-5D Mean change from baseline

EQ-5D was not assessed in the study.

5.2.2.10.3 Adverse events

5.2.2.10.3.1 Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4

Grade ≥3 AEs, regardless of attribution occurred in 50 patients (43.8%). The outcome is not reported specifically for the PV cohort.(20)

5.2.2.10.3.2 Proportion experiencing at least one treatment related adverse events of grade 3-4

The publication does not report the proportion experiencing at least one treatment related adverse events of grade 3-4. Please see section 5.2.2.7.3.3 Qualitative review of adverse reaction profile for information available.

5.2.2.10.3.3 Qualitative review of adverse reaction profile

Yacoub et al. 2019 reported seventy-two percent of patients remained on therapy for over 12 months, with a median duration of 82 (range: 4-209) weeks for PV. The mean (SD) weekly dose of IFN-alfa-2a was 128.7 (46.4) for PV. The 2 most common reasons for discontinuation of therapy were study closure (30.4%) and completion of the planned 4-year follow-up (26.1%). Discontinuation of IFN-alfa-2a because of AEs occurred in 13.9% of patients. Cumulative incidence of a second cancer (excluding nonmelanoma skin cancers) at 2 years was 4% (95% CI: 1%-10%). These consisted of lung adenocarcinoma (PV: 2; ET: 0), spindle cell sarcoma (ET: 1) and melanoma (PV: 1). Four patients discontinued treatment because of secondary cancer (1 each with lung adenocarcinoma, melanoma, spindle cell sarcoma, and pre-existing renal cell cancer).(20)
All patients (N=114) who received IFN-alfa-2a were evaluated for AEs. One ET patient withdrew from the study before receiving treatment. AEs of any grade, regardless of attribution, were reported in 90.4% of patients. Grade ≥3 AEs, regardless of attribution occurred in 50 patients (43.8%). No deaths occurred in patients during treatment, but 3 deaths occurred in patients who had been taken off study. Reasons for discontinuation of the study in these 3 patients were substance abuse, adenocarcinoma of the lung, and the patient's decision.(20)

5.2.3 Comparative analyses

As highlighted in section 5.2.1 the available evidence for IFN-alfa-2a/b is limited for the treatment of PV patients. There is significant heterogeneity in study design, reported end points and patient populations included in the identified studies, which makes it difficult to do formal comparative statistics for the comparison of ropeg-IFN-alfa-2b and IFN-alfa-2a/b. Hence, the comparison analyses for clinical question 2 will mostly be narrative.

The only end point reported by the majority of studies is the proportion of patients experiencing hematological response. Hence, only the proportion of patients experiencing hematological response will be compared quantitively. Based on dialogue with the DMC secretariate a naïve indirect treatment comparison (ITC) has been performed on the proportion of patients experiencing hematological response using available data from the PROUD-PV and CONTINUATION-PV studies for ropegIFN alfa-2b and data from Mascarenhas et al. 2022 for pegIFN alfa-2a. The ITC uses the Buchers method although the underlying heterogeneity of the studies means that the normal assumptions for a Bucher analysis is not met. Hence, the analysis should be interpreted with caution, but the results can serve as supportive information to the narrative comparison.

The following analyses are provided:

- proportion of patients experiencing complete hematological response (excl spleen criterion) at 12 months in Table 18
- proportion of patients experiencing complete hematological response (incl spleen criterion) at 12 months in Table 19
- proportion of patients experiencing complete hematological response (incl spleen criterion) at 36 months in Table 20. Data for complete hematological response without spleen criterion is not available in Mascarenhas et al. 2022

The point estimates of the ITCs indicates that treatment with ropegIFN alfa-2b (Besremi) results in a larger proportion of patients experiencing complete hematological response than pegIFN alfa-2a (Pegasys) irrespective of inclusion of the spleen criterion and time horizon, as supported by the risk ratios presented in the tables below, which ranges from 0.81 to 0.83. None of the analyses results in statistically significant differences.

The response estimates for HU and pegIFN alfa-2a (Pegasys) decreases at 36 months while the response to ropegIFN alfa-2b (Besremi) increases from the 12 months timepoint to the 36 months timepoint, supporting a potential long-term benefit from treatment with ropegIFN alfa-2b compared to HU and pegIFN alfa-2a.

Table 18 ITC - Proportion experiencing complete hematological response (excl spleen criterion) - 12 months

Trial	Besremi - n/N (%)	HU - n/N (%)	Absolute risk difference, % (95% CI)	Risk ratio/OR (95% CI)
PROUD-PV	53/123 (43%)	57/125 (46%)	-2.5% (-14.9%;9.9%)	0.94 (0.71 - 1.25)
Trial	**Pegasys - n/N (%)**	**HU - n/N (%)**	**Absolute risk difference, % (95% CI)**	**Risk ratio/OR (95% CI)**
Mascarenhas	39/82 (48%)	36/86 (42%)	5.7% (-9.3%;20.7%)	1.14 (0.81 - 1.59)
Indirect Comparison - Proportion experiencing complete hematological response (excl spleen criterion) - 12 mo			-8.0% (-22.2%;14.1%) p=0.3948	RR: 0.83 (0.53 - 1.30) p=0.4243

Table 19 ITC - Proportion experiencing complete hematological response (incl spleen criterion) - 12 months

Trial	Besremi - n/N (%)	HU - n/N (%)	Absolute risk difference, % (95% CI)	Risk ratio/OR (95% CI)

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PROUD-PV	27/127 (21%)	35/127 (28%)	-6.3% (-16.8%;4.2%)	0.77 (0.50 - 1.19)
Trial	**Pegasys - n/N (%)**	**HU - n/N (%)**	**Absolute risk difference, % (95% CI)**	**Risk ratio/OR (95% CI)**
Mascarenhas	29/82 (35%)	32/86 (37%)	-1.8% (-16.4%;12.7%)	0.95 (0.64 - 1.42)
Indirect Comparison - Proportion experiencing complete hematological response (incl spleen criterion) - 12 mo			-6.7% (-19.7%;17.1%) p=0.4870	RR: 0.81 (0.44 - 1.48) p=0.5077

Table 20 ITC - Proportion experiencing complete hematological response (incl spleen criterion) - 36 months

Trial	**Besremi - n/N (%)**	**HU - n/N (%)**	**Absolute risk difference, % (95% CI)**	**Risk ratio/OR (95% CI)**
PROUD-PV	38/90 (42%)	21/69 (30%)	11.8% (-3.1%;26.7%)	1.39 (0.90 - 2.13)
Trial	**Pegasys - n/N (%)**	**HU - n/N (%)**	**Absolute risk difference, % (95% CI)**	**Risk ratio/OR (95% CI)**
Mascarenhas	5/17 (29%)	3/17 (18%)	11.8% (-16.5%;40.0%)	1,67 (0,47 - 5,90)
Indirect Comparison - Proportion experiencing complete hematological response (incl spleen criterion) - 36 mo			-4.9% (-23.1%;65.6%) p=0.8386	RR: 0.83 (0.21 - 3.23) p=0.8030

The hematological responses across the included IFN studies are depicted Table 21, which clearly shows the varying estimates across type of interferon alfa, dosing, populations and time of assessment, ranging from 22% to 95%. The results from PROUD-PV and CONTINUATION-PV indicates that ropegIFN alfa-2b is within the range found in other IFN studies. Based on the development over time from the PROUD-PV to the CONTINUATION-PV the proportion of patients with hematological response increases, which aligns with the molecular structure and pharmacodynamics of ropegIFN alfa-2b.

Table 21 Overview of reported hematological response across IFN studies

Study	**Patient number/ IFN type**	**Dosing**	**Duration (median months)**	**Haemato-logical response (%)**	**Definition of hematologic response**
Clinical studies with ropegIFN alfa-2b					
PROUD-PV	127 PV ropegIFN alfa-2b	Starting dose: 100 µg increasing slowly to 450 µg every 2 weeks	12	43 (53/123)	Hct<45% without phlebotomy (at least 3 months since the last phlebotomy), PLTs<400 x 10^9 /L, WBCs<10 x 10^9/L
CONTINUATION-PV	95 PV ropegIFN alfa-2b	Median dose at 36 months: 425 µg every 2-4 weeks	36	71	Hct<45% without phlebotomy (at least 3 months since the last phlebotomy), PLTs<400 x 10^9 /L, WBCs<10 x 10^9/L

PEGINVERA	42 PV ropegIFN alfa-2b	Median dose: 227 µg every 2-4 weeks	7.8	64	Hct < 45% (without phlebotomy in the previous two months), PLT count ≤ 400≤10^9 /L, leukocyte count ≤ 10x10^9 cells/L, normal spleen size (measured via ultrasound), and absence of the thromboembolic events
Clinical studies with marketed IFN alfa preparations					
Masarova et al., 2017	ET = 40 PV = 43 (pegIFN alfa-2a)	450 µg/wk Reduced to 90 µg/wk	69	29 ET 33 PV	Hemoglobin <15.0 g/L without phlebotomy with complete resolution of palpable splenomegaly/symptoms in the absence of a thrombotic event
Quintas-Cardama et al., 2009	ET = 39 PV = 40 (pegIFN alfa-2a)	450 µg/wk Reduced to 90 µg/wk	21	80	<45% and <42% in females, WBC and platelet counts, and spleen size, without the use of phlebotomies, hydroxyurea, or anagrelide and in the absence of thromboembolic events
Kiladjian et al., 2008a	PV=37 (pegIFN alfa-2a)	90 µg/wk	31	95	Hematocrit (Hct) level lower than 45% in males and 42% in females without phlebotomy, absence of splenomegaly, and normal white blood cell (WBC) (<10x 10^9/L) and platelet counts (<400 x10^9/L)
Samuelsson et al., 2006	ET=21 PV = 21 (pegIFN alfa-2b)	30 µg/wk [0.5 µg/kg/wk]	24	69	Platelet count <400 x 10^9/L in patients who had a previous thromboembolic episode or ongoing microcirculatory symptoms or achieving a platelet count <600 x 10^9/L in asymptomatic patients who were without previous thromboembolic complications
Mascarenhas et al. 2022	PV = 43 (HU resistant and/or intolerant) (pegIFN alfa-2a)	45 µg/wk increasing to 180 µg/wk	12	28	<400 x 10^9/L, HCT to <45% without phlebotomy (for PV patients only), and WBC to <10 x 10^9/L; resolution of splenomegaly; and resolution of disease-related symptoms
	PV = 43 ET = 39 (HU resistant and/or intolerant) (pegIFN alfa-2a)	45 µg/wk increasing to 180 µg/wk	12	48	<400 x 10^9/L, HCT to <45% without phlebotomy (for PV patients only), and WBC to <10 x 10^9/L; resolution of splenomegaly; and resolution of disease-related symptoms **without spleen normalization**
Crisa et al. 2017	PV = 65	90 µg/wk	50	70	European LeukemiaNet 2009 criteria: hematocrit less than 45% without phlebotomy, platelet count less than or equal to 400 × 10^9/L, white blood cell count less than or equal to 10 ×

					10^9/L, and no disease-related symptoms
Huang et al. 2014	ET = 123 PV = 64 (IFN-alfa-2b) PV = 59 (Hydroxyurea)	3 million units three times a week	60	70.3 All 29.7 PV	Normalization of platelet counts (≤400 × 10^9/L) without thromboembolic events
Stauffer Larsen et al. 2013	ET = 19 PV = 75 PMF = 4 MPNu = 4 (pegIFN alfa-2a/b)	74 g/wk	42	95 ET 68 PV	Normalization of platelet and white cell counts, hematocrit <0.45 and no need of phlebotomy 3 months prior to date of follow-up

Adverse events were heterogeneous reported across the included studies. Based on the rates of discontinuation due to adverse events reported in PROUD-PV (5.5%) and CONTINUATION-PV (8%) for ropegIFN alfa-2b has lower rates of discontinuation compared to other pegIFN (MPN-RC 112: 13.9%(20); PVN1: 35.1%(4); Samuelsson et al.: 38.1%(9)).

6. Other considerations

6.1 JAK mutational burden on transformation risk to MF or AML for Besremi and comparators

As of the 60-month analysis, in the PROUD-PV/CONTINUATION-PV studies, there was only one case of disease progression: a patient who developed myelofibrosis. In contrast, in the control arm 2 patients had leukemic transformation and 2 developed myelofibrosis.

This generally compares favorably with data from PEGASYS studies:

- **Mascarenhas et al 2022**: no progression reported in IFN arm (N=82 in IFN arm, 39 ET and 43 PV; median duration 94.6 weeks – this study had a shorter period of follow-up and a smaller PV population than AOP's studies)(21)
- **Yacoub et al 2019**: Transformation to MF occurred in 1 PV patient. Of note, the population was smaller (N=50 PV)) and the follow-up time on this study was much shorter (82 weeks for PV) than in PROUD-PV/CONTINUATION-PV)(20)
- **Masarova et al 2017**: Seven (8%) of 83 PV/ET patients had disease progression while on therapy: six patients progressed to myelofibrosis and one patient's disease transformed to acute myeloid Leukaemia.(18)
- **Crisa et al 2017**: Disease progression to myelofibrosis or acute myeloid leukemia occurred in 1 patient only in peg-INF (MF), compared to three in HU (MF, 2 of these later developed AML) (median follow-up 75 months, N=30 peg-INF and 35 HU - non-randomised study)(8)

To determine progression of PV a very long observational period is required, which explains the scarcity of prospective data. A retrospective study by Abu-Zeinah et al. 2021 analysed MF-free survival and overall survival in 470 PV patients receiving IFNa, hydroxyurea or phlebotomy alone.(6) In both high and low-risk PV patients, a numerical difference between the groups was seen with the longest rates of 20-year MF-free survival and overall survival among INFa-treated patients, and in low-risk patients the difference was statistically significant: In low-risk patients, 20-year MFS

for rIFNα, HU, and PHL-O was 84%, 65% and 55% respectively (p < 0.001) and 20-year OS was 100%, 85% and 80% respectively (p = 0.44). In high-risk patients, 20-year MFS for rIFNα, HU, and PHL-O was 89%, 41% and 36% respectively (p = 0.19) and 20-year OS was 66%, 40%, 14% respectively (p = 0.016).(6) Furthermore, longer treatment duration with IFNa was associated with a lower risk of MF (HR: 0.91, p < 0.001), leading the authors to conclude that IFNa treatment of PV may prevent development of MF and prolong survival.(6)Figure from Abu-Zeinah et al, 2021(6):

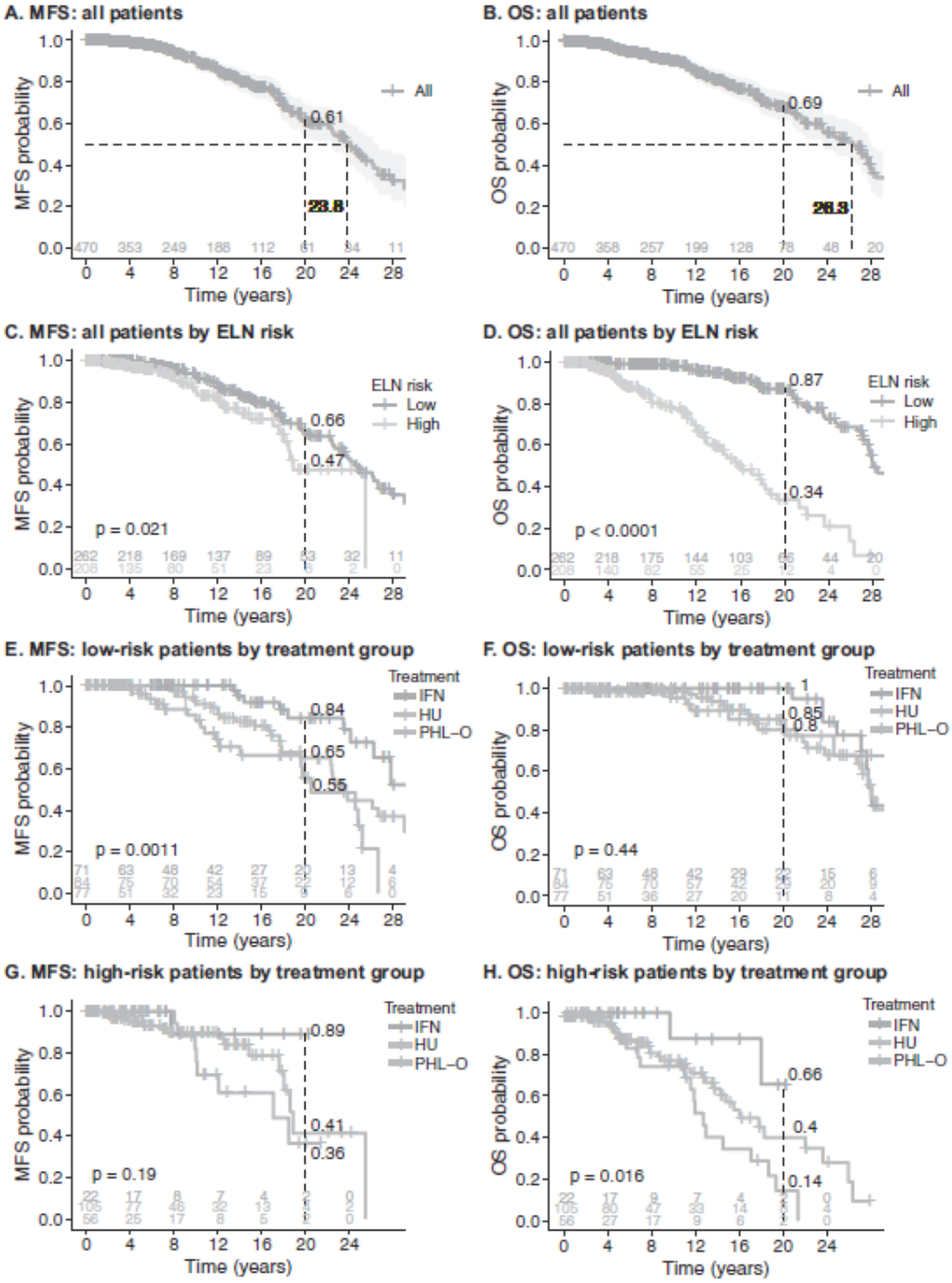


Fig. 1 Myelofibrosis-free survival (MFS) and overall survival (OS) of PV patients. A MFS of all patients, **B** OS of all patients, **C** MFS of all patients by ELN risk, **D** OS of all patients by ELN risk, **E** MFS of low-risk patients by treatment group, **F** OS of low-risk patients by treatment group, **G** MFS of high-risk patients by treatment group, **H** OS of high-risk patients by treatment group.

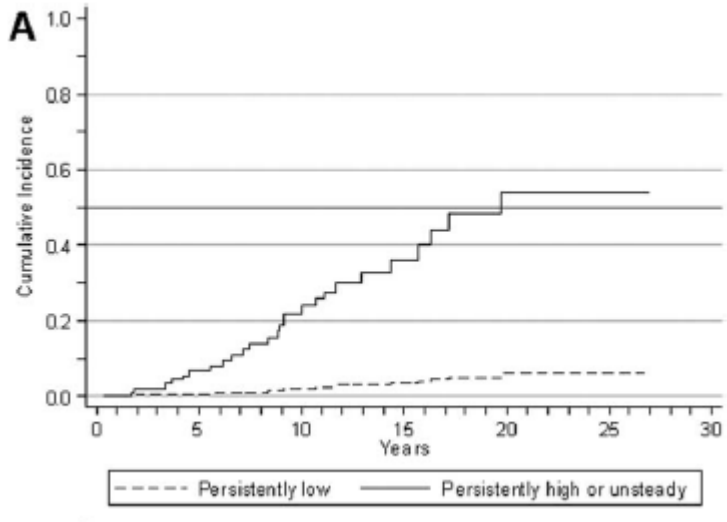
6.2 Correlation between JAK mutational burden and patient relevant clinical outcomes

In *JAK2*V617F-positive MPNs including PV, accumulating genomic instability generated by the gradually increasing pool of homozygous mutant *JAK2*V617F clones may promote disease progression.(22) In PV specifically, high *JAK2*V617F allele burden has been identified as a risk factor for the development of secondary myelofibrosis.(23, 24) Ropeginterferon alfa-2b has been shown to induce a sustained reduction of the *JAK2*V617F allele burden in patients with PV, and thus may potentially modify the natural course of the disease.(25)

Progression of PV to myelofibrosis or acute leukemia can occur many years after the original diagnosis, hindering the feasibility of prospective trials evaluating the impact of ropeginterferon alfa-2b treatment on these clinical outcomes. In a long-term retrospective study, an improved 20-year myelofibrosis-free survival (MFS) rate was reported among interferon alfa-treated patients with PV compared to those receiving hydroxyurea or phlebotomy only: 84%, 65% and 55% for rIFNα, HU, and PHL-O respectively ($p < 0.001$) in low-risk patients and 89%, 41% and 36% respectively ($p = 0.19$) in high-risk patients.(6) Results from the after 5 years of treatment with ropeginterferon alfa-2b in the prospective PROUD-PV/CONTINUATION-PV trials appear consistent with these findings; disease progression (including myelofibrosis and leukemic transformation) was observed in only a single patient treated with ropeginterferon alfa-2b compared with four patients the control arm. It should be noted that the PROUD-PV/CONTINUATION-PV studies were conducted in an early-stage PV population, and disease progression events within 5 years of follow-up were too rare to allow statistical comparison.

Given the difficulty of conducting interventional studies of a sufficient duration to evaluate disease progression in PV, there has been continued interest in the utility of *JAK2*V617F allele burden as a surrogate marker with prognostic potential.(24, 26, 27) An analysis of the correlation between *JAK2*V617F allele burden and myelofibrotic transformation conducted over more than 2400 years of cumulative patient follow up by Alvarez-Larran et al. 2014 demonstrated a higher risk of MF among PV patients with a persistently high or unstable *JAK2*V617F allele burden compared with patients who has a persistently low allele burden (<50%) (incidence rate ratio: 20.7, 95% CI: 6.5–65.4; $p < 0.001$) (Figure 7**)**.(24)

Figure 7 Risk of transformation to myelofibrosis according to the assessment of the JAK2V617F allele burden by monitoring the evolutionary pattern(24)



(24)Risk of transformation to myelofibrosis according to the assessment of the JAK2V617F allele burden by monitoring the evolutionary pattern. The cumulative incidence of transformation was computed taking death as a competing risk and further

adjusted for age, gender, type of diagnosis, time under P32, busulphan or melphalan. Persistently low refers to an allele burden <50%.

[redacted]

7. Conclusion

The documentation provided for ropegIFN alfa-2b (Besremi) has focused on the clinical questions raised by DMC in the protocol. Since the DMC protocol itself handles information on the disease and current treatment practice this has been given limited focus in the submitted documentation. The systematic literature search has been conducted as per instructions.

The present documentation has certain limitations. These include that the clinical questions only take into account comparison to HU and off-label pegIFN (Pegasys). Clinical practice and current Nordic MPN study group guidelines also include ruxolitinib (Jakavi) as a possible 3rd line option. Further, for clinical question 2, limited data are available and no head-to- head studies have been performed. vs. pegylated (or non-pegylated) interferon (which would have been considered an investigational medical product in clinical studies, requiring an additional treatment arm, and further increasing complexity of the study design).
Although there has not been any previously approved interferon available for PV, the need for the clinical benefit of interferons as cytoreductive therapy has made off-label interferons an important treatment option. However conventional interferons developed for other diseases and used off-label for PV do have limitations with respect to dosing interval and tolerability when used long-term for a chronic disease. Interferon is theoretically superior to other therapies for treating PV as long-standing molecular remissions can be achieved.(2-4). Interferon does not increase the risk of leukemia(5). Further, it follows from Abu-Zeinah et al. 2021(6) that interferon-alpha is the only disease-

modifying treatment for PV, also preventing the developing of myelofibrosis and has the potential of prolonging survival. Accordingly, interferons serve as an obvious treatment option for PV.

RopegIFN alfa-2b (Besremi) has been specifically developed and approved for PV in order to meet the need of an interferon with improved tolerability to be able to maintain effective long-term therapy. Structural innovations of RopegIFN alfa-2b (Besremi) with a single positional isomer and larger PEG molecule results in an extended elimination half-life compared to conventional interferons. This enables less frequent dosing (every other week, or monthly during maintenance therapy) and improved tolerability, supporting long-term patient compliance. RopegIFN alfa-2b (Besremi) is administered via a dose adjustable pen, suitable for home administration.

RopegIFN alfa-2b (Besremi) was approved in EU February 2019 and has since launch been introduced in several European countries with Austria and Germany being the most mature markets. Recently ropegIFN alfa-2b (Besremi) has also received approval by FDA. Reports from the clinical experience concludes that ropegIFN alfa-2b (Besremi) is a valuable addition to the treatment of patients with PV. Treatment with ropegIFN alfa-2b (Besremi) results in high and sustained haematological response rates and disease-modifying effects. This is corroborated by the fact that the allele burden of the JAK2 mutation, known as the driver mutation in PV, is significantly decreased in most patients treated with ropegIFN alfa-2b (Besremi) and in some patients is no longer detectable. From clinical practice it is reported that patients suffering from tolerability issues with Pegasys has been successfully switched to ropegIFN alfa-2b (Besremi) with better tolerability and compliance as outcome.(7)

As discussed in the DMC protocol PV is a chronic blood cancer that frequently leads to thrombosis and may transform into MF or AML. Consequently, it is crucial for these patients to have access to available and adequate treatment options. RopegIFN alfa-2b (Besremi) represents a therapeutic option developed specifically for treating PV, and provides improvement compared to conventional cytoreductive therapies performed either with hydroxyurea or off-label conventional interferons. Hence ropegIFN alfa-2b (Besremi) serves an important addition to the treatment options in PV. AOP Orphan would like to support Danish patients with availability of ropegIFN alfa-2b (Besremi) and hope for a positive outcome of the DMC with approval for patients in clinical question 1 and clinical question 2. AOP Orphan would like to stress that we are open for discussions on how ropegIFN alfa-2b (Besremi) could be introduced in Denmark.

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9. Appendices

9.1 Literature search

Table A1 Inclusion and exclusion criteria	
Inclusion criteria	Population: Patients with PV
	Intervention(s): Ropeginterferon alfa-2
	Comparator(s): peginterferon alfa-2a or b; Hydroxyurea
	Outcomes: as specified in the protocol
	Settings (if applicable): NA
	Study design: as specified in the protocol
	Language restrictions: as specified in the protocol
	Other search limits or restrictions applied: NA
Exclusion criteria	Population: NA
	Intervention(s): NA
	Comparator(s): NA
	Outcomes: NA
	Settings (if applicable): NA
	Study design: NA
	Language restrictions: NA
	Other search limits or restrictions applied: NA

Table 22 PubMed search results

Search number	Query	Search Details	Results
26	#16 AND #24 AND #25	((("myeloproliferative neoplasm*"[Title] OR "MPN"[Title] OR ("polycythemia rubra vera"[Title/Abstract] OR "polycythaemia rubra vera"[Title/Abstract] OR "polycythemia vera"[Title/Abstract] OR "polycythaemia vera"[Title/Abstract] OR "primary polycythemia"[Title/Abstract] OR "primary polycythaemia"[Title/Abstract]) OR "polycythemia vera"[MeSH Terms]) AND ("ropeginterferon*"[Title/Abstract] OR "besremi*"[Title/Abstract] OR "peginterferon*"[Title/Abstract] OR "pegasys*"[Title/Abstract] OR ("peginterferon alfa 2a"[Supplementary Concept] OR "peginterferon alfa 2b"[Supplementary Concept]) OR (("interferon alpha"[MeSH Terms] OR "interferon alpha 2"[MeSH Terms]) AND "polyethylene glycols"[MeSH Terms]) OR (("PEG"[Title/Abstract] OR "pegylated"[Title/Abstract] OR "monopegylated"[Title/Abstract] OR "polyethylene glycol*"[Title/Abstract]) AND ("interferon*"[Title/Abstract] OR "IFN"[Title/Abstract] OR "rIFN"[Title/Abstract] OR "ifnalpha*"[Title/Abstract] OR "ifnalfa*"[Title/Abstract] OR "ifnalpha*"[Title/Abstract])) OR (("interferon*"[Title/Abstract] OR "IFN"[Title/Abstract] OR "rIFN"[Title/Abstract]) AND ("alpha"[Title/Abstract] OR "alpha2a"[Title/Abstract] OR "alpha2b"[Title/Abstract] OR "alfa*"[Title/Abstract] OR "alpha*"[Title/Abstract])) OR ("ifnalpha*"[Title/Abstract] OR "ifnalfa*"[Title/Abstract] OR "ifnalpha*"[Title/Abstract]) OR ("interferon alpha"[MeSH Major Topic] OR "interferon alpha 2"[MeSH Terms]))) NOT ("case reports"[Publication Type] OR	101

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		"Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Guideline"[Publication Type] OR "Letter"[Publication Type] OR "News"[Publication Type] OR "Review"[Publication Type] OR "case report"[Title] OR "animal*"[Title] OR "mouse"[Title] OR "mice"[Title] OR "rat"[Title] OR "rats"[Title] OR ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))) AND ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR ("Controlled"[Title/Abstract] OR "group*"[Title/Abstract] OR "random*"[Title/Abstract] OR "placebo"[Title/Abstract] OR "Trial"[Title]) OR ("clinical trial"[Publication Type] OR "comparative study"[Publication Type] OR "multicenter study"[Publication Type] OR "observational study"[Publication Type] OR "cohort studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "retrospective studies"[MeSH Terms]) OR "clinical trial"[Title/Abstract] OR (("phase 2*"[Title/Abstract] OR "phase ii*"[Title/Abstract] OR "phase 3*"[Title/Abstract] OR "phase iii*"[Title/Abstract] OR "Comparative"[Title/Abstract]) AND ("Trial"[Title/Abstract] OR "Study"[Title/Abstract])) OR (("Observational"[Title/Abstract] OR "cohort*"[Title/Abstract] OR "prospective"[Title/Abstract] OR "retrospective*"[Title/Abstract] OR "Multicenter"[Title/Abstract] OR "multi-center"[Title/Abstract]) AND ("Study"[Title/Abstract] OR "analy*"[Title/Abstract])) OR ("registries"[MeSH Terms] OR "registry"[Title/Abstract] OR "nation-wide"[Title/Abstract] OR "nationwide"[Title/Abstract] OR "real-world"[Title/Abstract] OR "real-life"[Title/Abstract])) AND ("english"[Language] AND "hasabstract"[All Fields])	
25	eng[la] AND hasabstract	"english"[Language] AND "hasabstract"[All Fields]	21,150,046
24	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	"randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR ("Controlled"[Title/Abstract] OR "group*"[Title/Abstract] OR "random*"[Title/Abstract] OR "placebo"[Title/Abstract] OR "Trial"[Title]) OR ("clinical trial"[Publication Type] OR "comparative study"[Publication Type] OR "multicenter study"[Publication Type] OR "observational study"[Publication Type] OR "cohort studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "retrospective studies"[MeSH Terms]) OR "clinical trial"[Title/Abstract] OR (("phase 2*"[Title/Abstract] OR "phase ii*"[Title/Abstract] OR "phase 3*"[Title/Abstract] OR "phase iii*"[Title/Abstract] OR "Comparative"[Title/Abstract]) AND ("Trial"[Title/Abstract] OR "Study"[Title/Abstract])) OR (("Observational"[Title/Abstract] OR "cohort*"[Title/Abstract] OR "prospective"[Title/Abstract] OR "retrospective*"[Title/Abstract] OR "Multicenter"[Title/Abstract] OR "multi-center"[Title/Abstract]) AND ("Study"[Title/Abstract] OR "analy*"[Title/Abstract])) OR ("registries"[MeSH Terms] OR "registry"[Title/Abstract] OR "nation-wide"[Title/Abstract] OR "nationwide"[Title/Abstract] OR "real-world"[Title/Abstract] OR "real-life"[Title/Abstract])	8,735,181
23	Registries[mh] OR registry[tiab] OR nation-wide[tiab] OR nationwide[tiab] OR real-world[tiab] OR real-life[tiab]	"registries"[MeSH Terms] OR "registry"[Title/Abstract] OR "nation-wide"[Title/Abstract] OR "nationwide"[Title/Abstract] OR "real-world"[Title/Abstract] OR "real-life"[Title/Abstract]	319,288
22	(observational[tiab] OR cohort*[tiab] OR prospective[tiab] OR retrospective*[tiab] OR multicenter[tiab] OR multi-center[tiab]) AND (study[tiab] OR analy*[tiab])	("observational"[Title/Abstract] OR "cohort*"[Title/Abstract] OR "prospective"[Title/Abstract] OR "retrospective*"[Title/Abstract] OR "multicenter"[Title/Abstract] OR "multi-center"[Title/Abstract]) AND ("study"[Title/Abstract] OR "analy*"[Title/Abstract])	1,761,768
21	(phase 2*[tiab] OR phase II*[tiab] OR phase 3*[tiab] OR phase III*[tiab] OR comparative[tiab]) AND (trial[tiab] OR study[tiab])	("phase 2*"[Title/Abstract] OR "phase ii*"[Title/Abstract] OR "phase 3*"[Title/Abstract] OR "phase iii*"[Title/Abstract] OR "comparative"[Title/Abstract]) AND ("trial"[Title/Abstract] OR "study"[Title/Abstract])	313,637

20	clinical trial[tiab]	"clinical trial"[Title/Abstract]	172,59
19	Clinical Trial[pt] OR Comparative Study[pt] OR Multicenter Study[pt] OR Observational Study[pt] OR Cohort Studies[mh] OR Prospective Studies[mh] OR Retrospective Studies[mh]	"clinical trial"[Publication Type] OR "comparative study"[Publication Type] OR "multicenter study"[Publication Type] OR "observational study"[Publication Type] OR "cohort studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "retrospective studies"[MeSH Terms]	4,486,715
18	controlled[tiab] OR group*[tiab] OR random*[tiab] OR placebo[tiab] OR trial[ti]	"controlled"[Title/Abstract] OR "group*"[Title/Abstract] OR "random*"[Title/Abstract] OR "placebo"[Title/Abstract] OR "trial"[Title]	5,291,664
17	Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt]	"randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type]	645,707
16	#13 NOT (#14 OR #15)	(("myeloproliferative neoplasm*"[Title] OR "MPN"[Title] OR ("polycythemia rubra vera"[Title/Abstract] OR "polycythaemia rubra vera"[Title/Abstract] OR "polycythemia vera"[Title/Abstract] OR "polycythaemia vera"[Title/Abstract] OR "primary polycythemia"[Title/Abstract] OR "primary polycythaemia"[Title/Abstract]) OR "polycythemia vera"[MeSH Terms]) AND ("ropeginterferon*"[Title/Abstract] OR "besremi*"[Title/Abstract] OR "peginterferon*"[Title/Abstract] OR "pegasys*"[Title/Abstract] OR ("peginterferon alfa 2a"[Supplementary Concept] OR "peginterferon alfa 2b"[Supplementary Concept]) OR (("interferon alpha"[MeSH Terms] OR "interferon alpha 2"[MeSH Terms]) AND "polyethylene glycols"[MeSH Terms]) OR (("PEG"[Title/Abstract] OR "pegylated"[Title/Abstract] OR "monopegylated"[Title/Abstract] OR "polyethylene glycol*"[Title/Abstract]) AND ("interferon*"[Title/Abstract] OR "IFN"[Title/Abstract] OR "rIFN"[Title/Abstract] OR "ifnalpha*"[Title/Abstract] OR "ifnalfa*"[Title/Abstract] OR "ifnalpha*"[Title/Abstract])) OR (("interferon*"[Title/Abstract] OR "IFN"[Title/Abstract] OR "rIFN"[Title/Abstract]) AND ("alpha"[Title/Abstract] OR "alpha2a"[Title/Abstract] OR "alpha2b"[Title/Abstract] OR "alfa*"[Title/Abstract] OR "alpha*"[Title/Abstract])) OR ("ifnalpha*"[Title/Abstract] OR "ifnalfa*"[Title/Abstract] OR "ifnalpha*"[Title/Abstract]) OR ("interferon alpha"[MeSH Major Topic] OR "interferon alpha 2"[MeSH Terms]))) NOT ("case reports"[Publication Type] OR "Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Guideline"[Publication Type] OR "Letter"[Publication Type] OR "News"[Publication Type] OR "Review"[Publication Type] OR "case report"[Title] OR "animal*"[Title] OR "mouse"[Title] OR "mice"[Title] OR "rat"[Title] OR "rats"[Title] OR ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))	196
15	Animals[mh] NOT Humans[mh]	"animals"[MeSH Terms] NOT "humans"[MeSH Terms]	4,936,802
14	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti] OR animal*[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti]	"case reports"[Publication Type] OR "Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Guideline"[Publication Type] OR "Letter"[Publication Type] OR "News"[Publication Type] OR "Review"[Publication Type] OR "case report"[Title] OR "animal*"[Title] OR "mouse"[Title] OR "mice"[Title] OR "rat"[Title] OR "rats"[Title]	8,508,779
13	#4 AND #12	("myeloproliferative neoplasm*"[Title] OR "MPN"[Title] OR ("polycythemia rubra vera"[Title/Abstract] OR "polycythaemia rubra vera"[Title/Abstract] OR "polycythemia vera"[Title/Abstract] OR "polycythaemia vera"[Title/Abstract] OR "primary polycythemia"[Title/Abstract] OR "primary polycythaemia"[Title/Abstract]) OR "polycythemia vera"[MeSH Terms]) AND ("ropeginterferon*"[Title/Abstract] OR "besremi*"[Title/Abstract] OR "peginterferon*"[Title/Abstract] OR "pegasys*"[Title/Abstract] OR ("peginterferon alfa 2a"[Supplementary Concept] OR "peginterferon alfa 2b"[Supplementary Concept]) OR (("interferon alpha"[MeSH Terms] OR	411

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		"interferon alpha 2"[MeSH Terms]) AND "polyethylene glycols"[MeSH Terms]) OR (("PEG"[Title/Abstract] OR "pegylated"[Title/Abstract] OR "monopegylated"[Title/Abstract] OR "polyethylene glycol*"[Title/Abstract]) AND ("interferon*"[Title/Abstract] OR "IFN"[Title/Abstract] OR "rIFN"[Title/Abstract] OR "ifnalpha*"[Title/Abstract] OR "ifnalfa*"[Title/Abstract] OR "ifnalpha*"[Title/Abstract])) OR (("interferon*"[Title/Abstract] OR "IFN"[Title/Abstract] OR "rIFN"[Title/Abstract]) AND ("alpha"[Title/Abstract] OR "alpha2a"[Title/Abstract] OR "alpha2b"[Title/Abstract] OR "alfa*"[Title/Abstract] OR "alpha*"[Title/Abstract])) OR ("ifnalpha*"[Title/Abstract] OR "ifnalfa*"[Title/Abstract] OR "ifnalpha*"[Title/Abstract]) OR ("interferon alpha"[MeSH Major Topic] OR "interferon alpha 2"[MeSH Terms]))	
12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	"ropeginterferon*"[Title/Abstract] OR "besremi*"[Title/Abstract] OR "peginterferon*"[Title/Abstract] OR "pegasys*"[Title/Abstract] OR ("peginterferon alfa 2a"[Supplementary Concept] OR "peginterferon alfa 2b"[Supplementary Concept]) OR (("interferon alpha"[MeSH Terms] OR "interferon alpha 2"[MeSH Terms]) AND "polyethylene glycols"[MeSH Terms]) OR (("PEG"[Title/Abstract] OR "pegylated"[Title/Abstract] OR "monopegylated"[Title/Abstract] OR "polyethylene glycol*"[Title/Abstract]) AND ("interferon*"[Title/Abstract] OR "IFN"[Title/Abstract] OR "rIFN"[Title/Abstract] OR "ifnalpha*"[Title/Abstract] OR "ifnalfa*"[Title/Abstract] OR "ifnalpha*"[Title/Abstract])) OR (("interferon*"[Title/Abstract] OR "IFN"[Title/Abstract] OR "rIFN"[Title/Abstract]) AND ("alpha"[Title/Abstract] OR "alpha2a"[Title/Abstract] OR "alpha2b"[Title/Abstract] OR "alfa*"[Title/Abstract] OR "alpha*"[Title/Abstract])) OR ("ifnalpha*"[Title/Abstract] OR "ifnalfa*"[Title/Abstract] OR "ifnalpha*"[Title/Abstract]) OR ("interferon alpha"[MeSH Major Topic] OR "interferon alpha 2"[MeSH Terms])	91,618
11	Interferon-alpha[majr] OR Interferon alpha-2[mh]	"interferon alpha"[MeSH Major Topic] OR "interferon alpha 2"[MeSH Terms]	21,824
10	IFNα*[tiab] OR IFNalfa*[tiab] OR IFNalpha*[tiab]	"ifnalpha*"[Title/Abstract] OR "ifnalfa*"[Title/Abstract] OR "ifnalpha*"[Title/Abstract]	18,807
9	(interferon*[tiab] OR IFN[tiab] OR rIFN[tiab]) AND (α[tiab] OR α2a[tiab] OR α2b[tiab] OR alfa*[tiab] OR alpha*[tiab])	("interferon*"[Title/Abstract] OR "IFN"[Title/Abstract] OR "rIFN"[Title/Abstract]) AND ("alpha"[Title/Abstract] OR "alpha2a"[Title/Abstract] OR "alpha2b"[Title/Abstract] OR "alfa*"[Title/Abstract] OR "alpha*"[Title/Abstract])	81,534
8	(PEG[tiab] OR pegylated[tiab] OR monopegylated[tiab] OR polyethylene glycol*[tiab]) AND (interferon*[tiab] OR IFN[tiab] OR rIFN[tiab] OR IFNα*[tiab] OR IFNalfa*[tiab] OR IFNalpha*[tiab])	("PEG"[Title/Abstract] OR "pegylated"[Title/Abstract] OR "monopegylated"[Title/Abstract] OR "polyethylene glycol*"[Title/Abstract]) AND ("interferon*"[Title/Abstract] OR "IFN"[Title/Abstract] OR "rIFN"[Title/Abstract] OR "ifnalpha*"[Title/Abstract] OR "ifnalfa*"[Title/Abstract] OR "ifnalpha*"[Title/Abstract])	8,783
7	(Interferon-alpha[mh] OR Interferon alpha-2[mh]) AND Polyethylene Glycols[mh]	("interferon alpha"[MeSH Terms] OR "interferon alpha 2"[MeSH Terms]) AND "polyethylene glycols"[MeSH Terms]	5,962
6	peginterferon alfa-2a[nm] OR peginterferon alfa-2b[nm]	"peginterferon alfa 2a"[Supplementary Concept] OR "peginterferon alfa 2b"[Supplementary Concept]	5,494
5	ropeginterferon*[tiab] OR besremi*[tiab] OR peginterferon*[tiab] OR pegasys*[tiab]	"ropeginterferon*"[Title/Abstract] OR "besremi*"[Title/Abstract] OR "peginterferon*"[Title/Abstract] OR "pegasys*"[Title/Abstract]	3,36
4	#1 OR #2 OR #3	"myeloproliferative neoplasm*"[Title] OR "MPN"[Title] OR "polycythemia rubra vera"[Title/Abstract] OR "polycythaemia rubra vera"[Title/Abstract] OR "polycythemia vera"[Title/Abstract] OR "polycythaemia vera"[Title/Abstract] OR "primary polycythemia"[Title/Abstract] OR "primary polycythaemia"[Title/Abstract] OR "polycythemia vera"[MeSH Terms]	10,232

3	Polycythemia Vera[mh]	"polycythemia vera"[MeSH Terms]	6,308
2	polycythemia rubra vera[tiab] OR polycythaemia rubra vera[tiab] OR polycythemia vera[tiab] OR polycythaemia vera[tiab] OR primary polycythemia[tiab] OR primary polycythaemia[tiab]	"polycythemia rubra vera"[Title/Abstract] OR "polycythaemia rubra vera"[Title/Abstract] OR "polycythemia vera"[Title/Abstract] OR "polycythaemia vera"[Title/Abstract] OR "primary polycythemia"[Title/Abstract] OR "primary polycythaemia"[Title/Abstract]	7,102
1	Myeloproliferative Neoplasm*[ti] OR MPN[ti]	"myeloproliferative neoplasm*"[Title] OR "MPN"[Title]	2,462

Table 23 Cochrane CENTRAL search results

ID	Search	Hits
#1	(myeloproliferative next neoplasm* or MPN):ti	105
#2	((polycythemia or polycythaemia) near/2 (vera or primary)):ti,ab,kw	424
#3	#1 or #2	491
#4	(ropeginterferon next alpha2b or peginterferon next alpha* or recombinant next alpha2 next interferon):kw	500
#5	(alpha2* next interferon):kw	325
#6	(ropeginterferon* or besremi* or peginterferon* or pegasys*):ti,ab	2365
#7	((PEG or pegylated or monopegylated or polyethylene next glycol*) near/3 (interferon* or IFN or rIFN or IFNα* or IFNalfa* or IFNalpha*)):ti,ab	2825
#8	((interferon* or IFN or rIFN) near/3 (α or α2a or α2b or alfa* or alpha*)):ti,ab	7114
#9	(IFNα* or IFNalfa* or IFNalpha*):ti,ab	1549
#10	#4 or #5 or #6 or #7 or #8 or #9	9532
#11	#3 and #10	73
#12	(clinicaltrials.gov or trialsearch):so	391103
#13	NCT*:au	221718
#14	#12 or #13	391289
#15	#11 not #14	63
#16	pubmed:an	745634
#17	#15 not #16	44

Table 24 References excluded based on full-text screening

Reference	Title	Exclusion criteria
Them 2015	Molecular responses and chromosomal aberrations in patients with polycythemia vera treated with peg-proline-interferon alpha-2b	Wrong outcomes
Ianotto 2018	Benefits and pitfalls of pegylated interferon-α2a therapy in patients with myeloproliferative neoplasm-associated myelofibrosis: a French Intergroup of Myeloproliferative neoplasms (FIM) study	Wrong outcomes
Abu-Zeinah 2021	Interferon-alpha for treating polycythemia vera yields improved myelofibrosis-free and overall survival.	Wrong outcomes

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Gowin 2017	Pegylated interferon alpha - 2a is clinically effective and tolerable in myeloproliferative neoplasm patients treated off clinical trial	Wrong patient population
Landtblom 2021	Risk of infections in patients with myeloproliferative neoplasms-a population-based cohort study of 8363 patients.	Wrong outcomes
Stasi 1997	Efficacy and safety of human leucocyte interferon-alpha treatment in patients younger than 60 years of age with polycythaemia vera	Wrong patient population (only 14 patients)
Nand 1996	Leukemogenic risk of hydroxyurea therapy in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis	Wrong comparator
Masarova 2017	Histomorphological responses after therapy with pegylated interferon α-2a in patients with essential thrombocythemia (ET) and polycythemia vera (PV).	Wrong outcomes

9.2 Main characteristics of included studies

Table A2 Main study characteristics	
Trial name	PROUD-PV and CONTINUATION-PV
NCT number	NCT01949805 and NCT02218047
Objective	Demonstrate non-Inferiority of ropegIFN alfa-2b versus hydroxyurea in terms of disease response rate in patients diagnosed with PV with the mandatory presence of JAK2 V617F mutation, either HU naïve or currently treated or pre-treated with HU
Publications – title, author, journal, year	Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomized, non-Inferiority, phase 3 trial and its extension study, Gisslinger et al., Lancet Haematol, 2020
Study type and design	Open-label, randomized, multicentre, controlled, parallel-arm, phase III study (PROUD-PV). CONTINUATION-PV was an open-label extension study of PROUD-PV.
Follow-up time	Median follow-up was 182.1 weeks (IQR 166.3-201.7) in the ropeginterferon alfa-2b and 164.5 weeks (144.4-169.3) in the standard therapy group in PROUD-PV. CONTINUATION-PV provided additional five year follow-up data.
Population (inclusion and exclusion criteria)	Inclusion Criteria: 1. 18 years or older 2. Diagnosis of Polycythemia Vera according to the WHO 2008 criteria (Barbui et al, 2011) with the mandatory presence of JAK2V617F mutation as the major disease criterion. 3. For previously cytoreduction untreated patients - documented need of cytoreductive treatment o leukocytosis (WBC>10G/L for two measurements within one week) 4. For patients currently treated or pre-treated with HU, all of the following criteria:

Table A2 Main study characteristics

- being non responders (as defined by the response criteria for primary endpoint)
- total HU treatment duration shorter than three years
- no documented resistance or intolerance as defined by modified Barosi et al, 2009 criteria

5. Hospital Anxiety and Depression Scale (HADS) score 0-7 on both subscales
6. Patients with HADS score of 8-10 inclusive on either or both of the subscales may be eligible following psychiatric assessment that excludes clinical significance of the observed symptoms in the context of potential treatment with an interferon alfa
7. Signed written informed consent

Exclusion Criteria:

1. Any systematic cytoreduction for PV prior study entry with exception of HU for shorter than 3 years (see respective inclusion criterion)
2. Any contraindication to any of the IMPs (pegylated interferon or hydroxyurea) or their excipients
3. Any systemic exposure to a non-pegylated or pegylated interferon alfa
4. Documented autoimmune disease at screening or in the medical history
5. Clinically relevant pulmonary infiltrates, pneumonia, and pneumonitis at screening
6. Systemic infections, e.g. hepatitis B, hepatitis C, or HIV at screening
7. Known PV-related thromboembolic complications in the abdominal area (e.g. portal vein thrombosis, Budd-chiari syndrome) and/or splenectomy in the medical history
8. Any investigational drug less than 6 weeks prior to the first dose of study drug or not recovered from effects of prior administration of any investigational agent
9. History or presence of depression requiring treatment with antidepressant
10. HADS score equal to or above 11 on either or both of the subscales
11. Any risk of suicide at screening or previous suicide attempts
12. Any significant morbidity or abnormality which may interfere with the study participation
13. Pregnancy and breast-feeding females of reproductive potential and males not using effective means of contraception
14. History of active substance or alcohol abuse within the last year
15. Evidence of severe retinopathy (e.g. cytomegalovirus retinitis, macular degeneration) or clinically relevant ophthalmological disorder (due to diabetes mellitus or hypertension)
16. Thyroid dysfunction not adequately controlled

Table A2 Main study characteristics	
	17. Patients tested positively with TgAb and / or TPOAb at screening 18. History of major organ transplantation 19. History of uncontrolled severe seizure disorder 20. Leukocytopenia at the time of screening 21. Thrombocytopenia at the time of screening 22. History of malignant disease, including solid tumours and hematological malignancies (except basal cell and squamous cell carcinomas of the skin and carcinoma in situ of the cervix that have been completely excised and are considered cured) within the last 3 years
Intervention	Patients were randomly assigned 1:1 to ropeginterferon alfa-2b (n=127 subcutaneously every 2 weeks, starting at 100 µg) or hydroxyurea (n= 127 orally starting at 500 mg/day).
Baseline characteristics	

	PROUD-PV		CONTINUATION-PV*	
	Ropeginterferon alfa-2b (n=127)	Hydroxyurea (n=127)	Ropeginterferon alfa-2b (n=95)	Best available treatment (n=76
Female	68 (54%)	67 (53%)	48 (51%)	40 (53%)
Male	59 (46%)	60 (47%)	47 (49%)	36 (47%)
Age, years				
Median	60·0 (52·0–66·0)	60·0 (48·0–67·0)	58·0 (50·0–64·0)	59·0 (49·0–65·5)
Range	30–85	21–81	30–85	32–79
Hydroxyurea pretreated	45 (35%)	37 (29%)	30 (32%)	20 (26%)
Median duration of previous hydroxyurea therapy, months†	10·2 (2·1–21·3)	7·9 (2·7–19·2)	9·5 (2·8–25·1)	8·2 (2·6–23·0)
Median duration of polycythaemia vera, months†	1·9 (0·7–11·2)	3·6 (0·7–20·0)	1·8 (0·6–6·8)	1·6 (0·7–15·1)
Previous thromboembolic event	25 (20%)	23 (18%)	21 (22%)	14 (18%)
Positive status for *JAK2* Val617Phe mutation§				
Number	126 (99%)	125 (98%)	94 (99%)	74 (97%)
Mean allele burden, %	41·9% (24)	42·8% (24)	42·8% (23)	42·9% (23)
Median haematocrit, %	47·1% (44·2–51·3)	48·0% (45·0–52·2)	47·7% (44·4–52·0)	49·9% (46·2–53·1)
Median platelet count, 10^9/L	485·0 (350·0–671·0)	452·0 (329·0–666·0)	488·0 (350·0–701·0)	451·0 (329·0–678·5)
Median leucocyte count, 10^9/L	10·6 (8·0–13·4)	10·5 (7·9–14·5)	10·9 (8·0–14·6)	11·3 (8·7–15·1)
Median spleen size, cm	13·1 (11·0–15·0)	13·0 (11·5–15·2)	13·5 (11·5–15·0)	12·8 (11·3–15·5)
Presence of splenomegaly¶	12 (9%)	15 (12%)	7 (7%)	8 (11%)

Primary and secondary endpoints	The primary endpoint in PROUD-PV was disease response rate at Month 12 defined as haematocrit <45% without phlebotomy (at least 3 months since last phlebotomy), platelets <400x109/L, leukocytes <10x109/L (these 3 variables defining the complete haematological response) and normal spleen size (defined as longitudinal diameter ≤12 cm for females and ≤13 cm for males). Secondary endpoints were: • Efficacy: disease response rate over time, time to first disease response, disease response duration, number of phlebotomies performed, molecular response and haematological parameters (haematocrit, leukocytes, platelets, erythrocytes) and spleen size change from baseline to last patient visit. • Safety. • Quality of life (assessed on EQ-5D-3L questionnaire) and change of JAK2 V617F allelic burden over time were also analysed.

Table A2 Main study characteristics	
	A post-hoc non-Inferiority analysis of the disease response rate defined as the complete haematological response (without spleen size normality) was performed with a non-Inferiority margin of -20.0%. The reason for changing the primary endpoint was that significant splenomegaly was only present in a few patients at baseline and spleen size fluctuations observed during the trial were small in the range of that observed also in a healthy population.
Method of analysis	Analysis of the primary endpoint (disease response defined as complete haematological response with spleen size normality) was performed in the FAS population via a non-Inferiority unilateral test (α = 2.5%) using the Cochran-Mantel-Haenszel method for estimation, with: • H0: ropegIFN alfa-2b inferior to HU: pT ≤pR - 0,1050 (95% CI upper limit of the response rate difference between both arms ≤-10,5%), where pT was the response rate in ropegIFN alfa-2b arm et pR the response rate in hydroxyurea arm. • H1: non-Inferiority of ropegIFN alfa-2b versus HU: pT >pR - 0,1050 (95% CI lower limit of the response rate difference >-10,5%). • The chosen non-Inferiority margin was based on an assumed overall response rate of 25% after 12 months of study treatment and allowing a random fluctuation of response rates of 4%. A post-hoc non-Inferiority analysis of the disease response rate defined as the complete haematological response (without spleen size normality) was performed with a non-Inferiority margin of -20.0%. Secondary efficacy endpoints analysis was performed for exploratory purposes using descriptive analysis and standard statistical tests.
Subgroup analyses	NA

Table A2 Main study characteristics	
Trial name	PEGINVERA
NCT number	NCT01193699
Objective	Identification of the maximum tolerated dose (MTD) of the investigational medicinal product. Moreover, the safety and tolerability will be assessed and an exploratory analysis of efficacy and biomarker modulation will be performed.
Publications – title, author, journal, year	Ropeginterferon alfa-2b, a novel IFNa-2b, induces high response rates with low toxicity in patients with polycythemia vera, Gisslinger et al., Blood, 2015
Study type and design	Open-label, Prospective, Multicentre, Phase I/II Dose Escalation Study
Follow-up time	Median follow-up duration reported in this study is 80 weeks (range, 4-174)

Table A2 Main study characteristics	
Population (inclusion and exclusion criteria)	Inclusion Criteria: 1. Written informed consent obtained prior to any study specific screening activities and able to comply with this protocol. 2. Patients age ≥18 years 3. Confirmed diagnosis of PV according to either the WHO criteria (2008, appendix 6) or the PSVG (appendix 7) criteria plus JAK-2 positivity, including newly diagnosed, pre-treated and on cytoreductive therapy. 4. Eastern Cooperative Oncology Group performance status ≤ 2 5. If female of childbearing potential - have a negative urine pregnancy test result within 7 days prior to the scheduled first application of investigational product and agree to employ adequate birth control measures for the duration of the study Exclusion Criteria: 1. Diagnosis of any other myeloproliferative disorder 2. Any clinically significant illness or surgery within 4 weeks prior to dosing 3. Systemic infections, e.g. hepatitis B, hepatitis C, or HIV at screening 4. Uncontrolled hypertension (systolic > 150 mmHg and diastolic > 100 mmHg, or clinically significant (i.e. active) cardiovascular disease: CVA/stroke (≤ 3 months prior to enrolment), myocardial infarction (≤ 3 months prior to enrolment), significant coronary artery stenosis, unstable angina, New York Heart Association (NYHA) Class 2 or greater Congestive heart failure, or serious cardiac arrhythmia requiring medication. 5. Previous treatment with Interferon for PV 6. Concurrent treatment with cytoreductive agents other than Hydroxyurea and investigational agents of any type 7. History of malignant disease, including solid tumours and haematological malignancies (except basal cell and squamous cell carcinomas of the skin and carcinoma in situ of the cervix that have been completely excised and are considered cured) within the last 3 years 8. History of severe allergic (like anaphylaxis) or hypersensitivity reactions (like angioedema), any known or suspected intolerance to the investigational product. 9. Use of any investigational drug or participation in any investigational drug study within the last 4 weeks 10. Clinically significant history or known presence of psychiatric disorders, including but not limited to depression, anxiety and sleep disorders 11. Organ transplant, past or planned 12. Inadequate liver function defined by serum (total) bilirubin > 2,5 x ULN and/ or AST and ALT > 2,5 x ULN 13. Clinically significant ECG findings

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Table A2 Main study characteristics	
	14. History of renal disease requiring haemodialysis or seizure disorder requiring anticonvulsant therapy 15. Pregnant or lactating females (pregnancy test to be assessed within 7 days prior to study treatment start) 16. Acute or chronic infections or autoimmune diseases (collagen diseases, polyarthritis, immune thrombocythemia, thyroiditis, psoriasis, lupus nephritis or any other autoimmune disorder).
Intervention	RopegIFN alfa-2b (n=51) The starting dose in phase 1 was 50mg, based on preclinical toxicology data. Intrapatient dose escalation was allowed throughout the entire study, but the dose administered to the patients could not exceed the highest dose under the exploration (before defining the MTD) or the MTD. After the MTD was defined, ropeginterferon alfa-2b dosing was adjusted based primarily on efficacy and long-term tolerability. The mean administered dose in the study was 263 mg (±104) every 14 days.
Baseline characteristics	**Table 1. Baseline characteristics** **Parameter** / **Value** Safety population, patients (all treated) — 51 Age at study entry (y), median (min-max) — 56 (35-82) Male, n (%) — 31 (61%) Splenomegaly (length >12 cm on sonograph), patients (%) — 31 (61%) Spleen length on sonograph, median in cm (min-max) — 13.1 (8.0-22.0) Patients with phlebotomies in 3 mo before screening, n (%) — 31 (61%) Number of phlebotomies in 3 mo before screening, median (range) — 2 (1-8) PV history before entry (mo), median (Q1-Q3) — 17.0 (3.6-68.8) Major cardiovascular events in the med history, patients (%) — 11 (22%) HU pretreated, patients (%) — 17 (33%) Hct, %, median (min-max) — 44.8 (36.9-53.8) Platelets, G/L, median (min-max) — 429 (148-1016) WBC, G/L, median (min-max) — 11.1 (4.7-30.9) *JAK2* V617F–positive — 100% %V617F allelic burden, median (min-max) — 41% (2-100) Hct, hematocrit; WBC, white blood cells.
Primary and secondary endpoints	Primary endpoint: • Maximum tolerated dose (MTD) Secondary endpoints: • Hematologic and molecular response. For the hematologic response, complete response (CR) was defined using the modified European Leukemia Net criteria.
Method of analysis	Methods of descriptive analysis were used for analysis of preliminary study data. Pearson's and Spearman correlation coefficients and corresponding p-values were calculated in order to evaluate correlation between dose (or treatment exposure) and safety or efficacy data. Change from baseline in JAK2 allelic burden was tested by Wilcoxon Signed Rank test. In addition, current study data were used for exploration of dose effect, effect of previous HU treatment and duration of PV on hematological

Table A2 Main study characteristics	
	and molecular variables using regression methods. Specifically, hematological response and molecular response (as class variables) were analyzed using ordinal logistic regression. JAK2-V617F allelic burden was analyzed using linear regression. Generalized estimating equations method was used for computation of the models in order to consider the longitudinal character of the data. Further, times to responses were analyzed using the Kaplan-Meier method. The statistical tests performed were carried out for exploratory purposes
Subgroup analyses	NA

Table A2 Main study characteristics (Complete this table for each included study)	
Trial name	NA
NCT number	NCT00452023
Objective	Establish the efficacy and tolerability of PEG-IFN-alfa-2a in patients with MPNs and the impact of this therapy on the dynamics of JAK2V617F mutation
Publications – title, author, journal, year	Pegylated interferon alfa-2a in patients with essential thrombocythaemia or polycythaemia vera: a post-hoc, median 83 month follow-up of an open-label, phase 2 trial, Masarova et al., Lancet Haematol., 2017 Molecular analysis of patients with polycythemia vera or essential thrombocythemia receiving pegylated interferon alfa-2a, Quintas-Cardama et al., Blood, 2013 Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera, Quintas-Cardama et al., J Clin Oncol, 2009.
Study type and design	Prospective, open-label, single-center, phase II study.
Follow-up time	Median follow-up of 84 months (IQR: 69–94 months)
Population (inclusion and exclusion criteria)	Inclusion Criteria: 6. Following diagnoses: -ET: Patients with PLT > 600 x10 9 /l documented in the past 12 months; hyperplasia of marrow megakaryocytes in the absence of identifiable cause of thrombocytosis and in the absence of Ph chromosome. Patients with ET and lower PLT will be eligible if attributable to prior ET therapy. --PV: Patients should have Hb >/= 15g/dl (except if patient is having phlebotomies done) and documented past diagnosis. 7. Performance status </= 2 (ECOG scale).

Table A2 Main study characteristics (Complete this table for each included study)	
	8. Age greater than 18 years since disease is extremely rare in younger age group. 9. Adequate liver function: total bilirubin of </= 2.0 mg/dl (except for patients with Gilbert's Syndrome) and AST (SGOT) or ALT (SGPT) < 3 X ULN (or < 5 X ULN if considered due to tumor), and renal function (serum creatinine </= 2.0 mg/dl). 10. Signed informed consent indicating that patients are aware of the investigational nature of this study in keeping with the policies of the M.D. Anderson Cancer Center. The only acceptable consent form is the one approved by the M.D. Anderson Cancer Center IRB. 11. Willingness and ability to comply with the requirements of the protocol for the duration of the study. 12. Patients must have been off chemotherapy for 1 week prior to beginning Pegasys and have recovered from the toxic effects of that therapy. Patients may have received hydroxyurea or anagrelide immediately before study entry, and may continue into therapy if treating physician determines this is in the best interest of the patient. Exclusion Criteria: 17. Pregnant or lactating women. 18. Patients with prior history of another malignancy or concurrent malignancy, except for the following: basal cell carcinoma of the skin, carcinoma in situ of the cervix, or other malignancies if the patient is disease free >3 years. 19. Patients with history of ischemic retinopathy. 20. Patients with history of severe cardiac disease: NYHA Functional Class III or IV, myocardial infarction within 6 months, uncontrolled ventricular tachyarrhythmias or unstable angina. 21. Patients with history of medically significant psychiatric disease if not controlled, especially endogenous depression (does not include reactive depression post-cancer diagnosis), psychosis and bipolar disease. 22. Patients with seizure disorders requiring anticonvulsant therapy. 23. Patients with known infection with HBV, HIV, or other active systemic infection. 24. Patients with known autoimmune disease except for rheumatoid arthritis. 25. Patients with renal disease on hemodialysis. 26. Patients taking continuous or chronic high-dose systemic steroids; if discontinued, there must be a minimum washout period of one month before study drug is begun. 27. Patients with known hypersensitivity to PEG-IFN alfa-2a or its components.
Intervention	IFN-alfa2a Starting dose 90 µg injection under the skin once a week.

Table A2 Main study characteristics (Complete this table for each included study)	
	The first three patients in the study received PEG-IFN-alfa-2a subcutaneously at 450 µg weekly. As a result of poor tolerance, the starting dose was decreased in a stepwise manner by 90-µg decrements based on tolerance (360 µg weekly, n=3; 270 µg weekly, n=19; 180 µg weekly, n=26) to 90 µg weekly, which was subsequently used as a starting dose in the remainder of patients (n=28) accrued to the study. PEG-IFN-alfa-2a was administered for as long as the patient obtained a clinical benefit
Baseline characteristics	

Table 1. Baseline Demographics and Clinical Characteristics of Patients With PV or ET Receiving Therapy With PEG-IFN-α-2a

Characteristic	PV (n = 40) No. of Patients	PV (n = 40) %	ET (n = 39) No. of Patients	ET (n = 39) %
Age, years				
Median	53		50	
Range	23-77		18-75	
Months from diagnosis				
Median	54		33	
Range	0-360		0-285	
JAK2^{V617F} positive	38	95	19	49
JAK2^{V617F} allele burden, %				
Median	64		23	
Range	18.5-94.6		2.9-55.5	
Abnormal karyotype	2	5	7	18
Splenomegaly	5	13	0	0
Spleen span below left costal margin for five patients, cm				
Median	5			
Range	4-12			
WBC, $\times 10^9$/L				
Median	12.1		7.2	
Range	3.7-49.3		2.8-13.3	
Hemoglobin, g/dL				
Median	14.4		13.2	
Range	11.1-18.8		8.9-16.6	
Platelets, $\times 10^9$/L				
Median	491		698	
Range	128-1,087		236-2,690	
No. of prior therapies				
Median	1		2	
Range	0-4		0-4	
Prior therapy				
Phlebotomy	30	75	0	0
Hydroxyurea	18	45	27	69
Anagrelide	3	8	21	54
Interferon alfa	7	18	5	13
Previously untreated	6	15	9	23

Abbreviations: PV, polycythemia vera; ET, essential thrombocythemia; PEG-IFN-α-2a, pegylated interferon alfa-2a.

Primary and secondary endpoints	Primary endpoint:

Table A2 Main study characteristics (Complete this table for each included study)	
	• Number of Patients with Complete Response (CR) or Partial Response (PR) [Time Frame: 3 months] CR = Reduction of PLT to <440x109/l and disappearance of thromboembolic events, without the use of anagrelide or hydroxyurea. PR = Reduction of PLT by 50% but still >440x109/l or reduction of thromboembolic events by 50%, without the use of anagrelide or hydroxyurea Secondary endpoints: • Toxicity
Method of analysis	Responses and clinical data were analyzed using descriptive statistics. Fisher's exact test was used to compare responses in different groups for categorical variable. The Mann-Whitney U or Kruskal-Wallis tests were used to compare continuous variables, as indicated. Evaluations included complete physical examination every 3 to 6 months; CBC and comprehensive biochemistry panel every other week for 4 weeks, then every 1 to 2 months for 12 months, and then every3 months; thyroid function tests every6 to 12 months; and BM aspiration and biopsy every 3 to 6 months, with JAK2V617F quantitation and cytogenetics when in complete remission. Toxicity was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). CHRin patients with ET was defined as normalization of platelet counts (≤ $400x10^9$/L) without the use of hydroxyurea or anagrelide and in the absence of thromboembolic events. Partial hematologic response required at least a 50% reduction in platelet counts (but still >$400x10^9$/L). CHR in patients with PV was defined as normalization of hematocrit (<45% in males and <42% in females),WBC and platelet counts, and spleen size, without the use of phlebotomies, hydroxyurea, or anagrelide and in the absence of thromboembolic events. Partial hematologic response required the documentation of at least a 50% reduction in phlebotomy requirements or spleen size.
Subgroup analyses	NA

Table A2 Main study characteristics	
Trial name	Crisa et al. 2017
NCT number	NA
Objective	Not reported
Publications – title, author, journal, year	Can pegylated interferon improve the outcome of polycythemia vera patients?, Crisa et al., J Hematol Oncol., 2017
Study type and design	Observational study comparing peg-IFN with HU in a population of PV patients below 65 years
Follow-up time	Median follow-up of 75 months (range 14–80 months).

Table A2 Main study characteristics	
Population (inclusion and exclusion criteria)	Inclusion Criteria: 1. WHO 2008 classification 2. aged 65 years or younger 3. normal cardiac, renal, and liver function 4. without history of autoimmune disease. Exclusion Criteria not reported
Intervention	Peg-IFN (n=30) Hydroxyurea (n=35) Dosing not reported
Baseline characteristics	**Table 1** Patients characteristics

	peg-INF group	HU group	*p* value
Sex, *n* (%)			
Male	19 (63)	23 (66)	0.841
Female	11 (37)	12 (34)	
Age at diagnosis (years)			
Median (range)	49 (18–64)	53 (29–65)	0.180
Age at treatment start			
Median (range)	54 (32–65)	55 (36–65)	0.645
Time from diagnosis to study entry (months)			
Median (range)	11 (0–179)	18 (0–169)	0.631
Palpable spleen			
N (%)	16 (55)	14 (42)	0.316
Cardiovascular risk factors			
N (%)	16 (53)	20 (57)	0.758
Previous thrombosis			
N (%)	5 (17)	9 (26)	0.376

Primary and secondary endpoints	Primary endpoint: • Complete response Secondary endpoints: • safety
Method of analysis	Patients' characteristics were compared using Fisher's exact test for the categorical variables and the Kruskal-Wallis test for the continuous ones. Overall survival was estimated from the study start until death or last follow-up by Kaplan-Meier method; any statistical difference between curves was assessed by log-rank test
Subgroup analyses	NA

Table A2 Main study characteristics	
Trial name	Stauffer Larsen et al. 2013
NCT number	NA
Objective	This study aimed to report on clinical and molecular data in the largest cohort o JAK2V617F mutant MPN patients being treated long-term with rIFN-alfa2
Publications – title, author, journal, year	Long term molecular responses in a cohort of Danish patients with essential thrombocythemia, polycythemia vera and myelofibrosis treated with recombinant interferon alfa, Stauffer Larsen et al., Leuk Res., 2013
Study type and design	Open-label, retrospective, observational single center
Follow-up time	The median follow-uptime was 42 months (range12–146months), and the intervals median disease duration was 51 months (95% CI: 44–65).
Population (inclusion and exclusion criteria)	JAK2V617F mutated ET, PV or PMF according to either WHO 2001 or 2008 criteria / treatment with IFN-alfa2a for a period of at least 12 months
Intervention	IFN-alfa-2a/b n = 102 (19 ET; 75 PV) Treatment with rIFN-alfa2 was initiated in the first patient August 1996 and in the last patient 2011. The majority of patients were treated with peg-IFN-2a (n=70) or 2b (n=19), whereas 13 patients were treated with at least two different types of interferon. Dosing schedules varied considerably, both in respect to the administered dose and the dosing intervals. The median weekly dose of peg-IFN-alfa2a was 74 µg/week (range: 26-157) and the median pegIFN-alfa2b dose was 38 µg/week (range: 30–100).
Baseline characteristics	There was an equal gender distribution (49 males and 53 females), with a male:female ratio according to diagnosis: ET 1:1.5; PV 1:1; PMF 3:1 and MPNu 3:1. The median age was 52 years (range: 17–75 years). Patients who initiated therapy IFN within 6 months from diagnosis was defined as newly diagnosed patients. Fifty-one patients met this criterion (11 with ET, 38 with PV,1 with PMF and one with MPNu).
Primary and secondary endpoints	Primary endpoint: • Hematologic response
Method of analysis	The Chi2 and Fischer's exact test were used for comparing categorical variables, whereas Wilcoxon rank sum test was used for continuous variables.
Subgroup analyses	NA

Table A2 Main study characteristics	
Trial name	PVN1
NCT number	NCT00241241.
Objective	This study aimed to report results of the completed PVN1 study, including clinical, molecular responses, and tolerance in the whole cohort of 40 patients
Publications – title, author, journal, year	Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera, Kiladjian et al., Blood, 2008
Study type and design	Prospective, open-label, single-arm, phase II
Follow-up time	Median follow-up of 31.4 months.
Population (inclusion and exclusion criteria)	Inclusion criteria 1. polycythemia vera diagnosed according to PVSG criteria, modified by Pearson 2. Previously untreated patients or patients treated by phlebotomy only or HU or pipobroman for less than 2 years 3. Age 18 to 65 years 4. Signed informed consent Exclusion criteria 1. Contra indication for interferon 2. Severe renal or liver disease 3. ECOG performance status > 2 4. Pregnancy 5. Uncontrolled endocrine disorders except well-regulated hyperthyroidism and diabetes 6. Severe concomitant heart failure or psychiatric disorder 7. Patients receiving another investigational treatment
Intervention	IPeg-IFN-alfa-2a (n=37) was started subcutaneously at 90 µg weekly for 2 weeks, with a dose escalation (every 2 weeks, and in the absence of toxicity) to 135 µg/wk and to 180 µg/wk in the absence of hematologic response.
Baseline characteristics	

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Table A2 Main study characteristics	

Table 1. Main baseline characteristics of included patients

	No. (%) or median (Q1-Q3)
No. of patients	37
Age at diagnosis, y	49 (42-53)
Male sex	16, 43%
Splenomegaly	13/37 (35%)
Spleen enlargement below costal margin (in cm, in 7 patients with palpable splenomegaly)	2 (2-2)
Spleen size by ultrasound (in cm, in 6 patients with splenomegaly by imaging)	14 (13.2-14)
Time since diagnosis, mo	5 (1-11)
History of major thrombosis	5 (14%)
Patients with previous phlebotomies	20 (54%)
No. of phlebotomies in the past 3 mo*	3 (3-5)
Previously on HU	12 (32%)
Hematocrit,† %	51 (49-56.5)
Hemoglobin,† g/dL	16.9 (15.6-19.2)
Leukocytes,† $\times 10^9$/L	10.0 (7.3-13.4)
ANC,† $\times 10^9$/L	7.3 (5.9-10)
Platelets,† $\times 10^9$/L	720 (471-910)
JAK2V617F positive	29 (83%)
%V617F	45 (35-60)

ANC indicates absolute neutrophil count.
*In phlebotomized patients.
†Correspond to values at diagnosis.

Primary and secondary endpoints	Primary endpoint: • response rate after one year of treatment Secondary endpoints: • safety • molecular response
Method of analysis	For continuous variables, median (Q1-Q3) values are given. Distributions of time to response and time to treatment discontinuation were estimated by the Kaplan-Meier method and compared across groups using the log-rank test. Comparisons of Eastern Cooperative Oncology Group staging and %V617F at 12 months vs baseline were based on the MacNemar test and the Wilcoxon sign test, respectively. Mean decrease of %V617F over time was tested using a mixed effect model, accounting for intrapatient correlation of serial measures. This allowed further testing for predictive factors of response. All statistical tests were 2-sided, with P values of .05 or less denoting statistical significance.
Subgroup analyses	NA

Table A2 Main study characteristics	
Trial name	Samuelsson et al. 2006
NCT number	NA

Table A2 Main study characteristics	
Objective	This study aimed to investigate the feasibility of PEG-IFN therapy, its biologic effects, and its impact on quality of life (QoL).
Publications – title, author, journal, year	A phase II trial of pegylated interferon alfa-2b therapy for polycythemia vera and essential thrombocythemia: feasibility, clinical and biologic effects, and impact on quality of life, Samuelsson et al., Cancer, 2006
Study type and design	Prospective, open label, Phase II clinical
Follow-up time	All patients were followed for 24 months
Population (inclusion and exclusion criteria)	Inclusion criteria were a diagnosis of PV or ET and a platelet count >400 x 10^9/L in patients who had a previous thromboembolic episode or ongoing microcirculatory symptoms, a platelet count >1000 x 10^9/L in asymptomatic patients aged 18 years and older, and signed informed consent. Exclusion criteria were previous IFN therapy; ongoing therapy with another myelosuppressive agent; previous severe autoimmune disease; previous endogenous depression requiring medical therapy; pregnancy; cardiac failure (New York Heart Association Grades III and IV); serum creatinine or alanine aminotransferase levels >1.5 and >3 times the upper normal reference value, respectively; or another concurrent malignancy.
Intervention	All 42 patients who were included in the current trial received PEG-IFN therapy.
Baseline characteristics	The median age was 54 years (mean, 53 years; range, 29-77 years), and the median disease duration was 0.80 years (mean, 3.1 years; range, 0.01-30.2 years). Twenty-two patients had a previous thromboembolic event, which included stroke in 9 patients, transient ischemic attack in 2 patients, pituitary apoplexy in 1 patient, myocardial infarction in 1 patient, peripheral arterial thrombosis in 1 patient, splenic infarction in 1 patient, deep vein thrombosis in 3 patients, pulmonary embolism in 1 patient, sinus thrombosis in 1 patient, retinal vein thrombosis in 1 patient, and superficial thrombophlebitis in 1 patient. The time from these complications to study inclusion was 30 months (mean range, 0.5132 months). Four patients had ongoing microcirculatory symptoms, and 16 patients were asymptomatic. Twenty-seven patients had not received prior cytoreductive treatment, whereas 7 patients had received anagrelide, 6 patients had received hydroxyurea, 1 patient had received busulfan, and 1 patient had received radioactive phosphorus. Twenty-eight patients were on low-dose aspirin at study inclusion. In patients with PV, phlebotomy was used to maintain a venous hematocrit <45%
Primary and secondary endpoints	The primary objective of this study was to evaluate the feasibility of PEG-IFN therapy in patients with PV and ET with regard to reaching preset objectives of platelet reductions, which were defined as achieving a platelet count <400 x 10^9/L in patients who had a previous thromboembolic episode or ongoing microcirculatory symptoms or achieving a platelet count <600 x 10^9/L in asymptomatic patients who were without previous thromboembolic complications. Having achieved this objective for at least 4 weeks was defined as a complete platelet response (CR), and all other patient outcomes were defined as failures. Secondary objectives were to evaluate efficacy with regard to thromboembolic events, cessation of phlebotomy requirement in patients with PV, overall survival, spleen size, polycythemia rubra vera-1 (PRV-1) expression, and bone marrow cytogenetics. Another secondary objective was to delineate the impact of PEG-IFN treatment on QoL.

Table A2 Main study characteristics	
Method of analysis	Platelet response rates at 6 months and 24 months were analyzed by using the Fisher exact test according to the following subgroups: patients with PV versus patients with ET, female patients versus male patients, and previously treated patients versus previously untreated patients. QoL questionnaires were analyzed according to the manual for the EORTC QLQ-C30 and the original HAD publication. QoL data are presented descriptively. Changes in mean values ≥5 were considered clinically significant.
Subgroup analyses	NA

Table A2 Main study characteristics	
Trial name	MPN-RC 112
NCT number	NCT01259856
Objective	This study aimed to look at the effectiveness of giving participants who have been diagnosed with ET or PV one of two different study regimens over time
Publications – title, author, journal, year	Results of the Myeloproliferative Neoplasms - Research Consortium (MPN-RC) 112 Randomized Trial of Pegylated Interferon Alfa-2a (PEG) Versus Hydroxyurea (HU) Therapy for the Treatment of High Risk Polycythemia Vera (PV) and High Risk Essential Thrombocythemia (ET), Mascarenhas et al., Blood, 2018 Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea, Yacoub et al., Blood, 2019 Symptom burden and quality of life in patients with high-risk essential thrombocythaemia and polycythaemia vera receiving hydroxyurea or pegylated interferon alfa-2a: a post-hoc analysis of the MPN-RC 111 and 112 trials, Mazza et al., Lancet Haematol., 2022
Study type and design	Randomized, open label, phase 3
Follow-up time	Median follow-up time was 19.6 months (range, 0.6-56.6)
Population (inclusion and exclusion criteria)	Inclusion Criteria: 1. A diagnosis of Essential Thrombocythemia (ET) or Polycythemia Vera (PV) shall be made in accordance with the WHO (2008) criteria (Swerdlow 2008) as shown below. 2. Diagnosis < 5 years prior to entry. 3. Polycythemia Vera (2 major criteria required) o Hb >18.5g/dl (men) or 16.5g/dl (women) or HCT >99 percentile reference range or Elevated red cell mass (>25% above mean predicted value) or Hb >17g/dl (men) or 15g/dl (women) if associated with a sustained rise from baseline with no apparent cause (e.g. treated iron deficiency). o Presence of JAK2V617F

Table A2 Main study characteristics

1. If source documentation of diagnostic criterion #1 cannot be obtained, then diagnosis can be made with (1) the addition of an erythropoietin level below the reference range of normal AND (2) bone marrow biopsy showing hypercellularity for age with trilineage (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation.

4. Essential Thrombocythemia (all 6 criteria required)
   - Platelets count ≥ 450 x 10 to 9/L
   - Megakaryocyte proliferation with large and mature morphology. No significant increase or left shift of neutrophil granulopoiesis or erythropoiesis. Patients may have up to and including 2+ marrow reticulin fibrosis (0, 1 or 2 on scale 0 -4).
   - Not meeting WHO criteria for CML, PV, MDS, PMF or other myeloid neoplasm
   - Demonstration of clonal cytogenetic marker or no evidence of reactive thrombocytosis.
   - Absence of a leukoerythroblastic blood picture.
   - May participate in study without presence of JAK2V617F.Patients must have high risk disease as defined below:
   - High risk PV ANY ONE of the following:
     1. Age ≥ 60 years
     2. Previous documented thrombosis, erythromelalgia or migraine (severe, recurrent, requiring medications, and felt to be secondary to the MPN) either after diagnosis or within 10 years before diagnosis and considered to be disease related
     3. Significant splenomegaly (> 5cm below the left costal margin on palpitation) or symptomatic splenomegaly (splenic IFNarcts or requiring analgesia)
     4. Platelets ≥ 1000 x 10 to 9/L
     5. Diabetes or hypertension requiring pharmacological therapy for > 6 months
   - High risk ET ANY ONE of the following:
     1. Age ≥ 60 years
     2. Platelet count ≥ 1500 x 10 to 9/L
     3. Previous documented thrombosis, erythromelalgia or migraine headaches (severe, recurrent, requiring medications, and felt to be secondary to the MPN) either after diagnosis or within 10 years before diagnosis and considered to be disease related
     4. Previous hemorrhage related to ET

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Table A2 Main study characteristics

5. Diabetes or hypertension requiring pharmacological therapy for > 6 months

Exclusion Criteria:

(ANY of the following, both strata)

1. Known to meet the criteria for primary myelofibrosis (as opposed to ET) by WHO 2008
2. Patients with a prior malignancy within the last 5 years (except for basal or squamous cell carcinoma, or in situ cancer of the cervix)
3. Any contraindications to pegylated interferon or hydroxyurea
4. Presence of any life-threatening co-morbidity
5. History of active substance or alcohol abuse within the last year
6. Subjects who are pregnant, lactating or of reproductive potential and not practicing an effective means of contraception
7. History of psychiatric disorder (e.g. depression) Subjects with a history of mild depression may be considered for entry into this study, provided that a pretreatment assessment of the subject's affective status supports that the subject is clinically stable based on the investigator's normal practice for such subject.
8. History of autoimmune disorder (e.g. hepatitis)
9. Hypersensitivity to interferon alfa
10. Hepatitis B or C infection (HBV), or untreated systemic infection
11. Known HIV disease
12. Evidence of severe retinopathy (e.g. CMV retinitis, macular degeneration) or clinically relevant ophthalmological disorder (e.g. due to diabetes mellitus or hypertension)
13. History or other evidence of decompensated liver disease
14. History or other evidence of chronic pulmonary disease associated with functional limitation
15. Thyroid dysfunction not adequately controlled
16. Neutrophil count <1.5 x 10 to 9/L
17. JAK2 exon 12 mutation: PV that lacks the JAK2V617F mutation but is characterized by the exon 12 mutation.
18. Meets criteria for post PV or post ET-MF

Table A2 Main study characteristics	
	19. Subjects with any other medical condition, which in the opinion of the investigator would compromise the results of the study by deleterious effects of treatment. 20. Previous exposure to any formulation of pegylated interferon 21. History of major organ transplantation 22. History of uncontrolled severe seizure disorder 23. Inability to give informed written consent 24. Total bilirubin >1.5 x ULN (patients that have an isolated indirect bilirubin that causes total bilirubin to be elevated beyond 1.5 x ULN due to documented Gilbert's syndrome or hemolysis may be included). No detectable PNH (paroxysmal nocturnal hemoglobinuria) clone where tested
Intervention	The study included 65 patients with ET and 50 patients with PV. Pegylated interferon alfa-2a was administered subcutaneously at a starting dose of 45 mg weekly and titrated monthly in 45-mg increments for response up to a maximum of 180 mg weekly. Dose escalation occurred when the criteria for CR and dose limiting toxicity were not met. Subjects with a CR or PR at month 12 were eligible to continue treatment at the same dose until loss of response, unacceptable toxicity, patient/physician decision, or completion of the study period at 4 years. Subjects with no response or stable disease at month 12 did not continue receiving treatment.

Table A2 Main study characteristics

Baseline characteristics

Table 1. Baseline characteristics

Characteristic	ET (n = 65)	PV (n = 50)	Total (N = 115)
Sex			
Female	33 (50.8)	24 (48.0)	57 (49.6)
Male	32 (49.2)	26 (52.0)	58 (50.4)
Age >60 y*	38 (58.5)	33 (66.0)	71 (61.7)
Race			
White	54 (83.1)	47 (94.0)	101 (87.8)
Black or African American	6 (9.2)	2 (4.0)	8 (7.0)
Asian	2 (3.1)	0	2 (1.7)
Not reported	3 (4.6)	1 (2.0)	4 (3.5)
ECOG performance status (grade)			
0	44 (67.7)	33 (66.0)	77 (67.0)
1	21 (32.3)	16 (32.0)	37 (32.2)
2	0 (0.0)	1 (2.0)	1 (0.9)
Previous thrombosis	21 (32.3)	11 (22.0)	32 (27.8)
Previous hemorrhage	7 (10.8)	6 (12)	13 (11.2)
Splenomegaly	12 (18.5)	28 (56.0)	40 (34.8)
Disease duration in months since diagnosis, median (range)	37.3 (0.4-291)	54.8 (0.5-394)	42.3 (0.5-394)
HU resistant	20 (31.3)	17 (34.0)	37 (32.5)
Not achieving platelet count <600 × 10^9/L†	15 (75)	4 (23.5)	19 (51.4)
Progressive splenomegaly or hepatomegaly or new splenomegaly or hepatomegaly†	2 (10)	7 (44.2)	9 (24.3)
Not achieving a HCT <45 without phlebotomy†	2 (10)	5 (29.4)	7 (18.9)
Not achieving a WBC <10 × 10^9/L†	5 (29.4)	2 (10)	7 (18.9)
Development of a major thrombotic episode†	7 (35.0)	2 (11.8)	9 (24.3)
HU intolerant	44 (68.8)	33 (66.0)	77 (67.5)
WBC < 2.5 × 10^9/L or hemoglobin <11 g/dL at any dose of HU	11 (25.0)	6 (18.2)	17 (22.1)
Having a platelet count <100 × 10^9/L	1 (2.3)	3 (9.1)	4 (5.2)
Presence of leg ulcers or other unacceptable HU-related nonhematological toxicities	37 (84.1)	25 (75.8	62 (80.5)
HU therapy discontinued	26 (40.0)	16 (32.0)	42 (36.5)
HU therapy ongoing	39 (60.0)	34 (68.0)	73 (63.5)‡
WBC (×10^9/L), median (range)	7.4 (2.4-55.7)	11.1 (2.3-45.3)	8.5 (2.3-55.7)
Platelets (×10^9/L), median (range)	609 (124-1899)	378 (15.2-1698)	485 (15.2-1899)
HCT %, median (range)	39.4 (40-53.7)	44 (27.5-55.8)	41 (40-55.8)
Driver mutations, n			
JAK2V617F	31	48	—
CALR	23	—	—
MPL	4	1	—
Triple negative or unavailable	8	2	—

Primary and secondary endpoints

Primary endpoint:

1. Number of Participants With Complete Remission (CR) [Time Frame: 12 months]
2. Number of Participants With Partial Remission (PR) [Time Frame: 12 months]

Secondary endpoints:

1. Number of Participants With Grade 3 and Grade 4 Hematological and Non-hematological Events [Time Frame: 4 years]
2. Change in the Total Symptom Score (TSS) [Time Frame: baseline and 12 months]
3. JAK2 Allele Burden [Time Frame: 4 years]
4. Allele Burden [Time Frame: 4 years]

Table A2 Main study characteristics	
	5. Number of Participants With Progression of Disease or Death [Time Frame: 4 years] 6. Number of Participants With Major Cardiovascular Events After Therapy [Time Frame: 4 years]
Method of analysis	For each disease cohort, a 50%ORR achieved during the first 12 months was considered acceptable. With the original sample size of 84 patients in each cohort, a difference in ORR from 35% to 50% provided 80% power (a 5 0.05). Patients who dropped out prior to 12 months for lack of response, tolerability, or complications were considered nonresponders (NRs). Baseline demographics, clinical characteristics, and baseline mutational status were reported for ET and PV patients. Maximum grade adverse events (AEs) were summarized, regardless of attribution. Responses at 12 months were reported and ORR (CR1PR) along with exact 95% confidence intervals (CIs) were reported. For each cohort, an independent z test was conducted to test the null hypothesis that the ORR was equal to 35%. Clinical variables were examined according to clinical response using the independent-samples Student t test or the x^2 test for frequency data. Logistic regression was used to examine the association of CR at 12 months with patient demographic and clinical characteristics. Incidence of vascular events and second cancers were estimated using cumulative incidence. Patient-reported outcome measurements were scored according to published scoring algorithms. Within-group changes and between-group differences over time were assessed by mixed models adjusted for age. Analysis of covariance (ANCOVA) adjusting for baseline scores compared 12-month score between patients with a CR vs those with PR/NR.
Subgroup analyses	NA

Table A2 Main study characteristics	
Trial name	MPN-RC 111
NCT number	NCT01259817
Objective	Evaluate the ability of Pegylated Interferon Alfa-2a to achieve Complete Response or Partial Response in patients with (1) high risk polycythemia vera or (2) high risk essential thrombocythemia or (3) splanchic vein thrombosis
Publications – title, author, journal, year	Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea, Yacoub et al., Blood, 2019
Study type and design	Prospective, open-label, single-arm, phase II
Follow-up time	Median follow-up time was 19.6 months (range, 0.6-56.6)
Population (inclusion and exclusion criteria)	Inclusion Criteria:

Table A2 Main study characteristics

5. A diagnosis of ET or PV shall be made in accordance with the WHO (2008) criteria (Swerdlow 2008) as shown below (Values below are at the time of diagnosis, not study entry):
    - Polycythemia Vera (2 major criteria required)
        1. Hb >18.5g/dl (♂) or 16.5g/dl (♀) or HCT >99 percentile reference range or Elevated red cell mass (>25% above mean predicted value) or Hb >17g/dl (♂) or 15g/dl (♀) if associated with a sustained rise from baseline with no apparent cause (e.g. treated iron deficiency).
        2. Presence of JAK2V617F

           If source documentation of diagnostic criterion #1 cannot be obtained, then diagnosis can be made with (1) the addition of an erythropoietin level below the reference range of normal AND (2) bone marrow biopsy showing hypercellularity for age with trilineage (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation.
    - Essential Thrombocythemia (all 6 criteria required)
        1. Platelets count ≥ 450 x 10 to 9/L
        2. Megakaryocyte proliferation with large and mature morphology. No significant increase or left shift of neutrophil granulopoiesis or erythropoiesis. Patients may have up to and including 2+ marrow reticulin fibrosis (0, 1 or 2 on scale 0 -4).
        3. Not meeting WHO criteria for CML, PV, MDS, PMF or other myeloid neoplasm
        4. Demonstration of clonal cytogenetic marker or no evidence of reactive thrombocytosis.
        5. Absence of a leukoerythroblastic blood picture.
        6. May participate in study without presence of JAK2V617F.

Patients must have high risk disease as defined below:

- High risk PV ANY ONE of the following:
    1. Age ≥ 60 years
    2. Platelet count ≥ 1500 x 10 to 9/L
    3. Previous documented thrombosis, erythromelalgia or migraine (severe, recurrent, requiring medications, and felt to be secondary to the MPN) either after diagnosis or within 10 years before diagnosis and considered to be disease related
    4. Previous hemorrhage related to ET
    5. Diabetes or hypertension requiring pharmacological therapy for ≥ 6 months

Table A2 Main study characteristics

In addition patients must EITHER be intolerant or resistant to Hydroxyurea according to established criteria as follows:

- Platelet count ≥ 600 x 10 to 9/L after 3 months of at least 2 g/day of Hydroxyurea (2.5 g/day in patients with a body weight>80 kg)
- WBC < 2.5 x 109/L or Hgb < 11g/dl at any dose of hydroxyurea not to exceed 2g/day.
- Progressive splenomegaly or hepatomegaly (> 5cm from initiation of hydroxyurea) or the appearance of new splenomegaly or hepatomegaly while on MTD of hydroxyurea.
- Not achieving a Hct < 45% in order to eliminate the need for supplemental phlebotomies after 3 months of at least 2g/day or MTD of hydroxyurea.
- Not achieving a WBC of < 10 x 109/L after 3 months of at least 2g/day or MTD of hydroxyurea.
- Having a platelet count < 100 x 109/L on hydroxyurea at any dose without eliminating the need for supplemental phlebotomy or having progressive splenomegaly as defined above.
- Development of a major thrombotic episode (CVA, myocardial infarction, severe migraines requiring medication, abdominal vein thrombosis, deep vein thrombosis) while being treated with maximal tolerated doses of hydroxyurea.
- Presence of leg ulcers or other unacceptable Hydroxyurea-related non-hematological toxicities, such as unacceptable mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of Hydroxyurea.

OR have Splanchnic Vein Thrombosis (SVT) (includes Budd-Chiari, abdominal vein thrombosis, portal vein thrombosis, splenic vein thrombosis). For these patients the following additional inclusion/exclusion criteria apply:

- > 3 months since onset of SVT
- SVT treated with oral anticoagulants but no aspirin
- Liver enzymes not > 2 times the normal value
- Absence of encephalopathy, refractory or infected ascites, esophageal varicose of grade > 1 at time of trial entry
- Bone marrow biopsy confirmed diagnosis of PV or ET
- JAK2-V617F mutations present
- These patients may have a normal blood count at trial entry
- Age over 18 years (no upper age limit)
- Able and willing to comply with study criteria
- Signed and informed consent to participant in this study
- Willing to participate in associated correlative science biomarker study

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Table A2 Main study characteristics

- Serum creatinine < 1.5 x upper limit of normal
- AST and ALT < 2 x upper limit of normal
- Total bilirubin within normal limits

Exclusion Criteria:

(ANY of the following, both strata)

1. Patients cannot have any other form of chemotherapy for their MPD (other than hydroxyurea). Specifically prior interferon or JAK2 inhibitors are prohibited.
2. If a patient has received prior hydroxyurea, they should be tapered off hydroxyurea over a period of the first 2 months of Pegylated interferon alfa-2a therapy. Taper is at the treating physician's discretion, but must be absent (completed) by the start of the third month.
3. Patients with a prior malignancy within the last 5 years (except for basal or squamous cell carcinoma, or in situ cancer of the cervix)
4. Presence of any life-threatening co-morbidity
5. History of active substance or alcohol abuse within the last year
6. Any contraindications to pegylated or non-pegylated interferon
7. Subjects who have a positive pregnancy test, are pregnant, lactating or of reproductive potential and not practicing an effective means of contraception
8. History of psychiatric disorder (e.g. depression; suicidal ideation; psychosis) Subjects with a history of mild depression may be considered for entry into this study, provided that a pretreatment assessment of the subject's affective status supports that the subject is clinically stable based on the investigator's normal practice for such subject.
9. History of autoimmune disorder (e.g. hepatitis; ITP; scleroderma; severe psoriasis affecting > 10% of the body, rheumatoid arthritis requiring more than intermittent NSAID for management)
10. Hypersensitivity to IFN-α
11. HBV or untreated systemic infection
12. Known HIV disease
13. Evidence of severe retinopathy (e.g. CMV retinitis, macular degeneration) or clinically relevant ophthalmological disorder (e.g. due to diabetes mellitus or hypertension)
14. History or other evidence of decompensated liver disease
15. History or other evidence of chronic pulmonary disease associated with functional limitation
16. Thyroid dysfunction not adequately controlled
17. Any investigational drug <6 weeks prior to the first dose of study drug or not recovered from effects of prior investigational agent.
18. Presence of JAK2 exon 12 mutation
19. Patients should not meet criteria for post PV or post ET-MF (see appendix B)
20. Previous exposure to any formulation of interferon
21. Subjects with any other medical condition, which in the opinion of the investigator would compromise the results of the study by deleterious effects of treatment.
22. History of major organ transplantation
23. History of uncontrolled severe seizure disorder

Table A2 Main study characteristics	
	24. Inability to give informed written consent 25. Serum creatinine > 1.5 x upper limit of normal 26. AST and ALT > 2 x upper limit of normal 27. Total bilirubin > 1.5 mg/ml 28. No detectable PNH (paroxysmal nocturnal hemoglobinuria) clone where tested 29. Concurrent hormonal contraceptive use
Intervention	The study included 65 patients with ET and 50 patients with PV. Pegylated interferon alfa-2a was administered subcutaneously at a starting dose of 45 mg weekly and titrated monthly in 45-mg increments for response up to a maximum of 180 mg weekly. Dose escalation occurred when the criteria for CR and dose limiting toxicity were not met. Subjects with a CR or PR at month 12 were eligible to continue treatment at the same dose until loss of response, unacceptable toxicity, patient/physician decision, or completion of the study period at 4 years. Subjects with no response or stable disease at month 12 did not continue receiving treatment.
Baseline characteristics	**Table 1. Baseline characteristics**

Characteristic	ET (n = 65)	PV (n = 50)	Total (N = 115)
Sex			
Female	33 (50.8)	24 (48.0)	57 (49.6)
Male	32 (49.2)	26 (52.0)	58 (50.4)
Age >60 y*	38 (58.5)	33 (66.0)	71 (61.7)
Race			
White	54 (83.1)	47 (94.0)	101 (87.8)
Black or African American	6 (9.2)	2 (4.0)	8 (7.0)
Asian	2 (3.1)	0	2 (1.7)
Not reported	3 (4.6)	1 (2.0)	4 (3.5)
ECOG performance status (grade)			
0	44 (67.7)	33 (66.0)	77 (67.0)
1	21 (32.3)	16 (32.0)	37 (32.2)
2	0 (0.0)	1 (2.0)	1 (0.9)
Previous thrombosis	21 (32.3)	11 (22.0)	32 (27.8)
Previous hemorrhage	7 (10.8)	6 (12)	13 (11.2)
Splenomegaly	12 (18.5)	28 (56.0)	40 (34.8)
Disease duration in months since diagnosis, median (range)	37.3 (0.4-291)	54.8 (0.5-394)	42.3 (0.5-394)
HU resistant	20 (31.3)	17 (34.0)	37 (32.5)
Not achieving platelet count <600 × 10^9/L†	15 (75)	4 (23.5)	19 (51.4)
Progressive splenomegaly or hepatomegaly or new splenomegaly or hepatomegaly†	2 (10)	7 (44.2)	9 (24.3)
Not achieving a HCT <45 without phlebotomy†	2 (10)	5 (29.4)	7 (18.9)
Not achieving a WBC <10 × 10^9/L†	5 (29.4)	2 (10)	7 (18.9)
Development of a major thrombotic episode†	7 (35.0)	2 (11.8)	9 (24.3)
HU intolerant	44 (68.8)	33 (66.0)	77 (67.5)
WBC < 2.5 × 10^9/L or hemoglobin <11 g/dL at any dose of HU	11 (25.0)	6 (18.2)	17 (22.1)
Having a platelet count <100 × 10^9/L	1 (2.3)	3 (9.1)	4 (5.2)
Presence of leg ulcers or other unacceptable HU-related nonhematological toxicities	37 (84.1)	25 (75.8	62 (80.5)
HU therapy discontinued	26 (40.0)	16 (32.0)	42 (36.5)
HU therapy ongoing	39 (60.0)	34 (68.0)	73 (63.5)‡
WBC (×10^9/L), median (range)	7.4 (2.4-55.7)	11.1 (2.3-45.3)	8.5 (2.3-55.7)
Platelets (×10^9/L), median (range)	609 (124-1899)	378 (15.2-1698)	485 (15.2-1899)
HCT %, median (range)	39.4 (40-53.7)	44 (27.5-55.8)	41 (40-55.8)
Driver mutations, n			
JAK2V617F	31	48	—
CALR	23	—	—
MPL	4	1	—
Triple negative or unavailable	8	2	—

Table A2 Main study characteristics	
Primary and secondary endpoints	Primary endpoint: 3. Number of Participants With Complete Remission (CR) [Time Frame: 12 months] 4. Number of Participants With Partial Remission (PR) [Time Frame: 12 months] Secondary endpoints: 7. Number of Participants With Grade 3 and Grade 4 Hematological and Non-hematological Events [Time Frame: 4 years] 8. Change in the Total Symptom Score (TSS) [Time Frame: baseline and 12 months] 9. JAK2 Allele Burden [Time Frame: 4 years] 10. Allele Burden [Time Frame: 4 years] 11. Number of Participants With Progression of Disease or Death [Time Frame: 4 years] 12. Number of Participants With Major Cardiovascular Events After Therapy [Time Frame: 4 years]
Method of analysis	For each disease cohort, a 50%ORR achieved during the first 12 months was considered acceptable. With the original sample size of 84 patients in each cohort, a difference in ORR from 35% to 50% provided 80% power (a 5 0.05). Patients who dropped out prior to 12 months for lack of response, tolerability, or complications were considered nonresponders (NRs). Baseline demographics, clinical characteristics, and baseline mutational status were reported for ET and PV patients. Maximum grade adverse events (AEs) were summarized, regardless of attribution. Responses at 12 months were reported and ORR (CR1PR) along with exact 95% confidence intervals (CIs) were reported. For each cohort, an independent z test was conducted to test the null hypothesis that the ORR was equal to 35%. Clinical variables were examined according to clinical response using the independent-samples Student t test or the x^2 test for frequency data. Logistic regression was used to examine the association of CR at 12 months with patient demographic and clinical characteristics. Incidence of vascular events and second cancers were estimated using cumulative incidence. Patient-reported outcome measurements were scored according to published scoring algorithms. Within-group changes and between-group differences over time were assessed by mixed models adjusted for age. Analysis of covariance (ANCOVA) adjusting for baseline scores compared 12-month score between patients with a CR vs those with PR/NR.
Subgroup analyses	NA

Table A2 Main study characteristics	
Trial name	Huang et al. 2014
NCT number	NA
Objective	This study aimed to evaluate treatment response, efficacy therapy and safety to IFN-alfa-2b for the essential thrombocythemia (ET) and polycythemia vera (PV) with JAK2V617F positive mutation
Publications – title, author, journal, year	Interferon alfa-2b gains high sustained response therapy for advanced essential thrombocythemia and polycythemia vera with JAK2V617F positive mutation, Huang et al., Leuk Res., 2014
Study type and design	Open-label, observational, multicenter
Follow-up time	Not reported
Population (inclusion and exclusion criteria)	Patients with a diagnosis of advanced ET or PV (hematocrit >45% or extreme thrombocytosis >1000 × 109/L) either newly diagnosed or previously treated; (2) Patients with extreme thrombocytosis risks or thrombosis history; (3) The Karnofsky performance status (KPS) scores were at least 60; (4) A serum total bilirubin concentration was found to be no higher than twice the upper limit of the normal range; (5) A serum concentration of alanine aminotransferase was no higher than 2.5 times the upper limit of the normal range; (6) Patients with symptoms of congestive heart failure were excluded.
Intervention	IFN-alfa-2b therapy regimen: original dose was three million units SC three times a week for two years, and maintenance dose was five million units SC two times a week until the termination of the study. HU therapy regimen: the starting dose of HU is 15–20 mg/kg/day until response is obtained, the maintenance dose is titrated to keep platelet count in the normal range and leukocyte count >2.5 × 109/L] until the termination of the study.
Baseline characteristics	Only data regarding the PV cohort is presented

PV arm with JAK2V617F+	IFN α-2b $n = 64$	
	Median	Range
Age	47	26–64
WBC × 10^9/L	26.1	6.6–50.1
Hemoglobin, g/L	197	185–213
Platelets	600	423–900

Primary and secondary endpoints	Primary endpoint: • Complete hematologic response (CHR) in patients with ET was defined as normalization of platelet counts (≤400 × 109/L) without thromboembolic events Secondary endpoints: • Partial hematologic response (PHR) • Complete molecular response (CMR)

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Table A2 Main study characteristics	
	• PFS • OS • Safety
Method of analysis	Complete hematologic response (CHR) in patients with ET was defined as normalization of platelet counts (≤400 × 109/L) without thromboembolic events. Partial hematologic response (PHR) required at least a 50% reduction in platelet counts (but still >400 × 109/L). CHR in patients with PV was defined as normalization of hematocrit (<45% in males and <42% in females), WBC and platelet counts, and spleen size, without the absence of thromboembolic events. PHR required the documentation of at least a 50% reduction in phlebotomy requirements or spleen size. Complete molecular response (CMR) required undetectable levels of JAK2V617F mutation; partial molecular response (PMR) required ≥50% reduction of baseline JAK2V617F mutation level; and minor molecular response (MMR) required 20% to 49% reduction of baseline JAK2V617F mutation level. Progression-free survival (PFS) was defined as the time from the diagnosis to progression, including thrombosis, bleeding, spleen enlargement, severe myelofibrosis or death from any cause in the treatment. Overall response (OS) was measured from diagnosis until death from any cause. Patients who were still alive at the date of last contact were then censored. Adverse drug events were monitored and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (National Cancer Institute, 2003) at each visit after the end of the consolidation treatment. The features of patients (stratifications of WBC, hemoglobin, platelets and age distribution) were evaluated by t-test; complete response, phlebotomy rate, vasomotor symptoms and adverse-event response were evaluated using a Chi-square test; PFS and OS were estimated using the Kaplan–Meier method. A P value of <0.05 was considered statistically significant.
Subgroup analyses	NA

9.3 Results per study

Table A3a Results of study PROUD-PV

Trial name:	PROUD-PV
NCT number:	NCT01949805

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients experiencing at least one thromboembolic event	Ropeginterferon alfa-2b Hydroxyurea	127 127	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion experiencing complete hematological response	Ropeginterferon alfa-2b	123 (data missing in 4 patients)	53/123 (43.09%)	-2,51	-9.85 to 14.87	0,7	RR: 1.06	0.8 to 1.4		CHR without spleen criterion; discontinued patients are considered non-responders. Cochran-Mantel test	

Table A3a Results of study PROUD-PV

	Hydroxyurea	125 (data missing in 4 patients)	57/125 (45.60%)								
MPN-SAF mean change from baseline in total symptom score	Ropeginterferon alfa-2b	NA	NA	NA	NA	NA	NA	NA	NA		
	Hydroxyurea	NA	NA								
EQ-5D Mean change from baseline	Ropeginterferon alfa-2b	105	0,2	NA	NA	NA	[redacted]				
	Hydroxyurea	109	0,1								
Proportion of patients experiencing at least one treatment emergent adverse	Ropeginterferon alfa-2b	127	Grade 3: 21 (16.5%); Grade 4: 1 (0.8%); Grade 5: 1 (0.8%)	NA	NA	NA	NA	NA	NA		

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Table A3a Results of study PROUD-PV											
events of grade 3-4	Hydroxyurea	127	Grade 3: 26 (20.5%); Grade 4: 1 (0.8%); Grade 5: 0								
Proportion experiencing at least one treatment related adverse events of grade 3-4	Ropeginterferon alfa-2b	127	Grade 3: 9 (7.1%) Grade 4: 0 Grade 5: 0	NA	NA	NA	NA	NA	NA		
	Hydroxyurea	127	Grade 3: 17 (13.4%) Grade 4: 0 Grade 5: 0								

Table A3a Results of study CONTINUATION-PV at 60 months						
Trial name:	CONTINUATION-PV					
NCT number:	NCT02218047					
				Estimated absolute difference in effect	**Estimated relative difference in effect**	**Description of methods used for estimation**	**References**

Table A3a Results of study CONTINUATION-PV at 60 months

Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Proportion of patients experiencing at least one thromboembolic event	Ropeginterferon alfa-2b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Hydroxyurea	[redacted]	[redacted]								
Proportion experiencing complete hematologic al response	Ropeginterferon alfa-2b	[redacted]	53 (55.79%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
	Hydroxyurea	[redacted]	33 (44.00%)								
MPN-SAF mean	Ropeginterferon alfa-2b	NA	NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study CONTINUATION-PV at 60 months

change from baseline in total symptom score	Hydroxyurea	NA	NA							
EQ-5D Mean change from baseline	Ropeginterferon alfa-2b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Hydroxyurea	[redacted]	[redacted]							
Proportion of patients experiencing at least one treatment emergent	Ropeginterferon alfa-2b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table A3a Results of study CONTINUATION-PV at 60 months												
adverse events of grade 3-4	Hydroxyurea	Xxx	xxxxxx xxxxxxxxx (xxxxx) xxxxx xxxx xxxxxxx xxxxx									
Proportion experiencing at least one treatment related adverse events of grade 3-4	Ropeginterferon alfa-2b	Xxx	xxxxxx xxxxxxxx (xxxxxx) xxxxx xxx xxxxxxxx xxxxxx	[redacted]								
	Hydroxyurea	Xxx	xxxxxx xxxxxxxx (xxxxx) xxxxx xxx xxxxxxxx xxxxx									

Table A3a Results of study PEGINVERA	
Trial name:	PEGINVERA
NCT number:	NCT02218047

Table A3a Results of study PEGINVERA

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Proportion of patients experiencing at least one thromboembolic event	Ropeginterferon alfa-2b		NA NA	NA	NA	NA	NA	NA	NA		
Proportion experiencing complete hematologic al response	Ropeginterferon alfa-2b	42	27 (64.4%)	NA	NA	NA	NA	NA	NA		(10)
MPN-SAF mean change from baseline in total symptom score	Ropeginterferon alfa-2b	NA	NA	NA	NA	NA	NA	NA	NA		

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Table A3a Results of study PEGINVERA											
EQ-5D Mean change from baseline	Ropeginterferon alfa-2b	NA	NA	NA	NA	NA	NA	NA	NA		
Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4	Ropeginterferon alfa-2b	NA	NA	NA	NA	NA	NA	NA	NA		
Proportion experiencing at least one treatment related adverse events of grade 3-4	Ropeginterferon alfa-2b	NA	NA	NA	NA	NA	NA	NA	NA		Data on file

Table A3a Results of study Masarova et al. 2017; Quintas-Cardama et al. 2013; Quintas-Cardama et al. 2009											
Trial name:	Masarova et al. 2017; Quintas-Cardama et al. 2013; Quintas-Cardama et al. 2009										
NCT number:	NCT00452023										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients experiencing at least one thromboembolic event	Pegylated interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Proportion experiencing complete hematologic al response	Pegylated interferon alfa-2a	66	26/66 39%	NA	NA	NA	NA	NA	NA	Responses and clinical data were analyzed using descriptive statistics. Fisher's exact test was used to compare responses in different groups for categorical variable.	Masarova et al. 2017
	NA	NA	NA								
MPN-SAF mean change from	Pegylated interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study Masarova et al. 2017; Quintas-Cardama et al. 2013; Quintas-Cardama et al. 2009											
baseline in total symptom score	NA	NA	NA								
EQ-5D Mean change from baseline	Pegylated interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4	Pegylated interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Proportion experiencing at least one	Pegylated interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study Masarova et al. 2017; Quintas-Cardama et al. 2013; Quintas-Cardama et al. 2009			
treatment related adverse events of grade 3-4	NA	NA	NA

Table A3a Results of study Crisa et al. 2017	
Trial name:	Crisa et al. 2017
NCT number:	NA

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients experiencing at least one thromboembolic event	Pegylated interferon alfa-2a	NA	NR	NA	NA	NA	NA	NA	NA		
	Hydroxyurea	NA	NR								
Proportion experiencing complete	Pegylated interferon alfa-2a	30	21/30 70%	21.43%	*-18.8 to 44.73	0.0715	RR: 1.44	0.95–2.17	0.0833	Only complete respons reported. Patients' characteristics were compared	Crisa et al. 2017

Table A3a Results of study Crisa et al. 2017											
hematologic al response	Hydroxyurea	35	17/35 49%							using Fisher's exact test for the categorical variables.	
MPN-SAF mean change from baseline in total symptom score	Pegylated interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA		
	Hydroxyurea	NA	NA								
EQ-5D Mean change from baseline	Pegylated interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA		
	Hydroxyurea	NA	NA								
Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4	Pegylated interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA		
	Hydroxyurea	NA	NA								

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Table A3a Results of study Crisa et al. 2017											
Proportion experiencing at least one treatment related adverse events of grade 3-4	Pegylated interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA		
	Hydroxyurea	NA	NA								

Table A3a Results of study Huang et al. 2014											
Trial name:	Huang et al. 2014										
NCT number:	NA										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients experiencing at least one thromboembolic event	Interferon alfa-2b	NA	NR	NA	NA	NA	NA	NA	NA		
	Hydroxyurea	NA	NR								

Table A3a Results of study Huang et al. 2014											
Proportion experiencing complete hematologic al response	Interferon alfa-2b	64	19/64 29.68%	-0,87%	-16.31 to 14.58	0.9123	RR: 0.97	0.58–1.62	0.9124	Complete hematologic response (CHR) in patients with ET was defined as normalization of platelet counts (≤400 × 109/L) without thromboembolic events. Complete response was evaluated using a Chi-square test	Huang et al. 2014
	Hydroxyurea	72	22/72 30.55%								
MPN-SAF mean change from baseline in total symptom score	Interferon alfa-2b	NA	NA	NA	NA	NA	NA	NA	NA		
	Hydroxyurea	NA	NA								
EQ-5D Mean change from baseline	Interferon alfa-2b	NA	NA	NA	NA	NA	NA	NA	NA		
	Hydroxyurea	NA	NA								
Proportion of patients	Interferon alfa-2b	NA	NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study Huang et al. 2014											
experiencing at least one treatment emergent adverse events of grade 3-4	Hydroxyurea	NA	NA								
Proportion experiencing at least one treatment related adverse events of grade 3-4	Interferon alfa-2b	NA	NA	NA	NA	NA	NA	NA	NA		
	Hydroxyurea	NA	NA								

Table A3a Results of study Stauffer Larsen et al. 2013											
Trial name:	Stauffer Larsen et al. 2013										
NCT number:	NA										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		

Table A3a Results of study Stauffer Larsen et al. 2013											
Proportion of patients experiencing at least one thromboembolic event	Interferon alfa-2a/b	NA	NR	NA	NA	NA	NA	NA	NA		
	NA	NA	NR								
Proportion experiencing complete hematological response	Interferon alfa-2a/b	75	51/75 68%	NA	NA	NA	NA	NA	NA		Stauffer Larsen et al. 2013
	NA	NA	NR								
MPN-SAF mean change from baseline in total symptom score	Interferon alfa-2a/b	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
EQ-5D Mean change from baseline	Interferon alfa-2a/b	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								

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Table A3a Results of study Stauffer Larsen et al. 2013										
Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4	Interferon alfa-2a/b	NA	NA	NA	NA	NA	NA	NA	NA	
	NA	NA	NA							
Proportion experiencing at least one treatment related adverse events of grade 3-4	Interferon alfa-2a/b	NA	NA	NA	NA	NA	NA	NA	NA	
	NA	NA	NA							

Table A3a Results of study PVN1					
Trial name:	PVN1				
NCT number:	NCT00241241				
		Estimated absolute difference in effect	**Estimated relative difference in effect**	**Description of methods used for estimation**	**References**

Table A3a Results of study PVN1

Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Proportion of patients experiencing at least one thromboembolic event	Interferon alfa-2a	NA	NR	NA	NA	NA	NA	NA	NA		
	NA	NA	NR								
Proportion experiencing complete hematologic al response	Interferon alfa-2a	37	35/37 94.65%	NA	NA	NA	NA	NA	NA	Complete hematologic response (CR) was defined by a hematocrit (Hct) level lower than 45% in males and 42% in females without phlebotomy, absence of splenomegaly, and normal white blood cell (WBC) (< 10x 109/L) and platelet counts (< 400x109/L).	Kiladjian et al. 2008
	NA	NA	NR								
MPN-SAF mean change from baseline in total symptom score	Interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								

Table A3a Results of study PVN1											
EQ-5D Mean change from baseline	Interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4	Interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Proportion experiencing at least one treatment related adverse events of grade 3-4	Interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								

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Table A3a Results of study MPN-RC 112												
Trial name:	MPN-RC 112											
NCT number:	NCT01259856											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients experiencing at least one thromboembolic event	Hydroxyurea	NA	NR	NA	NA	NA	NA	NA	NA		
	Pegylated interferon alfa-2a	NA	NR								
Proportion experiencing complete hematologic al response	Hydroxyurea	37	35/37 94.65%	NA	NA	NA	NA	NA	NA	Complete hematologic response (CR) was defined by a hematocrit (Hct) level lower than 45% in males and 42% in females without phlebotomy, absence of splenomegaly, and normal white blood cell (WBC) (< 10x 109/L) and platelet counts (< 400x109/L).	https://clinicaltrials.gov/ct2/show/results/NCT01259856
	Pegylated interferon alfa-2a	NA	NR								
	Hydroxyurea	NA	NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study MPN-RC 112											
MPN-SAF mean change from baseline in total symptom score	Pegylated interferon alfa-2a	NA	NA								
EQ-5D Mean change from baseline	Hydroxyurea	NA	NA	NA	NA	NA	NA	NA	NA		
	Pegylated interferon alfa-2a	NA	NA								
Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4	Hydroxyurea	NA	NA	NA	NA	NA	NA	NA	NA		
	Pegylated interferon alfa-2a	NA	NA								

Table A3a Results of study MPN-RC 112											
Proportion experiencing at least one treatment related adverse events of grade 3-4	Hydroxyurea	NA	NA	NA	NA	NA	NA	NA	NA		
	Pegylated interferon alfa-2a	NA	NA								

Table A3a Results of study MPN-RC 111											
Trial name:	MPN-RC 111										
NCT number:	NCT01259817										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients experiencing at least one thromboembolic event	Pegylated interferon alfa-2a	NA	NR	NA	NA	NA	NA	NA	NA		
	NA	NA	NR								

Table A3a Results of study MPN-RC 111										
Proportion experiencing complete hematological response	Pegylated interferon alfa-2a NA	50 NA	11/50 (22%) NR	NA	NA	NA	NA	NA	NA	Complete hematologic response (CR) was defined by a hematocrit (Hct) level lower than 45% in males and 42% in females without phlebotomy, absence of splenomegaly, and normal white blood cell (WBC) (< 10x 109/L) and platelet counts (< 400x109/L).	
MPN-SAF mean change from baseline in total symptom score	Pegylated interferon alfa-2a NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		
EQ-5D Mean change from baseline	Pegylated interferon alfa-2a NA	NA NA	NA NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study MPN-RC 111											
Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4	Pegylated interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA	NA	
	NA	NA	NA								
Proportion experiencing at least one treatment related adverse events of grade 3-4	Pegylated interferon alfa-2a	NA	NA	NA	NA	NA	NA	NA	NA	NA	
	NA	NA	NA								

Table A3a Results of study Samuelsson et al. 2006	
Trial name:	Samuelsson et al. 2006
NCT number:	NA

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Table A3a Results of study Samuelsson et al. 2006

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients experiencing at least one thromboembolic event	Pegylated interferon alfa-2b	NA	NR	NA	NA	NA	NA	NA	NA		
	NA	NA	NR								
Proportion experiencing complete hematologic al response	Pegylated interferon alfa-2b	42	29/42 69.0%	NA	NA	NA	NA	NA	NA	Platelet response rates at 6 months and 24 months were analyzed by using the Fisher exact test according to the following subgroups; patients with PV versus patients with ET, female patients versus male patients, and previously treated patients versus previously untreated patients	Samuelsson et al. 2006
	NA	NA	NR								
MPN-SAF mean change from	Pegylated interferon alfa-2b	NA	NA	NA	NA	NA	NA	NA	NA		

Table A3a Results of study Samuelsson et al. 2006											
baseline in total symptom score	NA	NA	NA								
EQ-5D Mean change from baseline	Pegylated interferon alfa-2b	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Proportion of patients experiencing at least one treatment emergent adverse events of grade 3-4	Pegylated interferon alfa-2b	NA	NA	NA	NA	NA	NA	NA	NA		
	NA	NA	NA								
Proportion experiencing at least one	Pegylated interferon alfa-2b	NA	NA	NA	NA	NA	NA	NA	NA		

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Table A3a Results of study Samuelsson et al. 2006			
treatment related adverse events of grade 3-4	NA	NA	NA

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9.4 Results per PICO (clinical question)

The results per PICO related to clinical question 1 is identical to the results per study for PROUD-PV and CONTINUATION-PV presented in section 9.3. Hence no additional table has been developed for this section.
Given the heterogeneity of the available comparator data regarding clinical question 2 the comparison conducted is of a narrative nature and cannot be inserted into the table A4 template in a meaningful manner.

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Cost- and budget impact model for Besremi

Technical document – application for the Danish Medicines Council

28-02-2022

Version 1.0

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Table of content

1 Background

AOP Orphan Sweden AB applies for the recommendation of the DMC concerning ropeginterferon-alfa-2b (Besremi®) as possible standard treatment for patients with polycythaemia vera (PV).

Besremi will be available as a 250 mcg pens for injection for subcutaneous administration. AOP Orphan is considering bringing a 500 mcg pen onto the market in 2023.

The full indication for Besremi:

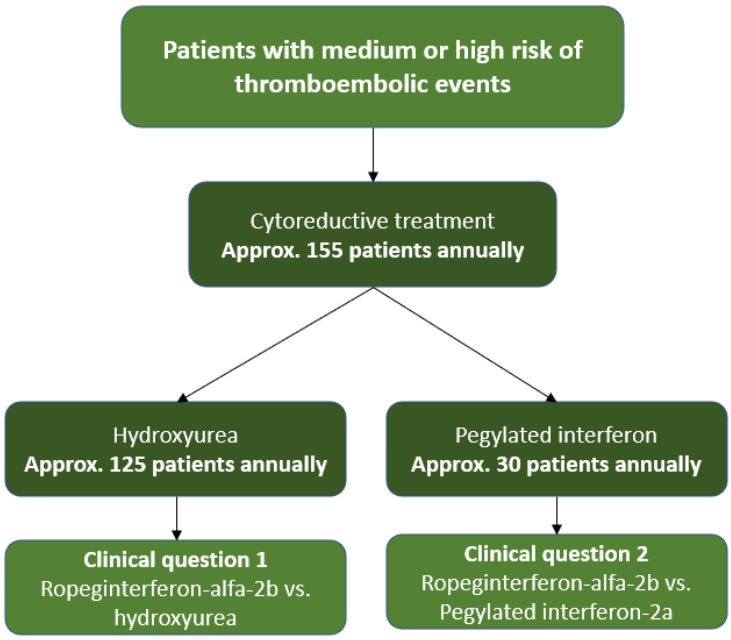
Besremi is indicated as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly(1)

The dose is titrated individually with a recommended starting dose of 100 micrograms. The dose should be gradually increased by 50 micrograms every two weeks (in parallel, other cytoreductive therapy should be decreased gradually, as appropriate) until stabilisation of the haematological parameters is achieved (haematocrit <45%, platelets <400 x 109 /L and leukocytes <10 x 109 /L). The maximum recommended single dose is 500 micrograms injected every two weeks. During the course of treatment, the dosing interval can be increased to 4 weeks(1)

.

Treatment of patients with polycythaemia vera in Denmark
As per the DMC protocol, current standard treatment for medium to high-risk PV patients are pegylated interferon, if patients are under 60 years, and hydroxyurea (HU) if patients are above 60 years.

Figure 1. Diagram of treatment algorithm of patients with polycythaemia vera and the relevant clinical questions provided by the expert committee in the protocol(2).



1.1 Clinical Questions:

The DMC's protocol for assessment of Besremi as treatment of PV includes two clinical questions*(2)*. The clinical questions are:

1.1.1 Clinical question 1

What is the value of ropeginterferon-alfa-2b (Besremi) compared to hydroxyurea for PV patients above 60 years?

- Population: Patients with PV above 60 years
- Intervention: Ropeginterferon-alfa-2b, dosing as described in the **Background**-section.
- Comparator: Hydroxyurea in 500 mg capsules. 10-30 mg/kg daily.

1.1.2 Clinical question 2

What is the value of ropeginterferon-alfa-2b (Besremi) compared to pegylated interferon-alfa-2a for PV patients below 60 years?

- Population: Patients with PV below 60 years
- Intervention: Ropeginterferon-alfa-2b, dosing as described in the **Background**-section.
- Comparator: Pegylated interferon-alfa-2a (Pegasys) as subcutaneous injection. Starting dose is 45 mcg per week. Dose is gradually increased by 45 mcg once monthly if hematological response is not achieved, until a max dose of 180 mcg per week.

The relevant comparison for the population in this application is presented in **Table 1**:

Table 1: Intervention and comparators in the model

	Administration form	Dosing	Population
Intervention			
Ropeginterferon-alfa-2b (Besremi)	s.c.	Startdose: 100 microgram every other week, gradually increase dosis by 50 microgram every administration until stabilisation of haematological values*(2)*	PV patients above and below 60 years
Comparators			
Hydroxyurea	p.o.	10-30 mg/kg daily*(2)*	Clinical question 1
Pegylated interferon-alfa-2a (Pegasys)	s.c.	Starting dose is 45 mcg per week. Dose is gradually increased by 45 mcg once monthly if haematological response is not achieved, until a max dose of 180 mcg per week. *(2)*	Clinical question 2

2 Cost per patient analysis

2.1 Model description

A simple cost-per-patient analysis was developed to assess the incremental cost of Besremi in clinical question 1 and 2. With the objective of model parsimony and to avoid any unnecessary complexity, disease progression was not directly modelled, and only events such as administration and monitoring were modelled. Adverse events were not included since no significant differences were demonstrated in the overall clinical safety data.

2.1.1 Comparators and efficacy

The model includes two comparators, one for each clinical question, based on the DMC's protocol for assessment of Besremi for PV patients. The two comparators included are HU and pegylated interferon-alfa-2a.

In the model dashboard, it is possible to select the clinical question. If clinical question 1 is selected, the model will automatically change the comparator to HU. If clinical question 2 is selected, the model will select pegylated interferon-alfa-2a as the comparator.

As the model does not capture disease progression, nor disease events, no efficacy estimates are needed for this model and have therefore been omitted from the model.

2.1.2 Resources and costing perspective

The model applies a Danish restricted societal perspective in line with DMC guidelines(3). All interventions are fixed dose, and consequently no patient characteristics have been applied in this model with the objective of model parsimony.

The analysis includes drug cost, administration cost, monitoring cost, patient costs and transportation costs. Drug costs were accounted for by identifying the AIP at medicinpriser.dk. The Danish DRG tariff system (Interaktiv DRG 2022(4)) was used to account for administration- and monitoring cost. The DMC's methods guideline for unit cost was applied to account for patient cost.

2.1.3 Time horizon

The time horizon was chosen to be 5 years in the base-case, as this aligns with the 60 month analysis of CONTINUATION-PV used for the discontinuation rates. As only the drug cost and discontinuation rate differ between the 3 comparators, a 5-year time horizon was deemed reasonable, however, to test the impact of the time horizon, scenario analyses have been conducted.

Cost are discounted 3.5% per year in accordance with DMC's methods guideline.(3)

2.2 Model input

2.2.1 Drug cost

The unit costs for the included drugs are found and sourced from Medicinpriser.dk. These are applied in Table 2**.**

Table 2: The drug prices applied in the model (AIP DKK).

Drug	Formulation	Packing	Price*	Source
Ropeginterferon alfa-2b	250 mcg	1 injection pen	17,509.29	Medicinpriser.dk (Besremi) 084535
Hydroxyurea	500 mg	100 pc	295.00	Medicinpriser.dk (Hydroxyurea "Medac") 464545
Pegylated interferon-alfa-2a	135 mcg	4 injection pens	4,282.55	Medicinpriser.dk (Pegasys) 008767/372067
	180 mcg	4 pre-filled synringe	4,996.28	

*Identified and sourced February 8th, 2022.

2.2.1.1 Dosing

2.2.1.1.1 Besremi dosing

During the titration phase the dose is titrated individually with a recommended starting dose of 100 micrograms (or 50 micrograms in patients under another cytoreductive therapy). The dose should be gradually increased by 50 micrograms every two weeks (in parallel, other cytoreductive therapy should be decreased gradually, as appropriate) until stabilisation of the hematological parameters is achieved (hematocrit <45%, platelets <400 x 109/L and leukocytes <10 x 109/L). The maximum recommended single dose is 500 micrograms injected every two weeks(1). After 18 months, dosing interval can be increased to every 4 weeks.(1)

2.2.1.1.1.1 Drug utilization in clinical practice

Based on clinical experience with Besremi (named patient use in Austria, Hungary, UK and France), approx. [redacted] to [redacted] pens are expected to be used every 4 weeks in real world clinical practice. Additionally, following 1.5 years of treatment, the dose can be reduced to once every 4 weeks. This was evident in the phase II Peginvera study(5), where the mean dose received by patients was [redacted] mcg, supporting the assumption of a lower dose in clinical practice. The study reported that patients could extend the interval between Besremi administration and still maintain the hematologic response at the level before the dose reduction.

Therefore, in the base case analysis, the dosing of Besremi will be based on long-term data from the Peginvera study, as the pen Besremi is dosed with allows for multiple usage, therefore for splitting up doses if stored correctly. [redacted] To calculate the drug utilization in the model, number of doses per week was calculated as mean number of doses divided by mean duration of treatment. Mean mcg per week was then calculated as number of doses per week multiplied by mean dosage. Finally, number of pens per year was calculated as mean mcg per week multiplied with number of weeks per year, divided by mcg per pen, resulting in approximately [redacted] pens per year. To calculate the pens per model cycle, the pens per year were divided by 13 (13 cycles per year) and in the base case, this would result in a total cost per cycle of [redacted].

Table 3. Dosing of Besremi based on data from the Peginvera study

Mean number of doses	Mean treatment duration	Mean dosage	Mcg per week	Pens per year
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.2.1.1.2 Dosing hydroxyurea

HU is administered p.o. daily, at 10-30 mg/kg. In the PROUD-PV trial, the mean baseline weight was 76.11 kg(6). For this model, a dosing of 15 mg/kg was applied. This results in a dose per administration of 1,141.56 mg (76.11 kg * 15 mg/kg), however, as the treatment is p.o. and the capsules cannot be divided, the dosing is rounded up to the number of pills necessary to achieve the calculated dosing. Therefore, a dosing of 1,500.00 mg per administration is in the model, this results in a total cost per cycle of 247.80 DKK.

2.2.1.1.3 Dosing pegylated interferon-alfa-2a

Dosing with pegylated interferon-alfa-2a is defined as "45 mcg every week, and gradually increase dose to a maximum of 180 mcg per week. Dose is increased once monthly by 45 mcg if hematological response is not achieved" in the DMC protocol(2). However, as the 'Pegasys'-syringe is single use(7), it is not possible to administer the content over multiple administrations, and a full pen is utilised at every administration. Therefore, for the base-case, the cost of a full syringe is applied each administration week, resulting in a total cost per cycle of 4,282.55 DKK.

2.2.1.2 Treatment discontinuation

2.2.1.2.1 Besremi

Discontinuation for Besremi was based on the 60 month analysis of Continuation-PV study(6) (Table 4). We considered all discontinuation that was observed in the clinical trial.

Table 4. Estimation of treatment discontinuation rates per 4-week cycle for Besremi

Treatment	Period	Number of patients (%) with discontinuation	Probability of discontinuation per cycle*
Besremi	60 month analysis	[redacted]	[redacted]

Source: *CONTINUATION-PV 60 months CSR Table 14.1.1.4*. **Note**: *, converted from rates to 4-week probability using provided in Box 3.1 in 'Decision Modelling for Health Economic Evaluations', Andrew Briggs et al.

2.2.1.2.2 Hydroxyurea

Discontinuation for HU was based on the 60 month analysis of Continuation-PV study(6) (Table 5). We considered all discontinuation that was observed in the clinical trial.

Table 5. Estimation of treatment discontinuation rates per 4-week cycle for Besremi

Treatment	Period	Number of patients (%) with discontinuation	Probability of discontinuation per cycle*
Hydroxyurea	60 month analysis	[redacted]	[redacted]

Source: *CONTINUATION-PV 60 months CSR Table 14.1.1.4*. **Note**: *, converted from rates to 4-week probability using provided in Box 3.1 in 'Decision Modelling for Health Economic Evaluations', Andrew Briggs et al.(8)

2.2.1.2.3 Pegylated interferon-alfa-2a

Besremi is the only approved INF therapy for PV. It was designed to overcome limitations with the current available off-label pegylated interferons regarding dosing and tolerability. When approved, the European Medicine Agency committee for Medicinal Product for Human use considered that Besremi is a new active substance as it differs significantly form INF previously approved within the European Union. In contrast to other pegylated IFN compounds Besremi consist of a single positional isomer resulting in an extended elimination half-life. Considering that Besremi exhibits a prolonged half-life which result in an extended dosing interval, it can significantly improve patient tolerability, ensuring

better compliance and therefore having a significant impact on the efficacy and safety of the product. Recent clinical experience report benefit related to improved tolerability and compliance of Besremi compared to conventional interferons such as Pegasys. Unfortunately, no head to head studies – comparing Besremi vs Pegasys has been conducted. Consequently, due to lack of data, the input in the model assumes similar discontinuation rates for both alternatives. Hence not taking assumptions of better tolerability and lower discontinuation rate of Besremi into consideration, could favor Pegasys and be a limitation in the model.

Therefore, in order to reflect the differences between Besremi and Pegasys, the discontinuation rate of pegylated interferon-alfa-2a have been based on data from the clinical trial MPD-RC 111(9).

Table 6. Estimation of treatment discontinuation rates per 4-week cycle for pegylated interferon-alfa-2a

Treatment	Period	Number of patients (%) with discontinuation	Probability of discontinuation per cycle*
Pegylated interferon-alfa-2a	Median follow-up: 19.6 month	[redacted]	[redacted]

Source: MPD-RC 111, Yacoub et al., 2019 **Note**: *, converted from rates to 4-week probability using provided in Box 3.1 in 'Decision Modelling for Health Economic Evaluations', Andrew Briggs et al.

2.2.2 Administration and monitoring (hospital cost)

Besremi and Pegylated interferon-alfa-2a is intended for self-administration. It is expected that training in s.c. self-administration will be provided at the initial hospital visit. Therefore, an administration cost visit has been applied in the first model cycle for Besremi and Pegylated interferon-alfa-2a. For HU, the p.o. administration is not expected to result in any administration cost.

All PV patients are expected to be attend two clinical monitoring visits every year(10). The model will therefore include 2 annual monitoring visits for all patients.

The frequency of visits presented above were applied in the model along with the cost of each administration or monitoring visit. The costs were sourced from the Danish DRG 2022(4). The costs applied are listed below in 7.

Table 7: Cost applied for administration and monitoring (hospital cost). The costs are based on 2022 DRG (DKK).

Type	Price (DKK)	Note	Source
Training of subcutaneous self-administration	3,225	DRG 2022, 17MA98: MDC17 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD459 Polycythaemia vera Procedure: BWAA31: Medicingivning ved subkutan injektion.	DRG 2022, interaktiv DRG
Monitoring visit	3,225	DRG 2022, 17MA98: MDC17 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD459 Polycythaemia vera.	DRG 2022, interaktiv DRG

2.2.3 Patient and transportation cost

Patient costs were included in line with DMC guideline, as DKK 179 is estimated per hour used. Patient costs were included for monitoring and administration. A monitoring visit was assumed to be one hour for all PV patients. No patient time was estimated for p.o. administration and for s.c. administration 10 minutes was assumed. In the model, patient cost is applied at every occurrence of an hospital visit or a s.c. administration.

Transportation costs are included in the model in line with DMC guidelines. An average rate of DKK 3.52 per km is assumed with an average distance of 28 km per hospital visit in line with DMC's methods guideline.(11) In the model, transportation cost is applied at the occurrence of hospital visits.

2.3 Summary of base-case assumptions

Table 8: Summary of the assumptions applied in the base-case

Element	Base-case
Intervention	Ropeginterferon-alfa-2b
Comparators	Hydroxyurea (clinical question 1) Pegylated interferon-alfa-2a (clinical question 2)
Time horizon	5 years (60 months)
Discount rate	XXXX
Included costs	Drug acquisition Administration Monitoring Patient time Transportation
Wastage assumed	Yes
Other key assumptions	Safety profiles are assumed similar for all included interventions, therefore no cost have been modelled for adverse events

2.5 Results

2.5.1 Base-case

For clinical question 1, Besremi represents an incremental cost of DKK 1,131,696 per patient compared to hydroxyurea using AIP-prices over a 60-month time horizon. For clinical question 2, Besremi presented an incremental cost of DKK [redacted] per patient compared to pegylated interferon-alfa-2a using AIP-prices prices over a 60-month time horizon.

Besremi represents a cost of DKK [redacted], hydroxyurea represents a cost of DKK 45,898, and pegylated interferon-alfa-2a a cost of DKK 148,558 using AIP prices over the 60-month time horizon.

Table 9: Base-case costs for the clinical question 1 over 60 months (AIP DKK)

Drug	Besremi	Hydroxyurea	Incremental vs. Besremi
Drug cost	[redacted]	13,162.83	[redacted]
Hospital cost	30,141.36	30,141.36	0.00
Patient cost	3,244.99	1,672.96	1,572.03
Transportation cost	921.16	921.16	0
Total	[redacted]	**45,898.31**	[redacted]

Table 10: Base-case costs for clinical question 2 over 36 months (AIP DKK)

Drug	Besremi	Pegylated interferon-alfa-2a	Incremental vs. Besremi
Drug cost	[redacted]	112,682.42	[redacted]
Hospital cost	30,141.36	30,141.36	0.00
Patient cost	3,244.99	4,812.86	-1,567.87
Transportation cost	921.16	921.16	0.00
Total	[redacted]	**148,557.79**	[redacted]

2.5.2 Sensitivity analyses

To investigate the impact of main variables in the analysis, scenario analyses were conducted. The following scenario analyses were conducted: the time horizon varied to 1 and 3 years. The scenario analyses for clinical question 1 are presented in Tavle 11, while the scenario analyses for clinical question 2 are presented in Table 12.

Table 11: Scenario analysis for the pairwise comparison between Besremi and hydroxyurea (Clinical question 1) (AIP DKK).

Scenario	Incremental cost vs. hydroxyurea
Time horizon of 12 months	[redacted]
Time horizon of 36 months	[redacted]
Time horizon of 60 months – Base case	[redacted]

Table 2: Scenario analysis for the pairwise comparison between Besremi and pegylated interferon-alfa-2a (Clinical question 2) (AIP DKK).

Scenario	Incremental cost vs. pegylated interferon-alfa-2a
Time horizon of 12 months	[redacted]
Time horizon of 36 months	[redacted]
Time horizon of 60 months – Base case	[redacted]

3 Budget Impact model

3.1 Methods

A budget impact model (BIM) was conducted to compare the regional expenses in the current scenario (without the recommendation of Besremi) with the regional expenses in a future scenario with the recommendation of Besremi as possible standard treatment. The budget impact is presented per year over a five-year period without discounting.

The BIM is embedded in the cost per patient model, and consequently, any updates of the assumptions in the costs per patient model will impact the results of the BIM.

In the base-case an average annual cost per patient approach has been applied as is standard in budget impact models. Using this approach, the average cost per year over the chosen time horizon is calculated and applied per year. This approach is naturally a simplification, since this will not directly reflect the cost per patient for the stratified patient cohort in any given year, however, this approach is necessary since we do not have any robust data on treatment switching for all the interventions included. By using this approach, all the interventions can compete for the total prevalent population in any given year, which aligns with the assumptions applied for the market shares.

3.2 Patient numbers

For clinical question 1, the expert committee noted that approx. 125 patients annually would be within the defined population of the clinical question, while approx. 30 patients would be within the defined population of clinical question 2 annually(2).

This estimate appears to be at the upper limit of the incidence estimate observed in Europe (12), where the incidence number ranges between 0.4-2.8 per 100,000 (approx. 23.2-162.4 incident patients per year in total). Importantly, not all patients are in need of cytoreductive therapy. Studies have shown that the proportion of patients in need of cytoreductive therapy ranges from 73-84%(13), resulting in maximally 136.4 new patients (162.4 * 84%), who are candidates for cytoreductive treatment of PV annually.

However, in order to stay consistent with the protocol, the expert committees estimates have been used in the base case of the budget impact analysis (**Table 13**).

Table 13: Estimated patient count for clinical question 1 and 2.

	Clinical question 1					Clinical question 2				
Year	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1	Year 2	Year 3	Year 4	Year 5
No. of patients who candidate for treatment annually	125	125	125	125	125	30	30	30	30	30
Total number of patients	*125*	*250*	*375*	*500*	*625*	*30*	*60*	*90*	*120*	*150*

3.3 Market shares

3.3.1 Clinical question 1

AOP Orphan expect approx. [redacted] of the incident patients will be eligible for treatment with Besremi in the scenario with a recommendation of Besremi, resulting in a market uptake of [redacted] from year 1.

Table 14: Estimated market shares per year

	Without recommendation of Besremi					With recommendation of Besremi				
Treatment	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Besremi	0%	0%	0%	0%	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxyurea	100%	100%	100%	100%	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3.2 Clinical question 2

AOP Orphan expect approx. a [redacted] uptake of patients in year 1 for Besremi, and that this number will increase over time to [redacted] in year 5, [redacted]

Table 15: Estimated market shares per year

	Without recommendation of Besremi					With recommendation of Besremi				
Treatment	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Besremi	0%	0%	0%	0%	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated interferon-alfa-2a	100%	100%	100%	100%	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.4 Results

3.4.1 Base-case

Using AIP-prices, the estimated budget impact of recommending Besremi as standard treatment for the population in clinical question 1 is DKK [redacted] mil. in year 1, and DKK [redacted] mil. is expected in year 5. The results are illustrated in Table 16.

Table 16: Result from the base case. Estimated budget impact per year for the next five years for the population in clinical question 1 (AIP DKK).

	1st year	2nd year	3rd year	4th year	5th year
Recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Using AIP-price, the estimated budget impact of recommending Besremi as standard treatment for the population in clinical question 2 is expected to be approximately DKK [redacted] mil. in year 1 and DKK [redacted] mil. in year 5. The results are illustrated in Table 5.

Table 5: Result from the base case. Estimated budget impact per year for the next five years for population in clinical question 2 (AIP DKK).

	1st year	2nd year	3rd year	4th year	5th year
Recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4 Conclusion

Using AIP-prices, Besremi is associated with a higher cost per patient compared to hydroxyurea for the patient population defined in clinical question 1 over a 5-year time horizon. In the patient population defined in clinical question 2, Besremi is associated with higher cost per patient compared to pegylated interferon-alfa-2a over a 5-year time horizon.

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Medicinrådet

Medicinrådets protokol for vurdering vedrørende ropeginterferon-alfa-2b til behandling af polycytæmia vera

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 protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet sammenligner med, og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

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 den ansøgende virksomhed få besked.

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1. Begreber og forkortelser

AML	Akut myeloid leukæmi
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EPAR:	*European Public Assessment Report*
EUnetHTA:	*European Network for Health Technology Assessment*
FDA:	*The Food and Drug Administration*
FINOSE:	Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HTA:	Medicinsk teknologivurdering (*Health Technology Assessment)*
IQWIG:	*The Institute for Quality and Efficiency in Healthcare*
ITT:	*Intention to treat*
JAK2	Janus kinase-2
MKRF:	Mindste klinisk relevante forskel
MPN-SAF	*Myeloproliferative Neoplasm Symptom Assessment Form*
NICE:	*The National Institute for Health and Care Excellence*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*
PP:	*Per Protocol*
PV	Polycytæmia vera
RR:	Relativ risiko
SMD:	*Standardized Mean Difference*
VAS	Visuel analog skala

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra AOP Pharma, som ønsker, at Medicinrådet vurderer ropeginterferon-alfa-2b (Besremi) til polycytæmia vera. Medicinrådet modtog den foreløbige ansøgning den 16. december 2020. Ansøger fik forhåndsgodkendelse (positive opinion) i Det Europæiske Lægemiddelagentur (*European Medicines Agency,* EMA) i november 2018 og markedsføringstilladelse af Europakommissionen i februar 2019.

2.1 Polycytæmia vera

Polycytæmia vera (PV) er en kronisk myeloproliferativ sygdom, hvor der sker en overproduktion af hovedsageligt røde blodlegemer (erythrocytter), men eventuelt også hvide blodlegemer (leukocytter) og blodplader (trombocytter). Stort set alle patienter med PV har en underliggende mutation i enzymet, Janus kinase-2 (JAK2), hvoraf langt størstedelen har en specifik mutation, JAK2 V617F [1,2]. JAK2-mutationen medfører en øget signalering fra receptorer, der kontrollerer dannelsen af røde blodlegemer, hvide blodlegemer og blodplader, og mutationen anses for at være den overordnede driver for udviklingen af PV [3].

I Danmark diagnosticeres ca. 170 patienter årligt med PV. Ca. halvdelen diagnosticeres i 64-79-års alderen, men en fjerdedel er yngre og en fjerdedel er ældre [4]. 5-års overlevelsen i Danmark er ca. 80 % [4], og den samlede medianoverlevelse er opgjort til omkring 19 år [5]. PV betragtes dermed som en kronisk sygdom, dog med en vis overdødelighed [5]. Sygdommen opdages oftest under udredning af andre symptomer, herunder cirkulationsproblemer eller blodpropper, som kan forekomme i alle dele af kredsløbet, men hos en del patienter opdages sygdommen pga. blodprøveresultater taget i anden sammenhæng.

PV indledes med en stabil fase af mange års varighed. I den stabile fase har patienterne en betydelig højere risiko for tromboemboliske hændelser med dertilhørende komorbiditet, sammenlignet med raske jævnaldrende, men patienterne kan også have en blødningstendens. Samlet set udvikler ca. 25 % tromboemboliske hændelser i sygdomsforløbet, men almindelige risikofaktorer for blodpropper har stor betydning for den enkelte patients samlede risiko [2]. Udviklingen af tromboemboliske- og andre kardiovaskulære hændelser er sandsynligvis en væsentlig faktor for overdødeligheden ved PV [5]. Patienternes sygdomssymptomer varierer meget i den stabile fase. De fleste patienter har ingen symptomer på diagnosetidspunktet, mens nogle oplever sygdomsrelateret hovedpine, svimmelhed, synsforstyrrelse, træthed, hudkløe, føleforstyrrelse i hænder eller fødder, hurtig mathed eller komplikationer i form af blodprop eller blødning. De symptomer vil fortsætte med at påvirke patientens livskvalitet afhængig af behandlingsrespons.

Efter den stabile fase kan nogle patienter udvikle myelofibrose (6-10 %), som er en bindevævsdannelse i knoglemarven med fortrængning af blodproduktionen, eller akut myeloid leukæmi (AML) (3-5 %). Disse er alvorlige sygdomme med høj dødelighed og kan bidrage til en generel forringet overlevelse for patienter med PV [5,6].

2.2 Ropeginterferon-alfa-2b

Ropeginterferon-alfa-2b markedsføres under handelsnavnet Besremi® og har indikation som monoterapi til behandling af PV uden symptomatisk splenomegali (forstørret milt) hos voksne patienter. Lægemidlet fik markedsføringstilladelse i EMA i februar 2019. Fagudvalget vurderer, at symptomatisk splenomegali forekommer meget sjældent i patienter med PV, og at der ikke findes et klinisk ræsonnement for denne opdeling af patienter. Derfor fører dette kriterium i praksis ikke til en indskrænkning af den mulige patientpopulation.

Ropeginterferon-alfa-2b er et pegyleret interferon. Behandling med lægemidlet medfører både sænkede blodværdier og en reduktion af patientens JAK2V617F-mutationsbyrde (det molekylære mål for sygdomsmængden) [7,8]. Den bagvedliggende virkningsmekanisme er ikke fuldt klarlagt. Ved lægemidlets binding til cellemembranen initierer interferon en kompleks intracellulær kaskade, der bl.a. hæmmer cellevækst og differentiering og øger immunrespons. Virkningen synes altså at kunne tilskrives dels en effekt på celledeling, og dels en mulig effekt på kroppens immunrespons over for de sygdomsramte celler [9].

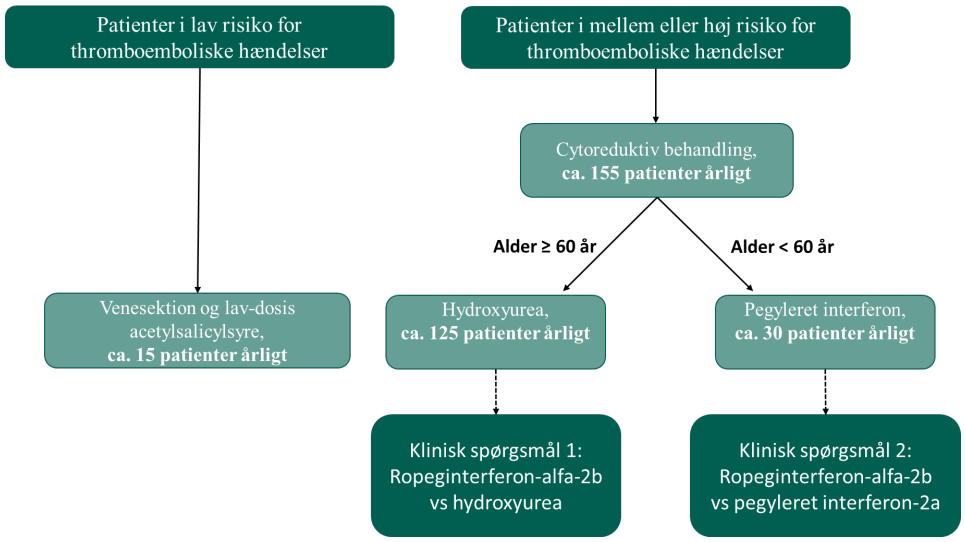
Ropeginterferon-alfa-2b er formuleret som en injektionsvæske (opløsning) i penne og administreres subkutant hver anden uge.

Startdosis er 100 µg og øges gradvist hver anden uge med 50 µg indtil stabilisering af hæmatologiske parametre (hæmatokrit < 45 %, blodplader < $400 \cdot 10^9$/L og hvide blodlegemer < $10 \cdot 10^9$/L). Doseringsintervallet kan forøges til hver 4. uge. Den maksimale enkeltdosis er 500 µg administreret hver 2. uge.

2.3 Nuværende behandling

Behandlingen af PV foregår typisk ambulant på hæmatologiske afdelinger. Behandlingen i den stabile fase er afhængig af risikofaktorer (alder, tidligere tromboemboliske hændelser, blodpladetal, andre risikofaktorer for tromboser og antallet af hvide blodlegemer) [10]. Generelt fokuserer den på at reducere risikoen for at udvikle tromboemboliske hændelser ved at sænke hæmatokritværdien (volumenfraktionen af røde blodlegemer) til 45 % eller derunder [11]. For patienter i lav-risikogruppen (patienter uden nogen af de ovennævnte risikofaktorer) kan dette ofte håndteres ved venesektioner (blodtapninger) samt lav-dosis acetylsalicylsyre (se Figur 1 nedenfor) [10]. Fagudvalget vurderer, at dette gælder knap 10 % af patienterne.

Såkaldt cytoreduktiv behandling med lægemidler, der kan normalisere eller nærnormalisere blodværdierne, tilbydes i dag flere patienter end tidligere (omkring 90 % af patienterne), dels for at sænke de forhøjede blodværdier, og dels med henblik på at reducere behovet for venesektion. Cytoreduktiv behandling foregår normalt enten med lægemidlerne hydroxyurea eller pegyleret interferon-alfa-2a [11]. Lægemidlerne har forskellig virkningsmekanisme, administrationsform og bivirkningsprofil. Som hovedregel er standardbehandlingen pegyleret interferon, hvis patienten er under 60 år (knap 20 % af patienterne), mens hydroxyurea kan anvendes, hvis patienten er over 60 år (omkring 70-75 % af patienterne) (se Figur 1 nedenfor for behandlingsalgoritme og forventede patientantal) [10]. Opdelingen efter alder skyldes, at hydroxyurea er mistænkt for at kunne øge risikoen for sekundære neoplasier, og derfor ønsker man som udgangspunkt ikke at behandle yngre patienter med dette, Pegyleret interferon-alfa-2a er ikke indiceret af EMA til behandling af PV, men anvendes som standard i klinisk praksis både i Danmark og internationalt [2,10,11].



Figur 1: Oversigt over behandlingsalgoritmen for patienter med polycytæmia vera og de deraf afledte kliniske spørgsmål.

Ved cytoreduktiv behandling kan der opnås en normalisering af blodværdierne (hæmatologisk remission/komplet hæmatologisk respons). Dette kan dog ikke sidestilles med helbredelse, idet den underlæggende JAK2-mutation, og derved sygdomsdriver, er uforandret. Behandling med pegylerede interferoner kan dog reducere antallet af celler, der bærer forandringen [12–14]. Det er uvist, hvad dette betyder for langtidsoverlevelse og livskvaliteten [2], men studier, der vil kunne dokumentere en eventuel effekt på overlevelsen, vil kræve meget lang observationstid og byde på udfordringer med hensyn til at holde populationerne separerede.

3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, Medicinrådet undersøger (interventionen), af den behandling, Medicinrådet sammenligner med (komparator(er)), og af effektmålene.

Medicinrådet har stillet to kliniske spørgsmål, hvor ropeginterferon-alfa-2b sammenlignes med hhv. hydroxyurea og pegyleret interferon-alfa-2a.

3.1 Klinisk spørgsmål 1

Hvilken værdi har ropeginterferon-alfa-2b sammenlignet med hydroxyurea for patienter over 60 år med polycytæmia vera?

Population
Patienter over 60 år med polycytæmia vera.

Intervention
Ropeginterferon-alfa-2b, som beskrevet i afsnit 2.2.

Komparator
Hydroxyurea i kapsler på 500 mg. 10-30 mg/kg dagligt.

Effektmål
De valgte effektmål fremgår af Tabel 1.

3.2 Klinisk spørgsmål 2

Hvilken værdi har ropeginterferon-alfa-2b sammenlignet med pegyleret interferon-alfa-2a for voksne patienter under 60 år med polycytæmia vera?

Population
Voksne patienter under 60 år med polycytæmia vera uden symptomatisk splenomegali.

Intervention
Ropeginterferon-alfa-2b, som beskrevet i afsnit 2.2.

Komparator
Pegyleret interferon-alfa-2a som subkutan injektion. Startdosis er 45 µg per uge, hvorefter dosis øges gradvist til maksimalt 180 µg per uge. Øgning af dosis sker månedligt med 45 µg per gang, hvis der ikke er opnået hæmatologisk respons.

Effektmål
De valgte effektmål fremgår af Tabel 1.

3.3 Effektmål

Det optimale overordnede effektmål til at vurdere behandlingen havde været samlet overlevelse. PV betragtes som en kronisk tilstand med generel lang overlevelse, og derved er det ikke realistisk at kunne måle en behandlingseffekt på overlevelsen uden at have en meget stor patientgruppe med meget lang opfølgningstid (> 10 år).

Medicinrådet mener, at vurderingen af lægemidlets værdi for begge kliniske spørgsmål bedst bliver understøttet af de effektmål, der er nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

Tabel 1: Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Tromboemboliske hændelser	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel af patienterne, der oplever minimum en tromboembolisk hændelse	5 %-point
			Kvalitativ gennemgang af hændelserne	-
Bivirkninger	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andelen af patienter, der oplever minimum én uønsket hændelse af grad 3-4, samt andelen, der oplever minimum én bivirkning af grad 3-4	5 %-point
			Kvalitativ gennemgang af bivirkningsprofil	-

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	MPN-SAF: Gennemsnitlig ændring fra baseline i *total symptom score* samt en kvalitativ gennemgang af domænescorer EQ-5D: Gennemsnitlig ændring fra baseline.	Ved MPN-SAF: 10 point på *Total symptom score* Ved EQ-5D: 0,1 point eller 10 point på EQ-5D VAS
Komplet hæmatologisk respons	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel der oplever komplet hæmatologisk respons	15 %-point

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
** Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.

3.3.1 Kritiske effektmål

Tromboemboliske hændelser
Tromboemboliske hændelser er en væsentlig årsag til øget sygdomsbyrde og overdødelighed for patienter med PV. Derfor betragter fagudvalget det som kritisk at mindske antallet af tromboemboliske hændelser. Samlet set forekommer tromboemboliske hændelser dog relativt sjældent. Fagudvalget estimerer, at ca. 25 % af patienterne oplever en tromboembolisk hændelse i løbet af deres sygdomsforløb, heraf dog en del inden diagnosen stilles. Da sygdomsforløbene ofte er langstrakte, er det begrænset, hvor mange hændelser, der vil kunne observeres i løbet af et randomiseret klinisk studie med 3-5 års opfølgningstid. Derfor vurderer fagudvalget, at en forskel på 5 %-point observeret i et randomiseret klinisk studie vil være klinisk relevant. Den mindste klinisk relevante forskel skal ses i det lys, at tromboemboliske hændelser dækker over både alvorlige hændelser, der kan medføre svær morbiditet eller død (eksempelvis lungeemboli og slagtilfælde), og milde hændelser (eksempelvis tromboflebit). Den kvantitative opgørelse kan derved give et indblik i patienternes samlede trombosetendens, men inklusionen af milde tromboemboliske hændelser medfører samtidig, at den mindste klinisk relevante forskel skal sættes højere for at repræsentere en værdi for patienterne.

Den forskellige alvorlighed af tromboemboliske hændelser betyder også, at en samlet kvantitativ vurdering alene ikke nødvendigvis er retvisende. Derfor ønsker fagudvalget en opgørelse over hvilke tromboemboliske hændelser, patienterne har oplevet, således

at fagudvalget kan udføre en kvalitativ vurdering af disse. Vurderingen af effektmålet vil bero på en samlet vurdering af den kvalitative og kvantitative gennemgang.

Livskvalitet
Ændring i livskvalitet er et patientrelevant effektmål, som kan afveje, hvordan lægemidlernes fordele og ulemper samlet set påvirker patienten. En populationsundersøgelse i Danmark, der inkluderede 910 patienter med PV, viste en svagt nedsat overordnet livskvalitet i patienter med PV sammenlignet med den almene befolkning [15]. Derfor vurderer fagudvalget, at en behandling, der minimerer patienternes symptomer, kan have potentialet til at forbedre deres overordnede livskvalitet. Modsat kan bivirkninger og gener ved en aktiv behandling i sig selv medføre et fald i patienternes livskvalitet. Da sygdommen betragtes som kronisk, og patienterne kan have meget lange behandlingsforløb, betragter fagudvalget livskvalitet som et kritisk effektmål.

Helbredsrelateret livskvalitet kan måles ved det sygdomsspecifikke redskab, *Myeloproliferative Neoplasm Symptom Assessment Form* (MPN-SAF), der er udviklet og valideret til myeloproliferative neoplasier, herunder PV [16]. MPN-SAF evaluerer en række karakteristiske symptomer ved PV og resulterer i scorer fra 0-10 for de enkelte symptomgrupper samt en samlet *total symptom score* fra 0-100. Fagudvalget foretrækker, at livskvaliteten opgøres vha. dette effektmål, og betragter en ændring i *total symptom score på 10 point* som den mindste klinisk relevant forskel. Desuden ønsker fagudvalget data for de enkelte underlæggende symptomgrupper for at kunne udføre en kvalitativ gennemgang af profilerne.

Hvis ikke der er data tilgængeligt fra dette måleinstrument, vil fagudvalget vurdere data opsamlet ved et generisk spørgeskema, eksempelvis EQ-5D. Dette består af fem dimensioner (bevægelighed, personlig pleje, sædvanlige aktiviteter, smerte/ubehag og angst/depression). Spørgeskemaet indeholder desuden en visuel analog skala (VAS), der går fra 0 (værst tænkeligt helbred) til 100 (bedst tænkeligt helbred) [17]. Fagudvalget betragter en ændring på 0,1 eller 10 point på EQ-5D VAS som klinisk relevant.

Uønskede hændelser og bivirkninger
Forekomst af uønskede hændelser (*treatment emergent adverse events*) og bivirkninger (*treatment related adverse events*) af grad 3-4 er et udtryk for alvorlig toksicitet af lægemidlet. På den baggrund vurderer fagudvalget, at uønskede hændelser og bivirkninger er et kritisk effektmål. Fagudvalget ønsker data på nedenstående måleenheder:

- Andelen af patienter, der oplever mindst én uønsket hændelse af grad 3 eller 4.
- Andelen af patienter, der oplever mindst én bivirkning af grad 3 eller 4.

Uønskede hændelser af grad 3-4 er defineret i henhold til National Cancer Institute CTCAE, version 4.03 [18]. Fagudvalget vurderer, at en forskel på 5 %-point er klinisk relevant, da selv en lille øgning af bivirkningshyppigheden kan have stor betydning for patienterne i et langvarigt behandlingsforløb. Fagudvalget ønsker at se frekvensen af både uønskede hændelser og bivirkninger, da uønskede hændelser ikke er påvirket af en subjektiv vurdering, ift. om en given uønsket hændelse er relateret til selve lægemidlet.

Opdeling i bivirkninger og uønskede hændelser kan samtidig være relevant for at danne et billede af, hvilke hændelser som skyldes lægemidlet, og hvilke hændelser som skyldes sygdommen.

- Kvalitativ gennemgang af bivirkninger og uønskede hændelser.

Ansøger bedes indsende en opgørelse over frekvensen af alle uønskede hændelser og bivirkninger. Fagudvalget vil gennemgå alle uønskede hændelser og bivirkninger, der opstår ved behandling med ropeginterferon-alfa-2b overfor komparatorerne, med henblik på at vurdere hændelsernes type, håndterbarhed og reversibilitet, samt i hvor høj grad uønskede hændelser og bivirkninger medfører behandlingsstop. Eftersom det ofte kan være vanskeligt at sammenligne kvantitative bivirkningsopgørelser på tværs af studier, vil fagudvalget lægge stor vægt på den kvalitative gennemgang i den samlede vurdering af effektmålet.

3.3.2 Vigtige effektmål

Komplet hæmatologisk respons
Komplet hæmatologisk respons anvendes ofte som det primære effektmål ved kliniske studier omhandlende PV [12–14,19], og det anses som et direkte behandlingsmål for alle behandlinger for PV [2,11]. Definitionen af komplet hæmatologisk respons kan variere mellem studier, men som oftest defineres det som sænkning af blodværdierne til hæmatokrit < 45 %, blodplader < $400 \cdot 10^9$/L, og hvide blodlegemer < $10 \cdot 10^9$/L, og nogle gange ledsages dette af fravær af forstørret milt og fravær af øget sygdomsbyrde. Fagudvalget betragter sænkningen af hæmatokritværdien som den vigtigste af disse parametre, da patienter med hæmatokrit > 45 % har en øget risiko for kardiovaskulære dødsfald [20]. Dette retfærdiggør også, at effektmålet i sig selv anses for vigtigt.

Frekvensen for komplet hæmatologisk respons varierer meget mellem studier. For behandling med pegyleret interferon-alfa-2a eller -2b rapporteres responsrater mellem 20 og 90 % [19], mens rater mellem 20 og 70 % er rapporteret ved behandling med hydroxyurea [12,21]. Dette illustrerer vanskeligheden i at sammenligne responsrater på tværs af studier.

Fagudvalget betragter en forskel på 15 %-point som klinisk relevant. Fagudvalget ønsker at vurdere effektmålet som sænkning af blodværdierne uden tilhørende udmåling af miltstørrelsen, da det vigtigste parameter er at sænke patientens hæmatokritværdi.

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Herudover kan data fra Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (fx NICE, EUnetHTA, FINOSE og IQWiG)

indgå i vurderingen. Medicinrådet kan også inddrage upublicerede og eventuelt fortrolige data – se Medicinrådets principper for anvendelse af upublicerede data.

Vedr. klinisk spørgsmål 1:
Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der findes et studie, hvor ropeginterferon-alfa-2b er sammenlignet direkte med hydroxyurea. Studiet er rapporteret i følgende publikation:

- Gisslinger et al. 2020: Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study [22] (EudraCT, 2012-005259 og 2014-001357-17)

Det er tilstrækkeligt datagrundlag til at besvare det kliniske spørgsmål. Ansøger skal derfor ikke søge efter yderligere data, men skal konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er). Fagudvalget er bekendt med, at der præsenteres 5-års opfølgningsdata fra PROUD-PV – CONTINUATION-PV på *American Society of Hematology Annual Meeting and Exposition* i december 2021, og ønsker at disse data medtages i ansøgningen. Fagudvalget bemærker derudover, at patienterne i PROUD-PV og CONTINUATION-PV ikke alle var over 60 år, hvorved patientpopulationen ikke fuldstændig svarer til den definerede population i klinisk spørgsmål 1. Fagudvalget forventer dog ikke, at patienternes alder i studiet påvirker behandlingernes effekt forskelligt, så længe alderen er balanceret mellem studiearmene. Derfor ønsker fagudvalget at vurdere data fra hele studiepopulationen uagtet patienternes alder.

Vedr. klinisk spørgsmål 2:
Medicinrådet er ikke bekendt med studier, hvor ropeginterferon-alfa-2b er sammenlignet direkte med pegyleret interferon-alfa-2a. Derfor skal ansøger søge efter studier til en indirekte sammenligning.

Søgestrengene fremgår af bilag 1. Derudover skal ansøger konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er).

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i klinisk spørgsmål 2, og artikler, der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål. Ligesom ved klinisk spørgsmål 1 forventer fagudvalget dog ikke, at patientpopulationernes alder påvirker behandlingernes resultater, så længe alderen er balanceret mellem studiearmene. Derfor ønsker fagudvalget ikke, at alder under 60 år indgår som et inklusionskriterie for litteratursøgningen.

Fagudvalget vurderer, at effekten af pegyleret interferon-alfa-2a og -2b overordnet set er ligeværdig. Derfor ønsker fagudvalget, at ansøger skal søge efter litteratur for både pegyleret interferon-alfa-2a og -2b, selvom kun -2a er tilgængelig i dansk klinisk praksis.

Kriterier for litteratursøgning
Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, fx i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur
Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med det/de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler først ekskludere på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement.

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal virksomheden anvende et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen skal vurderes.

5. Den endelige ansøgning

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.

- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (fx intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jf. appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'-modeller og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).

- Beskriv forskelle mellem studier, og vurdér, hvorvidt resultaterne er sammenlignelige.

Særlige forhold i denne protokol
Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

Sundhedsøkonomiske analyser
En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men er en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, fx behandlingslængde eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.
- Udfør følsomhedsanalyser, som belyser, hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

6. Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

Fagudvalget er beviste om, at det potentielt kan have en værdi at reducere JAK2-mutationsbyrden. Derfor ønsker fagudvalget at ansøger indsender data til at belyse dette både for interventionen og komparatorerne.

Nogle patienter vil opleve transformation til AML eller myelofibrose. Forekomsten er dog i begge tilfælde meget lav, og det vil kræve lang opfølgningstid og en stor studiepopulation at dokumentere forskelle i transformationsrisikoen. Derfor betragter fagudvalget ikke sygdomstransformation som et effektmål, men ønsker alligevel, at ansøger indsender data for dette for intervention og komparatorer, hvis der forefindes data. Fagudvalget ønsker at se data for dette, også selvom data stammer fra retrospektive kohortestudier.

8. Relation til behandlingsvejledning

Medicinrådet har publiceret en Behandlingsvejledning vedrørende cytoreduktiv behandling af Essentiel Trombocytose og Polycytæmia Vera. Behandlingsvejledningen er imidlertid ikke godkendt af Medicinrådet, da den omhandler anvendelse af lægemidler uden for den godkendte indikation. Medicinrådet kunne på daværende tidspunkt ikke udfærdige en generel anbefaling om, at der til en bestemt patientgruppe skal anvendes et bestemt lægemiddel, som ikke er godkendt til den pågældende indikation, medmindre der ikke findes godkendte lægemidler. Behandlingsvejledningen har derfor ikke dannet grundlag for et udbud eller en lægemiddelrekommandation, og derfor vil fagudvalget ikke foretage en indplacering af ropegingerferon-alfa-2b i forbindelse med nuværende vurdering.

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kroniske myeloproliferative sygdomme (inkl. kronisk myeloid leukæmi).

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Jesper Stentoft *Professor, overlæge*	Indstillet som formand af Dansk Hæmatologisk Selskab og Region Midtjylland samt udpeget som medlem af Region Midtjylland
Medlemmer	**Udpeget af**
Gitte Thomsen *Afdelingslæge*	Region Nordjylland
Andreja Dimitrijevic *Overlæge*	Region Syddanmark
Lene Udby *Overlæge*	Region Sjælland
Bo Kok Mortensen *Afdelingslæge*	Region Hovedstaden
Sidsel Marcussen *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Andreas Brønden *1. reservelæge*	Dansk Selskab for Klinisk Farmakologi
Mette Munk *Sygeplejerske*	Dansk Sygepleje Selskab
Michael Olsen	Danske Patienter
Annette Johansen	Danske Patienter

Medicinrådets sekretariat

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11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	21. december 2021	Godkendt af Medicinrådet

12. Bilag

Bilag 1: Søgestrenge

Klinisk spørgsmål 2

Søgestreng til PubMed: https://pubmed.ncbi.nlm.nih.gov/advanced/

#	Søgestreng	Kommentar
#1	Myeloproliferative Neoplasm*[ti] OR MPN[ti]	Population
#2	polycythemia rubra vera[tiab] OR polycythaemia rubra vera[tiab] OR polycythemia vera[tiab] OR polycythaemia vera[tiab] OR primary polycythemia[tiab] OR primary polycythaemia[tiab]	
#3	Polycythemia Vera[mh]	
#4	#1 OR #2 OR #3	
#5	ropeginterferon*[tiab] OR besremi*[tiab] OR peginterferon*[tiab] OR pegasys*[tiab]	Behandling
#6	peginterferon alfa-2a[nm] OR peginterferon alfa-2b[nm]	
#7	(Interferon-alpha[mh] OR Interferon alpha-2[mh]) AND Polyethylene Glycols[mh]	
#8	(PEG[tiab] OR pegylated[tiab] OR monopegylated[tiab] OR polyethylene glycol*[tiab]) AND (interferon*[tiab] OR IFN[tiab] OR rIFN[tiab] OR IFNα*[tiab] OR IFNalfa*[tiab] OR IFNalpha*[tiab])	
#9	(interferon*[tiab] OR IFN[tiab] OR rIFN[tiab]) AND (α[tiab] OR α2a[tiab] OR α2b[tiab] OR alfa*[tiab] OR alpha*[tiab])	
#10	IFNα*[tiab] OR IFNalfa*[tiab] OR IFNalpha*[tiab]	
#11	Interferon-alpha[majr] OR Interferon alpha-2[mh]	
#12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	
#13	#4 AND #12	
#14	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti] OR animal*[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti]	Irrelevante publikationstyper/ dyrestudier
#15	Animals[mh] NOT Humans[mh]	
#16	#13 NOT (#14 OR #15)	

#17	Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt]	Studiedesign
#18	controlled[tiab] OR group*[tiab] OR random*[tiab] OR placebo[tiab] OR trial[ti]	
#19	Clinical Trial[pt] OR Comparative Study[pt] OR Multicenter Study[pt] OR Observational Study[pt] OR Cohort Studies[mh] OR Prospective Studies[mh] OR Retrospective Studies[mh]	
#20	clinical trial[tiab]	
#21	(phase 2*[tiab] OR phase II*[tiab] OR phase 3*[tiab] OR phase III*[tiab] OR comparative[tiab]) AND (trial[tiab] OR study[tiab])	
#22	(observational[tiab] OR cohort*[tiab] OR prospective[tiab] OR retrospective*[tiab] OR multicenter[tiab] OR multi-center[tiab]) AND (study[tiab] OR analy*[tiab])	
#23	Registries[mh] OR registry[tiab] OR nation-wide[tiab] OR nationwide[tiab] OR real-world[tiab] OR real-life[tiab]	
#24	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	
#25	eng[la] AND hasabstract	Afgrænsning til artikler på engelsk og som har abstracts
#26	#16 AND #24 AND #25	Endelig søgning

Søgestreng til CENTRAL: https://www.cochranelibrary.com/advanced-search/search-manager

#	Søgestreng	Kommentar
#1	(myeloproliferative next neoplasm* or MPN):ti	Population
#2	((polycythemia or polycythaemia) near/2 (vera or primary)):ti,ab,kw	
#3	#1 or #2	
#4	(ropeginterferon next alpha2b or peginterferon next alpha* or recombinant next alpha2 next interferon):kw	Behandling
#5	(alpha2* next interferon):kw	
#6	(ropeginterferon* or besremi* or peginterferon* or pegasys*):ti,ab	
#7	((PEG or pegylated or monopegylated or polyethylene next glycol*) near/3 (interferon* or IFN or rIFN or IFNα* or IFNalfa* or IFNalpha*)):ti,ab	
#8	((interferon* or IFN or rIFN) near/3 (α or α2a or α2b or alfa* or alpha*)):ti,ab	

#9	(IFNα* or IFNalfa* or IFNalpha*):ti,ab	
#10	#4 or #5 or #6 or #7 or #8 or #9	
#11	#3 and #10	
#12	(clinicaltrials.gov or trialsearch):so	Irrelevante publikationstyper
#13	NCT*:au	
#14	#12 or #13	
#15	#11 not #14	
#16	pubmed:an	Eksklusion af referencer fra PubMed
#17	#15 not #16	Endelig søgning, afgræns til Trials