Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende avatrombopag til behandling af kronisk immun trombocytopeni

Vers. 1.0

Bilagsoversigt

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Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Avatrombopag

Kronisk immun trombocytopeni

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*.

Dokumentoplysninger	
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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
ITP	Immun trombocytopeni
SAIP	Sygehusapotekernes indkøbspris
TPO-RA	Trombopoietin-receptoragonist

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for avatrombopag ca. [redacted] DKK pr. patient pr. år sammenlignet med eltrombopag. Det vil sige, at der estimeres en gennemsnitlig [redacted] på ca. [redacted] DKK pr. patient pr. år ved brug af avatrombopag i stedet for eltrombopag. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 11.000 DKK pr. patient. Tidshorisonten i analysen er på 1 år, svarende til at patienterne er i behandling i 1 år.

Analysen er en omkostningsminimeringsanalyse, som kun sammenligner lægemiddelomkostningerne for avatrombopag og eltrombopag, da alle andre omkostninger forventes at være ens. Behandlingsvarigheden er usikker, da patienter kan opstarte og seponere behandling gennem hele livet. Der er også usikkerhed omkring de gennemsnitlige doser med avatrombopag og eltrombopag, da patienter ofte dosisjusteres i dansk praksis. Ved behandling med avatrombopag forventes dog samme grad af dosisjustering som ved behandling med eltrombopag.

Medicinrådet estimerer, at budgetkonsekvenserne for regionerne ved anbefaling af avatrombopag som mulig standardbehandling vil være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 1,6 mio. DKK i det femte år.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af avatrombopag som mulig standardbehandling på danske hospitaler til kronisk ITP.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Swedish Orphan Biovitrum A/S. Medicinrådet modtog ansøgningen den 23. november 2021.

3.1 Patientpopulation

Immun trombocytopeni (ITP) er en autoimmun sygdom, som forårsager øget nedbrydning af blodplader (trombocytter). Blodpladerne er nødvendige, for at blodet kan størkne (koagulere), og patienter med ITP har pga. det lave antal blodplader en øget risiko for blødninger. Sygdommen betegnes som kronisk, når patienten har haft vedvarende ITP i ≥ 12 måneder. Kronisk ITP forekommer i Danmark hos ca. 10 ud af 100.000 indbyggere med en incidens hos voksne på ca. 2,8 pr. 100.000 om året [1]. Fagudvalget anslår ud fra forbrugsopgørelser, at omkring 150 patienter i dag er i behandling med en TPO-RA, og at der årligt vil være omkring 30 nye patienter, der kandiderer til behandlingen.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af avatrombopag på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har avatrombopag sammenlignet med eltrombopag for patienter med primær kronisk ITP, som er refraktære over for tidligere behandlinger med glukokortikoider og evt. rituximab?

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 avatrombopag sammenlignet med eltrombopag. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

Ansøger har sammenlignet avatrombopag med eltrombopag på baggrund af en netværksmetaanalyse, hvor data fra studierne AVA-302 [1] og RAISE [2] indgår. AVA-302 er et randomiseret, dobbeltblindet, fase III-studie, der undersøgte avatrombopag over for placebo. RAISE er et randomiseret, dobbeltblindet, fase III-studie, der undersøgte eltrombopag over for placebo. På baggrund af netværksmetaanalysen konkluderer ansøger, at der ikke er forskel i effekten mellem avatrombopag og eltrombopag, og har derfor indsendt en omkostningsminimeringsanalyse.

Medicinrådets vurdering af antagelser og forudsætninger for modellen
Medicinrådet vælger ikke at anvende netværksmetaanalysen for at sammenligne de to lægemidler, da den er forbundet med usikkerhed, som følge af metodiske udfordringer i studierne. I stedet foretages der en naiv sammenligning af studiernes effekt og sikkerhedsdata i vurderingen af avatrombopag vs. eltrombopag. På baggrund af den naive sammenligning kommer Medicinrådet frem til samme vurdering som ansøger; at der ikke er betydelig forskel i effekten og/eller bivirkninger mellem avatrombopag og eltrombopag. Medicinrådet accepterer derfor ansøgers valg om at lave en omkostningsminimeringsanalyse. For yderligere information omkring det kliniske sammenligningsgrundlag, se Medicinrådets vurderingsrapport.

4.1.1 Modelbeskrivelse og analyseperspektiv.

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 1 år, og omkostningerne er derfor ikke diskonteret.

Medicinrådets vurdering af ansøgers model og analyseperspektiv
Ifølge fagudvalget er der stor variation i behandlingsvarigheden mellem patienter. Fagudvalget forventer ikke, at der vil være forskel i behandlingsvarigheden mellem eltrombopag og avatrombopag. Ved stabilt blodpladetal vil man forsøge at nedtrappe og seponere behandlingerne, men behandlingerne kan genopstartes ved behov. Medicinrådet accepterer derfor ansøgers valg af tidshorisont på 1 år. Omkostningerne til begge behandlinger vil være konstante for hvert år, patienterne yderligere er i behandling.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af avatrombopag sammenlignet med eltrombopag. Ansøgers analyse estimerer lægemiddelomkostningerne og yderligere omkostninger til monitorering ved eltrombopag i forhold til avatrombopag, da de to lægemidlers produktresuméer beskriver forskellige monitoreringsforløb, hvor det anbefales at tage test af levefunktionen ved patienter, som modtager eltrombopag. Fagudvalget vurderer dog, at monitoreringstest vil være ens for avatrombopag og eltrombopag. Medicinrådet accepterer derfor ansøgers analyse, hvor levertest er ekskluderet, og kun lægemiddelomkostningerne er inkluderet.

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).

Jf. produktresuméet doseres avatrombopag med 20 mg pr. dag, mens eltrombopag doseres med 50 mg pr. dag. Begge doseringer kan op- og nedjusteres baseret på blodpladerespons. Ansøger anvender de gennemsnitlige doser fra AVA-302 og et studie, som undersøgte den langsigtede effekt af og sikkerhed ved eltrombopag [3]. For avatrombopag var den gennemsnitlige dosis 22,3 mg pr. dag, mens den for eltrombopag var 50,2 mg pr. dag. Ansøger estimerer lægemiddelomkostningerne ved at beregne lægemiddelomkostningen pr. mg, og spild er derfor ikke medregnet i ansøgers analyse.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 1.

Tabel 1. Anvendte lægemiddelpriser, SAIP (december 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Pris pr. tablet [DKK]	Kilde
Avatrombopag	20 mg	10 stk.	[redacted]	[redacted]	Amgros
	20 mg	15 stk.	[redacted]	[redacted]	Amgros
	20 mg	30 stk.	[redacted]	[redacted]	Amgros
Eltrombopag	25 mg	28 stk.	[redacted]	[redacted]	Amgros
	50 mg	28 stk.	[redacted]	[redacted]	Amgros
	75 mg	14 stk.	[redacted]	[redacted]	Amgros

De gennemsnitlige doser for avatrombopag og eltrombopag virker rimelige ifølge fagudvalget. Fagudvalget forventer, at man i dansk praksis vil dosisjustere avatrombopag i samme grad som eltrombopag. Jf. produktresuméet for avatrombopag kan lægemidlet doseres med op til 40 mg dagligt. For eltrombopag er den maksimale dosis 75 mg dagligt jf. produktresuméet. Ifølge fagudvalget får nogle patienter op til 75 mg eltrombopag dagligt i dansk praksis, og fagudvalget vurderer, at nogle patienter vil få op til 40 mg avatrombopag dagligt. Betydningen af forskellige doseringer undersøges i følsomhedsanalyser. Der kan forekomme spild i forbindelse med dosisjusteringen, men dette vurderes af fagudvalget at være ubetydeligt.

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 ikke lavet følsomhedsanalyser.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Der er usikkerhed omkring de gennemsnitlige doser for eltrombopag og avatrombopag pga. høj grad af dosisjustering. Medicinrådet præsenterer derfor tre følsomhedsanalyser, hvor doserne for avatrombopag og eltrombopag varieres. I en følsomhedsanalyse, øges de gennemsnitlige doser til de maksimale doser (40 mg avatrombopag og 75 mg eltrombopag dagligt). I en anden følsomhedsanalyse øges doserne med 50 % ift. de anbefalede doser for begge lægemidler (30 mg avatrombopag og 75 mg eltrombopag dagligt). I en tredje følsomhedsanalyse reduceres doserne med 50 % ift. de anbefalede doser for begge lægemidler (10 mg avatrombopag og 25 mg eltrombopag dagligt).

4.4 Opsummering af basisantagelser

I Tabel 2 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 2. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	1 år	1 år
Inkluderede omkostninger	Lægemiddelomkostninger	Lægemiddelomkostninger
Gennemsnitlige doser:		
Avatrombopag Eltrombopag	22,3 mg 50,2 mg	22,3 mg 50,2 mg
Inkludering af spild	Nej	Nej

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i Medicinrådets hovedanalyse. Det vil sige, at der estimeres en gennemsnitlig [redacted] på ca. [redacted] DKK pr. patient pr. år ved brug af avatrombopag i stedet for eltrombopag.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 11.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 3.

Tabel 3. Resultatet af Medicinrådets hovedanalyse ved sammenligning med eltrombopag, DKK

	Avatrombopag	Eltrombopag	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
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 4.

Tabel 4. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen 22,3 mg avatrombopag og 50,2 mg eltrombopag	[redacted]
Maksimale doser: 40 mg avatrombopag og 75 mg eltrombopag	[redacted]
Doser øges med 50 % ift. de anbefalede doser: 30 mg avatrombopag og 75 mg eltrombopag	[redacted]
Doser reduceres med 50 % ift. de anbefalede doser: 10 mg avatrombopag og 25 mg eltrombopag	[redacted]

6. Budgetkonsekvenser

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

- Avatrombopag bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Avatrombopag 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 estimerer antallet af patienter, der kandiderer til behandling med avatrombopag på baggrund af data on file omkring prævalensen i Europa på 10 patienter pr. 100.000 indbyggere og en årlig stigning på 2,5 % i patientpopulationen. Ansøger antager heraf, at 7 % af patienterne vil modtage behandling med TPO-RA-lægemidler. Dette svarer til følgende patientantal: år 1: 192 patienter, år 2: 209 patienter, år 3: 230 patienter, år 4: 253 patienter og år 5: 271 patienter.

Ansøger antager, at avatrombopag vil være et alternativ til patienter, der har manglende effekt eller uacceptable bivirkninger ved behandling med eltrombopag. Ansøger anslår, at dette svarer til følgende markedsoptag: år 1: [redacted] %, år 2: [redacted] %, år 3: [redacted] %, år 4: [redacted] % og år 5: [redacted] %.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget anslår ud fra forbrugsopgørelser, at omkring 150 patienter i dag er i behandling med en TPO-RA, og at der årligt vil være omkring 30 nye patienter, der

kandiderer til behandlingen. Fagudvalget vil som udgangspunkt være tilbageholdende med at skifte velbehandlede patienter, der modtager eltrombopag, til avatrombopag. For nye patienter vælges den billigste behandling. Medicinrådet vurderer derfor, at hvis avatrombopag anbefales som standardbehandling, vil 30 nye patienter årligt modtage avatrombopag i stedet for eltrombopag. Medicinrådets estimat for patienter pr. år, der modtager hhv. avatrombopag eller eltrombopag, kan ses i Tabel 5.

Tabel 5. Medicinrådets estimat af antal patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Avatrombopag	30	60	90	120	150
Eltrombopag	150	150	150	150	150
			Anbefales ikke		
Avatrombopag	0	0	0	0	0
Eltrombopag	180	210	240	270	300

6.2 Medicinrådets budgetkonsekvensanalyse

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

- Ændret patientantallet på baggrund af fagudvalgets vurdering
- Ændret markedsoptaget for avatrombopag, hvis behandlingen anbefales, så alle nye patienter starter behandling med avatrombopag.

Medicinrådet estimerer, at anvendelse af avatrombopag vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 6. Det vil sige, at der estimeres en [redacted] på ca. [redacted] DKK i det femte år ved brug af avatrombopag i stedet for eltrombopag.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 1,6 mio. DKK i år 5.

Tabel 6. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

7. Diskussion

Behandling med avatrombopag er forbundet med inkrementelle omkostninger på ca. [redacted] DKK pr. patient pr. år sammenlignet med behandling med eltrombopag. Det vil sige, at der estimeres en gennemsnitlig [redacted] på ca. [redacted] DKK pr. patient pr. år ved brug af avatrombopag i stedet for eltrombopag. Tidshorisonten i analysen er på 1 år svarende til, at patienterne er i behandling i 1 år. Den sundhedsøkonomiske analyse er en omkostningsminimeringsanalyse, da fagudvalget vurderer, at avatrombopag har sammenlignelig effekt og sikkerhedsprofil med eltrombopag. Analysen inkluderer kun lægemiddelomkostninger, da alle andre omkostninger forventes at være ens for de to behandlinger.

De gennemsnitlige doser pr. dag har betydning for analysens resultat. I dansk klinisk praksis er det almindeligt at dosisjustere patienter. Fagudvalget vurderer, at man vil dosisjustere begge lægemidler i samme grad, og hvis forholdet mellem dosisjusteringen er ens mellem avatrombopag og eltrombopag, har dosisjusteringen mindre betydning for analysens resultat.

Jf. produktresuméet kan doseringen af avatrombopag øges med 100 % (fra 20 mg til 40 mg dagligt), mens doseringen af eltrombopag kan øges med 50 % (fra 50 mg til 75 mg). Det har væsentlig betydning, hvis de daglige doser sættes til de maksimale doser (40 mg avatrombopag og 75 mg eltrombopag dagligt). De inkrementelle omkostninger stiger da fra ca. [redacted] DKK til ca. [redacted] DKK, og der er i dette scenarie ikke tale om [redacted]. Det er usikkert, hvor mange patienter der vil få den højeste dosis med avatrombopag.

8. Referencer

1. Jurczak W, Chojnowski K, Mayer J, Krawczyk K, Jamieson BD, Tian W, et al. Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia. Br J Haematol. 2018;183(3):479–90.

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3. Wong RSM, Saleh MN, Khelif A, Salama A, Portella MSO, Burgess P, et al. Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: Final results of the EXTEND study. Blood. 2017;130(23):2527–36.

9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	27. januar 2022	Godkendt af Medicinrådet

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK pr. år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 7.

Tabel 7. Resultatet af ansøgers hovedanalyse, DKK

	Avatrombopag	Eltrombopag	Inkrementelle omkostninger
Lægemiddelomkostninger	[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.

Med ansøgers antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af avatrombopag vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 8.

Tabel 8. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

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Forhandlingsnotat

Dato for behandling i Medicinrådet	Januar 2022 (skriftlig 7-ugers proces)
Leverandør	Swedish Orphan Biovitrum A/S (SOBI)
Lægemiddel	Doptelet (Avatrombopag)
Ansøgt indikation	Primær kronisk immun trombocytopeni hos voksne patienter, som er refraktære over for andre behandlinger (f.eks. glukokortikoider og immunglobuliner

Forhandlingsresultat

Amgros har opnået følgende pris på Doptelet (Avatrombopag):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Avatrombopag	20 mg / tabletter	10 stk.	4.092,99	[redacted]	[redacted]
Avatrombopag	20 mg / tabletter	15 stk.	6.139,49	[redacted]	[redacted]
Avatrombopag	20 mg / tabletter	30 stk.	12.278,97	[redacted]	[redacted]

Prisen er ikke betinget af en anbefaling fra Medicinrådet.

[redacted]

[redacted]

[redacted]

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

[redacted]

Tabel 2: Sammenligning af lægemiddelpriser

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år (DKK)
Avatrombopag	20 mg / tabletter	10 stk.	[redacted]	36,5	[redacted]
Avatrombopag	20 mg / tabletter	15 stk.	[redacted]	24,4	[redacted]
Avatrombopag	20 mg / tabletter	30 stk.	[redacted]	12,2	[redacted]
Eltrombopag	25 mg / tabletter	28 stk.	[redacted]	13	[redacted]
Eltrombopag	50 mg / tabletter	28 stk.	[redacted]	13	[redacted]
Eltrombopag	75 mg / tabletter	14 stk.	[redacted]	26,8	[redacted]
Avatrombopag 22,3 mg / dag (gns. dosis fra vurderingsrapporten)					[redacted]
Eltrombopag 50,2 mg / dag (gns. dosis fra vurderingsrapporten)					[redacted]

Status fra andre lande

Norge: Anbefalet[1].

Sverige: Anbefalet[2]

England: Afventer beslutning. Vurdering sat på hold pga. ressourceudfordring i NICE[3].

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/avatrombopag-doptelet-indikasjon-ii

[2] https://www.tlv.se/beslut/beslut-lakemedel/begransad-subvention/arkiv/2021-06-18-doptelet-ingar-i-hogkostnadsskyddet-med-begransning.html

[3] https://www.nice.org.uk/guidance/indevelopment/gid-ta10738

Fra:	Dorthea Elise Christiansen
Til:	"Karin Sennfält"
Cc:	Katrine Jürs; Mai Clifford
Emne:	Udkast til vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for avatrombopag til jeres gennemgang
Dato:	15. december 2021 10:17:00
Vedhæftede filer:	image001.png Udkast Medicinrådets sundhedsøkonomiske afrapportering vedr. avatrombopag-vers. 1.0-X.pdf Udkast Medicinrådets vurderingsrapport vedr. avatrombopag til kronisk immun trombocytopeni-vers. 1.0.pdf

Kære Karin og Mai

Sekretariatet fremsender hermed udkast til Medicinrådets vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for avatrombopag til kronisk ITP.
Medicinrådet følger 7 ugers processen i denne sag. Det betyder, at Medicinrådet først drøfter både vurdering og anbefaling af lægemidlet efter jeres høring og forhandling med Amgros.
I har i alt 5 hverdage til at sende eventuelle bemærkninger til kategoriseringen af lægemidlets værdi og den sundhedsøkonomiske afrapportering. **Jeres frist for at indgive kommentarer er derfor senest den 22. december.** I er selvfølgelig velkomne til at sende eventuelle bemærkninger inden denne dato. I må også gerne meddele, hvis I ikke har kommentarer til kategoriseringen.
Vurderer sekretariatet og fagudvalget, at jeres kommentarer giver anledning til at revurdere kategoriseringen af lægemidlets værdi, skal sagen tilbage til fagudvalget, og beslutning om anbefaling vil blive forsinket.
Jeres eventuelle kommentarer indgår i det materiale, som bliver fremlagt for Medicinrådet i forbindelse med deres behandlingen af sagen. Jeres eventuelle kommentarer bliver offentliggjort sammen med anbefalingen.

Vh Katrine og Dorthea

Dorthea E. Christiansen
Sundhedsvidenskabelig konsulent
+45 50 45 51 56
dec@medicinraadet.dk

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Fra:	Karin Sennfält
Til:	Dorthea Elise Christiansen
Cc:	Katrine Jürs; Mai Clifford
Emne:	RE: Udkast til vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for avatrombopag til jeres gennemgang
Dato:	15. december 2021 10:23:37

Kära Dorthea,

Tack för meddelande.

Jag kan dock inte öppna det bifogade meddelandet, det säger att jag inte har tillåtelse att öppna.

Jag skulle därför vara tacksam om du vill skicka dokumentet direkt till oss.

Tack så mycket!

Hälsningar
Karin

-----Original Message-----
From: Dorthea Elise Christiansen <DEC@medicinraadet.dk>
Sent: den 15 december 2021 10:18
To: Karin Sennfält <Karin.Sennfalt@sobi.com>
Cc: Katrine Jürs <KJU@medicinraadet.dk>; Mai Clifford <Mai.Clifford@sobi.com>
Subject: Udkast til vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for avatrombopag til jeres gennemgang

[EXTERNAL SENDER]

Fra: Karin Sennfält
Til: Dorthea Elise Christiansen
Cc: Katrine Jürs; Mai Clifford
Emne: RE: eftersending af dokumenter for avatrombopag
Dato: 22. december 2021 10:06:58
Vedhæftede filer: image001.png

Kära Dorthea,

Tack så mycket för bekräftelse, det låter bra.

Önskar dig också en underbar jul!

Hälsningar
Karin

From: Dorthea Elise Christiansen <DEC@medicinraadet.dk>
Sent: den 21 december 2021 20:13
To: Karin Sennfält <Karin.Sennfalt@sobi.com>
Cc: Katrine Jürs <KJU@medicinraadet.dk>; Mai Clifford <Mai.Clifford@sobi.com>
Subject: RE: eftersending af dokumenter for avatrombopag

[EXTERNAL SENDER]

Kære Karin,

Det er modtaget.
Jeg vil gerne bekræfte, at den konfidentielle pris ni har forhandlet med Amgros ikke publiceras (men bliver blændet i den offentlige version, som publiceras på vor hjemmesiden)

Med ønsket om en trevlig jul

Vh Dorthea

From: Karin Sennfält <Karin.Sennfalt@sobi.com>
Sent: 21. december 2021 18:23
To: Dorthea Elise Christiansen <DEC@medicinraadet.dk>
Cc: Katrine Jürs <KJU@medicinraadet.dk>; Mai Clifford <Mai.Clifford@sobi.com>
Subject: RE: eftersending af dokumenter for avatrombopag

Kära Dorthea,

Tack så mycket igen för dokumenten.

Vi har tittat igenom dem och vi har inga ytterligare kommentarer.

Jag skulle dock vara tacksam för bekräftelse att de delar som innehåller det konfidentiella pris som vi har överenskommit med Amgros kommer att tas bort innan dokumenten publiceras.

Tack igen, och önskar dig en trevlig kväll.

Hälsningar
Karin

From: Dorthea Elise Christiansen <DEC@medicinraadet.dk>
Sent: den 15 december 2021 10:31
To: Karin Sennfält <Karin.Sennfalt@sobi.com>
Cc: Katrine Jürs <KJU@medicinraadet.dk>; Mai Clifford <Mai.Clifford@sobi.com>
Subject: eftersending af dokumenter for avatrombopag

[EXTERNAL SENDER]

Kære Karin

Lykkes det at åbne dokumenterne nu?

Vh Dorthea

Dorthea E. Christiansen
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Medicinrådet

Medicinrådets vurdering vedrørende avatrombopag til behandling af kronisk immun trombocytopeni

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	27. januar 2022
Dokumentnummer	132821
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet anbefaler avatrombopag til patienter med blodsygdommen primær kronisk immuntrombocytopeni, som ikke responderer tilstrækkeligt over for tidligere behandlinger med glukokortikoider og evt. rituximab.

Medicinrådet vurderer, at avatrombopag ikke ser ud til at være hverken dårligere eller bedre end den behandling, patienterne får i dag. Derudover vil sundhedsvæsenets omkostninger til lægemidlet være rimelige.
Medicinrådet anbefaler, at regionerne bruger det lægemiddel, der er forbundet med de laveste omkostninger.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 28. januar 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

CI: Konfidensinterval

EMA: Det Europæiske Lægemiddelagentur (*European Medicines Agency)*

FAS: *Full analysis set*

GRADE: System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)

ITT: *Intention to treat*

ITP: Immun trombocytopeni

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

TEAE: *Treatment emergent adverse events*

TPO-RA: Trombopoietin-receptoragonister

SD: Standard deviation

SOBI: *Swedish Orphan Biovitrum A/S*

3. Introduktion

Formålet med Medicinrådets vurdering af avatrombopag til kronisk immun trombocytopeni er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Swedish Orphan Biovitrum A/S (SOBI). Medicinrådet modtog ansøgningen den 23. november 2021.

Avatrombopag vurderes efter Medicinrådets 7-ugers proces, da foreløbige data fra ansøger understøtter, at avatrombopag kan ligestilles med eltrombopag (hvilket er præmissen for, at lægemidlet kan indgå i en 7-ugers proces).

Det kliniske spørgsmål er:

Hvilken værdi har avatrombopag sammenlignet med eltrombopag for patienter med primær kronisk ITP, som er refraktære over for tidligere behandlinger med glukokortikoider og evt. rituximab?

3.1 Kronisk immun trombocytopeni

Immun trombocytopeni (ITP) er en autoimmun sygdom, som forårsager øget nedbrydning af blodplader (trombocytter) og forstadier hertil (megakaryocytter), hvilket resulterer i et nedsat antal af cirkulerende blodplader. Blodpladerne er nødvendige, for at blodet kan størkne (koagulere), og patienter med ITP har pga. det lave antal blodplader en øget risiko for blødninger.

ITP er en udelukkelsesdiagnose, som stilles på baggrund af blodprøver og diagnostiske tests, der har til formål at udelukke andre årsager til blodpladeмangel. Som led i udredningen foretages også ofte ultralydsscanning af milten og evt. knoglemarvsundersøgelse. Diagnosen kan stilles, når blodpladetallet er < 100 x 10^9 pr. liter, selvom den nedre grænse i normalområdet er højere end dette (150 x 10^9 pr. liter). Dette skyldes dels, at der først er behandlingsindikation ved betydeligt lavere værdier (typisk 20-30 x 10^9 pr. liter), samt at personer med et blodpladetal mellem 100-150 x 10^9 pr. liter har en god prognose og sjældent falder til lavere værdier. Der skelnes mellem primær ITP (ingen kendt årsag) og sekundær ITP, som opstår ved andre kendte autoimmune sygdomme og visse knoglemarvssygdomme. ITP betegnes som *persisterende,* når den nedsatte mængde af blodplader varer over 3 måneder, og *kronisk*, når den har varet i over 12 måneder.

Sygdommen findes både hos børn, hvor den ofte er forbigående, og hos voksne, hvor sygdommen oftest er kronisk med varierende sværhedsgrad og behandlingsbehov. Medianalderen ved diagnose er 55 år, men varierer meget.

Kronisk ITP forekommer i Danmark hos ca. 10 ud af 100.000 indbyggere med en incidens hos voksne på ca. 2,8 pr. 100.000 om året [1]. Fagudvalget anslår ud fra forbrugsopgørelser, at omkring 150 patienter i dag er i behandling med en TPO-RA, og at der årligt vil være omkring 30 nye patienter, der kandiderer til behandlingen.

Patienternes symptomer inkluderer hudblødninger (purpura) i form af 1-2 mm store røde pletter på huden (petekkier) eller større blå mærker (ekkymoser) og blødning fra slimhinder i næse, mund, urinveje, tarm mv. Almindelige manifestationer er derfor også kraftige menstruationer (menoragi), mens blødning fra mave-tarmkanalen i form af synligt blod i afføring eller blødning fra urinveje med blod i urin er sjældnere. Af størst alvorlighed for patienter med ITP er deres forhøjede risiko for indre blødninger, herunder transfusionskrævende tarmblødninger og intrakranielle blødninger. Alvorlige blødninger forekommer sjældent, men risikoen stiger med alderen. Således har patienter > 60 år højere risiko end yngre. I Danmark har patienter med kronisk ITP en 1-års risiko for hospitalisering af enhver årsag på 15 %, hvilket er 4,5 gange højere end alders- og kønsmatchede personer. 5-års risikoen for intrakranielle blødninger er 1,4 %, hvilket er 3,2 gange højere end alders- og kønsmatchede borgere, mens risikoen for andre alvorlige blødninger, der kræver indlæggelse, er 3,6 %, hvilket er 4,4 gange baggrundsbefolkningens [2]. Patienter, som tidligere har haft alvorlig blødning, har en højere risiko for en ny blødning [3].

Patienternes livskvalitet kan påvirkes af blødningerne, men desuden også af træthed, af frygten for alvorlige blødninger samt af bivirkninger og ulemper ved behandling af sygdommen. Livskvaliteten hos patienter med kronisk ITP er betydeligt forringet, sammenlignet med baggrundsbefolkningen, og er på niveau med en række andre kroniske sygdomme som f.eks. leddegigt og cancer [4].

Patienter med kronisk ITP har en dødelighed på ca. 1,5 i forhold til en dansk baggrundsbefolkning [5], hvilket svarer til, at den forventede middellevetid sænkes med knap 4 år. Den forhøjede dødelighed hænger bl.a. sammen med, at sygdommen er forbundet med risiko for andre hæmatologiske komplikationer og kardiovaskulær sygdom, forhøjet risiko for tromboser og hæmatologisk kræft. Trombosetendensen er sandsynligvis multifaktoriel og muligvis relateret til autoimmunitet, men kan også skyldes, at patienterne, på grund af frygten for blødninger, i mindre omfang bliver behandlet med antikoagulerende behandling og trombocythæmmere, som ellers ville have været indiceret. Forklaringen på den øgede forekomst af hæmatologisk kræft er formentlig, at ITP er en eksklusionsdiagnose, hvor en evt. underliggende knoglemarvssygdom ikke altid er synlig til stede på diagnosetidspunktet. Derudover kan de immunsuppressive behandlinger, der benyttes som standardbehandling til ITP, også være kræftfremkaldende. Blandt andet af disse grunde forbliver patienter med ITP ofte i langvarig opfølgning.

3.2 Nuværende behandling

Behandlingsbehovet ved ITP vurderes på baggrund af kliniske symptomer og blodpladetallet. Et blodpladetal på < 20-30 x 10^9/L er en typisk behandlingsindikation hos nydiagnosticerede patienter.

Nydiagnosticerede patienter behandles oftest i 2-3 måneder med glukokortikoider eller i kombination med rituximab i 4 uger, som anvendes off-label. Behandlingsbehovet er ofte tilbagevendende hos 60-75 %. Tiltagende sygdomsaktivitet viser sig ved blødning i slimhinderne eller faldende trombocyttal og defineres som et markant fald i trombocyttal til udgangspunktet før behandling eller lavere.

Har patienten haft et godt respons på den første behandling, vil dette oftest gentages ved tilbagevendende behandlingsbehov, indtil responset ikke længere er tilfredsstillende, eller tilbagefaldene er hurtige eller mange. I princippet ophører en virksom behandling af kronisk ITP først, hvis der er tegn på spontan remission af den autoimmune sygdom, eller hvis respons tabes, eller der opstår bivirkninger.

Behandling af kronisk ITP er individualiseret og afhænger af effekt og bivirkninger ved tidligere behandlinger samt en vurdering af alder, blødningsrisiko, komorbiditeter (herunder samtidige lægemidler), risiko for traumer mm. [3].

Behandlingsmuligheder efter glukokortikoider og evt. rituximab inkluderer først og fremmest trombopoietin-receptoragonister (TPO-RA), som omfatter lægemidlerne eltrombopag (daglig tabletbehandling) og romiplostim (subkutan injektion én gang om ugen) [6]. Flest patienter behandles med eltrombopag som følge af administrationsvejen. Har patienten ikke effekt af eltrombopag, udelukker det ikke en effekt af romiplostim eller omvendt [7–9]. Typisk afprøves en anden TPO-RA-behandling ved svigt af den første. Hvis TPO-RA ikke har en effekt, kan øvrige behandlingsmodaliteter såsom dapson, danazol, mycophenolate mofetil, azathioprin eller ciclosporin også anvendes [3]. I den nyeste American Society of Hematology (ASH) guideline bliver behandling med TPO-RA'er eller rituximab anbefalet som 2. linjebehandling, mens de øvrige behandlingsmodaliteter anbefales i senere behandlingslinjer [6]. Ikke alle øvrige behandlingsmodaliteter har indikation til ITP og anvendes derfor off-label. Evidensen for de øvrige behandlingsmodaliteter ved ITP er dårlig, men den kliniske erfaring er lang, og nogle patienter har god effekt af disse lægemidler.

Behandling med både TPO-RA'er og andre behandlingsmodaliteter er længerevarende (ofte flere år). TPO-RA'er virker hurtigt (typisk indenfor uger), mens de øvrige behandlingsmodaliteter har mere langsomt indsættende effekt (ofte uger til måneder). Valg af behandling sker bl.a. på baggrund af overvejelser om behovet for hurtigt indsættende effekt, alder og vurdering af den forventede behandlingsvarighed, idet langvarig immunsuppressiv behandling kan være kontraindiceret på grund af risiko for infektioner og kræft.

Hos patienter med kronisk ITP vil behandlingsbehovet være vedvarende eller tilbagevendende resten af livet, men sjældent ses spontan remission. Fagudvalget vurderer, at det sker hos ca. 5 %.

En behandlingsmulighed er også at fjerne milten (splenektomi). Tidligere har splenektomi været en almindelig anvendt behandlingsmulighed til kronisk ITP, men splenektomi anvendes sjældnere i dag og aldrig til børn.

I akutte situationer, ved behov for hurtigt indsættende effekt, kan immunglobuliner eller transfusion med blodplader anvendes. [3] Effekten af behandlingerne er hurtigt indsættende (indenfor timer), men meget kortvarig. Transfusion med blodplader bør kun anvendes ved kritisk blødning eller forud for akut operation.

Monitorering
Patienter med ITP trænes i selvobservation (f.eks. for blå mærker) og monitoreres i klinikken med patientrapporteret blødningstendens, synlige tegn på blødningstendens og blodprøvekontrol. Patienternes kontrolbehov varierer meget, men typisk tages en blodprøve hver 6. måned. Patienter i vedvarende behandling vil typisk monitoreres oftere.

3.3 Avatrombopag

Avatrombopag er en trombopoietin-receptoragonist (TPO-RA), som stimulerer dannelse og udvikling af megakaryocytter i knoglemarven og derved fremmer dannelsen af blodplader.

Avatrombopag er i European Medicines Agency (EMA) godkendt til følgende indikationer:

- Svær trombocytopeni hos voksne patienter med kronisk leversygdom, for hvem et invasivt indgreb er planlagt. (*Positive Opinion* i EMA den 26. april 2019).
- Primær kronisk immun trombocytopeni hos voksne patienter, som er refraktære over for andre behandlinger (f.eks. glukokortikoider og immunglobuliner). (*Positive Opinion* i EMA den 10. december 2020).

Denne vurdering omhandler sidstnævnte indikation vedr. ITP.

Fagudvalget bemærker, at betegnelsen *refraktær* har en uaktuel definition i nuværende klinisk praksis, idet definitionen forudsætter, at milten er fjernet (splenektomi).

I dag anvendes betegnelsen *refraktær* mere uspecifikt om patienter, der ikke responderer tilfredsstillende over for en eller flere almindeligt anvendte behandlinger.

Fagudvalget bemærker desuden, at immunglobuliner kun anvendes i akutte situationer, og mener, at avatrombopag bør placeres som en 2. linjebehandling efter glukokortikoider og evt. rituximab på linje med de øvrige TPO-RA'er. Af samme årsag vurderer Medicinrådet, at eltrombopag er en relevant komparator til avatrombopag.

Avatrombopag indtages oralt som tabletter á 20 mg en gang dagligt. Tabletterne indtages i forbindelse med et måltid. Avatrombopag er ifølge EMA's produktresumé ikke forbundet med måltidsrestriktioner i forbindelse med indtag [10]. Dette gør sig dog gældende for eltrombopag, hvor man skal være opmærksom på kation-interaktion, hvilket betyder, at fx mejeriprodukter skal undgås 4 timer før dosering og 2 timer efter dosering [11].

Avatrombopag doseres efter antallet af trombocytter i blodet. Generelt skal den laveste mulige dosis anvendes for at opnå og vedligeholde et trombocyttal på ≥ 50 x 10^9/L. Initialdosis er 20 mg (dvs. én tablet) pr. dag. Dosis kan både optitreres (til 40 mg) og nedtitreres.

Avatrombopag kan gives i kombination med anden ITP-behandling, f.eks. glukokortikoider.

Hos patienter med øget tromboserisiko bør behandling med avatrombopag overvejes nøje og foregå med særlig omhyggelig monitorering [10].

Fagudvalget forventer som udgangspunkt, at behandling med avatrombopag er længerevarende, men at varigheden kan variere fra måneder til livslang.

4. Metode

Medicinrådets protokol for vurdering af avatrombopag til behandling af kronisk immun trombocytopeni 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

5.1.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt to placebokontrollerede studier (AVA-302 og RAISE).

Derudover har ansøger også fundet et yderligere studie på clinicaltrials.gov, hvor avatrombopag er sammenlignet direkte med eltrombopag. Studiet blev ikke identificeret i litteratursøgningen (studiet AVA-305).

Tabel 1 viser oversigten over de tre studier.

Tabel 1. Oversigt over studier

	AVA-302	AVA-305	RAISE
Publikation	Jurczak, W., et al., 2018 [12]	Tarantino, M D., et al., 2020 (abstract) [13]	Cheng, G., et al., 2011 [14]
NCT-nummer	NCT01438840	NCT01433978	NCT00370331
Studietype	Randomiseret, dobbeltblindet, fase III-studie	Randomiseret, dobbeltblindet, fase III-studie	Randomiseret, dobbeltblindet, fase III-studie
Population	49 voksne patienter med kronisk ITP	Voksne med kronisk ITP *Ønske om at rekruttere 286 patienter, men det lykkedes kun at inkludere 23*	197 voksne patienter med kronisk ITP
Intervention	Avatrombopag vs. placebo	Avatrombopag vs. eltrombopag	Eltrombopag vs. placebo
Opfølgningstid	26 uger	*Afsluttet for tidligt; designet til at vare 6 måneder, efterfuldt af et optil 104 ugers ekstensionsfasestudie. Gennemsnitlig behandlingslængde var 15,6 uger for avatrombopag og 10,5 uger for eltrombopag*	26 uger
Dato for studie (start – slutdato)	Februar 2012 – november 2013	Marts 2012 – september 2013 *(afsluttet tidligere end forventet, som følge af rekrutteringsproblemer)*	November 2006 – juli 2008
Primære respons-evaluering	Blodplade-respons	Blodplade-respons	Blodplade-respons

***AVA-302*:** Studiet inkluderede 49 voksne med kronisk ITP, hvilket blev defineret som en varighed ≥ 12 måneder. Patienterne skulle for at kunne blive inkluderet i studiet foruden deres sygdom have modtaget tidligere ITP-behandling, det var også tilladt at anvende samtidig ITP-behandling med kortikosteroider og azatioprin (stabil dosis op til fire uger

inden randomisering), mycophenolate mofetil, ciclosporin eller danazol (stabil dosis op til 12 uger inden randomisering) og protonpumpe inhibitorer (stabil dosis op til 6 uger inden randomisering) under studieperioden. Patienterne blev stratificeret til enten avatrombopag eller placebo baseret på miltstatus (splenektomi), blodpladetal ved baseline og anvendelse af samtidig ITP-medicin.

Studiet inkluderede 49 patienter, som blev randomiseret i en ratio 2:1 til enten placebo (n = 17) eller avatrombopag (n = 32) i 26 uger. Avatrombopag blev givet som startdosis af 20 mg i tillæg til standardbehandling. Dosis kunne justeres, alt efter om den enkelte patient oplevede et respons på behandlingen. Justeringen blev baseret på blodpladetallet målt hver 2. uge. Patienter med et blodpladetal < 50 x 10^9/L eller > 250 x 10^9/L kunne få justeret deres dosis på ugentlig basis. Dosis kunne titreres til maksimum 40 mg dagligt til minimum 5 mg dagligt. Det primære endepunkt var det kumulative antal uger med blodpladerespons (blodpladetal ≥ 50 x 10^9/L uden brug af rescue-behandling).

Behandlingsophør: I studiet så man et stort frafald, særligt i placeboarmen. Der var 16/17 patienter (94 %) i placeboarmen, som ophørte studiet, enten som følge af utilstrækkelig effekt (n = 15) eller andre årsager (n = 1). For avatrombopagarmen ophørte 10/32 patienter (31 %) studiet, enten som følge af utilstrækkelig effekt (n = 7) eller uønskede hændelser (n = 3). Det store behandlingsophør i placeboarmen medførte, at patienter behandlet med avatrombopag havde en længere gennemsnitlig eksponering, som var ca. 2,6 gange længere end placebogruppens (22,8 uger vs. 8,9 uger).

Sikkerhedsanalyserne er foretaget på baggrund af patienter, som havde modtaget mindst én dosis af enten avatrombopag eller placebo i studiet, og som kom til opfølgning enten i det primære studie eller i ekstensionsfasen. Effektanalyser i studiet er foretaget på *full analysis set* (FAS)-populationen (dvs. alle randomiserede patienter).

***AVA-305*:** Studiet var et direkte sammenlignede randomiseret, non-inferiørt dobbeltblindet, fase III-studie mellem avatrombopag og eltrombopag. Det bestod af to dele; del 1 var det primære studie (6 måneder), hvis formål var at undersøge avatrombopag mod eltrombopag ift. blodpladerespons. Del 2 omfattede en ublindet ekstensionsfase (OLE), hvor formålet var at undersøge sikkerhed og tolerabilitet for avatrombopag. Ekstensionsfasen varede i op til 104 uger. Patienterne blev ved randomiseringen stratificeret baseret på splenektomistatus, blodpladetal ved baseline og anvendelse af samtidig ITP-medicin. Studiet led under alvorlige rekrutteringsproblemer, målet var at inkludere 286 patienter i alt, men kun 23 patienter blev indrulleret. Studiet blev derfor afsluttet før tid (i løbet af ekstensionsfase-studiet). Ifølge clinicaltrials.gov gennemførte kun én patient det primære studie, og ingen patienter gennemførte ekstensionsfase-studiet. De 23 patienter blev randomiseret til enten 20 mg avatrombopag (n=12) eller 50 mg eltrombopag (n=11) dagligt. Det var tilladt at justere dosis for at opretholde et blodpladetal på mellem 50-150 x 10^9/L og for at nedbringe behovet af samtidig ITP-medicin. Det primære endepunkt var ændring fra baseline i blodpladetal i den 6 måneder lange behandlingsperiode.

Som følge af at studiet blev afsluttet tidligere end planlagt og kun formåede at inkludere en lille studiepopulation, er datagrundlaget sparsomt og spinkelt. Gennemsnitlig

behandlingslængde i studiet var hhv. 15,6 uger (median 13,1 uger) for avatrombopag og 10,5 uger (median 6,9 uger) for eltrombopag.

RAISE: Inkluderede 197 voksne patienter, som havde haft ITP i mere end 6 måneder, og som havde et blodpladetal < 30.000/µL. For at kunne blive inkluderet i studiet skulle patienterne tidligere have modtaget og responderet på mindst en ITP-behandling. Anvendelse af samtidig ITP-behandling var også tilladt, hvor følgende medikamenter var tilladte: Kortikosteroider og azatioprin (stabil dosis op til fire uger inden randomisering), mycophenolate mofetil, ciclosporin eller danazol (stabil dosis op til 12 uger inden randomisering), dosis skulle for samtlige medikamenter forblive uændret de første 6 uger af studiet. Patienterne blev randomiseret i en ratio 2:1 til behandling med enten 50 mg eltrombopag eller matchende placebo én gang dagligt i 6 måneder. Patienterne blev ved randomiseringen stratificeret baseret på splenektomistatus, blodpladetal ved baseline og anvendelse af samtidig ITP-behandling. Det var tilladt at lave dosisjusteringer baseret på blodpladetallet. Det var også tilladt at anvende rescue-medicin.

Behandlingsophør: 13/135 (9,6 %) patienter behandlet med eltrombopag ophørte behandlingen som følge af uønskede hændelser. I placeboarmen ophørte 4/62 (6,5 %) patienter som følge af uønskede hændelser. Der var ingen andre årsager til behandlingsophør.

Analyserne i studiet er lavet på *intention to treat (*ITT)-populationen.

Medicinrådet har i Tabel 2 angivet baselinekarakteristika for studierne. Til dette er ansøgers ansøgning og clinicaltrials.gov anvendt.

Tabel 2. Baselinekarakteristika af AVA-302, AVA-305 og RAISE

	AVA-302		**AVA-305**		**RAISE**	
	Placebo (n = 17)	**Avatrom-bopag (n = 32)**	**Avatrom-bopag (n = 12)**	**Eltrom-bopag (n = 11)**	**Placebo (n = 62)**	**Eltrom-bopag (n = 135)**
Alder (år), gennemsnit (SD)	41,2 (14,7)	46,6 (14,2)	50,8 (NA)	45,4 (NA)	51 (14,72)	46,5 (15,61)
Køn, kvinde, n (%)	8 (47,1)	23 (71,9)	7 (58,3)	7 (63,6)	43 (69,4)	93 (68,9)
Etnicitet, n (%) Kaukasisk Sort Asiatisk Andre	 15(88,2) 1 (15,9) 1 (5,9) 0	 31 (96,9) 0 1 (3,1) 0	NA	NA	 44 (71) 1 13 (21) 4	 101 (75) 2 21 (16) 11
Baseline blodpladetal, n (%) ≤ 15*10^9/L	 10 (58,8)	 18 (56,3)	NA	NA	 30 (49)	 67 (50)

	AVA-302		AVA-305		RAISE	
	Placebo (n = 17)	Avatrom-bopag (n = 32)	Avatrom-bopag (n = 12)	Eltrom-bopag (n = 11)	Placebo (n = 62)	Eltrom-bopag (n = 135)
15-30*10^9/L ≥ 30*10^9/L	7 (41,2) 0	13 (40,6) 1 (3,1)				
Splenektomi, n (%)	5 (29,4)	11 (34,4)	NA	NA	21 (34)	50 (37)
Brug af samtidig ITP-medicin ved baseline, n (%)*	7 (41,2)	15 (46,9)	NA	NA	31 (50)	63 (47)

*Det var I AVA-302 og RAISE tilladt at anvende kortikosteroider, azatioprin, mycophenolate mofetil, ciclosporin, danazol eller protonpumpe-inhibitorer (sidstnævnte kun i AVA-302), den præcise fordeling mellem medikamenterne kendes ikke. Forkortelser: NA = Not applicable.

Vurdering af forskelle i baselinekarakteristika

Fagudvalget vurderer, at baselinekarakteristika er balanceret mellem grupperne i studierne og sammenlignelig med danske patienter. AVA-305 opgør meget få baselinekarakteristika, hvilket vanskeliggør studiets sammenlignelighed med RAISE og AVA-302.

Der mangler information om baseline blodpladetal i RAISE, hvor kun andelen som har en blodpladetal ≤ 15*109/L kendes. Det antages dog at de resterende patienter (hhv. 51 % i placeboarmen og 50 % i eltrombopagarmen) må have et blodpladetal mellem 15-30*10^9/L, da patienter ikke blev inkluderet, hvis blodpladetallet var ≥ 30*10^9/L. Derfor vurderes det ikke at have nogen betydning i sammenligneligheden mellem studierne.

I screeningsperioden for AVA-302 fejlede 42/100 screening til studiet pga. inklusions- og eksklusionskriterierne. I RAISE gjorde det samme sig gældende for 88/285 patienter, hvilket kan betyde, at de mest behandlingskrævende patienter blev sorteret fra. Der ses dog ikke forskelle mellem studierne, hvorfor det ikke tillægges betydning.

Forskelle mellem studierne

RAISE, AVA-302 og AVA-305 adskiller sig ved definitionen af kronisk ITP. I RAISE var kronisk ITP defineret som en varighed på ≥ 6 måneder (baseret på daværende definition), mens det i AVA-302 og -305 var defineret som en varighed på ≥ 12 måneder (nuværende definition). Det kan have betydet, at sværhedsgraden i RAISE har været mindre end i AVA-302 og -305. Fortolkning af studiernes resultater skal også tages med forbehold som følge af alderen på studierne; i årene (2006-2007), hvor RAISE blev gennemført, var der ikke mange alternativer til lægemidler, hvis et lægemiddel ikke havde nogen effekt eller var forbundet med uacceptable bivirkninger. Fagudvalget vurderer derfor, at det kan have betydet, at færre ophørte behandlingen i RAISE sammenlignet med patienter i AVA-302 (udført i 2012-2015), fordi der i forsøgsperioden 2006-2007 ikke har været noget bedre alternativ.

5.1.2 Databehandling og analyse

Ansøger har udarbejdet en netværksmetaanalyse for en indirekte sammenligning mellem avatrombopag og eltrombopag på baggrund af data fra de placebokontrollerede studier AVA-302 og RAISE.

Fagudvalgets valg af analyse

Det store behandlingsophør for især placebogruppen i AVA-302 bidrager til stor usikkerhed i fortolkning af resultaterne, og gør det ikke muligt at lave en indirekte sammenligning via placebo mellem RAISE og AVA-302-studiet. Derfor vælger fagudvalget ikke at anvende ansøgers netværksmetaanalyse, da den er forbundet med for store usikkerheder og usikre antagelser pga. det skæve behandlingsophør i især AVA-302. Fagudvalget vælger i stedet at lave en naiv sammenligning af avatrombopag ved at sammenligne interventionsgrupperne (dvs. eltrombopag- og avatrombopag-gruppen) og se bort fra placebogrupperne i hhv. AVA-302 og RAISE.

Resultaterne fra AVA-305 fremgår af et abstract [13] og vedrører blodpladerespons og uønskede hændelser. Fagudvalget vurderer, at studiet AVA-305 er behæftet med stor usikkerhed og lav statistisk styrke som følge af en meget lille studiepopulation. Fagudvalget anvender derfor kun disse resultater som supplement til den naive sammenligning mellem AVA-302 og RAISE under effektmålet *blodpladerespons*.

Analyserede effektmål

Vedrørende effektmålet *blødninger*, som fagudvalget i protokollen ønskede opgjort i både alvorlige og mindre blødninger, har det ikke været muligt for ansøger at opdele hændelserne i mindre blødninger. I stedet har ansøger inkluderet *blødninger af enhver grad* og *alvorlige blødninger*, hvilket Medicinrådet accepterer.

Derudover har ansøger indsendt et yderligere effektmål for *blodpladerespons*, hvor ansøger har valgt at inkludere effektmålet *durable platelet response* (dansk: varigt blodpladerespons). Dette var muligt, da studierne RAISE og AVA-302 havde effektmålet tilfælles, i RAISE var effektmålet dog ikke prædefineret og blev først undersøgt i en post hoc-analyse. Fagudvalget ønsker at lade dette effektmål indgå i deres vurdering, da det giver en indikation af, hvor vedvarende en effekt af behandlingen er.

Ansøger har ikke udført en analyse for andelen, som ophørte behandlingen grundet uønskede hændelser, Medicinrådet vælger derfor at opgøre disse andele selv, da de angives i studierne.

Ubalancen i opfølgningstid i AVA-302 kan have medført en underestimering i forskellen mellem effektmålene blødninger og bivirkninger for avatrombopag og placebo.

For at sammenligne data mellem AVA-302 og RAISE er effektmålene opgjort efter 26 ugers opfølgning.

5.1.3 Evidensens kvalitet

Medicinrådet har ikke anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Det skyldes, at fagudvalget ikke vælger at tage

højde for placeboarmene i de to studier, som ligger til grund for vurderingen, som følge af meget stort frafald i placeboarmene. Det betyder i praksis, at fagudvalget kun anvender de aktive interventionsarme i sammenligningen mellem avatrombopag og eltrombopag, hvilket kan sammenlignes med enkeltarms-studier. Et enkeltarms-studiedesign medfører som udgangspunkt, at evidensen er af meget lav kvalitet.

Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at der er forbehold i vurderingen af risiko for bias i RAISE og risiko for bias i AVA-302 er høj. For begge studier gælder det, at der kan være risiko for, at patienter kan have gættet deres behandling som følge af symptomer, der manifesterer sig på baggrund af for lave blodplader, og at dette kan være årsag til studieophør. Samtidig kan anvendelsen af rescue-medication og optitrering i dosis som følge af manglende blodpladerespons også være årsager til, at blindingen potentielt ophæves. Det er dog ikke til at sige med sikkerhed, om dette var tilfældet i studierne. I AVA-302 medføre det skæve behandlingsophør mellem avatrombopag og placebo yderligere, at de to arme ikke umiddelbart kan sammenlignes, hvorved konsekvensen også bliver, at studiet ikke kan indgå i en indirekte statistisk sammenligning med RAISE-studiet.

Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 1.

5.1.4 Effektestimater og kategorier

Det er ikke muligt at rapportere de absolutte og relative effektforskelle, da sammenligningen mellem avatrombopag og eltrombopag er naiv. Derfor kan de enkelte effektmål eller den samlede værdi *ikke kategoriseres*, og evidensens kvalitet vurderes at være meget lav.

Resultater for hvert af effektmålene bliver herunder gennemgået.

Livskvalitet
Som beskrevet i protokollen er effektmålet *livskvalitet* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi behandlingen kan forventes at være langvarig, og patienternes livskvalitet er forringet af både symptomer, frygt for symptomer og behandlingen.

Livskvalitet var målt med SF-36 i både AVA-302 og RAISE, resultater for forskel i gennemsnitlig ændring fra baseline ses af Tabel 3.

Tabel 3. Resultater for livskvalitet målt ved SF-36, gennemsnitlig ændring fra baseline i AVA-302 og RAISE

Studie	Behandlingsarm	SF-36 fysiske komponent		SF-36 mentale komponent	
		Resultat	Absolut forskel	Resultat	Absolut forskel
AVA-302	Avatrombopag	0,71 [-2,49; 3,91]	-0,21 [-4,55; 4,13]	3,11 [-0,65; 6,88]	3,97
	Placebo	0,92 [-2; 3,85]		-0,85 [-3,82; 2,11]	
RAISE	Eltrombopag	1,5 *	-	1,7 *	-
	Placebo	-1,4 *		-0,6 *	

*RAISE rapporterede ikke estimater for standardafvigelser (SD) og beskrev ikke analysemetoden.

Fagudvalget kan ikke på det foreliggende datagrundlag udtale sig om, der er forskel mellem de to lægemidler i effekten på livskvalitet, men den mindste klinisk relevante forskel på 8 points forskel fra baseline er ikke i nærheden af at være opnået, heller ikke når lægemidlerne sammenlignes direkte med placebo.

Alvorlige blødninger

Som beskrevet i protokollen er effektmålet *alvorlige blødninger* kritisk for vurderingen af lægemidlets værdi for patienterne. Det skyldes, at alvorlige blødninger er det mest frygtede symptom ved ITP, selvom alvorlige blødninger er sjældne.

Blødninger var i AVA-302 og RAISE bestemt ved hjælp af WHO blødningsskala (grad 0: ingen; grad 1: petekkier; grad 2: mildt blodtab; grad 3: stort blodtab; grad 4: livstruende blodtab). Blødningstab af grad 2-4 blev defineret som alvorlige.

Hændelsesraterne for alvorlige blødninger i RAISE og AVA-302 ses af Tabel 4. Af tabellen ses det at hhv. 32,6 % i eltrombopagarmen og 9,4 % i avatrombopagarmen får en grad 2-4 blødning, hvilket giver en absolut forskel på 23,2 %-point til avatrombopags fordel. Dette overstiger den mindste klinisk relevante forskel på 1 %-point.

Tabel 4. Hændelsesrater for alvorlige blødninger i RAISE og AVA-302

	RAISE	AVA-302
Intervention (eltrombopag eller avatrombopag)	44/135 (32,6 %)	3/32 (9,4 %)
Komparator (placebo)	32/62 (51,7 %)	0/17 (0 %)

Fagudvalget vurderer, at WHO's blødningsskala er grov, og inddelingen i grad 2-4 er meget bred sammenlignet med, hvad fagudvalget vurderer er alvorlige blødninger (fx intrakranielle blødninger eller indlæggelseskrævende). Der er således stor forskel på, om

en blødning er af grad 2 eller 4 i WHO's definition, hvorfor fordelingen i de enkelte grader kunne være en værdifuld information.

Fra AVA-302 vides det, at ud af de tre patienter (i avatrombopagarmen), som oplevede en WHO grad 2-4 blødning, var der to patienter, som oplevede en grad 2, og en patient, som oplevede en grad 3 (epistaxis/næseblødning) [12]. Fra RAISE-studiet vides det ikke, hvorledes blødningerne fordeler sig i WHO's grad 2-4 definition. Dog rapporteres det, at oddsene for at få en blødning med eltrombopag er 65 % mindre sammenlignet med placebo (OR = 0,35, 95 % CI 0,19; 0,64) i studiet [14]. Derudover vides det fra sikkerhedsprofilen i RAISE, at uønskede hændelser ≥ grad 3 for fire patienter skyldtes blødninger i placeboarmen vs. tre patienter i eltrombopagarmen, hvilket styrker argumentet om, at mange af de resterende blødningerne rapporteret i RAISE er hvad man vil betegne som mindre alvorlige.

Alvorlige blødninger betegner fagudvalget som alvorlige, og i særdeleshed livstruende blødninger er erfaringsmæssigt sjældne ved ITP, hvilket vil kræve studier med lang tidshorisont for at vise en forskel. Fagudvalget bemærker, at ingen studier inden for ITP-området til dato har haft statistisk styrke til at vise en forskel.

Fagudvalget finder det vanskeligt at sammenligne og konkludere på hændelsesraterne for alvorlige blødninger anført i Tabel 4. Det skyldes, at fagudvalget har en mere streng definition af alvorlige blødninger, manglende oplysninger om fordelingen af grad 2-4 blødninger i RAISE, samt usikre resultater i AVA-302 som følge af få patienter i behandlingsarmen.

Mindre blødninger

Mindre blødninger er i protokollen defineret som et *vigtigt* effektmål. Disse blødninger er ofte generende for patienten og har betydning for patienternes livskvalitet og potentielt for deres vedholdenhed i forhold til deres behandling.

Blødninger var AVA-302 og RAISE bestemt ved hjælp af WHO's blødningsskala. Ansøger har afveget fra effektmålet *mindre blødninger* og rapporterer *blødninger af enhver grad* (grad 1-4). Resultaterne inkluderer altså for dette effektmål både mindre og alvorlige blødninger. Fagudvalget bemærker, at WHO-skalaen for definition af blødninger er meget unuanceret, da selv milde blødninger kan være generende og har stor betydning for patienternes livskvalitet.

Af Tabel 5 ses hændelsesrater for antal blødninger i RAISE og AVA-302.

Tabel 5. Hændelsesrater for alle typer blødninger i RAISE og AVA-302

	RAISE	AVA-302
Intervention (eltrombopag eller avatrombopag)	106/135 (78,5 %)	14/32 (43,8 %)
Komparator (placebo)	56/62 (90,3 %)	9/17 (52,9 %)

I AVA-302 var den hyppigste rapporterede blødning, blødning fra tandkødet og petekkier, alle var af WHO grad 1, bortset fra de tre patienter anført i Tabel 4, som oplevede blødninger af grad 2 og 3 [12]. Typen af blødning fra RAISE vides ikke.

Forskellen mellem behandlingsarmene i RAISE og AVA-302 er 35 %-point, hvilket overstiger den fastsatte mindste klinisk relevante forskel på 10 %-point. Fagudvalget vurderer dog, at det er svært at sammenligne resultaterne som følge af forskelle i studiestørrelserne, men vurderer, at der ikke er grund til at antage en forskel i klinisk praksis, trods forskellen mellem studierne.

Blodpladerespons

Blodpladerespons er i protokollen defineret som et vigtigt effektmål. Blodpladetallet er et surrogat for patientens blødningsrisiko. Fagudvalget anser effektmålet som relevant, fordi det er et tal, der monitoreres i klinikken, og er brugbart i forhold til at kunne vurdere, hvor hurtigt effekten af avatrombopag indsætter. Derudover indgår effektmålet også i vurderingen af, hvad patienterne ellers kan modtage af medicin, og om de kan gennemgå kirurgiske indgreb. Ansøger har indsendt data for det i protokollen efterspurgte effektmål vedr. blodpladerespons (andel, der opnår et blodpladetal ≥ 50 x 10^9 /L, opgjort efter 6 måneders behandling) samt suppleret med effektmålet varigt blodpladerespons, som fagudvalget vælger at tage med i sin vurdering af effektmålet.

Af Tabel 6 ses hændelsesraterne for varigt blodpladerespons, og andelen som opnår et blodpladetal ≥ 50 x 10^9 /L opgjort efter 6 måneders behandling for hhv. RAISE og AVA-302.

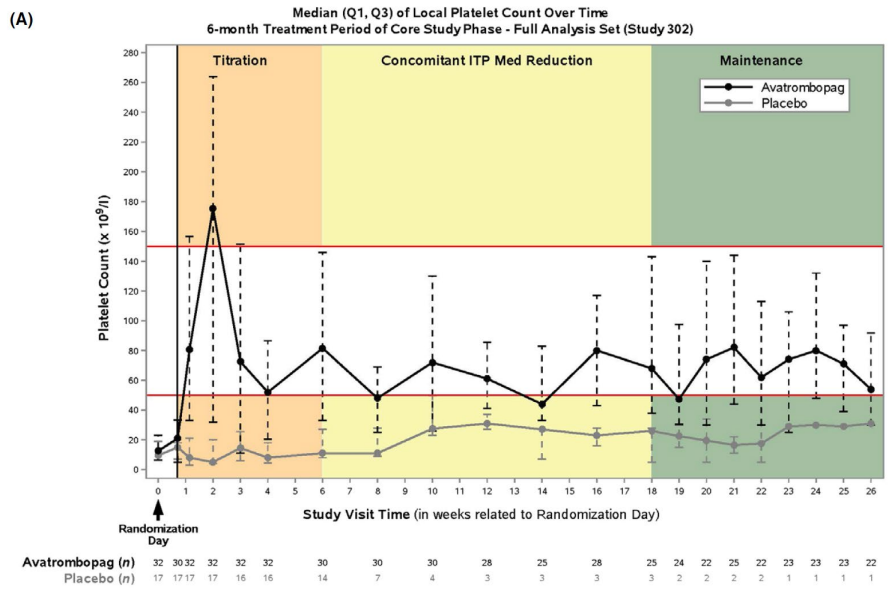
Fagudvalget vurderer, at avatrombopag og eltrombopag har en sammenlignelig effekt vedr. andelen, som opnår et blodpladetal ≥ 50 x 10^9 /L, da den absolutte forskel ikke overstiger den mindste klinisk relevante forskel på 10 %-point.
Fagudvalget vurderer, at resultaterne for varigt blodpladerespons er positive for begge studier, men tager forbehold i den naive sammenligning af interventionsarmene, da resultaterne i RAISE er opgjort ved en post-hoc analyse af tilgængelige blodpladetal.

Tabel 6. Hændelsesrater for blodpladetal i RAISE og AVA-302

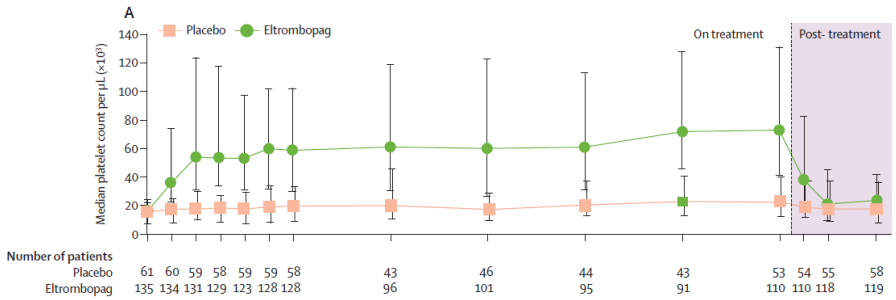
		RAISE	AVA-302
Andel, som opnår et blodpladetal ≥ 50 x 10^9 /L, opgjort efter 6 måneders behandling	Intervention (eltrombopag eller avatrombopag)	52/135 (38,5 %)	13/32 (41 %)
	Komparator (placebo)	17/62 (27,4 %)	0/17 (0 %)
Varigt blodpladerespons	Intervention (eltrombopag eller avatrombopag)	57/95 (60 %) *	11/32 (34 %)
	Komparator (placebo)	4/39 (10 %) *	0/17 (0 %)

*Post-hoc analyse af tilgængelige blodpladetal.

Fagudvalget har yderligere ønsket at vurdere blodpladeresponskurver. Disse ses for hhv. RAISE og AVA-302 i Figur 1 og Figur 2.



Figur 1. blodpladerespons kurve fra AVA-302 [12]



Figur 2. blodpladerespons kurve fra RAISE [14]

Fagudvalget vurderer, at kurverne for hhv. avatrombopag og eltrombopag er sammenlignelige med en medianværdi på ca. 60 x 10^9/L for begge. Kurven for avatrombopag i Figur 1 svinger meget i starten, hvilket fagudvalget mener kan være et udtryk for dosisjusteringer.

Fagudvalget vurderer, at avatrombopag har sammenlignelig effekt med eltrombopag.

Supplerende data vedr. blodpladerespons fra AVA-305
Af Tabel 7 ses det gennemsnitlige antal kumulative uger med blodpladerespons (≥ 50 x 10^9 /L).

Tabel 7. Gennemsnitlige antal kumulative uger med blodpladerespons [13]

	Avatrombopag (n = 12)	Eltrombopag (n = 11)
Gennemsnitlig kumulative antal uger med respons (SD)	5,4 (4,4)	4,3 (6,3)

Fagudvalget vurderer, at resultaterne fra AVA-305 indikerer, at avatrombopag har samme effekt som eltrombopag, hvilket understøtter fagudvalgets vurdering vedr. sammenligningen af avatrombopag med eltrombopag ud fra studierne RAISE og AVA-302. Fagudvalget vurderer, at studiet skal tolkes med forbehold, da studiepopulationen er meget lille, og opfølgningstiden kort.

Behandlingsophør som følge af uønskede hændelser
Behandlingsophør er i protokollen defineret som et *vigtigt* effektmål. Behandlingsophør grundet uønskede hændelser er relevant, da det belyser tyngden og alvorligheden af bivirkninger. Eftersom behandling med en TPO-RA forventes at være langvarig, er effektmålet også relevant, da det belyser, hvor godt lægemidlet tolereres af patienten.

Ansøger har ikke lavet nogen sammenlignende analyse mellem avatrombopag og eltrombopag vedr. behandlingsophør. Resultaterne er dog rapporteret i begge studiepublikationer fra AVA-302 og RAISE. I AVA-302 ophørte 0/17 (0 %) patienter behandlingen som følge af uønskede hændelser i placeboarmen, mens 3/32 (9,3 %) patienter i avatrombopagarmen ophørte som følge af uønskede hændelser. I RAISE ophørte 13/135 (9,6 %) patienter behandling med eltrombopag som følge af uønskede hændelser. I placeboarmen var andelen 4/62 (6,5 %) patienter.

Den absolutte forskel mellem interventionsarmene er dermed 0,3 %-point, hvilket ikke overstiger den mindste klinisk relevante forskel på 10 %-point. Fagudvalget vurderer, at lægemidlerne er sammenlignelige vedr. behandlingsophør som følge af uønskede hændelser.

Kvalitativ gennemgang af bivirkningsprofilerne
I AVA-302-studiet blev uønskede hændelser målt som *treatment-emergent adverse events* (TEAE), og i RAISE-studiet målt som *on-treatment adverse events*.

I AVA-302 oplevede 6,6 % af patienterne behandlet med placebo en TEAE, mens det gjorde sig gældende for 4,3 % af patienterne behandlet med avatrombopag (justeret for behandlingslængde). Den mest almindelige TEAE (≥ 20 % af patienterne) var blå mærker, hovedpine og øvre luftvejsinfektion. Incidensen af alvorlige uønskede hændelser (justeret for behandlingslængde) var højere for avatrombopag (1,2 %) sammenlignet med placebo (0,7 %).

I RAISE-studiet var incidensen af bivirkninger den samme for begge grupper og typisk milde af sværhedsgrad (grad 1-2). Den mest almindelig uønskede hændelse (≥ 20 % af patienterne) var hovedpine. Kvalme og opkast blev rapporteret i ≥ 5 % flere patienter behandlet med eltrombopag sammenlignet med placebo. Smerter i øvre maveregion

(dyspepsi), perifer hævelse, søvnløshed, næseblødning og blå mærker var rapporteret i ≥ 5 % flere patienter behandlet med placebo sammenlignet med eltrombopag.

Uønskede hændelser ≥ grad 3 skete i 20/135 (15 %) af patienterne behandlet med eltrombopag, versus 7/61 (11 %) af patienterne behandlet med placebo. De fleste (7 %) i placebogruppen skyldtes blødninger, heriblandt én patient, som døde af en blødning i hjernen. Kun 2 % af tilfældene hos patienterne behandlet med eltrombopag skyldtes blødninger, heraf fandt alle sted hos patienter med et blodpladetal < 50 x 10^9/L.

I RAISE-studiet var der derudover 7 % af patienterne behandlet med eltrombopag, som oplevede en stigning i alanin aminotransferase koncentrationen, mod 3 % af patienterne behandlet med placebo. 4 % af patienterne behandlet med eltrombopag oplevede også en stigning i koncentrationen af bilirubin mod 0 % af patienterne behandlet med placebo.

Den samlede bivirkningsprofil for AVA-302 og RAISE-studiet ses af bilag 2.

Overordnet vurderer fagudvalget, at der ikke er nogen bekymrende signaler ved sikkerhedsprofilerne for begge lægemidler, og sikkerhedsprofilerne er sammenlignelige. Fagudvalget bemærker, at selvom der ikke er nogen bekymrende signaler, kan de observerede uønskede hændelser godt være generende for den enkelte patient og derved have en betydning for den enkeltes livskvalitet.

5.1.5 Fagudvalgets konklusion

Værdien af avatrombopag sammenlignet med eltrombopag kan ikke kategoriseres i henhold til Medicinrådets metoder. Vurderingen er baseret på en naiv sammenligning mellem de aktive behandlingsarme fra to forskellige studier, da de to studier, som er anvendt i vurderingen, har været metodemæssigt udfordret med bl.a. små studiepopulationer og et omfattende og tidligt behandlingsophør i placebogruppen for avatrombopag-studiet AVA-302.

Fagudvalget vurderer på baggrund af det foreliggende datagrundlag, at avatrombopag har en sammenlignelig effekt med eltrombopag vedr. blødninger, blodpladerespons og bivirkninger. Det var ikke muligt at sammenligne livskvalitet for behandlingerne, men fagudvalget vurderer, at der ikke ses signaler på, at der skulle være forskelle i livskvalitet ved de to behandlinger.

Fagudvalget fremhæver, at administrationen af avatrombopag er forbundet med en lille fordel, da indtag af lægemidlet ikke er forbundet med måltidsrestriktioner, som ellers er tilfældet med eltrombopag.

6. Andre overvejelser

Skifte imellem TPO-RA-behandling

Fagudvalget bemærker, at der ikke er studier, som belyser effekt, dosering og bivirkninger ved et eventuelt skift fra en velfungerende behandling med én TPO-RA til en alternativ TPO-RA. Et sådant skift vil dermed kræve samme indsats fra patient og behandlende afdeling med hensyn til blodprøver og kliniske kontroller som en nyinstitueret behandling.

Betydning for behandlingssekvensen

Fagudvalget ønskede i protokollen viden om, hvorvidt der var en klasseeffekt ved behandling med to TPO-RA'er efter hinanden.

Ansøger referer i deres ansøgning til, at man i AVA-302 ikke så nogen forskel i effekt for de patienter, som tidligere havde været behandlet med en TPO-RA i forhold til de patienter, som ikke før havde været i en sådan behandling [15]. I AVA-302 havde 12/32 patienter i avatrombopag-gruppen før modtaget en TPO-RA, og man observerede ingen forskel i andelen, som opnåede blodpladerespons i løbet af de 6 måneder ift. tidligere TPO-RA-behandling eller ej, hvilket også ses af Tabel 8.

Tabel 8. Blodpladerespons i avatrombopagarmen i AVA-302 studiet, baseret på tidligere TPO-RA-behandling [15]

		Tidligere TPO-RA, N = 12	Ingen tidligere TPO-RA, N = 20
Kumulative antal uger med blodpladerespons	Median	12,7	12,4
	Gennemsnit (SD)	11,8 (9,11)	12,0 (8,77)
Blodpladerespons på dag 8		7/12 (58,3 %)	14/20 (70 %)
Blodpladerespons på dag 28		5/12 (41,7 %)	9/20 (45 %)
Blodpladerespons i måned 6		6/9 (66,7 %)	7/13 (53,9 %)

Medicinrådet vurderer, at der for nuværende ikke foreligger tilstrækkelig evidens for sekventiel behandling mellem eltrombopag og avatrombopag. Derfor anbefales det ikke at anvende de to behandlinger efter hinanden.

Behov for supplerende behandling

I AVA-302-studiet var der en reduktion i behovet for supplerende behandling. Ved baseline var det 15/32 (46,9 %) af patienterne behandlet med avatrombopag, som var i supplerende behandling, i placebogruppen var 7/17 (41,2 %) på supplerende behandling. 5/15 (33,3 %) i avatrombopag-gruppen kunne i løbet af studiet reducere deres behov for supplerende behandling. I placebogruppen var der ingen, som fik reduceret deres behov. Forskellen var dog ikke signifikant [CI 95 % 9,48; 57,19] som følge af et lavt antal patienter ved baseline, som anvendte supplerende behandling (hhv. 15 vs. 7 patienter).

I RAISE-studiet modtog 31/62 patienter randomiseret til placebo (50 %) ved baseline supplerende behandling, tilsvarende modtog 63/135 (47 %) af patienterne randomiseret til eltrombopag supplerende behandling ved baseline. 37/63 (59 %) patienter behandlet med eltrombopag fik reduceret deres behov for supplerende behandling i løbet af studiet, mod 10/31 (32 %) af patienterne i placeboarmen. Forskellen var dog ikke signifikant forskellig [CI 1,24; 7,75].

Lægemiddeladministration

Der er ingen restriktioner i forbindelse med indtag af avatrombopag, modsat eltrombopag. Avatrombopag skal jf. EMA's produktresumé indtages i forbindelse med et måltid, altid på samme tidspunkt af dagen. Fagudvalget vurderer, at det kan være en fordel for nogle patienter at vælge behandling med avatrombopag frem for eltrombopag, da avatrombopag ikke er forbundet med måltidsrestriktioner.

Dosisintensitet

Dosisjusteringer foretages på baggrund af blodpladetallet. Jf. EMA's respektive produktresuméer for avatrombopag og eltrombopag skal dosisjusteringer ske som beskrevet i Tabel 9.

Tabel 9. Dosisjusteringer af eltrombopag og avatrombopag

Blodpladetal (x 10^9/L)	Dosisjustering eller handling
Avatrombopag	
< 50 efter mindst 2 uger med behandling	Øg dosis et niveau. Vent 2 uger med at vurdere virkningen af dette regime og eventuelle efterfølgende justeringer
> 150 og ≤ 250	Sænk et niveau. Vent 2 uger med at vurdere virkningen af dette regime og eventuelle efterfølgende justeringer
> 250	Stop avatrombopag. Øg overvågning af blodpladetal til x 2 ugentligt. Når blodpladetallet er ≤ 100, så sænk et niveau og genstart behandling
< 50 efter 4 uge med avatrombopag 40 mg dagligt	Seponer
> 250 efter 2 uger med avatrombopag 20 mg dagligt	Seponer

Eltrombopag	
< 50 efter mindst 2 uger med behandling	Øg dosis med 25 mg dagligt til maksimum 75 mg/dag*
≥ 50 til ≤ 150	Anvend laveste eltrombopagdosis og/eller anden ITP-medicin for at fastholde et trombocyttal, hvor blødning undgås eller reduceres
> 150 til ≤ 250	Nedsæt den daglige dosis med 25 mg. Vent derefter 2 uger for at vurdere virkningen af dette og evt. efterfølgende dosisjusteringer**
> 250	Seponer. Øg monitoreringen af blodpladetallet til 2 gange om ugen. Hvis blodpladetallet ≤ 100, sættes behandlingen i gang igen med en daglig dosis nedsat med 25 mg.

*For patienter, der tager 25 mg eltrombopag én gang hver 2. dag, øges dosis til 25 mg én gang dagligt.
**For patienter, der tager 25 mg eltrombopag én gang dagligt, bør det overvejes at dosere med 12,5 mg én gang dagligt eller alternativt en dosis på 25 mg én gang hver 2. dag.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende benign hæmatologi

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Jesper Stentoft *Professor, overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Kaper Røikjær Jensen *Afdelingslæge*	Region Nordjylland
Henrik Frederiksen *Professor, overlæge*	Region Syddanmark
Birgitte Lausen *Overlæge*	Region Hovedstaden
Eva Birgitte Leinøe *Overlæge*	Region Hovedstaden
Mikkel Helleberg Dorff *Overlæge*	Region Sjælland
Klaus Reineck *Afdelingslæge*	Dansk Selskab for Klinisk Immunologi
Ane Hornbæk Mortensen *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Deltager ikke	Dansk Selskab for Trombose og Hæmostase
Udpegning i gang	Dansk Sygepleje Selskab
Ann Kjersgaard Meldal *Patient/patientrepræsentant*	Danske Patienter
Anders Vidstrup *Patient/patientrepræsentant*	Danske patienter

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	27. januar 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 10. Vurdering af risiko for bias, Cheng et al. 2011, *Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study*, NCT00370331

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	*All randomisations were done with RAMOS, an automated interactive voice recognition telephone randomisation and drug ordering system. Patients, investigators, and those assessing the data were masked to allocation.*
Effekt af tildeling til intervention	**Forbehold**	*Patients, investigators, and those assessing the data were masked to allocation.* Der kan være risiko for, at patienter og investigator er blevet klar over, hvilken behandlingsarm patienten var allokeret til. Det skyldes, at respons på behandlingen blev monitoreret og det samme med anvendelsen af rescue-medication.
Manglende data for effektmål	**Lav**	The primary analysis used data from nominal visits (weeks 1 – 6 inclusive, and weeks 10, 14, 18, 22, and 26), in case a nominal visit was not available, information from the immediately preceding, non-nominal visit was used, had the patient not withdrawn from the study. Assessments for patients who withdrew from the study were classified as negative from the time of withdrawal and for all subsequent nominal visits.
Risiko for bias ved indsamlingen af data	**Lav**	Patientrapporteret effektmål såsom livskvalitet kan være påvirket, da patienterne kan have gættet deres behandling undervejs. Det har dog ikke været muligt at evaluere på livskvalitet i vurderingsrapporten.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Sammenligning af artikel med information på clinicaltrials.gov viser primære og sekundære effektmål.
Overordnet risiko for bias	**Forbehold**	Der kan dog være risiko for, at blindingen af visse patienter er ophørt, som følge af dårlig respons på (placebo)behandlingen. Uvist hvilken påvirkning det har haft for risikoen for bias, men det primære respons (blodpladetal) er objektivt, derfor vurderes den overordnede risiko for bias at være lav.

Tabel 11. Vurdering af risiko for bias, Jurczak et al. 2018, *Phase 3 randomised study of avatrombopag, a novel thombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia* (AVA-302), NCT01438840

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Patienterne blev randomiseret ved hjælp af et *interactive voice and web response system.* *Randomisation data were kept strictly confidential, filed securely at each site, and were accessible only to authorized persons until the time of unblinding. A master list of all treatments was maintained in a sealed envelope with the sponsor. Corresponding patient numbers associated with a specific treatment were blinded in the interactive voice and web response system database*
Effekt af tildeling til intervention	**Forbehold**	Der kan være risiko for at patienter og investigator er blevet klar over, hvilken behandlingsarm patienten var allokeret til. Det skyldes, at respons på behandlingen blev monitoreret, og det samme med anvendelsen af rescue-medication.
Manglende data for effektmål	**Høj**	Der mangler information om, hvordan manglende data håndteres. Effektanalyser er baseret på *full analysis set (FAS),* dvs. samtlige randomiserede patienter. Det store frafald i placebogruppen bevirker at der mangler meget data for disse patienter.
Risiko for bias ved indsamlingen af data	**Lav**	Patientrapporteret effektmål såsom livskvalitet kan være påvirket, da patienterne kan have gættet deres behandling undervejs. Det har dog ikke været muligt at evaluere på livskvalitet i vurderingsrapporten.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	*The study protocol was amended in March 2013, changing the primary endpoint from durable platelet response to the cumulative number of weeks of platelet response over 6 months of treatment in order to support a planned regulatory filing of avatrombopag in Japan. Platelet response at day 8 was also changed from a secondary to an exploratory endpoint, and the anticipated sample size was reduced from 100 to 45 subjects.*
Overordnet risiko for bias	**Høj**	Der kan dog være risiko for, at blindingen af visse patienter er ophørt, som følge af dårlig respons på (placebo)behandlingen. Uvist hvilken påvirkning det har haft for risikoen for bias, men det primære respons (blodpladetal) er objektivt, derfor vurderes den overordnede risiko for bias at være lav.

Bilag 2: Bivirkningsprofil for avatrombopag og eltrombopag baseret på studierne AVA-302 og RAISE

Table 12. Reports of adverse events amongst avatrombopag and eltrombopag treated patients in the AVA-302 and RAISE trials

Adverse events*, %	AVA-302		RAISE	
	Avatrombopag (N = 32)	Placebo (N = 17)	Eltrombopag (N = 135)	Placebo (N = 61)
Headache	37.5	11.8	30	33
Contusion	31.3	23.5	1	5
Upper respiratory tract infection	18.8	5.9	10	11
Arthralgia	12.5	0	7	5
Epistaxis	12.5	17.6	5	10
Fatigue	12.5	5.9	10	13
Gingival bleeding	12.5	0	n/a	n/a
Petechiae	12.5	5.9	n/a	n/a
Thrombocytopenia	6.3	0	n/a	n/a
Pharyngitis	0	5.9	6	1
Hypertension	6.3	5.9	3	5
Nasopharyngitis	9.4	0	10	13
Diarrhoea	n/a	n/a	13	10
Nausea	n/a	n/a	12	7
Limb pain	n/a	n/a	7	10
Increased ALT concentration	n/a	n/a	7	7
Vomiting	n/a	n/a	7	2
Urinary tract infection	n/a	n/a	7	7
Oropharyngeal pain	n/a	n/a	7	5
Myalgia	n/a	n/a	6	3
Increased AST concentration	n/a	n/a	5	3
Back pain	n/a	n/a	5	5
Influenza	n/a	n/a	5	5
Cough	n/a	n/a	4	7
Upper abdominal pain	n/a	n/a	4	8
Constipation	n/a	n/a	4	8
Dizziness	n/a	n/a	4	10
Pruritus	n/a	n/a	3	8
Cataract	n/a	n/a	3	7‡
Peripheral oedema	n/a	n/a	1	10‡§
Dyspepsia	n/a	n/a	1	7‡§
Ecchymosis	n/a	n/a	2	7
Insomnia	n/a	n/a	1	7‡

Adverse events*, %	AVA-302		RAISE	
Anxiety	n/a	n/a	1	5
Conjunctival haemorrhage	n/a	n/a	1	5
Neck pain	n/a	n/a	1	5
Non-cardiac chest pain	n/a	n/a	1	5
Abdominal distension	n/a	n/a	<1	5
Conjunctivitis	n/a	n/a	<1	7
Fall	n/a	n/a	<1	5
Face swelling	n/a	n/a	<1	5
Cellulitis	n/a	n/a	0	7‡
Eye swelling	n/a	n/a	0	5

Abbreviation: AST: asparagine aminotransferase; ALT: alanine amino transferase; GGT: gamma-glutamyl transferase; n/a: not available.

Note: *AVA-302 measured treatment-emergent adverse events, while RAISE measured on-treatment adverse events.
‡ Events typically associated with corticosteroid use.
§ Significantly lower for avatrombopag versus placebo using two-sided Fisher's exact test (p=0·01).

Application for the assessment of Doptelet (avatrombopag) for the treatment of adult patients with chronic immune thrombocytopenia (ITP) who are refractory to other treatments (e.g., corticosteroids, immunoglobulins)

Contents

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1. Basic information

Kontaktoplysninger	
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Overview of the pharmaceutical	
Proprietary name	Doptelet
Generic name	Avatrombopag
Marketing authorization holder in Denmark	Swedish Orphan Biovitrum A/S (SOBI)
ATC code	B02BX08
Pharmacotherapeutic group	Thrombopoietin receptor agonist (TPO-RA)
Active substance(s)	Avatrombopag
Pharmaceutical form(s)	Oral tablet
Mechanism of action	Small-molecule TPO-RA, which stimulates natural platelet production leading to a predictable increase in platelet count. Avatrombopag does not compete with TPO for binding to the TPO receptor and has an additive effect with TPO on platelet production
Dosage regimen	Initial dose regimen: Begin treatment with avatrombopag at a starting dose of 20 mg (1 tablet) once daily with food. Dose adjustments are performed based on platelet count response. Use the lowest dose of avatrombopag needed to achieve and maintain a platelet count greater than or equal to 50 $\times 10^9$/L as necessary to reduce the risk for bleeding. Do not use avatrombopag to normalize platelet counts. Do not exceed a daily dose of 40 mg (2 tablets).
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Treatment of adult patients with primary chronic immune thrombocytopenia (cITP) who are refractory to other treatments (e.g., corticosteroids, immunoglobulins)
Other approved therapeutic indications	Treatment of severe thrombocytopenia in adult patients with chronic liver disease that are scheduled to undergo an invasive procedure

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Overview of the pharmaceutical	
Will dispensing be restricted to hospitals?	No
Combination therapy and/or co-medication	Non-applicable
Packaging – types, sizes/number of units, and concentrations	20 mg per tablet available in a 30 tablet pack
Orphan drug designation	Yes

Abbreviations: mg = micrograms

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2. Abbreviations

AE	Adverse event
ALT	Alanine amino transferase
ASH	American Society of Haematology
AST	Asparagine aminotransferase
CI	Confidence interval
CsA	Cyclosporin A
DMC	Danish Medicines Council
EPAR	European Public Assessment Reports
FAS	Full set analysis
HRQoL	Health related quality of life
ITP	Immune thrombocytopenia
ITT	Intent-to-treat
IRR	Incidence rate ratio
ITC	Indirect treatment comparison
MMF	mycophenolate mofetil
NMA	Network meta-analysis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
QoL	Quality of life
SAS	Safety analysis set
SF-36	Short Form Health Survey
SLR	Systematic literature review
TEAE	Treatment emergent adverse event
TPO-RA	Thrombopoietin receptor agonist
WHO	World Health Organisation

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3. Summary

Population

Immune thrombocytopenia (ITP) is an autoimmune disorder involving the destruction of platelets and impaired platelet production, resulting in a reduction in platelet count (defined as a platelet count of below 100×10^9/L) (Provan and Newland 2015). ITP can be defined as either primary or secondary disease. Primary ITP refers to isolated thrombocytopenia in the absence of other causes, while secondary could be the result of an underlying disease or drug exposure (Rodeghiero, Stasi et al. 2009).

Patients with severe ITP (defined as a platelet count of below 100×10^9/L) have an increased risk of severe bleeding from trauma, as well as of spontaneous bleeding (especially for those with a platelet count of below 50×10^9/L), an increased risk of thrombosis, and are more likely to exhibit symptoms of fatigue (Kayal, Jayachandran et al. 2014, Matzdorff, Meyer et al. 2018). Furthermore, the symptomatology and treatment of ITP has an impact on patients' lifestyle and psychological wellbeing.

ITP is a rare condition, with the majority of diagnosed cases progressing to chronic disease (Neunert, Terrell et al. 2019). The prevalence in Denmark is approximately 10 per 100,000 people and an incidence rate of 2.8 per 100,000 people (Christiansen, Bahmanyar et al. 2019). According to recent guidelines (DSBH 2018, Matzdorff, Meyer et al. 2018) , patients with ITP are initially treated with corticosteroids and/or immunoglobulins. For patients with chronic (defined as having symptoms of a period longer than 12 months) or refractory (i.e., after splenectomy) ITP, TPO-RAs are the preferred choice.

Currently, there are two TPO-RA products available, eltrombopag (an oral tablet) and romiplostim (administered subcutaneously), that are used interchangeably, as they have been deemed of equal clinical efficacy and safety (Neunert, Terrell et al. 2019). Patients with ITP treated with TPO-RAs may need to discontinue therapy due to unfavourable adverse events, non-response or loss of response. For these patients, treatment cycling to an alternative TPO-RA can be an effective treatment management approach (Neunert, Terrell et al. 2019, Provan, Arnold et al. 2019). Avatrombopag will be available as an additional TPO-RA option for the treatment of patients with chronic ITP.

Intervention

Avatrombopag is a novel, oral, small-molecule TPO-RA, which stimulates natural platelet production leading to a predictable increase in platelet count. An approval from the European Commission (EC) was received in January 2021 for the treatment of primary chronic ITP in adult patients who are refractory to other treatments (e.g., corticosteroids, immunoglobulins).

Avatrombopag will be available in a strength of 20 mg per tablet. Treatment with avatrombopag should be initiated at 20 mg once daily with food. The dose should be adjusted in order to achieve and maintain platelet count $\geq50\times10^9$/L. A daily dose of 40 mg should not be exceeded.

Comparator

Eltrombopag is considered the relevant comparator of avatrombopag. Both treatments are oral tablets and eltrombopag is the TPO-RA predominantly used in Denmark (75%, compared with 25% for romiplostim, (SOBI data on file 2020)). The recommended starting dose of eltrombopag is 25 mg once daily, while a daily dose of 75 mg should not be exceeded. Treatment with eltrombopag is related to food restrictions, as patients have to abstain from consuming

food a few hours before and after treatment. Eltrombopag is also associated with a risk of hepatotoxicity and regular monitoring with liver tests is required.

Avatrombopag could be considered a more convenient TPO-RA option, as patients do not need to fast before or after administration of avatrombopag, and it is not associated with hepatotoxicity.

Outcomes

Due to a lack of head-to-head data an indirect treatment comparison (ITC) in the form of a network meta-analysis (NMA), is presented. The results of the NMA showed that there was no significant difference in clinical efficacy and safety between avatrombopag and eltrombopag.

There was between-trial heterogeneity in the proportion of patients prematurely discontinuing the allocated treatment. Due to this premature, imbalanced discontinuation the total exposure time in the included studies was significantly affected and therefore could impact the relative efficacy and safety results. To avoid this bias, an NMA based on estimated incidence rate ratio (IRR) accounts for the differences in the effective treatment duration across groups. For this reason, the results of the following outcomes are presented:

- Quality of life (QoL)
- Bleeding events (any and WHO grade 2-4)
- Platelet response rate and duration of response

Health economic evaluation

As avatrombopag and eltrombopag have been shown to have similar efficacy a cost-comparison analysis was conducted. The analysis concluded that there is a minimal added incremental cost of [redacted] for treating a patient with avatrombopag. The total budget impact of introducing avatrombopag to the Danish market is expected to [redacted] in year 2026 treating a total of [redacted].

The addition of avatrombopag to the currently available TPO-RAs would provide patients with an option that shares the same clinical efficacy and safety with eltrombopag. In addition, avatrombopag could be considered a more convenient option for patients, as it is not related to strict dietary restrictions or hepatotoxicity.

Finally, avatrombopag would be an additional option for those patients that switch between TPO-RA treatments due to lack of response or side effects.

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4. Literature search

A systematic literature review (SLR) was conducted to identify relevant publications to assess the clinical added value of avatrombopag for the treatment of ITP versus eltrombopag.
The search string used was defined in the protocol provided by the Danish Medicines Council. The search was performed on 3rd March 2021 in Medline and in CENTRAL. The search strings and results are presented in Table 1 and Table 2.

Table 1: Search string for strategic search for clinical and safety in CENTRAL (via Cochrane library)

#	Query	Search facet	No. of hits
#1	(idiopathic near/2 thrombocytopenic near/2 purpura):kw	Population	601
#2	ITP:ti,ab		720
#3	(purpura near thrombocytop*):ti,ab		589
#4	((idiopathic or autoimmun* or immun*) near thrombocytop*):ti,ab		892
#5	#1 or #2 or #3 or #4		1251
#6	(avatrombopag or AKR-501 or AKR501 or Doptelet* or E5501 or YM-477 or YM477):ti,ab,kw	Intervention	75
#7	(eltrombopag or Promacta* or Revolade* or SB-497115):ti,ab,kw	Comparator	281
#8	#6 or #7	Intervention and comparator	350
#9	NCT*:au	Exclusion of irrelevant publication	204 358
#10	("conference abstract" or review):pt		188 585
#11	(clinicaltrials.gov or trialsearch):so		356 147
#12	(abstract or conference or meeting or proceeding*):so		44 807
#13	#9 or #10 or #11 or #12		574 672
#14	(#5 and #8) not #13		66
#15	#14 not pubmed:an	Final search	30

Table 2: Search string for strategic search for clinical efficacy and safety in Medline (via PubMed)

#	Query	Search facet	No. of hits
#1	Purpura, Thrombocytopenic, Idiopathic[mh]	Population	6 512
#2	ITP[tiab] OR (werlhof*[tiab] AND disease[tiab]) OR (purpura[tiab] AND thrombocytop*[tiab]) OR ((idiopathic[tiab] OR autoimmun*[tiab] OR immun*[tiab]) AND thrombocytop*[tiab])		29 541
#3	#1 OR #2		30 200
#4	Avatrombopag[nm]	Intervention	27
#5	avatrombopag[tiab] OR AKR-501[tiab] OR AKR501[tiab] OR Doptelet*[tiab] OR E5501[tiab] OR YM-477[tiab] OR YM477[tiab]		57
#6	Eltrombopag[nm]	Comparator	521
#7	eltrombopag[tiab] OR Promacta*[tiab] OR Revolade*[tiab] OR SB-497 115[tiab]		792
#8	#4 OR #5 OR #6 OR #7	Intervention and comparator	926
#9	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans [mh])	Cochrane RCT-filter	1 292 418
#10	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]	Exclusion of irrelevant publication	6 745 411
#11	#3 AND #8		548

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#12	#11 AND #9		122
#13	#12 NOT #10	Final search	57

The eligibility criteria used for the SLR are defined in terms of the population, intervention, comparator, outcomes, and study design (PICOS) framework, as well as language and time frame (see Table 19 in section 7.1).
A total of 87 records were identified through CENTRAL and MEDLINE. With duplicates removed (n = 6), 81 records were left to be screened. Abstracts identified by the search according to the PICOS selection criteria were reviewed for inclusion by title or abstract according to the PICOS selection criteria, resulting in 65 excluded records. The 16 full-text publications that passed the first screening underwent a more rigorous screening to assess any data of interest according to PICOS. Of these, two publications corresponding to two clinical studies were found relevant and are further described in Table 3.
The process of study identification and selection is summarized in Section 7.1 with a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1). All excluded records after the full-text review are presented with explanation in Appendix Table 20.

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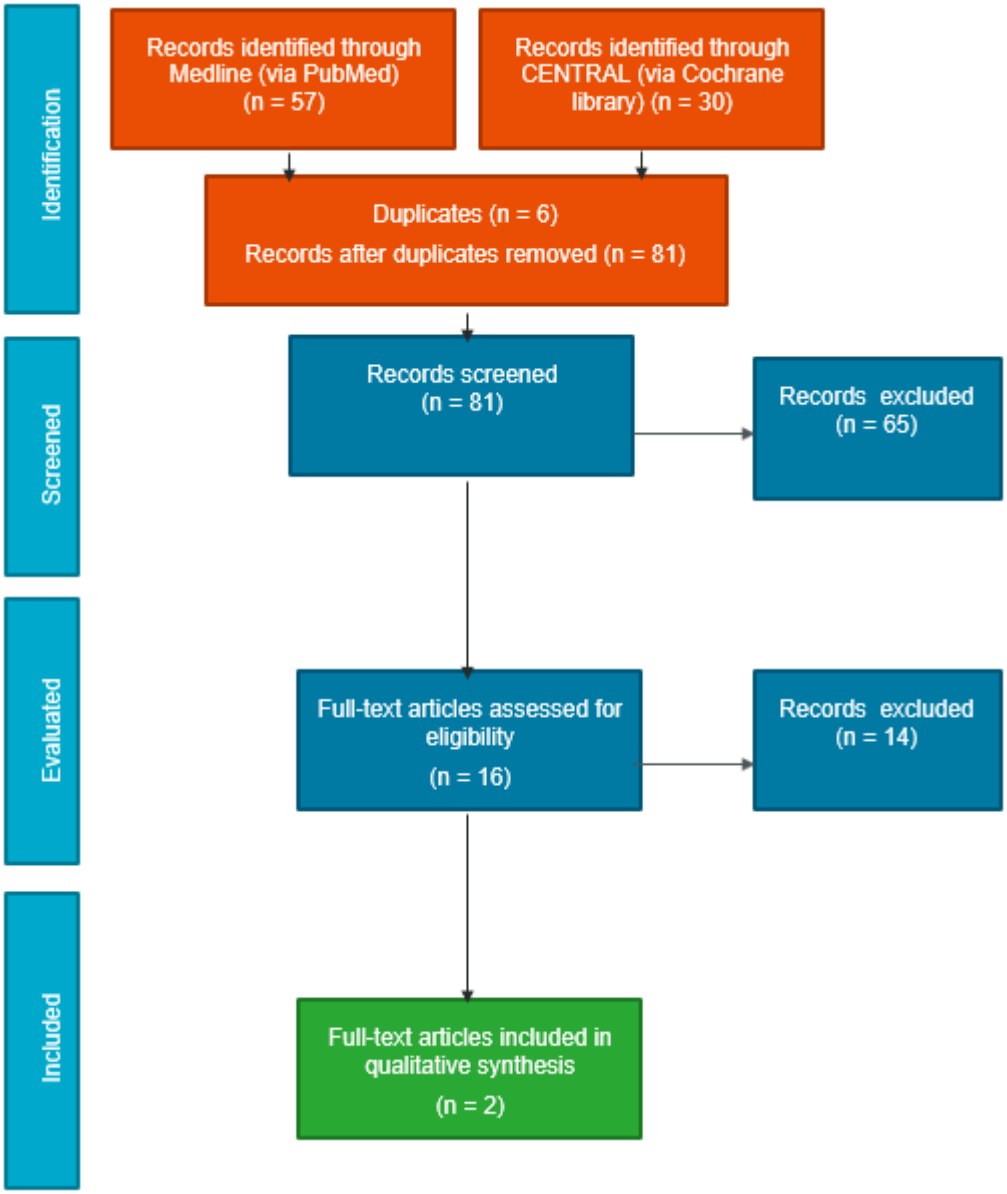
Figure 1: PRISMA flow diagram of Medline (via PubMed) and CENTRAL (via Cochrane library)



European Public Assessment Reports (EPARs) and Summary of Product Characteristics (SmPCs) for avatrombopag and eltrombopag were also reviewed. Hand-searching on clinicaltrials.gov identified one relevant study not captured by database searching, this was included in the qualitative synthesis.

4.1 Relevant studies

Table 3 presents the relevant clinical trials and respective references captured in the SLR and included in this assessment of avatrombopag. The identified comparator was eltrombopag. Hand-searching identified one relevant study not captured in the SLR (AVA-305: NCT01433978).

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Table 3: Relevant studies included in the assessment

Reference (title, author, journal, year)	NCT number	Dates of study (start and expected completion)
Avatrombopag		
Jurczak, W., et al., Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia. Br J Haematol, 2018. **183**(3): p. 479-490.	**NCT01438840**	FEB 2012 – NOV 2013
AVA-305: A Phase 3, Multicenter, Randomized, Double-blind, Active-controlled, Parallel-group Trial With an Open-label Extension Phase to Evaluate the Efficacy and Safety of Oral E5501 Versus Eltrombopag, in Adults With Chronic Immune Thrombocytopenia (Idiopathic Thrombocytopenic Purpura)	**NCT01433978**	MAR 2012 – SEP 2013 (terminated early due to recruitment problems)
Eltrombopag		
Cheng, G., et al., Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet, 2011. **377**(9763): p. 393-402.	**NCT00370331**	NOV 2006 – JUL 2008

4.2 Main characteristics of included studies

The following tables describe the main characteristics of the three studies included in the review.

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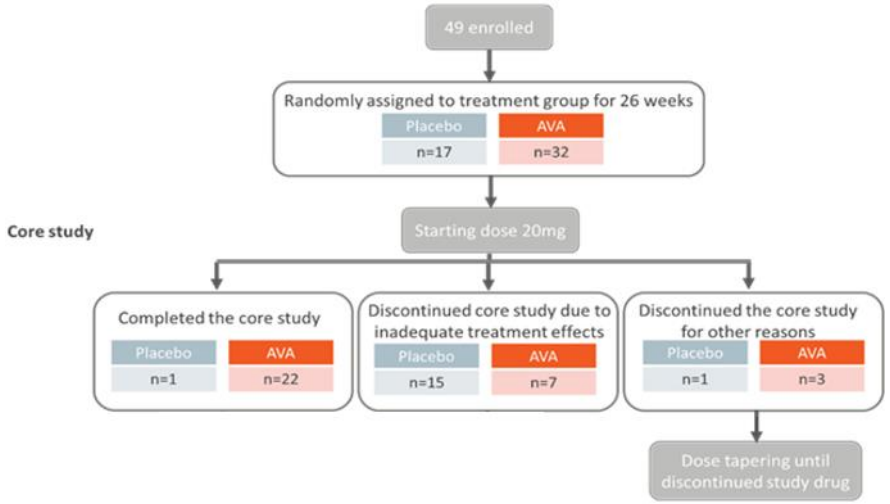
Table 4: Main study characteristics of AVA-302 (NCT01438840)

AVA-302 NCT01438840	
Trial name	Efficacy and safety of oral E5501 plus standard of care for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP)
NCT number	NCT01438840
Objective	To demonstrate that the efficacy of avatrombopag (in addition to standard of care) is superior to placebo (in addition to standard of care) for the treatment of adult participants with chronic immune thrombocytopenia (idiopathic thrombocytopenic purpura) (ITP) as measured by cumulative number of weeks of platelet response over 6 months of once daily treatment in adults participants who received at least 1 prior ITP therapy.
Publications – title, author, journal, year	Jurczak, W., et al., Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia. Br J Haematol, 2018. 183(3): p. 479-490.
Study type and design	The pivotal study was a Phase III randomised, international, multicentre, and parallel group study. The study has been completed. Adult chronic ITP patients (n=49) were enrolled in the trial, having met the eligibility requirements. These patients were stratified based upon splenectomy status, baseline platelet count, and use of concomitant ITP treatments. They were then randomised to receive either placebo (n=17) or avatrombopag (n=32) for 26 weeks, at a starting dose of 20 mg and in a double-blind fashion. Treatment doses were titrated up or down dependent on the individual's response to treatment. The figure below provides a summary of the study design and methodology.

AVA-302 NCT01438840	
	Figure: Study design and methodology of the pivotal Phase III avatrombopag study 302 
Follow-up time	26 weeks

Population (inclusion and exclusion criteria)	<u>Core study</u>
	Inclusion criteria
	• Adults with chronic ITP confirmed as per ASH guidelines
	• Previously received at least one ITP therapy
	• Some concurrent medication allowed:
	  ○ Stable treatment with corticosteroids within 4 weeks,
	  ○ Stable treatment with MMF, CsA or danazol within 12 weeks
	  ○ Proton pump inhibitors/H2-receptor antagonist therapy within 6 weeks of randomisation
	
	Exclusion criteria
	• Some concurrent medication not allowed:
	  ○ Rituximab within 12 weeks of randomisation
	  ○ Immunoglobulins within 1 week of randomisation

AVA-302 NCT01438840	
	○ TPO-RAs or cyclophosphamide/vinca alkaloids within 4 weeks of randomisation • Splenectomy within 12 weeks of randomisation • Known secondary thrombocytopenia • Significant medical conditions or medical history: ○ Hepatitis ○ Lymphoproliferative disease ○ Cardiovascular disease or CHF ○ Thrombosis
Intervention	Thirty-two patients received avatrombopag (plus standard of care) for 26 weeks, at a starting dose of 20 mg and in a double-blind fashion. Treatment doses were titrated up or down dependent on the individual's response to treatment. Dose adjustment was carried out based upon platelet count every two weeks and was targeted to maintain a platelet count of ≥50×10^9/L and ≤150×10^9/L. Patients with a platelet count of <50×10^9/L or >250×10^9/L were eligible for dose adjustment weekly. This dosing pattern was similar to that of the FDA SPC for avatrombopag in ITP patients, which differs only in the requirement for stopping avatrombopag treatment at >400×10^9/L rather than >250×10^9/L (FDA 2019). The mean daily dose of avatrombopag was recorded. The most common dosage was between 10 mg and 20 mg, and doses ranged from 5 mg to 40 mg of avatrombopag. Dose-tapering was carried out in those patients who did not proceed to the extension trial, with a follow-up period of 30 days. This involved weekly visits at which the study drug was down-titrated one dose level per week until the study drug was discontinued. Table 2 below describes the dose adjustment of the study. **Table 2. Dose adjustment based upon platelet count during for Study 302** **Platelet count** — **Dose adjustment** **<50×10^9/L** — Up titrate one dose level **≥50×10^9/L to ≤150×10^9/L** — Keep on the current dose **>150×10^9/L to ≤250×10^9/L** — Down titrate one dose level **>250×10^9/L** — Stop dose, return for twice weekly platelet counts, then down titrate study drug one dose level when platelet count is ≤150×10^9/L Reference: (Eisai Inc 2016)

AVA-302 NCT01438840

Baseline characteristics

Figure 2: Baseline characteristics

	Placebo (n = 17)	Avatrombopag (n = 32)	Total (N = 49)
Age (years), mean (SD)	41.2 (14.7)	46.4 (14.2)	44.6 (14.4)
<65 years, n (%)	16 (94.1)	29 (90.6)	45 (91.8)
Female, n (%)	8 (47.1)	23 (71.9)	31 (63.3)
Race, n (%)			
White	15 (88.2)	31 (96.9)	46 (93.9)
Black or African American	1 (5.9)	0	1 (2.0)
Asian	1 (5.9)	1 (3.1)	2 (4.1)
Weight (kg), mean (SD)	84.97(20.48)	81.90 (22.71)	82.97 (21.79)
Height (cm), mean (SD)	170.53 (7.46)	167.89 (8.00)	168.81 (7.84)
BMI (kg/m2), mean (SD)	29.24 (6.64)	28.99 (7.32)	29.08 (7.02)
Baseline platelet count, n (%)			
≤15 x 10^9/L	10 (58.8)	18 (56.3)	28 (57.1)
15 – 30 x 10^9/L	7 (41.2)	13 (40.6)	20 (40.8)
≥ 30 x 10^9/L	0	1 (3.1)	1 (2.0)
Splenectomy, n (%)	5 (29.4)	11 (34.4)	16 (32.7)
Use of concomitant ITP medication at baseline, n (%)	7 (41.2)	15 (46.9)	22 (44.9)

Abbreviations: BMI, body mass index; FAS, full analysis set; ITP, immune thrombocytopenia; N, number of patients; SD, standard deviation.

Primary and secondary endpoints

<u>Core study</u>

Primary endpoint

Cumulative number of weeks of platelet response over 26 weeks (i.e., platelet count greater than or equal to 50 x 10^9/L during 26 weeks of treatment in the core study in the absence of rescue therapy)

Secondary endpoints

- Platelet response at day 8 (i.e., number of participants with platelet response at day 8 defined as those with a platelet count greater than or equal to 50 x 10^9/L at day 8 in the absence of rescue therapy on or before day 8)
- Proportion of patients with reduction in concomitant ITP medication use (time frame: week 1 through week 26)
- Safety of avatrombopag compared with placebo (adverse events throughout the core study period)

Main exploratory endpoints

- Durable platelet response (i.e., proportion of patients who had at least 6 out of 8 weekly platelet responses during the last 8 weeks of treatment, in the absence of rescue therapy)

AVA-302 NCT01438840	
	• Bleeding minimisation (incidence and severity of bleeding events as assessed by the WHO Bleeding Scale during the 6 months of treatment) • Use of rescue therapy (assessed by the use of concomitant ITP medication, during the 6 months of treatment)
Method of analysis	The full analysis set (FAS) included all randomised patients, and the safety analysis set (SAS) included all patients who received at least one dose of study medication and had a post-dose safety assessment in either the core study or extension phase. All patients who received study medication and who provided at least one platelet count and corresponding efficacy assessment during the extension phase were included in the modified full analysis set (mFAS). Baseline demographics and characteristics of the FAS and SAS were summarized for each group using descriptive statistics and categorical variables summarised by treatment group and by frequency distribution.
Subgroup analyses	Subgroup analyses were performed based on the following criteria: • Status of splenectomy (splenectomised, non-splenectomised) • Baseline platelet count (≤15 x 10^9/L, >15 to <30 x 10^9/L) • Use of concomitant ITP medication at baseline (yes, no)

Table 5: Main study characteristics of AVA-305 (NCT01433978)

AVA-305 NCT01433978	
Trial name	A Phase 3, Multicenter, Randomized, Double-blind, Active-controlled, Parallel-group Trial With an Open-label Extension Phase to Evaluate the Efficacy and Safety of Oral E5501 Versus Eltrombopag, in Adults With Chronic Immune Thrombocytopenia (Idiopathic Thrombocytopenic Purpura).
NCT number	NCT01433978
Objective	**Core study:** To compare the efficacy of avatrombopag in addition to standard of care, to eltrombopag (in addition to standard of care) for the treatment of adult participants with chronic immune thrombocytopenia as measured by durable platelet response. **Open-label Extension Phase:** To evaluate the safety and tolerability of long-term therapy with avatrombopag in participants with chronic ITP (cITP).
Publications – title, author, journal, year	Terminated early due to significant enrolment challenges.

AVA-305 NCT01433978	
Study type and design	The study consisted of three phases: Prerandomization, Randomization (Core Study) and Extension Phase. Participants 18 years of age and over, who met all the eligibility requirements were randomized into the study. Requirement that splenectomised participants make up at least 35% of the study population and no single platelet count is greater than $35x10^9$/L. Participants were centrally stratified at randomization by splenectomy status, baseline platelet count, and use of concomitant ITP medication at baseline and randomized to receive either double-blind avatrombopag or eltrombopag in a 1:1 ratio. Participants received blinded therapy at a starting dose of 20 mg avatrombopag once daily or 50 mg eltrombopag once daily. Participants were able to have their dose titrated up (maximum dose 40 mg avatrombopag and 75 mg for eltrombopag) or down (minimum dose 5 mg for avatrombopag and 25 mg for eltrombopag) depending on their response to study drug. The goal of dose modification was to maintain the platelet count at levels greater than or equal to $50x10^9$/L and less than or equal to $150x10^9$/L, and to decrease the need for ITP-directed concomitant medications. Participants who meet the eligibility requirements for the Open-label Extension (OLE) Phase or who discontinue the Core Study early because of lack of treatment effect will be eligible to continue into the OLE Phase for up to 104 weeks of open-label avatrombopag therapy.
Follow-up time	Terminated early.
Population (inclusion and exclusion criteria)	<u>Core study</u> **Inclusion criteria** • Adults diagnosed with cITP (≥12 months duration) according to the ASH/BCSH guidelines, and an average of 2 platelet counts less than $30x10^9$/L. • Participants who previously received and initially responded to one or more ITP therapies (including, but not limited to corticosteroids, immunoglobulins, azathioprine, danazol, cyclophosphamide and/or rituximab). • PT/INR and aPTT must have been within 80% - 120% of the normal range with no history of hypercoagulable state. • A complete blood count within the reference range with the following exceptions: • Haemoglobin: participants with haemoglobin levels between 10 g/dL (100 g/L) and the lower limit of normal are eligible for inclusion, if anaemia was clearly attributable to ITP. • Absolute neutrophil count (ANC) ≥1500/uL ($1.5x10^9$/L) (elevated WBC/ANC due to corticosteroid treatment is acceptable). **Exclusion criteria** • Participants with known secondary immune thrombocytopenia. • Participants with concurrent malignant disease. • Splenectomy or use of rituximab within 12 weeks of randomization.

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AVA-305 NCT01433978	

	• Participants with significant medical conditions:
	• Acute hepatitis, active chronic hepatitis.
	• Lymphoproliferative disease; myeloproliferative disorders, leukaemia.
	• Participants with a history of;
	  ○ MDS
	  ○ Pernicious anaemia, or participants with vitamin B12 deficiency who have not had pernicious anaemia excluded as a cause.
	  ○ Arterial or venous thrombosis (stroke, transient ischemic attack, myocardial infarction, deep vein thrombosis, or pulmonary embolism).
	  ○ Significant cardiovascular disease (e.g., congestive heart failure [CHF]), arrhythmia (e.g., atrial fibrillation), participants with a QT interval corrected for heart rate of >450 msec, angina, unstable angina, coronary artery stent placement, angioplasty, or coronary artery bypass grafting.
	  ○ Cirrhosis, portal hypertension, and chronic active hepatitis.

Intervention	**Core study** Avatrombopag administered orally as 5 mg, 10 mg, 20 mg, 30 mg, or 40 mg in a flexible dose design for 26 weeks. Participants received blinded therapy at a starting dose of 20 mg avatrombopag, once daily and allow to have their dose titrated up (maximum dose of 40 mg avatrombopag) or down (minimum dose of 5 mg avatrombopag) depending on their response to study drug. Eltrombopag administered orally as 25 mg, 50 mg, or 75 mg in a flexible dose design for 26 weeks. Participants received blinded therapy at a starting dose of 50 mg eltrombopag once daily and allow to have their dose titrated up (maximum dose of 75 mg eltrombopag) or down (minimum dose of 25 mg eltrombopag) depending on their response to study drug. **Extension study** Participants who enter the OLE from the Core Study will receive a starting dose of open-label avatrombopag which will be determined by the last dose of study drug at the End of Treatment (EOT) Visit (Visit 22) of the Core Study. Participants who discontinue the Core Study early because of lack of treatment effect and enter the OLE will receive open-label avatrombopag at a starting dose of 20 mg once daily of open-label avatrombopag.
Baseline characteristics	**Figure 3: Baseline characteristics** **Avatrombopag (n = 12)** | **Eltrombopag (n = 11)**

AVA-305 NCT01433978		
Median age (years)	50.8	45.4
Female, n (%)	7 (58.3)	7 (63.6)

Primary and secondary endpoints	<u>Core study</u> **Primary endpoint** Change from baseline in local platelet count for the 6-month treatment period.
Method of analysis	The Full Analysis Set (FAS) included all participants who were randomized into the study. Only participants with non-missing data at both baseline and the relevant post-baseline visit are included in the change from baseline summary statistics. Standard deviation is not applicable for some of the categories, from Visit 14 to Visit 22, as the number of participants analysed for that visit was 1 individual.

Table 6: Main study characteristics of RAISE (NCT00370331)

RAISE NCT00370331	
Trial name	A Randomized, Double-blind, Placebo-controlled Phase III Study, to Evaluate the Efficacy, Safety and Tolerability of Eltrombopag Olamine (SB-497115-GR), a Thrombopoietin Receptor Agonist, administered for 6 Months as Oral Tablets Once Daily in Adult Subjects With Previously Treated Chronic ITP.
NCT number	NCT00370331
Objective	To evaluate the 6-month safety and efficacy of eltrombopag in the treatment of previously treated subjects with chronic ITP.
Publications – title, author, journal, year	Cheng, G., et al., Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet, 2011. 377(9763): p. 393-402.
Study type and design	Phase 3, double-blind, placebo-controlled study in adults with previously treated ITP of more than 6 months' duration who had baseline platelet counts lower than 30 000/µL. Patients were randomly allocated (in a 2:1 ratio) treatment with local standard of care plus 50 mg eltrombopag or matching placebo once daily for 6 months. Randomisation was stratified by baseline platelet count (≤15 000/µL), use of treatment for immune thrombocytopenia, and splenectomy status. Patients, investigators, and

RAISE NCT00370331	
	those assessing data were masked to allocation. Dose modifications were made on the basis of platelet response. Analysis was by intention to treat.
Follow-up time	6 months
Population (inclusion and exclusion criteria)	**Inclusion criteria:** • Adults (≥18 years) diagnosed with chronic ITP, and platelet count < 30,000/µL on Day 1 (or within 24 hours prior to dosing on Day 1). • Previously received one or more prior ITP therapies • Either initially responded (platelet count > 100,000/µL) to a previous ITP therapy or have had a bone marrow examination consistent with ITP within 3 years • Previous therapy for ITP with immunoglobulins (IVIg and anti-D) completed at least 1 week prior to randomization and the platelet count shows a clear downward trend after the last treatment with immunoglobulins; Previous treatment for ITP with splenectomy, rituximab and cyclophosphamide must completed at least 4 weeks prior to randomization, or clearly be ineffective • Subjects treated with concomitant ITP medication receiving a dose that has been stable for at least 4 weeks prior to randomization. Subjects treated with cyclosporine A, mycophenolate mofetil or danazol receiving a dose that has been stable for at least 3 months prior to randomization. The medication should be continued with a stable dose for the initial 6 weeks of study • Prothrombin time (PT/INR) and activated partial thromboplastin time within 80 to 120% of the normal range with no history of hypercoagulable state • A CBC within the reference range, with the following exceptions: <30,000 platelets/µL on Day 1 (or within 24 hours of Day 1) • Haemoglobin: levels between 10 g/dL (100 g/L) and the lower limit of normal are eligible for inclusion, if anaemia is clearly attributable to ITP (excessive blood loss) • ANC ≥ 1500/µL ($1.5x10^9$/L) is required for inclusion (elevated WBC/ANC due to steroid treatment is acceptable) • Clinical chemistries must not exceed the upper limit of normal reference range by more than 20%: creatinine, ALT, AST, total bilirubin, and alkaline phosphatase; total albumin must not be below the lower limit of normal by more than 10% • Female subjects (or female partners of male subjects) must either be of non-childbearing potential, or of childbearing potential and use highly effective methods of contraception from two weeks prior to administration of study medication, throughout the study, and 28 days after completion or premature discontinuation from the study **Exclusion criteria:**

RAISE NCT00370331	
	• Any clinically relevant abnormality, other than ITP, identified on the screening examination or any other medical condition or circumstance, which in the opinion of the investigator makes the subject unsuitable for participation in the study or suggests another primary diagnosis • Concurrent malignant disease and/or history of cancer treatment with cytotoxic chemotherapy and/or radiotherapy • Any prior history of arterial or venous thrombosis, AND ≥2 of the following risk factors: hormone replacement therapy, systemic contraception (containing oestrogen), smoking, diabetes, hypercholesterolemia, medication for hypertension, cancer, hereditary thrombophilic disorders, or any other family history of arterial or venous thrombosis • Pre-existing cardiovascular disease (congestive heart failure, NYHA Grade III/IV), or arrhythmia known to increase the risk of thromboembolic events, or subjects with a QTc >450 msec • Female subjects who are nursing or pregnant at screening or pre-dose on Day 1 • History of alcohol/drug abuse • Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication • Subject treated with drugs that affect platelet function or anti-coagulants for >3 consecutive days within 2 weeks of the study start and until the study end • History of platelet agglutination abnormality that prevents reliable measurement of platelet counts • Secondary immune thrombocytopenia, including those with laboratory or clinical evidence of HIV infection, anti-phospholipid antibody syndrome, chronic hepatitis B infection, hepatitis C virus infection, or any evidence for active hepatitis at the time of subject screening • Previous participation in a clinical study with eltrombopag • Patients planning to have cataract surgery
Intervention	The initially administered dose was 50 mg oral tablets of eltrombopag once daily for six months. Dose adjustments were made based on individual platelet response. Dose increases (up to 75 mg once daily) were allowed after day 22 if platelet count fell below 50 000/µL. Dose decreases (to 25 mg once daily) were required if platelet counts reached above 200 000/µL. If platelet counts reached above 400 000/µL, study treatment was interrupted for the respective patient and was resumed at the lowest dose once platelet count fell below 150 000/µL. After 6 weeks of treatment, patients who had platelet counts of 100 000/µL or more for at least 2 successive weeks, could reduce or discontinue concomitant treatments. Patients were eligible to receive rescue mediation, in which case patients were regarded as non-responders for the duration of rescue treatment and until platelet counts fell below 50 000/µL.
Baseline characteristics	**Figure 4: Baseline characteristics**

	Placebo (n = 62)	Eltrombopag (n = 135)
Median age (years)	52.5 (43 – 63)	47.0 (34 – 56)

RAISE NCT00370331

Female, n (%)	43 (69)	93 (69)
Race, n (%)		
White	44 (71)	101 (75)
Asian	13 (21)	21 (16)
Other	5 (8)	13 (10)
Stratification variables, n (%)		
Platelet count ≤15 000/µL*	30 (49)	67 (50)
Splenectomy	21 (34)	50 (37)
Concomitant CITP treatment	31 (50)	63 (47)
Median platelet count (platelets per µL)	16 000 (9000 – 24000)	16 000 (8000 – 22000)
Bleeding symptoms†, n (%)	47 (77)	98 (73)
Clinically significant bleeding symptoms†, n(%)	17 (28)	30 (22)
Number of previous CITP treatments‡, n (%)		
Two or more	50 (81)	105 (78)
Three or more	32 (52)	75 (56)
Four or more	20 (32)	51 (38)
Five or more	11 (18)	35 (26)

Note: Data are number (%) or median (IQR). Bleeding symptoms included WHO bleeding scale grades 1–4; clinically significant bleeding symptoms included grades 2–4. CITP=chronic immune thrombocytopenia. *Placebo, n=61; one patient had a missing baseline platelet count. †Placebo, n=61; one patient did not have a baseline bleeding assessment. ‡Corticosteroids were the most frequently reported previous CITP treatment (eltrombopag, n=119, 88%; placebo, n=56, 90%).

Primary and secondary endpoints

Primary outcome

- Percentage of responders

  The percentage of evaluable participants who achieved a platelet response (defined as a platelet count between 50,000 and 400,000 microliter) at each nominal on-therapy day and 4 weeks post-treatment

Secondary Outcome

- Summary of median platelet counts [Baseline; Day 8 through Week 26 on-treatment; and 1, 2, 4 week follow-up visits]
- Percentage of participants initiating rescue treatment On-therapy [Anytime from Day 1 to Week 26]
- Maximum and total weeks of platelet response [Day 1 through Week 26 on-treatment]
- Percentage of participants with a reduction in use of baseline ITP medication [From Day 1 through Week 26 on-treatment]
- WHO Bleeding Scale [Baseline, all nominal visits on-therapy defined as Day 8, Day 15, Day 22, Day 29, Day 36, Day 43, Week 10, Week 14, Week 18, Week 22, Week 26, and 1, 2 and 4 week follow-up visits]
- HR-QoL Instrument and Domain Scores from the SF-36v2 Questionnaire at Baseline, Week 6, Week 14, and Week 26 or early discontinuation from study

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	• HR-QoL Instrument and Domain Scores from the FACIT-F Questionnaire at Baseline, Week 6, Week 14, and Week 26 or early discontinuation from study • HR-QoL Instrument and Domain Scores for the FACT-Th Questionnaire at Baseline, Week 6, Week 14, and Week 26 or early discontinuation from study • HR-QoL Instrument and Domain Scores from the MEI-SF Questionnaire at Baseline, Week 6, Week 14, and Week 26 or early discontinuation from study
Method of analysis	Descriptive statistics summarised demographic and baseline characteristics and safety data. The ITT population included all patients randomly allocated treatment; the safety population included all patients who received at least one dose of study drug. Odds of a response to treatment at any time during the 6-month treatment period between groups for the ITT population was compared using a repeated-measures model for binary data adjusted for the randomisation stratification variables. Generalised estimating equation methodology was used to estimate the parameters of the regression model, with an exchangeable working correlation structure that assumed the correlation between any two measures within a patient were the same. The primary analysis used data from nominal visits (weeks 1 – 6 inclusive, and weeks 10, 14, 18, 22, and 26), in case a nominal visit was not available, information from the immediately preceding, non-nominal visit was used, had the patient not withdrawn from the study. Assessments for patients who withdrew from the study were classified as negative from the time of withdrawal and for all subsequent nominal visits. Logistic regression model adjusted for the stratification variables evaluated between group differences for: proportions of patients who achieved a response at 75% or more of on-treatment assessments; reduced baseline concomitant treatments; and received rescue treatment. Odds of any or significant bleeding were compared between treatment groups using a repeated measures model for binary data adjusted for the stratification variables and dichotomised baseline bleeding grade. Changes from baseline in HRQoL scores were analysed with a repeated-measures model adjusted for baseline score. The predictive strength of association between either SF-36v2 or FACT-Th6 scores and platelet counts, and bleeding symptoms was estimated by use of unadjusted linear longitudinal regression models. All p-values were two sided with no adjustments were made for multiple testing.
Subgroup analyses	Prespecified subgroup analyses of primary endpoint assessed interactions between response to treatment and splenectomy status, baseline platelet count, and baseline treatment for ITP. The outcomes were evaluated at the 10% significance level.

5. Clinical questions

5.1 Clinical question 1: What value does avatrombopag have compared to eltrombopag for patients with primary chronic ITP who are refractory to previous treatments with glucocorticoids and e.g., rituximab?

5.1.1 Presentation of relevant studies

The following studies are used in the assessment of clinical question #1:

Avatrombopag

- NCT01438840
- NCT01433978

Eltrombopag

- NCT00370331
- NCT01433978

Limitations of identified studies

The above identified studies were presented with some limitations, which resulted in challenges with comparing the generated results. Consequently, it has not been feasible to present all outcomes and to perform all analysis according to the requirements sent by the DMC (additional details can be seen in section 5.1.2 and 0).

The main limitations of this analysis include the following:

- Discontinuation from the placebo arms of recent studies

Most patients allocated to the placebo arm of AVA-302 trial discontinued prematurely, predominantly leading to an imbalanced follow-up between groups. As a result, the treatment duration of the placebo group was significantly reduced, which likely led to an underestimation of the change in bleeding events and safety outcomes in these groups. It is worth noting that the discontinuation from the recent clinical trials may not reflect inherent limitations within the trial protocols but rather may be associated with changes in clinical practice and better availability of treatment alternatives for non-responders, since eltrombopag was already available in clinical practice. Due to this, patients with suboptimal outcomes could not remain in the placebo groups as in previous trials, when better alternatives were unavailable. To avoid bias associated with imbalanced discontinuation an NMA was conducted based on estimated incidence rate ratio (IRR), rather than relative risk (RR), thus accounting for the differences in the treatment duration across groups.

- Assumptions related to estimates of incidence rates

To calculate IRR, the incidence rates were estimated based on data regarding number of patients with at least one event. For this estimation it was assumed that one patient could have only one event. Thus, the analysis did not consider that one patient could potentially experience several events of the same kind; however, this approach should not favour any intervention, since it was adopted for both the AVA-302 and RAISE studies.

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Table 7: Availability of outcome data for the comparative analyses and notes

Outcome				AVA-302 NCT01438840	RAISE NCT00370331
As requested by DMC		**Suggested alternative**	**Rationale**		
Quality of life	**Difference in average change from baseline measured by SF-36** **Proportion of patients achieving an increase of > 8 points**	**Descriptive**	Formal comparison between AVA and ELT may not be feasible due to insufficient reporting of the QoL results in RAISE trial.	Available	Available (average change from baseline without dispersion, i.e., SD, SE, 95% CI)
Bleeding	**Percentage of patients experiencing serious bleeds**	**WHO 2 – 4 (clinically significant)** **WHO 1 – 4 (any)**	The number of patients experiencing minor and serious bleeding events were not reported in RAISE trial. The comparison might be feasible regarding grade 1-4 and grade 2-4 (clinically significant) bleeding events. In the trials, severity of bleeding episodes is defined based on the WHO Grade scale.	Available Assessed per the WHO bleeding scale	
Platelet response	**Proportion of patients with platelet counts ≥ 50 x 10^9/L after 6 months**	**Durable platelet response**	Durable response is a clinically relevant endpoint, taking into account the maintenance of platelet response, and not just a response at random time points.	Available Platelet response for ≥6 of the last 8 weeks of treatment Platelet response at 6 months of treatment	Available Platelet response for ≥6 of the last 8 weeks of treatment and patient never received rescue treatment Platelet response at 6 months of treatment
Adverse events	**Proportion that ceases treatment due to adverse events** **Qualitative review of the adverse reaction profile**	**Qualitative review of the adverse reaction profile**	In RAISE trial, proportion of patients not completing treatment due to various reasons is reported; outcomes based on this compete and interact with each other. In addition, circumstances in which AVA 302 and RAISE trials were conducted have influenced the rate and reason for discontinuation	Available	Available; proportion of patients not completing treatment due to various reasons

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Abbreviations: DMC, Danish Medicines Council; SF-36, Short Form Health Survey; WHO, World Health Organization.
Source: (Cheng, Saleh et al. 2011, Jurczak, Chojnowski et al. 2018)
Note: Outcome data for any bleeding event and bleeding event assessed per WHO bleeding scale were also available for study AVA-305(NCT01433978).

5.1.2 Results per study

Results by study are presented in Table 8, Table 9 and Table 10.

Additional information on the statistical methodology used for the calculation of outcomes , such as bleeding episodes, is included in the NMA report (Doptelet ITP NMA report DMC) that is attached to this submission document.

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Table 8: Results of AVA-302 (NCT01438840) study

NCT01428840											
Trial name:	AVA-302										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
QoL (Mean change from baseline in SF-36; Physical component summary)	Avatrombopag	30	0.71 (-2.49, 3.91)	-0.21	-4.55, 4.13	n/a	n/a	n/a	n/a	Mean change from baseline was calculated based on data from AVA-302	**(Eisai Inc 2016)**
	Placebo	17	0.92 (-2, 3.85)								
QoL (Mean change from baseline in SF-36; Mental component summary)	Avatrombopag	30	3.11 (-0.65, 6.88)	3.97	-0.83, 8.76	n/a	n/a	n/a	n/a	Mean change from baseline was calculated based on data from AVA-302	(Eisai Inc 2016)
	Placebo	17	-0.85 (-3.82, 2.11)								
Bleeding (WHO 1 – 4)	Avatrombopag	14/32 (14.02 patient-years)	IR = 1.00/ patient-years*	n/a	n/a	n/a	IRR = 0.32	0.14, 0.75	n/a	* After continuity correction for zero events, proportional to	(Jurczak, Chojnowski et al. 2018);

NCT01428840										
	Placebo	9/17 (2.92 patient-years)	IR = 3.08/ patient-years*							total duration of treatment additional analysis was performed on the above published data
Bleeding (WHO 2 – 4)	Avatrombopag	3/32 (14.02 patient-years)	IR = 0.27/ patient-years*	n/a	n/a	n/a	IRR = 4.63	0.04, 575.58	n/a	* After continuity correction for zero events, proportional to total duration of treatment (Jurczak, Chojnowski et al. 2018) additional analysis was performed on the above published data
	Placebo	0/17 (2.92 patient-years)	IR = 0.06/ patient-years*							
Durable platelet response	Avatrombopag	11/32	36.42%*	0.34	0.18 - 0.51	n/a	RR = 17.84**	0.64, 496.07	n/a	*After continuity correction for zero events proportional to sample size; zero correction used to calculate RR, but not RD **RR calculated using frequentist methods with the correction for zero cells (Jurczak, Chojnowski et al. 2018) additional analysis was performed on the above published data
	Placebo	0/17	2.04%*							

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NCT01428840											
Platelet response at 6 months	Avatrombopag	13/32	42.7%*	0.41	0.24, 0.58	n/a	RR = 20.91**	0.76, 577	n/a	*After continuity correction for zero events proportional to sample size. Zero correction used to calculate RR but not RD **RR calculated using frequentist methods with the correction for zero cells	(Jurczak, Chojnowski et al. 2018) additional analysis was performed on the above published data
	Placebo	0/17	2.0%*								

Abbreviations: CI; confidence interval; IR, incidence rate; IRR, incidence rate ratio; RR, relative risk; WHO, World health organization

Table 9: Results of AVA-305 (NCT01433978) study

NCT01433978											
Trial name:	AVA-305										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (IR) (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Bleeding (WHO 2 – 4)	Avatrombopag	4/13 (3.62 patient-years*)	1.11/ patient-years*	n/a	n/a	n/a	IRR = 0.62	0.15, 2.47	n/a	IRR was used, instead of RR, to account for the discontinuation bias	(Tarantino, Vredenburg et al. 2020)
	Eltrombopag	4/11 (2.23 patient-years*)	1.79/ patient-years*								

NCT01433978										
Any bleeding (WHO 1 – 4)	Avatrombopag	6/13 (3.62 patient-years*)	1.66/ patient-years	n/a	n/a	n/a	IRR = 0.41	0.15, 1.16	n/a	(Tarantino, Vredenburg et al. 2020)
	Eltrombopag	9/11 (2.23 patient-years*)	4.03/patient-years							

Abbreviations: CI; confidence interval; IR, incidence rate; IRR, incidence rate ratio; RR, relative risk; WHO, World health organization

Table 10: Results of RAISE (NCT00370331) study

NCT00370331										
Trial name:	RAISE									
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
QoL (Mean change from baseline in SF-36; Physical component summary)	Eltrombopag	135	1.5	n/a	n/a	n/a	n/a	n/a	n/a	Mean change from baseline; repeated measures model. No additional information was available	
	Placebo	62	-1.4								

NCT00370331										
QoL (Mean change from baseline in SF-36; Mental component summary)	Eltrombopag	135	1.7	n/a	n/a	n/a	n/a	n/a	n/a	Mean change from baseline; repeated measures model. No additional information was available	(Cheng, Saleh et al. 2011)
	Placebo	62	-0.6								
Bleeding (WHO 1 – 4)	Eltrombopag	106/135 (58.62 patient-years)	1.81/patient-years	n/a	n/a	n/a	IRR = 0.90	0.65, 1.24	n/a	Additional analysis was performed on the above published data IRR was used, instead of RR, to account for the discontinuation bias	(Cheng, Saleh et al. 2011)
	Placebo	56/62 (27.68 patient-years)	2.01/patient-years								
Bleeding (WHO 2 – 4)	Eltrombopag	44/135 (58.62 patient-years)	0.75/patient-years	n/a	n/a	n/a	IRR=0.65	0.41, 1.03	n/a	Additional analysis was performed on the above published data IRR was used, instead of RR, to account for the discontinuation bias	(Cheng, Saleh et al. 2011)
	Placebo	32/62 (27.68 patient-years)	1.15/patient-years								

NCT00370331											
Durable platelet response	Eltrombopag	57/95	60.0%	0.5	0.36, 0.63	n/a	RR = 5.85**	2.28, 15.02	n/a	Additional analysis was performed on the above published data **RR calculated using frequentist methods	(Cheng, Saleh et al. 2011)
	Placebo	4/39	10.26%								
Platelet response at 6 months	Eltrombopag	52/135	38.52%	0.11	-0.03, 0.25	n/a	RR = 1.40**	0.89, 2.22	n/a	Additional analysis was performed on the above published data **RR calculated using frequentist methods	(Cheng, Saleh et al. 2011)
	Placebo	17/62	27.42%								

Abbreviations: CI; confidence interval; IRR, incidence rate ratio; RR, relative risk; WHO, World health organization

Forest plots for the results related to bleeding events that were presented above can be found in Figure 5, and Figure 6 below.

Figure 5: Forest plot for the incidence rate ratio for comparison of TPO-RAs vs placebo regarding any bleed

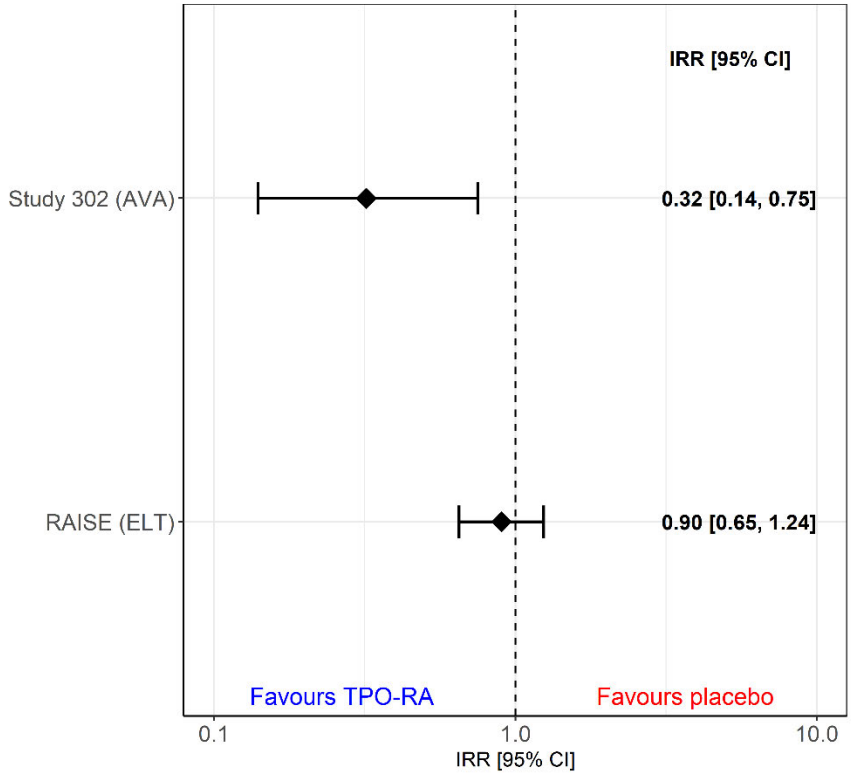
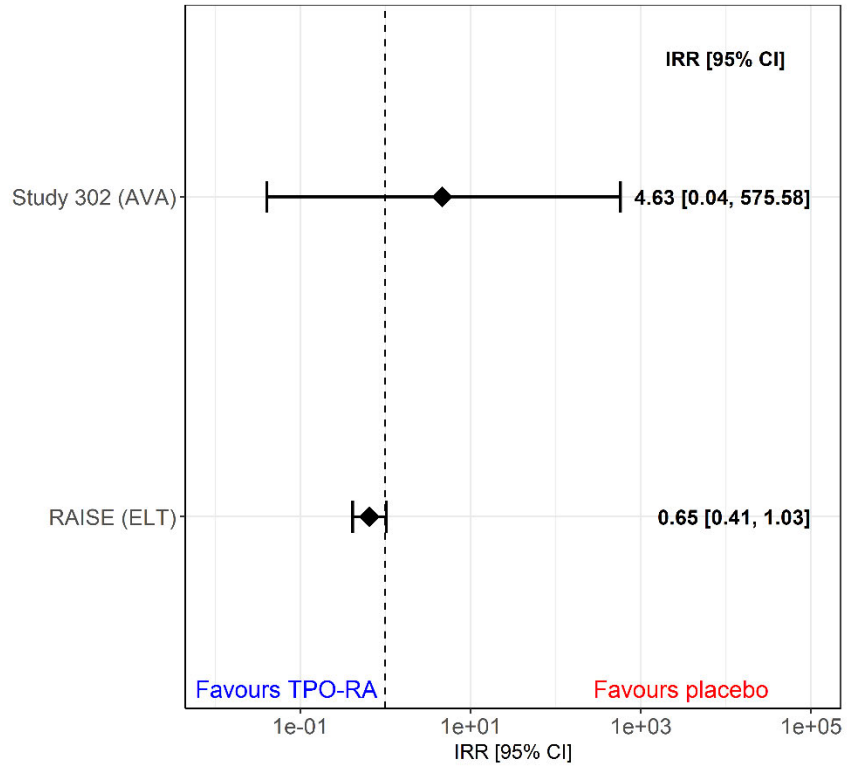


Figure 6: Forest plot for the incidence ratio for comparison of TPO-RAs vs placebo regarding bleed WHO grade 2-4



5.1.3 Comparative analyses

As described, the trials that were most relevant for the clinical question are AVA-302 for avatrombopag (Jurczak, Chojnowski et al. 2018) and RAISE for eltrombopag (Cheng, Saleh et al. 2011). Table 11 presents outcomes that were available and used for the comparative analysis as requested by the DMC. The table also presents salient differences in definition of outcomes.

To match the data available for avatrombopag from the AVA-302 trial, all endpoints from both the AVA-302 and RAISE trials are presented for the study duration of 6 months.

Table 11 provides an overview of the comparative analysis results.

5.2 Results per PICO

Table 11: Results per outcome for avatrombopag and eltrombopag

		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Bleeding (WHO 1 – 4)	AVA-302 RAISE	n/a	n/a	n/a	IRR = 0.38	0.19, 0.75	n/a	IRR was used, instead of RR, to account for the discontinuation bias in the trials
Bleeding (WHO 2 – 4)	AVA-302 RAISE	n/a	n/a	n/a	IRR = 0.74	0.20, 2.83	n/a	IRR was used, instead of RR, to account for the discontinuation bias in the trials
Durable platelet response	AVA-302 RAISE*	RD= 0.19**	-0.24, 0.93	n/a	RR = 1.81**	0.30, 92.0	n/a	* Assumed event rate: 2.41% (95% CI: 0.002 – 64.14); Baseline risk estimated using Bayesian analysis in accordance with NICE DSU TSD 5 (TSD5-Baseline.final-report.08.05.12.pdf (nicedsu.org.uk)) ** estimated using Bayesian analysis

		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
Platelet response at 6 months	AVA-302 RAISE*	RD= 0.51**	0.002, 0.97	n/a	RR = 7.81**	1.08, 563.20	n/a	* Assumed event rate: 4.09% (95% CI: 0.00004 – 84.22); Baseline risk estimated using Bayesian analysis in accordance with NICE DSU TSD 5 (TSD5-Baseline.final-report.08.05.12.pdf (nicedsu.org.uk)) ** estimated using Bayesian analysis

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; RD, risk difference; RR, relative risk; WHO, World health organization

5.2.1.1 QoL

Quality of life was measured in both AVA-302 and RAISE trials. However, the available information for eltrombopag was not sufficient to allow for a comparative analysis between avatrombopag and eltrombopag, as there was no reporting of SD estimates, nor of a detailed description of the methodology used (repeated-measures model).

5.2.1.2 Bleeding

Percent of patients experiencing bleeding WHO grade 2 – 4 (clinically significant)

Bleeding events and safety outcomes are highly impacted due to imbalanced discontinuation in the clinical trials presented. This leads to an underestimation of the true risk of events in the placebo arm. Relative risk (RR) does not take into consideration the discontinuation bias and will result in skewed results from the indirect comparison (ITC) if RR is used as the basis. As an alternative, data is presented as estimated incidence rate ratio (IRR), to adjust for the imbalanced exposure time in both arms (e.g., patient years) and to take into account the discontinuation bias. IRR was considered statistically significant, if the corresponding 95% credible intervals (CIs) did not include 1.

Bleeding was assessed with the WHO bleeding scale (grade 0, no bleeding; grade 1, petechiae; grade 2, mild blood loss; grade 3, gross blood loss; grade 4, debilitating blood loss) in both the AVA-302 and RAISE studies (Cheng, Saleh et al. 2011, Jurczak, Chojnowski et al. 2018). Bleeding of WHO grades 2 – 4 were considered clinically significant. Results from the NMA showed that there was no significant difference in bleeding between avatrombopag and eltrombopag (IRR=0.74 [0.20, 2.83]) (Table 12).

Table 12: Percent of patients experiencing bleeding WHO grade 2 – 4 (severe)

WHO grade 2 – 4	Incidence rate ratio (95% CI)	Absolute risk difference (percent; 95% CI)	Reference
AVA-302 vs RAISE	0.74 (0.20, 2.83)	n/a	(Cheng, Saleh et al. 2011, Jurczak, Chojnowski et al. 2018)

Abbreviation: CI, confidence interval; WHO, World Health Organization

Percent of patients experiencing bleeding WHO grade 1 – 4 (any)

As described above, bleeding was assessed with the WHO bleeding scale. Avatrombopag was associated with significantly lower incidence rate of any bleeding compared with eltrombopag (IRR = 0.38 [0.19, 0.75]) (Table 13).

Table 13: Percent of patients experiencing bleeding WHO grade 1 – 4 (any)

WHO grade 1 – 4	Incidence rate ratio (95% CI)	Absolute risk difference (percent; 95% CI)	Reference
AVA-302 vs RAISE	0.38 (0.19, 0.75)	n/a	(Cheng, Saleh et al. 2011, Jurczak, Chojnowski et al. 2018)

Abbreviation: CI, confidence interval; WHO, World Health Organization

5.2.1.3 Platelet response

Percent of patients achieving a durable platelet response

Platelet level may fluctuate during the treatment, therefore the assessment of platelet response at a single time-point has limited clinical relevance. Durable platelet response is more clinically relevant. In both studies, durable platelet response was defined as the proportion of patients who had a platelet response for ≥6 of the last 8 weeks of treatment (Cheng, Saleh et al. 2011, Jurczak, Chojnowski et al. 2018). In addition, both studies had specified a similar threshold of platelet count (≥50 x 10^9/L). This outcome was defined to assess maintenance of platelet response and was therefore less prone to random fluctuations of platelet level over time. The imbalanced discontinuation may have limited impact on durable platelet response, since it is unlikely that patients who discontinued due to insufficient efficacy would get the response. According to the results, there was no significant difference between avatrombopag and eltrombopag in durable platelet response (RR = 1.81 [0.30, 92]; i.e., CIs included 1). Outcomes are presented in Table 14.

Table 14: percent of patients achieving a durable platelet response

Durable platelet response	Relative risk (95% CI)	Absolute risk difference (percent; 95% CI)	Reference
AVA-302 vs RAISE	1.81 (0.30, 92)	0.19 (-0.24, 0.93)	(Cheng, Saleh et al. 2011, Jurczak, Chojnowski et al. 2018)

Abbreviation: CI, confidence interval

In addition, the percent of patients achieving a platelet response at 6 months was also analysed. According to the results, avatrombopag was associated with significantly higher probability of reaching platelet response compared with eltrombopag (RR = 7.81 [1.08, 563.20]. Outcomes are presented in Table 15.

Table 15: percent of patients achieving a platelet response at 6 months of treatment

Platelet response at 6 months	Relative risk (95% CI)	Absolute risk difference (percent; 95% CI)	Reference
AVA-302 vs RAISE	7.81 (1.08, 563.20)	0.51 (0.002, 0.97)	(Cheng, Saleh et al. 2011, Jurczak, Chojnowski et al. 2018)

Abbreviation: CI, confidence interval

5.2.1.4 Adverse events

Percent of patients experiencing adverse events

Adverse events were reported as treatment-emergent adverse events in the AVA-302 and as on-treatment adverse events in the RAISE study (as opposed to post-treatment adverse events) (Cheng, Saleh et al. 2011, Jurczak, Chojnowski et al. 2018). Treatment-emergent adverse events in the AVA-302 study were defined as any adverse event that had onset or worsened in severity, on or after the first dose of avatrombopag study treatment, and up to 30 days after the last dose of study medication during the study (Jurczak, Chojnowski et al. 2018). Of note, the RAISE study considered on-treatment adverse events separate from the post-treatment period.

As mentioned in Table 7, no comparative analysis was performed, due to the fact that such analysis would have resulted in a biased outcome, as a result of the imbalanced discontinuation rate in the AVA-302 trial.

Qualitative description of safety profiles

Table 16 presents a description of adverse events from the avatrombopag AVA-302 and eltrombopag RAISE trials. As mentioned above, the rate of adverse events in the AVA-302 trial was likely affected by the discontinuation bias in the trial.

The safety profile for the AVA-302 study (Jurczak, Chojnowski et al. 2018) shows that the incidence of exposure adjusted treatment emergent adverse events (TEAEs) was slightly lower in the avatrombopag group (4.3%) versus the placebo group (6.6%) per subject weeks. The TEAEs most commonly experienced (≥20% of patients) were contusion (bruising), headache, and upper-respiratory tract infection (Jurczak, Chojnowski et al. 2018).

The incidence of Common Toxicity Criteria for Adverse Events (CTCAE) grade 3/4 exposure-adjusted TEAEs was slightly higher in the avatrombopag group (0.8%) versus the placebo group (0%) per subject-weeks. The incidence of exposure-adjusted serious adverse events (SAEs) was slightly higher in the avatrombopag group (1.2%) versus the placebo group (0.7%) per subject weeks (Jurczak, Chojnowski et al. 2018).

The safety profile for the RAISE study (Cheng, Saleh et al. 2011) shows that the incidence of on-treatment adverse events (AEs) was similar for both groups, with AEs mainly of grade 1–2 severity. The AE most commonly reported (≥20% of patients) was headache. AEs that were reported for ≥5% more for patients receiving eltrombopag than placebo were nausea and vomiting. AEs that were reported for ≥5% more for patients receiving placebo than eltrombopag were: dyspepsia, peripheral oedema, insomnia, epistaxis, and ecchymosis. Grade 3+ AE occurred in 14% versus 11% of patients receiving eltrombopag versus placebo, respectively. Grade 3 AE of bleeding occurred for 7% of placebo patients, compared to 2% of eltrombopag patients (Cheng, Saleh et al. 2011).

An increase in alanine aminotransferase concentration to ≥3 times the upper limit (UL) of normal occurred in 7% and 3% of patients receiving eltrombopag and placebo, respectively. Increases of total bilirubin to >1.5 times the UL of normal occurred in 4% patients receiving eltrombopag and no patients receiving placebo. One patient receiving eltrombopag and one patient receiving placebo were withdrawn from the study due to an increase in alanine aminotransferase concentration of grade 3+ severity. All alanine aminotransferase abnormalities resolved, both during treatment with eltrombopag or after treatment interruption or discontinuation (Cheng, Saleh et al. 2011).

Table 16: Reports of adverse events amongst avatrombopag and eltrombopag treated patients in the AVA-302 and RAISE trials

Adverse events*, %	AVA-302		RAISE	
	Avatrombopag (N=32)	Placebo (N=17)	Eltrombopag (N=135)	Placebo (N=61)
Headache	37.5	11.8	30	33
Contusion	31.3	23.5	1	5
Upper respiratory tract infection	18.8	5.9	10	11
Arthralgia	12.5	0	7	5
Epistaxis	12.5	17.6	5	10
Fatigue	12.5	5.9	10	13
Gingival bleeding	12.5	0	n/a	n/a
Petechiae	12.5	5.9	n/a	n/a
Thrombocytopenia	6.3	0	n/a	n/a
Pharyngitis	0	5.9	6	1
Hypertension	6.3	5.9	3	5
Nasopharyngitis	9.4	0	10	13
Diarrhoea	n/a	n/a	13	10
Nausea	n/a	n/a	12	7
Limb pain	n/a	n/a	7	10
Increased ALT concentration	n/a	n/a	7	7
Vomiting	n/a	n/a	7	2
Urinary tract infection	n/a	n/a	7	7
Oropharyngeal pain	n/a	n/a	7	5
Myalgia	n/a	n/a	6	3
Increased AST concentration	n/a	n/a	5	3
Back pain	n/a	n/a	5	5
Influenza	n/a	n/a	5	5
Cough	n/a	n/a	4	7
Upper abdominal pain	n/a	n/a	4	8
Constipation	n/a	n/a	4	8
Dizziness	n/a	n/a	4	10
Pruritus	n/a	n/a	3	8
Cataract	n/a	n/a	3	7‡
Peripheral oedema	n/a	n/a	1	10‡§
Dyspepsia	n/a	n/a	1	7‡§
Ecchymosis	n/a	n/a	2	7
Insomnia	n/a	n/a	1	7‡
Anxiety	n/a	n/a	1	5
Conjunctival haemorrhage	n/a	n/a	1	5

Adverse events*, %	AVA-302		RAISE	
	Avatrombopag (N=32)	Placebo (N=17)	Eltrombopag (N=135)	Placebo (N=61)
Neck pain	n/a	n/a	1	5
Non-cardiac chest pain	n/a	n/a	1	5
Abdominal distension	n/a	n/a	<1	5
Conjunctivitis	n/a	n/a	<1	7
Fall	n/a	n/a	<1	5
Face swelling	n/a	n/a	<1	5
Cellulitis	n/a	n/a	0	7‡
Eye swelling	n/a	n/a	0	5

Abbreviation: AST; asparagine aminotransferase; ALT, alanine amino transferase; GGT gamma-glutamyl transferase; n/a, not available
Note: *AVA-302 measured treatment-emergent adverse events, while RAISE measured on-treatment adverse events. ‡Events typically associated with corticosteroid use. §Significantly lower for avatrombopag versus placebo using two-sided Fisher's exact test (p=0 01).
Source: (Cheng, Saleh et al. 2011, Jurczak, Chojnowski et al. 2018)

5.3 Other considerations

This section presents additional available evidence on avatrombopag and eltrombopag, as suggested in Section 7 in the DMC protocol (andre overvejelser).

Implications on sequence of treatment

Based on the results of the NMA, avatrombopag has the same clinical efficacy as eltrombopag. Avatrombopag will be introduced as another available TPO-RA treatment for patients with chronic ITP.

Based on the results from the AVA-302 study, previous treatment with another TPO-RA does not have any effect on the clinical efficacy of avatrombopag (McCrae, Allen et al. 2019).

Duration of treatment

The pooled safety data from available trials includes 128 patients who were exposed to avatrombopag for a median duration of 29 weeks.

Chronic ITP is a life-long disease, and the treatment is considered chronic. No comparative data is currently available on treatment duration between avatrombopag and eltrombopag.

Concomitant ITP medication

According to the results of the AVA-302 trial, there was a reduction in concomitant ITP medication usage from baseline in avatrombopag treated patients that was greater than for placebo treated patients, -33.3% versus a 0% change, respectively (Jurczak, Chojnowski et al. 2018).

Drug administration and interactions

Avatrombopag is for oral use and should be taken with food (European Medicines Agency 2021).

Eltrombopag is for oral use. The tablets should be taken at least two hours before or four hours after any products such as antacids, calcium containing food products, or mineral supplements containing polyvalent cations (e.g., iron, calcium, magnesium, aluminium, selenium, and zinc) (European Medicines Agency 2021)

Hypersensitivity to either avatrombopag or eltrombopag or any of their excipients are possible contraindications.

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Dose intensity

Avatrombopag should be administered at the lowest dose needed to achieve and maintain a platelet count ≥ 50 x 10^9/L as necessary to reduce the risk for bleeding. The recommended starting dose of avatrombopag is 20 mg (1 tablet) once daily with food. After initiating therapy, platelet counts should be assessed at least once weekly until a stable platelet count ≥ 50 x 10^9/L to ≤ 150 x 10^9/L has been achieved. Twice weekly platelet count monitoring should be conducted during the first weeks of therapy in patients receiving avatrombopag only once or twice weekly. Twice weekly monitoring should also be conducted after dose adjustments during the treatment. Due to the potential risk of platelet counts above 400 x 10^9/L within the first weeks of treatment patients should be carefully monitored for any signs or symptoms of thrombocytosis. After discontinuation of avatrombopag, platelet counts should be obtained weekly for at least four weeks. Dose adjustments (Table 17) are based on the platelet count response. A daily dose of 40 mg (2 tablets) should not be exceeded.

Table 17: Dose adjustments of avatrombopag

Platelet count (x10^9/L)	Dose adjustment or action
<50 following at least 2weeks of therapy	Increase one dose level. Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
>150 to ≤250	Decrease one dose level. Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
>250	Stop avatrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤100 x 10^9/L, decrease one dose level and reinitiate therapy.
<50 after 4 weeks of avatrombopag 40 mg once daily	Discontinue avatrombopag.
>250 after 2 weeks of avatrombopag 20 mg weekly	Discontinue avatrombopag.

SOURCE: Doptelet Summary of Product Characteristics

The lowest dose of eltrombopag to achieve and maintain a platelet count ≥50 x 10^9/L should be used. Dose adjustments are based upon the platelet count response. Eltrombopag must not be used to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting eltrombopag and decreased within 1 to 2weeks after discontinuation. The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East-/Southeast-Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily. After initiating eltrombopag, the dose must be adjusted to achieve and maintain a platelet count ≥50 x 10^9/L as necessary to reduce the risk for bleeding (Table 18). A daily dose of 75 mg must not be exceeded.

Table 18: Dose adjustments of eltrombopag

Platelet count (x10^9/L)	Dose adjustment or response
<50 following at least 2weeks of therapy	Increase daily dose by 25 mg to a maximum of 75mg/day.*
≥50 to ≤150	Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
>150 to ≤250	Decrease the daily dose by 25 mg. Wait 2weeks to assess the effects of this and any subsequent dose adjustments.**
>250	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤100 x 10^9/L, reinitiate therapy at a daily dose reduced by 25 mg.

SOURCE: Revolade Summary of Product Characteristics
*For patients taking 25mg eltrombopag once every other day, increase dose to 25mg once daily.
**For patients taking 25mg eltrombopag once daily, consideration should be given to dosing at 12.5mg once daily or alternatively a dose of 25mg once every other day

5.4 Conclusions

The results presented in this application have shown that avatrombopag is of similar clinical efficacy as eltrombopag, with regards to durable platelet response and severe bleeding events. In addition, avatrombopag may be associated with a reduced rate of any bleeding compared with eltrombopag.

No comparative analysis was feasible for QoL and adverse events, mainly due to the fact that there was limited published information on these outcomes for the RAISE trial, and there was an imbalanced discontinuation rate in the AVA-302 trial.

With regards to dietary restrictions, eltrombopag is associated with food restrictions, as patients have to fast a few hours before and after the treatment, while avatrombopag is an oral tablet without significant food restrictions (should be taken with food), and as such could be perceived by patients as a more convenient alternative.

The addition of avatrombopag to the currently available TPO-RAs would provide patients with an option that shares the same clinical efficacy and similar safety profile as eltrombopag, while being considered as a potentially more convenient option. In addition, avatrombopag would be an additional option for those patients that switch between TPO-RA treatments due to lack of response or side effects.

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7. Appendix

7.1 Literature search

Table 19: Literature search inclusion and exclusion criteria for question 1

Inclusion criteria	**Population:**
	Adult patients with primary chronic ITP who are refractory to previous treatment with glucocorticoids and at least one other immunosuppressant (such as rituximab)
	Intervention(s):
	Avatrombopag 20 mg per day, which can be titrated to 40 mg per day
	Eltrombopag 50 mg per day, which can be titrated to 75 mg per day
	Comparator(s):
	Placebo
	Outcomes:
	• QoL
	  ○ SF-36
	• Efficacy
	• Severe and/or minor bleeding
	• Platelet count
	• Safety
	  ○ Adverse events
	• Discontinuation
	• Outcomes at 6 months
	Settings (if applicable):
	N/A
	Study design:
	Randomised control trials
	Phase II studies only considered when no phase III studies are available
	Language restrictions:
	English, Norwegian, Swedish, or Danish
	Other search limits or restrictions applied:
	n/a

Exclusion criteria	**Population:** Patients who are not Adults with primary chronic ITP who are refractory to previous treatment with glucocorticoids and at least one other immunosuppressant (such as rituximab) **Intervention(s):** Not avatrombopag nor eltrombopag Other doses of treatment that not defined by the Danish Medicines Council in the protocol **Comparator(s):** Not placebo **Outcomes:** Others not specified by the Danish Medicines Council in the protocol Data not available at 6 months **Settings (if applicable):** N/A **Study design:** Not randomized control trial, Animal, non RCTs, case reports, editorials & opinion pieces, reviews, conference abstract poster **Language restrictions:** Not English, Norwegian, Danish, or Swedish **Other search limits or restrictions applied:** n/a

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The following publications/studies were excluded during the full-text systematic literature review.

Table 20: Full text publications excluded during the Systematic Literature Review

	Publication	Reason for exclusion	Comment
1	Al-Samkari, H. and S. Nagalla, Efficacy and safety evaluation of avatrombopag in immune thrombocytopenia: analyses of a phase III study and long-term extension. Platelets, 2021: p. 1-8.	Study design	Not RCT
2	Perioperative oral eltrombopag versus intravenous immunoglobulin in patients with immune thrombocytopenia: a non-inferiority, multicentre, randomised trial Arnold et al. Lancet Hemaetology (2020)	Population	Perioperative
3	Long-Term Safety and Efficacy of Oral Eltrombopag for the Treatment of Subjects with Idiopathic Thrombocytopenic Purpura (ITP): Preliminary Data from the EXTEND Study. Bussel et al. Blood (2007)	Study design	Conference abstract
4	Analysis of Bleeding in Patients with Immune Thrombocytopenic Purpura (ITP): A Randomized, Double-Blind, Placebo-Controlled Trial of Eltrombopag, an Oral Platelet Growth Factor. Bussel et al. Blood (2006)	Study design	Conference abstract
5	Oral Eltrombopag for the Long-Term Treatment of Patients with Chronic Idiopathic Thrombocytopenic Purpura: Results of a Phase III, Double- Blind, Placebo-Controlled Study (RAISE) Cheng et al. Blood (2008)	Study design	Conference abstract
6	A Randomized, Double-Blind, Placebo-Controlled Phase II Trial on the Efficacy, Safety and Tolerability of E5501 (AKR501) In Subjects with Chronic Immune Thrombocytopenia (ITP) Bussel et al. Blood (2010)	Study design	Conference abstract
7	Repeated short-term use of eltrombopag in patients with chronic immune thrombocytopenia (ITP) Bussel et al. BJH (2013)	Study design	Phase 2 RCT
8	A randomized trial of avatrombopag, an investigational thrombopoietin-receptor agonist, in persistent and chronic immune thrombocytopenia Bussel et al. Blood (2014)	Study design	Phase 2 RCT
9	Bussel, J.B., et al., Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med, 2007. **357**(22): p. 2237-47.	Study outcomes	No 6-month data
10	Bussel, J.B., et al., Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. Lancet, 2009. **373**(9664): p. 641-8.	Study outcome	No 6-month data
11	Spotlight on Eltrombopag in Treatment-Refractory Chronic Primary Immune Thrombocytopenia Garnock-Jones Biodrugs (2011)	Study design	Review
12	Efficacy and safety of eltrombopag in Chinese patients with chronic immune thrombocytopenia: stage 2 results from a multicenter phase III study Lui et al. Platelets (2020)	Intervention	Dosage not approved
13	Tarantino, M.D., et al., Efficacy of eltrombopag in management of bleeding symptoms associated with chronic immune thrombocytopenia. Blood Coagul Fibrinolysis, 2013. **24**(3): p. 284-96.	Study design	Not RCT
14	Multicentre, randomised phase III study of the efficacy and safety of eltrombopag in Chinese patients with chronic immune thrombocytopenia Yang et al. BJH (2017)	Intervention	Dosage not approved

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Network meta-analysis of efficacy and safety of avatrombopag versus comparators in adult patients with chronic immune thrombocytopenia who have had an insufficient response to a previous treatment

Date: 04-11-2020

Version 1

Prepared for:
SOBI

sobi
rare strength

1. Table of contents

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4. Abbreviations

AVA	Avatrombopag
ELT	Eltrombopag
IRR	Incidence rate ratio
ITP	Immune thrombocytopenia
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PLC	Placebo
RCT	Randomised controlled trial
RR	Relative risk

5. Objective

The objective of this project was to assess the relative efficacy and safety of avatrombopag (AVA) compared to eltrombopag (ELT) in adult patients with chronic immune thrombocytopenia (cITP), who have had an insufficient response to a previous treatment.

The assessment was performed using a network meta-analysis (NMA) in a Bayesian framework based on studies identified through a systematic literature review or randomised controlled trials (RCTs).

5.1. Outputs of the NMA

A network diagram representing all direct comparisons between treatments included in the analysis were produced for each outcome.

Results are presented with summary statistics:

- Median and mean relative risks or incidence rate ratios with associated 95% credible intervals (95% CrI) are reported for AVA versus other treatments for binary outcomes

A difference in the mean change from the baseline is considered statistically significant when the associated 95% credible interval does not include zero. A relative risk is considered statistically significant when the associated 95% confidence interval does not include 1.

Forest plots with relative risks (for binary outcomes) and incidence rate ratios, and associated 95% CrI for AVA versus ELT, have been prepared.

5.1.1. Discontinuation rate

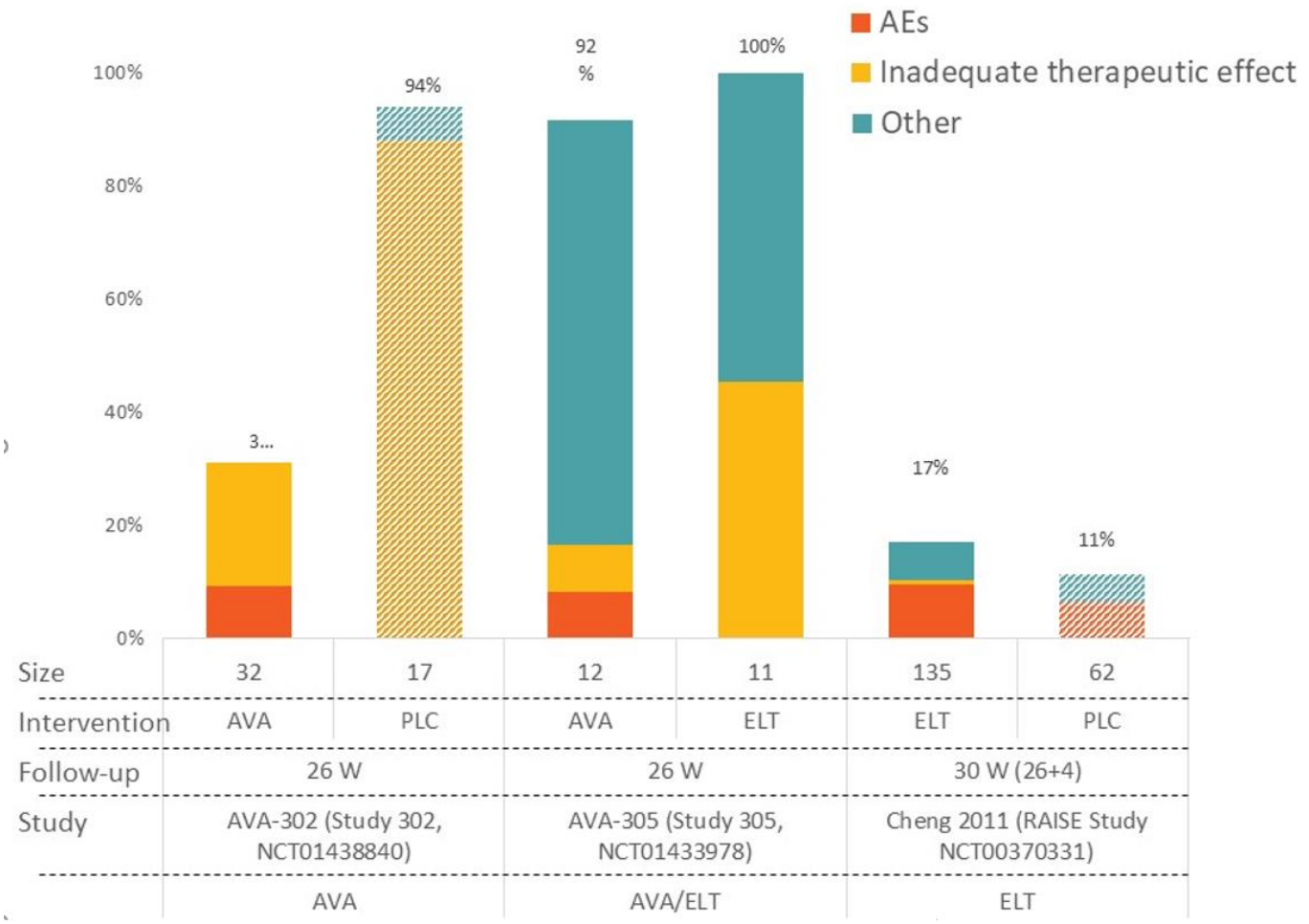
There was a noticeable between-trial heterogeneity in the proportion of patients prematurely discontinuing allocated treatment. In the pivotal AVA-302 trial 94% of patients allocated discontinued prematurely from the PLC arm, predominantly due to inadequate therapeutic effect, while 31% of patients dropped out from the AVA arm at the same time.[1] On the contrary, much lower rates of premature discontinuation was observed in the RAISE trial with 11% of patients discontinued from the PLC group, mainly due to adverse events and consent withdrawal (Figure 1).

The noticeable discontinuation from AVA-302 trial was likely due to availability of treatment alternatives for not responding patients. This relatively recent study was registered after ELT had been approved in the treatment of patients with ITP, therefore participants with suboptimal response during AVA-302 could not be maintained in the trial due to ethical concerns. Therefore, they were allowed to discontinue allocated regimens and receive best available alternative therapy, which explains that nearly all participants, who were allocated to PLC groups of the AVA-302 trial discontinued treatment, most often due to inadequate effect (Figure 1).

Premature, imbalanced discontinuation significantly affected the total exposure time in the included studies and therefore could interact with the results for relative efficacy and safety. For example, the mean reported duration of

exposure with avatrombopag was approximately 2.6-fold longer than that in PLC group (22.78 weeks versus 8.93 weeks in the AVA and PLC groups, respectively). This large disproportion in the effective treatment duration highly likely influenced the risk of bleeding by decreasing the chance of events to occur in the PLC group. It is therefore highly likely that PLC group in AVA-302 trial was favoured, since massive drop out reduced the chance for bleeding events or adverse events. Thus, observed percentages of patients with such outcomes may underestimate the true risk of events in the PLC groups.

Figure 1. Proportion of patients who discontinued from respective clinical trials



5.2. Adjustment for premature discontinuation

As discussed in Section 5.1.1, the rates and reasons for premature discontinuations differed across included studies, so that large early drop-out was observed from PLC group of the AVA-302 trial. This significant and imbalanced discontinuation reduced the effective treatment periods leading to underestimation of the true event risks. Since vast majority of early dropouts occurred due to inadequate efficacy, it is highly unlikely that it would affect durable platelet response. On the contrary, the risk of bleeding is likely to be affected by the drop out (Table 1).

Table 1. Impact of the premature drop-out on the efficacy and safety outcomes

Outcome	Impact of discontinuation due to suboptimal efficacy	Comment on the impact of premature discontinuation	Analysed effect measure
Durable platelet response	Low	The impact is considered limited since the likelihood for achieving durable platelet response in patients, who discontinue due to insufficient response is marginal	Analysis based on observed events with relative risk
Platelet response at 6 months	Low	The impact is considered limited since the likelihood for achieving platelet response at 6 months in patients, who discontinue due to insufficient response is marginal	Analysis based on observed events with relative risk
Bleeding events	High	The impact is considered high since reduced effective exposure highly likely led to underestimation of the true event risk	Analysis based on estimated incidence with incidence rate ratio
Adverse events	High	The impact is considered high since reduced effective exposure highly likely led to underestimation of the true event risk	Analysis based on estimated incidence with incidence rate ratio

To avoid bias associated with imbalanced premature discontinuation we conducted an NMA based on estimated incidence rate ratio, thus accounting for the differences in the effective treatment duration across groups.

First, the time on treatment in all arms of respective studies will be estimated assuming exponential survival curve for time to discontinuation.

$$c(t) = e^{-\lambda t}$$

Where, *c(t)* – proportion of patients, who remained on treatment

λ - rate of discontinuation

t - time

The mean exposure was estimated by calculating the surface below the survival curve for time to discontinuation:

$$\text{mean exposure time} = \int_0^{observation\ time} c(t)dt = -\frac{1}{\lambda}\left(e^{\left(\frac{observation\ time}{\lambda}\right)} - 1\right)$$

Incidence rate ratios (IRR) for the comparison between groups within each study were then calculated by dividing incidence rates estimated for the treatment and control groups, respectively. The 95% confidence intervals around IRR were calculated as follows:

$$CI_{95\%}(IRR) = \mathrm{e}^{ln\,IRR \pm z_{2.5\%}\sqrt{var(ln(IR_{active}))+var(ln(IR_{control}))}},$$

Where, $z_{97.5\%}$ – the inverse of the standard normal distribution at 97.5%

$var(ln(IR_i))$ – variance of the natural logarithm of incidence rate estimated for arm *i*.

Assuming that the number of patients with events in group i (n_i) is equal to the total number of events observed in this group, the variance of the natural logarithm of incidence rate estimated for arm *i* is approximated by the equation:

$$var(ln(IR_i)) = \frac{1}{n_i}$$

Mean exposure duration in AVA-302 trial was reported by the authors as 22.78 weeks and 8.93 weeks in the AVA and PLC groups, respectively.

Table 2. Estimated exposure durations in the included studies

Study	Treatment	Percentage of non-completers	Mean exposure [years]	Total exposure [patient-years]
AVA-302 [1]	AVA	10/32 (31%)	0.44*	14.02
	PLC	16/17 (94%)	0.17*	2.92
AVA-305 (NCT01433978)	AVA	11/12 (92%)	0.30	3.62
	ELT	11/11 (100%)	0.20	2.23
Cheng 2011[2] **(RAISE Study)**	ELT	23/135 (17%)	0.46	61.57
	PLC	7/62 (11%)	0.47	29.22

*True exposure reported in the trial report[1]

5.3. Outcomes reporting

The definition of the primary outcome differed across included studies. The objective of the AVA-302 trial was to compare maintenance of the platelet response within the treatment period, while AVA-305 was initially designed to assess change from baseline in platelet count from baseline. The RAISE trial was powered for the assessment of the percentage of patients with the response. Therefore, the response assessed in the included studies was heterogeneous in terms of definition and time of evaluation. (Table 3)

Table 3. Primary efficacy outcome definition in included trials

Trial	Primary efficacy outcome
Study 302	**Number of weeks with platelet count greater than or equal to 50 x 10^9/l** during 6-month treatment period [Time frame: week 1 to week 26] The cumulative number of weeks of platelet response is defined as the total numbers of weeks in which the platelet count is greater than or equal to 50 x 10^ 9/L during 6 months of treatment of core study in the absence of rescue therapy.
Study 305	**Change from baseline** in local platelet count for the 6 month treatment period [Time frame: day 5, Day 8, Week 2, Week 3, Week 4, Week 6, Week 8, Week 10, Week 12, Week 14, Week 16, Week 18, Week 19, Week 20, Week 22, Week 23, Week 24, Week 25, Week 26] Platelet responses to avatrombopag was evaluated using the platelet counts determined at local clinical laboratories. Only participants with non-missing data at both baseline and the relevant post-baseline visit are included in the change from baseline summary statistics. Standard deviation is not applicable for some of the categories, from Visit 14 to Visit 22, as the number of participants analyzed for that visit was 1 individual.
RAISE	Percentage of responders [Time frame: baseline; each on-therapy treatment day; Weeks 10, 14, 18, 22, and 26; and Weeks 1, 2, and 4 post-treatment] The percentage of evaluable participants who achieved a platelet response (defined as a platelet count between 50,000 and 400,000 microliter) at each nominal on-therapy day and 4 weeks post-treatment

Despite noticeable between-trial differences regarding assessed parameters there were several outcomes with reasonably consistent definition across studies, which allowed for the indirect treatment comparison using Bayesian NMA. The outcomes with reasonably consistent definitions are described below.

Durable response was assessed in 2 studies (1 for AVA and ELT) with relatively similar definitions based on:

- Similar threshold of platelet count (≥50 × 10^9/L, 50-400 × 10^9/L),
- Similar observation period (last 8 weeks),
- Similar maintenance of improvement (6 out of 8 weeks).

The proportion of patients with durable platelet response were reported in all trials except AVA-305 trial, although it is worth noting that the durable response in the RAISE trial was not pre-specified and was assessed within a post-hoc analysis based on available data only.[2]

Figure 2 presents definitions of durable (stable) platelet response used in included trials.

Figure 2. Durable response definition in trials

Bleeding episodes were reported in all included studies, although the definitions of events varied across studies:

- Studies AVA-302 and AVA-305 adopted WHO bleeding scale,

- RAISE study adopted two bleeding scales:
    - WHO bleeding scale,
    - bleeding adverse events reporting by physicians, using the National Cancer Institute Common Toxicity Criteria for Adverse Events scale,

Taking this into account the **proportion of patients with bleeding events of all severities** (WHO 1-4) and **bleeding events grades 2-4** according to WHO were reported in studies assessing AVA (AVA-302, AVA 305) and ELT (RAISE, AVA 305).

The number of patients experiencing **any adverse events** emerging during the treatment were reported in all trials.

6. Methods

A network meta-analysis (NMA) in a Bayesian framework was conducted to compare clinical efficacy and safety of AVA versus ELT. The analysis was conducted in accordance with the methodological guidelines and tutorials developed by NICE Decision Support Unit.[3]

6.1. NMA overview

NMAs have been presented as an extension of a traditional meta-analysis (where all included studies compare the same intervention with the same comparator) by including multiple pair-wise comparisons across a range of different interventions. The key value of an NMA is that the efficacy of a particular intervention versus competing interventions can be obtained in the absence of head-to-head comparisons; indirect treatment comparison (ITC) of two interventions is made via a common comparator.

A meta-analysis of RCTs comparing drug A and drug B (AB studies) provides a direct estimate of the *true* relative effect of A versus B (d_{AB}). A meta-analysis of AC-studies provides a direct estimate of the true relative effect d_{AC}. If the included AB and AC studies are sufficiently similar, then the true relative efficacy of the different types of comparisons are mathematically related, as illustrated in Figure 3.

In the absence of 'head-to-head' evidence comparing drugs B and C, an indirect estimate for the relative *true* effect of B versus C (d_{BC}) can be obtained from the *true* effect d_{AB} and from the *true* effect d_{AC}. In essence, this implies that the same true d_{BC} is obtained as would have been estimated in a meta-analysis focusing on drug B versus C using three-arm ABC studies, if available. Under the same condition, indirect evidence contains more uncertainty than direct evidence. For example, in Figure 3 the variance for the indirect comparison of d_{BC} would be the sum of variances of d_{AB} and d_{AC}. Therefore, by definition, the variance (and uncertainty) is greater for the indirect comparison when compared to the direct evidence for either d_{AB} or d_{AC}. As for the example illustrated in Figure 4, the meta-analyses for AB studies and AC studies can be performed separately (a step wise approach) or simultaneously with a model taking into account the structure of the network.

Figure 4 represents the situation when, in addition to interventions B and C, the intervention D is of interest as well. For this latter intervention, direct estimates from BD studies are available. Given the network of direct comparisons across the range of interventions, indirect estimates can be obtained for d_{AB}, d_{AC}, d_{BC}, d_{CD}, and d_{AD}. Given the mathematical relations between the true underlying estimates of the different comparisons in the network, there is direct and indirect evidence available for all the pair-wise comparisons, except for the CD comparisons (only indirect evidence) and the BD comparisons (only direct evidence; See Figure 4). The evidence network consists of 'loops' of evidence and the analysis is called a Network Meta-Analysis (NMA). Hence, the advantages of the simultaneous analysis with NMA are that 1) estimates for indirect comparisons are obtained, and 2) indirect comparisons can support evidence for direct estimates. If there are inconsistencies between direct and indirect evidence for particular 'loops', there will be bias in the estimates.

Figure 3. Network of evidence reflecting an anchored indirect treatment comparison of AB studies with AC studies

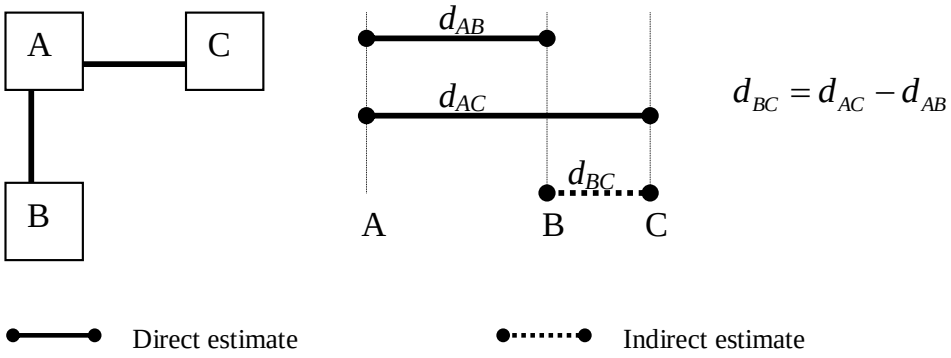
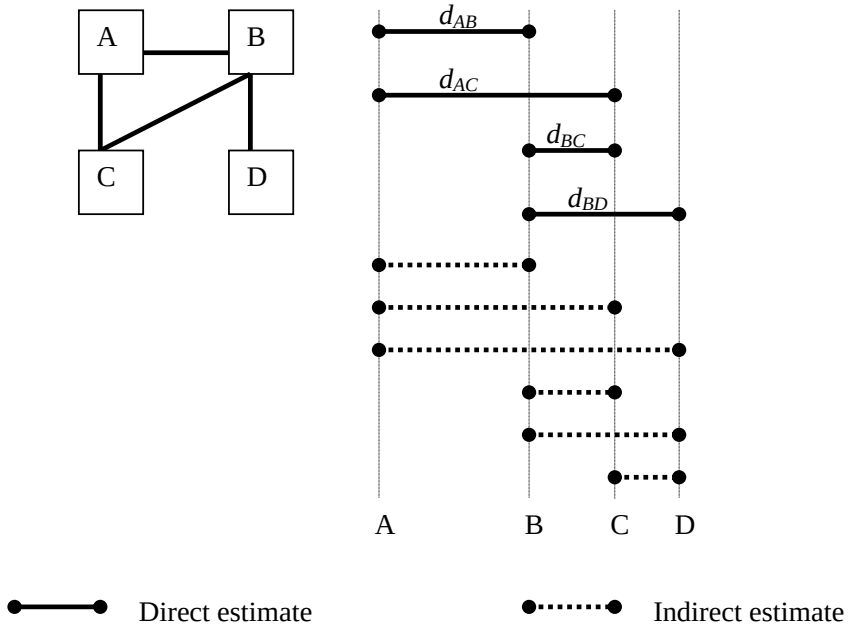


Figure 4. Network of evidence reflecting mixed treatment comparisons of AB studies, AC studies, BC studies, and BD studies



6.2. Data inputs

- **Model inputs for incidence**: the estimated incidence rate ratios (IRR) together with 95% confidence intervals. IRR follows log-normal distribution, therefore the estimates were logarithmised prior to the analysis and pooled together using the model with normal likelihood and identity link dedicated for treatment differences. (Example 7 from NICE DSU TSD2 guidelines[4]).
- **Model inputs for dichotomous data:** the number of patients experiencing the outcomes and the total number of patients by different arms were used and pooled using models with binomial likelihood and logit link (Example 1 from NICE DSU TSD2 guidelines[4])

6.3. Correction for zero events

Computational problems could occur when no events were observed in one or both groups in an individual study. Problematic zero counts were carefully checked, and fixed values were added to cells presenting a number of events proportionally to the number of patients recruited to a given arm or, in a case of considering incidence rate ratio, proportionally to the number of patient weeks in a given arm.[5]

6.4. Likelihood and link-functions

To perform the NMA within a Bayesian framework, likelihood distributions needed to be defined to relate the data to the parameters of the models. An overview of the likelihood and link function for the different types of outcome data in the available evidence base is provided in Table 4.

Table 4. Likelihood and link functions for different types of outcome data

	Likelihood	Link function
Normally distributed continuous data	$y_{jk} \sim normal(\theta_{jk}, \sigma_{jk}^2)$	Identity
Binary data	$r_{jk} \sim binomial(p_{jk}, n_{jk})$	$\text{logit}(p_{jk})$

6.5. Prior distributions

In order not to influence the observed results by the prior distribution, non-informative prior distributions were used for the model parameter(s). With such a 'flat' prior, it is assumed that before seeing the data any parameter value is 'equally' likely. As a consequence, posterior results are not influenced by the prior distribution but driven by the data as with a conventional frequentist meta-analysis. This approach is consistent with NICE requirements as stated in the NICE DSU technical support document[3] and Table 5presents the prior distributions to be used in the planned Bayesian analysis.

Table 5. Prior distributions for model parameters used for analysis in a Bayesian framework

Model parameters	Prior distribution
Nuisance parameters	$\mu_{jb} \sim normal(0,\ 10000)$
Treatment effect parameters	$d_{Ak} \sim normal(0,\ 10000)$
Heterogeneity parameters	$\sigma \sim uniform(0,\ 5)$

6.6. Selection of FE versus RE model

In order to identify the most appropriate model given the evidence base, the goodness-of-fit of model predictions to the observed data can be measured by calculating the posterior mean residual deviance, $\overline{D}$. The deviance information criterion (DIC) provided a measure of model fit that penalises model complexity according to $DIC = \overline{D} + pD, pD = \overline{D} - \widehat{D}$[6]. pD is the 'effective number of parameters' and $\widehat{D}$ is the deviance evaluated at the posterior mean of the model parameters.

The model with the lower DIC has been selected as it is the best compromise between adequacy and complexity[7]. However, a small difference in DIC between the fixed and random effects models (3-5 points) implies that the better fit obtained by adding random effects does not justify the additional complexity. If the difference in DIC between the fixed and random effect models was lower than 5 points, then the fixed effect model was selected, as it contains a lower number of parameters and is easier for clinical interpretation compared with the random effects model.[8]

6.7. Calculation of baseline risk

The estimation of the relative risks in the NMA requires to feed the model with the estimate of absolute risk attributable to the reference treatment encoded as d_1, referred as baseline risk. The baseline risk was calculated in accordance with the NICE DSU TSD 5 methodological guidelines with a random-effect model with binomial distribution and logit link. The model estimating the baseline risk was integrated with models used to calculate relative effects (See Section 10.1.1).

6.8. Analysis of consistency

As described in the NICE TSD 4, the inconsistency in NMAs refers to the conflict between direct comparison and indirect evidence within closed loops of the evidence network. Therefore, the assessment of network consistency makes sense only for a network of evidence containing closed loops formed by different studies. [9]

Except for AVA-305, all studies assessing the interventions of interest in the treatment of thrombocytopenia compare versus the placebo and form a star-like network with the placebo as the common comparator. Therefore, the consistency was tested only for networks with closed loops formed by studies AVA-302, AVA-305 and RAISE. The analysis of consistency was conducted using Bucher's approach and test for heterogeneity as described in the NICE TSD 4 guidelines.

6.9. Assessment of convergence

The convergence of models has been assessed based on two diagnostics tools:

- Trace plot:

- If the model has converged, the trace plot moves around the mode of the distribution.
- A clear sign of non-convergence with a trace plot occurring when we observe some trending in the sample space.
- The scale of the trace plot can be used to identify instability in the chains with very high values

- Brooks-Gelman-Rubin diagnostic tool:
  - The green is the width of an 80% credible interval from the simulations pooled from all chains (a measure of the between-chain variability); the blue line is the average width of the 80% credible intervals for each chain separately (a measure of the within-chain variability), the red line is the ratio of the between- and within-chain measures.
  - Convergence is reached when the red line settles down too close to 1 and the blue and green lines converge together to stability.

In case of convergence issues, several technics were considered such as increasing the number of iterations, reducing the variance of the prior distributions or removing some studies from the analyses.

This report would inform further if the convergence occurred for all parameters in each analysis.

6.10. Planned number of iterations

Three independent Monte-Carlo chains were run for each analysis.

For fixed effect models, an initial burn-in of 25,000 iterations were discarded and all the results are based on a further sample of 25,000 iterations.

For random effect models, an initial burn-in of 50,000 iterations were discarded and all the results are based on a further sample of 50,000 iterations.

6.11. Software

The parameters of the different models were estimated within a Bayesian framework using a Markov Chain Monte Carlo (MCMC) method as implemented in the WinBUGS software package [10].

7. NMA Results

7.1.1. Durable response (binary data)

7.1.1.1. Overall information and input data

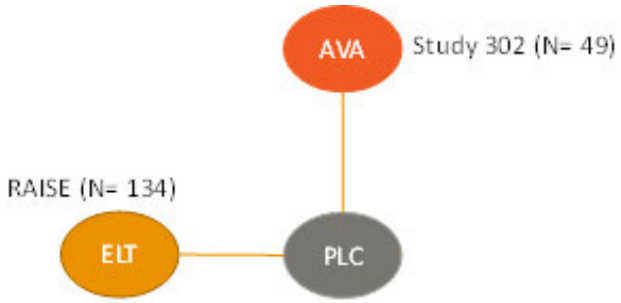
There were 2 studies (3 treatments; 207 patients) included in the NMA. Input data for the NMA are presented in Table 6 and the network of evidence for this outcome is depicted in Figure 5.

Table 6. Input data for the NMA of the proportion of patients with durable response

Study	Treatment	Event rate n/N (%)	RR [95%CI]**
Study 302	AVA	11/32 (34.38%)	17.84 * [0.64, 496.07]
	PLC	0/17 (0.00%)	
RAISE	ELT	57/95 (60.00%)	5.85 [2.28, 15.02]
	PLC	4/39 (10.26%)	

RR – relative risk; IRR – incidence rate ratio
* Continuity correction for zero cells was applied. For details see Table 22
** RRs were calculated using frequentist methods with the correction for zero cells

Figure 5. Network of evidence for the proportion of patients with durable response



7.1.1.2. NMA results

Results of the NMA regarding the proportion of patients with durable response are depicted in Figure 6 and summarised in Table 7. Additional results (random effect model) from the NMA are provided in Table 16 (Appendix 1).

Although the estimates from this analysis were highly imprecise due to low number of events, this NMA showed that all treatments were associated with significantly higher probability of durable response compared with PLC. No significant differences regarding the proportion of patients with durable response were observed between AVA and ELT.

The mean and median posterior distribution for the proportion of patients reaching platelet response estimated across both PLC groups from the included trials were 8.1% and 2.4%, respectively.

Figure 6. Forest plot for relative risk for comparison AVA vs comparators regarding durable response – fixed effect model

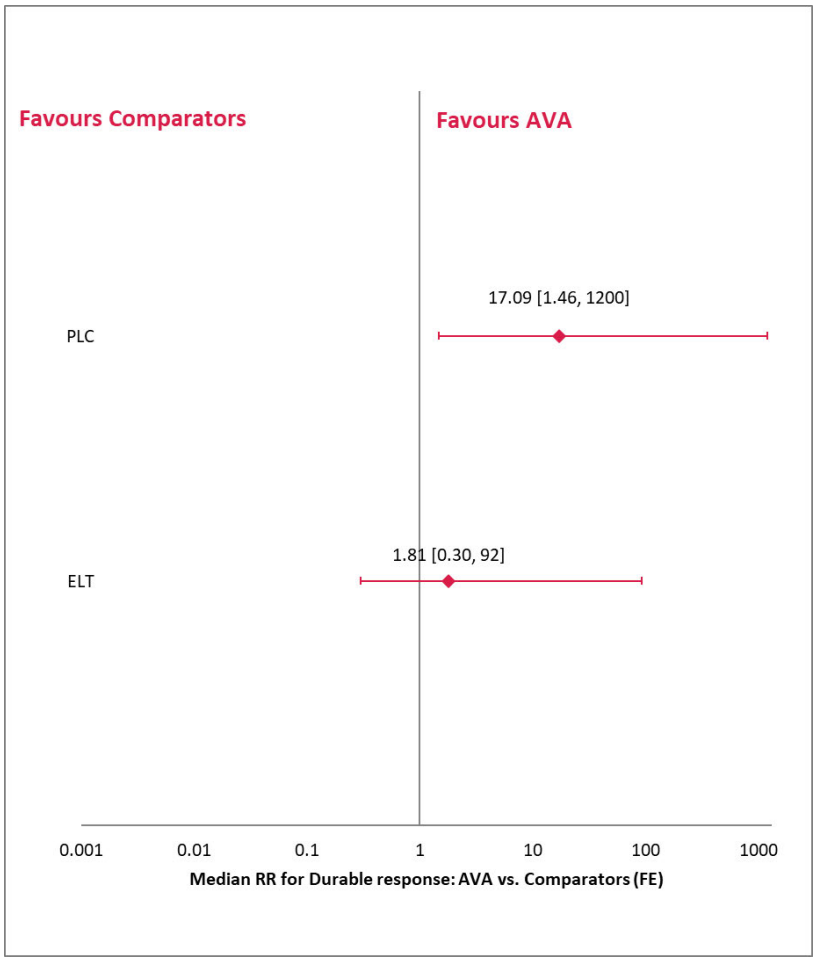


Table 7. Relative risk for durable response – fixed effect model

	Relative risks for all comparisons (FE model)		
	vs. PLC	vs. AVA	vs. ELT
PLC	PLC	**0.04 [0.00, 0.29]**	**0.09 [0.03, 0.23]**
AVA	**24.68 [3.41, 417.70]**	AVA	2.34 [0.28, 35.01]
ELT	**10.58 [4.26, 32.10]**	0.43 [0.03, 3.60]	ELT

RR – relative risk; IRR – incidence rate ratio; statistically significant valuers were presented in bold;

7.1.2. Platelet response at 6 months (binary data)

7.1.2.1. Overall information and input data

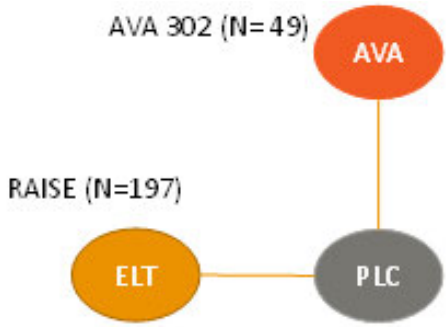
There were 2 studies (3 treatments; 246 patients) included in the NMA. Input data for the NMA are presented in Table 6 and the network of evidence for this outcome is depicted in Figure 5.

Table 8. Input data for the NMA of the proportion of patients with durable response

Study	Treatment	Event rate n/N (%)	RR [95%CI]**
Study 302	AVA	13/32 (40.63%)	20.91 * [0.76, 577.00]
	PLC	0/17 (0.00%)	
RAISE	ELT	52/135 (38.52%)	1.40 [0.89, 2.22]
	PLC	17/62 (27.42%)	

RR – relative risk; IRR – incidence rate ratio
* Continuity correction for zero cells was applied. For details see Table 22
** RRs calculated using frequentist methods with the correction for zero cells

Figure 7. Network of evidence for the proportion of patients with durable response



7.1.2.2. NMA results

Results of the NMA regarding the proportion of patients with durable response are depicted in Figure 6 and summarised in Table 9. Relative risk for platelet response at 6 months – fixed effect model. Additional results (random effect model) from the NMA are provided in Table 17 Relative risk and rankings for proportion of patients with platelet response - random effect model (Appendix 1).

Although the estimates from this analysis were highly imprecise due to low number of events, this NMA showed that all treatments were associated with significantly higher probability of platelet response at 6 months compared with PLC. Moreover, AVA was associated with significantly higher probability of reaching platelet response compared with ELT (RR = 7.81 [1.08, 563.20]).

The mean and median posterior distribution for the proportion of patients reaching platelet response estimated across both PLC groups from the included trials were 13.6% and 4.1%, respectively.

Figure 8. Forest plot for relative risk for comparison AVA vs comparators regarding platelet response at 6 months – fixed effect model

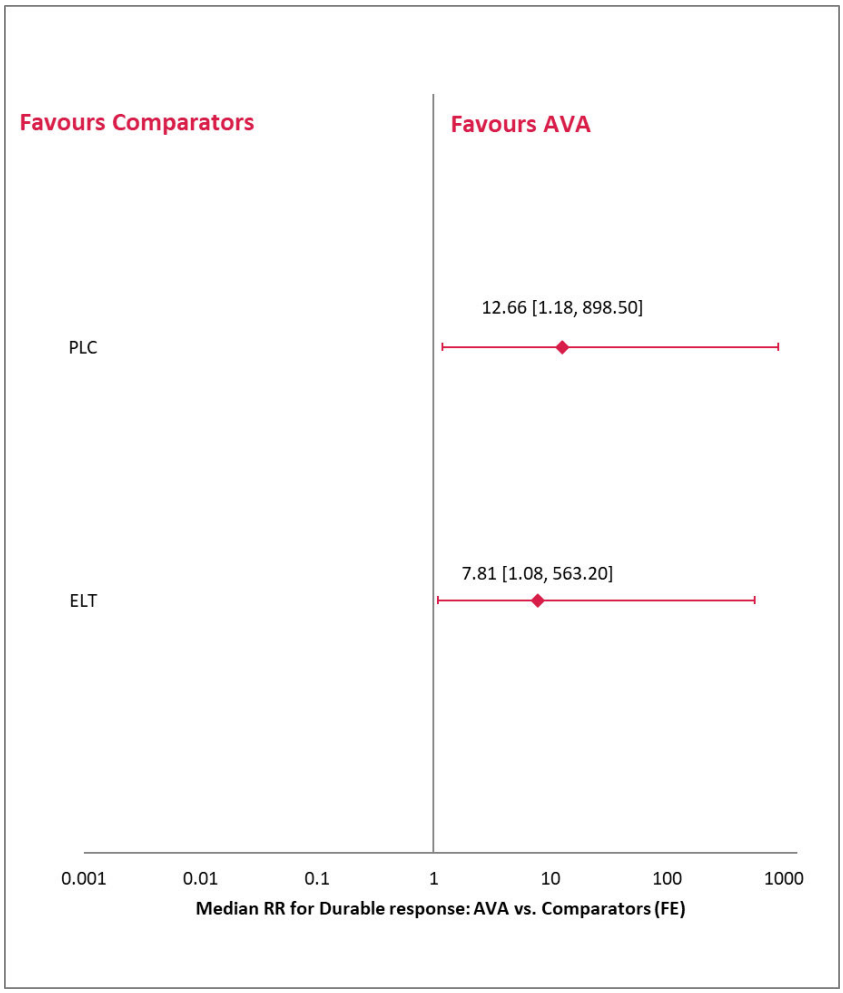


Table 9. Relative risk for platelet response at 6 months – fixed effect model

Relative risks for all comparisons (FE model)			
	vs. PLC	vs. AVA	vs. ELT
PLC	PLC	**0.08 [0.001, 0.85]**	0.66 [0.33, 1.12]
AVA	**12.66 [1.18, 898.50]**	AVA	**7.81 [1.08, 563.20]**
ELT	1.52 [0.89, 3.01]	**0.13 [0.002, 0.92]**	ELT

Statistically significant valuers were presented in bold;

7.1.3. Any bleeding events (estimated incidence)

7.1.3.1. Overall information and input data

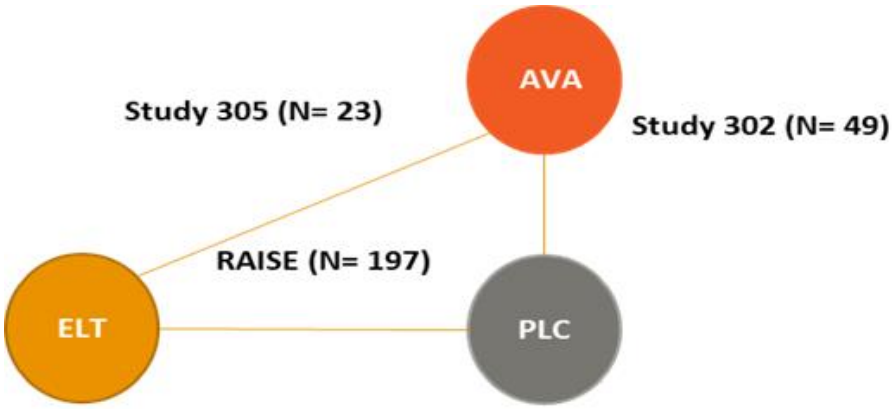
There were 3 studies (3 treatments; 270 patients) included in the NMA reporting grade 1-4 WHO bleeds. Input data for the NMA are presented in Table 10 and the network of evidence for this outcome is depicted in Figure 9.

Table 10. Input data for the NMA of proportion of patients with any bleed (grade 1-4 WHO)

Study	Treatment	Event rate n/N (%)	RR * [95%CI]	Mean exposure [years]	Total pts-years	Incidence rate [/pts-yrs.]	IRR [95%CI]
Study 302	AVA	14/32 (43.8%)	0.83 [0.46, 1.5]	0.44	14.02	0.9986	0.32 [0.14, 0.75]
	PLC	9/17 (52.9%)		0.17	2.92	3.0789	
Study 305	AVA	6/13 (46.2%)	0.56 [0.29, 1.08]	0.30	3.62	1.6596	0.41 [0.15, 1.16]
	ELT	9/11 (81.8%)		0.20	2.23	4.0345	
RAISE	ELT	106/135 (78.5%)	0.87 [0.77, 0.98]	0.43	58.62	1.8084	0.90 [0.65, 1.24]
	PLC	56/62 (90.3%)		0.45	27.86	2.0103	

RR – relative risk; IRR – incidence rate ratio
* RRs were calculated using frequentist methods

Figure 9. Network of evidence for proportion of patients with any bleed

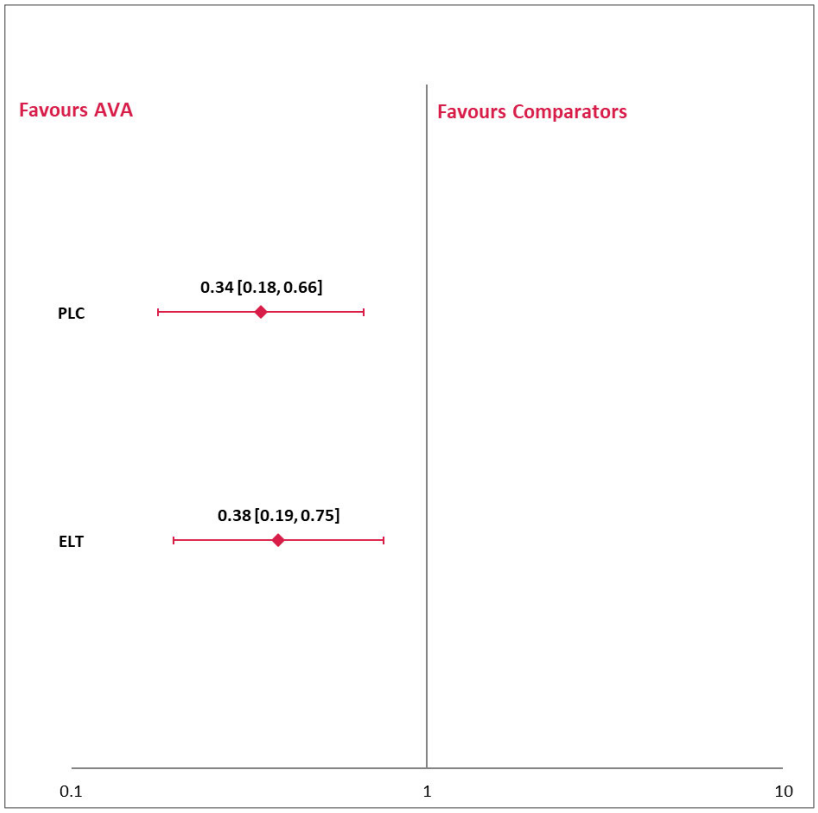


7.1.3.2. NMA results

Results of the NMA regarding proportion of patients with any bleed are depicted in Figure 10 and summarised in Table 11. Additional results (random effect model) from the NMA are provided in Table 18.

AVA was associated with significantly lower estimated incidence of any bleeding compared with PLC. Additionally, AVA was associated with significantly lower incidence rate of any bleeding compared with ELT (IRR = 0.38 [0.19, 0.75]).

Figure 10. Forest plot for the incidence rate ratio for comparison AVA vs comparators regarding any bleed – fixed effect model



Median IRR for proportion of patients with any bleed: AVA vs. comparators (FE)

Table 11. Incidence rate ratios for any bleed – fixed effect model

IRR for all comparisons (FE model)			
	vs. PLC	vs. AVA	vs. ELT
PLC	PLC	2.94 [1.52, 5.71]	**1.12 [0.82, 1.53]**
AVA	**0.34 [0.18, 0.66]**	AVA	**0.38 [0.19, 0.75]**
ELT	0.89 [0.65, 1.22]	**2.63 [1.33, 5.17]**	ELT

Significant results were reported in bold

7.1.4. Bleeding events WHO grade 2-4 (estimated incidence)

7.1.4.1. Overall information and input data

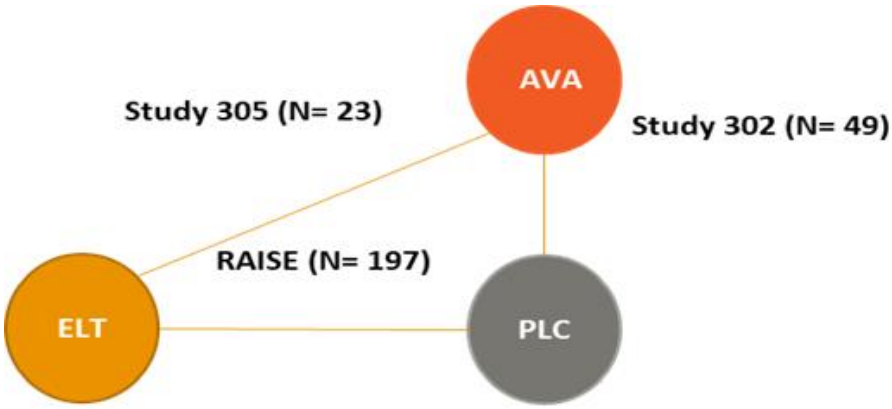
There were 3 studies (3 treatments; 270 patients) included in the NMA. Input data for the NMA are presented in Table 12 and the network of evidence for this outcome is depicted in Figure 11.

Table 12. Input data for the NMA of proportion of patients with bleed WHO grade 2-4

Study	Treatment	Event rate n/N (%)	RR [95%CI]*	Mean exposure	Total pts-years	Incidence rate [/pts-yrs.]	IRR [95%CI]
Study 302	AVA	3/32 (9.4%)	5.59 [0.18, 173.05]	0.44	14.02	0.2730	4.63 [0.04, 575.58]*
	PLC	0/17 (0.0%)		0.17	2.92	0.0590	
Study 305	AVA	4/13 (30.8%)	0.85 [0.27, 2.62]	0.30	3.62	1.1064	0.62 [0.15, 2.47]
	ELT	4/11 (36.4%)		0.20	2.23	1.7931	
RAISE	ELT	44/135 (32.6%)	0.63 [0.45, 0.89]	0.43	58.62	0.7506	0.65 [0.41, 1.03]
	PLC	32/62 (51.6%)		0.45	27.86	1.1488	

RR – relative risk; IRR – incidence rate ratio
* Continuity correction for zero cells was applied. For details see Table 22
** RR calculated using frequentist methods with the correction for zero cells

Figure 11. Network of evidence for proportion of patients with bleed WHO grade 2-4

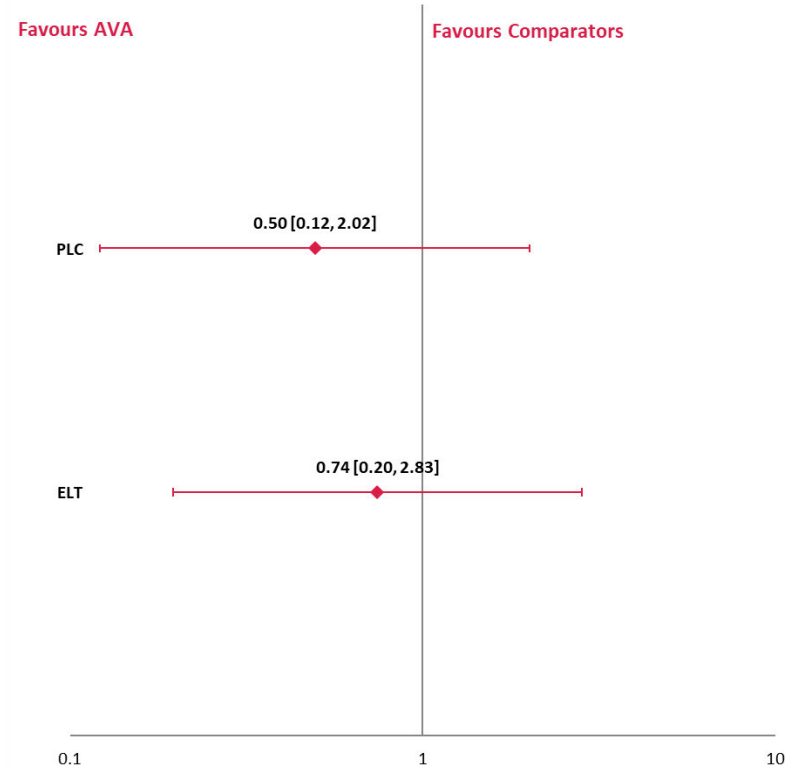


7.1.4.2. NMA results

Results of the NMA regarding proportion of patients with bleed WHO grade 2-4 are depicted in Figure 12 and summarised in Table 13. Additional results (random effect model) from the NMA are provided in Table 19.

No significant differences regarding the proportion of patients with bleed WHO grade 2-4 were observed between AVA and comparators.

Figure 12. Forest plot for proportion of patients with bleed WHO grade 2-4, avatrombopag vs comparators – fixed effect model



Median IRR for proportion of patients with bleed WHO grade 2-4: AVA vs. comparators (FE)

Table 13. Incidence rate ratios for bleeding events WHO grade 2-4 – fixed effect model

IRR for all comparisons (FE model)			
	vs. PLC	vs. AVA	vs. ELT
PLC	PLC	2.01 [0.50, 8.20]	1.50 [0.95, 2.36]
AVA	0.50 [0.12, 2.02]	AVA	0.74 [0.20, 2.83]
ELT	0.67 [0.42, 1.05]	1.34 [0.35, 5.10]	ELT

Significant results were reported in bold

7.1.5. Adverse events

7.1.5.1. Overall information and input data

There were 3 studies (3 treatments; 268 patients) included in the NMA.

Input data for the NMA are presented in Table 14 and the network of evidence for this outcome is depicted in Figure 13.

Table 14. Input data for the NMA of the estimated incidence of any adverse event

Study	Treatment	Event rate n/N (%)	RR [95%CI]	Mean exposure [years]	Total pts-years	Incidence rate [/pts-yrs.]	IRR [95%CI]
Study 302	AVA	31/32 (96.9%)	1.65 [1.1, 2.46]	0.44	14.02	2.2112	0.65 [0.32, 1.32]
	PLC	10/17 (58.8%)		0.17	2.92	3.4211	
Study 305	AVA	11/12 (91.7%)	0.92 [0.77, 1.09]	0.30	3.62	3.0426	0.62 [0.27, 1.42]
	ELT	11/11 (100.0%)		0.20	2.23	4.9310	
RAISE	ELT	118/135 (87.4%)	0.95 [0.86, 1.05]	0.46	61.57	1.9165	0.98 [0.72, 1.35]
	PLC	56/61 (91.8%)		0.47	28.74	1.9482	

The number of patients experiencing any adverse events during the study were reported in all trials.

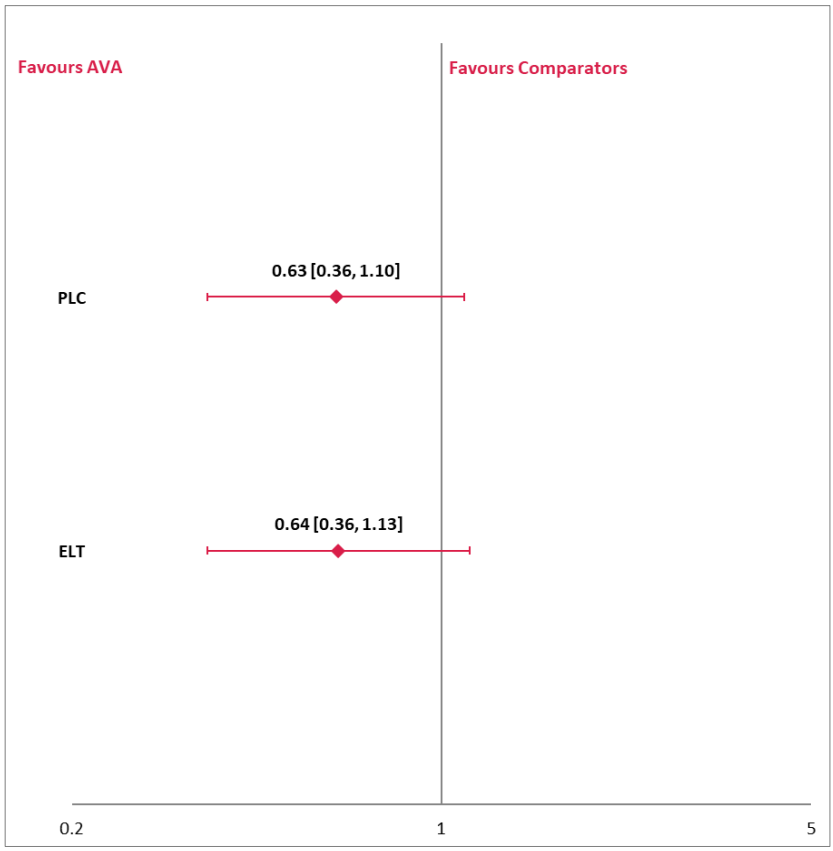
Figure 13. Network of evidence for the incidence of any adverse event

7.1.5.2. NMA results

Results of the NMA regarding estimated incidence of any adverse event are depicted in Figure 14 and summarised in Table 15. Additional results (random effect model) from the NMA are provided in Appendix 1.

No significant differences regarding the estimated incidence of any adverse event were observed between AVA and comparators.

Figure 14. Forest plot for the incidence rate ratio for comparison AVA vs comparators regarding any adverse event – fixed effect model



Median IRR for proportion of patients with adverse events: AVA vs. comparators (FE)

Table 15. Incidence rate ratios and rankings for any adverse event – fixed effect model

	IRR for all comparisons (FE model)		
	vs. PLC	vs. AVA	vs. ELT
PLC	**PLC**	1.58 [0.91, 2.77]	1.01 [0.75, 1.37]
AVA	0.63 [0.36, 1.10]	**AVA**	0.64 [0.36, 1.13]
ELT	0.99 [0.73, 1.34]	1.57 [0.88, 2.77]	**ELT**

Significant results were reported in bold

8. References

1. Jurczak W, Chojnowski K, Mayer J, et al. Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia. *British Journal of Haematology* 2018;183(3):479-90. doi: 10.1111/bjh.15573

2. Cheng G, Saleh MN, Marcher C, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *The Lancet* 2011;377(9763):393-402. doi: 10.1016/S0140-6736(10)60959-2

3. Dias S, Sutton AJ, Ades AE, et al. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Medical decision making : an international journal of the Society for Medical Decision Making* 2013;33(5):607-17. doi: 10.1177/0272989x12458724 [published Online First: 2012/10/30]

4. Dias S, Welton N, Sutton A, et al. NICE DSU Technical Support Document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials 2016

5.

9. Appendix 1: Results of random-effect models

9.1. Proportion of patients with durable response

Table 16. Relative risk and rankings for proportion of patients with durable response – random effect model

Relative risks for all comparisons (RE model)			
	vs. PLC	vs. AVA	vs. ELT
PLC	PLC	**0.04 [0.00, 0.54]**	**0.09 [0.02, 0.80]**
AVA	**24.52 [1.85, 416.40]**	AVA	2.28 [0.12, 64.16]
ELT	**10.57 [1.24, 58.26]**	0.44 [0.02, 8.15]	ELT

Significant results were reported in bold

9.2. Proportion of patients with platelet response

Table 17 Relative risk and rankings for proportion of patients with platelet response - random effect model

Relative risks for all comparisons (RE model)			
	vs. PLC	vs. AVA	vs. ELT
PLC	PLC	**0.09 [0.001, 0.94]**	0.68 [0.08, 6.96]
AVA	**11.01 [1.06, 788.80]**	AVA	7.01 [0.68, 857.30]
ELT	1.47 [0.14, 11.82]	0.14 [0.001, 1.47]	ELT

Significant results were reported in bold

9.3. Incidence of any bleeding events

Table 18. Incidence rate ratios and rankings for any bleed – random effect model

IRR for all comparisons (RE model)			
	vs. PLC	**vs. AVA**	**vs. ELT**
PLC	PLC	2.93 [0.08, 110.31]	1.14 [0.03, 42.92]
AVA	0.34 [0.01, 12.70]	AVA	0.39 [0.01, 15.45]
ELT	0.88 [0.02, 33.69]	2.57 [0.06, 102.00]	ELT

Significant results were reported in bold

9.4. Incidence of bleeding events WHO grade 2-4

Table 19. Incidence rate ratios and rankings for bleeding events WHO grade 2-4 – random effect model

IRR for all comparisons (RE model)			
	vs. PLC	vs. AVA	vs. ELT
PLC	PLC	1.47 [0.48, 4.50]	**1.55 [1.11, 2.18]**
AVA	0.68 [0.22, 2.10]	AVA	1.06 [0.36, 3.12]
ELT	**0.64 [0.46, 0.90]**	0.94 [0.32, 2.77]	ELT

Significant results were reported in bold

9.5. Incidence of adverse event

Table 20 Incidence rate ratios for adverse events - random effect model

IRR for all comparisons (RE model)			
	vs. PLC	vs. AVA	vs. ELT
PLC	PLC	1.58 [0.04, 62.45]	1.00 [0.03, 40.13]
AVA	0.63 [0.02, 24.32]	AVA	0.63 [0.02, 25.89]
ELT	1.00 [0.02, 38.56]	1.58 [0.04, 62.51]	ELT

10. Appendix 2: Statistical model

Below, the NMA models are presented that were evaluated for the evidence set. For educational purposes, a fixed effects model for a meta-analysis of treatment B versus A comparison is presented, and then built upon for multiple treatment comparisons[11]. The model is based upon the NICE Decision Support Unit (DSU) work. All WinBUGS codes for continuous and binary outcomes are based on the NICE DSU TSD2 document (Dias S. 2011). The models are described in more detail below for both the fixed and random effects.

In equation 1 the fixed effects meta-analysis model for RCTs is presented.

$$\theta_{jk} = \begin{cases} \mu_j & k = A \\ \mu_j + d & k = B \end{cases}$$

(1)

θ_{jk} reflects the 'underlying' outcome for treatment *k* in study *j* and the link function to transform this outcome to a normally distributed scale: $\theta_{jk} = g(\gamma_{jk})$ with $g(.)$ the link function and γ_{jk} the unknown parameters of the likelihood function. μ_j represents this (transformed) outcome in study *j* with comparator treatment A. *d* is the underlying *treatment effect* of B versus A on a normal scale that is the same for each study *j*. With the random effects meta-analysis model δ_j is the study-specific relative treatment effect of B relative to A. These study-specific relative effects are drawn from a random effect's distribution $\delta_j \sim N(d\ ,\sigma^2)$

$$\theta_{jk} = \begin{cases} \mu_j & k = A \\ \mu_j + \delta_j & k = B \end{cases}$$

$$\delta_j \sim normal(d\ ,\sigma^2)$$(2)

When the available evidence consists of a network of multiple pairwise comparisons (i.e. AB-trials, AC-studies, BC studies, etc.) the standard fixed effects model for an NMA can be specified as follows:

$$\theta_{jk} = \begin{cases} \mu_{jb} & b = \text{A,B,C,} \quad \text{if } k = b \\ \mu_{jb} + d_{bk} = \mu_{jb} + d_{Ak} - d_{Ab} & \text{if } k \text{ alphabetically after } b \end{cases}$$

$$d_{AA} = 0$$(3)

There are *k* treatments labelled as A, B, C, etc., and treatment A is taken to be the reference treatment for the analysis. μ_{jb} is the (transformed) outcome in study *j* on the 'baseline' treatment *b*, which varies across studies. d_{bk} is the fixed effect of treatment *k* relative to the 'baseline treatment' *b*. d_{bk} are identified by expressing them in terms of the reference treatment A: $d_{bk} = d_{Ak} - d_{Ab}$ with $d_{AA} = 0$.

NMAs can be performed within a frequentist or Bayesian framework.

Within the frequentist framework, estimation of model parameters and inference are based on some form of maximum likelihood. The output of the analysis is a point estimate, along with a p-value or a 95% confidence interval as a

measure of uncertainty. The 95% confidence intervals cannot be interpreted in terms of probabilities. The 95% confidence interval does not mean there is a 95% probability that the true value is between the boundaries of the interval[6].

Within the Bayesian framework, parameters are considered random variables. The 'belief' regarding the possible values of a model parameter before looking at the data can be summarised with a probability distribution: the prior distribution. This probability distributions were updated after having observed the data, resulting in the posterior distribution summarising the updated probabilities of the values for this parameter. Hence, within the Bayesian framework, the analysis not only involves data, a likelihood distribution, and a model with parameters reflecting the treatment effects and impact of covariates, but also prior probability distributions for these parameters. In other words: Bayesian methods involve a formal combination of a prior probability distribution, with a (likelihood) distribution to obtain a posterior probability distribution of model parameters [12].

The output of the Bayesian NMA is a complex posterior distribution of all relative treatment effects between interventions included in the network. The posterior distribution for each relative treatment effect can be summarised with a mean or median to reflect the most likely value for the effect size, as well as the 2.5th and 97.5th percentile: the 95% credible interval. Unlike the 95% confidence interval of the frequentist framework, the 95% credible interval can be interpreted in terms of probabilities: there is a 95% chance that the true parameter value falls between the boundaries of the credible interval.

A major advantage of the Bayesian approach is that the method naturally leads into a decision framework to support decision-making [10,12,13]. With the Bayesian approach for an NMA, the multiple inferences based on confidence intervals or p-values can be replaced with probability statements: For example "there is x% probability that treatment C is better than B", or "there is a y% probability that treatment D is the most efficacious out of treatment A, B, C, D, and E regarding this outcome". The probability that each treatment ranks 1st, 2nd, 3rd, etc. out of all interventions compared can be summarised. Therefore, this analysis was conducted in a Bayesian framework according to methodological guidelines and tutorials developed by NICE and described in the NICE DSU TSD2 document. [3]

10.1. WinBUGS models used for NMA

10.1.1. Models used for the NMA of binary data

10.1.1.1. Fixed-effect model

The code used to calculate baseline risk (absolute event risk in the placebo group) is presented in blue.

```
model{
  for (i in 1:ns){
    r1[i,1] ~ dbin(p1[i,1],n[i,1])
    logit(p1[i,1]) <- mu1[i]
    mu1[i] ~ dnorm(m,tau.m)
  }
  m ~ dnorm(0,.0001)
  var.m <- 1/tau.m
  tau.m <- pow(sd.m,-2)
```

```
  logit(R) <- m

  for(i in 1:ns){
    mu[i] ~ dnorm(0,.0001)

    for (k in 1:na[i]) {
      r[i,k] ~ dbin(p[i,k],n[i,k])
      logit(p[i,k]) <- mu[i] + d[t[i,k]]-d[t[i,1]]
      rhat[i,k] <- p[i,k] * n[i,k]
      dev[i,k] <- 2*(r[i,k]*(log(r[i,k])-log(rhat[i,k]))
                    + (n[i,k]-r[i,k])*(log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
     resdev[i] <- sum(dev[i,1:na[i]])
  }
  totresdev <- sum(resdev[])
  d[1]<- 0
  for (k in 2:nt){ d[k] ~ dnorm(0,.0001)}
  for (k in 1:nt){ logit(T[k]) <- m + d[k]}
  for (c in 1:nt){
    for (k in 1 :nt) {
      rr[c,k] <- T[c] /T[k]
    }
  }
}
```

10.1.1.2. Random-effect model

The code used to calculate baseline risk (absolute event risk in the placebo group) is presented in blue.

```
model{
  for (i in 1:ns){
    r1[i,1] ~ dbin(p1[i,1],n[i,1])
    logit(p1[i,1]) <- mu1[i]
    mu1[i] ~ dnorm(m,tau.m)
  }
  m ~ dnorm(0,.0001)
  var.m <- 1/tau.m
  tau.m <- pow(sd.m,-2)
  logit(R) <- m

for(i in 1:ns){
  w[i,1] <- 0
  delta[i,1] <- 0
  mu[i] ~ dnorm(0,.01)
  for (k in 1:na[i]) {
    r[i,k] ~ dbin(p[i,k],n[i,k])
    logit(p[i,k]) <- mu[i] + delta[i,k]
     rhat[i,k] <- p[i,k] * n[i,k]
     dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
  }
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {
     delta[i,k] ~ dnorm(md[i,k],taud[i,k])
     md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
     taud[i,k] <- tau *2*(k-1)/k
     w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
     sw[i,k] <- sum(w[i,1:k-1])/(k-1)
   }
}
```

```
  totresdev <- sum(resdev[])
  d[1]<- 0
  for (k in 2:nt){ d[k] ~ dnorm(0,.0001)}
  for (k in 1:nt){ logit(T[k]) <- m + d[k]}
  sd ~ dunif(0, 5)
  tau <- pow(sd,  -2)


  for (c in 1:nt){
    for (k in 1 :nt) {
      rr[c,k] <- T[c] /T[k]
    }
  }
}
```

10.1.2. Models used for the NMA of incidence rates

10.1.2.1. Fixed-effect model

```
model{
  for( i in 1 : ns2 ) {
    y[i , 2] ~ dnorm(delta[i , 2], prec[i , 2])
    var[i , 2] <- pow(se[i , 2], 2)
    prec[i , 2] <- 1 / var[i , 2]
    dev[i] <- (y[i , 2] - delta[i , 2]) * (y[i , 2] - delta[i , 2]) * prec[i , 2]
    delta[i , 2] <- d[t[i , 2]] - d[t[i , 1]]
  }

  totresdev <- sum(dev[])
  d[1] <- 0

  for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

  for( c in 1 : nt) {
    for( k in 1 : nt) {
      hr[c , k] <- exp(d[c] - d[k])
      lhr[c , k] <- d[c] - d[k]
    }
  }
}
```

10.1.2.2. Random-effect model

```
model{
  for( i in 1 : ns2 ) {
    y[i , 2] ~ dnorm(delta[i , 2], prec[i , 2])
    var[i , 2] <- pow(se[i , 2], 2)
    prec[i , 2] <- 1 / var[i , 2]
    resdev[i] <- (y[i , 2] - delta[i , 2]) * (y[i , 2] - delta[i , 2]) * prec[i , 2]
    delta[i,2] ~ dnorm(md[i,2],tau)
    md[i , 2] <- d[t[i , 2]] - d[t[i , 1]]
  }

  totresdev <- sum(resdev[])
  d[1] <- 0
  for( k in 2 : nt ) {
    d[k] ~ dnorm(0, 1.0E-4)
  }
```

```
  sd ~ dunif(0, 5)
  tau <- pow(sd,  -2)

  for( c in 1: nt ) {
    for( k in 1: nt ) {
      hr[c , k] <- exp(d[c] - d[k])
      lhr[c , k] <- d[c] - d[k]
    }
  }
}
```

11. Appendix 3: Analysis of consistency

There was no evidence for the inconsistency between direct and indirect evidence within the analysed networks of evidence.

Table 21. Analysis of consistency for evidence networks with closed loop.

Indirect evidence			Direct exidecne		Heterogeneity test for direct vs. indirect evidence
Study	IRR [95%CI]	Bucher's ITC AVA vs ELT	Study	IRR [95%CI]	
Any bleeding episodes					
AVA-302 RAISE	0.32 [0.14, 0.75] 0.9 [0.65, 1.24]	0.36 [0.14, 0.87]	AVA-305	0.41 [0.15, 1.16]	I^2 = 0 p = 0.8375
Bleeding episodes grade 2+					
AVA-302 RAISE	4.63 [0.04, 575.58] 0.65 [0.41, 1.03]	7.12 [0.06, 873.56]	AVA-306	0.62 [0.15, 2.47]	I^2 = 0 p = 0.3394

12. Appendix 4: Continuity corrections

Table 22. Details regarding continuity correction for binary outcomes

Study	Intervention	Total	Number of events without continuity correction	% without continuity correction	Number of events with continuity correction	% with continuity correction
Durable platelet response						
AVA-302	AVA	32	11	11/32=**34.38%**	11 + 32/(32+17) = **11.65**	11.65/32=**36.4%**
	PLC	17	0	0/17=**0%**	0 + 17/(32+17) = **0.35**	0.35/17=**2.0%**
Platelet response at 6 months						
AVA-302	AVA	32	13	13/32=**40.6%**	13 + 32/(32+17) = **13.65**	13.65/32=**42.7%**
	PLC	17	0	0/17=**0%**	0 + 17/(32+17) = **0.35**	0.35/17=**2.0%**

Table 23. Details regarding continuity correction for estimated incidence

Study	Intervention	Total	Number of events without continuity correction	Total patient-years	Incidence rate without continuity correction [/pts-yrs.]	Incidence rate with continuity correction [/pts-yrs.]	Incidence rate ratio [95%CI]
Bleeding events WHO grade 2-4							
AVA-302	AVA	32	3	14.02	0.214	(3+ 14.02/(2.92+14.02))/14.02 =**0.273**	4.63 [0.04, 575.58]
	PLC	17	0	2.92	0	(0 + 2.92/(2.92+14.02))/2.92 =**0.059**	

Health Economic Evidence for Doptelet® (avatrombopag) for the treatment of chronic immune thrombocytopenia in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)

Questions around this document may be posed to:

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Table of contents

Glossary of terms

Abbreviation	Description of abbreviation
AE	Adverse event
AIP	Pharmacy purchasing price
AUP	Pharmacy selling price
AVA	Avatrombopaag
DB	Twice daily
DKK	Danish kDSBHrona
EC	European comission
ELT	Eltrombopag
EMA	European Medicines Agency

EQ	EuroQol
ITP	Immune thrombocytopenia
MMF	Mycophenolate mofetil
NMA	Network meta-analysis
PPP	Pharmacy purchasing price
PSP	Pharmacy selling price
TPO-RA	Thrombopoietin receptor agonist

Executive Summary

Population

Immune thrombocytopenia (ITP) is an autoimmune disorder involving the destruction of platelets and impaired platelet production, resulting in a reduction in platelet count (defined as a platelet count of below 100×10^9/L) (Provan and Newland 2015). ITP can be defined as either primary or secondary disease. Primary ITP refers to isolated thrombocytopenia in the absence of other causes, while secondary could be the result of an underlying disease or drug exposure (Rodeghiero, Stasi et al. 2009).

Patients with severe ITP (defined as a platelet count of below 100×10^9/L) have an increased risk of severe bleeding from trauma, as well as of spontaneous bleeding (especially for those with a platelet count of below 50×10^9/L), an increased risk of thrombosis, and are more likely to exhibit symptoms of fatigue (Kayal, Jayachandran et al. 2014, Matzdorff, Meyer et al. 2018). Furthermore, the symptomatology and treatment of ITP has an impact on patients' lifestyle and psychological wellbeing.

ITP is a rare condition, with the majority of diagnosed cases progressing to chronic disease (Neunert, Terrell et al. 2019). The prevalence in Denmark is approximately 10 per 100,000 people and an incidence rate of 2.8 per 100,000 people (Christiansen, Bahmanyar et al. 2019). According to recent guidelines (DSBH 2018, Matzdorff, Meyer et al. 2018) , patients with ITP are initially treated with corticosteroids and/or immunoglobulins. For patients with chronic (defined as having symptoms of a period longer than 12 months) or refractory (i.e., after splenectomy) ITP, TPO-RAs are the preferred choice.

Currently, there are two TPO-RA products available, eltrombopag (an oral tablet) and romiplostim (administered subcutaneously) that are used interchangeably, as they have been deemed of equal clinical efficacy and safety (Neunert, Terrell et al. 2019). Patients with ITP treated with TPO-RAs may need to discontinue therapy due to unfavourable adverse events, non-response or loss of response. For these patients, treatment cycling to an alternative TPO-RA can be an effective treatment management approach (Neunert, Terrell et al. 2019, Provan, Arnold et al. 2019). Avatrombopag will be available as an additional TPO-RA option for the treatment of patients with chronic ITP.

Intervention

Avatrombopag is a novel, oral, small-molecule TPO-RA, which stimulates natural platelet production leading to a predictable increase in platelet count. An approval from the European Commission (EC) was received in January 2021 for the treatment of primary chronic ITP in adult patients who are refractory to other treatments (e.g., corticosteroids, immunoglobulins).

Avatrombopag will be available in a strength of 20 mg per tablet. Treatment with avatrombopag should be initiated at 20 mg once daily with food. The dose should be adjusted in order to achieve and maintain platelet count $\geq50\times10^9$/L. A daily dose of 40 mg should not be exceeded.

Comparator

Eltrombopag is considered the relevant comparator of avatrombopag. Both treatments are oral tablets and eltrombopag is the TPO-RA predominantly used in Denmark (75%, compared with 25% for romiplostim, (SOBI data on file 2020)). The recommended starting dose of eltrombopag is 25 mg once

daily, while a daily dose of 75 mg should not be exceeded. Treatment with eltrombopag is related to food restrictions, as patients have to abstain from consuming food a few hours before and after treatment. Eltrombopag is also associated with a risk of hepatotoxicity and regular monitoring with liver tests is required.

Avatrombopag could be considered a more convenient TPO-RA option, as it does not have strict dietary restrictions (i.e., patients do not need to fast before or after administration of avatrombopag), and it is not associated with hepatotoxicity.

Outcomes

Due to a lack of head-to-head data an indirect treatment comparison (ITC) in the form of a network meta-analysis (NMA), is presented. The results of the NMA showed that there was no significant difference in clinical efficacy and safety between avatrombopag and eltrombopag.

There was between-trial heterogeneity in the proportion of patients prematurely discontinuing the allocated treatment. Due to this premature, imbalanced discontinuation the total exposure time in the included studies was significantly affected and therefore could impact the relative efficacy and safety results. To avoid this bias, an NMA based on estimated incidence rate ratio (IRR) accounts for the differences in the effective treatment duration across groups. For this reason, the results of the following outcomes are presented:

Quality of life (QoL)

Bleeding events (any and WHO grade 2-4)

Platelet response rate and duration of response

Health economic evaluation

As avatrombopag and eltrombopag have been shown to have similar efficacy a cost-comparison analysis was conducted. The analysis concluded that there is a minimal added incremental cost of [redacted] for treating a patient with avatrombopag. The total budget impact of introducing avatrombopag to the Danish market is expected to be [redacted] in year 2026 treating a total of [redacted]

The addition of avatrombopag to the currently available TPO-RAs would provide patients with an option that shares the same clinical efficacy and safety with eltrombopag. In addition, avatrombopag could be considered a more convenient option for patients, as it is not related to strict dietary restrictions or hepatotoxicity.

Finally, avatrombopag would be an additional option for those patients that switch between TPO-RA treatments due to lack of response or side effects.

1. Health economic analysis

1.1 Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder involving the destruction of platelets and impaired platelet production, resulting in a reduction in platelet count (Provan and Newland 2015).

ITP is defined by a platelet count below 100×10^9/L and many ITP patients present with increased susceptibility to bleeding, and skin haemorrhage or purpura (purple-spotted rash caused by bleeding from small blood vessels) (Kayal, Jayachandran et al. 2014). ITP is thought to be caused by an autoimmune response against platelets (Swinkels, Rijkers et al. 2018), potentially triggered by prior infection (Rose 2017) or genetic risk factors (Li, Ma et al. 2017).

Currently, clinical guidelines distinguish between three phases in the ITP clinical course (Michel 2013): newly diagnosed (<3 months), persistent (3–12 months) and chronic (>12 months). In addition, refractory ITP is considered a separate phase, as it develops after splenectomy (DSBH 2018).

ITP is a rare condition, with the majority of diagnosed cases progressing to chronic disease (Neunert, Terrell et al. 2019). In Denmark, the prevalence of ITP has been estimated to be around 10 per 100,000 people, with an incidence rate of 2.8 per 100,000 people (Christiansen, Bahmanyar et al. 2019). In addition, according to the Danish guidelines, the prevalence of ITP is between 9.5 to 23.6 per 100,000 and the incidence rate is between 1.6 to 4 per 100,000 (DSBH 2018).

According to current international guidelines (Matzdorff, Meyer et al. 2018, Neunert, Terrell et al. 2019, Provan, Arnold et al. 2019) an initial short term treatment of ITP with corticosteroids is recommended. Patients whose ITP doesn't resolve rapidly move onto TPO-RA treatment. Currently available TPO-RAs, eltrombopag and romiplostim, are considered of similar clinical efficacy and are used interchangeably (Neunert, Terrell et al. 2019). The treatment of ITP in Denmark follows similar national guidelines (DSBH 2018). Apart from glucocorticosteroids, first line treatment could include immunoglobins (IVIg), platelet transfusion or rituximab. TPO-RAs can be given to patients with persistent, chronic, or refractory ITP (after splenectomy), and to patients not eligible for splenectomy.

Eltrombopag is considered to be the relevant comparator to avatrombopag, since they are both oral tablets, and eltrombopag is the TPO-RA predominantly used in Denmark (SOBI data on file 2020).

1.2 Patient population

Avatrombopag has received European Commission (EC) approval in January 2021 for the treatment of patients with primary chronic ITP that are refractory to other treatments (e.g. corticosteroids, immunoglobulins etc) (Committee for Medicinal Products for Human Use (CHMP) 2020). As such, this is the target population of the present health economic analysis.

In Denmark, the prevalence of ITP has been estimated to be around 10 per 100,000 people, with an incidence rate of 2.8 per 100,000 people (Christiansen, Bahmanyar et al. 2019). In addition, according

to the Danish guidelines, the prevalence of ITP is between 9.5 to 23.6 per 100,000 and the incidence rate is between 1.6 to 4 per 100,000 (DSBH 2018).

Based on a Danish population of 4 842 272 adults (5 806 081persons, in 2019), an annual population growth of 2.5%, and an ITP prevalence of 10 per 100 000 inhabitants, the total number of persons with chronic ITP is expected to be 521 in 2022, 234 in 2023, 547 in 2024, 561 in 2025, and 575 in 2026 (SOBI data on file 2020). TPO-RAs are assumed to be used in [redacted] of the total chronic ITP population, with a yearly increase of [redacted] Avatrombopag is expected to be used in [redacted] of patients with chronic ITP in 2022. (SOBI data on file 2020)(Ref)

1.3 Intervention

Avatrombopag is a novel, oral, small-molecule TPO-RA, which stimulates natural platelet production leading to a predictable increase in platelet count. Avatrombopag does not compete with TPO for binding to the TPO receptor and has an additive effect with TPO on platelet production (European Medicines Agency 2021). Activation of the TPO receptor results in an increase in mature megakaryocyte numbers (Kaushansky 2009, Długosz-Danecka, Zdziarska et al. 2019) and subsequently platelet production (Fisher and Di Paola 2018). Avatrombopag has the same mechanism of action as eltrombopag (Peck-Radosavljevic 2017).

An overview of avatrombopag is presented in Table 1 below.

Table 1: Product description of avatrombopag

Product description	
Name of preparation/pharmaceutical	Doptelet®
Active ingredient	Avatrombopag (TPO-RA)
Indication	Avatrombopag is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)[a]
Pharmaceutical form	Film-coated tablet
Strength	20 mg per tablet
Recommended daily dose	Use the lowest dose of avatrombopag needed to achieve and maintain a platelet count greater than or equal to 50 $\times 10^9$/L as necessary to reduce the risk for bleeding. Dose adjustments are based on platelet count response. Do not use avatrombopag to normalize platelet counts. Do not exceed a daily dose of 40 mg (2 tablets). Initial Dose Regimen: Begin avatrombopag at a starting dose of 20 mg (1 tablet) once daily with food.
Should the intervention be used with other drugs?	Avatrombopag can be used with other ITP medication
Treatment length/criteria for termination of treatment	Discontinue avatrombopag if the platelet count does not increase to ≥ $50x10^9$ /L after 4 weeks of dosing at the maximum dose of 40 mg once daily. Discontinue Doptelet if the platelet count is greater than $250x10^9$ /L after 2 weeks of dosing at 20 mg once weekly.
Required monitoring, under administration or during treatment period	After initiating therapy, assess platelet counts at least once weekly until a stable platelet count ≥ $50x10^9$ /L and ≤ $150x10^9$ /L has been achieved. Twice weekly platelet count monitoring should be conducted during the first weeks of therapy in patients receiving

	avatrombopag only once or twice weekly. Twice weekly monitoring should also be conducted after dose adjustments during the treatment. Due to the potential risk of platelet counts above 400 x 10^9 /L within the first weeks of treatment patients should be carefully monitored for any signs or symptoms of thrombocytosis. After a stable platelet count has been achieved, obtain platelet counts at least monthly. After discontinuation of avatrombopag, platelet counts should be obtained weekly for at least 4 weeks
Requirements of diagnostics or other tests	No testing required
Medically approved indication /-s	Doptelet is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure Doptelet is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)

Abbreviations: TPO-RA, thrombopoietin reactive agent
Reference: (European Medicines Agency 2021)

Avatrombopag will be available as an additional TPO-RA option for patients with chronic ITP. Availability of an additional TPO-RA option could further delay the need for splenectomy, with the associated patient and budgetary benefits. In addition, avatrombopag should be taken with food, contrary to eltrombopag, which could increase patient adherence.

In details, patients should abstain from consuming specific products, such as antacids, daily products, or mineral supplements containing polyvalent cations two hours before or four hours after taking eltrombopag (European Medicines Agency 2021). On the contrary, avatrombopag should be taken with food and no additional dietary restrictions are associated with its intake (European Medicines Agency 2021).

1.4 Comparator

In Denmark, both eltrombopag and romiplostim are used for the treatment of patients with chronic ITP that are refractory to other treatments. For the purpose of this submission, eltrombopag is considered the relevant comparator for avatrombopag. The reasons are multifold. First, both eltrombopag and avatrombopag share the same route of administration, as they are both oral tablets. Secondly, eltrombopag is the TPO-RA predominantly used in Denmark (SOBI 2020).

An overview of eltrombopag is presented in Table 2 below.

Table 2: Description of eltrombopag

Product description	
Name of preparation/pharmaceutical	Revolade
Active ingredient	Eltrombopag (TPO-RA)
Pharmaceutical form	Film-coated tablet
Strength	12.5 mg, 25 mg, 50 mg, 75 mg per tablet

Product description	
Recommended daily dose	Use the lowest dose of eltrombopag needed to achieve and maintain a platelet count greater than or equal to 50 $\times 10^9$/L as necessary to reduce the risk for bleeding. Eltrombopag must not be used to normalise platelet counts The recommended starting dose of eltrombopag is 25 mg once daily. A daily dose of 75 mg must not be exceeded.
Should the intervention be used with other drugs?	Eltrombopag can be used with other ITP medication
Treatment length/criteria for termination of treatment	Treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of eltrombopag therapy at 75mg once daily
Required monitoring, under administration or during treatment period	Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag. In addition, full blood counts (FBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count (≥50 $\times 10^9$/L for at least four weeks) has been achieved. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter.
Requirements of diagnostics or other tests	No
Medically approved indication /-s	Revolade is indicated for the treatment of patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy Revolade is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation

Reference: (European Medicines Agency 2021)

1.5 Indirect comparison

Since there was no head-to-head data of the relative efficacy of avatrombopag to the existing TPO-RAs, an NMA in a Bayesian framework was conducted to provide comparative data.

The outcomes used in the NMA were the following:

- Durable response
- Reduction in bleeding events (any)
- Reduction in bleeding event (WHO 2-4 level)

According to the results patients treated with avatrombopag is significantly less likely to experience bleeding (any), there were no significant differences in the remaining outcomes between avatrombopag

and eltrombopag. See the clinical report for avatrombopag for detailed results of the indirect comparison.

1.6 Health economic evaluation methods

In this health technology assessment (HTA), avatrombopag is compared with eltrombopag, which constitutes the most relevant comparator for the reasons outlined in section 1.4 above.

Since avatrombopag and eltrombopag are considered to be of similar clinical efficacy and safety, a simple cost-comparison approach is presented, and no model is presented in this HTA.

1.6.1 Cost- comparison analysis: assumptions and inputs

The population of interest in this analysis consists of adult patients with primary chronic ITP who are refractory to other treatments (e.g. corticosteroids, immunoglobulins), i.e. patients who are eligible for avatrombopag treatment (based on the approvedindication and the clinical trial data).

The annual drug acquisition costs are estimated based on the mean doses used in relevant clinical trials (i.e. 22.34 mg for avatrombopag, and 50.20 mg for eltrombopag) (Jurczak, Chojnowski et al. 2018) (NICE 2013, Wong RSM 2017), and as such these are the doses linked to the clinical efficacy of the drugs in question. In addition, this approach was used to compare the clinical efficacy of avatrombopag and eltrombopag in the conducted NMA. It should also be mentioned that the presented mean doses are very close to the recommended doses for avatrombopag and eltrombopag (20 mg and 50 mg, respectively), according to their Summary of Product Characteristics (SPC) (European Medicines Agency 2021, European Medicines Agency 2021).

The results in Table 4 are presented as annual costs and are not assumed to change over time, hence no specific time horizon is adopted in this cost comparison analysis.

1.6.1.1 Cost analysis

As both eltrombopag and avatrombopag are oral treatments administered at home they are not assumed to incur any administration costs. Moreover, any difference in the monitoring costs between these two products is considered negligible.

The price per package for avatrombopag and eltrombopag are presented in Table 3.

Table 3: Drug costs used in the analysis

Treatment	PPP per pack (DKK)	Strength	Pack size	Reference
Avatrombopag	12 278.97	20 mg	30 pack	(SOBI 2020)
Eltrombopag	12 236.65	50 mg	28 pack	(www.medicinpriser.dk; Revolade, Novartis)

Abbreviation : PPP, pharmacy purchasing price

The average daily dose reported in the main clinical trials of each treatment was used to calculate average daily and annual drug acquisition costs (assuming no wastage and multiplying the estimated

daily cost by 365.25 for the yearly cost). Table 4 presents a breakdown of the estimated annual drug costs of avatrombopag and eltrombopag in pharmacy purchasing price (PPP).

Table 4. Annual costs of avatrombopag and eltrombopag (drug costs only)

	Dose per day (mg)	Cost per mg (DKK)	Daily cost (DKK)	Annual cost (DKK)
Avatrombopag	22.34	20.46	457.19	166 988
Eltrombopag	50.20	8.74	438.77	160 261

Abbreviation : PPP, pharmacy purchasing price

According to the SPC for eltrombopag, patients are required to perform liver function tests once every month (Medicin.dk 2021). The cost for liver function test per year is presented in Table 5. Annual costs for liver function test

Table 5. Annual costs for liver function test

Treatment	Occurrence per month	Yearly cost (DKK)	Reference
Avatrombopag	0	0	
Eltrombopag	1	2 556	Rigshospitalets Labportal (2021). Test code for hepatic tests included (codes): NPU19651, NPU19654, NPU27783, NPU19673, NPU01370, NPU03278.

Abbreviation : PPP, pharmacy purchasing price

2. Results

2.1 Base case results

Table 6 presents the base-case results for the comparison of avatrombopag versus eltrombopag using the average doses reported in the main clinical trial of each treatment. The annual cost of treatment per patient is estimated to DKK 166 988 with avatrombopag and DKK 162 817 with eltrombopag, i.e. DKK 4 170 higher for avatrombopag compared with eltrombopag.

Table 6: Base case results

Cost component	Avatrombopag arm (DKK)	Eltrombopag arm (DKK)	Incremental results (DKK)
Drug costs (PPP)	166 988	160 261	6 726
Liver function test cost (yearly)	0	2 556	-2 556
Total	166 988	162 817	4 170

Abbreviation : PPP, pharmacy purchasing price

No scenarios are presented in this report.

3. Budget impact

A budget impact analysis was developed in order to assess the impact of avatrombopag compared to current SoC (eltrombopag) in the next five years.

The current budget impact analysis does not include any additional costs related to health and care services, as the budget impact of these is expected to be negligible.

3.1 Budget impact on the drug budget of the national insurance scheme

3.1.1 Number of patients

As mentioned in section 2.2, based on a Danish population of 4 842 272 adults (5 806 081 persons, in 2019), an annual population growth of 2.5%, and an ITP prevalence of 10 per 100 000 inhabitants, the total number of persons with chronic ITP is expected to be 522 in 2022, 535 in 2023, 548 in 2024, 562 in 2025, and 576 in 2026.

Assuming 37% of the total chronic ITP population are using TPO-RA in 2021 with a yearly increase of 7%, the total number of patients using any TPO-RA is expected to be 192 in 2022, 209 in 2023, 230 in 2024, 253 in 2025 and 271 in 2026.

It is estimated that if avatrombopag is introduced in January 2022 it would make up [redacted] of the total TPO-RA market during the first year, with an increase to [redacted] the next four years, which would correspond to [redacted] patients 2022-2026.

Table 7. Number of patients using each TPO-RA if avatrombopag is not introduced

	2022	2023	2024	2025	2026
Avatrombopag	0	0	0	0	0
Eltrombopag	192	209	230	253	271
Total	192	209	230	253	271

Abbreviations: TPO-RA: Thrombopoietin receptor agonist

Table 8. Number of patients using each TPO-RA if avatrombopag is introduced

	2022	2023	2024	2025	2026
Avatrombopag	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eltrombopag	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	192	209	230	253	271

Abbreviations: : TPO-RA: Thrombopoietin receptor agonist

3.1.2 Expenditure per patient

The maximum pharmacy retail price was calculated based on instructions provided by the Danish Medicines Council.

The annual cost per patient for eltrombopag and avatrombopag are described in Section 1.

3.1.3 Budget impact

Table 9 and Table 10 describes the annual expenditures in the scenarios of avatrombopag not being reimbursed or reimbursed.

Table 9. Annual drug expenditure if avatrombopag is not reimbursed

	2022 (DKK)	2023 (DKK)	2024 (DKK)	2025 (DKK)	2026 (DKK)
Avatrombopag	0	0	0	0	0
Eltrombopag	31 260 906	34 028 799	37 447 961	41 192 757	44 123 467
Total cost	31 260 906	34 028 799	37 447 961	41 192 757	44 123 467

Table 10. Annual expenditure if avatrombopag is reimbursed

	2022 (DKK)	2023 (DKK)	2024 (DKK)	2025 (DKK)	2026 (DKK)
Avatrombopag	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eltrombopag	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The budget impact of introducing avatrombopag is estimated to [redacted] in year 5.

Table 11 describes the annual budget impact for the next five years.

Table 11. Expected annual budget impact for avatrombopag

	2022 (DKK)	2023 (DKK)	2024 (DKK)	2025 (DKK)	2026 (DKK)
Avatrombopag	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No avatrombopag	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4. Discussion

Avatrombopag, a new TPO-RA, represents a new treatment option for patients with chronic ITP who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Avatrombopag has been shown to be of similar clinical efficacy and safety as eltrombopag, the other oral TPO-RA that is currently available in many countries, including Denmark.

As it has already been mentioned, treatment with eltrombopag has limitations that could negatively affect patient adherence. Eltrombopag is associated with food restrictions, as patients have to fast before and after administration. Avatrombopag is an oral tablet which should be taken with food, and as such could be perceived by patients as a more convenient choice.

In this assessment, a cost-comparison analysis was conducted, as avatrombopag and eltrombopag have been shown to have similar efficacy and safety. The analysis concluded that there is a minimal added incremental cost of [redacted] for treating a patient with avatrombopag. The total budget impact of introducing avatrombopag to the Danish market is expected to be [redacted] in year 2026.

The addition of avatrombopag to the currently available TPO-RA would provide patients with an option of similar clinical efficacy and safety with eltrombopag, while being considered as a potentially more convenient option. In addition, avatrombopag would be an additional option for those patients that switch between TPO-RA treatments due to lack of response or side effects.

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Medicinrådet

Medicinrådets protokol for vurdering af avatrombopag til behandling af kronisk immun trombocytopeni

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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Indholdsfortegnelse

1. Begreber og forkortelser

ASH	*American Society of Hematology*
CTCAE	*Common Terminology Criteria for Adverse Events*
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*
ISTH:	*International Society on Thrombosis and Haemostasis*
ITP:	*Immun trombocytopeni*
ITT:	*Intention-to-treat*
MKRF:	Mindste klinisk relevante forskel
NICE:	*The National Institute for Health and Care Excellence*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*
PP:	*Per Protocol*
RR:	Relativ risiko
SAE:	*Serious adverse event*
SMD:	*Standardized Mean Difference*
TPO-RA:	Thrombopoetin receptor-agonist

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2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Swedish Orphan Biovitrum A/S (SOBI), som ønsker, at Medicinrådet vurderer avatrombopag til patienter med primær kronisk immun trombocytopeni, som er refraktære over for andre behandlinger. Medicinrådet modtog den foreløbige ansøgning den 19. november 2020.

2.1 Kronisk immun trombocytopeni

Immun trombocytopeni (ITP) er en autoimmun sygdom, som forårsager øget nedbrydning af blodplader (trombocytter) og forstadier hertil (megakaryocytter), hvilket resulterer i et nedsat antal af cirkulerende blodplader. Blodpladerne er nødvendige, for at blodet kan størkne (koagulere), og patienter med ITP har pga. det lave antal blodplader en øget risiko for blødninger.

ITP er en eksklusionsdiagnose, som stilles på baggrund af blodprøver og diagnostiske tests, der har til formål at udelukke andre årsager til blodplademan gel. Som led i udredningen foretages også ofte ultralydsscanning af milten og evt. knoglemarvsundersøgelse. Diagnosen kan stilles, når blodpladetallet er < 100 x 10^9 pr. liter, selvom den nedre grænse i normalområdet er højere end dette (150 x 10^9 pr. liter). Dette skyldes dels, at der først er behandlingsindikation ved betydeligt lavere værdier (typisk 20-30 x 10^9 pr. liter), samt at personer med et blodpladetal mellem 100-150 x 10^9 pr. liter har en god prognose og sjældent falder til lavere værdier. Der skelnes mellem primær ITP (ingen kendt årsag) og sekundær ITP, som opstår ved andre kendte autoimmune sygdomme og visse knoglemarvssygdomme. ITP betegnes som *persisterende,* når den nedsatte mængde af blodplader varer over 3 måneder, og *kronisk*, når den har varet i over 12 måneder.

Sygdommen findes både hos børn, hvor den ofte er forbigående, og hos voksne, hvor sygdommen oftest er kronisk med varierende sværhedsgrad og behandlingsbehov. Medianalderen ved diagnose er 55 år, men varierer meget.

Kronisk ITP forekommer i Danmark hos ca. 10 ud af 100.000 indbyggere med en incidens hos voksne på ca. 2,8 pr. 100.000 om året [1]. Fagudvalget anslår ud fra forbrugsopgørelser, at omkring 150 patienter kandiderer til behandling med avatrombopag, og at der årligt vil være omkring 30 nye patienter, der kandiderer til behandlingen.

Patienternes symptomer inkluderer hudblødninger (purpura) i form af 1-2 mm store røde pletter på huden (petekkier) eller større blå mærker (ekkymoser) og blødning fra slimhinder i næse, mund, urinveje, tarm mv. Almindelige manifestationer er derfor også kraftige menstruationer (menoragi), mens blødning fra mave-tarmkanalen i form af synligt blod i afføring eller blødning fra urinveje med blodig urin er sjældnere. Af størst alvorlighed for patienter med ITP er deres forhøjede risiko for indre blødninger, herunder transfusionskrævende tarmblødninger og intrakranielle blødninger. Alvorlige

blødninger forekommer sjældent, men risikoen stiger med alderen. Således har patienter > 60 år højere risiko end yngre. I Danmark har patienter med kronisk ITP en 1-års risiko for hospitalisering af enhver årsag på 15 %, hvilket er 4,5 gange højere end alders- og kønsmatchede personer. 5-års risikoen for intrakranielle blødninger er 1,4 %, hvilket er 3,2 gange højere end alders- og kønsmatchede borgere, mens risikoen for andre alvorlige blødninger, der kræver indlæggelse, er 3,6 %, hvilket er 4,4 gange baggrundsbefolkningens [2]. Patienter, som tidligere har haft alvorlig blødning, har en højere risiko for en ny blødning [3].

Patienternes livskvalitet kan påvirkes af blødningerne, men desuden også af træthed, af frygten for alvorlige blødninger samt af bivirkninger og ulemper ved behandling af sygdommen. Livskvaliteten hos patienter med kronisk ITP er betydeligt forringet, sammenlignet med baggrundsbefolkningen, og er på niveau med en række andre kroniske sygdomme som f.eks. leddegigt og cancer [4].

Patienter med kronisk ITP har en dødelighed på ca. 1,5 i forhold til en dansk baggrundsbefolkning [5], hvilket svarer til, at den forventede middellevetid sænkes med knap 4 år. Den forhøjede dødelighed hænger bl.a. sammen med, at sygdommen er forbundet med risiko for andre hæmatologiske komplikationer og kardiovaskulær sygdom, forhøjet risiko for tromboser og hæmatologisk kræft. Trombosetendensen er sandsynligvis multifaktoriel og muligvis relateret til autoimmunitet, men kan også skyldes, at patienterne, på grund af frygten for blødninger, i mindre omfang bliver behandlet med antikoagulerende behandling og trombocythæmmere, som ellers ville have været indiceret. Forklaringen på den øgede forekomst af hæmatologisk kræft er formentlig, at ITP er en eksklusionsdiagnose, hvor en evt. underliggende knoglemarvssygdom ikke altid er synligt til stede på diagnosetidspunktet. Derudover kan de immunsuppressive behandlinger, der benyttes som standardbehandling til ITP, også være kræftfremkaldende. Blandt andet af disse grunde forbliver patienter med ITP ofte i langvarig opfølgning.

2.2 Nuværende behandling

Behandlingsbehovet ved ITP vurderes på baggrund af kliniske symptomer og blodpladetallet. Et blodpladetal på < 20-30 x 10^9/L er en typisk behandlingsindikation hos nydiagnosticerede patienter.

Nydiagnosticerede patienter behandles oftest i 2-3 måneder med glukokortikoider eller i 4 uger med rituximab, som anvendes off-label (evt. i kombination). Behandlingsbehovet er ofte tilbagevendende (hos 60-75 %), hvilket skyldes tilbagefald af sygdommen. Tilbagefald viser sig ved blødning i slimhinderne eller faldende trombocyttal og defineres som et markant fald i trombocyttal til udgangspunktet før behandling eller lavere.

Har patienten haft et godt respons på den første behandling, vil dette oftest gentages ved tilbagevendende behandlingsbehov, indtil responset ikke længere er tilfredsstillende, eller tilbagefaldene er hurtige eller mange. I princippet ophører en

virksom behandling af kronisk ITP først, hvis der er tegn på spontan remission af den autoimmune sygdom, eller hvis respons tabes, eller der opstår bivirkninger.

Behandling af kronisk ITP er individualiseret og afhænger af effekt og bivirkninger ved tidligere behandlinger samt en vurdering af alder, blødningsrisiko, komorbiditeter (herunder samtidige lægemidler), risiko for traumer mm. [3].

Behandlingsmuligheder efter glukokortikoider og evt. rituximab inkluderer først og fremmest trombopoetin-receptor agonister (TPO-RA), som omfatter lægemidlerne eltrombopag (daglig tabletbehandling) og romiplostim (subkutan injektion én gang om ugen) [6]. Flest patienter behandles med eltrombopag som følge af administrationsvejen. Har patienten ikke effekt af eltrombopag, udelukker det ikke en effekt af romiplostim eller omvendt [7–9]. Typisk afprøves en anden TPO-RA-behandling ved svigt af den første. Hvis TPO-RA ikke har en effekt, kan immunsuppressive behandlinger såsom dapson, danazol, mycophenolate mofetil, azathioprin eller ciclosporin også anvendes [3]. I den nyeste American Society of Hematology (ASH) guideline bliver behandling med TPO-RA'er eller rituximab anbefalet som 2. linjebehandling, mens de øvrige immunsuppressiva anbefales i senere behandlingslinjer [6]. Samtlige immunsuppressive behandlinger har dog ikke indikation til ITP og anvendes derfor off-label. Evidensen for behandling af ITP med immunsuppressiva er dårlig, men den kliniske erfaring er lang, og nogle patienter har god effekt af disse lægemidler.

Behandling med både TPO-RA'er og immunsuppressiva er længerevarende (ofte flere år). TPO-RA'er virker hurtigt, mens immunsuppressiva har mere langsomt indsættende effekt (ofte uger til måneder). Valget mellem immunsuppressive behandlinger og TPO-RA-behandling sker bl.a. på baggrund af overvejelser om behovet for hurtigt indsættende effekt, alder og vurdering af den forventede behandlingsvarighed, idet langvarig immunsuppressiv behandling kan være kontraindiceret på grund af risiko for infektioner og kræft.

Hos patienter med kronisk ITP vil behandlingsbehovet være vedvarende eller tilbagevendende resten af livet, men sjældent ses spontan remission. Fagudvalget vurderer der sker hos ca. 5 %.

I akutte situationer, ved behov for hurtigt indsættende effekt, kan immunglobuliner eller transfusion med blodplader anvendes. [3] Effekten af behandlingerne er hurtigt indsættende, men meget kortvarig. Transfusion med blodplader bør kun anvendes ved kritisk blødning eller forud for akut operation.

Monitorering

Patienter med ITP trænes i selvobservation (f.eks. for blå mærker) og monitoreres med kliniske oplysninger og blodprøver. Patienternes kontrolbehov varierer meget, men typisk tages en blodprøve hver 6. måned. Patienter i vedvarende behandling vil typisk monitoreres oftere.

2.3 Avatrombopag

Avatrombopag er en thrombopoietin receptor-agonist (TPO-RA), som stimulerer proliferering og differentiering af megakaryocytter i knoglemarven og derved fremmer dannelsen af blodplader.

Avatrombopag har i forvejen i European Medicines Agency (EMA) indikation til svær trombocytopeni hos voksne patienter med kronisk leversygdom, for hvem et invasivt indgreb er planlagt.

Denne vurdering omhandler indikationsudvidelse til voksne patienter med primær kronisk immun trombocytopeni, som er refraktære over for andre behandlinger (f.eks. glukokortikoider og immunglobuliner).

Fagudvalget bemærker, at betegnelsen *refraktær* har en uaktuel definition i nuværende klinisk praksis, idet definitionen forudsætter, at milten er fjernet (splenektomi). Tidligere var splenektomi en almindelig anvendt behandlingsmulighed til kronisk ITP, men splenektomi anvendes sjældnere i dag og aldrig til børn.
I dag anvendes betegnelsen *refraktær* mere uspecifikt om patienter, der ikke responderer tilfredsstillende over for en eller flere almindeligt anvendte behandlinger.

Fagudvalget bemærker desuden, at immunglobuliner kun anvendes i akutte situationer, og mener, at avatrombopag bør placeres som en 2. linjebehandling efter glukokortikoider og evt. rituximab på linje med de øvrige TPO-RA'er.

Avatrombopag indtages oralt som tabletter á 20 mg en gang dagligt. Tabletterne indtages i forbindelse med et måltid.

Avatrombopag doseres efter antallet af trombocytter i blodet. Generelt skal den laveste mulige dosis anvendes for at opnå og vedligeholde et trombocyttal på ≥ 50 x 10^9/L. Initialdosis er 20 mg (dvs. én tablet) pr. dag. Dosis kan både optitreres (til 40 mg) og nedtitreres.

Avatrombopag kan gives i kombination med anden ITP-behandling, f.eks. glukokortikoider.

Hos patienter med øget tromboserisiko bør behandling med avatrombopag overvejes nøje og foregå med særlig omhyggelig monitorering [10].

Fagudvalget forventer som udgangspunkt, at behandling med avatrombopag er længerevarende, men at varigheden kan variere fra måneder til livslang.

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.

3.1 Klinisk spørgsmål 1

Hvilken værdi har avatrombopag sammenlignet med eltrombopag for patienter med primær kronisk ITP, som er refraktære over for tidligere behandlinger med glukokortikoider og evt. rituximab?

Population
Patienter ≥ 18 år med primær kronisk ITP, som er refraktære over for tidligere behandling med glukokortikoider og minimum ét andet immunsuppressivum som f.eks rituximab?

Intervention
Avatrombopag 20 mg pr. dag (startdosis), som kan optitreres til 40 mg pr. dag.

Komparator
Eltrombopag 50 mg pr. dag (startdosis), som kan optitreres til 75 mg pr. dag.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 1. For hver 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
Livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Forskel i gennemsnitlig ændring fra baseline målt ved SF-36	8 point
			Andelen af patienter, der opnår en stigning på ≥ 8 point	10 %-point
Alvorlige Blødninger	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel, der oplever alvorlige blødninger	1 %-point
Mindre blødninger	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Andel, der oplever mindre blødninger	10 %-point
Blodplade-respons	Vigtigt	Ikke-alvorlige symptomer og bivirkninger	Andel af patienter med blodpladetal > 50 x 10^9/L efter 6 måneder	10 %-point
Bivirkninger	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Andel, der ophører behandling pga. uønskede hændelser	5 %-point
			Kvalitativ gennemgang af bivirkningsprofilen	-

*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.

3.2.1 Kritiske effektmål

Livskvalitet
I denne patientpopulation, hvor behandlingen kan forventes at være langvarig, og patienternes livskvalitet er forringet af både symptomer, frygt for symptomer og behandlingen, betragter fagudvalget effektmålet som kritisk for vurderingen.

I dansk klinisk praksis måles patienternes livskvalitet ikke rutinemæssigt. Fagudvalget vurderer, at SF-36 vil være et relevant værktøj at anvende i denne vurdering, da værktøjet er valideret i patienter med blødersygdom og anvendt i tidligere studier af livskvalitet hos ITP-patienter. SF-36 indeholder 8 domæner, som hver kan scores fra 0-100. 8 point anvendes typisk som en klinisk relevant forskel. Fagudvalget ønsker at se resultater for livskvalitet opgjort samlet og for hvert domæne og betragter en forskel i gennemsnitlig ændring fra baseline på 8 point som mindste klinisk relevante forskel. Fagudvalget ønsker som supplement også at se andelen af patienter, der opnår en

stigning på ≥ 8 point og betragter en forskel på 10 %-point som en mindste klinisk relevant forskel.

Alvorlige blødninger
Alvorlige blødninger er sjældne, men er det mest frygtede symptom ved ITP, især intrakraniel blødning, da det kan lede til død eller varige mén. Det er derfor kritisk for patienten, at behandlingen forhindrer alvorlige blødninger. Alvorlig blødning kan defineres i henhold til en række definitioner, herunder f.eks. CTCAE *(Common Terminology Criteria for Adverse Events)* eller *WHO Bleeding scale,* som er en skala med fem niveauer fra 0-4.

Fagudvalget ønsker andelen af patienter, der oplever alvorlige blødninger, opgjort efter længst mulig opfølgningstid med CTCAE og *WHO Bleeding Scale* eller andre skalaer, der er sammenlignelige. Et dansk retrospektivt studie har estimeret 5-års risikoen for hospitalisering som følge af intrakranielle blødninger til 1,4 % blandt patienter med kronisk ITP, hvor især patienter > 60 år var i højest risiko. Derudover var 5-års risikoen for hospitalisering som følge af blødning (andre end intrakraniel blødning) 3,6 % [2]. Sidenhen er TPO-RA blevet en tilgængelig behandling, som yderligere har kunnet reducere risikoen. Derfor anser fagudvalget i dag risikoen for alvorlig blødning hos patienter i behandling med en TPO-RA som endnu mindre. Af den årsag fastsætter fagudvalget den mindste klinisk relevante forskel til 1 %-point. Fagudvalget ønsker effektmålet opgjort med længst mulig opfølgningstid.

3.2.2 Vigtige effektmål

Mindre blødninger
Fagudvalget finder det relevant at vurdere effektmålet *mindre blødninger* defineret i overensstemmelse med CTCAE eller *WHO bleeding scale*. Mindre blødninger omfatter blødninger, som ikke møder kriterierne for en alvorlig blødning, men som enten kræver medicinsk intervention, indlæggelse eller fremmøde hos en læge for at blive vurderet. Disse blødninger er ofte generende for patienten og har betydning for patienternes livskvalitet og potentielt for deres vedholdenhed i forhold til deres behandling. Baseret på studiedata oplever, omkring 20 % af patienterne i behandling med eltrombopag mindre blødninger i løbet af 6 måneder [11]. På den baggrund vurderer fagudvalget, at den mindste klinisk relevante forskel er 10 %-point.

Andel af patienter med blodpladetal ≥ 50 x 10^9/L
Blodpladetallet er et surrogat for patientens blødningsrisiko og af mindre betydning for patienten, derfor har fagudvalget anvendt effektmålsgruppen Ikke-alvorlige symptomer og bivirkninger. Til trods for dette anser fagudvalget effektmålet som relevant, fordi det er et tal, der monitoreres i klinikken og er brugbart i forhold til at kunne vurdere, hvor hurtigt effekten af avatrombopag indsætter. Derudover indgår effektmålet også i vurderingen af, hvad patienterne ellers kan modtage af medicin, og om de kan gennemgå kirurgiske indgreb.

Fagudvalget ønsker andelen, som opnår et *blodpladetal* ≥ 50 x 10^9/L, opgjort efter 6 måneders behandling, med og uden behov for supplerende medicin. Omkring 60 % opnår tilstrækkeligt respons på de TPO-RA, som anvendes i dag. Derfor vurderer fagudvalget, at mindste klinisk relevante forskel skal være 10 %-point. Som supplement ønsker fagudvalget, at ansøger bidrager med kurver, der viser udviklingen af blodpladetallene over hele opfølgningstiden samt en opgørelse af varigheden af responset.

Bivirkninger

Behandlingsophør pga. uønskede hændelser
Fagudvalget ønsker at vurdere behandlingsophør på grund af uønskede hændelser, da det er et effektmål, der belyser tyngden og alvorligheden af bivirkninger. Behandlingen med TPO-RA forventes at være langvarig, og behandlingsophør belyser, hvor godt interventionen og komparator tolereres af patienterne.

Fagudvalget vurderer, at effektmålet er vigtigt for vurderingen og ønsker effektmålet opgjort som andelen af patienter, som ophører behandling på grund af uønskede hændelser med længst mulig opfølgningstid. Baseret på studiedata ophører ca. 15 % med nuværende behandling inden for 6 måneder [11]. Fagudvalget vurderer derfor, at en forskel på 5 %-point er klinisk relevant.

Kvalitativ gennemgang
Fagudvalget ønsker som supplement til effektmålet behandlingsophør grundet uønskede hændelser, at ansøger opgør bivirkningsprofilen med henblik på en kvalitativ gennemgang. Opgørelsen skal indeholde alle bivirkninger af enhver grad rapporteret i de kliniske studier. Bivirkninger af grad 3-4 bedes opgjort separat.
Fagudvalget vil ud fra denne opgørelse vurdere håndterbarhed og tyngde af bivirkningsprofilen. Fagudvalget er særligt opmærksomme på andelen, som får tromboser.

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 (f.eks. NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Hvis disse data er tilstrækkelige til at kunne vurdere lægemidlet, vil Medicinrådet som hovedregel ikke anvende andre data[1]. Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data,

[1] For yderligere detaljer se Medicinrådets kriteriepapir om anvendelse af upublicerede data

der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets kriteriepapir.

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der ikke findes studier, hvor avatrombopag er sammenlignet direkte med eltrombopag. 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.

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler, der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

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, f.eks. 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 (f.eks. 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.

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, f.eks. 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

7.1 Betydning for behandlingssekvensen

Medicinrådet ønsker, at det i den sundhedsøkonomiske analyse imødekommes, hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlingssekvensen, hvad angår type, varighed og forventet effekt.
Fagudvalget ønsker at ansøger belyser evidensen for at behandle med avatrombopag og eltrombopag efter hinanden.

7.2 Behandlingsvarighed

Fagudvalget ønsker, at ansøger redegør for, hvor længe patienterne kan forventes at være i behandling med avatrombopag og komparator. Den forventede behandlingsvarighed bedes afspejlet i tidshorisonten i den sundhedsøkonomiske model.

7.3 Supplerende behandling

Fagudvalget ønsker, at ansøger bidrager med data, der belyser, hvorvidt patienter i behandling med avatrombopag har et reduceret behov for supplering med glukokortikoider og immunglobuliner i sammenligning med komparator.

7.4 Forhold omkring lægemiddeladministration og interaktioner

Ved administration af eltrombopag skal man være opmærksom på kation-interaktion, som betyder, at det ikke bør indtages sammen med divalente kationer såsom calcium, magnesium og jern, og patienten derfor ikke må indtage f.eks. mejeriprodukter 4 timer før og 2 timer efter dosering af eltrombopag. Fagudvalget beder ansøger redegøre for, om der er restriktioner forbundet med dosering af avatrombopag.

7.5 Dosisintensitet

Da både avatrombopag og komparator kan dosisjusteres, og der i klinisk praksis er behandlingspause, bedes ansøger redegøre for den forventede dosisintensitet for avatrombopag og komparator, samt belyse hvor stor en del af patienterne, der forventes i perioder at kunne ophøre behandling med avatrombopag henholdsvis eltrombopag.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

9. Referencer

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende benign hæmatologi

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Jesper Stentoft *Professor, overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Kaper Røikjær Jensen *Afdelingslæge*	Region Nordjylland
Henrik Frederiksen *Professor, overlæge*	Region Syddanmark
Birgitte Lausen *Overlæge*	Region Hovedstaden
Eva Birgitte Leinøe *Overlæge*	Region Hovedstaden
Mikkel Helleberg Dorff *Overlæge*	Region Sjælland
Klaus Reineck *Afdelingslæge*	Dansk Selskab for Klinisk Immunologi
Ane Hornbæk Mortensen *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Udpegning i gang	Dansk Selskab for Trombose og Hæmostase
Kan ikke udpege en kandidat	Danske Patienter

Medicinrådets sekretariat
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11. Versionslog

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

12. Bilag

Bilag 1: Søgestrenge

Søgestreng til PubMed:

#	Søgestreng	Kommentar
#1	Purpura, Thrombocytopenic, Idiopathic[mh]	
#2	ITP[tiab] OR (werlhof*[tiab] AND disease[tiab]) OR (purpura[tiab] AND thrombocytop*[tiab]) OR ((idiopathic[tiab] OR autoimmun*[tiab] OR immun*[tiab]) AND thrombocytop*[tiab])	
#3	#1 OR #2	Samlet søgning for populationen
#4	Avatrombopag[nm]	Søgetermer for interventionen
#5	avatrombopag[tiab] OR AKR-501[tiab] OR AKR501[tiab] OR Doptelet*[tiab] OR E5501[tiab] OR YM-477[tiab] OR YM477[tiab]	
#6	Eltrombopag[nm]	Søgetermer for komparator
#7	eltrombopag[tiab] OR Promacta*[tiab] OR Revolade*[tiab] OR SB-497 115[tiab]	
#8	#4 OR #5 OR #6 OR #7	Intervention + komparator
#9	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans [mh])	Cochrane RCT-filter
#10	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]	Eksklusion af ikke-relevante publikationstyper
#11	#3 AND #8	
#12	#11 AND #9	
#13	#12 NOT #10	Endelig søgning

Søgestreng til CENTRAL:

#	Søgestreng	Kommentar
#1	(idiopathic near/2 thrombocytopenic near/2 purpura):kw	
#2	ITP:ti,ab	
#3	(purpura near thrombocytop*):ti,ab	
#4	((idiopathic or autoimmun* or immun*) near thrombocytop*):ti,ab	
#5	#1 or #2 or #3 or #4	Samlet søgning for populationen
#6	(avatrombopag or AKR-501 or AKR501 or Doptelet* or E5501 or YM-477 or YM477):ti,ab,kw	Søgetermer for interventionen
#7	(eltrombopag or Promacta* or Revolade* or SB-497 115):ti,ab,kw	Søgetermer for komparator
#8	#6 or #7	Intervention + komparator
#9	NCT*:au	Eksklusion af ikke-relevante publikationstyper
#10	("conference abstract" or review):pt	
#11	(clinicaltrials.gov or trialsearch):so	
#12	(abstract or conference or meeting or proceeding*):so	
#13	#9 or #10 or #11 or #12	
#14	(#5 and #8) not #13	
#15	#14 not pubmed:an	Endelig søgning