Medicinrådet

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

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. fostamatinib, version 1.0
2. Forhandlingsnotat fra Amgros vedr. fostamatinib
3. Høringssvar fra ansøger
4. Medicinrådets vurdering vedr. fostamatinib til behandling af kronisk immun trombocytopeni, version 1.0
5. Ansøgers endelige kliniske ansøgning vedr. fostamatinib
6. Ansøgers tekniske dokument til den sundhedsøkonomiske
7. Medicinrådets protokol for vurdering vedr. vedr. fostamatinib til behandling af kronisk immun trombocytopeni, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Fostamatinib

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*.

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1. Begreber og forkortelser

AIP: Apotekernes indkøbspris

DKK: Danske kroner

DRG: Diagnose Relaterede Grupper

SAIP: Sygehusapotekernes indkøbspris

ITP: Kronisk immun trombocytopeni

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
Som følge af betydelige usikkerheder om varighed af respons, og dermed om behandlingslængde, har Medicinrådet anvendt to scenarier i sin hovedanalyse. Scenarierne har forskellige antagelser om behandlingslængde, hvorfor de resulterer i forskellige inkrementelle omkostninger.

I scenarie 1 er de inkrementelle omkostninger ca. [redacted] DKK pr. patient sammenlignet med *watch and rescue (placebo)*. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 229.000 DKK pr. patient.

I scenarie 2 er de inkrementelle omkostninger ca. [redacted] DKK pr. patient sammenlignet med *watch and rescue*. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 1,9 mio. DKK pr. patient.

Ansøger har i sin sundhedsøkonomiske ansøgning kun besvaret klinisk spørgsmål 1 fra Medicinrådets protokol, hvor den definerede komparator er placebo (*watch and rescue*). Baggrunden for dette er, at det ikke har været muligt for ansøger at identificere tilstrækkeligt relevant data. Den sundhedsøkonomiske afrapportering undersøger derfor ikke de inkrementelle omkostninger ved anvendelse af fostamatinib sammenlignet med immunsuppressive behandlinger.

3. Introduktion

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

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Grifols. Medicinrådet modtog ansøgningen den 21. marts 2022.

3.1 Patientpopulation

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. Diagnosen kan stilles, når blodpladetallet er < $100*10^9$ pr. liter, selvom den nedre grænse i normalområdet er højere end dette ($150*10^9$ pr. liter). Dette skyldes dels, at der først er behandlingsindikation ved betydeligt lavere værdier (typisk 20-30

*10^9 pr. liter), dels at personer med et blodpladetal mellem 100-150 * 10^9 pr. liter har en god prognose og sjældent falder til lavere værdier.

Sygdommen findes både hos børn, hvor den ofte er forbigående, og hos voksne, hvor den 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]. De fleste af disse vil være tilstrækkeligt hjulpet af de nuværende behandlinger, og fagudvalget vurderer, at der er ca. 10 patienter, som ikke vil have gavn af de nuværende behandlinger, og som dermed er kandidater til behandling med fostamatinib. Derudover skønner fagudvalget, at der vil være 1-5 nye patienter om året.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

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

Klinisk spørgsmål 1:

Hvilken værdi har fostamatinib sammenlignet med placebo for patienter med primær kronisk behandlingsrefraktær ITP?

Klinisk spørgsmål 2:

Hvilken værdi har fostamatinib sammenlignet med immunsuppressive behandlinger såsom dapson, danazol, mycophenolate mofetil, azathioprin eller ciclosporin for patienter med primær kronisk ITP?

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 fostamatinib sammenlignet med placebo. Der er ikke indsendt en sundhedsøkonomisk analyse, der viser de inkrementelle omkostninger ved anvendelse af fostamatinib sammenlignet med immunsuppressive behandlinger, da det ikke har været muligt for ansøger at identificere det nødvendige data.

Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

Sammenligningen med placebo er lavet på baggrund af data fra FIT-1 og FIT-2[2], der undersøgte effekt og sikkerhed af fostamatinib. Begge studier var randomiserede, dobbeltblindede og placebokontrollerede.

For at blive inkluderet i studierne skulle patienterne have haft ITP i ≥ 3 måneder og have modtaget behandling for deres sygdom med mindst ét lægemiddel tidligere. Yderligere skulle patienternes gennemsnitlige blodpladetal være < $30*10^9$pr. liter baseret på tre målinger inden for tre måneder op til studiestart. Patienterne blev randomiseret i en ratio på 2:1 til enten fostamatinib eller placebo i 24 uger. 101 patienter modtog fostamatinib versus 49, som modtog placebo i FIT-1 og FIT-2 tilsammen. Det var tilladt at modtage samtidig ITP-behandling (enten glukokortikoider < 20 mg/dag, azathioprin eller danazol) med enten fostamatinib eller placebo. Derudover var *rescue*-behandling også tilladt efter behov (øget dosis af samtidig ITP-behandling, IVIg, IV Anti-D, steroider og blodtransfusion).

Yderligere information om studierne kan findes i Medicinrådets vurderingsrapport.

4.1.1 Modelbeskrivelse

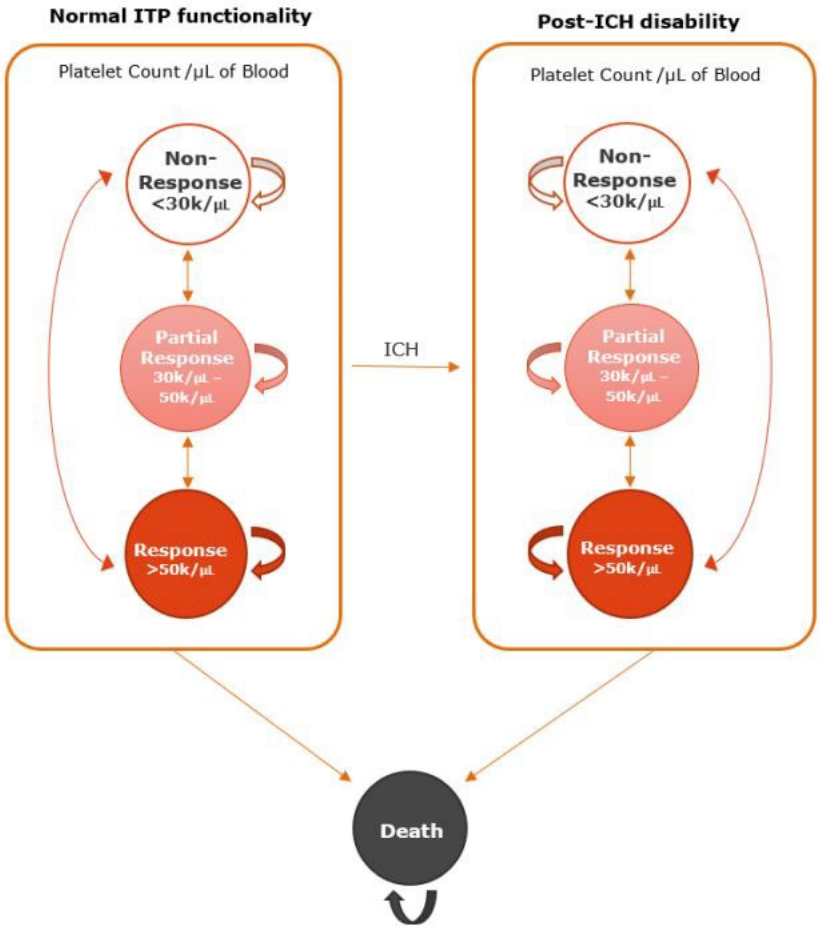
Ansøger har indsendt en Markov-model til at estimere omkostningerne forbundet med behandling med fostamatinib.

Modellen består af en række stadier, som patienten kan befinde sig i på et givet tidspunkt af modellens tidshorisont. De forskellige stadier repræsenterer forskellige niveauer af blodpladetal, hvor hvert stadie er associeret med en given risiko for at modtage *rescue*-behandling og for at opleve blødninger. Modellens stadier er non-respons, partielt respons og respons samt død. Non-respons dækker over de patienter, som har et blodpladetal > 30 * 10^9 pr. liter, mens partielt respons dækker over patienterne med et blodpladetal på 30-50 * 10^9 pr. liter. Respons dækker over de patienter, som har et blodpladetal > 50 * 10^9 pr. liter. Derudover skelnes der i modellen mellem, om en intrakraniel blødning er forekommet, da patienter, som ellers har et tilsvarende blodpladetal, vil være associeret med forskellige omkostninger, afhængigt af om de har haft en intrakraniel blødning eller ej. Modellen har derfor i alt seks stadier ud over det absorberende stadie død (non-respons, partielt respons og respons med og uden intrakraniel blødning). Transitionssandsynligheder er estimeret ud fra FIT-1 og FIT-2, hvor der på baggrund af interventions- og placebogruppen estimeres transitionssandsynligheder for patienter, der hhv. behandles og ikke behandles med fostamatinib.

Figur 1 viser de forskellige sygdomsstadier, og hvordan patienten kan bevæge sig mellem de forskellige stadier. I forenelighed med inklusionskriteriet fra FIT-studierne starter patienterne i non-respons-stadiet. Herfra kan de opnå et fuldt eller partielt respons og bevæge sig til et af de respektive stadier. Hvis dette ikke opnås, forbliver de i non-respons-stadiet. Patienter, som har bevæget sig til et af de andre stadier som følge af fuldt eller partielt respons, har i hver cyklus en risiko for at miste deres respons og bevæge sig tilbage til non-respons-stadiet. Hvis dette forekommer for en patient, der

modtager fostamatinib, afsluttes denne behandling, og de overgår til *watch and rescue*, hvor der kun gives *rescue*-behandling og behandling i tilfælde af blødninger.

Modellen har en cykluslængde på 4 uger. Ansøger argumenterer for, at dette er passende, siden dette interval er kort nok til, at det ikke kan forventes, at mere end ét blødningsevent kan nå at forekomme.



Figur 1. Beskrivelse af modelstrukturen i omkostningsanalysen

Medicinrådets vurdering af ansøgers model
Medicinrådet accepterer ansøgers valg af modeltype og struktur.

4.1.2 Modelantagelser og -beskrivelse

Transitionssandsynligheder anvendt i modellen
Transitionssandsynlighederne, der determinerer patienternes bevægelse gennem modellens stadier, er baseret på individuelt patientdata fra FIT-1 og FIT-2. Blodpladetal blev i studiet målt ved uge 5, 13 og 24 efter påbegyndt behandling. Der er således rater tilgængelige for, hvor mange patienter der i dette tidsrum falder eller stiger i blodpladetal inden for de respektive stadier i modellen. Raterne fra uge 5-12 og uge 13-

24 bliver omregnet til 4-ugers transitionssandsynligheder, så de passer med modellens cykluslængde.

Da FIT-1 og FIT-2 kun havde 24 ugers opfølgningstid, er det nødvendigt at gøre sig antagelser om, hvordan patienterne bevæger sig i stadierne for det resterende af modellens tidshorisont. I ansøgers hovedanalyse antages det, at de estimerede transitionssandsynligheder fra uge 13-24 gælder resten af modellens tidshorisont. Antagelsen betyder, at hvis det fx i uge 13-24 blev estimeret, at en patient i stadiet non-respons havde en sandsynlighed på 29,2 % for at opnå et partielt respons inden for 4 uger, så antages det, at sandsynligheden også vil være gældende i den resterende tid af modellens tidshorisont.

Yderligere antages det, at hvis patienterne opnår et respons fra uge 13-24, vil de ikke miste deres respons i den efterfølgende tid af modellen (svarende til at antage en 0 % risiko for relaps). Denne antagelse er valgt i ansøgers hovedanalyse, men modellen tillader også at anvende en alternativ tilgang, hvor der ekstrapoleres på tab af respons efter uge 24 ud fra det observerede gennemsnitlige tab af respons fra uge 5-24 i FIT-1-2.

Sammenhæng mellem blodpladetal og dødelighed

Det er i den indsendte model inkorporeret, at et lavere blodpladetal er forbundet med en højere dødelighed, siden man i stadierne partielt respons og non-respons, sammenlignet med patienter i respons, har en højere risiko for at bevæge sig til stadiet død.

Det antages, at dødelighed blandt patienter i respons ikke er højere end risikoen hos den generelle befolkning. For non-respons er risikoen for død baseret på Portielje et al.[3], der undersøgte dødeligheden blandt hollandske ITP-patienter. Studiet estimerede, at risiko for død blandt ITP-patienter med blodpladetal < 30 $*10^9$ pr. liter var 4,2 gange højere end hos den generelle befolkning. Denne risiko anvendes i modellen til at estimere den øgede risiko for at dø i non-respons sammenlignet med respons. Risikoen for død i partielt respons er modelleret ud fra Adelborg et al.[4], et registerstudie, der undersøgte dødelighed blandt skandinaviske patienter. Det blev her fundet, at patienter med blodpladetal < 50 * 10^9 pr. liter havde en 2,5 gange større risiko for død sammenlignet med den generelle befolknings risiko. Denne risiko anvendes i modellen til at modellere den højere risiko for død i stadiet partielt respons sammenlignet med respons.

Patienter, der oplever en intrakraniel blødning har, uafhængigt af blodpladetal, også en øget risiko for at dø i modellen. Der anvendes en hazard ratio på 2,02 relativt til patienter, der ikke har haft dette event. Estimatet er baseret på Gonzalez-Perez et al.[5], der undersøgte øget mortalitet på kort og langt sigt hos engelske patienter efter en intrakraniel blødning var forekommet.

Sammenhæng mellem blodpladetal og blødninger

Ansøger har anvendt data fra forskellige studer til at modellere risiko for blødning på tværs af modellens stadier. Patienter kan i modellen blive udsat for intrakranielle, gastrointestinale og andre indlæggelseskrævende blødninger samt blødninger, der kræver ambulant besøg.

For patienter med blodpladetal < 30 * 10^9 pr. liter er frekvenser for intrakranielle, gastrointestinale og ambulant håndterede blødninger baseret på et klinisk studie, der undersøgte lægemidlet romiplostim mod placebo over 24 uger[6]. Frekvenserne for patienter med blodpladetal > 50 * 10^9 pr. liter er baseret på en peer-reviewed sundhedsøkonomisk analyse af Allen et al.[7], der undersøgte omkostningseffektiviteten af eltrombopag over for romiplostim. Frekvenserne for patienter med et blodpladetal på 30-50 * 10^9 pr. liter er baseret på den gennemsnitlige værdi af frekvenserne for patienterne med hhv. < 30 og > 50, da det ikke var muligt for ansøger at identificere relevante studier for denne population. Andre indlæggelseskrævende blødningsfrekvenser baseres på tværs af alle blodpladeintervaller i modellen på Adelborg et al., der undersøgte blødningsrisiko blandt nordiske patienter.

Medicinrådets vurdering af ansøgers modelantagelser

Fagudvalget vurderer, at studierne, der bruges til at estimere dødelighed i modellens forskellige stadier, godt kan anvendes, men gør opmærksom på, at den kausale sammenhæng mellem ITP og overdødelighed er usikker, bl.a. som følge af, at årsagerne til overdødeligheden er uafklaret. Medicinrådet accepterer derfor ansøgers tilgang til at estimere dødelighed i modellen, men præsenterer også en følsomhedsanalyse, hvor dødeligheden sættes til at være lig den generelle befolknings dødelighed på tværs af alle modellens stadier.

Da opfølgningstiden i FIT-1-2 kun var 24 uger, og behandling potentielt kan være livslang, er estimering af gennemsnitlig behandlingslængde med fostamatinib i tilfælde af anbefaling behæftet med stor usikkerhed. Det vurderes af fagudvalget, at den faktiske behandlingslængde med fostamatinib nok vil ligge et sted mellem de to tilgange til tab af respons efter uge 24, der er mulige at anvende i ansøgers indsendte model. Antagelsen om vedblivende respons i resten af patienternes levetid, hvis denne blev opnået i uge 13-24, vurderer fagudvalget er for optimistisk, når der tages højde for, at disse patienter er svære at behandle og ikke har opnået tilstrækkelig effekt af andre lægemidler. Samtidig vurderer fagudvalget, at det nok leder til et for hurtigt tab af respons i modellen, hvis ansøgers alternative tilgang anvendes, hvor der ekstrapoleres på tab af respons efter uge 24 på baggrund af det observerede gennemsnitlige tab af respons fra uge 5-24 i FIT-1-2. Denne antagelse leder i modellen til en gennemsnitlig behandlingslængde på 8,28 måneder, som vurderes at være underestimeret i forhold til resultaterne fra FIT-3 [8], hvor 62 % af patienterne havde en median responsvarighed > 28 måneder og fortsat var i behandling ved studiets afslutning (opfølgningstid var 2 år i FIT-3). Som følge af denne vurdering om, at de respektive antagelser hhv. overestimerer og underestimerer behandlingslængden, anvender Medicinrådet begge antagelser i hovedanalysen, så de inkrementelle omkostninger præsenteres for begge scenarier. Den gennemsnitlige tid i modellens stadier samt gennemsnitlig tid i behandling ved de to metoder fremgår af hhv. Tabel 1 og Tabel 2.

Fagudvalget vurderer, at registerstudiet af Adelborg et al., der undersøger blødningsrisiko blandt skandinaviske patienter, bør anvendes fremfor de kliniske studier, ansøger har anvendt, da registerstudier passer bedre med den danske patientpopulation, inkluderer flere patienter og har længere opfølgningstid. Medicinrådet bemærker yderligere, at Adelborg et al. definerer blødningsevent som

blødninger, der kræver hospitalskontakt. Det vurderes derfor, at anvendelse af dette studie til udelukkende at estimere andre indlæggelseskrævende blødninger vil overestimere prævalensen af blødninger samlet set, da det anvendte data dækker alle typer af blødninger (ambulant håndterede, gastrointestinale, intrakranielle etc.). Som følge deraf er det kun studiet af Adelborg et al., der anvendes til at estimere risiko for blødninger i Medicinrådets hovedanalyse. Dette vurderes at have moderat betydning for analysens resultater.

Tabel 1. Gennemsnitlig tid i modellens stadier ved de to anvendte scenarier i Medicinrådets hovedanalyse om varighed af respons på fostamatinib

Behandling	Non-respons (år)	Partielt respons (år)	Respons (år)
Antagelse om intet tab af respons i uge 24+	7,8	2,6	11,3
Tab af respons uge 24+ baseret på data fra uge 5-25 i FIT-1-2	12,1	4,1	1,8

Tabel 2. Gennemsnitlig tid i behandling med fostamatinib ved de to anvendte scenarier i Medicinrådets hovedanalyse om varighed af respons på fostamatinib

Behandling	Gennemsnitlig tid i behandling (år)	Gennemsnitlig tid uden behandling	Gennemsnitlig levealder
Antagelse om intet tab af respons i uge 24+	10,77	11,06	76,84
Tab af respons uge 24+ baseret på data fra uge 5-25 i FIT-1-2	0,69	17,36	73,05

Medicinrådet præsenterer i sin hovedanalyse begge antagelser om tab af respons efter uge 24.

4.1.3 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 40 år. Det antages, at patienterne ved baseline er 60 år.

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

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet accepterer ansøgers valgte tidshorisont. Da der, som beskrevet i afsnit 3.1, er betydelig variation i alder ved diagnose, præsenteres følsomhedsanalyser, hvor baselinealderen varieres.

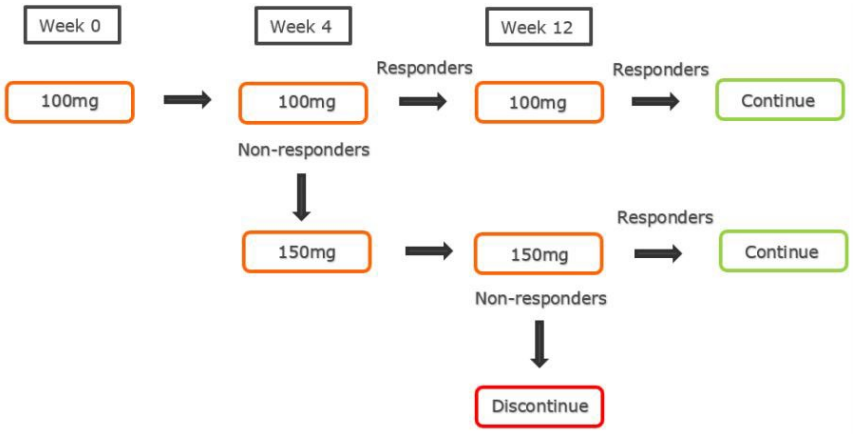
4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af fostamatinib sammenlignet med *watch and rescue*-behandling. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, patientomkostninger og kommunale omkostninger.

Omkostningerne er cyklusbestemt, hvilket betyder, at omkostningerne påregnes for hver cyklus, patienten befinder sig i stadiet.

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). Dosering af fostamatinib er baseret på lægemidlets produktresumé. Patienter modtager initialt 100 mg 2 gange dagligt og kan øges til 150 mg 2 gange dagligt efter 4 ugers behandling. Dette inkorporeres i ansøgers model, hvor andelen af patienter, der ikke responderer efter 4 ugers behandling, øges til 150 mg. Hvis patienterne da opnår et respons ved uge 12, fortætter de i behandlingen, mens den seponeres, hvis et respons fortsat ikke er opnået. Det antages i modellen, at de patienter, der opnår respons ved øgning af dosis til 150 mg, fortsætter med denne dosis i 12 måneder, hvorefter der reduceres til 100 mg. Doseringsalgoritmen fremgår grafisk af Figur 2.



Figur 2. Doseringsalgoritme anvendt i den sundhedsøkonomiske analyse

Ud over behandling med fostamatinib inkluderer modellen også lægemiddelomkostninger til *rescue*-behandling. Hvert af modellens stadier er associeret med en given risiko for at modtage *rescue*-behandling, baseret på observeret data fra FIT-1 og FIT-2. I FIT-1 og FIT-2 bestod *rescue*-behandling af immunglobuliner og methylprednisolon. Ansøger antager, at der i forbindelse med *rescue*-behandling gives 5 behandlinger med immunglobulin i doseringen 0,4 g/kg, mens der gives 1 gram methylprednisolon peroralt dagligt i syv dage.

Ansøger antager, at samme behandling med immunglobuliner og dexamethason gives som forebyggende behandling ved operationer hos patienter i stadiet non-respons.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 2.

Fagudvalget vurderer, at man i praksis muligvis vil fortsætte længere end 12 uger, før man seponerer behandling hos de patienter, der ikke har opnået et respons. Det er dog usikkert, hvor meget længere, hvorfor Medicinrådet accepterer ansøgers antagelse vedrørende dette.

Fagudvalget vurderer ligeledes, at det i praksis vil være et mindretal af patienterne, der nedjusteres til 100 mg i dosis efter 12 måneder, hvis de fortsat har gavn af behandlingen, og et respons først blev opnået, da dosis blev øget til 150 mg. Som følge deraf ændrer Medicinrådet denne antagelse, så 80 % af disse patienter fortsætter på 150 mg, så længe de er i behandling med fostamatinib. For at undersøge denne antagelses indvirkning på resultatet præsenteres en følsomhedsanalyse, hvor ansøgers antagelse om nedjustering er bibeholdt.

Medicinrådet accepterer den estimerede risiko for at modtage *rescue*-behandling, der anvendes i modellen, men justerer den behandling, der gives. I dansk klinisk praksis bliver immunglobuliner generelt kun anvendt til denne patientpopulation i tilfælde af blødninger. Som følge deraf er omkostninger til immunglobuliner i Medicinrådets hovedanalyse determineret af blødningsfrekvenser fremfor andel, der modtager *rescue*-behandling. Fagudvalget vurderer, at immunglobuliner som udgangspunkt altid vil blive anvendt ved intrakranielle og gastrointestinale blødninger samt i 25 % af andre indlæggelseskrævende blødninger. Som beskrevet i afsnit 4.1.2 anvender Medicinrådet kun Adelborg et al. til estimering af blødningsrisiko, og dette studie stratificerer ikke på type af blødning. Til fordeling af type af blødninger vurderer fagudvalget det rimeligt at tage udgangspunkt i den sundhedsøkonomiske analyse af Allen et al., der undersøgte romiplostim over for eltrombopag. Denne analyse finder på basis af individuelt patientdata, at 93 % af blødningerne, der forekom, blev håndteret ambulant, mens de resterende 7 % krævede en indlæggelse. Medicinrådet antager derfor, at immunglobuliner bliver anvendt ved alle indlæggelseskrævende blødninger. Dette vurderes at være en rimelig antagelse, da indlæggelseskrævende blødninger overvejende vil være intrakranielle og gastrointestinale.

Yderligere ændres doseringen af den immunglobulinbehandling, der anvendes i modellen, da fagudvalget påpeger, at man i dansk klinisk praksis giver 1 g/kg over 1-2 behandlinger (et gennemsnit på 1,5 er anvendt i modellen).

Medicinrådet ændrer også antagelsen om methylprednisolon i 7 dage peroralt til 4 behandlinger af 40 mg dexamethason i forbindelse med *rescue*-behandling.

Risiko pr. cyklus for at modtage *rescue*-behandling tværs af modellens stadier fremgår af Tabel 4.

Tabel 3. Anvendte lægemiddelpriser, SAIP (Oktober 2022)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
J06BA02 - Immunoglobuliner, normal human til intravasc. brug	100 mg/ml	25 ml	[redacted]	Amgros
J06BA02 - Immunoglobuliner, normal human til intravasc. brug	100 mg/ml	50 ml	[redacted]	Amgros
J06BA02 - Immunoglobuliner, normal human til intravasc. brug	100 mg/ml	100 ml	[redacted]	Amgros
J06BA02 - Immunoglobuliner, normal human til intravasc. brug	100 mg/ml	200 ml	[redacted]	Amgros
J06BA02 - Immunoglobuliner, normal human til intravasc. brug	100 mg/ml	400 ml	[redacted]	Amgros
H02AB04 - Methylprednisolon	100 mg	20 stk. (blister)	[redacted]	Amgros
H02AB04 - Methylprednisolon	32 mg	60 stk.	[redacted]	Amgros
H02AB04 - Methylprednisolon	100 mg	20 stk.	[redacted]	Amgros
H02AB04 - Methylprednisolon	32 mg	50 stk.	[redacted]	Amgros
B02BX09 - Fostamatinib	150 mg	60 stk.	[redacted]	Amgros
B02BX09 - Fostamatinib	100 mg	60 stk.	[redacted]	Amgros
H02AB02 - Dexamethason	4 mg/ml	10 x 1 ml	[redacted]	Amgros

Tabel 4. Risiko for at modtage *rescue*-behandling samt omkostninger pr. cyklus

Stadie	Risiko for at modtage *rescue*-behandling pr. cyklus
Non-respons (<30 * 10^9/L)	19,5 %
Partielt respons (30-50 *10^9 /L)	11,8 %
Respons (> 50*10^9 /L)	9,2 %

Tabel 5. Risiko for behandling med immunogluboliner pr. cyklus

Stadie	Risiko for blødning pr. Cyklus	Andel blødninger, hvor immunglobuliner anvendes
Non-respons (<30 * 10^9/L)	2,27 %	7 %
Partielt respons (30-50 *10^9 /L)	0,75 %	7 %
Respons (> 50*10^9 /L)	0,46 %	7 %

Medicinrådet ændrer andelen, der nedjusteres fra 150 mg til 100 mg efter 12 måneder fra 100 % til 20 %. Ligeledes fjernes omkostninger til immunglobuliner i forbindelse med rescue-behandling og tilføjes til omkostninger i forbindelse med blødninger.

4.2.2 Hospitalsomkostninger

I den sundhedsøkonomiske model har ansøger inkluderet hospitalsomkostninger i forbindelse administrationsomkostninger til blødninger, monitoreringsomkostninger og bivirkningsomkostninger.

Administrationsomkostninger

Administrationsomkostninger i forbindelse med blødninger
Patienter kan i ansøgers model blive udsat for fire typer blødninger, hvor hver type blødning er blevet tillagt en enhedsomkostning på baggrund af en DRG-takst:

- Intrakraniel blødning (DRG: Sammedagspakke: Blodprop i hjernen, udredning (01SP01) og forbigående utilstrækkelig blodforsyning til hjerne og okklusion af præcerebrale arterier (01MA13)).

- Gastrointestinal blødning (DRG: Blødning fra mave-tarmkanal, pat. mindst 18 år, m. kompl. bidiag. (06MA06)).
- Andre indlæggelseskrævende blødninger (DRG: Blødning fra mave-tarmkanal, pat. mindst 18 år, u. kompl. Bidiag (06MA07)).
- Blødning, der kræver et ambulant besøg (DRG: Næseblødning (03MA03)).

Til administration af intravenøse lægemidler har ansøger anvendt Medicinrådets enhedsomkostninger, som indgår i udgiften til administration af immunglobuliner. Ligeledes indgår udgift til blodpladetransfusion baseret på DRG takst (16PR02 Transfusion af blod, øvrig), som ansøger også antager bliver anvendt i forbindelse med *rescue*-behandling for 20 % af patienterne.

For patienter, der oplever ICH er der inkluderet yderligere omkostninger i de tilfælde, hvor blødningen leder til invalidering, svarende til score 4 eller 5 på *Modified Rankin Scale* (MRS). Ansøger estimerer, at det er 8 % af patienterne med ICH, som oplever denne grad af invalidering efter eventet, på basis af et retrospektivt studie af spanske patienter udført af Rodriguez-Castro et al[9]. Til at estimere hospitalsomkostninger forbundet med denne grad af invalidering anvender ansøger et svensk registerstudie af Lekander et al., der undersøgte omkostninger som følge af en blodprop eller blødning i hjernen.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Som beskrevet i afsnit 4.1.2 anvender Medicinrådet kun Adelborg et al. til estimering af blødningsrisiko. Eftersom studiet ikke stratificerer på typer af blødninger, anvender Medicinrådet en gennemsnitsberegning af relevante DRG-takster til at estimere enhedsomkostning i tilfælde af blødning. Ligesom for estimeringen af udgifter til immunglobuliner estimeres det, at 94 % af blødningerne håndteres ambulant, mens de resterende 7 % kræver indlæggelse. Baseret på disse andele og fra DRG-takster, som Medicinrådet vurderer mest relevante, udregnes et vægtet gennemsnit for enhedsomkostningen anvendt til blødninger i modellen, se Tabel 6.

På samme vis som for immunglobuliner vurderer fagudvalget, at man i klinisk praksis ikke vil give blodpladetransfusion i forbindelse med *rescue*-behandling, men at dette kan forekomme i forbindelse med indlæggelseskrævede blødninger. Medicinrådet vurderer dog, at DRG-taksterne for blodpladetransfusion allerede er afspejlet i DRG-takst for intrakranielle og gastrointestinale blødninger, hvorfor udgiften til blodpladetransfusioner sættes til nul i Medicinrådets hovedanalyse.

For administrationsomkostninger i forbindelse med administration af intravenøse lægemidler anvender Medicinrådet DRG-taksten for et ambulant besøg (01MA98) i stedet for Medicinrådets enhedsomkostninger, som er anvendt i ansøgers analyse. Dette gøres, da ansøger ikke har taget højde for utensilier.

En yderligere implikation af kun at anvende studiet af Adelborg et al. er, at det ikke er muligt at estimere andelen, der oplever svær invalidering som følge af ICH, hvorfor denne omkostning ekskluderes fra modellen. Til trods for at en sådan invalidering

medfører meget høje omkostninger, har denne eksklusion minimal betydning for modellens resultat, da risikoen for dette event er ekstremt lav. Et dansk registerstudie fandt en 5-års risiko på 1,4 % for ICH hos ITP-patienter med blodpladetal > 30 *10^9 pr. liter[10], hvoraf det altså kun estimeres, at 8 % af disse patienter vil blive svært invalideret. Medicinrådet finder det derfor rimeligt ikke at tage højde for denne omkostning.

Tabel 6. Administrationsomkostninger til blødninger anvendt i Medicinrådets hovedanalyse

Event	Vægt	Omkostning	DRG-kode og beskrivelse
Blødning håndteret ambulant	93 %	3.618 DKK	1-dagsgruppe, pat. Mindt 7 år (01MA98)
Intrakraniel blødning	3,5 %	34.693 DKK	Hovedtraumer eksl. hjernerystelse (01MA11)
Gastrointestinal blødning	3,5 %	33.836 DKK	Blødning fra mave-tarmkanal, pat. mindst 18 år, m. kompl. bidiag. (06MA06)
Enhedsomkostning anvendt for administrationsomkostninger ifm. blødningsevent		**5.766 DKK**	

Medicinrådet benytter alternativt studiedata til at estimere blødningsrisiko samt andre DRG-takster til at estimere enhedsomkostning.

Monitoreringsomkostninger

Ansøger inkluderer monitoreringsomkostninger til kontrolbesøg samt blodprøvetagning og analyse. På basis af input fra en *key opinion leader* er frekvens af disse besøg på tværs af modellens stadie estimeret. Til at estimere omkostningen for disse er der taget udgangspunkt i Medicinrådets enhedsomkostninger, hvor det af ansøger antages, at konsultationen varetages af en overlæge.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger

Fagudvalget vurderer, at der er stor variation i, hvor meget patienterne monitoreres inden for de givne blodpladeintervaller, og bemærker, at der vil være hyppigere konsultationer ved opstart af behandling, men finder ikke de antagede frekvenser urimelige. Medicinrådet accepterer derfor de antagede frekvenser for monitoreringsbesøg. Det vurderes af fagudvalget, at blodprøvetagninger muligvis er en anelse overestimeret for patienter med blodpladetal < 30. Frekvensen accepteres dog af Medicinrådet, da det har lille betydning for det samlede resultat af den

sundhedsøkonomiske analyse. Ligesom for administrationsomkostninger anvender Medicinrådet DRG-taksten for ambulant besøg i stedet Medicinrådets enhedsomkostninger.

Tabel 7. Antal monitoreringsbesøg årligt fordelt på modellens respektive stadier

	Antal monitoreringsbesøg pr. år
Non-respons (< 10^9/L)	9,75
Partielt respons (30-50 *10^9 /L)	4,29
Respons (> 50*10^9 /L)	1,04

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger for bivirkninger, der blev observeret hos minimum 5 % af patienterne i en givet behandlingsarm i FIT-1 og FIT-2. Til at udregne omkostninger til behandlingen af bivirkningerne har ansøger anvendt DRG-takster for et udvalg af bivirkningerne. For de resterende bivirkninger har ansøger anvendt Medicinrådets enhedsomkostning for et ambulant besøg hos en ikke-ledende overlæge.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Medicinrådet accepterer metoden til at estimere bivirkningsfrekvenser. For de bivirkninger, hvor ansøger har anvendt enhedsomkostningen for en ikke-ledende overlæge, anvender Medicinrådet i stedet DRG-taksten for et ambulant besøg, så alle inkluderede bivirkningsomkostninger er baseret på DRG-takster. Bivirkningsfrekvenser og anvendte takster kan ses i Tabel 8.

Tabel 8. Rapporterede bivirkningsfrekvenser ved behandling med fostamatinib og *watch and rescue* samt enhedsomkostninger for bivirkningerne

	Fostamatinib [%]	*Watch and rescue* [%]	Enhedsomkostning [DKK]	Kilde
Diarré	29 %	7 %	3.176	16MA98: Ambulant besøg (DRG)
Hypertension	20 %	4 %	3.176	16MA98: Ambulant besøg (DRG)
Kvalme	19 %	4 %	3.176	16MA98: Ambulant besøg (DRG)

	Fostamatinib [%]	*Watch and rescue* [%]	Enhedsomkostning [DKK]	Kilde
Forhøjet alanintransaminase	9 %	0 %	3.176	16MA98: Ambulant besøg (DRG)
Forhøjet aspartattransaminase	8 %	0 %	3.176	16MA98: Ambulant besøg (DRG)
Svimmelhed	9 %	4 %	5,091	03MA02 Svimmelhed (DRG)
Epistaxis	15 %	5 %	3.176	16MA98: Ambulant besøg (DRG)
Infektion i øvre luftvej	8 %	1 %	51,542	04MA05 Infektioner og betændelse i luftveje, pat. mindst 65 år (DRG)
Urinvejsinfektion	3 %	0 %	3.176	16MA98: Ambulant besøg (DRG)
Abdominalsmerter	3 %	0 %	3.176	16MA98: Ambulant besøg (DRG)
Fatigue	6%	1%	3176	16MA98: Ambulant besøg (DRG)
Pyrexia	2 %	2 %	18,889	18MA04 Feber af ukendt årsag, pat. mindst 18 år, uden biopsi og/eller scopi (DRG)
Hovedpine	10 %	9 %	3.176	16MA98: Ambulant besøg (DRG)
Udslæt	7 %	1 %	3.176	16MA98: Ambulant besøg (DRG)

	Fostamatinib [%]	*Watch and rescue* [%]	Enhedsomkostning [DKK]	Kilde
Brystsmerter	4 %	1 %	3.176	16MA98: Ambulant besøg (DRG)
Anæmi	2 %	2 %	69,514	16MP06 Mangelanæmier (DRG)
Petekkier	2 %	2 %	3.176	16MA98: Ambulant besøg (DRG)

Medicinrådet ændrer omkostning anvendt for et udvalg af de inkluderede bivirkninger.

4.2.3 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrations- og monitoreringsbesøg på hospitalet og inkluderer patientens og pårørendes effektive tid på hospitalet, ventetid og transporttid. I de tilfælde, hvor en patient er blevet svært invalideret som følge af ICH, antages det, at patienten er ledsaget af en pårørende på hospitalet. Ansøger antager i modellen, at en patient – og eventuelt en pårørende bruger 4 timer på et ambulant besøg inkl. transport. Der anvendes en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 100 DKK pr. besøg, jf. Medicinrådets værdisætning af enhedsomkostninger.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet accepterer ansøgers estimerede patienttid. Dog indgår pårørendetid ikke i Medicinrådets hovedanalyse, da invalidering på baggrund af ICH ekskluderes fra modellen som beskrevet i 4.2.2. Omkostning pr. cyklus for modellens respektive stadier fremgår af Tabel 9.

Tabel 9. Estimerede patientomkostninger pr. cyklus for modellens stadier

	Omkostning pr. cyklus
Non-respons (<30 * 10^9/L)	1.433 DKK
Partielt respons (30-50 *10^9 /L)	545 DKK
Respons (> 50*10^9 /L)	205 DKK

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostninger.

4.2.4 Omkostninger i primærsektoren

Omkostninger i primærsektoren er inkluderet i ansøgers analyse i forbindelse med de patienter, der invalideres af ICH. Til at estimere omkostninger som følge af dette anvender ansøger det førnævnte svenske registerstudie, der estimerer omkostninger til egen læge, hjemmepleje, specialbolig m.m.

Medicinrådets vurdering af ansøgers antagelser vedr. kommunale omkostninger
Medicinrådet accepterer ansøgers antagelser vedr. omkostninger i primærsektoren. Dog indgår denne omkostning ikke i Medicinrådets hovedanalyse, da invalidering på baggrund af ICH ekskluderes fra modellen som beskrevet i 4.2.2.

Medicinrådet accepterer ansøgers tilgang vedr. omkostninger i primærsektoren.

4.3 Følsomhedsanalyser

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

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Følgende følsomhedsanalyser er udført:

Tabel 10. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Ændring af tidshorisont	Ændres fra 40 år til 20 år
Ændring af tidshorisont	Ændres fra 40 år til 50 år
Ændring af diskonteringsrate	Ændres fra 3,5 % årligt til 0 %
Ændring af diskonteringsrate	Ændres fra 3,5 % årligt til 5 %

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Medicinrådet vælger at præsentere egne følsomhedsanalyser, der belyser de usikkerheder i modellen, der findes mest centrale.

Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser.

4.4 Opsummering af ændringer fra ansøgers analyse til Medicinrådets hovedanalyse

Tabel 11. Forskellen mellem ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Varighed af respons uge 24+	Antagelse om intet tab af respons efter uge 24 (hvis dette blev opnået i uge 13-24)	Hovedanalyse inkluderer to scenarier. I første scenarie er tab af respons for uge 24+ ekstrapoleret på basis af gennemsnitligt tab af respons observeret fra uge 5-24 i FIT-1 og FIT-2. I det andet scenarie antages intet tab af respons (hvis dette blev opnået i uge 13-24).
Andel af *non-responders* ved uge 4, hvor opjustering fra 100 til 150 mg fostamatinib resulterer i respons målt ved uge 12, som bliver nedjusteret til 100 mg efter 12 måneders behandling	100 %	20 %
Data anvendt til estimering af risiko for blødning i modellens stadier	Gernsheimer et al. Allen et al. Adelborg et al.	Adelborg et al.
Omkostninger til immunglobuliner	Anvendes i forbindelse med *rescue*-behandling	Anvendes i forbindelse med blødninger
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Patientomkostninger Omkostninger i primærsektoren	Lægemiddelomkostninger Hospitalsomkostninger Patientomkostninger

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådet præsenterer to scenarier for sammenligningen af fostamatinib over for *watch and rescue*. I scenarie 1 er varighed af respons efter uge 24 hos de patienter, der opnåede respons i uge 13-24, estimeret ud fra det gennemsnitlige tab af respons observeret fra uge 5-24 for den samlede patientpopulation i FIT-1-2.

I scenarie 2 er det antaget, at patienter ikke taber deres respons efter uge 24, hvis dette bliver opnået i uge 13-24 (svarende til at antage en risiko for relaps på 0 %). Resultatet af Medicinrådets hovedanalyse er således præsenteret som et spænd, som de inkrementelle omkostninger ved anvendelse af fostamatinib forventes at ligge inden for. Baggrunden for valget om at præsentere Medicinrådets hovedanalyse i to scenarier er beskrevet i yderligere detaljer i afsnit 4.1.2.

I scenarie 1 estimeres det, at anvendelse af fostamatinib vil resultere i inkrementelle omkostninger pr. patient på ca. [redacted] DKK, når der sammenlignes med *watch and rescue*-behandling. Er analysen udført med AIP, bliver den inkrementelle omkostning ca. 229.000 DKK. Resultaterne af scenarie 1 fremgår af Tabel 12.

I scenarie 2 estimeres det, at anvendelse af fostamatinib vil resultere i inkrementelle omkostninger pr. patient på ca. [redacted] DKK, når der sammenlignes med *watch and rescue*-behandling. Er analysen udført med AIP, bliver den inkrementelle omkostning ca. 1,9 mio. DKK. Resultaterne af scenarie 1 fremgår af Tabel 13.

Tabel 12. Medicinrådets hovedanalyse i scenarie 1, hvor respons efter uge 24 estimeres ud fra gennemsnitligt tab af respons i FIT-1-2, ved sammenligning med *watch and rescue*

	Fostamatinib (DKK)	*Watch and rescue* (DKK)	Inkrementelle omkostninger (DKK)
Lægemiddelomkostninger til fostamatinib	[redacted]	[redacted]	[redacted]
Omkostninger til *rescue*-behandling	[redacted]	[redacted]	[redacted]
Omkostninger til forebyggende behandling ved operationer	[redacted]	[redacted]	[redacted]
Omkostninger til blødninger og monitorering	[redacted]	[redacted]	[redacted]
Bivirkningsomkostninger	10.460	7.431	3.029
Patientomkostninger	155.715	159.892	-4.177
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 13. Medicinrådets hovedanalyse i scenarie 2, hvor der ikke antages tab af respons efter uge 24, hvis dette blev opnået i uge 13-24

	Fostamatinib (DKK)	*Watch and rescue* (DKK)	Inkrementelle omkostninger (DKK)
Lægemiddelomkostninger til fostamatinib	[redacted]	[redacted]	[redacted]

	Fostamatinib (DKK)	*Watch and rescue* (DKK)	Inkrementelle omkostninger (DKK)
Omkostninger til *rescue*-behandling	[redacted]	[redacted]	[redacted]
Omkostninger til forebyggende behandling ved operationer	[redacted]	[redacted]	[redacted]
Omkostninger til blødninger og monitorering	[redacted]	[redacted]	[redacted]
Bivirkningsomkostninger	10.460	7.431	3.029
Patientomkostninger	116.214	159.892	-43.678
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Medicinrådet præsenterer en række følsomhedsanalyser af de mest centrale parametre, der indgår i den sundhedsøkonomiske analyse, for at belyse deres indvirkning på resultatet. De udførte følsomhedsanalyser bliver præsenteret for både scenarie 1 og scenarie 2.

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 14.

Tabel 14. Resultatet af Medicinrådets følsomhedsanalyser sammenlignet hovedanalysens Scenarie 1, DKK

Scenarie	Baggrund	Inkrementelle omkostninger
Resultatet af scenarie 1		[redacted]
Baselinealder ændres fra 60 år til 40 år (samtidig med at tidshorisont ændres til 60 år)	Stor variation i alder ved diagnosticering af ITP	[redacted]
Dødelighed på tværs af modellens stadier sættes lig dødelighed for den generelle befolkning	Usikkerhed vedrørende grad af øget dødelighed blandt ITP- patienter	[redacted]
Andel i behandling med 150 mg fostamatinib, der nedjusteres efter 12 måneders behandling, ændres fra 20 % til 100 %	Usikkerhed om faktisk andel, hvor dette vil forekomme i tilfælde af anbefaling	[redacted]

Tabel 15. Resultatet af Medicinrådets følsomhedsanalyser sammenlignet hovedanalysens scenarie 2, DKK

Scenarie	Baggrund	Inkrementelle omkostninger
Resultatet af scenarie 2		[redacted]
Baselinealder ændres fra 60 år til 40 år (samtidig med at tidshorisont ændres til 60 år)	Stor variation i alder ved diagnosticering af ITP	[redacted]
Dødelighed på tværs af modellens stadier sættes lig dødelighed for den generelle befolkning	Usikkerhed vedrørende grad af øget dødelighed blandt ITP- patienter	[redacted]
Andel i behandling med 150 mg fostamatinib, der nedjusteres efter 12 måneders behandling, ændres fra 20 % til 100 %	Usikkerhed om faktisk andel, hvor dette vil forekomme i tilfælde af anbefaling	[redacted]

6. Budgetkonsekvenser

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

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

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

6.1 Estimat af patientantal og markedsandel

Ansøger har antaget, at der vil være ca. 15 patienter i år 1 og 35 patienter i år 5, der ved anbefaling vil blive behandlet med fostamatinib.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Medicinrådet accepterer ansøgers estimat af patientantal, da det er i overensstemmelse med fagudvalgets estimat angivet i Medicinrådets protokol. Patientantal fremgår af Tabel 16.

Tabel 16. Medicinrådets estimat af antal nye patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Fostamatinib	15	5	5	5	5
Watch and rescue	0	0	0	0	0
			Anbefales ikke		
Fostamatinib	0	0	0	0	0
Watch and rescue	15	5	5	5	5

Medicinrådet accepterer ansøgers antagelser om patientantal.

6.2 Medicinrådets budgetkonsekvensanalyse

I scenarie 1 estimerer Medicinrådet, at anvendelse af fostamatinib vil resultere i budgetkonsekvenser på ca. [redacted]. DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 17. Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 0,03 mio. DKK i år 5.

I scenarie 2 estimerer Medicinrådet, at anvendelse af fostamatinib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 18. Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 2,83 mio. DKK i år 5.

Tabel 17. Medicinrådets analyse af totale budgetkonsekvenser i scenarie 1, mio. DKK, ikke-diskonterede tal*

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

*Som følge af den estimerede gennemsnitlige behandlingslængde er ca. 8 måneder i Scenarie 1 er det her antaget at patienter frafalder behandling i løbet af det første års behandling.

Tabel 18. Medicinrådets analyse af totale budgetkonsekvenser i scenarie 2, mio. DKK, ikke-diskonterede tal

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

7. Diskussion

Resultatet af Medicinrådets hovedanalyse viser, at de inkrementelle omkostninger ved anvendelse af fostamatinib næsten udelukkende er drevet af omkostningerne til lægemidlet. Da opfølgningen i studierne, der ligger til grund for analysen, kun havde 24 ugers opfølgning, og behandlingen potentielt er livslang, er der stor usikkerhed om den gennemsnitlige behandlingslængde. Anvendelsen af FIT-1-2 vanskeliggøres yderligere af det høje frafald af patienter (se Medicinrådets vurderingsrapport for yderligere information). Derfor valgte Medicinrådet at præsentere to scenarier i sin hovedanalyse, hvor antagelser om varighed af respons er forskellige og resulterer i meget forskellige resultater for de inkrementelle omkostninger.

I scenarie 1 var de inkrementelle omkostninger ca. [redacted]. Den lave inkrementelle omkostning ved anvendelse af fostamatinib i dette scenarie er et resultat af antagelsen om varighed af respons efter studieopfølgningstiden, som leder til en meget kort gennemsnitlig behandlingsvarighed i modellen (ca. 8 måneder). I scenarie 2 var de inkrementelle omkostninger ca. [redacted] DKK, da antagelsen vedrørende varighed af respons ledte til en længere behandlingsvarighed i modellen (ca. 11 år i gennemsnit).

Det bør bemærkes, at hverken scenarie 1 eller scenarie 2 er plausible scenarier for den faktiske behandlingslængde. Scenarie 1 resulterer i en gennemsnitlig behandlingslængde, der er kortere, end hvad extension-studiet FIT-3 har vist (se afsnit 4.1.2 for beskrivelse af, hvorfor FIT-3 ikke kan anvendes til estimering af behandlingsvarighed). Ligeledes er antagelsen i scenarie 2, om at ingen patienter taber respons efter uge 24, hvis respons blev opnået i uge 13-24, heller ikke plausibel.

Selvom det ikke er muligt at estimere den gennemsnitlige behandlingslængde, fremgår det af FIT-3, at der er betydelig variation i varighed af respons, siden median responstid var 6,7 måneder, mens 44 % af patienterne havde en responsvarighed på > 28 måneder. Den betydelige variation i varighed af respons og implikationen for de inkrementelle omkostninger understreger dermed vigtigheden af, at patienter seponeres ved manglende respons, hvis fostamatinib anvendes.

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	20. december 2022	Godkendt af Medicinrådet.

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 40 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 19.

Tabel 19. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Fostamatinib (DKK)	*Watch and rescue* (DKK)	Inkrementelle omkostninger (DKK)
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

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

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af fostamatinib vil resultere i budgetkonsekvenser på ca. [redacted]. DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 20.

Tabel 20. 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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29.11.2022

MGK/ECH

Forhandlingsnotat

Dato for behandling i Medicinrådet	14.12.2022
Leverandør	Instituto Grifols S.A.
Lægemiddel	Tavlesse (fostamatinib)
Ansøgt indikation	Behandling af kronisk immun trombocytopeni (ITP)

Forhandlingsresultat

Amgros har opnået følgende pris på Tavlesse (fostamatinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP	Nuværende SAIP	Forhandlet SAIP	Rabatprocent ift. AIP
Tavlesse (fostamatinib)	100 mg	60 stk.	26.568	[redacted]	[redacted]	[redacted]
Tavlesse (fostamatinib)	150 mg	60 stk.	39.852	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

[redacted]

Tabel 2: Årlige lægemiddelomkostninger for Tavlesse (fostamatinib)

Lægemiddel	Behandlingsår	Dosis	Pakningsstørrelse	Pakningspris SAIP	Antal pakninger/år	Årlige lægemiddelomkostninger SAIP
Tavlesse (fostamatinib)	Første års behandling inkl. startdosis	100 mg 2 gange dagligt	[redacted]	[redacted]	~ 1	[redacted]
		Efter 4 ugers behandling 150 mg 2 gange dagligt	[redacted]	[redacted]	~ 11	
Tavlesse (fostamatinib)	Vedligeholdelsesår	150 mg 2 gange dagligt	[redacted]	[redacted]	12	[redacted]

Status fra andre lande

Norge: Anbefalet [1]
Sverige: [redacted]
England: Anbefalet [2]

Konklusion

Amgros vurderer ikke det er muligt at opnå en bedre pris på nuværende tidspunkt.

[1] Fostamatinib (Tavlesse) (nyemetoder.no)
[2] 1 Recommendations | Fostamatinib for treating refractory chronic immune thrombocytopenia | Guidance | NICE

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Attn: Danish Medicines Council

To whom it may concern,

We would like to thank the Danish Medicines Council for the opportunity to review and comment on the clinical and health economic reports for fostamatinib in the treatment of chronic Immune Thrombocytopenia (ITP).

We would like to clarify the following aspects related to the content of the assessment reports:

1. ***Duration of treatment with fostamatinib and evaluation of response prior to the decision to discontinue treatment at 8 weeks, and it should be 12 weeks***

The Danish Medicines Council committee in the economic report, states that: *"Fagudvalget vurderer, at man i praksis muligvis vil fortsætte længere end 12 uger, før man seponerer behandling hos de patienter, der ikke har opnået et respons". Furthermore, w*e would like to point out that according to the European Medicines Agency (EMA) Summary of Product Characteristics for fostamatinib[1]: "*Treatment with fostamatinib should be discontinued after 12 weeks of fostamatinib therapy if the platelet count does not increase to a level sufficient to avoid clinically important bleeding.*" This statement is supported by evidence from the FIT-1 and FIT-2 trials, in which a number of patients who responded to fostamatinib, only showed a first response to therapy (defined as a first platelet count ≥50 000/µL) between weeks 8 and 12:

- Among patients who had a stable response[1] to fostamatinib within trial duration (n=18), 1 had a first platelet response between weeks 8 and 10, and 2 had a first platelet response between weeks 10 and 12.
- Among patients who had an overall response[2] to fostamatinib within trial duration (n=43), 4 had a first platelet response between weeks 8 and 10, and 3 had a first platelet response between weeks 10 and 12.

It should be noted that the primary efficacy endpoint (stable response) in the FIT program (as well as the overall response endpoint), is much more restrictive than that reflected in the regulatory recommendations in the EMA guideline (2014)[2] which recommends using a primary endpoint of response of 30,000 platelets/µL (together with at least doubling of the baseline platelet count and absence of bleeding).

In addition, the EMA recommends that platelet counts should be confirmed on at least two separate occasions (at least 7 days apart)[2] while in FIT studies, this was required in 4 out of 6 visits within 10 weeks, to consider that the patient had responded to treatment.

[1] Stable response was defined as platelets ≥50 000/µL at ≥4 of 6 biweekly visits, weeks 14-24, without rescue therapy
[2] Overall platelet response was defined as ≥1 platelet count ≥50 000/µL within the first 12 weeks on treatment

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The stable response criteria used in the FIT program is also more restrictive than what is recommended in the ASH 2019 guidelines (i.e. stable response: platelet count ≥ 30,000 /µL and at least doubling the basal count at 6 months)[3], and in the ITP International Working Group recommendations (i.e. maintenance of a target platelet level > 20,000-30,000 /µL at least for symptomatic patients).[4]

2. Evidence available on the long term use of fostamatinib

We would like to clarify that the information reported in the documents regarding the long term use of fostamatinib in the FIT-3 trial[5] corresponds to an interim data analysis, and has been more recently updated in a new publication.[6]

In this publication the authors reported a durable treatment efficacy up to 5 years and a very low incidence of thromboembolic events (0.7%, or 0.44 events/ 100,000 patient-years) in patients receiving long term fostamatinib treatment.

Stockholm November 30, 2022

Sincerely,

Anki Book
Director Biopharma
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Medicinrådet

Medicinrådets vurdering vedrørende fostamatinib 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	23. november 2022
Dokumentnummer	158412
Versionsnummer	1.0

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1. Medicinrådets konklusion

Medicinrådet vurderer, at værdien af fostamatinib til behandling af patienter med svær behandlingsrefraktær ITP ikke kan kategoriseres. Medicinrådet bemærker, at en lille gruppe patienter ser ud til at respondere på behandlingen. For denne gruppe patienter ser fostamatinib ud til at have et hurtigt indsættende respons.

Fostamatinibs anvendelsesområde er 3. linjebehandling, hvor værdien af de nuværende medicinske behandlingsmuligheder mest hviler på langvarig klinisk erfaring. Sammenlignet hermed er dokumentationen for fostamatinib mere solid, men direkte sammenligninger af disse lægemidler kan ikke forventes at blive udført. Medicinrådets vurdering er, at fostamatinib, på linje med de nuværende behandlinger i 3. linje, kan være effektivt for en lille gruppe patienter. Det drejer sig om patienter, der har været behandlet med steroid, rituximab og TPO-RA, og som ikke længere har dokumenterbar effekt. Der er tale om kroniske ITP-patienter med vedvarende behandlingsbehov pga. aktiv blødning eller uacceptabel blødningsrisiko og et meget lavt trombocyttal, eller patienter, der skal have blodfortyndende medicin pga. atrieflimren, og som derfor skal have et højere trombocyttal end det normalt acceptable. Medicinrådet bemærker, at patienterne skal have respons i form af en klinisk relevant stigning af trombocyttal indenfor de første 8 uger af behandlingen. Hvis det ikke opnås, bør behandlingen seponeres.

Vurderingerne er baseret på evidens af meget lav kvalitet.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 24. november 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

AE:	*Adverse Event*
Anti-D:	Anti-D immunglobulin
CI:	Konfidensinterval
CsA:	Ciclosporin
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
ITP:	Immuntrombocytopeni
ITT:	*Intention to treat*
IV:	Intravenøs
IVIg:	Intravenøs immunglobulin
MMF:	Mycophenolate mofetil
MKRF:	Mindste klinisk relevante forskel
OR:	*Odds ratio*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
SAE:	*Serious adverse event*
SmPC:	Produktresumé fra EMA
TPO-RA:	Trombopoietin-receptoragonister

3. Introduktion

Formålet med Medicinrådets vurdering af fostamatinib 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 Instituto Grifols S.A. Medicinrådet modtog ansøgningen den 21. marts 2022.

De kliniske spørgsmål er:

1) *Hvilken værdi har fostamatinib sammenlignet med placebo for patienter med primær kronisk behandlingsrefraktær ITP?*
2) *Hvilken værdi har fostamatinib sammenlignet med immunsuppressive behandlinger såsom dapson, danazol, mycophenolate mofetil, azathioprin eller ciclosporin for patienter med primær kronisk ITP?*

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 stilles først, 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.

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].

Patienternes symptomer er meget varierende fra ingen til betydelig blødning og 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 indlæggelse 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 personer, 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 derfor 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, hvilket svarer til, at den forventede middellevetid sænkes med knap 4 år [5]. 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.

3.2 Nuværende behandling hos voksne

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

Behandling af kronisk ITP er individualiseret og sker bl.a. på baggrund af overvejelser om behovet for hurtigt indsættende effekt, samt en vurdering af effekt og bivirkninger ved tidligere ITP-behandlinger, alder, blødningsrisiko og den forventede behandlingsvarighed, idet langvarig immunsuppressiv behandling kan være kontraindiceret på grund af risiko for infektioner og kræft [3].

Den nuværende behandling består af tre linjer. I hver linje er der flere behandlingsmuligheder, som kan bruges sekventielt (Tabel 1). Behandlinger i 2. linje har generelt en effekt, der er mere solidt dokumenteret end behandlinger i 3. linje.

Tabel 1. Lægemidler i de nuværende behandlingslinjer

		Responsrate	Tid til initialt respons
Primær behandling			
1. linje	Prednisolon	Initialt: 70-80 % Varigt: Usikkert, ca. 10-25 %	4 – 14 dage
	Dexamethason	Initialt: Op til 90 % Varigt: Som prednisolon	2 – 14 dage
	IVIG	Initialt: Op til 80 % Varigt: Overgang til persisterende/kronisk ITP	1 – 3 dage
Behandling af persisterende og kronisk ITP			
2. linje	Rituximab	Initialt: 60 % Varigt: 15-20 % (3-5 år)	1 -8 uger
	Avatrombopag	Initialt: 66 % Varigt: Kun så længe beh. foregår	3 – 5 dage
	Romiplostim	Initialt: 80-90 % Varigt: Kun så længe beh. foregår	1 – 2 uger
	Eltrombopag	Initialt: 70-80 % Varigt: Kun så længe beh. foregår	1 – 2 uger
	Splenektomi[a]	Initialt: 80 % Varigt: Omkring 65 %	1 – 56 dage
3. linje[b]	Dapson	Initialt: 50 %	3 uger
	Danazol	Initialt: 40-70 %	2 – 12 uger
	Mycophenolatmorfetil	Initialt: 40-80 %	2 – 6 uger
	Azathioprin	Initialt: 40-60 %	4 – 12 uger
	Ciclosporin-A	Initialt: Usikkert, op til 50-80 %	3 – 4 uger

	Responsrate	Tid til initialt respons
Hydroxychloroquin	Initialt: Op til 60 %	
Cyklofosfamid		2 – 4 uger

Informationer fra [6] samt fagudvalgets vurdering. A) Fagudvalget tager forbehold for, om det citerede tal kan genfindes i den population, som i dag tilbydes indgrebet. B) For behandlingerne i 3. linje er studierne små, så responsrater er anekdotiske.

1. linjebehandling af nydiagnosticerede patienter består af glukokortikoider oftest i 2-3 måneder evt. i kombination med rituximab i 4 uger, som anvendes off-label. Hvis patienten kan trappes ned til 5 mg prednisolon, kan behandlingen fortsætte hos udvalgte patienter, men ellers skifter man til en af behandlingsmulighederne i 2. linje efter 6 – 8 uger.

Responset vurderes ud fra målinger af blodpladetal og en vurdering af den rapporterede og observerede blødningstendens. Har patienten haft et tilfredsstillende respons på den første behandling, vil dette oftest gentages ved tilbagevendende behandlingsbehov, indtil responset ikke længere er tilfredsstillende, eller tilbagefaldene er hurtige eller mange. Behandlingsbehovet er tilbagevendende hos 60-75 % af patienterne. Tiltagende sygdomsaktivitet viser sig ved blødning i slimhinderne og/eller faldende trombocyttal til udgangspunktet før behandling eller lavere.

Behandlingsmuligheder i 2. linje inkluderer rituximab og trombopoietin-receptoragonister (TPO-RA), der omfatter lægemidlerne eltrombopag, avatrombopag og romiplostim [7]. Har patienten ikke effekt af en type TPO-RA, udelukker det ikke effekt af en anden TPO-RA [8–10]. Typisk afprøves anden TPO-RA-behandling ved svigt af den første. Responsrater afhænger af, hvor godt patienterne tidligere har responderet på behandling, men anvendt som 2. eller 3. linje opnås ca. 66 % respons, hvoraf over halvdelen er vedvarende under pågående behandling (jf. skemaet ovenfor).

Hvis behandlingsmulighederne i 2. linje ikke har en effekt, kan behandlingsmulighederne i 3. linje anvendes (Tabel 1) [3]. Ingen af disse behandlinger har indikation til ITP og anvendes derfor off-label. Evidensen for behandlingerne i 3. linje er mangelfuld, men den kliniske erfaring er lang, og nogle patienter har god effekt af disse lægemidler.

Flere af behandlingerne i både 2. og 3. linje er længerevarende (ofte flere år). TPO-RA'er virker hurtigt (typisk indenfor uger), mens de øvrige behandlinger har langsomt indsættende effekt (ofte uger til måneder).

Behandlingsmålet ved ITP er altid individuelt. Højeste prioritet er frihed for blødninger og frihed for bivirkninger af behandling. En reduktion af kontrolbehov og en stabilisering af trombocyttal på et mere sikkert niveau er også værdifuldt for patienterne.

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 ikke-medicinsk behandlingsmulighed er at fjerne milten (splenektomi). Tidligere har splenektomi været en almindelig anvendt behandling til kronisk ITP, men splenektomi anvendes sjældnere i dag og aldrig til børn. Patienter er mindre tilbøjelige til at acceptere et operativt indgreb. Ud over de umiddelbare gener og risici pådrager patienterne sig en vedvarede risiko for alvorlige infektioner, herunder blodforgiftning med pneumokokker, hvilket nødvendiggør vaccinationer og skærpet opmærksomhed ved feber.

I akutte situationer, ved behov for hurtigt indsættende effekt uanset underliggende behandling, kan immunglobuliner eller transfusion med blodplader anvendes[3]. Effekten af behandlingerne er hurtigt indsættende (indenfor timer), men 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 blive monitoreret oftere.

3.3 Fostamatinib

Fostamatinib er en milt-tyrosinkinase (SYK)-inhibitor, der modvirker nedbrydelsen af blodplader gennem den aktive metabolit, R406. R406 reducerer den antistof-medierede destruktion af trombocytter ved at hæmme signaleringen hos B-cellereceptorer og Fc-aktiverende receptorer.

Fostamatinib blev i december 2020 godkendt af det europæiske lægemiddelagentur (EMA) til kronisk immuntrombocytopeni hos voksne patienter, der er refraktære over for andre behandlinger.

ITP er den eneste indikation, som fostamatinib er godkendt til. Lægemidlet er dog tidligere blevet undersøgt ved patienter med leddegigt, hvilket bidrager med yderligere data vedr. sikkerhed, som EMA anvender i deres gennemgang af sikkerhed for lægemidlet [11].

Betegnelsen refraktær anvendes i dag uspecifikt om patienter, der ikke responderer tilfredsstillende over for 2. linjebehandlinger.

Fagudvalget vurderer, at fostamatinib bør anvendes efter behandlinger med glukokortikoider, rituximab og TPO-RA'er på linje med de øvrige 3. linjebehandlinger. De fleste af patienterne vil være tilstrækkeligt hjulpet af 1. og 2. linjebehandlingerne, men fagudvalget vurderer, at der er ca. 10-20 patienter, som ikke vil have gavn af disse, og dermed være kandidater til behandling med fostamatinib. Derudover vurderer fagudvalget, at der vil være 1-5 nye patienter om året til behandlingen.

Fostamatinib indtages oralt som tabletter à 100 mg eller 150 mg to gange dagligt. Lægemidlet doseres, så den laveste dosis for at opnå et trombocyttal på > 50 x 10^9 pr.

liter anvendes. Den anbefalede dosis er 100 mg to gange dagligt. Dosis kan efter 4 uger øges til 150 mg baseret på trombocyttal og tolerabilitet. Dosis må ikke overskride 300 mg dagligt, og patienter med nyreinsufficiens bør ikke få foretaget dosisjusteringer.

Ifølge EPAR'en skal behandlingen seponeres efter 12 uger, hvis trombocyttallet ikke er steget til et tilstrækkeligt niveau [12]. Fagudvalget vurderer dog, at seponering kan foretages allerede ved 8 uger, hvis trombocyttallet ikke er begyndt at stige. Behandling med fostamatinib forventes at fortsætte, så længe der er tilstrækkelig effekt. Vurdering af effekt beror på en individuel vurdering og afhænger af patienternes behov.

Klinisk hæmatologi, blodtryk og leverfunktion overvåges regelmæssigt i løbet af behandling med fostamatinib. Fostamatinib bør ikke anvendes hos patienter med svært nedsat leverfunktion.

4. Metode

Medicinrådets protokol for vurdering vedrørende fostamatinib 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.

For klinisk spørgsmål 1 baserer ansøgningen sig på to artikler, der også er angivet i protokollen; FIT 1 og FIT 2. Derudover har ansøger også inkluderet yderligere ét studie, FIT 3, til besvarelse af klinisk spørgsmål 1 (se Bilag 1: Oversigt over studier).

Fagudvalget har yderligere konsulteret EMAs produktresumé (SmPC) [13] og *assessment report* (EPAR) [11] for fostamatinib.

FIT1 og FIT2: har begge identiske studiedesigns. De er randomiserede, dobbeltblindede, placebokontrollede studier, som sammenligner effekt og sikkerhed af fostamatinib med placebo. Forskellen mellem studierne er tidspunktet for udførelse, samt hvilke lande studierne foregik i. FIT1 inkluderede patienter fra juli 2014 til april 2015 fra 35 centre i Nordamerika, Australien og Europa. FIT2 inkluderede patienter fra januar 2015 til august 2016 fra 23 centre i Europa.

For at blive inkluderet i studierne skulle patienterne have haft ITP i ≥ 3 måneder samt tidligere være behandlet for deres sygdom med mindst ét lægemiddel. Patienternes gennemsnitlige blodpladetal skulle være < 30 x 10^9/L baseret på tre målinger inden for tre måneder op til studiestart.

Patienter blev randomiseret i en ratio 2:1 til enten fostamatinib eller placebo i 24 uger. Tilsammen modtog 101 patienter fostamatinib versus 49, som modtog placebo i FIT1 og FIT2. Randomiseringen blev stratificeret på baggrund af tidligere splenektomi, sværhedsgrad af ITP (dvs. blodpladetal < 15 x 10^9/L eller ≥ 15 x 10^9/L). Det var tilladt at modtage anden behandling (enten glukokortikoider < 20 mg/dag, azathioprin eller danazol) sammen med enten fostamatinib eller placebo, derudover var *rescue*-behandling også tilladt efter behov (øget dosis af samtidig ITP-behandling, IVIg, IV Anti-D, steroider, blodtransfusion).

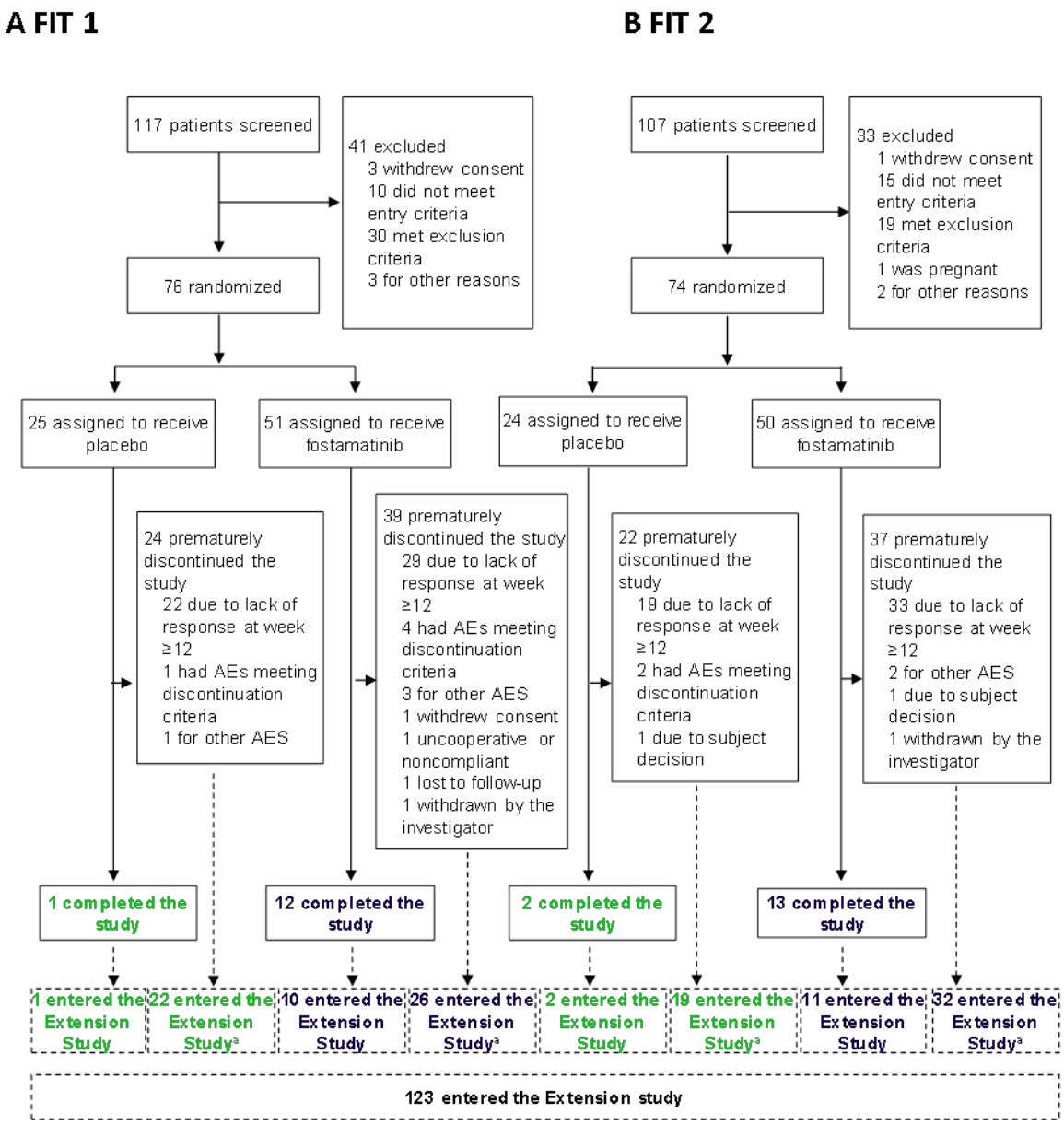
Startdosis for fostamatinib var 100 mg to gange dagligt, og det var tilladt at dosisjustere til 150 mg to gange dagligt efter uge 4. Dette blev doseringen hos 86 % af patienterne. Patienterne kom til monitoreringsbesøg hver 2. uge igennem den 24 ugers behandlingsperiode.

Det primære effektmål var stabilt blodpladerespons ved uge 24 (defineret som et blodpladetal ≥ 50 x 10^9/L i mindst fire ud af de seks klinikbesøg, som forekom i uge 14-24).

Behandlingsophør: Generelt gælder det for både FIT1 og FIT2, at der var mange, som ophørte behandlingen. Andelen, der ophørte, ses af Tabel 2. De fleste patienter ophørte behandlingen inden for de første 12 uger. Patienter, som ved uge 12 havde utilstrækkeligt respons, kunne overgå til opfølgningsstudiet FIT3. Da både patienter og læger var blindede i FIT1 og FIT2, vurderer fagudvalget, at den del af de patienter, der ikke havde respons på fostamatinib, kan være stoppet efter 12 uger, i håb om at de var i placebo-armen og efterfølgende kunne prøve fostamatinib i FIT3.

Tabel 2. Andel, som ophørte i behandling med enten fostamatinib eller placebo i FIT1 og FIT2. [11]

	FIT1		FIT2	
	Fostamatinib	**Placebo**	**Fostamatinib**	**Placebo**
Totalt antal (n/N)	**39/51 (76 %)**	**24/25 (96 %)**	**37/50 (74 %)**	**22/24 (92 %)**
Utilstrækkeligt respons	28/39	22/24	33/37	19/22
Uønskede hændelse	7/39	2/24	2/37	2/22
Eget valg	1/39	0	1/37	1/22
Andre årsager	3/39	0	1/37	0



Figur 1. Oversigt over FIT1-, FIT2- og FIT3-studierne

a) Patienter, der går ind i forlængelsesundersøgelsen på grund af manglende respons i uge ≥ 12. Grøn) Patienter, der går ind i forlængelsesundersøgelsen og blev behandlet med placebo i de randomiserede forsøg. Blå) Patienter, der deltager i forlængelsesundersøgelsen og blev behandlet med fostamatinib i de randomiserede forsøg .

FIT3: Er et ublindet opfølgningsstudie af FIT1 og FIT2. Patienter, som havde afsluttet 24 ugers behandling i disse to studier, eller patienter, som ikke responderede på deres behandling efter 12 uger, måtte deltage i studiet. Patienter, som oprindeligt var randomiseret til placebo i enten FIT1 eller FIT2, krydsede over til behandling med fostamatinib i FIT3. Studiet inkluderede i alt 123 patienter, heraf havde 44 patienter tidligere modtaget placebo (se Figur 1).

Median behandlingsvarighed med fostamatinib var 8,9 måneder (spredning 1,5 – 41,3) ved interimanalysen i marts 2018. På det tidspunkt var 42/123 patienter (34 %) fortsat i behandling med fostamatinib. Årsager til ophør skyldes manglende blodpladerespons og uønskede hændelser [14].

Af Tabel 3 ses baselinekarakteristika for hhv. FIT1 og FIT2.

Tabel 3. Baselinekarakteristika

	FIT1 (n=76)		FIT2 (n=74)		Samlet	
	Fostamatinib (n=51)	Placebo (n=25)	Fostamatinib (n=50)	Placebo (n=24)	Fostamatinib (n=101)	Placebo (n=49)
Alder, median (min-max), år	57 (20-88)	57 (26-77)	50 (21-82)	50 (20-78)	54 (20-88)	53 (20-78)
Køn, n (%)						
Kvinde	30 (59)	17 (68)	31 (62)	13 (54)	61 (60)	30 (61)
Mand	21 (41)	8 (32)	19 (38)	11 (46)	40 (40)	19 (39)
Etnicitet, n (%)						
Kaukasisk	44 (86)	21 (84)	50 (100)	24 (100)	94 (93)	45 (92)
Asiatisk	3 (6)	2 (8)	0	0	3 (3)	2 (4)
Afroamerikansk	2 (4)	2 (8)	0	0	2 (2)	2 (4)
Andre	2 (4)	0	0	0	2 (2)	0
Levested, n (%)						
Nordamerika	17 (33)	8 (32)	0	0	17 (17)	8 (16)
Europa	25 (49)	13 (52)	50 (100)	24 (100)	75 (74)	37 (76)
Australien	9 (18)	4 (16)	0	0	9 (9)	4 (8)
ITP-klassificering, n (%)						
Persisterende	3 (6)	3 (12)	3 (6)	1 (4)	6 (6)	4 (8)
Kronisk	48 (94)	22 (88)	47 (94)	23 (96)	95 (94)	45 (92)

	FIT1 (n=76)		FIT2 (n=74)		Samlet	
Varighed af ITP, median (min-max), år	7,5 (0,6–53,0)	5,5 (0,4-45,0)	8,8 (0,3-50,2)	10,8 (0,9-29,1)	8,7 (0,3-53)	7,8 (0,4-45)
Varighed af ITP i ≥ 3 år, n (%)	38 (75)	17 (68)	38 (76)	18 (75)	76 (75)	35 (71)
Tidligere behandlinger for ITP, median (min-max)	3,0 (1-9)	5,0 (1-10)	3,0 (1-13)	3,0 (1-10)	3,0 (1-13)	3,0 (1-10)
Type, tidligere behandlinger, n (%)						
Kortikosteroider	46 (90)	25 (100)	48 (96)	22 (92)	94 (93)	47 (96)
IVIg eller IV Anti-D	33 (65)	17 (68)	19 (38)	10 (42)	52 (51)	27 (55)
TPO-RA	27 (53)	15 (60)	20 (40)	10 (42)	47 (47)	25 (51)
Immunosuppressiva	22 (43)	12 (48)	22 (44)	10 (42)	44 (44)	22 (45)
Splenektomi	20 (39)	10 (40)	14 (28)	9 (38)	34 (34)	19 (39)
Rituximab	26 (51)	11 (44)	8 (16)	3 (13)	34 (34)	14 (29)
Danazol	7 (14)	4 (16)	13 (26)	5 (21)	20 (20)	9 (18)
Kemoterapi	4 (8)	2 (8)	5 (10)	4 (17)	9 (9)	6 (12)
Andre (Dapsone)	10 (20)	3 (12)	0	0	10 (10)	3 (6)
Baseline blodpladetal, gennemsnit, /µL (min-max)	16,202 (1000-51,000)	15,844 (1000-48,000)	15,900 (1000-33,000)	23,958 (1000-156,000)	16,052 (1000-51,000)	19,818 (1000-156,000)
Antal med baseline blodpladetal < 15,000 /µL, n (%)	25 (49)	12 (48)	22 (44)	9 (38)	47 (47)	21 (43)

Forkortelser: ITP = immuntrombocytopeni; TPO-RA = trombopoietin receptoragonist; IVIg = intravenøs immunoglobulin; IV = intravenøs; Anti-D = Anti-D-immunoglobulin.

Inklusionskriterierne i FIT-studierne afspejler ikke den population, man ville behandle med fostamatinib i Danmark, idet der kun kræves én tidligere behandling og varighed af ITP ned til 3 måneder. I Danmark vil man i overensstemmelse med indikationen afprøve fostamatinib ved kronisk ITP (min. 12 måneders varighed) og efter mindst 3 tidligere behandlinger.

Fagudvalget vurderer, at de fleste patienter i studierne reelt havde kronisk ITP, da mange patienter havde haft ITP i over 3 år på det tidspunkt, de blev inkluderet. Patienterne havde mediant fået min. 3 behandlinger i studierne. Blandt patienterne i dansk klinisk praksis ville en meget lavere andel have fået splenektomi, men fagudvalget vurderer, at det primært skyldes forskellig praksis i de inkluderende lande, og at det ikke påvirker vurderingen. Fagudvalget vurderer derfor, at patienterne er sammenlignelige med den gruppe, man i Danmark ville tilbyde fostamatinib.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for klinisk spørgsmål 1 beskrevet:

FIT1 og FIT2 anvendes til at besvare klinisk spørgsmål 1, FIT3-studiet anvendes supplerende til at beskrive sikkerhed. FIT-studierne udgør en direkte sammenligning mellem fostamatinib og placebo.

Effektanalyser er lavet på baggrund af intention to treat-populationen (dvs. alle randomiserede patienter). Sikkerhedsanalyser er baseret på alle randomiserede patienter, som har modtaget mindst én dosis fostamatinib (*safety* population). Analyserne er baseret på den *samlede* population, det vil sige, at data fra patienter i FIT1 og FIT2 er lagt sammen og derefter analyseret.

Effektmålet livskvalitet opgøres fra baseline til hhv. uge 4 og uge 12. Der var [redacted] placeboarmene, som udfyldte SF-36-spørgeskemaet ved uge 24, [redacted] fostamatinibarmene udfyldte spørgeskemaet ved uge 24. Det er derfor for usikkert at opgøre forskellen mellem placebo og fostamatinib for uge 24.

Effektmålet blødninger blev i FIT-studierne opgjort som uønsket hændelse, og analysen er derfor baseret på *safety*-populationen.

Effektmålet blodpladerespons baserer sig på forskellen mellem uge 0-16, da der i uge 20 kun var tre patienter i behandling med placebo, og der i uge 24 kun var én patient i behandling med placebo.

Bivirkningsgennemgangen baserer sig på *safety*-populationen. For at belyse den kvalitative gennemgang af bivirkningerne ved fostamatinib bedre, har fagudvalget ønsket at inddrage data fra leddegigtstudier, som fostamatinib tidligere har været undersøgt i.

5.1.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten for klinisk spørgsmål 1, hvor evidensen beror på to direkte sammenlignende studier (FIT1 og FIT2) mellem fostamatinib og placebo.

Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for klinisk spørgsmål 1. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (Bilag 2: Cochrane – risiko for bias).

5.1.4 Effektestimater og kategorier

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

Tabel 4. Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Livskvalitet	Forskel i gennemsnitlig ændring fra baseline målt ved SF-36 (8 point)	Kritisk		-	-	-	Kan ikke kategoriseres
	Andel, der opleveren stigning på ≥ 8 point i SF-36 (5 %-point)		-	-	-	-	Kan ikke kategoriseres
Alvorlige blødninger	Andel, der oplever alvorlige blødninger (1 %-point)	Kritisk	-5,5 %-point (-15,1; 4,1)	Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
Mindre blødninger	Andel, der oplever mindre blødninger (10 %-point)	Vigtigt	-2,5 %-point (-17,1; 12,2)	Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
Blodpladerespons	Andel med blodpladetal ≥ 30 x 10^9/L (10 %-point)	Vigtigt	19,5 %-point* (-13,5; 52,4)	Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
Bivirkninger	Andel, der ophører behandling pga. uønskede hændelser (10 %-point)	Vigtigt	1,5 %-point (-8,3; 11,2)	Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
	Kvalitativ gennemgang af bivirkningsprofilen		-	-	-	-	-

Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres.
Kvalitet af den samlede evidens	

Forkortelser: CI = konfidensinterval. *Opgjort ved 16 uger.

Livskvalitet

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

I protokollen ønskede fagudvalget livskvalitet opgjort ved hjælp af SF-36 som en samlet gennemsnitlig ændring fra baseline samt for hvert af de 8 domæner i SF-36. Derudover ønskede fagudvalget også at se, hvor mange der opnåede en stigning i SF-36 på ≥ 8 point, og havde defineret en forskel på 5 %-point som mindste klinisk relevante forskel.

Af Tabel 5 ses den gennemsnitlige forskel mellem fostamatinib og placebo i ændringer fra baseline i SF-36 for hvert af de 8 domæner. Ansøger har ikke rapporteret en samlet gennemsnitlig ændring fra baseline, hvorfor effektmålet ikke kan kategoriseres.

Tabel 5. Forskel i ændring fra baseline mellem fostamatinib og placebo i FIT1 og FIT2, opgjort for hvert SF-36 domæne

Domæne	Gennemsnitlig ændring fra baseline til uge 4 (95 % CI)	Gennemsnitlig ændring fra baseline til uge 12 (95 % CI)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

En positiv score betyder, at patienter behandlet med fostamatinib oplever en forbedring i livskvalitet ift. placebo. (Kilde: Grifols data on file)

Fagudvalget vurderer, at resultaterne i Tabel 5 er inkonklusive. Konfidensintervallerne er meget brede for samtlige domæner, og punktestimaterne viser, at ændringer i livskvalitet fra baseline på tværs af domæner kan være både højere og lavere med fostamatinib sammenlignet med placebo. Der er således ikke evidens for, at fostamatinib hverken forbedrer eller forværrer livskvaliteten sammenlignet med placebo. Fagudvalget bemærker, at bivirkningerne ved behandlingen kan have en betydning for det brogede billede, som ses af Tabel 5. Derudover baserer resultaterne sig på en meget tidlig

opgørelse (uge 4 og uge 12 fra behandlingsstart), som generelt er for kort, til at en ændring i livskvalitet kan nå at indfinde sig hos patienten.

Af Tabel 6 ses forskellen i andelen af patienter, der oplever en forbedring på mindst 8 point i SF-36.

Tabel 6. Forskellen i andelen af patienter med mindst 8-points forbedring i SF-36 fra baseline til hhv. uge 4 og uge 12

Domæne	Andel med mindst 8-points forbedring fra baseline til uge 4, %-point (95 % CI)	Andel med mindst 8-points forbedring fra baseline til uge 12, %-point (95 % CI)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Tabellen viser forskellen mellem andelen af patienter med mindst 8-points forbedring i fostamatinibarmen vs. placeboarmen. I protokollen havde fagudvalget defineret en ændring på 5%-point som den klinisk relevante forskel. (Kilde: Grifols data on file).

Fagudvalget vurderer, at resultaterne i **Fejl! Henvisningskilde ikke fundet.**6 er inkonklusive. Konfidensintervallerne er meget brede for samtlige domæner, og der er store forskelle på resultaterne, når målingerne laves i hhv. uge 4 og uge 12. Der er således ikke evidens for, at forskellen i andelen, der oplever en stigning på 8 point, ikke overstiger 5 %-point. Den fastsatte mindste klinisk relevante forskel var 5 %-point samlet for SF-36, men da ansøger ikke har opgjort en samlet andel, kan effektmålet *ikke kategoriseres*.

Blødninger

Fagudvalget ønskede blødninger opdelt i alvorlige og mindre alvorlige blødninger. Alvorlige blødninger er et frygtet symptom ved ITP, om end det forekommer sjældent. Mindre blødninger forekommer mere hyppigt og er ofte generende for patienten og dermed af betydning for patientens livskvalitet.

Fagudvalget ønskede i protokollen: ”andelen, som oplevede alvorlige og mindre blødninger” opgjort efter længst mulig opfølgningstid. Alvorlige blødninger blev i FIT-studierne defineret som:

- Blødninger, der førte til død.
- Blødninger, som var livstruende.
- Blødninger, som medførte behov for indlæggelse eller forlængelse af en eksisterende indlæggelse.
- Blødninger, som var persisterende eller invaliderende for patienten (fx blødninger, som førte til, at patienten ikke kunne udføre sine normale funktioner).

Milde blødninger er defineret som *ikke-alvorlige blødninger*. Det er alle de blødninger, der ikke mødte kriteriet for en alvorlig blødning. Det vil sige moderate blødninger, som inducerede en vis form for besvær eller bekymring for patienten, eller milde blødninger defineret som forbigående uden behov for behandling.

Af Tabel 7 ses forskel i andelen med alvorlige og ikke-alvorlige blødninger opgjort for den samlede population i FIT1 og FIT2.

Tabel 7. Andel, med alvorlige og ikke-alvorlige blødninger, samt forskel i andele (safety population)

	FIT1		FIT2		Fostamatinib samlet population (n=102)	Placebo samlet population (n=48)
	Fostamatinib (n=51)	Placebo (n=25)	Fostamatinib (n=51)	Placebo (n=23)		
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

[redacted] dog både positive og negative værdier, derfor er der ingen statistisk signifikant forskel mellem behandlingerne vedr. alvorlige blødninger, og effektmålet kan ikke kategoriseres. Der findes ingen opgørelser over hvorledes blødningerne fordeler sig ift. definitionerne af alvorlige blødninger.

Der var færre patienter behandlet med fostamatinib, som oplevede ikke-alvorlige blødninger sammenlignet med placebo (22,5 % vs. 25,0 %), med en forskel på -2,5 %-point til fostamatinibs fordel, hvilket ikke overgår den mindste klinisk relevante forskel på 10 %-point. Resultatet er ikke statistisk signifikant. Effektmålet kan ikke kategoriseres.

Andel patienter med blodpladerespons ≥ 30 x 10^9/L
Som beskrevet i protokollen er effektmålet *blodpladerespons* relevant for vurderingen af fostamatinibs værdi for patienterne. Det skyldes, at det er en vigtig parameter i klinikken, der bruges til at vurdere behandlingens effekt. Blodpladerespons er derfor en almindelig anvendt surrogatmarkør for patienternes blødningsrisiko.

I protokollen ønskede fagudvalget, at effektmålet blev opgjort som andelen, der opnår et blodpladetal ≥ 30 x 10^9/L efter 6 måneders behandling uden behov for supplerende medicin. Fagudvalget anser 10 %-point som den mindste klinisk relevante forskel.
Som supplement ønskede fagudvalget at se kurver for udvikling i blodpladetallene i hele studieperioden og en opgørelse af varigheden af responset.

Der findes ingen opgørelser over blodpladerespons opdelt på, om patienterne modtog supplerende ITP-behandling eller ej. Andelen, som opnåede et blodpladetal ≥ 30 x 10^9/, ses af Tabel 8.

Tabel 8. Andel, der opnåede et blodpladetal ≥ 30 x 10^9/L fra uge 0 til hhv. uge 4, 7, 12 og 16, opgjort samlet for FIT1 og FIT2

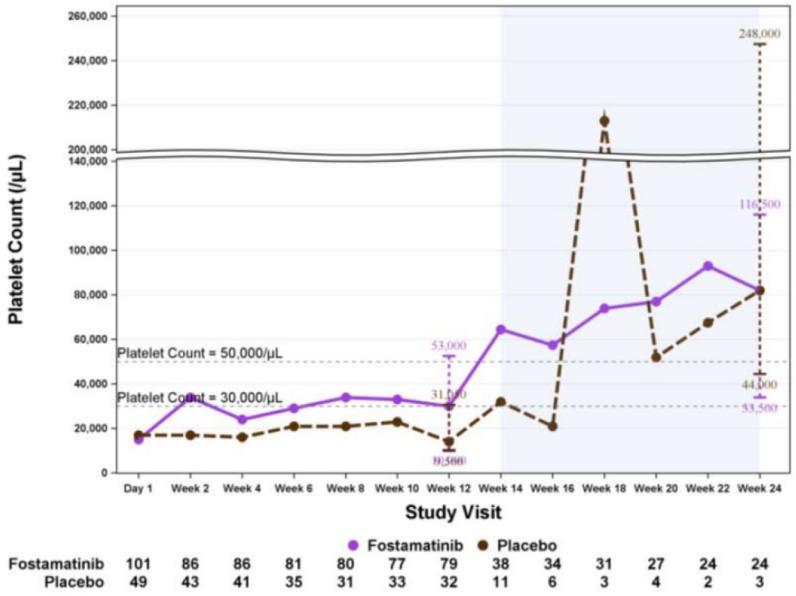
Behandlingsarm / uge	Fostamatinib	Placebo	Forskel
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Behandlingsarm / uge	Fostamatinib	Placebo	Forskel
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

*Der beregnes ingen forskel for uge 20 og 24, da der var meget få tilbage i placebogrupperne.

Fagudvalget ønskede forskellen opgjort efter 6 måneder (dvs. uge 24), [redacted], valgte fagudvalget i stedet at se på andelen ved uge 16. I uge 16 havde hhv. [redacted] i behandling med fostamatinib og [redacted] i behandling med placebo et blodpladetal på ≥ 30 x 10^9/L, hvilket giver en forskel på [redacted] til fostamatinibs fordel. Punktestimatet på [redacted] overstiger den mindste klinisk relevante forskel på 10 %-point, men konfidensintervallet afspejler både negative og positive værdier, hvorfor effektmålet ikke kan kategoriseres vedr. andelen, der opnår et blodpladetal ≥ 30 x 10^9/L. Fagudvalget bemærker, at der er et stort frafald af patienter ved uge 12, hvilket kan være fordi, patienterne havde mulighed for at fortsætte i FIT3-studiet. I begge arme var der formentlig en del patienter, der stoppede pga. manglende effekt, i håb om at de havde fået placebo og kunne prøve fostamatinib i FIT3. Det er med til at skabe usikkerhed om effektresultatet, da det i fostamatinibarmen kun er dem, der har effekt af lægemidlet, der bliver i studiet

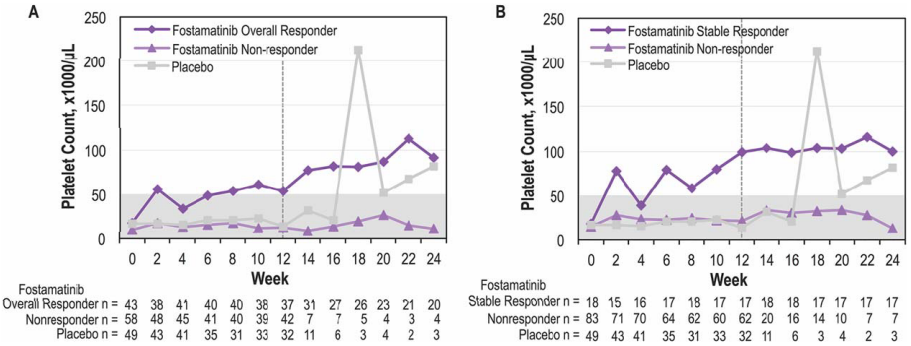
Ansøger har ikke bidraget med blodpladeresponskurver, derfor inddrager fagudvalget en kurve (Se Figur 2) som indgår i EPAR'en [11].



Figur 2. Median blodpladetal målt ved hvert studiebesøg, delt op i patienter behandlet med fostamatinib og placebo, samlet for FIT1 og FIT2 (kilde: EPAR[11] heri s. 92)

Interkvartil spredning (Q1-Q3) er vist for behandlingsgrupperne i uge 12 og 24, De patienter, som havde modtaget *rescue*-behandling, blev ikke inkluderet i figuren.

Det pludselige respons, som ses af figuren i uge 18 i placebogruppen, skyldes 3 patienter i placeboarmen, som har haft et fluktuerende blodpladetal. Fagudvalget har yderligere inddraget to kurver vedr. blodpladetal fra artiklen Bussel et al. 2018 [15], som ses af **Fejl! Henvisningskilde ikke fundet.**. Af figuren ses andelen, som opnåede hhv. *overall response* (billede A) og *stable response* (billede B) med fostamatinib.



Figur 3. Blodpladetal over tid, pooled data fra FIT1 og FIT2. A: Median blodpladetal hos *overall responders og non-responders* til fostamatinib samt placebopatienter. B: Median blodpladetal hos *stable responders* og *non-responders* til fostamatinib samt placebopatienter. Den stiplede linje ved uge 12 symboliserer tidspunktet, hvor *non-responders* (både i placebogruppen og i fostamatinibgruppen) måtte overgå til FIT3-studie-t. [15]

Overall response blev defineret post-hoc som mindst en måling med blodpladetal ≥ 50 x 109/L inden for de første 12 uger af behandlingen uden brug af *rescue*-behandling. *Stable response* var det primære effektmål i studierne defineret som et blodpladetal ≥ 50 x 109/L i mindst fire ud af de seks klinikbesøg, som forekom i uge 14-24 uden behov for *rescue*-behandling.

Baseret på blodpladeresponskurverne (Figur 2 og Figur 3) vurderer fagudvalget, at det ser ud til, at der er en lille gruppe af patienter, som opnår respons, og for disse ser responset ud til at være hurtigt indsættende og vedvarende. Ud fra det tilgængelige data er det dog ikke muligt at vurdere, om patienterne taber responset af fostamatinib på langt sigt, hvilket kan være en bekymring i en gruppe af patienter, der er svært behandlingsrefraktære.

Som følge af et stort frafald i antallet af patienter, som modtager behandling (patienter kunne fra uge 12 overgå til FIT3), er resultaterne meget usikre efter uge 12. Resultater fra FIT3 indikerer, at responset varer ved for dem, som initialt i enten FIT1 eller FIT2 havde opnået respons. I FIT3 havde 21/27 patienter (78 %) stadig stabilt respons (*stable response*) efter 12 måneders behandling med fostamatinib, efter 24 måneder var det gældende for 15/27 patienter (56 %) [14]. Fagudvalget kan ikke vurdere varigheden af effekten ud over studiets længde, men erfaringen med behandling af disse patienter viser, at dem, der responderer, har effekt i længere tid, og ved en lille del kan sygdommen forsvinde helt.

Bivirkninger
Fagudvalget ønskede effektmålet *bivirkninger* opgjort ved to deleffektmål: 1) behandlingsophør grundet uønskede hændelser og 2) en kvalitativ gennemgang af bivirkningsprofilen for fostamatinib.

Behandlingsophør grundet uønskede hændelser:
10/102 (9,8 %) patienter behandlet med fostamatinib ophørte behandlingen som følge af uønskede hændelser mod 4/48 (8,3 %) patienter behandlet med placebo, det giver en forskel på 1,5 %-point [95 % CI -8,3; 11,2) til placebos fordel. Punktestimatet overgår ikke den mindste klinisk relevante forskel på 10 %-point, og effektmålet kan ikke kategoriseres, som følge af at konfidensintervallet både indeholder positive og negative værdier). Årsagerne til behandlingsophør ses af Tabel 9.

Tabel 9. Uønskede hændelser, som ledte til behandlingsophør (placebo-kontrolleret periode*), hver række angiver et individ i FIT1 eller FIT2

Type uønsket hændelse, som ledte til behandlingsophør	Behandling	Studie
Bevidstløshed	Fostamatinib	FIT1
Pneumoni (lungebetændelse)	Fostamatinib	FIT1
Forhøjet alanin aminotransferase	Fostamatinib	FIT1
Diarré	Fostamatinib	FIT1
Brystsmerte	Fostamatinib	FIT1
Trombocytopeni (lavt niveau af blodplader)	Fostamatinib	FIT1
Smerter i maveregion	Fostamatinib	FIT1
Neutropeni (lavt antal hvide blodlegemer)	Fostamatinib	FIT1
Knoglemarvskræft	Fostamatinib	FIT2
Hovedpine	Fostamatinib	FIT2
Epistaxis (blødning fra næsen)	Placebo	FIT1
Ubehag i maveregion	Placebo	FIT1
Hypertension (forhøjet blodtryk)	Placebo	FIT2
Diarré	Placebo	FIT2

*Patienter behandlet med placebo kunne fra uge 12 i den placebo-kontrollerede periode af studierne overgå til FIT3 (ublindet). (Kilde: EPAR [11] s. 127 tabel 20)

Kvalitativ gennemgang af bivirkningsprofil:
Bivirkningsprofilen for fostamatinib er opsummeret i afsnit 0 (se

Bilag 4: Bivirkningsprofil) og gennemgås herunder. Henholdsvis 83 % af patienterne behandlet med fostamatinib og 75 % af patienterne behandlet med placebo oplevede en uønsket hændelse (samlet for FIT1 og FIT2). De mest almindelige rapporterede uønskede hændelser var diarré, hypertension, kvalme, svimmelhed samt påvirkede leverfunktionsprøver, se frekvenserne i

Bilag 4: Bivirkningsprofil. De fleste uønskede hændelser var milde og moderate af sværhedsgrad. Fagudvalget bemærker dog, at diarré og kvalme begge sædvanligvis er bivirkninger, der er intolerable for de fleste patienter selv i milde grader. Uønskede hændelser relateret til fostamatinib versus placebo var neutropeni (7 % vs. 0 %), gastrointestinale hændelser (41 % vs. 21 %), transaminase stigning til > 3 gange det normale (9 % vs. 0 %) og hypertension (28 % vs. 13 %).

Flere patienter behandlet med fostamatinib havde flere uønskede hændelser, som ledte til dosisreduktion (9 % vs. 2 %) og midlertidigt ophør af behandling (18 % vs. 10 %). De mest almindelige årsager til dosisreduktion var diarré og hypertension. De mest

almindelige årsager til midlertidigt ophør af behandlingen var stigning i levertal, diarré og influenzalignende sygdom.

Alvorlige uønskede hændelser (SAE) blev rapporteret hos 13 % af patienter behandlet med fostamatinib vs. 21 % på placebo, 3 typer SAE blev rapporteret mere end én gang i begge behandlingsgrupper: epitaxis (2 % vs. 2 %) trombocytopeni (1 % vs. 4 %) og kraftige menstruationsblødninger (0 % vs. 4 %). SAE'er blev antaget at skyldes behandlingen hos 4 % af patienterne behandlet med fostamatinib og 2 % af patienterne behandlet med placebo.

Der var to dødsfald i FIT-studierne; i FIT1 fik én placebo-patient blodforgiftning 19 dage efter at have forladt studiet pga. næseblødning. I FIT2 ledte en type knoglemarvskræft (plasma cell myeloma) på dag 19 til behandlingsophør hos én fostamatinib-patient og til død 71 dage efter. Fagudvalget vurderer, at patienten med knoglemarvskræft må have haft kræften ved inklusion i studiet og udgør derfor en fejlinklusion. EPAR'en slår ligeledes fast, at ingen af de 2 dødsfald var relateret til behandlingerne.

Tabel 10. Oversigt over sikkerhedsprofilen ved fostamatinib vs. placebo i FIT-studierne

Parameter	Fostamatinib (n=102), n (%)	Placebo (n=48), n (%)
Antal med mindst 1 AE	85	36
Alle AE'er	85 (83,3)	36 (75,0)
- Mild - Moderat - Svær	- 33 (32,4) - 36 (35,3) - 16 (15,7)	- 20 (41,7) - 9 (18,8) - 7 (14,6)
Behandlingsrelateret AE'er	60 (58,8)	13 (27,1)
Alvorlige AE'er (SAE'er)	13 (12,7)	10 (20,8)
AE'er, som ledte til dosisreduktion	9 (8,8)	1 (2,1)
AE'er, som ledte til midlertidigt ophør	18 (17,6)	5 (10,4)
AE'er, som ledte til studieophør	10 (9,8)	4 (8,3)
AE'er, som ledte til død	1 (1,0)	1 (2,1)

Forkortelser: AE = adverse events (dansk: uønskede hændelser), SAE = serious adverse events (dansk: alvorlige uønskede hændelser). (Kilde: EPAR [11] s. 127, tabel 16).

Supplerende sikkerhedsdata fra FIT3-studiet:
Uønskede hændelser observeret i FIT3-studiet er sammenlignelig med de randomiserede FIT1- og FIT2-studier.

Supplerende sikkerhedsdata fra leddegigtstudier:
Bivirkninger hos leddegigt-patienter behandlet med fostamatinib bekræfter de samme typer og frekvenser af bivirkninger, som blev observeret hos ITP-patienterne i FIT1- og -2-studierne [16].

Fagudvalget vurderer, at flere af bivirkningerne er af en type, som patienter med en kronisk sygdom som ITP ikke vil kunne tolerere, selvom de fleste af bivirkningerne er milde til moderate af sværhedsgrad (se

Bilag 4: Bivirkningsprofil).

5.2 Fagudvalgets konklusion

Vurderingen af klinisk spørgsmål 1 (fostamatinib vs. placebo) er baseret på to direkte sammenlignende dobbeltblindede randomiserede studier. Datagrundlaget er sparsomt, da studierne var forbundet med et stort og tidligt behandlingsophør i især placebogrupperne, hvilket gør det svært at sammenligne behandlingerne efter længst mulig opfølgningstid. Værdien af fostamatinib til behandling af patienter med svær behandlingsrefraktær ITP kan ikke kategoriseres.

Der var færre patienter behandlet med fostamatinib, som oplevede alvorlige blødninger sammenlignet med placebo (4,9 % vs. 10,4 %), med en forskel 5,5 %-point til fostamatinibs fordel, hvilket overgår den mindste klinisk relevante forskel på 1 %-point. Konfidensintervallet var dog meget bredt, og resultatet er ikke statistisk signifikant. Fagudvalget bemærker, at det helt generelt er svært at vise forskelle i forekomsten af blødningssymptomer ved ITP, da alvorlige blødninger forekommer sjældent, og kun en lille del af patienterne i studierne responderer på behandlingen. Trombocyttallet kan bruges som surrogat for blødninger, og fagudvalget bemærker, at behandlingen med fostamatinib medfører, at flere oplever en stigning i blodpladetallet til et stabilt og acceptabelt niveau. Fagudvalget mener derfor, at det er plausibelt, at blødningerne reduceres for patienter behandlet med fostamatinib sammenlignet med placebo.

Sammenlignet med placebo kan det på nuværende datagrundlag ikke vises, at fostamatinib forbedrer patienternes livskvalitet.

Der er flere bivirkninger forbundet med behandlingen med fostamatinib sammenlignet med placebo, og fagudvalget vurderer, at diarré og kvalme selv i milde grader er intolerable for de fleste patienter. Fagudvalget vurderer, at patienter uden stort behandlingsbehov, og som oplever bivirkninger, vil fravælge behandlingen som følge af bivirkningsprofilen, og det derfor kun er patienter med stort behandlingsbehov, som vil acceptere at prøve behandlingen.

Fagudvalget vurderer, at resultaterne er positive, da det hos en mindre gruppe af patienterne, nemlig dem, der ikke har responderet på anden behandling, kan være værdifuldt, at der kommer en ny behandlingsmulighed.

5.3 Klinisk spørgsmål 2

5.3.1 Litteratur

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

I Medicinrådets protokol vedr. fostamatinib blev der stillet to kliniske spørgsmål, hvor forskellen mellem dem er valget af komparator: I klinisk spørgsmål 1 er placebo komparator, og i klinisk spørgsmål 2 er nuværende 3. linje standardbehandlinger komparator. Klinisk spørgsmål 2 repræsenterer således dansk klinisk praksis.

For klinisk spørgsmål 2 har ansøger udført en systematisk litteratursøgning ved hjælp af søgestrengen angivet i protokollen, da der ikke findes direkte sammenlignende studier mellem fostamatinib og komparatorerne angivet i det kliniske spørgsmål. Søgningen resulterede i, at ansøger har inkluderet 4 studier vedr. komparatorerne; ciclosporin A og mycophenolate mofetil. Ansøger inkluderede kun studier, som opfyldte PICO-kriterierne defineret i protokollen.

Fagudvalget har yderligere konsulteret EMAs produktresumé (SmPC) [13] og *assessment report* (EPAR) [11] for fostamatinib.

Thabet 2020, Colovic 2011, Provan 2006, Zver 2006:
Disse fire studier har ansøger inkluderet vedr. komparator til besvarelse af klinisk spørgsmål 2. Thabet 2020 er et prospektivt studie, mens de øvrige tre er observationelle (case series) studier. Oversigt over studierne ses af Tabel 3, og studiekarakteristika ses af Tabel 11.

Tabel 11. Studiekarakteristik af Thabet 2020, Colovic 2011, Provan 2006 og Zver 2006

Studie (antal)	Thabet 2020 (n=20)	Colovic 2011 (n=16)	Provan 2006 (n=18)	Zver 2006 (n=6*)	
				Patient 3:	Patient 5:
Land	Egypten	Serbien	UK og USA	Slovenien	Slovenien
Alder	Gennemsnit (SD): 33,56 (9,81) år	Median (spredning): 55 (20-80) år	Median (spredning): 50,5 (25-66) år	61 år	56 år
Køn	Kvinder: 25/40 (62,5 %)	Kvinder: 10/16 (62,5 %)	Ikke-rapporteret	Kvinde	Kvinde

Studie (antal)	Thabet 2020 (n=20)	Colovic 2011 (n=16)	Provan 2006 (n=18)	Zver 2006 (n=6*)	
				Patient 3:	Patient 5:
Sygdoms-varighed	Ikke rapporteret	Median (spredning): 58 (24 – 280) måneder	Median (spredning): 8,5 (2-27) år	438 måneder	71 måneder
Antal tidligere behandlinger	65 % havde fejlet to tidligere behandlinger, 35 % havde fejlet ≥ 2 behandlinger	Median (spredning): 4 (3-8)	Ikke-rapporteret	Ikke-rapporteret	Ikke-rapporteret
Type tidligere behandling	Ikke-rapporteret	Kortikosteroid: 16/16 (100 %) IVIg: 6/16 (37,5 %) IS: 16/16 (100 %) splenektomi: 9/16 (81,82 %)	Kortikosteroid: 16/18 (88 %) IVIg: 14/18 (77 %) IS: 14/18 (77 %) Splenektomi: 15/18 (83 %) Rituximab: 3/18 (17 %)	Kortikoste-roid, IS, IVIg, splenektomi	Kortikoste-roid, IVIg, splenektomi
Baseline blodpladetal (x10^9/L)	Gennemsnit (SD): 14,85 (6,31)	Gennemsnit (SD): 7,19 (5,59)	Ikke-rapporteret	5	17

Forkortelser: IS = immunsupprimerende, IVIg = intravenøs immunglobulin. *I Zver 2006 indgik 6 patienter, men der benyttes kun data for 2 af patienterne, da de var de eneste, som opfyldte PICO-kriterierne beskrevet i protokollen.

Der er så store forskelle på patientpopulationerne, og data for baselinekarakteristika er så sparsomt i komparatorstudierne, at fagudvalget ikke finder det muligt at lave en meningsfuld sammenligning af data fra de fire studier med data fra FIT-studierne. Fagudvalget baserer den samlede konklusion på data fra FIT1 og -2-studierne.

5.4 Fagudvalgets samlede konklusion

Den samlede værdi af fostamatinib til behandling af patienter med svær behandlingsrefraktær ITP kan ikke kategoriseres. Fagudvalget bemærker dog, at en lille gruppe patienter ser ud til at respondere på behandlingen. For denne gruppe patienter ser fostamatinib ud til at have et hurtigt indsættende respons, og på baggrund af klinisk erfaring forventer fagudvalget, at responset fortsætter.

Fagudvalget vurderer, at det er lille gruppe patienter, der ville være målgruppe for behandlingen med fostamatinib. Det drejer sig om patienter, der har været behandlet med steroid, rituximab og TPO-RA, og som ingen dokumenterbar effekt har haft. Der er tale om kroniske ITP-patienter med vedvarende behandlingsbehov pga. aktiv blødning eller uacceptabel blødningsrisiko og et meget lavt trombocyttal eller patienter, der skal have blodfortyndende medicin pga. atrieflimren, og som derfor skal have et højere trombocyttal end det normalt acceptable.

Fagudvalget bemærker, at patienterne skal have respons i form af en klinisk relevant stigning af trombocyttal indenfor de første 8 uger af behandlingen. Hvis det ikke opnås, bør behandlingen seponeres.

Fagudvalget bemærker, at man i en femårsopfølgning af FIT1-, FIT2- og FIT3-studierne med 229 patientår kun registrerede et enkelt tromboembolisk event [17]. Selvom der ikke er en kontrolgruppe, styrker det antagelsen af, at fostamatinib har en klinisk relevant antitrombotisk effekt, jævnfør den velkendte overhyppighed af tromboser ved ITP [5].

Fostamatinibs anvendelsesområde er 3. linjebehandling, hvor de nuværende medicinske behandlingsmuligheder har sparsom dokumentation, der mest hviler på langvarig klinisk erfaring. Sammenlignet hermed er dokumentationen for fostamatinib mere solid, men direkte sammenligninger af disse lægemidler kan ikke forventes at blive udført. Fagudvalgets vurdering er, at fostamatinib, på linje med de nuværende behandlinger i 3. linje, kan være effektivt for en lille gruppe patienter.

6. Andre overvejelser

6.1 Behandlingsvarighed

Fagudvalget ønskede, jf. Medicinrådets protokol, at ansøger redegør for, hvor længe patienter kan forventes at være i behandling med fostamatinib og komparator i klinisk spørgsmål 2.

Ansøger giver ikke noget konkret svar på, hvor længe velbehandlede patienter kan forventes at være i behandling med fostamatinib, men skriver i deres ansøgning, at behandlingsvarigheden af kronisk ITP er forskellig fra patient til patient og mellem behandlende læge. Fagudvalget bemærker, at der er patienter, der har langvarig respons på deres behandling, og at de i nogle tilfælde kan behandles i mere end ti år, men at det er en meget lille gruppe.

6.2 Risiko for pneumokokinfektion

Fagudvalget ønskede, jf. Medicinrådets protokol, at ansøger beskriver risikoen for pneumokokinfektioner, ift. om SYK-hæmningen påvirker miltens funktion som forsvar mod disse infektioner.

Ansøger konkluderer i deres ansøgning, at risikoen for pneumokokinfektion ved behandling med fostamatinib er lav, det gør de på baggrund af bivirkningsdata.

Infektioner blev rapporteret i 30 % af patienterne behandlet med fostamatinib vs. 20 % af patienterne behandlet med placebo. Infektionerne inkluderer infektioner i luftvejene i 60 % af tilfældene for fostamatinib og 40 % af tilfældene for placebo. Pneumokokinfektioner blev rapporteret som ikke-almindelige (≥1/1000 to <1/100), mens infektioner i øvre luftveje, luftvejsinfektioner, bronkitis, infektion i nedre luftveje og virusinfektion i de øvre luftveje blev rapporteret som almindelige (≥1/100 to <1/10).

Fagudvalget finder ikke risikoen bekymrende, men gør opmærksom på, at behandlingsperioden i FIT-studierne er kort.

6.3 Betydning af splenektomi

Fagudvalget ønskede, jf. Medicinrådets protokol, at ansøger beskriver effekten af fostamatinib hos splenektomiserede patienter.

I FIT1 og FIT2 blev patienter med tidligere splenektomi undersøgt i en subgruppe. 34 % (34/101) af patienterne i fostamatinibgruppen havde fået fjernet milten (median 13 år før randomisering) mod 39 % (19/49) i placebogruppen. Subgruppeanalysen viste ingen tegn på respons baseret på tidligere splenektomi.

6.4 Supplerende behandling

Fagudvalget ønskede, jf. Medicinrådets protokol, at ansøger bidrager med data, som belyser, hvorvidt behandling med fostamatinib medfører reduceret behov for supplerende behandling med glukokortikoider og immunglobuliner, sammenlignet med komparator i klinisk spørgsmål 2.

Der findes ingen opgørelser over, hvor mange der kunne ophøre deres supplerende ITP-behandling i FIT-studierne.

Ansøger angiver, at færre patienter i fostamatinib-behandling modtog *rescue*-behandling i FIT1 og FIT2 sammenlignet med placebo (30 % vs. 45 %).

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

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9. Sammensætning af fagudvalg og kontaktinformation

Medicinrådets fagudvalg vedrørende benign hæmatologi

Sammensætning af fagudvalg	
Formand	**Indstillet af**
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Deltager ikke	Dansk Sygepleje Selskab
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Tidligere medlemmer, som har bidraget til arbejdet	**Udpeget af**
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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	23. november 2022	Godkendt af Medicinrådet

11. Bilag

Bilag 1: Oversigt over studier

	FIT1	FIT2	FIT3	Thabet 2020	Colovic 2011	Provan 2006	Zver 2006
Publikation	Bussel, J., et al., 2018 [15]: "Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials."			Thabet AF, Moeen SM., 2020 [18]: “More about the combination of rituximab, cyclosporine and dexamethasone in the treatment of chronic ITP. A useful option on an environment with limited resources.”	Colovic M, Suvajdzic N, Colovic N, Tomin D, Vidovic A, Palibrk V., 2011 [19]: “Mycophenolate mophetil thrombocytopenic purpura resistant to steroids, immunosupressants, and/or splenectomy in adults.”	Provan D, Moss AJ, Newland AC, Bussel JB., 2006 [20]: “Efficacy of Mycophenolate Mofetil as Single-Agent Therapy for Refractory Immune Thrombocytopenic Purpura.”	Zver S, Zupan IP, Cernelc P., 2006 [21]: “Cyclosporin A as an Immunosuppressive Treatment Modality for Patients with Refractory Autoimmune Thrombocytopenic Purpura after Splenektomy Failure.”

	FIT1	FIT2	FIT3	Thabet 2020	Colovic 2011	Provan 2006	Zver 2006
	Bussel, et al., 2019 [22]: ”Long-term fostamatinib treatment of adults with immune thrombocytopenia during the phase 3 clinical trial program.” Boccia et al., 2020 [23]: "Fostamatinib is an effective second-line therapy in patients with immune thrombocytopenia." Duliege, A-M., et al., 2018 [14]: “Two-Year Safety and Efficacy Outcomes with Fostamatinib in Adult Patients with Immune Thrombocytopenia (ITP): Open-Label Extension to Phase 3 Trial Program.”						
NCT-nummer	NCT02076399	NCT02076412	-	-	-	-	-
Studietype	Fase III-studie, randomiseret, dobbeltblindet og placebokontrollet		Ublindet, ekstensionsfase-studie	Prospektivt studie	Case series	Case series	Case series
Population	Voksne patienter med primær ITP, som tidligere har været behandlet for deres sygdom, og som har haft ITP i mindst 3 måneder.		Patienter fra FIT1 og -2, som havde færdiggjort 24 uger af deres behandling, eller som ikke responderede på behandling efter 12 uger, kunne blive inkluderet i FIT3.	Kroniske primære ITP-patienter uden tilstrækkeligt respons på mindst to tidligere behandlinger.	Kroniske ITP-patienter, som var resistente over for steroider, immunsupprimerende behandling og/eller splenektomi.	Refraktære ITP-patienter.	Kroniske, refraktære ITP.

	FIT1	FIT2	FIT3	Thabet 2020	Colovic 2011	Provan 2006	Zver 2006
Intervention	Fostamatinib (n=51)	Fostamatinib (n=50)	Fostamatinib (n=123), heraf havde 44 modtaget placebo i FIT1 og FIT2)^	Kombination af dexamethason (40 mg), CsA (2-3 mg/kg dagligt) og rituximab (100 mg) (n=40)	MMF (1,5-2 g/dag) (n=16)	MMF (opstartsdosis: 250 mg * 2/dag, efter 1. uge: 500 mg *2/dag. Vedligeholdelsesdosis: 1 g * 2/dag i 3 uger) (n=18)	CsA (1,5 mg/kg per dosis hver 12. time (n=6)
Komparator	Placebo (n=25)	Placebo (n=24)	-	-	-	-	-
Opfølgningstid	24 uger	24 uger	-	Februar 2016-januar 2019 (36 måneder)	-	-	1994-2004
Dato for studie	2014-2015	2015-2016	-	Februar 2016-januar 2019		-	1994-2006
Primære effektmål	Stabilt blodpladerespons* ved uge 24	Stabilt blodpladerespons* ved uge 24	-				
Anvendt i klinisk spørgsmål	1+2	1+2	1+2	2	2	2	2

Forkortelser: CsA = ciclosporin A, MMF = mycophenolate mofetil. *Stabilt blodpladerespons blev defineret som et blodpladetal ≥ 50 x 10^9 ved mindst fire ud af 6 besøg hver 2. uge mellem uge 14-24. ^data-cut marts 2018. [14]

Bilag 2: Cochrane – risiko for bias

Vurdering af risiko for bias ved Cochrane risk of bias tool 2,0,

Tabel 12. Vurdering af risiko for bias FIT1 (NCT02076399) og FIT2 (NCT02076412)

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Dobbeltblindede randomiserede studier. *Subjects were randomized (2:1, active:placebo) to receive fostamatinib or matching placebo for 24 weeks using permuted block randomization*.
Effekt af tildeling til intervention	**Forbehold**	Studierne var designet som dobbeltblindede studier. Men anvendelsen af rescue-medicin og den høje diskontinuering kan have afsløret behandlingen.
Manglende data for effektmål	**Lav**	Det primære effektmål var analyseret ved imputationsmetoden *last observation carried forward*.
Risiko for bias ved indsamlingen af data	**Lav**	Patientrapporteret effektmål såsom livskvalitet kan være påvirket, da patienterne kan have gættet deres behandling undervejs.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Clinicaltrials.gov viser, at nuværende og originale primære effektmål er ens. Det er ikke oplyst, hvad de originale sekundære effektmål har været.
Overordnet risiko for bias	**Lav**	Der kan være risiko for, at blindingen af visse patienter er ophørt som følge af det store frafald i studierne pga. dårlig respons og anvendelsen af *rescue*-medicin. Det primære effektmål (blodpladerespons) er dog objektivt, derfor vurderes den overordnede risiko for bias at være lav.

Bilag 3: GRADE

Klinisk spørgsmål 1 – Fostamatinib sammenlignet med placebo til behandling af patienter med primær kronisk behandlingsrefraktær ITP

Tabel 13. GRADE-evidensprofil for klinisk spørgsmål 1

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Intervention	Komparator	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Livskvalitet, Forskel i gennemsnitlig ændring fra baseline målt ved SF-36 (8 point)												
0	-	-	-	-	-	-					⨁◯◯◯ MEGET LAV	KRITISK
Livskvalitet, Andel, der opleveren stigning på ≥ 8 point i SF-36 (5 %-point)												
0	-	-	-	-	-	-					⨁◯◯◯ MEGET LAV	KRITISK
Alvorlige blødninger, Andel, der oplever alvorlige blødninger (1 %-point)												
2	RCT	Lav	Ikke-alvorligt[a]	Ikke-alvorligt	Alvorligt[b]	Ingen					⨁⨁⨁◯ MODERAT	KRITISK
Mindre blødninger, Andel, der oplever mindre blødninger (10 %-point)												
2	RCT	Lav	Ikke-alvorligt[c]	Ikke-alvorligt	Alvorligt[b]	Ingen					⨁⨁⨁◯ MODERAT	VIGTIGT

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Intervention	Komparator	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Blodpladerespons, andel med blodpladetal ≥ 30 x 109/L (10 %-point)												
2	RCT	Lav	Ikke-alvorligt[c]	Ikke-alvorlig	Alvorligt[b]	Ingen					⨁⨁⨁◯ MODERAT	VIGTIGT
Bivirkninger, andel, der ophører behandling pga. uønskede hændelser (10 %-point)												
2	RCT	Lav	Ikke-alvorligt[c]	Ikke-alvorlig	Alvorligt[b]	Ingen					⨁⨁⨁◯ MODERAT	VIGTIGT
Kvalitet af den samlede evidens MEGET LAV												

[a] Der er inkonsistens i effektforskel mellem FIT1 og FIT2, men der er små forskelle i baseline, som kan forklare effektforskellen. Derfor nedgraderes der ikke.

[b] Der er nedgraderet to niveauer, da konfidensintervallet er meget bredt og indeholder både positive og negative konklusioner.

[a] Det er ikke muligt at vurdere, om der er inkonsistens i effektforskel mellem FIT1 og FIT2. På baggrund af vurderingen i alvorlige blødninger nedgraderes der ikke.

Bilag 4: Bivirkningsprofil

Tabel 14. De mest almindelige rapporterede uønskede hændelser (≥5 %) hos patienter behandlet med fostamatinib i FIT1, FIT2 og FIT3 [22]

	Andel af patienter (n=146)			
	Milde	**Moderate**	**Svære**	**Total**
Diarré	18	16	1	35
Hypertension	10	10	1	21
Kvalme	17	2	0	19
Epitaxis	11	6	0	17
Petekkier	10	4	1	15
Hovedpine	9	4	0	13
Svimmelhed	9	1	1	11
Øvre luftvejsinfektion	7	3	0	10
ALT-stigning	6	4	0	10
Opkast	8	0	0	8
Mavesmerter	3	2	0	6
Nasopharyngitis	6	0	0	6
Hoste	4	1	0	6
Træthed	8	2	0	9
Dyspnø	3	1	1	5
Brystsmerter (non-kardiel)	3	2	1	6
AST-stigning	4	3	0	7
Neutropeni	2	3	1	6
Trombocytopeni	0	1	5	6
kontusion	6	1	1	8

Forkortelser: ALT = alanin aninotransferase, AST = aspartat aminotransferase.

Tabel 15. Uønskede hændelser rapporteret i ≥ 5 % af patienterne behandlet i FIT1 og FIT2, placebokontrolleret periode, (kilde EPAR s, 131 Tabel 19)

Most common AEs, preferred term	Randomized Studies (FIT1 og FIT2)	
	Fostamatinib (n=102), n (%)	Placebo (n=48), n (%)
Diarré	30 (29,4)	7 (14,6)
Hypertension	20 (19,6)	4 (8,3)
Kvalme	19 (18,6)	4 (8,3)
Epitaxis	16 (15,7)	5 (10,4)
ALT-stigning	11 (10,8)	0
AST-stigning	9 (8,8)	0
Udslet	9 (8,8)	1 (2,1)
Brystsmerter (non-kardiel)	6 (5,9)	1 (2,1)
Fatigue	6 (5,9)	1 (2,1)
Petikkier	4 (3,9	3 (6,3)
Hovedpine	11 (10,8)	9 (18,8)
Øvre luftvejsinfektioner	6 (5,9)	2 (4,2)
Svimmelhed	11 (10,8)	4 (8,3)
kontusion	6 (5,9)	0
Opkast	3 (2,9)	3 (6,3)

Forkoretelser: ALT = alanin aninotransferase, AST = aspartat aminotransferase.

Medicinrådet

Application for the assessment of Tavlesse® for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Tavlesse®
Generic name	Fostamatinib
Marketing authorization holder in Denmark	Instituto Grifols S.A.
ATC code	B02BX09
Pharmacotherapeutic group	Other systemic hemostatics
Active substance(s)	Fostamatinib disodium
Pharmaceutical form(s)	Film coated tablets
Mechanism of action	Fostamatinib mediates its activity effectively through its major metabolite, R406, which is a tyrosine kinase inhibitor with demonstrated activity against spleen tyrosine kinase (SYK).
Dosage regimen	Fostamatinib is administered orally by 100 mg or 150 mg orange film-coated tablets. The recommended initial dosage of fostamatinib for the treatment of ITP is 100 mg twice daily. Fostamatinib can be taken with or without food. The initial dose may be increased to 150 mg at week 4 based on platelet count and tolerability. The lowest dosage of fostamatinib to achieve platelet counts of at least 50,000/µL should be used.

Overview of the pharmaceutical	
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Tavlesse® is indicated for the treatment of chronic immune thrombocytopenia (cITP) in adult patients who are refractory to other treatments.
Other approved therapeutic indications	-
Will dispensing be restricted to hospitals?	Yes, BEGR
Combination therapy and/or co-medication	-
Packaging – types, sizes/number of units, and concentrations	100 mg, 60 tablets 150 mg, 60 tablets
Orphan drug designation	Not applicable. Although ITP is a rare disease

2. Abbrevations

Abbreviation	Explanation
AE	Adverse event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BID	Twice a day
CI	Confidence interval
cITP	chronic immune thrombocytopenia
DMC	Danish Medicines Council
EMA	European Medicines Agency
F	Female
g	Gram
ITP	Immune thrombocytopenia
IS	Immunosuppressants
IV	Intravenous

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IVIg	Intravenous immunoglobulin
IV anti-D IgG	Intravenous anti-D immunoglobulin
kg	Kilogram
M	Male
mg	Milligram
MMF	Mycophenolate mofetil
NE	Not estimable
NR	Not reported
OLE	Open-label extension
PC	Platelet count
RCT	Randomized controlled trials
SAE	Serious adverse event
SD	Standard deviation
SF-36	Short-form 36
SLR	Systematic literature review
SYK	Spleen tyrosine kinase
TPO-RA	Thrombopoietin receptor agonist
UK	United Kingdom
US	United States
WHO	World health organization

3. Summary

The protocol from the Danish Medicine's council identified two clinical questions to be addressed in the assessment of the clinical value of Tavlesse®:

1. What is the value of fostamatinib compared to placebo for patients with primary chronic treatment refractory ITP?

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2. What value does fostamatinib have compared to immunosuppressive therapies such as dapsone, danazol, mycophenolate mofetil, azathioprine or ciclosporin for patients with primary chronic ITP?

The following outcome measures were defined in the protocol (Table 1):

Table 1. Overview of outcome measures according to the protocol

Outcome measure	Outcome
Quality of life	Difference in average change from baseline in SF-36 (8 points) Proportion of patients who achieve an increase of ≥8 points (5%-point)
Serious bleeds	Proportion of patients who experience a serious bleed (1%-point)
Minor bleeds	Proportion of patients who experience a minor bleed (10%-point)
Platelet count	Proportion of patients with platelet count (PC) ≥30 x 10^9/L (10%-point)
Adverse events	Proportion of patients who discontinue due to an adverse event (10%-point) Qualitative description of adverse events

To respond to clinical question 1, the results from the two pivotal trials FIT1 and FIT2 were used as well as a pooled analysis of the two trials. Additionally, the results from the open label extension study FIT3 were used to describe safety outcomes comprehensively (long term). FIT1 and FIT2, are two identical designed studies randomized, double-blind, placebo-controlled studies comparing the efficacy and safety of fostamatinib to placebo in adult patients with previously treated persistent (3-12 months since diagnosis) or chronic (greater than 12 months since diagnosis) ITP. Rescue therapies (e.g., increased dosing of concomitant ITP therapy, IVIg, IV anti-D, steroids, platelet transfusion) were allowed in both studies. FIT3 is an open label extension study where patients from FIT1 and FIT2 who completed 24 weeks of treatment, or who did not respond to treatment after 12 weeks, were eligible to enroll.

The following results were obtained:

- XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXX.
- The difference in serious bleeds between the fostamatinib arm and the placebo arm was 5.5% and the difference in non-serious bleeds was 2.5%.
- The difference in the proportion of patients with platelet counts ≥ 30x10^9/L between the fostamatinib arm and placebo at week 12 and 16 was 22% and 20% respectively.
- In FIT1 and FIT2, 83% and 75% of patients experienced AEs in the fostamatinib and placebo groups, respectively. The most commonly reported AEs were diarrhea, nausea, hypertension, dizziness, and ALT and/or AST increases. Overall infections were slightly more frequent in patients on fostamatinib than placebo (30% vs. 21%, respectively), but rates of moderate or severe infections were similar (8% vs. 6%, respectively). Most cases of AEs were either mild (39% on fostamatinib and 56% on placebo) or moderate (42% on fostamatinib and 25% on placebo). Similar rates of AEs leading to treatment withdrawal were reported between treatment arms (9.8% fostamatinib vs. 8.3% placebo)

To respond to clinical question 2, a literature search was performed to identify available evidence to inform the answer. The literature review did not identify any studies comparing fostamatinib with any of the treatments identified in the protocol. Four studies were identified, one prospective trial and three case series. There were no randomized clinical trials (RCTs) identified in this SLR that fulfilled the PICO criteria described in the protocol supplied by the DMC. A narrative approach was deemed the most appropriate method for data synthesis and analysis because of the design of the included studies and their respective reported data. Due to not being able to quantify differences between fostamatinib and the comparators defined in clinical question 2 a economic evaluation was not performed. See secion 6 for the narrative comparison.

4. Literature search

4.1 Background

The DMC determined in the protocol that the studies FIT1 and FIT2 did not provide sufficient information to answer the clinical questions. There was a lack of data for the comparators specified in clinical question 2 as in the FIT1 and FIT2 trials fostamatinib is compared directly with placebo. Therefore, the DMC requested the applicant, Instituto Grifols SA, to perform a literature search to investigate whether there are other studies that contain the missing data. For this purpose, the DMC provided the search strings to be used to search for relevant literature in the databases PubMed and CENTRAL (via Cochrane Library).

4.2 Objective

The objective of the literature search was to investigate the existence of relevant and compatible clinical data to establish the additional clinical benefit of fostamatinib, studied in the clinical trials FIT1 and FIT2, compared to at least one of the drugs specified in clinical question 2 in order to give an answer to this question.

4.3 Methods

4.3.1 Search strategy

The DMC provided the search strings for the searches in PubMed and CENTRAL. The search strategy for PubMed is presented in Table 2. Only the studies in English and with abstracts were included. The search strategy for CENTRAL is presented in Table 3. No restrictions in terms of the time period covered were applied.

Table 2. Search strategy for PubMed

Row	Search term	Results
Search terms for the population		
1	Purpura, Thrombocytopenic, Idiopathic[mh]	7,015
2	ITP[ti] OR (werlhof*[ti] AND disease[ti]) OR (purpura[ti] AND thrombocytop*[ti]) OR ((idiopathic[ti] OR autoimmune[ti] OR immune[ti]) AND thrombocytop*[ti])	13,946

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3	#1 OR #2	15,549
Search terms for the intervention		
4	fostamatinib[nm]	123
5	fostamatinib[tiab] OR Tavalisse*[tiab] OR Tavlesse*[tiab] OR R-788[tiab] OR R788[tiab]	213
Search terms for the comparator		
6	Azathioprine[mh] OR Danazol[mh] OR Dapsone[mh] OR Mycophenolic Acid[mh] OR Cyclosporine[mh]	64,903
7	azathioprine[tiab] OR danazol[tiab] OR dapsone[tiab] OR mycophenolic acid[tiab] OR mycophenolate[tiab] OR cyclosporine[tiab]	60,256
Intervention + Comparator		
8	#4 OR #5 OR #6 OR #7	90,015
Population + Intervention + Comparator		
9	#3 AND #8	656
Exclusion of non-relevant populations and publication types		
10	child[ti] OR childhood[ti] OR children[tiab] OR pediatric[ti] OR paediatric[ti]	1,403,662
11	Child[mh] NOT (Adult[mh] OR Adolescent[mh])	883,352
12	Animals[mh] NOT Humans[mh]	4,943,361
13	animal[ti] OR animals[ti] OR rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] OR dog[ti] OR dogs[ti] OR primate[ti] OR primates[ti]	1,649,733
14	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti]	7,069,553
Final searches and exclusions		

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15	#10 OR #11 OR #12 OR #13 OR #14	13,278,944
16	#9 NOT #15	206
17	english[la] AND hasabstract	21,201,889
18	#16 AND #17	**148**

Table 3. Search strategy for CENTRAL

Row	Search term	Results
Search terms for the population		
1	(idiopathic near thrombocytopenic near purpura): kw	660
2	ITP: ti, ab	789
3	(purpura near thrombocytop*): ti, ab	604
4	((idiopathic or autoimmune or immune) near thrombocytop*): ti, ab	930
5	#1 or #2 or #3 or #4	1,324
Search terms for the intervention		
6	(fostamatinib or Tavalisse* or Tavlesse* or R-788 or R788): ti, ab, kw	107
Search terms for the comparator		
7	(azathioprine or danazol or dapsone or mycophenolic next acid or mycophenolate or cyclosporine): ti, ab, kw	12,053
Intervention + Comparator		
8	#6 or #7	12,155
Exclusion of non-relevant publication types		
9	NCT* au	219,055
10	("conference abstract" or review): pt	206,316
11	(clinicaltrials.gov or trialsearch): so	388,442

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	12	(Abstract or conference or meeting or proceeding*): so	45,201
	13	#9 or #10 or #11 or #12	625,023
Final searches			
	14	(#5 and #8) not #13	27
	15	# 14 not pubmed: an	**8**

4.3.2 Search Resources

The literature search was performed in the bibliographic databases PubMed and CENTRAL (see Table 4).

Table 4. Searched databases

Database	Interface/URL
PubMed	https://pubmed.ncbi.nlm.nih.gov/
Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley Cochrane Library

4.3.3 Study Selection

To be eligible for inclusion, studies had to meet all the following eligibility criteria for population, interventions, comparators, outcomes, study designs and limitations:

4.3.3.1 Population

To be eligible for inclusion, the studies had to assess patients ≥ 18 years of age with primary cITP who have no effect on other treatments (at least two or more previous treatment lines).

4.3.3.2 Interventions

Fostamatinib 100 mg twice daily. Can be adjusted to 150 mg daily after 4 weeks.

4.3.3.3 Comparators

To be eligible for inclusion, the studies had to evaluate at least one of the following interventions [1]:

- Danazol, 200 mg two to three times daily.
- Dapsone, 75–100 mg daily.
- Mycophenolate mofetil, up to 1 g twice a day.
- Azathioprine, 100 to 150 mg daily.
- Ciclosporin, 2–3 mg/kg/day in 2 divided doses.

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4.3.3.4 Outcomes

To be eligible for inclusion, the studies had to report at least one of the outcome measures specified in Table 1.

4.3.3.5 Study design

All studies were eligible for inclusion with the exception of:

- Case reports.
- Comments.
- Editorials.
- Guidelines.
- Letters.
- News.
- Reviews.

Limitations

- Only studies with at least title and abstract in English were considered for inclusion.

Table 5 summarizes the inclusion and exclusion criteria.

Table 5. Summary of inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Population	Patients ≥ 18 years of age with primary cITP who have no effect on other treatments (at least two or more previous treatment lines).	• Studies carried out only in paediatric and adolescent patients. • Studies that contain both the adult and paediatric population, but the subgroup results cannot be extracted. • Studies carried out in patients that had not previously been treated or had only received one line of treatment. • Studies carried out in patients without primary cITP. • Studies carried out in animals.
Intervention	Fostamatinib 100 mg twice daily. Can be adjusted to 150 mg daily after 4 weeks.	• None

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Comparator	At least one of the following [1]: • Danazol, 200 mg two to three times daily. • Dapsone, 75–100 mg daily. • Mycophenolate mofetil, up to 1 g twice a day. • Azathioprine, 100 to 150 mg daily. • Ciclosporin, 2–3 mg/kg/day in 2 divided doses.	• Studies not assessing any of the specified interventions. Studies assessing at least one of the specified interventions but given at a different dosage regimen.
Outcomes	Studies reporting at least one of the outcome measures specified in Table 1.	Studies not reporting any of the outcome measures specified in Table 1.
Study design	• No restriction	The following study designs were excluded: • Case reports. • Comments. • Editorials. • Guidelines. • Letters. • News. • Reviews.
Language	At least title and abstract in English.	Studies which have title, abstract and full text in a language other than English.

cITP: Chronic immune thrombocytopenia; kg: Kilogram; mg: Milligram; RCTs: Randomized controlled trials.

4.3.4 Identifying Search Results

Two researchers reviewed the titles, abstracts and, if necessary, the full texts were selected by the pre-defined list of inclusion and exclusion criteria detailed above.

4.4 Results of the Literature Search

4.4.1 Search Results

The searches were performed from April 6th to January 31st, 2022, and identified 156 records in 2 searched databases as shown in Table 6. The 156 records were screened for relevance.

Table 6. Results of the searched databases

Database	Results
PubMed	148
Cochrane Central Register of Controlled Trials (CENTRAL)	8
Total	156
Screened for relevance	156

4.4.2 Studies Identified and Selected

In this SLR update, a total of 156 records were screened for relevance (148 in the PubMed search, and eight in the CENTRAL search). Of these 148 records in the PubMed search, 105 records were excluded at title and abstract screening stage and 43 were sought for full-text review. Of these, 39 records were excluded after full-text screening and four studies were included in this SLR. The included studies are shown in Table 7. A list of the 39 excluded papers and respective reasons for exclusion is presented in section 8.2. In addition, there were eight records identified in the CENTRAL search. All these records were excluded at title and abstract screening stage. The full PRISMA for the PubMed and CENTRAL searches are presented in Figure 1 and Figure 2, respectively.

Table 7. List of the included studies

Study	Full reference
Colovic et al. 2011	Colovic M, Suvajdzic N, Colovic N, Tomin D, Vidovic A, Palibrk V. Mycophenolate mophetil therapy for chronic immune thrombocytopenic purpura resistant to steroids, immunosuppressants, and/or splenectomy in adults. Platelets. 2011;22(2):153-6. doi: 10.3109/09537104.2010.520372. Epub 2010 Dec 8.
Provan et al. 2006	Provan D, Moss AJ, Newland AC, Bussel JB. Efficacy of mycophenolate mofetil as single-agent therapy for refractory immune thrombocytopenic purpura. Am J Hematol. 2006 Jan;81(1):19-25. doi: 10.1002/ajh.20515.
Thabet et al. 2020	Thabet AF, Moeen SM. More about the combination of rituximab, cyclosporine and dexamethasone in the treatment of chronic ITP. A useful option on an environment with limited resources. Platelets. 2020 Aug 17;31(6):784-787. doi: 10.1080/09537104.2019.1678121. Epub 2019 Oct 11.
Zver et al. 2006	Zver S, Zupan IP, Cernelc P. Cyclosporin A as an immunosuppressive treatment modality for patients with refractory autoimmune thrombocytopenic purpura after splenectomy failure. Int J Hematol. 2006 Apr;83(3):238-42. doi: 10.1532/IJH97.05149.

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Figure 1. Study selection process for PubMed

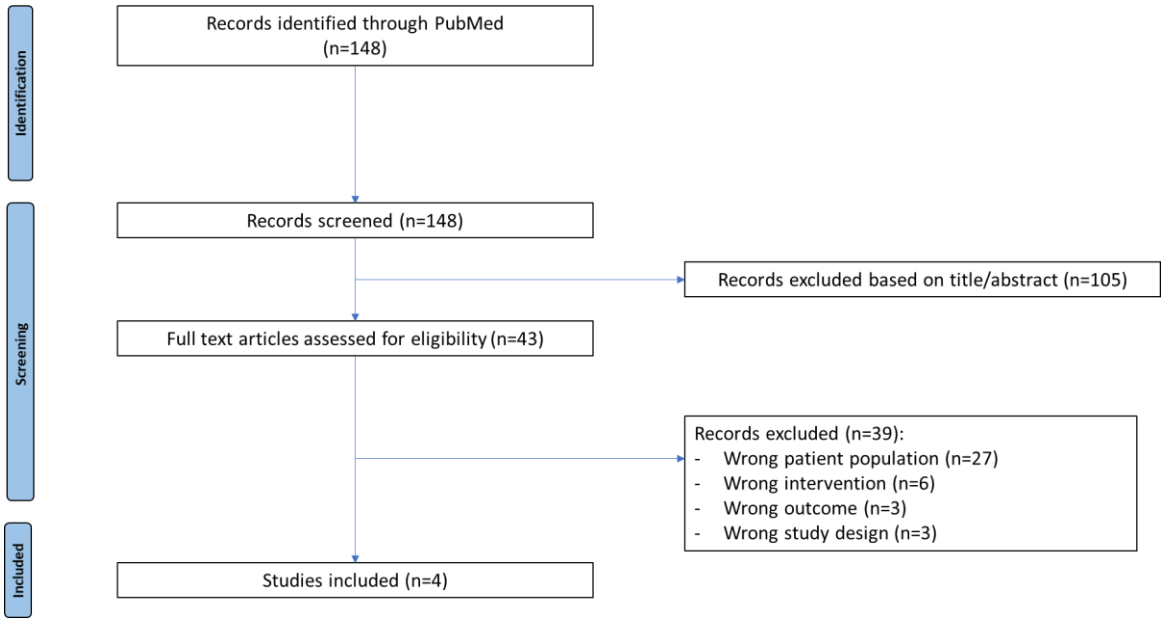
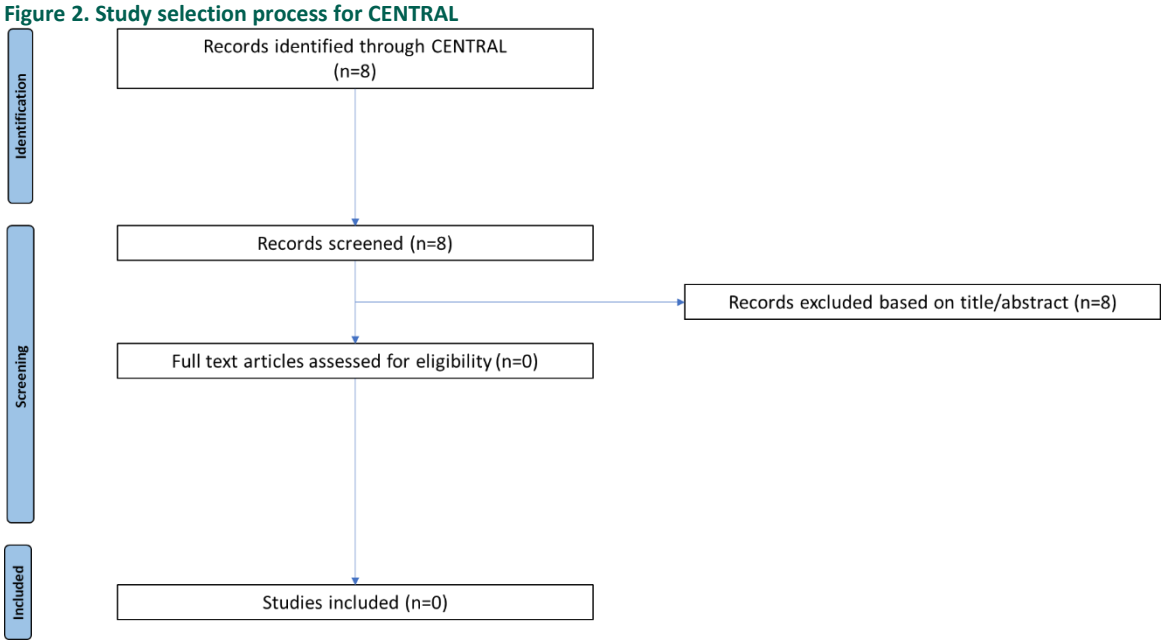


Figure 2. Study selection process for CENTRAL



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5. What is the value of fostamatinib compared to placebo for patients with primary chronic treatment refractory ITP?

5.1 Presentation of relevant studies

To respond to clinical question 1 the results from the two pivotal trials FIT1 and FIT 2 were used as well as a pooled analysis of the two trials. Additionally, the results from the open label extension study FIT3 were used for the safety narrative.

5.1.1 FIT clinical trial program

FIT1 and FIT2, are two identically designed, randomized, double-blind, placebo-controlled studies comparing the efficacy and safety of fostamatinib to placebo in adult patients with previously treated persistent (3-12 months since diagnosis) or chronic (greater than 12 months since diagnosis) ITP. FIT3 is a completed open label extension study where patients from FIT1 and FIT2 who completed 24 weeks of treatment, or who did not respond to treatment after 12 weeks, were eligible to enroll. Clinical question 1 were answered using data from the FIT clinical trial program, see Table 8.

Table 8. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
"Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials.", Bussel, J., et al., Am J Hematol., 2018 [2]	FIT1	NCT02076399	Start July 14, 2014 Completion April 21, 2016	Question 1/2
"Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials.", Bussel, J., et al., Am J Hematol., 2018 [2]	FIT2	NCT02076412	Start January 2015 Completion August 2016	Question 1/2

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Bussel, J.B., et al., *Long-term fostamatinib treatment of adults with immune thrombocytopenia during the phase 3 clinical trial program.* Am J Hematol, 2019. **94**(5): p. 546-553. [3]	FIT3	NCT02077192	Start July 2014 Completion June 1, 2020	Question 1/2

An overview of the FIT1 and FIT2 is presented in Table 9 and Table 10. FIT3 is presented in Table 14.

Table 9. Overview of FIT1 clinical trial

FIT1	An Efficacy and Safety Study of R935788 in the Treatment of Persistent/Chronic Immune Thrombocytopenic Purpura (ITP) (FIT1)
	"Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials.", Bussel, J., et al., Am J Hematol., 2018 [2] ”Long-term fostamatinib treatment of adults with immune thrombocytopenia during the phase 3 clinical trial program.”, Bussel, et al., Am J Hematol., 2019 [3] "Fostamatinib is an effective second-line therapy in patients with immune thrombocytopenia.", Boccia et al., British Journal of Haematology, 2020 [4]
NCT number	NCT02076399
Sample size (n)	76 (Fostamatinib n=51; Placebo n=25)
Study design	Phase 3, randomized, double blind, placebo-controlled study
Patient population	Patients 18 years of age or older (adults) with a primary ITP for at least 3 months. Eligible patients had persistent/cITP, in accordance with the American Society of Hematology 2011 Practice Guidelines and 2014 EMA guideline on clinical development of medicinal products for ITP. The average platelet counts had to be <30 000/µL, based on 3 qualifying counts (2 during screening) within the 3 months preceding study entry (and no counts >35 000/µL unless from rescue therapy). Other inclusion criteria included ≥ 1 prior treatment of ITP and Karnofsky score ≥ 70. Exclusion criteria included: secondary ITP, a major cardiovascular event, coagulopathy (including prothrombotic conditions such as Factor V Leiden, APC resistance, ATIII deficiency and lupus anticoagulant, or arterial or deep venous thrombosis) within 6 months, ITP Bleeding Scale Grade

	2 at the screening visit, poorly controlled hypertension, or disorders that, in the investigator's opinion, could affect the conduct of study.
Intervention(s)	Fostamatinib 100 mg BID. This could be increased to 150 mg BID after 4 weeks or later, depending on platelet count. Doses could be reduced to fostamatinib 100 or 150 mg once daily if a dose-limiting adverse event (AE) occurred.
Comparator(s)	Placebo combined with a watch and rescue strategy
Follow-up period	24 weeks
Is the study used in the health economic model?	Yes
Reasons for use / non-use of the study in model	Pivotal trial/ direct comparison of the intervention with the comparator
Primary endpoints reported include results	Stable platelet response by week 24 (≥50,000/µl on at least four of six clinic visits occurring every 2 weeks during weeks 14–24 inclusive)
Other outcomes reported include results	• Number of participants with platelet count ≥ 50,000/µL at week 12 and 24 • Platelet count ≥ 30,000/µL and ≥ 20,000/µL above baseline in subjects with baseline platelet count of <15,000/µL at week 12 and 24 • Mean of the ITP Bleeding Score • Mean of World Health Organization (WHO) Bleeding Scale
Inclusion criteria	• Age >18 years old • Clinical diagnosis of persistent/cITP for at least 3 months • ≥1 prior treatment of ITP • Average platelet count < 30,000/µL (and none > 35,000 unless as a result of rescue therapy) from at least 3 qualifying counts • Karnofsky score≥70
Exclusion criteria	• Secondary ITP • A major cardiovascular event, • Bleeding Scale Grade 2 at the screening • Clinical diagnosis of autoimmune hemolytic anemia • Uncontrolled or poorly controlled hypertension • History of coagulopathy including prothrombotic conditions
Method of analysis	All efficacy endpoints were analyzed based on the ITT population, and patients were analyzed according to their randomized treatment assignment. The efficacy analyses on the ITT population were considered the primary efficacy analyses. Safety analyses were performed on all randomized subjects who received any amount of fostamatinib. The primary endpoint was summarized by treatment group using counts and percentages, together with a 95% exact (Clopper-Pearson) confidence interval for the true percentage. The null and alternative hypotheses for the comparison of fostamatinib vs. placebo are as follows: H0: pF = pP vs. H1: pF ≠ pP where pF and pP denote the true proportions achieving a stable platelet response by 24 weeks for fostamatinib and placebo, respectively. The null hypothesis was tested using a 2-sided Fisher's Exact Test conducted with a significance level of 0.05. The same method was applied to the first two secondary endpoints. The remaining secondary endpoints (Mean ITP bleeding score and

	WHO bleeding scale) were analyzed using a 2-sided, 2-sampke t-test to test for a difference in means between the two arms. Safety was analyzed using descriptive statistics for the changes from baseline for systolic and diastolic blood pressure, each liver function test, and absolute neutrophil counts. The difference between fostamatinib and placebo in the mean change from baseline was also presented for each endpoint. For each treatment group, the 1 sample t-test was used to test whether the mean change from baseline equals 0 for each post-baseline time point. The 2-sample t-test was used to test whether the mean changes from baseline are equal for fostamatinib and placebo. The numbers and percentages of patients with GI complaints and infections at any time during the double-blind treatment period was presented by treatment group for the Safety Population. Fisher's Exact Test was used to test for a difference between fostamatinib and placebo in the proportions of patients experiencing GI complaints and infections. Missing data for the primary and secondary efficacy endpoints was imputed using the last observation carried forward (LOCF) method. Analysis populations included: (1) intent-to-treat (ITT): all randomized patients, primary population for efficacy analyses; and (2) safety: all randomized patients receiving a dose of study drug, the primary population for safety analyses. Sample size (75 patients per study: 50 fostamatinib, 25 placebo) was calculated to provide 90% power for the primary efficacy endpoint, using 2-sided, Fisher's Exact Test with alpha level of 0.05 and 2:1 fostamatinib:placebo allocation, assuming true proportions 0.40 for fostamatinib and 0.05 for placebo. One patient from FIT2, randomized to placebo, incorrectly received fostamatinib for 2 weeks; that patient's efficacy data were analyzed with the placebo group, but safety data with the fostamatinib group. The primary efficacy endpoint was analyzed using the prespecified imputation method of last observation carried forward (LOCF). A sensitivity analysis was conducted such that missing data were imputed as <50 000/µL (nonresponse). One patient in FIT2 randomized to fostamatinib had 5 consecutive study counts > 50 000/µL culminating at week 16; the patient then moved and thus had to leave the study. This patient was considered a stable responder in the prespecified analysis using LOCF and was a nonresponder in the sensitivity analysis. Efficacy endpoints were summarized using counts and percentages, and 95% exact (Clopper-Pearson) confidence intervals (CI). A 2-sided Fisher's Exact Test with significance level of 0.05 was used to evaluate efficacy. AEs were coded by the Medical Dictionary for Regulatory Activities.

Subgroup analyses	Subgroup analyses were conducted based on pre-specified subgroups for the pooled population (FIT1 and FIT2):
	
	• Baseline platelet count:
	  ○ ≥15k/ µl: n = 82
	  ○ <15k/ µl: n = 68
	• Prior splenectomy
	  ○ Yes: n = 53
	  ○ No: n = 97
	• Prior rituximab
	  ○ Yes: n = 48
	  ○ No: n = 102
	• Prior TPO-RA
	  ○ Yes: n = 71
	  ○ No: n = 79
	• Age
	  ○ <65 years: n = 111
	  ○ ≥65 years: n = 39

- Sex
  - Male: n = 59
  - Female: n = 91
- Duration of ITP at baseline
  - <8 years: n = 73
  - ≥8 years: n = 77

Both overall and stable response were analyzed.

Results	See Table 12

Table 10. Overview FIT2 clinical trial

FIT2	An Efficacy and Safety Study of Fostamatinib in the Treatment of Persistent/Chronic Immune Thrombocytopenic Purpura (ITP) (FIT2)
	"Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials.", Bussel, J., et al., Am J Hematol., 2018 [2] ”Long-term fostamatinib treatment of adults with immune thrombocytopenia during the phase 3 clinical trial program.”, Bussel, et al., Am J Hematol., 2019 [3] "Fostamatinib is an effective second-line therapy in patients with immune thrombocytopenia.", Boccia et al., British Journal of Haematology, 2020 [4]
NCT number	NCT02076412
Sample size (n)	74 (Fostamatinib n= 50, Placebo n=24)
Study design	Phase 3, randomized, double blind, placebo-controlled study
Patient population	Patients 18 years of age or older (adults) with a primary ITP for at least 3 months. Eligible patients had persistent/cITP, in accordance with the American Society of Hematology 2011 Practice Guidelines and 2014 EMA guideline on clinical development of medicinal products for ITP. The average platelet counts had to be <30 000/µL, based on _3 qualifying counts (2 during screening) within the 3 months preceding study entry (and no counts >35 000/µL unless from rescue therapy). Other inclusion criteria included ≥ 1 prior treatment of ITP and Karnofsky score ≥ 70. Exclusion criteria included: secondary ITP, a major cardiovascular event, coagulopathy (including prothrombotic conditions such as Factor V Leiden, APC resistance, ATIII deficiency and lupus anticoagulant, or arterial or deep venous thrombosis) within 6 months, ITP Bleeding Scale Grade 2 at the screening visit, poorly-controlled hypertension, or disorders that, in the investigator’s opinion, could affect the conduct of study.
Intervention(s)	Fostamatinib 100 mg BID. This could be increased to 150 mg BID after 4 weeks or later, depending on platelet count. Doses could be reduced to fostamatinib 100 or 150 mg once daily if a dose-limiting AE occurred.
Comparator(s)	Placebo combined with a watch and rescue strategy

Follow-up period	24 weeks
Is the study used in the health economic model?	Yes
Reasons for use / non-use of the study in model	Pivotal trial/ direct comparison of the intervention with the comparator
Primary endpoints reported include results	Stable platelet response by week 24 (≥50,000/µl on at least four of six clinic visits occurring every 2 weeks during weeks 14–24 inclusive)
Other outcomes reported include results	• Number of participants with platelet count ≥ 50,000/µL at week 12 and 24 • Platelet count ≥ 30,000/µL and ≥ 20,000/µL above baseline in subjects with baseline platelet count of <15,000/µL at week 12 and 24 • Mean of the ITP Bleeding Score • Mean of World Health Organization (WHO) Bleeding Scale
Inclusion criteria	• Age >18 years old • Clinical diagnosis of persistent/cITP for at least 3 months • ≥1 prior treatment of ITP • Average platelet count < 30,000/µL (and none > 35,000 unless as a result of rescue therapy) from at least 3 qualifying counts • Karnofsky score≥70
Exclusion criteria	• Secondary ITP • Clinical diagnosis of autoimmune hemolytic anemia • Uncontrolled or poorly controlled hypertension • A major cardiovascular event • History of coagulopathy including prothrombotic conditions • Bleeding Scale Grade 2 at the screening
Method of analysis	Same as FIT1, see Table 9.
Subgroup analyses	Subgroup analyses were conducted for the pooled population, see Table 9.
Results	See Table 13

FIT1 and FIT2 were two identically designed studies to investigate the efficacy and safety of fostamatinib versus placebo in achieving a response in patients with persistent or cITP (as defined by Rodeghiero et al., [5]) at biweekly timepoints during weeks 14 and 24. For each study, patients were randomized 2:1 to fostamatinib or placebo for 24 weeks; randomization was stratified with respect to prior splenectomy and severity of thrombocytopenia (baseline platelet count: <15,000/µL or ≥15,000/µL). Stable concurrent ITP therapy (glucocorticoids [less than 20 mg prednisone equivalent per day], azathioprine, or danazol) was allowed, and rescue therapy was permitted, if needed. All patients initially received study drug at 100 mg twice daily (or matching placebo). Based on platelet count and tolerability, dose escalation to 150 mg twice daily (or matching placebo) was undertaken in 86% of patients at Week 4 or later [6].

The primary efficacy analyses were based on the Intent-to-Treat (ITT) population which included all randomized subjects. Subjects were analyzed according to their randomized treatment assignments. A total of 146 patients received fostamatinib in any of the three FIT studies. Of them, 101 were assigned to receive fostamatinib in placebo-controlled

studies (FIT 1 or FIT2) and the rest received only fostamatinib in the FIT3 study. Patient disposition in the FIT1 and FIT 2 studies is shown in Figure 3. In both studies, patient characteristics at baseline were well-balanced between treatment groups in terms of age (median: 54 years fostamatinib vs 53 years placebo), sex (60% vs 61% female) and median number of prior ITP treatments (3 [1-13] vs 3 [1-10]). However, in FIT2, patients on fostamatinib had lower median platelet counts at baseline than patients on placebo (15,900/µL [1,000-33,000] vs 23,958/µL [1,000-156,000]) [2]. Patient characteristics are presented in Table 11.

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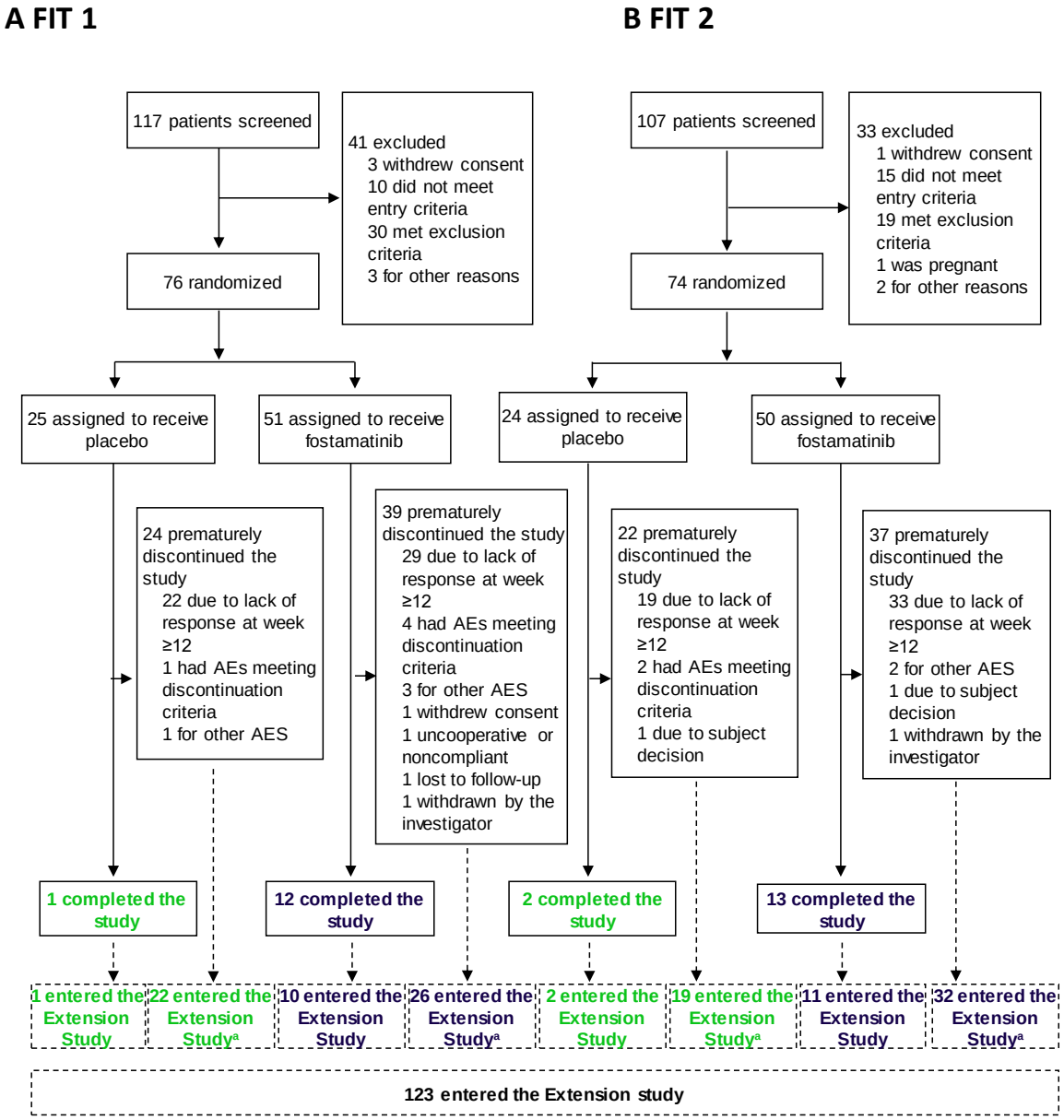
Figure 3. Disposition (ITT population)



[a] Patients who enter the Extension Study due to lack of response at week ≥12

Note: Patients who enter the Extension Study and were treated with placebo in the randomized trials are presented in green. Patients who enter the Extension Study and were treated with fostamatinib in the randomized trials are presented in blue. In FIT2, safety population differed from the ITT population because one patient was randomized to placebo but was mistakenly treated with fostamatinib. That is, one patient was included under placebo treatment in the ITT population and under fostamatinib treatment in the safety population. Source: [3]

Table 11. Patient demographics and characteristics at baseline in FIT1 and FIT2 [2]

	FIT1 (n=76)		FIT2 (n=74)		Pooled (n=150)	
	Fostamatinib (n = 51)	Placebo (n = 25)	Fostamatinib (n = 50)	Placebo (n = 24)	Fostamatinib (n = 101)	Placebo (n = 49)
Age, median (range), years	57 (20–88)	57 (26–77)	50 (21–82)	50 (20–78)	54 (20–88)	53 (20–78)
Sex, n (%)						
Female	30 (59)	17 (68)	31 (62)	13 (54)	61 (60)	30 (61)
Male	21 (41)	8 (32)	19 (38)	11 (46)	40 (40)	19 (39)
Race, n (%)						
White	44 (86)	21 (84)	50 (100)	24 (100)	94 (93)	45 (92)
Asian	3 (6)	2 (8)	0	0	3 (3)	2 (4)
Black/African American	2 (4)	2 (8)	0	0	2 (2)	2 (4)
Other	2 (4)	0	0	0	2 (2)	0
Region, n (%)						
North America	17 (33)	8 (32)	0	0	17 (17)	8 (16)
Europe	25 (49)	13 (52)	50 (100)	24 (100)	75 (74)	37 (76)
Australia	9 (18)	4 (16)	0	0	9 (9)	4 (8)
ITP Classification, n (%)						
Persistent	3 (6)	3 (12)	3 (6)	1 (4)	6 (6)	4 (8)
Chronic	48 (94)	22 (88)	47 (94)	23 (96)	95 (94)	45 (92)
Duration of ITP, median (range), years	7.5 (0.6–53.0)	5.5 (0.4–45.0)	8.8 (0.3–50.2)	10.8 (0.9–29.1)	8.7 (0.3–53)	7.8 (0.4–45)
Duration of ITP ≥3 years, n (%)	38 (75)	17 (68)	38 (76)	18 (75)	76 (75)	35 (71)
Prior unique treatments for ITP, median (range)	3.0 (1–9)	5.0 (1–10)	3.0 (1–13)	3.0 (1–10)	3.0 (1–13)	3.0 (1–10)
Prior treatments, n (%)						
Corticosteroids	46 (90)	25 (100)	48 (96)	22 (92)	94 (93)	47 (96)
IVIg or IV Anti-D	33 (65)	17 (68)	19 (38)	10 (42)	52 (51)	27 (55)
TPO-RA	27 (53)	15 (60)	20 (40)	10 (42)	47 (47)	25 (51)
Immunosuppressants	22 (43)	12 (48)	22 (44)	10 (42)	44 (44)	22 (45)
Splenectomy	20 (39)	10 (40)	14 (28)	9 (38)	34 (34)	19 (39)
Rituximab	26 (51)	11 (44)	8 (16)	3 (13)	34 (34)	14 (29)
Danazol	7 (14)	4 (16)	13 (26)	5 (21)	20 (20)	9 (18)
Chemotherapy	4 (8)	2 (8)	5 (10)	4 (17)	9 (9)	6 (12)
Other (Dapsone)	10 (20)	3 (12)	0	0	10 (10)	3 (6)

	FIT1 (n=76)		FIT2 (n=74)		Pooled (n=150)	
	Fostamatinib (n = 51)	Placebo (n = 25)	Fostamatinib (n = 50)	Placebo (n = 24)	Fostamatinib (n = 101)	Placebo (n = 49)
Baseline platelet count, mean, /µL (range)	16,202 (1000-51,000)	15,844 (1000-48,000)	15,900 (1000-33,000)	23,958 (1000-156,000)	16,052 (1000-51,000)	19,818 (1000-156,000)
Baseline Platelet count of <15,000 /µL, n (%)	25 (49)	12 (48)	22 (44)	9 (38)	47 (47)	21 (43)

Abbreviations: ITP: immune thrombocytopenia; TPO-RA: thrombopoietin receptor agonist; IVIg: intravenous immunoglobulins; IV: intravenous; Anti-D: Anti-D immunoglobulin.

The main results of FIT1 and FIT2 are presented in Table 12 and Table 13.

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Table **12. Results of study FIT1**

Trial name:	FIT1										
NCT number:	NCT02076399										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result n (%) (95% CI)	Difference %-point	95% CI	*P* value	Difference	95% CI	*P* value		
Stable platelet response by week 24	Fostamatinib	51	Yes: 9 (17.6) No: 42 (82.4) (8.4, 30.9)‡	17.6	(7.2, 28.1)†	NA	NA	NA	0.0261ʃ	‡ Clopper-Pearson exact confidence interval for a binomial proportion. †Confidence interval based on the normal approximation. ʃ p-value is from Fisher's Exact Test, testing for a difference in proportions between treatments.	[7, 8]
	Placebo	25	Yes: 0 (0.0) No: 25 (100.0) (0.0, 13.7) ‡								
Number of participants with platelet count ≥ 50,000/µL at week 12	Fostamatinib	51	Yes: 11 (21.6) No: 40 (78.4) (11.3, 35.3)‡	21.6	(10.3, 32.9)†	NA	NA	NA	0.0127ʃ	‡ Clopper-Pearson exact confidence interval for a binomial proportion. †Confidence interval based on the normal approximation. ʃ p-value is from Fisher's Exact Test, testing for a difference in proportions between treatments.	
	Placebo	25	Yes: 0 (0.0) No: 25 (100.0) (0.0, 13.7)‡								

Number of participants with platelet count ≥ 50,000/µL at week 24	Fostamatinib	51	Yes: 8 (15.7) No: 43 (84.3) (7.0, 28.6)‡	15.7	(5.7, 25.7)†	NA	NA	NA	0.0471∫	‡ Clopper-Pearson exact confidence interval for a binomial proportion. †Confidence interval based on the normal approximation. ∫ p-value is from Fisher's Exact Test, testing for a difference in proportions between treatments.	
	Placebo	25	Yes: 0 (0.0) No: 25 (100.0) (0.0, 13.7)‡								
Platelet count ≥ 30,000/µL and ≥ 20,000/µL above baseline in subjects with baseline platelet count of <15,000/µL at week 12	Fostamatinib	25*	Yes: 4 (16.0) No: 21 (84.0) (4.5, 36.1)‡	16.0	(1.6, 30.4)†	NA	NA	NA	0.2823∫	‡ Clopper-Pearson exact confidence interval for a binomial proportion. †Confidence interval calculated based on the normal approximation. ∫ p-value from Fisher's Exact Test, testing for a difference in proportions between treatments.	
	Placebo	12*	Yes: 0 (0.0) No: 12 (100.0) (0.0, 26.5)‡								
Platelet count ≥ 30,000/µL and ≥ 20,000/µL above baseline in subjects with baseline platelet count of <15,000/µL at week 24	Fostamatinib	25*	Yes: 4 (16.0) No: 21 (84.0) (4.5, 36.1)‡	16.0	(1.6, 30.4)†	NA	NA	NA	0.2823∫		
	Placebo	12*	Yes: 0 (0.0) No: 12 (100.0) (0.0, 26.5)‡								
Mean of the ITP Bleeding Score	Fostamatinib	51	Mean: 0.13 (0.1, 0.2) †	-0.01	(-0.1, 0.0)†	0.6642∫	NA	NA	NA		

	Placebo	25	Mean: 0.14 (0.1, 0.2) †							†Confidence interval calculated based on the t-distribution. ∫p-value from a two-sided two-sample t-test, testing for a difference in means between fostamatinib and placebo.	
Mean of the WHO Bleeding Scale Score	Fostamatinib	51	Mean: 0.61 (0.4, 0.8) †	0.15	(-0.2, 0.5)†	0.3365∫	NA	NA	NA	†Confidence interval calculated based on the t-distribution. ∫p-value from a two-sided two-sample t-test, testing for a difference in means between fostamatinib and placebo.	
	Placebo	25	Mean: 0.46 (0.2, 0.7)†								

*The sample size used was a subset of the sample size of the respective treatment arm.

Table 13. Results of study FIT2

Trial name:	FIT2										
NCT number	NCT02076412										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result n (%) (CI)	Difference %-point	95% CI	*P* value	Difference	95% CI	*P* value		
Stable platelet response by week 24	Fostamatinib	50	Yes: 9 (18.0) No: 41 (82.0) (8.6, 31.4) ‡	13.8	(0.5, 27.1)†	NA	NA	NA	0.1519∫	‡ Clopper-Pearson exact confidence interval for a binomial proportion. †Confidence interval based on the normal approximation.	[8]

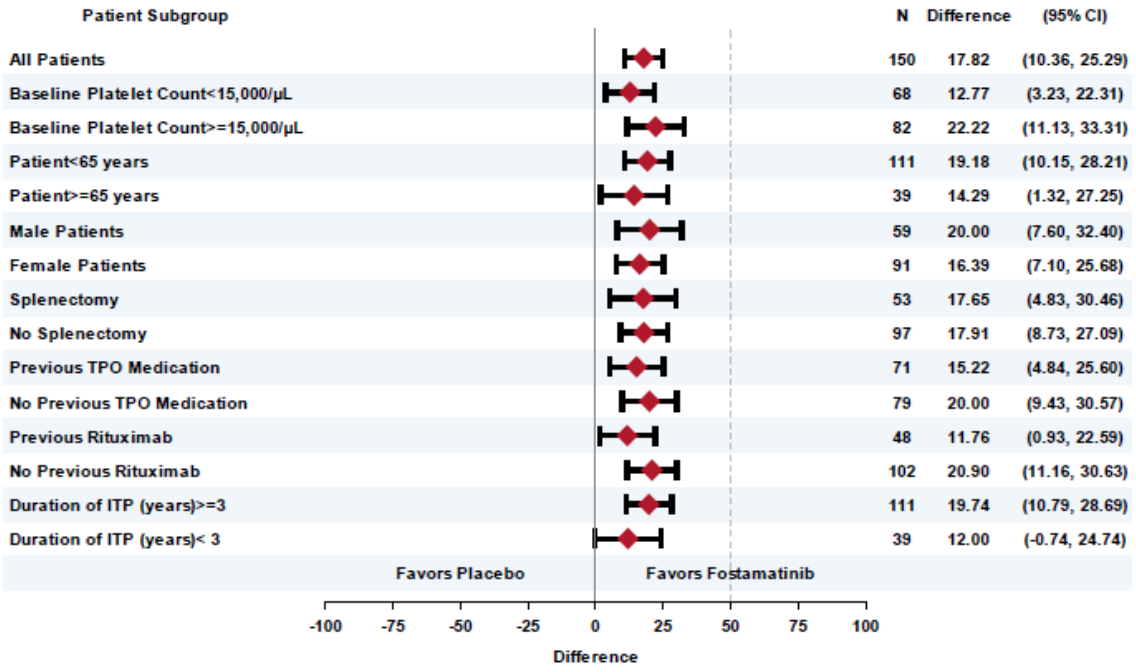
	Placebo	24	Yes: 1 (4.2) No: 23 (95.8) (0.1, 21.1)‡							∫) p-value is from Fisher's Exact Test, testing for a difference in proportions between treatments.	
Number of participants with platelet count ≥ 50,000/µL at week 12	Fostamatinib	50	Yes: 12 (24.0) No: 38 (76.0) (13.1, 38.2)‡	11.5	(-6,3, 29.3)†	NA	NA	NA	0.3581∫	‡ Clopper-Pearson exact confidence interval for a binomial proportion. †Confidence interval calculated based on the normal approximation ∫ p-value is from Fisher's Exact Test, testing for a difference in proportions between treatments.	
	Placebo	24	Yes: 3 (12.5) No: 21 (87.5) (2.7, 32.4)‡								
Number of participants with platelet count ≥ 50,000/µL at week 24	Fostamatinib	50	Yes: 8 (16.0) No: 42 (84.0) (7.2, 29.1)‡	11.8	(-1.1, 24.8)†	NA	NA	NA	0.2559∫		
	Placebo	24	Yes: 1 (4.2) No: 23 (95.8) (0.1, 21.1)‡								
Platelet count ≥ 30,000/µL and ≥ 20,000/µL above baseline in subjects with baseline platelet count of <15,000/µL at week 12	Fostamatinib	22*	Yes: 6 (27.3) No: 16 (72.7) (10.7, 50.2)‡	16.2	(-11.5, 43.9)†	NA	NA	NA	0.6395∫	†Confidence interval calculated based on the normal approximation for categorical variables. ‡ Clopper-Pearson exact confidence interval for a binomial proportion	
	Placebo	9*	Yes: 1 (11.1) No: 8 (88.9) (0.3, 48.2)‡								

Platelet count ≥ 30,000/µL and ≥ 20,000/µL above baseline in subjects with baseline platelet count of <15,000/µL at week 24	Fostamatinib	22*	Yes: 3 (13.6) No: 19 (86.4) (2.9, 34.9)‡	13.6	(-0.7, 28.0)†	NA	NA	NA	0.5375∫	∫ p-value is from Fisher's Exact Test, testing for a difference in proportions between treatments.	
	Placebo	9*	Yes: 0 (0.0) No: 9 (100.0) (0.0, 33.6)‡								
Mean of IBLS scores across 9 anatomical sites and across visits during the 24-week treatment period	Fostamatinib	50	Mean: 0.04 (0.02, 0.07) †	-0.01	(-0.05, 0.02)†	0.4927∫	NA	NA	NA	†Confidence interval calculated based on the t-distribution. ∫p-value from a two-sided two-sample t-test, testing for a difference in means between fostamatinib and placebo.	
	Placebo	24	Mean: 0.06 (0.03, 0.09) †								
Mean of WHO Bleeding Scale scores across visits during the 24-week treatment period	Fostamatinib	50	Mean: 0.26 (0.15, 0.36)†	-0.12	(-0.32, 0.09)†	0.2499∫	NA	NA	NA		
	Placebo	24	Mean: 0.38 (0.18, 0.57)†								

*The sample size used was a subset of the sample size of the respective treatment arm.

Subgroup analyses were conducted. Responses to fostamatinib were observed across all subgroups of age, sex, prior therapy (splenectomy, rituximab, or TPO-RA), baseline platelet count (15,000 ≤ vs. >15,000/µL), or duration of ITP at study entry (see Figure 4) [2, 9]. Stable responders had a stable platelet response by week 24 (≥50,000/µl on at least four of six clinic visits occurring every two weeks during weeks 14–24 inclusive) [2].

Figure 4. Subgroup analysis for stable responders in the pooled population [9]



5.1.2 FIT3

FIT3 is an open label extension study. Patients from FIT1 and FIT2 who completed 24 weeks of treatment, or who did not respond to treatment after 12 weeks, were eligible to enroll in this study. Patients remained blinded to their treatment assignment from the previous study (fostamatinib or placebo), so their starting dose in FIT3 was based on their final platelet count in FIT1 or FIT2. The presented results of this study correspond to an interim analysis (cut-off March 2018) as the study is still ongoing.

An overview of the open label extension study FIT3 is given below in Table 14

Table 14. Overview FIT3 clinical trial

FIT3	Open Label Study of R788 in the Treatment of Persistent/Chronic Immune Thrombocytopenic Purpura (ITP) (FIT3) (Extension study to FIT1 and FIT2)
	Duliege, A.-M., et al. (2018). "Two-Year Safety and Efficacy Outcomes with Fostamatinib in Adult Patients with Immune Thrombocytopenia (ITP): Open-Label Extension to Phase 3 Trial Program." Blood 132(Supplement 1): 736-736. [10]
Sample size (n)	N= 123

Study design	Open-label extension
Patient population	Patients 18 years of age or older (adults) with a primary ITP for at least 3 months. Eligible patients had persistent/cITP, in accordance with the American Society of Hematology 2011 Practice Guidelines and 2014 EMA guideline on clinical development of medicinal products for ITP. To enter the open-label extension (OLE) study, patients had to either have completed the full 24 weeks of treatment in the previous study (FIT1 or FIT2) or have discontinued the previous study due to lack of efficacy after completing at least 12 weeks of double-blind treatment including at least 4 weeks at 150 mg BID of study drug (active medication or placebo).
Intervention(s)	Fostamatinib either at the same dose and regimen as in the randomized studies in patients with platelet count ≥50,000/µL, or at 100 mg BID in those who entered the OLE study as non-responders in the randomized trials. Dose could be reduced to as low as 100mg QD if a dose-limiting event occurred
Comparator(s)	N/A
Follow-up period	5 years or until commercial availability of fostamatinib for all subjects is realized
Is the study used in the health economic model?	Yes
Reasons for use / non-use of the study in model	Complementation of trial data >24 weeks
Primary endpoints reported include results	Number of participants with platelet count of at least 50,000/µL as a measure of safety and efficacy, 5 years
Other outcomes reported include results	Placebo-Crossover: Placebo patients from the prior studies (FIT1 and FIT2) who crossed over to fostamatinib were evaluated for stable response for fostamatinib (from the first 24 weeks of the study) with their placebo data as the comparator for this objective measure.
Method of analysis	Analyses were performed on the treated population only, which included all enrolled and treated patients.

To address the questions in the protocol the pooled analysis of FIT1 and FIT2 was used. The results of the analyses are presented in Table 15.

Table 15. Results for clinical question 1

Results referring to clinical question 1								
Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	95% CI	*P* value	Difference	95% CI	*P* value	
Quality of Life: Change in SF-36 from baseline: PF, 4 weeks	FIT1 and FIT2 [7, 8]	XXX	XXXXXXXXXXX	NA	NA	NA	NA	Pooled weighted means, see section 5.2.1 95% confidence intervals assume normally distributed point estimates.
Quality of Life: Change in SF-36 from baseline: PF, 12 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
Quality of Life: Change in SF-36 from baseline: RP, 4 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
Quality of Life: Change in SF-36 from baseline: RP, 12 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
Quality of Life: Change in SF-36 from baseline: BP, 4 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
Quality of Life: Change in SF-36 from baseline: BP, 12 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
Quality of Life: Change in SF-36 from baseline: GH, 4 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	

Results referring to clinical question 1						
Quality of Life: Change in SF-36 from baseline: GH, 12 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
Quality of Life: Change in SF-36 from baseline: V, 4 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
Quality of Life: Change in SF-36 from baseline: V, 12 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
Quality of Life: Change in SF-36 from baseline: SF, 4 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
Quality of Life: Change in SF-36 from baseline: SF, 12 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
Quality of Life: Change in SF-36 from baseline: RE, 4 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
Quality of Life: Change in SF-36 from baseline: RE, 12 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
Quality of Life: Change in SF-36 from baseline: MH, 4 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
Quality of Life: Change in SF-36 from baseline: MH, 12 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA

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Results referring to clinical question 1							
Quality of Life: Change in SF-36 from baseline: PHS, 4 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
Quality of Life: Change in SF-36 from baseline: PHS, 12 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
Quality of Life: Change in SF-36 from baseline: MHS, 4 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
Quality of Life: Change in SF-36 from baseline: MHS, 12 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): PF, 4 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	The proportion of patients achieving an 8-point improvement in FIT1 and FIT2 was estimated using simulation based on the observed mean change from baseline. 95% CI assumed normally distributed point estimates. See section **Error! Reference source not found.** for details.
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): PF, 12 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): RP, 4 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	

Results referring to clinical question 1						
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): RP, 12 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): BP, 4 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): BP, 12 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): GH, 4 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): GH, 12 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): V, 4 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA

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Results referring to clinical question 1						
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): V, 12 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): SF, 4 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): SF, 12 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): RE, 4 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): RE, 12 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): MH, 4 weeks	XXX	XXXXXXXXXXX	NA	NA	NA	NA

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Results referring to clinical question 1							
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): MH, 12 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): PHS, 4 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): PHS, 12 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): MHS, 4 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
The difference in proportion of patients that achieve ≥8 point improvement (in %-point): MHS, 12 weeks		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
Proportion that experiences a serious bleed (%-point)*		XXX	XXXXXXXXXXX	NA	NA	NA	NA	Difference in %-point of pooled patients in FIT1 and FIT2 that experience a serious bleed. The 95% CI assumed a normal distribution of the point estimate. See section 5.2.3.

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Results referring to clinical question 1							
Proportion that experiences a minor bleed (%-point)†		XXX	XXXXXXXXXXX	NA	NA	NA	NA	Difference in %-point of pooled patients in FIT1 and FIT2 that experience a non-serious bleed (used as proxy for a minor bleed). The 95% CI assumed a normal distribution of the point estimate. See section 5.2.3.
Platelet count – proportion of patients with platelet counts ≥ $30x10^9$/L (%-point): week 0		XXX	XXXXXXXXXXX	NA	NA	NA	NA	Difference in %-point of pooled patients in FIT1 and FIT2 that achieve a platelet count of $30x10^9$ or above. The 95% CI assumed a normal distribution of the point estimate. Please note that less than four patients (three and one, respectively) remained in the placebo arm at timepoints Week 20 and Week 24 in the pooled analysis of FIT1 and FIT2. Thus, a difference between the two arms was only calculated for weeks 0-16. See section 5.2.4
Platelet count – proportion of patients with platelet counts ≥ $30x10^9$/L (%-point): week 4		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
Platelet count – proportion of patients with platelet counts ≥ $30x10^9$/L (%-point): week 8		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
Platelet count – proportion of patients with platelet counts ≥ $30x10^9$/L (%-point): week 12		XXX	XXXXXXXXXXX	NA	NA	NA	NA	
Platelet count – proportion of patients with platelet counts ≥ $30x10^9$/L (%-point): week 16		XXX	XXXXXXXXXXX	NA	NA	NA	NA	

Results referring to clinical question 1							
Adverse events: proportion that discontinue due to an adverse event (%-point)		XXX	XXXXXXXXXX	NA	NA	NA	NA	%-point difference between pooled arms of FIT1 and FIT2. The 95% CI assumed a normal distribution of the point estimate. See section 5.2.5.
Qualitative description of adverse events	FIT1, FIT2, and FIT3 [3, 10]	NA	NA	NA	NA	NA	NA	See section 5.2.5.

*See section 5.2.3 for definition of serious bleeds. †Minor bleeds are assumed to be non-serious bleeds,

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5.2 Study results.

5.2.1 XXXXXXXXXXXXXXXXX

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The change from baseline was reported for each domain of the SF-36 instrument for the fostamatinib and placebo arm in FIT1 and FIT2 (FIT1 and FIT2 clinical study reports). The difference in change from baseline was calculated using the following steps:

The weighted average of mean from baseline in FIT1 and FIT2 was calculated separately for fostamatinib and placebo using normalized weights for each timepoint. Below the calculation for mean change in physical functioning (PF) week 4 normalized weight for FIT1 ($w_{FIT1,week4,PF}$) is shown as an example:

$$w_{FIT1,week4,PF} = \frac{\frac{n_{FIT1,week4}}{N_{FIT1}}}{\frac{n_{FIT1,week4}}{N_{FIT1}} + \frac{n_{FIT2,week4}}{N_{FIT2}}}$$

The pooled mean-change is calculated by the addition of the weighted mean change from FIT1 and FIT2. In the next step the difference in mean change from baseline between fostamatinib and placebo was calculated by taking the difference in the pooled mean change between the two arms. The 95% CI is calculated using the sum of the variance of the pooled point estimates for FIT1 and FIT2. Below, example equations for the pooled variance as well as the 95% confidence interval for the difference in mean change in PF is given:

$$SE_{pooled}^{week4} = \sqrt{(w_{FIT1}^{week4} \cdot SE_{FIT1}^{week4})^2 + (w_{FIT2}^{week4} \cdot SE_{FIT2}^{week4})^2}$$

$$95\%\ CI = \widehat{\Delta\mu}_{week4,PF} \pm 1.96 \cdot \sqrt{SE_{Fosta}^2 + SE_{Placebo}^2}.$$

Where w is the weight for FIT1 and FIT2, respectively and SE is the associated standard deviation of the mean change.

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5.2.2 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

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5.2.3 Proportion that experiences a bleed

Proportion of patients with bleeds reported and graded as AEs were available from FIT1 and FIT2. A pooled analysis of the safety population is presented below in Table 16. The proportion of mild bleeds was not available, instead the proportion of non-serious bleeds is presented. The definition used for non-serious bleeds is:

All reported bleeds that did not meet the criteria for serious. I.e. moderate bleeds that are defined as experiences which introduce some level of inconvenience or concern to the subject and which may interfere with daily activities but are usually ameliorated by simple therapeutic measures and mild bleeds that are defined as experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities.

Additionally, the definition of serious bleeds, according to the reporting of AEs in FIT1 and FIT2 is:

- Results in death

- Is life-threatening. (With regards to determining if an AE is serious, “life-threatening” is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the Investigator or the Sponsor believes that an AE meets the definition of life threatening, it will be considered life-threatening.)
- Requires in-patient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity (e.g., the AE results in substantial disruption of the subject’s ability to conduct normal life functions)

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Table 16. Serious and non-serious bleeds (safety population)

	Fostamatinib FIT1	Placebo FIT1	Fostamatinib FIT2	Placebo FIT2	Fostamatinib Pooled*	Placebo Pooled	
N	51	25	51	23	102	48	[8]
Any bleed	20	7	8	10	28	17	
Serious bleed	3	3	2	2	5	5	
Non-serious bleed	17	4	6	8	23	12	
Proportion – serious bleed (95% CI)					4.9% (0.7, 9.1)	10.4% (1.8, 19.1)	
Difference %-point (95% CI)					-5.5 (-15.1, 4.1)		
Proportion – non-serious bleed (95% CI)					22.5% (14.4, 30.7)	25.0% (12.8, 37.3)	
%-point difference (95% CI)					-2.5% (-17.1, 12.2)		

*The safety population differs from the ITT population as one patient randomized to placebo received fostamatinib.

5.2.4 Proportion of patients with platelet counts ≥ 30,000/µL

The pooled proportion of patients in FIT1 and FIT2 with a platelet count above 30,000/µL is presented in Table 17. Please note that less than four patients (three and one, respectively) remained in the placebo arm at timepoints Week 20 and Week 24 in the pooled analysis of FIT1 and FIT2. Thus, a difference between the two arms was only calculated for weeks 0-16. The difference between the two arms in FIT1 and FIT2 increase in the first four weeks to become stable at 20 percentage points at Week 8 to Week 16.

Table 17. Proportion of patients with platelet counts ≥ 30x10^9/L per timepoint in FIT 1 and FIT 2

Treatment arm/Week	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Reference
Fostamatinib % (n/N) (95% CI)*	11.8 (12/102), (5.5, 18.0)	34.3 (35/102) (25.1, 43.5)	49.0 (47/96) (39.0, 59.0)	53.6 (45/84) (42.9, 64.2)	79.5 (31/39) (66.8, 92.2)	80.6 (25/31) (66.7, 94.6)	80.0 (16/20) (62.5, 97.5)	[8]
Placebo % (n/N) (95% CI)*	10.4 (5/48) (1.8, 19.1)	27.7 (13/47) (14.9, 40.5)	28.9 (13/45) (15.7, 42.1)	31.6 (12/38) (16.8, 46.4)	60.0 (6/10) (29.6, 90.4)	66.7 (2/3) (13.3, 100.0†)	100% (1/1) (100.0, 100.0)	
Difference %-point (95% CI)*	1.4 (-9.3, 12.0)	6.6 (-9.1, 22.4)	20.1 (3.5, 36.7)	22.0 (3.8, 40.2)	19.5 (-13.4, 52.4)	-	-	

*95% confidence intervals assume a normal distribution: $p \pm 1.96 \cdot \sqrt{p \cdot \frac{1-p}{n}}$ and $p_1 - p_2 \pm 1.96 \cdot \sqrt{p_1 \cdot \frac{1-p_1}{n_1} + p_2 \cdot \frac{1-p_2}{n_2}}$, †95% CI upper limit truncated to 100%

5.2.5 Adverse events

Study drug was withdrawn due to AEs in 10 (9.8%) fostamatinib treated subjects and 4 (8.3%) placebo treated subjects. AEs leading to study drug discontinuation is presented in Table 18 below. [CSR/EPAR]

Table 18. Adverse events leading to discontinuation in FIT 1 and FIT 2

Study	Treatment	Adverse event leading to discontinuation
FIT1	Fostamatinib	Syncope
FIT1	Fostamatinib	Pneumonia
FIT1	Fostamatinib	Alanine aminotransferase increased
FIT1	Fostamatinib	Diarrhoea
FIT1	Fostamatinib	Chest pain
FIT1	Fostamatinib	Thrombocytopenia
FIT1	Fostamatinib	Abdominal pain
FIT1	Fostamatinib	Neutropenia
FIT2	Fostamatinib	Plasma cell myeloma
FIT2	Fostamatinib	Headache
FIT1	Placebo	Epistaxis
FIT1	Placebo	Abdominal discomfort
FIT2	Placebo	Hypertension
FIT2	Placebo	Diarrhoea

FIT1

In FIT 1, AEs (294 events) occurred in 96.1% of subjects in the fostamatinib group compared with 90 events in 76.0% of subjects in the placebo group; the mean number of AEs per subject was 6.0 and 4.7, respectively. Serious AEs occurred in similar numbers of subjects in the fostamatinib and placebo groups (8 and 5 subjects, respectively). One placebo subject died during the study due to a serious AE (SAE) of sepsis. More fostamatinib-treated subjects than placebo subjects experienced AEs that were considered treatment-related. Higher proportions of subjects in the fostamatinib group had dose reductions, dose interruptions, or withdrawal of study drug due to AEs than subjects in the placebo group [8].

FIT2

In FIT2, AEs (141 events) occurred in 70.6% of subjects in the fostamatinib group and (53 events) in 78.3% of subjects in the placebo group; the mean number of AEs per subject was 3.9 and 2.9, respectively. Serious AEs occurred in 5/51 (9.8%) subjects in the fostamatinib group and 6/23 (26.1%) subjects in the placebo group. One subject in the fostamatinib group (Subject 048-433-005) died approximately 10 weeks after discontinuing the study, on study day 19, due to an SAE of plasma cell myeloma considered unlikely related to study drug. More of the AEs experienced by fostamatinib-treated subjects than placebo subjects were considered treatment-related (39.2% vs 26.1% of subjects, respectively). The AEs experienced by fostamatinib subjects led to a higher incidence of dose reduction or dose interruption due to AEs than in placebo subjects. A smaller proportion of subjects in the fostamatinib group experienced AEs that led to withdrawal of study drug than in the placebo group [8].

Pooled analysis FIT1 and FIT2

In FIT1 and FIT2, 83% and 75% of patients experienced AEs in the fostamatinib and placebo groups, respectively. The most commonly reported AEs were diarrhoea, nausea, hypertension, dizziness, and ALT and/or AST increases (Table 19). Overall infections were slightly more frequent in patients on fostamatinib than placebo (30% vs. 21%, respectively), but rates of moderate or severe infections were similar (8% vs. 6%, respectively). Most cases of AEs were either mild (39% on fostamatinib and 56% on placebo) or moderate (42% on fostamatinib and 25% on placebo). Similar rates of AEs

leading to treatment withdrawal were reported between treatment arms (9.8% fostamatinib vs. 8.3% placebo, see Table 13), but at different rates between studies (FIT1: 16% fostamatinib vs. 8% placebo; FIT2: 4% vs. 9%). Severe AEs leading to treatment withdrawal in the fostamatinib arm included 1 case each of non-serious chest pain and syncope, pneumonia, and thrombocytopenia. Patients on fostamatinib had higher rates of AEs leading to dose reductions (9% fostamatinib vs. 2% placebo) and temporary dose interruptions (18% vs. 10%). The most common AEs (2%) leading to fostamatinib dose reductions were diarrhoea and hypertension. The most common AEs leading to fostamatinib dose interruptions were ALT increased, diarrhea, and influenza-like illness. AEs known to occur with fostamatinib and assessed as groups of relevant preferred terms included: neutropenia (7% on fostamatinib vs 0% on placebo), gastrointestinal events (41% vs 21%), transaminase elevation to >3 times normal (9% vs 0%; no drug-induced liver injury in either group), and hypertension-type events (28% vs 13%). SAEs were experienced by 13% of patients on fostamatinib and 21% on placebo. Only 3 types of SAEs were reported in more than 1 patient in either treatment group: epistaxis (2% fostamatinib vs. 2% placebo), thrombocytopenia (1% vs. 4%), and menorrhagia (0% vs. 4%). SAEs were considered related to study drug in 4% of patients on fostamatinib and 2% on placebo. There were 2 fatalities. In FIT1, a patient on placebo died of probable sepsis 19 days after discontinuing the study due to epistaxis. In FIT2, plasma cell myeloma led to withdrawal of fostamatinib on Day 19 and death 71 days later. There were no thromboembolic events [2].

Table 19. Adverse events in FIT 1 and FIT 2 [11]

Most common AEs	Randomized Studies		Randomized + open-label extension
	Placebo N=48	Fostamatinib N=102	Fostamatinib N=146
Diarrhea	15%	29%	35%
Hypertension	8%	20%	21%
Nausea	8%	19%	19%
Epistaxis	10%	16%	17%
Petechiae	6%	4%	15%
Headache	19%	11%	13%
Upper respiratory tract infection	4%	6%	11%
Dizziness	8%	11%	10%
ALT increased	0%	11%	10%
Contusion	2%	6%	10%

Open label extension – FIT3

No new or more frequent toxicities or intolerabilities were detected with prolonged use of fostamatinib during the OLE study. AEs in the OLE study were similar to those observed in the randomized studies with the caveat that some of the patients from the randomized studies who could not tolerate fostamatinib or had side effects requiring discontinuation of treatment did not participate in the OLE study. The frequency of AEs in the OLE study alone (75%) was similar to the frequency reported in the randomized studies (83% with fostamatinib and 75% with placebo), notwithstanding the extended drug exposure (median of 5.9 months in the OLE study and 2.8 months in the randomized studies). The majority of AEs were mild to moderate and could be managed with medication, dose reduction, or interruption, or, in a small number of cases, including 2 of 27 stable responders, discontinuation of treatment [3].

5.3 Other considerations

Additional to the clinical questions presented above, four additional questions were included in the protocol regarding the treatment with Tavlesse®.

5.3.1 Treatment duration

The expert committee wants the applicant to explain how long the patients can be expected to be treated with fostamatinib and comparator. The expected duration of treatment should be reflected in the time horizon of the health economic model.

Treatment with fostamatinib should be discontinued after 12 weeks of fostamatinib therapy if the platelet count does not increase to a level sufficient to avoid clinically important bleeding [6]. Additionally, the management of some adverse reactions may require treatment discontinuation. The treatment of cITP differs across patients and treating physicians. Hence, treatment duration may vary accordingly. In the health economic analysis, a lifelong treatment duration was assumed for patients who achieve and maintain a sufficient treatment response.

5.3.2 Risk of pneumococcal infection

The spleen is an important defense against pneumococcal infection. However, the professional committee cannot assess whether the mechanism of action of fostamatinib in inhibition of SYK affects this function of spleen. The subject committee therefore wants the applicant to describe the risk of pneumococcal infections.

Infections, including pneumonia and respiratory tract infections, have been reported during clinical trials FIT1 and FIT2 [6]. In the placebo-controlled ITP population, infection adverse reactions were reported in 30% of patients receiving fostamatinib and 20% of patients receiving placebo. Infections involving the respiratory tract accounted for 60% of the AEs in the fostamatinib group and 40% of the events in the placebo group.

Together with other AEs, infections were ranked by frequency. Common infections (≥1/100 to <1/10) were upper respiratory tract infection, respiratory tract infection, bronchitis, lower respiratory tract infection, and viral upper respiratory tract infection. Pneumonia was reported as uncommon (≥1/1,000 to <1/100).

No systemic opportunistic infections were reported in the fostamatinib program. Serious adverse reactions for infection were uncommon. Severe infection events included pneumonia and influenza-like illness (1 patient each in the fostamatinib group) and sepsis (1 patient in the placebo group). One patient in the fostamatinib group discontinued study treatment due to an infection (pneumonia). Neutropenia was rarely associated with infection.

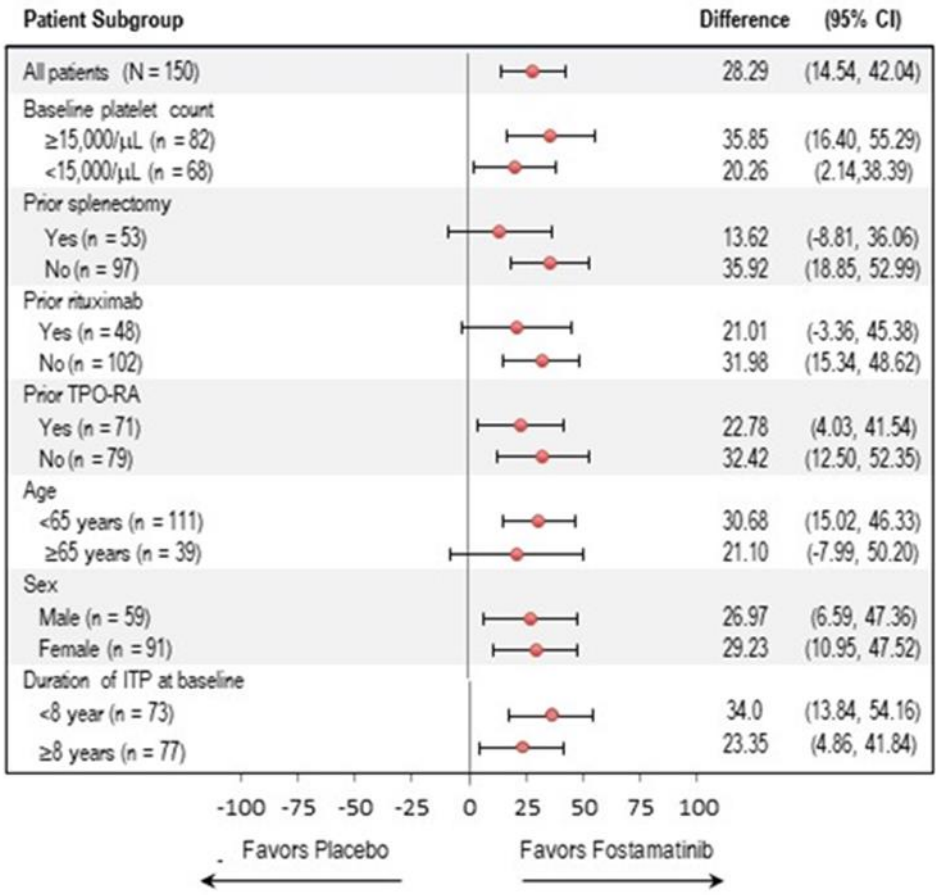
Based on this assessment, the risk of pneumococcal infection related to fostamatinib treatment is considered low.

5.3.3 Significance of splenectomy

The expert committee wants the applicant to describe how the effect of fostamatinib is affected in splenectomy patients.

Prior splenectomy was a prespecified subgroup in the FIT1 and FIT2 trials. Thirty-four percent (34/101) of the participants had a splenectomy (median 13 years earlier) in the fostamatinib group and thirty-nine percent (19/49) had splenectomy in the placebo group. The primary efficacy endpoint findings were robust and were generally consistent across subgroups including prior splenectomy (Figure 5). Hence, no clinically relevant difference in treatment effect in patients with prior splenectomy is expected.

Figure 5. Subgroup analysis for overall response in the pooled population [12]



Abbreviations: TPO-RA: thrombopoietin receptor agonist, CI: confidence interval; ITP: immune thrombocytopenia. Treatment effect, defined as an overall response (platelet count ≥50,000/µL in weeks 0-12), across subgroups categorized by baseline platelet count, prior treatment, age, and sex, and duration of ITP. Horizontal bars represent 95% CI.

5.3.4 Additional treatment

The expert committee wants the applicant to contribute data that sheds light on whether patients in treatment with fostamatinib has a reduced need for supplementation with glucocorticoids and immunoglobulins in comparison with comparator.

Certain therapeutic regimens for ITP were permitted for subjects in FIT1 and FIT2 with platelet counts <50,000/µL who needed 'rescue' support for their platelet count. Circumstances in which 'rescue' therapy was administered included [2]:

- Platelet count < 50,000/µL and at immediate risk of bleeding or with clinically significant bleeding or wet purpura

Allowed concomitant therapeutic regimens included:

- IVIg: up to 1 g/kg × 1 to 3 days, or
- IV anti-D IgG: up to 50 µg to 75 µg/kg × 1 to 2 days, or

- IV methylprednisolone up to 1 g/day for 1 to 3 days or oral dexamethasone up to 40 mg/day for 1 to 2 days or oral prednisone up to 1 mg/kg/day for 1 to 3 days

There is no specific data for the use of glucocorticoids and immunoglobulins, however there was a trend for patients on fostamatinib to receive rescue medication less often than those on placebo (30% vs. 45%, respectively). Among overall responders to fostamatinib, 7/43 (16%) received rescue medication vs. 20/58 (34%) non-responders and 22/49 (45%) patients on placebo. Among stable responders, 3/18 (17%) received rescue medication but only during the first week of treatment. In contrast, non-responders received rescue medication throughout the study period (weeks 0–24). Rescue therapies in the FIT program included increased dosing of concomitant ITP therapy, immunoglobulins, IV anti-D, steroids and platelet transfusion.

6. What value does fostamatinib have compared to immunosuppressive therapies such as dapsone, danazol, mycophenolate mofetil, azathioprine or ciclosporin for patients with primary chronic ITP?

6.1 Presentation of relevant studies

In the SLR attempting to inform clinical question 2 there were four full-text studies included. These studies were one prospective trial [13], and three case series [14-16]. There were no RCTs identified in this SLR that fulfilled the PICO criteria described in the protocol supplied by the DMC. A narrative approach was deemed the most appropriate method for data synthesis and analysis because of the design of the included studies and their respective reported data.

6.1.1 Study characteristics

The study characteristics of the four included studies varied in, among others, study design, geography, number of participants and study intervention [13-16]. A summary of the main study characteristics of the included studies is presented in Table 20. The prospective trial was conducted in Egypt for approximately 36 months and assessed the use of a combined immunotherapy of dexamethasone, cyclosporine and low-dose rituximab [13]. The trial included 40 chronic primary ITP patients who had failed previous two or more treatment options [13]. The first case series (Colovic et al. 2011) was conducted in Serbia and included 16 chronic ITP patients resistant to steroids, immunosuppressants, and/or splenectomy treated with MMF [14]. The second case series (Provan et al. 2006) was conducted in both the UK and USA and included 18 refractory ITP patients treated with MMF [15]. The third case series (Zver et al. 2006) was conducted in Slovenia and included six chronic refractory ITP patients treated with cyclosporine A [16].

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Table 20. Summary of study characteristics of the included studies

Study ID	Study design	Country/ies	Study period/duration	Study population	Number of study participants	Intervention (dosage)
Thabet_2020	Prospective trial	Egypt	February 2016 - January 2019 (36 months)	Chronic primary ITP patients who had failed previous 2 or more treatment options	40	Combination immunotherapy of dexamethasone (40 mg), cyclosporine (2–3 mg/kg daily) and rituximab (100 mg)
Colovic_2011	Case series	Serbia	NR	Chronic ITP patients resistant to steroids, immunosuppressants, and/or splenectomy	16	MMF (1.5–2 g/day)
Provan_2006	Case series	UK and USA	NR	Refractory ITP (idiopathic) patients	18	MMF (Loading dose: 250 mg twice daily, increased to 500 mg twice daily after week 1; Maintenance dose: 1 g twice daily by 3 week)
Zver_2006	Case series	Slovenia	1994 - 2004	Chronic refractory ITP	6	Cyclosporine A (1.5 mg/kg per dose every 12 hours)

g: Gram; ITP: Immune thrombocytopenia; kg: Kilogram; mg: Milligram; MMF: Mycophenolate mofetil; NR: Not reported; UK: United Kingdom; US: United States.

Comparatively, the FIT1 and FIT2 trials were phase 3, randomized, double-blind, placebo-controlled trials [2]. The trials included a similar number of participants; in FIT1 there were 76 included patients (Fostamatinib n=51; Placebo n=25), and 74 (Fostamatinib n= 50, Placebo n=24) in FIT2 [2].

The study design of the included studies differed from the ones used for the FIT1 and FIT2 trials (similar design). The study design of FIT1 and FIT2 were considerably more robust, when compared to a single-arm, non-randomised trial (interventional design) [13], and three case series (observational designs) [14-16]. Additionally, the number of included participants in the FIT1 and FIT2 trials was substantially higher, compared to the sample size of the included studies in this SLR.

6.1.2 Patient characteristics

The patient population of the four included studies was very similar in terms of its characteristics [13-16]. Following the PICO criteria described in the protocol, all studies included cITP patients (as per current definition, ITP lasting for > 12 months [1]). All studies stated that the origin of the ITP was unknown or a diagnosis of exclusion (i.e. other [secondary] causes of ITP were excluded) had been applied. Only data for patients aged > 18 years and with at least two previous treatments was extracted and reported here. A summary of the main patient characteristics of the included studies is presented in Table 21.

In the prospective trial, patients mean age (SD) was 33.56 (9.81) years and the age ranged between 20 and 49 years [13]. There were 62.50% females included in the trial [13]. There were 65% of patients who had failed two previous treatments and 35% who had failed more than two previous treatments [13]. Mean (SD) baseline PC count was 14.85 (6.31) x 10^9/L [13]. Ethnicity, disease duration and prior treatment types were not reported [13].

Colovic et al. 2011 included patients with a median (range) age of 55 (20-80) years and 62.50% of patients were females [14]. The median (range) disease duration was 58 (24-280) months, and the median (range) number of prior therapies was 4 (3-8) [14]. All patients had been previously treated with corticosteroids and immunosuppressants, 37.50% of patients with IVIg and 81.82% underwent splenectomy [14]. Mean (SD) baseline PC count was 7.19 (5.59) x 10^9/L [14]. Ethnicity was not reported and the number of prior therapies was not estimable [14].

Provan et al. 2006 included patients with a median (range) age of 50.5 (22-66) years, and a median (range) disease duration was 8.5 (2-27) years [15]. All patients had been previously treated with corticosteroids, 87.50% of patients with IVIg and immunosuppressants, 93.75% of patients underwent splenectomy and 18.75% of patients received rituximab [15]. Ethnicity and baseline PC count were not reported, and the number of prior therapies was not estimable [15].

From the Zver et al. 2006 study, data was extracted for only two patients (i.e. the only patients that fulfilled the PICO criteria). The first patient (patient 3) was a 61-year-old female, with baseline PC of 5.00 x 10^9/L [16]. The patient had ITP for 438 months and had been previously treated with methylprednisolone, cyclophosphamide, IVIg and splenectomy [16]. The second patient (patient 5) was a 56-year-old female, with a with baseline PC of 17.00 x 10^9/L [16]. The patient had ITP for 71 months and had been previously treated with methylprednisolone, IVIg and splenectomy [16].

Table 21. Summary of patient characteristics of the included studies

Study ID	Age	Gender	Disease duration	Number of prior treatments	Type of prior treatment	Baseline PC
Thabet_2020	Mean (SD): 33.56 (9.81) years Range: 20-49 years	Count, %: F: 25, 62.50% M: 15, 37.50%	NR	65.00% failed two previous treatments 35.00% failed more than two previous treatments	NR	Mean (SD): 14.85 (6.31) x 10^9/L

Study ID	Age	Gender	Disease duration	Number of prior treatments	Type of prior treatment	Baseline PC
Colovic_2011	Median (range): 55.00 (20-80) years	Count, %: F: 10, 62.50% M: 6, 37.50%	Median (range): 58 (24-280) months	Median (range): 4 (3-8)	Count, %: Steroids: 16, 100% IVIg: 6, 37.50% IS: 16, 100% Splenectomy: 9, 81.82%	Mean (SD): 7.19 (5.59) x 10^9/L
Provan_2006	Median (range): 50.50 (25-66) years	NR	Median (range): 8.5 (2-27) years	NE	Count, %: Steroids: 16, 100% IVIg: 14, 87.50% IS: 14, 87.50% Splenectomy: 15, 93.75% Rituximab: 3, 18.75%	NR
Zver_2006	Patient 3*: 61 years Patient 5*: 56 years	Patient 3: F Patient 5: F	Patient 3: 438 months Patient 5: 71 months	NE	Patient 3: Steroids, IS, IVIg, Splenectomy Patient 5: Steroids, IVIg, Splenectomy	Patient 3: 5.00 x 10^9/L Patient 5: 17.00 x 10^9/L

*Only data for patients 3 and 5 was extracted and reported as these patients were the only that fulfilled all the PICO criteria described in the protocol.

F: Female; IS: Immunosuppressants; IVIg; Intravenous immunoglobulin; M: Male; NE: Not estimable; NR: Not reported; PC: Platelet count; SD: Standard deviation.

In turn, in the FIT1 and FIT2 trials, patients had a clinical diagnosis of persistent/cITP for at least three months, and ≥1 prior treatment of ITP [2]. The trials excluded patients with a diagnosis of secondary ITP [2]. Furthermore, in both trials, in the fostamatinib arm, the median age was 54 years, 60% of patients were female, 93.00% of patients were white and 94% of patients had chronic ITP [2]. The median (range) number of prior ITP treatments was 3 (1-13), with 93% of patients having received corticosteroids, 51.00% IVIg, 44.00% immunosuppressants, 34.00% underwent splenectomy and 34.00% received rituximab [2]. The mean (range) baseline PC was 16.05 (1.00-51.00) x 10^9/L [2].

The patient populations in the four included studies, compared to the FIT1 and FIT2 patient populations, differed in several patient characteristics. As per protocol, the studies included had to report on cITP patients (e.g. studies including persistent ITP patients for which subgroup results for the chronic patients could not be extracted were excluded), as well as patients who were refractory to at least two previous treatment lines (e.g. studies reporting on ITP patients receiving second-line treatment were excluded). In the FIT1 and FIT2 trials, a minority of the patients had persistent ITP (6.00%) and some patients had only received one prior therapy. Furthermore, a higher proportion of patients had been splenectomised or received immunosuppressive therapy in the identified studies (varying from 81.82% and 93.75%, and

from 87.50 and 100%, respectively), compared to FIT1 and FIT2 trials (34.00% and 44.00%, respectively). Contrarily, rituximab had been administered to more patients in the FIT1 and FIT2 trials (34.00%), compared to the Colovic et al. 2011 study (18.75%; the only included study that reported on prior rituximab use). Additionally, no included study in this SLR reported prior treatment with TPO-RAs. The use of IVIg was highly variable across the studies. Notably, the median age and baseline PC were relatively similar among all studies. Ethnicity was not reported in the four included studies and therefore could not be compared.

6.2 Study results

The four included studies reported on the following outcomes: the proportion of patients with PC ≥30 x 10^9/L, the proportion of patients who discontinue due to an AE and a qualitative description of AEs. No outcomes concerning quality of life and bleeding were identified. A comparison between studies was difficult due to varying study interventions and timepoints used. A summary of the outcomes reported in the included studies is presented in Table 22.

Table 22. Summary of the outcomes reported in the included studies

Study ID	Timepoint	Proportion of patients with PC ≥30 x 10^9/L	Proportion of patients who discontinue due to an AE	Qualitative description of AEs
Thabet_2020	Week 4	82.50%	NR	No serious AEs. Three patients developed elevated random blood sugar (two with mild hypertension also). Two patients developed fever and chills with the first dose of rituximab.
Colovic_2011	Week 12	68.75%	NR	One patient had a bronchopneumonia requiring hospital admission, and a second patient had an episode of diarrhoea.
Provan_2006	Entire study period (not reported in the study)	43.75%	11.11%	Two patients discontinued treatment due to AEs: one had persistent headaches and the other had light-headedness. An additional patient could not tolerate a dose >1 g/day of MMF because of headache.

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Study ID	Timepoint	Proportion of patients with PC ≥30 x 10^9/L	Proportion of patients who discontinue due to an AE	Qualitative description of AEs
Zver_2006	Week 4	Patient 3: 104.00 x 10^9/L Patient 5: 190.00 x 10^9/L	NR	Patient 3: Leg oedema. Patient 5: Pain in leg muscles and leg oedema.

Note: the endpoints "Difference in average change from baseline in SF-36", "Proportion of patients who achieve an increase of ≥8 points", "Proportion of patients who experience a serious bleed" and "Proportion of patients who experience a minor bleed" were not reported in any of the four included studies.

AE: Adverse event; g: Gram; MMF: Mycophenolate mofetil; NR: Not reported; PC: Platelet count.

6.2.1 Platelet count ≥30 x 10^9/L

No evidence was retrieved on the proportion of patients achieving a PC ≥30 x 10^9/L after 6 months (approximately 26 weeks) of treatment without the need for additional medication. This was due to the fact that most of the included studies had short treatment durations. In turn, limited evidence was retrieved on the proportion of patients achieving a PC ≥30 x 10^9/L at different study timepoints and is presented below.

In the prospective trial, 82.50% of patients receiving combination therapy achieved a PC ≥30 x 10^9/L at week 4 [13]. In comparison, the pooled data for FIT1 and FIT2 showed 34.3% (95% CI: 25.10, 43.50) of patients on the fostamatinib arm achieved a PC ≥30 x 10^9/L at week 4 [2]. However, this comparison was not straightforward. In addition to the already mentioned differences in study design and population characteristics, the prospective trial treatment was a combination of dexamethasone, cyclosporine and low-dose rituximab; and did not allow for concomitant medication [13]; whereas in the FIT1 and FIT2 trials fostamatinib was not used in combination and there was a restriction on the allowed concomitant treatments (IVIg or anti-D Ig or IV corticosteroids or oral corticosteroids) [2].

Colovic et al. 2011 reported on patients' PC (x 10^9/L) at week 12, which allowed for a calculation of the proportion of patients who had achieved PC ≥30 x 10^9/L [14]. Notably, these patients were considered as non-responders in the study (that defined a complete response as PC >100 x 10^9/L, and a partial response as PC of >50 x 10^9/L with a >30 x 10^9/L increase from baseline) [14]. Colovic et al. 2011 demonstrated that 68.75% of patients receiving MMF reached a PC ≥30 x 10^9/L at week 12 (no concomitant medication was allowed) [14]. In comparison, the pooled data for FIT1 and FIT2 revealed 53.60% (95% CI: 42.90, 64.20) of patients on the fostamatinib arm achieved a PC ≥30 x 10^9/L at week 12 [2]. At study end (42 weeks; approximately 9.5 months), 90.91% of the responders (in week 12) maintained response (corresponding to 62.50% of the entire study population) [14].

Provan et al. 2006 reported on the following endpoints: maximum PC (x 10^9/L); maximum PC at week n (number of weeks to achieve maximum PC); and number of consecutive weeks with PC >30 x 10^9/L [15]. According to this study, 43.75% patients treated with MMF reached a PC ≥30 x 10^9/L throughout the study period (concomitant medication was allowed) [15]. Since each responder achieved a response at a different timepoint, the proportion calculated is presented for the whole study period (not reported in the study). The responses were achieved between week 1 and week 25 [15]. Contrarily to Colovic et al. 2011, these patients were considered responders in the study (that defined a good response as a stable PC > 30 x 10^9/L, and a partial response as no change in PC but a decrease in concomitant medication use) [15]. Notably, an additional four patients reached PC >30 x 10^9/L due to the administration of IVIg and were therefore

considered as non-responders [15]. In comparison, the pooled data for FIT1 and FIT2 revealed 79.50% (95% CI: 66.8, 92.2) of patients on the fostamatinib arm achieved a PC ≥30 x 10^9/L at week 16 [2].

Zver et al. 2006 showed patients 3 and 5 (the only ones that fulfilled the PICO criteria) treated with cyclosporin achieved a PC ≥30 x 10^9/L at week 4 (concomitant medication was allowed) [16]. Patient 5 further achieved a PC ≥30 x 10^9/L at weeks 8 and 16 [16]. Similarly to Colovic et al. 2011, these patients were considered as non-responders in the study (that defined a complete response as PC > 140 x 10^9/L maintained for at least a month; and a partial response as PC > 40 x 10^9/L maintained for at least a month) [16].

The different study design and small sample size of the three case series studies, compared to FIT1 and FIT2 trials, hindered a comparison in terms of efficacy between fostamatinib and its suggested comparators in treating primary cITP patients who failed at least two previous treatments.

6.2.2 Adverse events leading to treatment discontinuation

There was only one identified study informing on treatment discontinuation. Provan et al. 2006 reported 11.00% (n=2) of patients discontinued MMF treatment due to AEs (persistent headaches in one patient and light-headedness in a second patient) [15]. Comparatively, in the FIT1 and FIT2 trials, fostamatinib was withdrawn due to AEs in 10 (9.8%) fostamatinib-treated patients [2].

6.2.3 Qualitative description of adverse events

The identified evidence on AEs was limited. In the Provan et al. 2006 study, additionally to the two patients who discontinued treatment due to AEs, one patient received a low dose of MMF (lower than 1 g/day) to prevent headaches [15]. In the prospective trial, there were no serious AEs recorded [13]. There were three patients who developed elevated random blood sugar (two with mild hypertension associated) [13]. Furthermore, two patients developed fever and chills after their first rituximab dose [13]. Colovic et al. 2011 reported one patient suffered a bronchopneumonia requiring hospital admission, and a second patient had an episode of diarrhoea [14]. Zver et al. 2006 described patient 3 experienced leg oedema and patient 5 reported pain in the leg muscles and leg oedema [16]. It was not reported if treatment was discontinued in any of these three studies.

Comparatively, in the FIT1 and FIT2 trials, 83.00% of patients experienced AEs in the fostamatinib arm. The most commonly reported AEs were diarrhoea, nausea, hypertension, dizziness, and ALT and/or AST increases [2].

The diversity of registered AEs hindered a comparison between the four included studies and the FIT1 and FIT2 trial data. However, Provan et al. 2006 reported a similar proportion of patients who discontinue due to an AE (11.00%), compared to the FIT1 and FIT2 trials (9.8%).

Grade 3-4 adverse events were not reported in the included studies and therefore could not be calculated and presented here.

6.3 Conclusion

In conclusion, this SLR identified limited data on the suggested comparators of fostamatinib. There were only four studies identified that fulfilled the PICO criteria described in the protocol. In addition to the paucity of data, the identified studies differed in several PICO criteria, when compared to the FIT1 and FIT2 trials. For example, the included studies employed less robust study designs and included a lower sample size, compared to the trials. Notably, the treatment duration in most of the included studies was shorter than in the FIT1 and FIT2 trials.

In terms of the PICO, the patient populations included in the identified studies differed from the ones in the FIT1 and FIT2 trials. The latter allowed for a minority of persistent ITP patients to be included, as well as patients with only one line of treatment. There was also a heterogeneity in previous treatments, when comparing the included studies with the FIT1 and FIT2 trials. Importantly, only one study reported on patients previously treated with rituximab (18.75% of patients versus 34.00% in the FIT1 and FIT2 trials) and no identified study in this SLR reported on previous treatment with TPO-Ras. These differences could be explained by the different geographies or changes in clinical practice over the years.

Finally, clinical question 2 could not be answered properly since comparison between studies was difficult due to varying study interventions and timepoints used. The identified data was considered not sufficient to quantify the differences in terms of clinical efficacy between fostamatinib and its suggested comparators nor to populate the cost-per-patient model. Therefore, no health economic analysis comparing fostamatinib with any of the suggested comparators could be conducted.

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8. Appendices

8.1 Literature search

Table A1 Inclusion and exclusion criteria	
Inclusion criteria	Population: Patients ≥ 18 years of age with primary cITP who have no effect on other treatments (at least two or more previous treatments). Intervention(s): At least one of the following [1]: • Danazol, 200 mg two to three times daily. • Dapsone, 50 mg/day for 1 week, then 100 mg/day for 2 months. • Mycophenolate mofetil, 1.5–2 g/day for at least 12 weeks. • Azathioprine, 1–2 mg/kg (maximum: 150 mg/day). • Ciclosporin, 5 mg/kg/day for 6 days, then 2.5–3 mg/kg/day (titration to blood levels of 100–200 ng/mL). Comparator(s): No restrictions in terms of comparators were applied. Outcomes: Studies reporting at least one of the outcome measures specified in Table 1. Study design: RCTs, systematic Reviews as a source of reference to primary RCTs. Language restrictions: At least title and abstract in English.
Exclusion criteria	Population: Studies carried out only in pediatric and adolescent patients, studies that contain both the adult and pediatric population, but the subgroup results cannot be extracted, studies carried out in patients that had not previously been treated or had only received 1 line of treatment, studies carried out in patients without primary cITP. Intervention(s): Studies not assessing any of the specified interventions, studies assessing at least one of the specified interventions but given at a different dosage regimen. Comparator(s): No restrictions in terms of comparators were applied. Outcomes: Studies not reporting any of the outcome measures specified in Table 1. Study design: Single arm studies, non-randomized studies. Language restrictions: Studies which have title, abstract and full text in other language than English.

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8.2 List of excluded studies at full text with reasons for exclusion

Table A2 List of excluded studies at full text with reasons for exclusion

Full reference	Reason for exclusion
Abdallah GEM, Elbiih EAS, Sayed D, Moeen SM, Gafer S, Thabet AF. Revisiting the management of chronic ITP; a randomized controlled clinical trial. Platelets. 2021 Feb 17;32(2):243-249. doi: 10.1080/09537104.2020.1738367. Epub 2020 Mar 9.	The median number of prior therapies received by the patients included in the study was only one.
Ahn YS, Harrington WJ, Simon SR, Mylvaganam R, Pall LM, So AG. Danazol for the treatment of idiopathic thrombocytopenic purpura. N Engl J Med. 1983 Jun 9;308(23):1396-9. doi: 10.1056/NEJM198306093082306.	The study assessed an intervention drug included in the inclusion criteria of the protocol but that was not available in Denmark.
Ahn YS, Rocha R, Mylvaganam R, Garcia R, Duncan R, Harrington WJ. Long-term danazol therapy in autoimmune thrombocytopenia: unmaintained remission and age-dependent response in women. Ann Intern Med. 1989 Nov 1;111(9):723-9. doi: 10.7326/0003-4819-111-9-723.	The study included persistent and cITP patients, as well as ITP patients with none or only one prior therapy. Subgroup results for cITP patients with at least two prior therapies could not be extracted.
Arnold DM, Nazi I, Santos A, Chan H, Heddle NM, Warkentin TE, Kelton JG. Combination immunosuppressant therapy for patients with chronic refractory immune thrombocytopenic purpura. Blood. 2010 Jan 7;115(1):29-31. doi: 10.1182/blood-2009-06-222448. Epub 2009 Nov 6.	The study did not specify the classification of the included ITP population. Subgroup results for primary ITP patients could not be extracted.
Audia S, Godeau B, Bonnotte B. Is there still a place for "old therapies" in the management of immune thrombocytopenia? Rev Med Interne. 2016 Jan;37(1):43-9. doi: 10.1016/j.revmed.2015.08.007. Epub 2015 Oct 1.	The study design (review) was not of interest for this SLR.
Buelli M, Cortelazzo S, Viero P, Minetti B, Comotti B, Bassan R, Barbui T. Danazol for the treatment of idiopathic thrombocytopenic purpura. Acta Haematol. 1985;74(2):97-8. doi: 10.1159/000206176.	The study did not specify the classification of the included ITP population. Subgroup results for cITP patients could not be extracted.
Cervinek L. Diagnosis and treatment of immune thrombocytopenia. Vnitr Lek. Summer 2018;64(5):526-529.	The study design (guidelines) was not of interest for this SLR.
Choi PY, Roncolato F, Badoux X, Ramanathan S, Ho SJ, Chong BH. A novel triple therapy for ITP using high-dose dexamethasone, low-dose rituximab, and cyclosporine (TT4). Blood. 2015 Jul 23;126(4):500-3. doi: 10.1182/blood-2015-03-631937. Epub 2015 May 13.	The study included newly diagnosed, as well as secondary ITP patients. Subgroup results for the primary cITP patients could not be extracted.

Colella MP, Orsi FA, Alves ECF, Delmoro GF, Yamaguti-Hayakawa GG, de Paula EV, Annichino-Bizzacchi JM. A retrospective analysis of 122 immune thrombocytopenia patients treated with dapsone: Efficacy, safety and factors associated with treatment response. J Thromb Haemost. 2021 Sep;19(9):2275-2286. doi: 10.1111/jth.15396. Epub 2021 Aug 9.	The study included newly diagnosed, as well as secondary ITP patients. Subgroup results for the primary cITP patients could not be extracted.
Depre F, Aboud N, Mayer B, Salama A. Efficacy and tolerability of old and new drugs used in the treatment of immune thrombocytopenia: Results from a long-term observation in clinical practice. PLoS One. 2018 Jun 1;13(6):e0198184. doi: 10.1371/journal.pone.0198184. eCollection 2018.	The study included two patients with <18 years old and ITP patients with only one prior therapy. Subgroup results for ITP patients ≥18 years old with at least two prior therapies could not be extracted.
do Nascimento ACKV, Annichino-Bizzacchi JM, Maximo CA, Minowa E, Julian GS, Dos Santos RF. Patterns of care and burden of chronic idiopathic thrombocytopenic purpura in Brazil. J Med Econ. 2017 Aug;20(8):884-892. doi: 10.1080/13696998.2017.1341415. Epub 2017 Jul 4.	The outcomes for the intervention drugs included in the inclusion criteria could not be extracted.
Emilia G, Morselli M, Luppi M, Longo G, Marasca R, Gandini G, Ferrara L, D'Apollo N, Potenza L, Bertesi M, Torelli G. Long-term salvage therapy with cyclosporin A in refractory idiopathic thrombocytopenic purpura. Blood. 2002 Feb 15;99(4):1482-5. doi: 10.1182/blood.v99.4.1482.	The study assessed an intervention drug included in the inclusion criteria but this was administered in a different regimen than defined in the protocol.
Fujisawa K, Tani P, Piro L, McMillan R. The effect of therapy on platelet-associated autoantibody in chronic immune thrombocytopenic purpura. Blood. 1993 Jun 1;81(11):2872-7.	The number of prior therapies received by the cITP patients included in the study was not reported. Results for ITP patients treated with at least two prior therapies could not be extracted.
Godeau B, Durand JM, Roudot-Thoraval F, Tenneze A, Oksenhendler E, Kaplanski G, Schaeffer A, Bierling P. Dapsone for chronic autoimmune thrombocytopenic purpura: a report of 66 cases. Br J Haematol. 1997 May;97(2):336-9. doi: 10.1046/j.1365-2141.1997.412687.x.	The study included persistent and cITP patients. Subgroup results for cITP patients could not be extracted.
Hernandez F, Linares M, Colomina P, Pastor E, Cervero A, Perez A, Perella M. Dapsone for refractory chronic idiopathic thrombocytopenic purpura. Br J Haematol. 1995 Jun;90(2):473-5. doi: 10.1111/j.1365-2141.1995.tb05179.x.	The study did not specify if the included population had primary or secondary ITP. Subgroup results for primary ITP patients could not be extracted.
Hou M, Peng J, Shi Y, Zhang C, Qin P, Zhao C, Ji X, Wang X, Zhang M. Mycophenolate mofetil (MMF) for the treatment of steroid-resistant idiopathic thrombocytopenic purpura. Eur J Haematol. 2003 Jun;70(6):353-7. doi: 10.1034/j.1600-0609.2003.00076.x.	The outcomes for the intervention drugs included in the inclusion criteria could not be extracted.

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Howard J, Hoffbrand AV, Prentice HG, Mehta A. Mycophenolate mofetil for the treatment of refractory auto-immune haemolytic anaemia and auto-immune thrombocytopenia purpura. Br J Haematol. 2002 Jun;117(3):712-5. doi: 10.1046/j.1365-2141.2002.03430.x.	The study did not specify the classification of the included ITP population. Subgroup results for cITP patients could not be extracted.
Ikkala E, Kivilaakso E, Kotilainen M, Hastbacka J. Treatment of idiopathic thrombocytopenic purpura in adults. Long-term results in a series of 41 patients. Ann Clin Res. 1978 Apr;10(2):83-6.	The study did not specify the classification of the included ITP population. Subgroup results for cITP patients could not be extracted.
Kappers-Klunne MC, van't Veer MB. Cyclosporin A for the treatment of patients with chronic idiopathic thrombocytopenic purpura refractory to corticosteroids or splenectomy. Br J Haematol. 2001 Jul;114(1):121-5. doi: 10.1046/j.1365-2141.2001.02893.x.	The study assessed an intervention drug included in the inclusion criteria but this was administered in a different regimen than defined in the protocol.
Kondo H, Iseki T, Goto S, Takaso T, Ohto M, Okuda K. Danazol therapy in idiopathic thrombocytopenic purpura: the efficacy of low-medium dose therapy. Int J Hematol. 1992 Jun;55(3):293-300.	The study assessed an intervention drug included in the inclusion criteria of the protocol but that was not available in Denmark.
Kotb R, Pinganaud C, Trichet C, Lambotte O, Dreyfus M, Delfraissy JF, Tchernia G, Goujard C. Efficacy of mycophenolate mofetil in adult refractory auto-immune cytopenias: a single center preliminary study. Eur J Haematol. 2005 Jul;75(1):60-4. doi: 10.1111/j.1600-0609.2005.00437.x.	The study assessed an intervention drug included in the inclusion criteria but this was administered in a different regimen than defined in the protocol.
Kotlarek-Haus S, Podolak-Dawidziak M. Danazol in chronic idiopathic thrombocytopenic purpura resistant to corticosteroids. Folia Haematol Int Mag Klin Morphol Blutforsch. 1987;114(6):768-76.	The study included two patients with <18 years old and ITP patients with only one prior therapy. Subgroup results for ITP patients ≥18 years old and with at least two prior therapies could not be extracted.
Lee JY, Lee JO, Jung JY, Bang SM. Dapsone therapy for refractory immune thrombocytopenia patients: a case series. Blood Res. 2017 Jun;52(2):95-99. doi: 10.5045/br.2017.52.2.95. Epub 2017 Jun 22.	The study did not specify if the included population had primary or secondary ITP. Subgroup results for primary ITP patients could not be extracted.
Li J, Wang Z, Dai L, Cao L, Su J, Zhu M, Yu Z, Bai X, Ruan C. Effects of rapamycin combined with low dose prednisone in patients with chronic immune thrombocytopenia. Clin Dev Immunol. 2013;2013:548085. doi: 10.1155/2013/548085. Epub 2013 Dec 2.	The study included patients <18 years old and subgroup results according to age could not be extracted.
Liu W, Gu X, Fu R, Li Y, Lv M, Sun T, Lv C, Liu X, Xue F, Zhang L, Yang R. The Effect of Danazol in Primary Immune Thrombocytopenia: An Analysis of a Large Cohort From a Single Center in China. Clin Appl Thromb Hemost. 2016 Nov;22(8):727-733. doi: 10.1177/1076029615622002. Epub 2015 Dec 16.	The study included results for persistent or cITP patients. Subgroup results for only cITP patients could not be extracted.

Mazzucconi MG, Francesconi M, Falcione E, Ferrari A, Gandolfo GM, Ghirardini A, Tirindelli MC. Danazol therapy in refractory chronic immune thrombocytopenic purpura. Acta Haematol. 1987;77(1):45-7. doi: 10.1159/000205948.	The study included persistent and cITP patients, as well as ITP patients with only one prior therapy. Subgroup results for cITP patients with at least two prior therapies could not be extracted.
McVerry BA, Auger M, Bellingham AJ. The use of danazol in the management of chronic immune thrombocytopenic purpura. Br J Haematol. 1985 Sep;61(1):145-8. doi: 10.1111/j.1365-2141.1985.tb04070.x.	The study did not specify if the included population had primary or secondary ITP. Subgroup results for primary ITP patients could not be extracted.
Mylvaganam R, Ahn YS, Garcia RO, Kim CI, Harrington WJ. Very low dose danazol in idiopathic thrombocytopenic purpura and its role as an immune modulator. Am J Med Sci. 1989 Oct;298(4):215-20. doi: 10.1097/00000441-198910000-00002.	The study included persistent and cITP patients. Subgroup results for cITP patients could not be extracted.
Nozaki H, Tanaka K, Shimizu M, Satou Y, Tokunaga M, Usui T, Mishima K, Yonekura S, Shimizu H, Noguchi K, et al. A clinical study of patients with idiopathic thrombocytopenic purpura. Tokai J Exp Clin Med. 1989 Jun;14(3):231-6.	The study included only ITP patients with none or one prior therapy. Subgroup results for ITP patients with at least two prior therapies could not be extracted.
Pizzuto J, Ambriz R. Therapeutic experience on 934 adults with idiopathic thrombocytopenic purpura: Multicentric Trial of the Cooperative Latin American group on Hemostasis and Thrombosis. Blood. 1984 Dec;64(6):1179-83.	The study included patients <18 years old and subgroup results according to age could not be extracted.
Quiquandon I, Fenaux P, Caulier MT, Pagniez D, Huart JJ, Bauters F. Re-evaluation of the role of azathioprine in the treatment of adult chronic idiopathic thrombocytopenic purpura: a report on 53 cases. Br J Haematol. 1990 Feb;74(2):223-8. doi: 10.1111/j.1365-2141.1990.tb02569.x.	The outcomes for the intervention drugs included in the inclusion criteria could not be extracted.
Schiavotto C, Castaman G, Rodeghiero F. Treatment of idiopathic thrombocytopenic purpura (ITP) in patients with refractoriness to or with contraindication for corticosteroids and/or splenectomy with immunosuppressive therapy and danazol. Haematologica. 1993 Nov-Dec;78(6 Suppl 2):29-34.	The study included persistent and cITP patients. Subgroup results for cITP patients could not be extracted.
Wanachiwanawin W, Visudhiphan S, Pinankijagum A, Vatanavicharn S. Therapy of chronic idiopathic thrombocytopenic purpura in adults: experiences from Thailand. Southeast Asian J Trop Med Public Health. 1993;24 Suppl 1:71-5.	The study included persistent and cITP patients. Subgroup results for cITP patients could not be extracted.
Yang R, Lin L, Yao H, Ji O, Shen Q. Therapeutic options for adult patients with previously treated immune thrombocytopenia - a systematic review and network	None of the intervention drugs included in the inclusion criteria are assessed in the study.

meta-analysis. Hematology. 2019 Dec;24(1):290-299. doi: 10.1080/16078454.2019.1568659.	
Zaja F, Marin L, Chiozzotto M, Puglisi S, Volpetti S, Fanin R. Dapsone salvage therapy for adult patients with immune thrombocytopenia relapsed or refractory to steroid and rituximab. Am J Hematol. 2012 Mar;87(3):321-3. doi: 10.1002/ajh.22266. Epub 2011 Dec 21.	The study design (letter) was not of interest for this SLR.
Zhang WG, Ji L, Cao XM, Chen YX, He AL, Liu J, Zhao WH, Zou SP. Mycophenolate mofetil as a treatment for refractory idiopathic thrombocytopenic purpura. Acta Pharmacol Sin. 2005 May;26(5):598-602. doi: 10.1111/j.1745-7254.2005.00088.x.	The study included patients <18 years old and subgroup results according to age could not be extracted.
Zhou H, Fu R, Wang H, Zhou F, Li H, Zhou Z, Zhang L, Yang R. Immune thrombocytopenia in the elderly: clinical course in 525 patients from a single center in China. Ann Hematol. 2013 Jan;92(1):79-87. doi: 10.1007/s00277-012-1567-2. Epub 2012 Sep 6.	The study did not specify the classification of the included ITP population, nor the number of prior therapies. Subgroup results for cITP patients with at least two prior therapies could not be extracted.
Zimmer J, Andres E, Noel E, Koumarianou A, Blickle JF, Maloisel F. Current management of adult idiopathic thrombocytopenic purpura in practice: a cohort study of 201 patients from a single center. Clin Lab Haematol. 2004 Apr;26(2):137-42. doi: 10.1111/j.1365-2257.2004.00591.x.	The study included persistent and cITP patients, as well as ITP patients <18 years old. Subgroup results for cITP patients ≥18 years old could not be extracted.
Zulfiqar AA, Novella JL, Mahmoudi R, Pennaforte JL, Andres E. Treatment in idiopathic thrombocytopenic purpura in the elderly: about a retrospective study. Geriatr Psychol Neuropsychiatr Vieil. 2016 Jun 1;14(2):151-7. doi: 10.1684/pnv.2016.0608.	The study did not specify the classification of the included ITP population. Subgroup results for cITP patients could not be extracted.

cITP: Chronic immune thrombocytopenia; ITP: Immune thrombocytopenia; SLR: Systematic literature review.

8.3 Results per study - FIT1 and FIT2

8.3.1 Quality of life

Results for change in SF-36 per domain for FIT1 and FIT2 and the pooled analysis are presented in Table 24-Table 28.

Table 23. Change in SF36 from baseline for fostamatinib, FIT1

Scale	Mean change from baseline: 4 weeks (95% CI)	Mean change from baseline: 12 weeks (95% CI)	Mean change from baseline: 24 weeks (95% CI)	Proportion with 8-point improvement or more - 4 wks	Proportion with 8-point improvement or more - 12 wks	Proportion with 8-point improvement or more - 24 wks
Physical Functioning	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXX
Role Physical	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX
Bodily Pain	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX
General Health	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXX XXXX
Vitality	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX
Social Functioning	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXX XXXX
Role Emotional	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXX XXXX
Mental Health	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX
Physical Health Summary	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX
Mental Health Summary	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX

Table 24. Change in SF36 from baseline for fostamatinib, FIT2

Scale	Mean change from baseline: 4 weeks (95% CI)	Mean change from baseline: 12 weeks (95% CI)	Mean change from baseline: 24 weeks (95% CI)	Proportion with 8-point improvement or more - 4 wks	Proportion with 8-point improvement or more - 12 wks	Proportion with 8-point improvement or more - 24 wks
Physical Functioning	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX
Role Physical	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX
Bodily Pain	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX
General Health	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX	XXXXXXXXX XXXX
Vitality	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX
Social Functioning	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX
Role Emotional	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX
Mental Health	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX
Physical Health Summary	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX

Mental Health Summary	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX

Table 25. Change in SF36 from baseline for placebo, FIT1

Scale	Mean change from baseline: 4 weeks (95% CI)	Mean change from baseline: 12 weeks (95% CI)	Mean change from baseline: 24 weeks (95% CI)	Proportion with 8-point improvement or more - 4 wks	Proportion with 8-point improvement or more - 12 wks	Proportion with 8-point improvement or more - 24 wks
Physical Functioning	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXX	XXXXXXXXX XXXX	X
Role Physical	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXX XXXX	X
Bodily Pain	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXX XXXX	X
General Health	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXX XXXX	X
Vitality	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXX XXXX	X
Social Functioning	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXX	XXXXXXXX	XXXXXXXXX XXXX	X
Role Emotional	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXX	XXXXXXXX	XXXXXXXXX XXXX	X
Mental Health	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXX XXXX	X
Physical Health Summary	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXX XXXX	X
Mental Health Summary	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXX XXXX	X

Table 26. Change in SF36 from baseline for placebo, FIT2

Scale	Mean change from baseline: 4 weeks (95% CI)	Mean change from baseline: 12 weeks (95% CI)	Mean change from baseline: 24 weeks (95% CI)	Proportion with 8-point improvement or more - 4 wks	Proportion with 8-point improvement or more - 12 wks	Proportion with 8-point improvement or more - 24 wks
Physical Functioning	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXX
Role Physical	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXX	XXXXXXXXXX
Bodily Pain	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXXX
General Health	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXX	XXXXXX
Vitality	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXX XXXX	XXXXXX
Social Functioning	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXX XXXX	XXXXXXXXXX
Role Emotional	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXX XXXX	XXXXXXXXXX
Mental Health	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXX XXXX	XXXXXXXXXX
Physical Health Summary	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXXX
Mental Health Summary	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXX	XXXXXXXXXX

Table 27. Change in SF36 from baseline for fostamatinib – pooled FIT1 and FIT2

Scale	Mean change from baseline: 4 weeks (95% CI)	Mean change from baseline: 12 weeks (95% CI)	Mean change from baseline: 24 weeks (95% CI)	Proportion (%) with 8-point improvement or more - 4 wks	Proportion (%) with 8-point improvement or more - 12 wks	Proportion (%) with 8-point improvement or more - 24 wks
Physical Functioning	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXXX	XXXXXXXXXX
Role Physical	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX
Bodily Pain	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX
General Health	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXXX	XXXXXXXXX XXXX
Vitality	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX
Social Functioning	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX
Role Emotional	XXXXXXXXX XXXX	- XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX
Mental Health	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX
Physical Health Summary	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXXX
Mental Health Summary	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX

Table 28. Change in SF36 from baseline for placebo – pooled FIT1 and FIT2

Scale	Mean change from baseline: 4 weeks (95% CI)	Mean change from baseline: 12 weeks (95% CI)	Mean change from baseline: 24 weeks (95% CI)	Proportion with 8-point improvement or more - 4 wks	Proportion with 8-point improvement or more - 12 wks	Proportion with 8-point improvement or more - 24 wks (%)
Physical Functioning	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX	XXXXXXXXX	XXXX
Role Physical	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX	XXXXXXXXX XXXX	XXXXXXXXX
Bodily Pain	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX
General Health	XXXXXXXXX XXXX	XXXX XXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX
Vitality	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX
Social Functioning	XXXXXXXXX XXXX	XXXX XXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX	XXXXXXXXX XXXX	XXXXXXXXX
Role Emotional	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX	XXXXXXXXX XXXX	XXXXXXXXX
Mental Health	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX	XXXXXXXXX XXXX	XXXXXXXXX
Physical Health Summary	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX
Mental Health Summary	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX XXXX	XXXXXXXXX	XXXXXXXXX XXXX	XXXXXXXXX

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Technical report: Fostamatinib Denmark

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1 Executive Summary

1.1 Objective

The objective of this analysis was to evaluate the cost-per-patient and budget impact of fostamatinib (Tavlesse®) compared to Danish standard of care for the treatment of chronic immune thrombocytopenia (cITP) in adult patients who are refractory to other treatments over a lifetime horizon.

1.2 Methods

A previously developed *de novo* Markov model was adapted to the Danish setting and used to perform the health economic analysis. Key model inputs - the efficacy of fostamatinib, drug consumption, and adverse events – were sourced from the pivotal trials for fostamatinib in cITP, FIT1, FIT2, and FIT3. Costs and healthcare resource use were estimated from public sources and published literature. Cost-per-patient and the budget impact were estimated. Costs were discounted by 3.5% per annum [1]. Per-patient cost scenario analyses were conducted

1.3 Results

Fostamatinib was found to be associated with a cost per patient of DKK 5,209,648 over the lifetime time horizon. Compared to watch and rescue this translates into a budget impact of DKK 2,641,128 at five years after introduction.

1.4 Conclusions

Fostamatinib was shown to be a relevant treatment alternative to standard of care in the treatment of cITP in Denmark.

2 Definition of the decision problem

To investigate if fostamatinib represents a cost-effective alternative to standard of care in the treatment of patients with cITP in Denmark who are refractory to other treatments.

3 Previous cost-effectiveness analysis

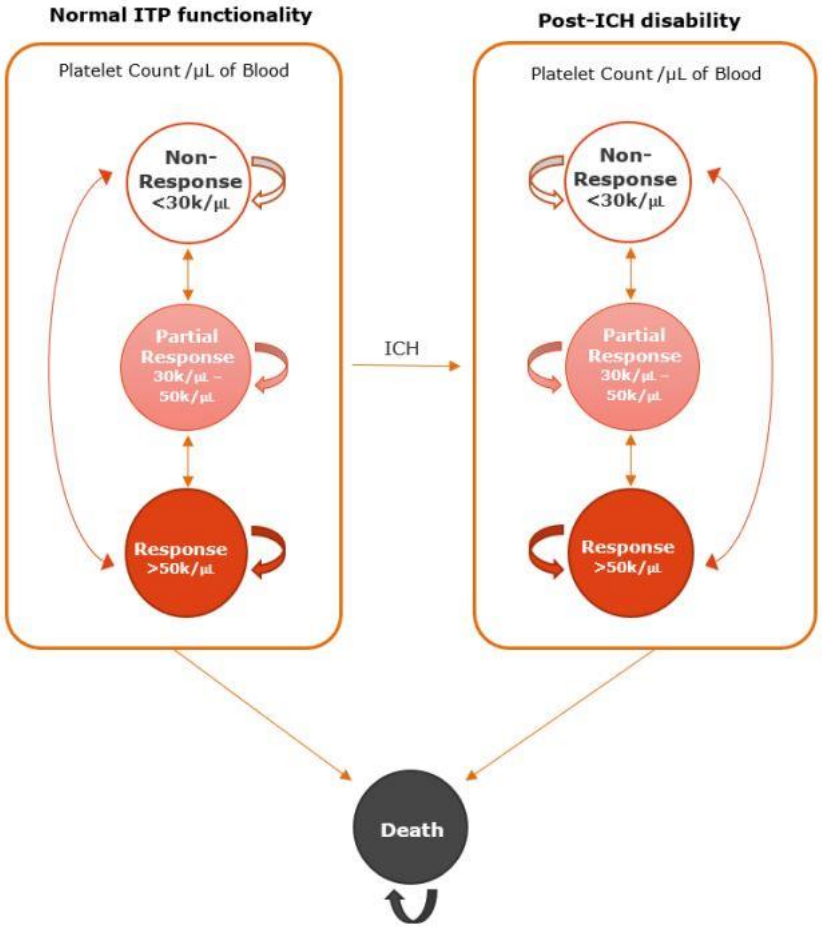
There are no previously published cost-effectiveness analyses of the use of fostamatinib to treat patients with cITP in Denmark. A *de novo* global economic model was adapted to the Danish setting.

4 Model and analysis

4.1 Model structure

A *de novo* Markov model was developed to explore the cost-effectiveness of Tavlesse®. The model structure is presented in (Figure 1). The model simulates a cohort of 1,000 patients per treatment arm over a lifetime analytic horizon. The model structure is designed to capture the significant clinical benefit in terms of increased platelet count that arises from response to treatment.

Figure 1. Model structure



ICH: intracerebral hemorrhage

All patients start with no response and without any previous ICH (termed 'normal ITP functionality'). Patients may continuously have a normal ITP function with one of the three included response levels (no response, partial response or response depending on the platelet count), experience an ICH or die. In the case of ICH occurrence, patients may remain alive with one of the three response levels or die. Once assigned to post-ICH disability, patients remain disabled until death. Patients in the model can either be on treatment with fostamatinib or be assigned to 'watch & rescue' treatment in case of loss of response (off active treatment).

The health states capture an individual's varying levels of platelet counts, as well as the long-term sequalae resulting from severe bleed events, given the following assumptions:

- Patients may not respond to fostamatinib or be under a 'watch and rescue' strategy, in which case their platelet counts are assumed to be <30k/µL of blood, based on data from the FIT clinical trials.
- Patients who respond to fostamatinib treatment move to either the response or partial response health states, with transition probabilities informed by the FIT clinical trials.

- Patients who have response after 24 weeks of treatment maintain the treatment response for the remaining follow-up time.
- Within each health state, the number of bleed events (rescue events, outpatient bleeds, and severe bleeds resulting in inpatient care) is captured to determine the differences in costs, and mortality.
- It is assumed that cycle length is short enough (four weeks) to be less than the shortest period in which two bleed events could realistically be assumed to take place, whilst still being long enough to capture the length of rescue treatment; therefore, it is only possible to have one bleed event per cycle.
- All patients will have a platelet count-dependent risk of ICH. A proportion of patients who experience ICH will subsequently have severe disability (modified Rankin scale 4 or 5) for the remainder of the time horizon.
- All patients have a risk of death, including the risk of death from severe bleed events and treatment-related thrombosis.

The model incorporates a dose escalation stopping rule whereby patients are assessed for response to 100 mg twice daily fostamatinib at week 4, when the following rubric is applied:

a) Responders continue post 4-weeks on 100 mg twice daily

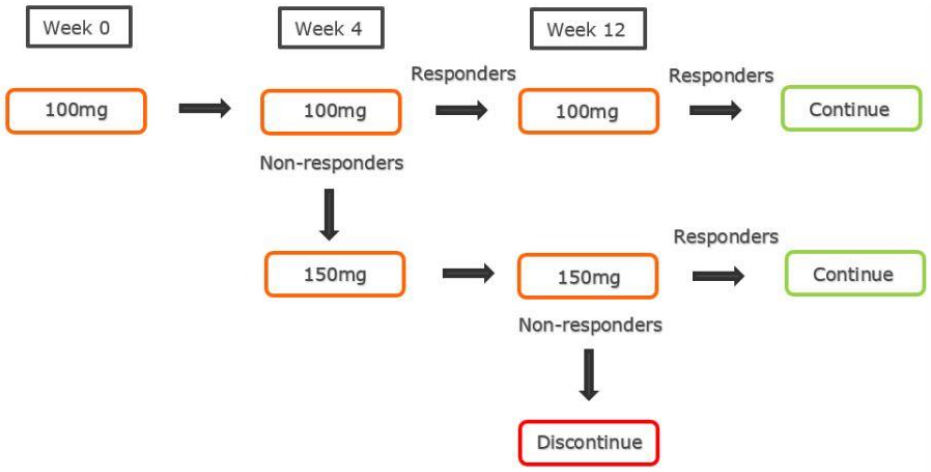
b) Non-responders' dose escalates to 150 mg twice daily for a further 8 weeks

After an additional 8 weeks (T0+12 weeks) patients receiving 150 mg twice daily will be assessed for response, and the following rubric is applied:

a) Responders continue post-12 weeks on 150 mg twice daily

b) Non-responders stop fostamatinib treatment and transition to the 'watch and rescue' strategy

Figure 2. Modelled dosing pathway for fostamatinib



It was assumed that patients who were escalated to receive 150 mg twice daily are titrated back down to a dose of 100 mg twice daily once they become stable responders after one year of treatment.

4.2 Cost-effectiveness analysis

4.2.1 Perspective

The base case included a limited societal perspective.

4.2.2 Population

The use of fostamatinib in Denmark is anticipated to be in adult patients with chronic ITP who have not had a sustained response to prior therapies including a TPO-RA, or where use of a TPO-RA is not appropriate. The relevant patient characteristics were validated by a clinical expert [2].

The baseline characteristics of patients entering the health economic analysis are in line with the patient population anticipated to be eligible for treatment with fostamatinib in Denmark [2]. These were based on literature and expert opinion.

Christiansen et al. [3] conducted a study utilizing the Nordic Country Patient Registry for Romiplostim (NCPRR) which currently follows the largest cITP1 cohort in the world with detailed data on almost 4,000 adults with confirmed cITP in Denmark, Sweden and Norway. The authors reported that the majority of patients with cITP were diagnosed aged 60 years or older (approximately 48% of patients in the Nordics) [3]. The age groups 60-69 years and 70-79 years constitute the proportionally largest groups at cITP diagnosis (17.76% and 17.14%, respectively). Additionally, it was reported that 56% of newly diagnosed cITP patients in the Nordics are women. Nordic clinical expert opinion states that relevant patient population is aged 60 years and approximately 50% are women [2].

4.2.3 Intervention

Fostamatinib (Tavlesse®) is indicated for the treatment of chronic ITP in adult patients who are refractory to other treatments.

4.2.4 Posology

Fostamatinib is administered orally in the form of a film-coated tablet. Dosing must be individualized based on the patient's platelet counts. The lowest dose of fostamatinib to achieve and maintain a platelet count of at least 50k/μL should be used. The recommended starting dose of fostamatinib is 100 mg twice daily. After initiating fostamatinib, the dose can be increased to 150 mg twice daily after 4 weeks based on platelet count and tolerability. A daily dose of 300 mg daily must not be exceeded [4].

Dose adjustments are based upon the platelet count response and tolerability (Table 1). Management of some adverse reactions may require dose interruption, reduction, or discontinuation. Clinical hematology, blood pressure and liver function tests should be monitored regularly throughout therapy with fostamatinib, and the dosing should be adjusted stepwise.

Treatment with fostamatinib should be discontinued after 12 weeks of fostamatinib therapy if the platelet count does not increase to a level sufficient to avoid clinically important bleeding.

Table 1. Dosing schedule

Daily dose	Administered as:	
	AM	PM
300 mg/day	150 mg	150 mg
200 mg/day	100 mg	100 mg

1 The authors defined chronic ITP as primary ITP lasting longer than 12 months with any platelet count <100 x 10^9/L.

150 mg/day	150 mg	-
100 mg/day[1]	100 mg	-

[1] If further dose reduction below 100 mg/day is required, fostamatinib should be discontinued.

4.2.5 Comparators

Fostamatinib was compared with a 'watch and rescue' strategy for the indicated patient population in the base case analysis. A 'watch and rescue' strategy is characterized by periods of no treatment punctuated by administration of intravenous steroids, IVIg, and platelet transfusions following hospitalization due to profound bleeds. Watch and rescue was assumed to reflect standard of care for patients that are refractory to other available treatments and thus eligible for treatment with fostamatinib. Rescues are also possible for the fostamatinib arm.

4.2.6 Outcomes

The model estimates total costs for the treatment with fostamatinib and 'watch and rescue'.
The outputs generated by the model are as follows:

- Platelet count
- Response rate
- Durable response
- Adverse effects of treatment
- Mortality
- Resource use associated with the treatment with fostamatinib
- Resource use associated with bleeding events
- Resource use associated with adverse events

4.2.7 Mortality

Mortality within the model is based on adjusted all-cause mortality probabilities, stratified by age and gender from the 2019 Danish national life tables [5] (See appendix 9.1).

The rate of all-cause mortality is adjusted for the decreased life expectancy linked to a low platelet count (Table 2). For non-responders, a standard mortality ratio was used based on a study by Portielje and colleagues [6]. The authors found that patients with severe cITP (platelet count <30k/µL) had a mortality risk of 4.2 compared to the general population irrespective of present hemorrhagic symptoms. The authors utilized both register and hospital specific data. In total 152 patients with ITP were included (age 15 and older). The mean age was 39 years. In total, 82% of patients were categorized as having severe ITP with platelet counts below <30k/µL. Generally, the population was considered to be representative for ITP patients at large. Data on long-term survival were obtained for 99% of patients for a mean of 10.5 years (median 9.4 years; range 2 months-22.6 years).
The authors found that patients with ITP with a persistent low platelet count (platelet count <30k/µL) 2 years after diagnosis (n=12) had a mortality risk of 4.2 compared to the general population irrespective of present hemorrhagic symptoms. The authors describe that the results are in line with other previous studies.
Despite a young patient population, few patient numbers and date of publication of the study (2001) the mortality risk of 4.2 was considered representative for the cITP population with a platelet count of <30k/µL in Denmark.

While the study includes a relatively broad patient population the mortality risk of 4.2 represents patients with a persistent and severe disease. Assuming the same mortality risk for the patient population eligible for fostamatinib may be conservative considering the disease severity of the relevant patient population.

For partial responders, a hazard ratio of 2.5 was applied based on a population-based study which assessed the cardiovascular and bleeding outcomes of 3584 patients with cITP in Norway, Denmark and Sweden [7].

In the study, occurrences of cardiovascular and bleeding events were associated with 4-fold to 5-fold increases in 1-year mortality, respectively. These events were strong prognostic factors for all-cause mortality. Patients with a platelet count <50k/µL had >2-fold (2.5) higher all-cause mortality rates than those with normal platelet counts (150-249 k /µL).
The study utilized data from the Nordic Country Patient Registry for Romiplostim. Patients were included in the register if they were ≥18 years old and had two or more ITP diagnoses at least 12 months apart, i.e., adult patients with cITP. The median age of the study population was 58 years.
About 50% had a platelet count of ≤149 k/µL and about 25% of the total population received glucocorticoids within 6 months prior to inclusion. In total, 18.3% had a splenectomy before inclusion. According to the main characteristics of the study population it is assumed that the study results are generalizable also for patients who may be eligible for the treatment with fostamatinib in Denmark.

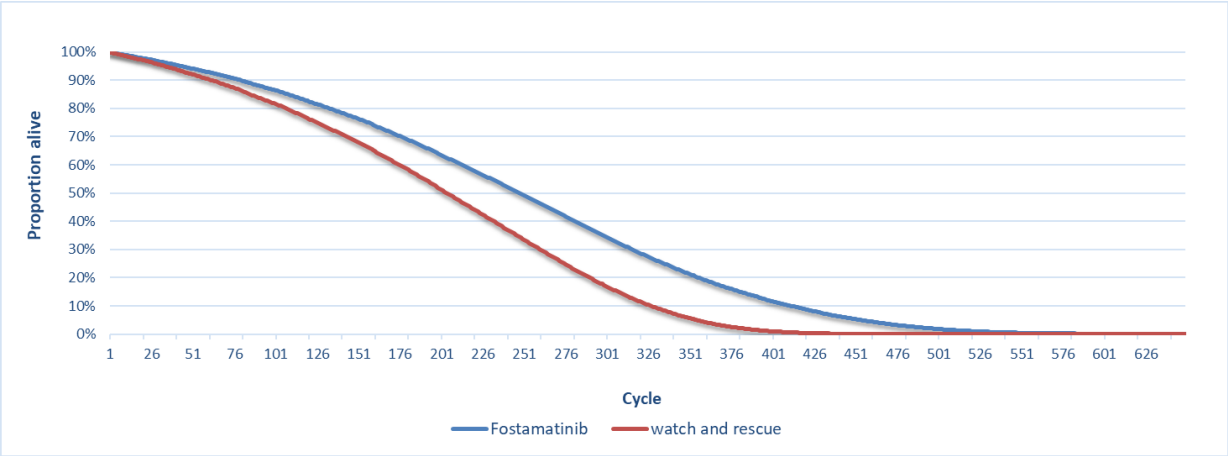
To account for increased mortality after an ICH, a hazard ratio of 2.02 was applied based on a case control study by Gonzalez-Perez et al. [8]. The authors investigated the short-term case fatality and long-term mortality after ICH and subarachnoid hemorrhage (SAH) using data from The Health Improvement Network database (UK).
Patients who were aged 20 to 89 years between January 2000 and December 2008 were included in the study cohort on the first day of the study period. Patients were excluded from the study if they had a diagnosis of ICH or SAH before their start date or if they were aged 70 years or older at the start date and were observed for more than 1 year but had no data recorded.
A total of 1,004 patients with ICH, 929 individuals with SAH, and 9,583 controls were available for follow-up until the end of 2010. The mean age at ICH diagnosis was 70.8 years.
The authors observed an elevated risk of death (HR 2.02) ICH among survivors at 1 year after an ICH. It was assumed that the study population is representative for the relevant patient population in Denmark.

Table 2. Hazard ratios applied according to platelet count

	Non-response <30k/µL	Partial response 30k/µL-50k/µL	Response >50k/µL
HR Inputs	4.20 [6]	2.50 [7]	1.00 [9]

HR: Hazard ratios, *The hazard ratio is the product of the HR applied for a stroke and the HR applied for the non-response state

Figure 3. Mortality applied in the model



4.2.8 Time horizon and cycle length

In this analysis, the treatment effect of fostamatinib was assumed to be a lifelong effect. Consequently, a lifetime horizon was selected. Based on the starting age of 60 years a time horizon of 40 years was assumed to be sufficient. The cycle length is four weeks (28 days). Half-cycle correction was applied.

4.2.9 Discounting

Cost and benefits were discounted by three percent (3.5%) per annum in line with the Danish reference case [1].

4.2.10 Uncertainty

Per-patient cost scenario analyses were conducted.

4.2.11 Assumptions on model parameters

Several assumptions have been made in parametrizing the model. The key assumptions are presented in Table 3.

Table 3. Assumptions on parameters in the model

Variable	Assumed value	Justification
Settings		
Time horizon	40 years	Patients entering the model have a mean age of 60 years based on clinical KOL feedback. Based on average life expectancy we do not expect any patients to live past 100 years old.
Markov assumption	NA	Patients will move through the health states as platelet count increases and decreases, suffer intra-cranial haemorrhage, or die. This is a reasonable assumption

		as the health states describe the patients' history, as ratified by KOL input [2].
Half cycle correction	NA	A half-cycle correction was applied to both costs and health outcomes in the Markov model to align with conventional modelling standards.
Baseline characteristics	Whole cohort: Age (years) = 60 % male = 50% Weight (kg) = 77	The baseline characteristics were based on KOL opinion [2].
Clinical inputs		
The transition probabilities from 'Response >50,000/µL' and 'Severe disability post ICH >50,000/µL' to other health states in the placebo arm, weeks 5 – 12.	NA	Due to zero patient numbers in the clinical trial, the transition probabilities of moving from 'Response >50k' were assumed to be the same as those for moving from 'Partial response 30-50,000/ µL', and transition probabilities of moving from ''Severe disability post ICH >50,000/µL' were assumed to be the same as those for 'Severe disability post ICH 30-50,000/µL' for the placebo arm, weeks 5-12
Hazard ratios for each health state	Non-response <30,000/µL': 4.2 'Partial Response 30- 50,000/µL': 2.5 'Response >50,000/µL': 1.0	It was assumed that responders have the same mortality as the general population while for partial and non-responders increased mortality was applied.
Adverse events per cycle	NA	It was assumed that adverse events would occur only during the first cycle for both fostamatinib and watch and rescue.
Loss of response	Loss of response from week 24	It was assumed that from week 24 patients do not lose response to fostamatinib.
Cost inputs		
Cost of administration of IV treatments (immunoglobulin and methylprednisolone)	NA	Due to zero patient numbers in the clinical trial, the transition probabilities of moving from 'Response >50k' were assumed to be the same as those for moving from 'Partial response 30-50,000/ µL', and transition probabilities of moving from ''Severe

		disability post ICH >50,000/μL' were assumed to be the same as those for 'Severe disability post ICH 30-50,000/μL' for the placebo arm, weeks 5-12
Health state costs	NA	It was assumed that only drug acquisition administration costs would be distinct between treatment arms. All other health state costs were assumed to apply to both arms, with frequency of their accrual determined by platelet count health state.
Cost of surgical prophylaxis – surgery rates for ITP patients	NA	It was assumed that Danish ITP patients have the same rate of surgery per age group as the general population of England & Wales.
Number of Hematologist consultations in post ICH health states	NA	Frequencies were based on KOL input [2].
Number of blood tests in post-ICH health states	NA	Frequencies were based on KOL input [2].
Number of biochemistry assays in post-ICH health states	NA	Frequencies were based on KOL input [2].
Vials wastage assumption	Wastage was only assumed for the use of the IVIg component	Wastage was included in the model as vial sharing of IVIg is not expected. All other treatments are either oral, supplied in small enough quantities to make up dosing, or supplied at dose.

5 Model inputs

Model inputs regarding effectiveness for fostamatinib were partly estimated from the pivotal clinical trials FIT1 and FIT2 (and in extension FIT3). Other model inputs were estimated based on data published in peer-reviewed journals or publicly available sources and supplemented with input from a Nordic clinical expert with experience in treating patients with cITP in the Nordics [2].

5.1 Population

Demographics used in the analysis are presented in Table 4 were sourced from literature [10] and KOL input. The inputs were discussed with and validated by a Nordic clinician [2].

Table 4. Demographics used in the cost-effectiveness model

Characteristics	Model population
Sex (% male)	50%
Mean age at start of analysis (years)	60
Mean body weight (kg)	77 kg

5.2 Effectiveness

The inputs regarding effectiveness for fostamatinib were derived from the pivotal trials FIT1 and FIT2, evaluating the effect and safety of fostamatinib in the treatment of individuals with cITP. Additionally, the open label extension study for fostamatinib (FIT3) was used [11]. The clinical trial data was used to inform:

- Transition probabilities among non-response, partial response, and response health states
- Discontinuation, either due to no response, adverse events, and compliance
- Rates of rescue events which occurred separated by platelet count
- Adverse event rates associated with fostamatinib, including thrombosis, occurring in at least 5% of any fostamatinib study arm

5.2.1 Fostamatinib

Patient level data from FIT1 and FIT2 were used to inform the transition matrices used in the model from baseline to Week 24. Patients' health states were defined according to their platelet counts, which is broadly in line with the two studies' primary efficacy endpoint, a stable platelet response (platelet count ≥ 50,000/μL for at least 4 of the 6 visits over Weeks 14 to 24). Transition matrices for the model were defined according to platelet count only. Patient level data from FIT1 and FIT2 were used to inform the transition matrices used in the model. For 'watch and rescue' patients the placebo data from FIT1 and FIT2 was used. Patients were categorized according to the health states defined in the model structure and their movements between health states was calculated. Patient movements were calculated from:

- Baseline to Week 4
- Week 5 to Week 12
- Week 13 to Week 24

This timing between calculation of health states is aligned with the anticipated intervals at which patients will be assessed for treatment response. Since the model uses four-weekly cycles, the rates of patient movement between health states from Week 5 to Week 12 and Week 13 to Week 24 were adjusted for the cycle length by transforming the 8-week and 12-week rates into 4-week rates (first rates were transformed into probabilities (formular 1) and then back into 4-week rates (formular 2)).

$$p = 1\text{-}EXP(-rt) \quad (1)$$
$$r = -(\ln(1-p))/t \quad (2)$$

Where there was no patient data to inform transition probabilities, the probability of moving between health states from a more severe health state was assumed to be the same probability of moving between health states from the next best health state, a conservative assumption.

The transition probabilities from week 24 + were based on a weighted average of the transition probabilities of the previous cycles. An alternative weighing using the average patient numbers and total row transitions was explored in a scenario analysis (Alternative weighing of transition probabilities from week 24+).

Beyond Week 24 of the model, the average of the Last Observation Carried Forward (LOCF) method can be also chosen. The average includes a weighted average of all transition matrices between Baseline and Week 24 for fostamatinib and 'watch and rescue' respectively. The weighted average is used since the transition matrices are applied a varying number of times. The LOCF methods utilizes the values from the transition matrix week 13 to 24.

The model includes the possibility to estimate loss of response beyond week 24 on a weighted average of loss of response during week 0 – 24. For the base case however, it was assumed that no loss of response would occur after week 24 – the 'exponential'. However, at the time of model development none of the responders to fostamatinib had sufficient follow-up to estimate an exponential function of loss of response – i.e., the model assumes no loss of response.

The resulting transition matrices are presented in **Appendix 9.2.**

5.2.2 Comparator - Watch and rescue

For 'watch and rescue' patients the placebo data from FIT1 and FIT2 was used. Similar to the fostamatinib arm, beyond Week 24 of the model, the weighted average of all transition matrices between Baseline and Week 24 is applied to 'watch and rescue'.

5.3 Adverse events

The analysis includes adverse events which occurred in at least 5% of one study arm over the entirety of the study in FIT1 or FIT2 regardless of severity. Table 5 presents the probability of adverse events for patients in the fostamatinib arm and in the watch and rescue arm. Adverse events including linked costs were applied during the first cycle in the model.

Table 5. Probability of adverse events for fostamatinib and 'watch and rescue' sourced from the FIT1 and FIT2 studies (pooled study populations)*

Resource item	Fostamatinib n (%)	Watch and rescue n (%)
Diarrhea	30 (29.4)	7 (14.6)
Hypertension	20 (19.6)	4 (8.3)
Nausea	19 (18.6)	4 (8.3)
ALT increased	9 (8.8)	0 (0)
AST increased	8 (7.8)	0 (0)
Diziness (with a fall)	9 (8.8)	4 (8.3)
Epistaxis	15 (14.7)	5 (10.4)
Upper RTI	8 (7.8)	1 (2.1)
Urinary Tract Infection	3 (2.9)	0 (0)
Abdominal pain	3 (2.9)	0 (0)
Fatigue	6 (5.9)	1 (2.1)
Pyrexia	2 (2)	2 (4.2)
Headache	10 (9.8)	9 (18.8)
Rash	7 (6.9)	1 (2.1)
Chest pain	4 (3.9)	1 (2.1)
Anemia	2 (2)	2 (4.2)
Petechiae	2 (2)	2 (4.2)

*AEs were included despite a probability of <5% in the pooled population (inclusion was based on probability per study arm in FIT1 or FIT2.
Source: [12, 13]

5.4 Resource use and unit costs

All costs in the model are expressed in DKK. The costs were derived from the diagnostic related groups list from 2021 [14] and the unit cost list published by the DMC [15]. Where applicable costs were inflated to 2021 cost level using consumer price index from Statistics Denmark (excl. electricity) [16].

Drug acquisition costs for rescue care were taken from the price list for drugs from the Danish Medicines Agency [17].

5.4.1 Drug acquisition costs

5.4.1.1 Fostamatinib

Fostamatinib is available as film-coated tablets in two strengths, 100 mg and 150 mg. See Table 6 for prices in the local currency.

Table 6. Drug acquisition cost

Product	Strength	Pharmacy purchasing price (DKK)	Cost of administration (DKK)
Tavlesse®	100 mg	26,568	0*
	150 mg	39,852	

*Assumption

5.4.1.2 Watch and rescue

Rescue treatment is given to all patients when platelet levels fall, and the patient becomes high risk for a bleeding event. For the frequencies for rescue events were derived from the FIT1 and FIT2 trial [18, 19].. The frequencies were calculated based on post- and pre-10-week data combing data for fostamatinib and placebo. The occurrences of the events were turned into a 4-weekly probability in similar fashion as it was done for bleed events (See section 5.4.2.1). The calculations are also presented in the data store of the cost-effectiveness model.

The frequency of rescue treatment per cycle is summarized in Table 7.

Table 7. Frequency of rescue events by health state in each 4-week cycle

Health states	Frequency of rescue treatment (per 4-weeks)
< 30,000µL	0.195
30,000-50,000µL	0.118
>50,000µL	0.092

The resource use of rescue treatment is summarised in Table 8. All patients receive immunoglobulin and methylprednisolone for rescue treatment for initial treatment, with 20% of patients additionally receiving a platelet transfusion. The frequency of the use of these resources was based on assumptions.

Table 8. Resource use associated with rescue treatment

	Probability of receiving one dose	Probability of receiving second dose
IV immunoglobulin	100%	0%

Oral methylprednisolone	100%	0%
Platelet transfusion (first and subsequent units)	20%	0%

The treatments used as rescue treatment are presented in Table 9.

Table 9. Drug acquisition and administration costs for rescue treatment

		Cost per unit (DKK)*	Cost per dose (DKK)	Administration cost (DKK)
Intravenous immunoglobulin	0.4g/kg – 5 times	612 per g	97155	712ǂ
Oral methylprednisolone	7g	138 - 158 per g	1025	0
Platelet transfusion†	1 transfusion	per transfusion	4628	712ǂ

*Treatment prices were taken from Medicinpriser.dk †DRG 2021: 16PR02 [14] ǂ Per administration

5.4.2 Healthcare utilization

5.4.2.1 Bleed events

Relevant healthcare services were included in the analysis. The selection of resource items for bleeding events were derived from the literature (**Table 10**).

Table 10. Health care utilization inputs for bleeding events

Resource item	Cost (DKK)	Comment	Source
Outpatient bleed	9418	Assumed to be the same as care for nose bleeding – 03MA03 Næseblødning	[14]
Gastrointestinal bleed	28340	Blødning fra mave-tarmkanal, pat. mindst 18 år, m. kompl. bidiag.	[14]
Intracranial hemorrhage	4977	Sammedagspakke: Blodprop i hjernen, udredning	[14]
Inpatient other bleed	21420	Assumed to be the same as gastrointestinal bleed (uncomplicated) - Blødning fra mave-tarmkanal, pat. mindst 18 år, u. kompl. bidiag.	[14]

Except for inpatient bleeds, frequency of bleed events for patients with a platelet count below 30,000/µL was taken from the romiplostim trial [20], whereas frequency of bleed events for patients above 50,000/µL was taken from Allen et al 2016 [21].

The romiplostim trial was considered a relevant source of information in terms of bleed events in patients with cITP. In total 41 patients received placebo; the mean age was 52 years. Concurrent therapy was allowed during the study. Since the frequencies were derived from the placebo arm the amount of bleed events during a 25-week duration was assumed to be representative for the patient population relevant to this analysis.

The study published by Allen et al. [21] was a cost-effectiveness analysis of eltrombopag vs. romiplostim for the treatment of cITP. Bleeding risks were estimated using patient-level data from the eltrombopag clinical trial program as the number of events experienced per unit time for patients with platelet counts of either $50x10^9$/L or more or less than $50x10^9$/L. Here, the frequencies for bleeds requiring either in- our outpatient care per four weeks for non-splenectomized patients were used. The inpatient bleeds were then categorized into "other bleed" (coagulation disorder, GI bleed and ICH) based on both splenectomized and non-splenectomized patients. The frequencies were derived from the RAISE (n=192) [22] and EXTEND trials (n = 299) [23], including patients both on placebo and eltrombopag. The estimated frequencies were included dependent on the health state, i.e., platelet count, and were hence used independent from treatment.

The frequency of bleed events for patients 30-50,000/µL was taken as an interpolation of the two sets of values. These frequencies were applied to both arms of the CE analysis.

Only for "inpatient other bleed" another study by Adelborg et al. was used [7]. The authors investigated the cardiovascular and bleeding outcomes in a population-based cohort of patients with cITP as described above (see description of HR – partial responders). The authors reported a 1-year risk of a bleed event (requiring hospital contact) of 25.8% (<25k), 9.8% (25 – 49 k) and 5.8% (50 – 149 k) for the respective platelet count. The platelet count categories were used as a proxy for the categories used in the model. The 1-year risk was transformed into per cycle probabilities.

All frequencies were applied to both arms of the cost-effectiveness analysis. Frequencies of severe bleed events are presented in Table 11**.**

Table 11.Severe bleed events related to immune thrombocytopenia applied per cycle in the model

Severe bleed event	Non-response <30k/µ L	Partial response 30k/µL - 50,000/µL	Response >50k /µ L	Severe disability post ICH <30k/µ L	Severe disability post ICH 30k/µL – 50k/µL	Severe disability post ICH >50k/µ L	Source
Intracranial haemorrhage	0.008	0.004	0	0	0	0	[20, 21]
Gastrointestinal bleed	0.004	0.002	0.0006	0.004	0.0023	0.0006	[20, 21]
Inpatient other bleed	0.02	0.008	0.005	0.02	0.008	0.005	[7]
Outpatient bleed	0.12	0.08	0.03	0.13	0.08	0.03	[20, 21]

The incidence of both bleed events and rescue events were first turned into a rate (1) and back into a probability (2) to account for the cycle length of the model.

$$r = -(\ln(1-p))/t \quad (1)$$

$$p = 1-EXP(-rt) \quad (2)$$

The frequencies of bleed events for patients with a platelet count of >50k were sourced as a 4-week rate. The probability of bleed events for patients with a platelet count of >50k/µ L was calculated by multiplying the 4-week rate of a hospitalization due to a bleed event and the proportion of the respective bleed event and then turning the rate into a probability (2).

Post-ICH disability was included for highly disabled patients (Modified Rankin Score[2] (mRS) 4 and 5) to reflect increased costs following an ICH. The probability of being categorized as mRS 4 or mRS 5 was derived from Rodríguez-Castro et al. [24]. According to the authors, 7.8% of women experiencing an ICH may be categorized as mRS 4 and 6.6% as mRS 5. Among men, 8% may be categorized as mrS 4 and 4.7% as mRS 5 [24]. These proportions were then weighted according to the proportion of men and women in the analysis (50%:50% in the base case). In the Danish analysis it was assumed that 7.9% of patients experiencing an ICH may be categorized as mRS 4 and 5.65% as mRS 5.

5.4.2.2 Emergency and care cost for ICH (Health and social care)

Emergency/ acute stroke care cost was applied in the model (Table 12). The frequencies for emergency/ acute stroke care cost are presented in Table 15.

Table 12. Emergency care cost

	Cost (DKK)	Comment/ Source
Emergency/ Acute Stroke Care	20,374	DRG: 01MA13 Forbigående utilstrækkelig blodforsyning til hjerne og okklusion af præcerebrale arterier [14]

To account for increased costs following an ICH due to an increased need of health and social care, costs were applied reflecting the first two years following the event of an ICH. Costs were derived from a Swedish study which investigated the relationship between functional disability following a stroke based on register data. For the actual estimation of costs during the first two years of an ICH in Denmark average costs for mRS 4 and mRS 5 were estimated, converted to DKK and inflated to 2021. Table 13 shows the used values from the publication. Table 14 shows the converted and inflated values which are currently applied in the model.

Table 13. Estimated post-ICH cost by year and category based on Lekander et al. [25]

		Inpatient stay (€)	Outpatient Speciality care (€)	Outpatient primary care (€)	Home care service (€)	Special housing (€)
Year 1	mRS 4	42,295	3,358	1,374	23,684	15,071
	mRS 5	5,537	1,605	1,069	23,264	31,476

[2] Modified Rankin Scale for Neurologic Disability

Year 2	mRS 4	4,899	954	674	65,931	12,448
	mRS 5	2,465	656	550	31,999	46,221

The total cost for post-ICH care is presented in Table 14. To differentiate between costs occurring in the primary or secondary sector, the post-ICH cost was divided into hospital and non-hospital cost.

Table 14. Values for post-ICH cost applied in the model

			Value
Post-ICH cost (average of year 1 and 2)	Total cost - Original (€)		157,765
	Total cost - Converted* to DKK and inflated to 2021†		1,216,533
	Post-ICH hospital costs (DKK)	Inpatient stay and outpatient specialty care	238,152
	Post-ICH non-hospital costs (DKK)	Outpatient primary care, home care services, and special housing	978,381

*Exchange rate: 7.436 [26], from 2021/03/24 †*Inflation rate: 1.003209243 2020 - March 2021 [16]

Table 15 shows the probabilities of acute and post-ICH 2-year cost applied for each cycle (see Table 11 for frequency of ICH). The cost is applied to the non-ICH states because it applies for a fixed period of time (2 years) from the moment an ICH occurs and not recurrently over the course of the rest of the patient's lifespan in the ICH state. As a result, the fixed 2-year cost of post-ICH care is applied as a cost to everyone in a non-ICH at risk health state, multiplied by ICH risk. This approach may underestimate the cost of post-ICH treatment, which favours the 'watch & rescue' strategy.

Table 15. Probabilities of acute post-ICH 2-year cost applied in the model

Cost item	Non-response <30k/µL	Partial response 30k/µL-50k/µL	Response >50k/µL	Severe disability post ICH <30k/µL	Severe disability post ICH 30k/µL-50k/µL	Severe disability post ICH >50k/µL
Emergency/Acute Stroke Care	0.008	0.004	0	0.008	0.004	0
Post-ICH 5-year cost of Health and Social Care	0.0011	0.0005	0	0	0	0

5.4.2.3 Routine care

The resource use associated with the routine management of chronic immune thrombocytopenia were discussed with and validated by a KOL [2]. Table 16 shows the frequencies for healtcare utilization linked to routine care. Unit costs linked to routine care which were sourced from a tariff list for specialized care (Table 17) [27].

Table 16. Frequencies of routine care – per cycle

Resource item	Non-response <30k/µL	Partial response 30k/µL-50k/µL	Response >50k/µL	Severe disability post ICH <30k/µL	Severe disability post ICH 30k/µL-50k/µL	Severe disability post ICH >50k/µL
Hematologist consultation	0.75	0.33	0.08	0.75	0.33	0.08
Blood test	1.00	0.33	0.17	1.00	0.33	0.17
Biochemistry	0.17	0.00	0.00	0.17	0.00	0.00

Applied unit costs for routine care are presented in Table 17.

Table 17. Unit costs for routine care

Resource item	Cost (DKK)	Comment	Source
Hematologist consultation	1,365	Overlæger, løntrinaflønnede (ikke ledende)	[15]
Blood test	49	Blodtagning fra blodåre pr. Forsendelse*	[28]
Biochemistry	255	Bioanalytikere (30 min)	[15]

*Inflated to 2021 (Inflation rate: 1.003209243, 2020 - March 2021 [16])

5.4.2.4 Adverse events

For each of the adverse events a unit cost was applied (Table 18). Costs were applied according to the frequencies for adverse events (Table 19).

Table 18. Health care utilization inputs for adverse events

Resource item	Cost (DKK)	Comment	Source/ Reference
Diarrhea	1,365	Physician visit: Overlæger, løntrinaflønnede (ikke ledende) - inflated to 2021*	[15]
Hypertension	1,365	Physician visit: Overlæger, løntrinaflønnede (ikke ledende) - inflated to 2021*	[15]
Nausea	1,365	Physician visit: Overlæger, løntrinaflønnede (ikke ledende) - inflated to 2021*	[15]
ALT increased	1,365	Physician visit: Overlæger, løntrinaflønnede (ikke ledende) - inflated to 2021*	[15]

AST increased	1,365	Physician visit: Overlæger, løntrinaflønnede (ikke ledende) - inflated to 2021*	[15]
Diziness (with a fall)	5,091	Care for diziness: 03MA02 Svimmelhed	[14]
Epistaxis	1,365	Physician visit: Overlæger, løntrinaflønnede (ikke ledende) - inflated to 2021*	[15]
Upper RTI	51,542	Treatment of inflamation of the respiratory tract: 04MA05 Infektioner og betændelse i luftveje, pat. mindst 65 år	[14]
Urinary Tract Infection	1,365	Physician visit: Overlæger, løntrinaflønnede (ikke ledende) - inflated to 2021*	[15]
Abdominal pain	1,365	Physician visit: Overlæger, løntrinaflønnede (ikke ledende) - inflated to 2021*	[15]
Fatigue	1,365	Physician visit: Overlæger, løntrinaflønnede (ikke ledende) - inflated to 2021*	[15]
Pyrexia	18,889	Treatment of fever: 18MA04 Feber af ukendt årsag, pat. mindst 18 år, uden biopsi og/eller scopi	[14]
Headache	1,365	Physician visit: Overlæger, løntrinaflønnede (ikke ledende) - inflated to 2021*	[15]
Rash	1,365	Physician visit: Overlæger, løntrinaflønnede (ikke ledende) - inflated to 2021*	[15]
Chest pain	1,365	Physician visit: Overlæger, løntrinaflønnede (ikke ledende) - inflated to 2021*	[15]
Anemia	69,514	Treatment of anemia: 16MP06 Mangelanæmier	[14]
Petechiae	1,365	Physician visit: Overlæger, løntrinaflønnede (ikke ledende) - inflated to 2021*	[15]

*Inflation rate: 1.003209243 2020 - March 2021 [16]

Table 19. Frequencies of adverse events applied in the model

Adverse event	Fostamatinib	Watch and rescue	Reference
Diarrhea	0.294	0.146	FIT1 and FIT2

Hypertension	0.196	0.083
Nausea	0.186	0.083
ALT increased	0.088	0.000
AST increased	0.078	0.000
Diziness (with a fall)	0.088	0.083
Epistaxis	0.147	0.104
Upper RTI	0.078	0.021
Urinary Tract Infection	0.029	0.000
Abdominal pain	0.029	0.000
Fatigue	0.059	0.021
Pyrexia	0.020	0.042
Headache	0.098	0.188
Rash	0.069	0.021
Chest pain	0.039	0.021
Anemia	0.020	0.042
Petechiae	0.020	0.042

Source: [12, 13]

5.4.2.5 Indirect costs

For the analysis, a limited societal perspective was applied including productivity loss linked to time spent due to treatment (alternative use of time). It was assumed that each healthcare visit (hematologist consultation or blood count) takes four hours. For one hour of time a value of DKK 180 was assumed as well as DKK 100 transportation cost per visit [15]. Table 20 shows the estimated use of time and linked unit costs. The frequencies presented in Table 21 were used for the calculations of the indirect costs. Table 22 shows the proportion of productivity losses applied for patients and caregivers. It was assumed that the productivity loss applies to 100% of the patients regardless of the health state. For caregivers, 0% spent time due to the patient's treatment in the Non-ICH-disability states and 100% for patients in the Post-ICH-disability states. The indirect costs were applied for each cycle in both arms.

Table 20. Overview of unit costs and values applied for indirect costs

Item	Value	Comment	Source

Hematologist: time use	4 h	Based on KOL opinion	[2]
Blood test: time use	4 h	Based on KOL opinion	[2]
Value per hour	180 DKK*	Applied for both patients and caregivers (see Table 22)	[15]
Transportation cost	100 DKK*	Applied only once	[15]

*Inflation rate: 1.003209243 2020 - March 2021 [16]

Table 21. Indirect cost calculations

	Non-response <30k/µL	Partial response 30k/µL-50k/µL	Response >50k/µL	Severe disability post ICH <30k/µL	Severe disability post ICH 30k/µL-50k/µL	Severe disability post ICH >50k/µL
Hematologist consultation	0.75	0.33	0.08	0.75	0.33	0.08
Blood count (incl. platelet count)	1.00	0.33	0.17	1.00	0.33	0.17
Biochemistry	0.17	0.00	0.00	0.17	0.00	0.00
Cost per healthcare visit	718	718	718	718	718	718
Transportation cost per visit	100	100	100	100	100	100
Total indirect cost per cycle	**1432.58**	**545.75**	**204.65**	**1432.58**	**545.75**	**204.65**

*Inflated to 2021 (Inflation rate: 1.003209243 2020 - March 2021 [16])

Table 22. Proportion of productivity loss linked to time spent due to treatment for patients and caregivers

Population	Proportion of time spent due to treatment	
	Non-ICH-disability states	Post-ICH-disability states
Patients	100%	100%
Caregivers	0%	100%

*Based on clinical expert opinion [2].

6 Results

6.1 Base case results

The base case analysis compares fostamatinib with 'watch and rescue'. The main settings of the analysis are presented below in Table 23.

Table 23. Base case settings

Item	Setting
Perspective	Limited societal perspective
Time horizon	40
Discounting	3.5% (2.5% from year 35)
Intervention	Fostamatinib combined with 'watch and rescue'
Comparator	'Watch and rescue'

6.1.1 Cost-per-patient

The base case cost-per-patient are presented below. Table 24 and Table 25 show total costs by category and health state. The summarized costs are shown in Table 26. Treatment with fostamatinib is associated with increased treatment costs compared to 'watch and rescue' (Table 24). The cost increase is driven by the drug acquisition cost while other cost items are decreasing. Considering a lifetime horizon, fostamatinib is linked to a cost of DKK 5,209,648 per patient.

Table 24. Base case results – Total cost-per-patient by category (discounted)

Category	Fostamatinib	Watch and rescue	Incremental difference
Drug acquisition (Fostamatinib)	2,290,214	0	2,290,214
Cost of rescue treatment	2,243,450	2,407,711	-164,261
Cost pre-surgical prophylaxis	212,138	337,647	-125,509
Health state cost (bleeding events and routine care)*	241,251	322,873	-81,623
Adverse event cost	8,046	6,149	1,897
Indirect cost	118,439	163,327	-44,888
Acute and two-year post ICH - Hospital costs	27,322	43,346	-16,024
Two-year post ICH - Non-hospital costs	68,789	109,134	-40,345

Total	5,209,648	3,390,188	1,819,459

*Excluding ICH

Costs by health state are presented in Table 25.

Table 25. Base case results – Total cost-per-patient by health state (discounted)

Health state	Fostamatinib	Watch and rescue	Incremental difference
Non-response <30,000/µL	1,674,493	2,584,195	-909,703
Partial response 30,000/µL-50,000/µL	331,784	484,118	-152,334
Response >50,000/µL	3,062,225	112,300	2,949,925
Severe disability post ICH <30,000/µL	107,480	172,341	-64,861
Severe disability post ICH 30,000/µL-50,000/µL	15,076	24,092	-9,016
Severe disability post ICH >50,000/µL	10,545	6,993	3,551
Adverse event cost	8,046	6,149	1,897
Total	5,209,648	3,390,188	1,819,459

Table 26. Base case results – Total cost-per-patient overview (discounted)

	Fostamatinib	Watch and rescue	Incremental
Total	5,209,648	3,390,188	1,819,459

6.1.2 Budget impact

The budget impact analysis is presented in Table 29 - Table 33. The cost estimations were based on the expected number of eligible patients (Table 27 and Table 28) and an assumed uptake of 100% in case of introduction of fostamatinib (i.e., all eligible patients would receive fostamatinib if introduced). Considering all costs including e.g., adverse event costs, rescue treatment costs and indirect costs, the introduction of fostamatinib would lead to DKK 2,641,128 additional costs at year five after introduction compared to watch and rescue.

Table 27. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5

Fostamatinib	15	20	25	30	35
Watch and rescue	0	0	0	0	0

Table 28. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is not introduced

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Fostamatinib	0	0	0	0	0
Watch and rescue	15	20	25	30	35

Table 29. Budget impact per patient per year - if the pharmaceutical is introduced

Treatment	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Fostamatinib	2,892,627	3,856,836	4,821,045	5,785,254	6,749,463
Watch and rescue	0	0	0	0	0

Table 30. Budget impact per patient per year - if the pharmaceutical is NOT introduced

Treatment	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Fostamatinib	0	0	0	0	0
Watch and rescue	1,760,715	2,347,620	2,934,524	3,521,429	4,108,334

Table 31. Disaggregated budget impact per patient per year - if the pharmaceutical is introduced

Item	Treatment	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Drug acquisition	Fostamatinib	1,281,593	1,708,790	2,135,988	2,563,186	2,990,383
	Watch and rescue	0	0	0	0	0
Rescue treatment	Fostamatinib	1,153,867	1,538,489	1,923,111	2,307,733	2,692,355
	Watch and rescue	0	0	0	0	0
Pre-surgical prophylaxis	Fostamatinib	109,345	145,793	182,241	218,690	255,138
	Watch and rescue	0	0	0	0	0
Health state costs (Bleed events & routine care)	Fostamatinib	120,964	161,286	201,607	241,929	282,250
	Watch and rescue	0	0	0	0	0
Adverse events	Fostamatinib	120,684	160,912	201,140	241,368	281,596
	Watch and rescue	0	0	0	0	0
Acute and two-year post ICH - Hospital costs	Fostamatinib	13,286	17,715	22,144	26,572	31,001
	Watch and rescue	0	0	0	0	0
Two-year post ICH - Non-hospital costs	Fostamatinib	33,451	44,602	55,752	66,903	78,053
	Watch and rescue	0	0	0	0	0
Indirect costs	Fostamatinib	59,437	79,249	99,061	118,874	138,686

	Watch and rescue	0	0	0	0	0

Table 32. Disaggregated budget impact per patient per year - if the pharmaceutical is not introduced

Item	Treatment	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Drug acquisition	Fostamatinib	0	0	0	0	0
	Watch and rescue	0	0	0	0	0
Rescue treatment	Fostamatinib	0	0	0	0	0
	Watch and rescue	1,180,977	1,574,636	1,968,294	2,361,953	2,755,612
Pre-surgical prophylaxis	Fostamatinib	0	0	0	0	0
	Watch and rescue	174,345	232,461	290,576	348,691	406,806
Health state costs (Bleed events & routine care)	Fostamatinib	0	0	0	0	0
	Watch and rescue	158,325	211,100	263,875	316,650	369,425
Adverse events	Fostamatinib	0	0	0	0	0
	Watch and rescue	92,230	122,973	153,716	184,459	215,202
	Fostamatinib	0	0	0	0	0

Acute and two-year post ICH - Hospital costs	Watch and rescue	21,125	17,715	22,144	26,572	31,001
Two-year post ICH - Non-hospital costs	Fostamatinib	0	0	0	0	0
	Watch and rescue	53,188	44,602	55,752	66,903	78,053
Indirect costs	Fostamatinib	0	0	0	0	0
	Watch and rescue	80,525	107,366	134,208	161,049	187,891

Table 33. Final budget impact

	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
The pharmaceutical under consideration is introduced	2,892,627	3,856,836	4,821,045	5,785,254	6,749,463
Minus:					
The pharmaceutical under consideration is NOT introduced	1,760,715	2,347,620	2,934,524	3,521,429	4,108,334
Difference	1,131,912	1,509,216	1,886,520	2,263,824	2,641,128

6.2 Scenario analyses

Table 34 shows the per-patient cost for different scenarios. The scenario analyses indicate that the model is stable to most changes, that is the scenario analyses do not change the cost-per-patient considerably.

Table 34. Scenario analysis fostamatinib vs. Watch and rescue

Parameter	Base case	New value	Fostamatinib – Per-patient cost	Watch and rescue – per patient cost	Incremental difference
Time horizon	40	20 years	4,613,281	3,245,385	1,367,897
		50 years	5,213,911	3,390,188	1,823,723
Discount rates	Costs 3.5% Benefits 3.5%	Costs 5%	4,601,291	3,063,598	1,537,693
		Costs 0%	7,366,699	4,455,387	2,911,312
Perspective	Limited societal perspective (Inclusion of time use due to treatment)	Payer	4,995,098	3,074,381	1,920,717

Additional to the scenario analysis, a deterministic sensitivity analysis was conducted exploring uncertainty linked to relevant variables.
The results for fostamatinib are presented in Figure 4. Here, the treatment cost for rescue medication per cycle (1+) for patients in the non-response state had the largest impact on the total cost per patient. This was followed by the treatment cost for rescue medication per cycle (1+) for patients in the partial-response state and the health state cost per cycle (6+) for patients in the non-response state .

Figure 4 Figure 5. Here, the treatment cost for rescue medication per cycle (1+) for patients in the non-response state had the largest impact on the total cost per patient. This was followed by the treatment cost for rescue medication per cycle (1+) for patients in the partial-response state and the health state cost per cycle (6+) for patients in the non-response state .

Figure 4. Tornado diagram – Cost per patient for fostamatinib

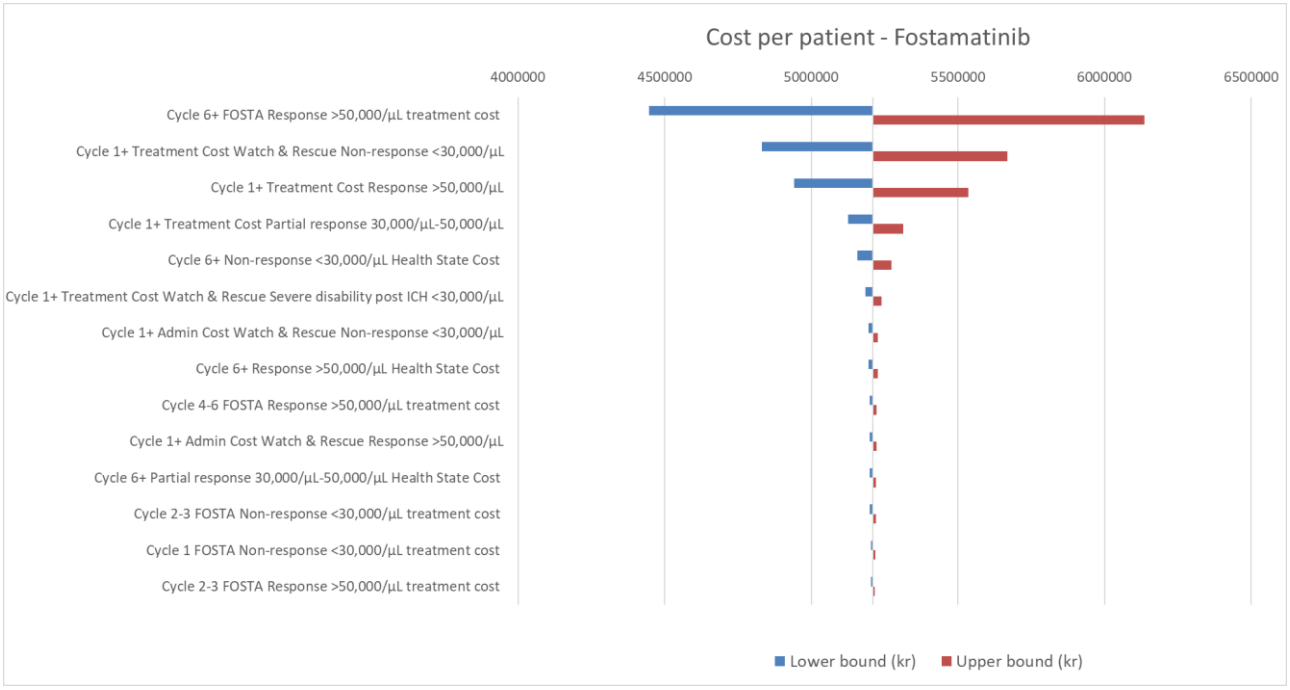
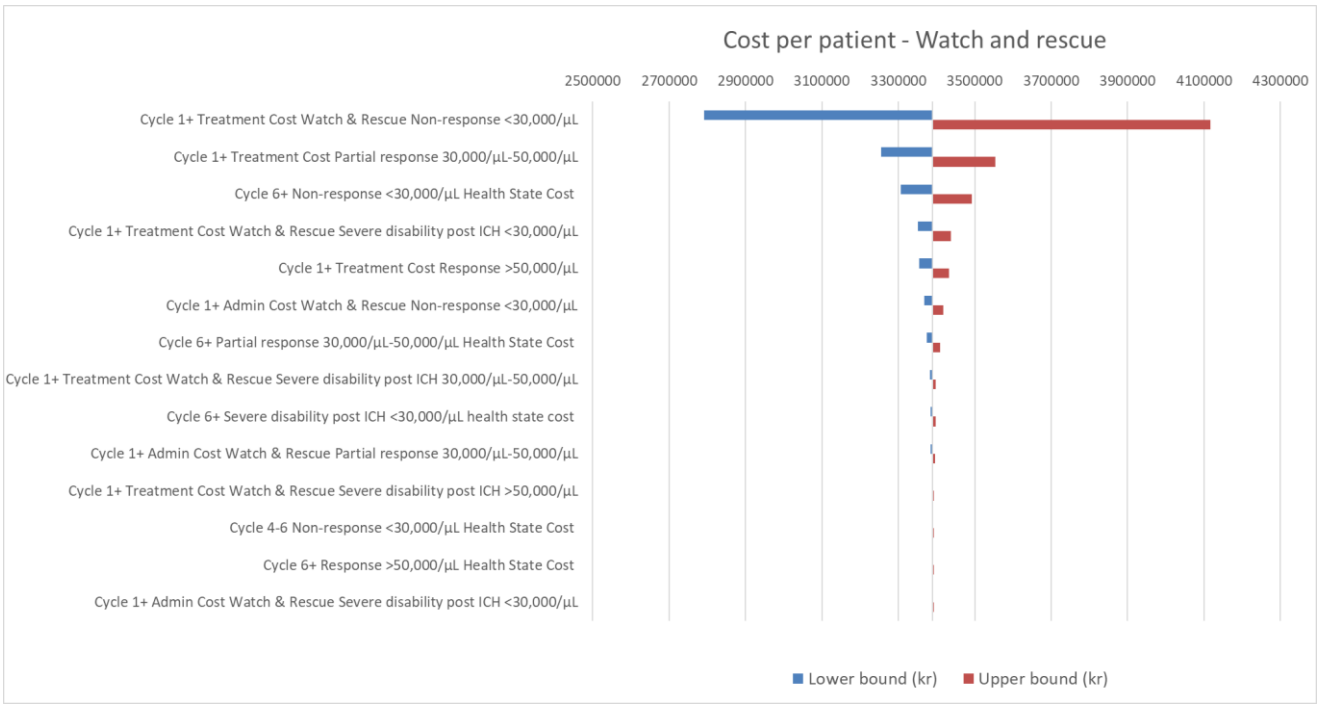


Figure 5. Tornado diagram – Cost per patient for watch and rescue



As mentioned above, the model appears to be robust regarding changes.

6.3 Scenario analysis – Alternative weighing of transition probabilities from week 24+

Alternative weighing of transition probabilities was explored in a scenario analysis. The results are presented below.

6.3.1 Cost-per-patient – Alternative weighing of transition probabilities from week 24+

The cost-per-patient for the alternative weighting are presented below. Table 24 and Table 25 show total costs by category and health state. The summarized costs are shown in Table 26. Treatment with fostamatinib is associated with increased treatment costs compared to 'watch and rescue' (Table 24). The cost increase is driven by the drug acquisition cost while other cost items are decreasing. Considering a lifetime horizon, fostamatinib is linked to a cost of DKK 5,229,395 per patient.

Table 35. Base case results – Total cost-per-patient by category (discounted)

Category	Fostamatinib	Watch and rescue	Incremental difference
Drug acquisition (Fostamatinib)	2,292,977	0	2,292,977
Cost of rescue treatment	2,251,294	2,420,661	-169,367
Cost pre-surgical prophylaxis	217,337	346,259	-128,922
Health state cost (bleeding events and routine care)*	243,066	325,964	-82,899
Adverse event cost	8,046	6,149	1,897
Indirect cost	119,696	165,441	-45,745
Acute and two-year post ICH - Hospital costs	27,569	43,777	-16,209
Two-year post ICH - Non-hospital costs	69,411	110,220	-40,810
Total	5,229,395	3,418,472	1,810,923

*Excluding ICH

Costs by health state are presented in Table 25.

Table 36. Base case results – Total cost-per-patient by health state (discounted)

Health state	Fostamatinib	Watch and rescue	Incremental difference
Non-response <30,000/µL	1,716,925	2,654,361	-937,437
Partial response 30,000/µL-50,000/µL	305,933	443,523	-137,590
Response >50,000/µL	3,063,114	107,222	2,955,893
Severe disability post ICH <30,000/µL	109,254	175,312	-66,058
Severe disability post ICH 30,000/µL-50,000/µL	14,459	23,119	-8,661

Severe disability post ICH >50,000/µL	11,664	8,786	2,878
Adverse event cost	8,046	6,149	1,897
Total	5,229,395	3,418,472	1,810,923

Table 37. Base case results – Total cost-per-patient overview (discounted)

	Fostamatinib	Watch and rescue	Incremental
Total	5,229,395	3,418,472	1,810,923

6.3.2 Budget impact – Alternative weighing of transition probabilities from week 24+

The budget impact analysis for the alternative weighting is presented in Table 29 - Table 33. The cost estimations were based on the expected number of eligible patients (Table 27 and Table 28) and an assumed uptake of 100% in case of introduction of fostamatinib (i.e., all eligible patients would receive fostamatinib if introduced). Considering all costs including e.g., adverse event costs, rescue treatment costs and indirect costs, the introduction of fostamatinib would lead to DKK 2,633,772 additional costs at year five after introduction compared to watch and rescue.

Table 38. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Fostamatinib	15	20	25	30	35
Watch and rescue	0	0	0	0	0

Table 39. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is not introduced

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Fostamatinib	0	0	0	0	0
Watch and rescue	15	20	25	30	35

Table 40. Budget impact per patient per year - if the pharmaceutical is introduced

Treatment	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Fostamatinib	2,901,460	3,868,613	4,835,766	5,802,919	6,770,072
Watch and rescue	0	0	0	0	0

Table 41. . Budget impact per patient per year - if the pharmaceutical is NOT introduced

Treatment	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Fostamatinib	0	0	0	0	0
Watch and rescue	1,772,700	2,363,600	2,954,501	3,545,401	4,136,301

Table 42. Disaggregated budget impact per patient per year - if the pharmaceutical is introduced

Item	Treatment	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Drug acquisition	Fostamatinib	1,283,197	1,710,930	2,138,662	2,566,395	2,994,127
	Watch and rescue	0	0	0	0	0
Rescue treatment	Fostamatinib	1,156,867	1,542,489	1,928,112	2,313,734	2,699,356
	Watch and rescue	0	0	0	0	0
Pre-surgical prophylaxis	Fostamatinib	111,876	149,168	186,460	223,753	261,045
	Watch and rescue	0	0	0	0	0
Health state costs (Bleed events & routine care)	Fostamatinib	121,735	162,314	202,892	243,470	284,049
	Watch and rescue	0	0	0	0	0
Adverse events	Fostamatinib	120,684	160,912	201,140	241,368	281,596
	Watch and rescue	0	0	0	0	0
Acute and two-year post ICH - Hospital costs	Fostamatinib	13,388	17,851	22,314	26,776	31,239
	Watch and rescue	0	0	0	0	0
Two-year post ICH - Non-hospital costs	Fostamatinib	33,708	44,944	56,180	67,416	78,652
	Watch and rescue	0	0	0	0	0
Indirect costs	Fostamatinib	60,004	80,005	100,006	120,007	140,009

	Watch and rescue	0	0	0	0	0

Table 43. Disaggregated budget impact per patient per year - if the pharmaceutical is not introduced

Item	Treatment	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Drug acquisition	Fostamatinib	0	0	0	0	0
	Watch and rescue	0	0	0	0	0
Rescue treatment	Fostamatinib	0	0	0	0	0
	Watch and rescue	1,185,853	1,581,137	1,976,421	2,371,705	2,766,990
Pre-surgical prophylaxis	Fostamatinib	0	0	0	0	0
	Watch and rescue	178,546	238,062	297,577	357,092	416,608
Health state costs (Bleed events & routine care)	Fostamatinib	0	0	0	0	0
	Watch and rescue	159,643	212,858	266,072	319,287	372,501
Adverse events	Fostamatinib	0	0	0	0	0
	Watch and rescue	92,230	122,973	153,716	184,459	215,202
	Fostamatinib	0	0	0	0	0

Acute and two-year post ICH - Hospital costs	Watch and rescue	21,306	17,851	22,314	26,776	31,239
Two-year post ICH - Non-hospital costs	Fostamatinib	0	0	0	0	0
	Watch and rescue	53,643	44,944	56,180	67,416	78,652
Indirect costs	Fostamatinib	0	0	0	0	0
	Watch and rescue	81,480	108,639	135,799	162,959	190,119

Table 44. Final budget impact

	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
The pharmaceutical under consideration is introduced	2,901,460	3,868,613	4,835,766	5,802,919	6,770,072
Minus:					
The pharmaceutical under consideration is NOT introduced	1,772,700	2,363,600	2,954,501	3,545,401	4,136,301
Difference	1,128,759	1,505,012	1,881,265	2,257,518	2,633,772

6.4 Scenario analyses – Alternative weighing of transition probabilities from week 24+

Table 34 shows the per-patient cost for different scenarios. The scenario analyses indicate that the model is stable to most changes, that is the scenario analyses do not change the cost-per-patient considerably.

Table 45. Scenario analysis fostamatinib vs. Watch and rescue

Parameter	Base case	New value	Fostamatinib – Per-patient cost	Watch and rescue – per patient cost	Incremental difference
Time horizon	40	20 years	4,633,519	3,275,428	1,358,092
		50 years	5,233,664	3,418,472	1,815,193
Discount rates	Costs 3.5% Benefits 3.5%	Costs 5%	4,619,695	3,090,335	1,529,359
		Costs 0%	7,390,212	4,487,354	2,902,858
Perspective	Limited societal perspective (Inclusion of time use due to treatment)	Payer	5,109,699	3,253,031	1,856,668

Additional to the scenario analysis, a deterministic sensitivity analysis was conducted exploring uncertainty linked to relevant variables.
The results for fostamatinib are presented in Figure 4. Here, the treatment cost for rescue medication per cycle (1+) for patients in the non-response state had the largest impact on the total cost per patient. This was followed by the treatment cost for rescue medication per cycle (1+) for patients in the partial-response state and the health state cost per cycle (6+) for patients in the non-response state .

Figure 4 Figure 5. Here, the treatment cost for rescue medication per cycle (1+) for patients in the non-response state had the largest impact on the total cost per patient. This was followed by the treatment cost for rescue medication per cycle (1+) for patients in the partial-response state and the health state cost per cycle (6+) for patients in the non-response state .

Figure 6. Tornado diagram – Cost per patient for fostamatinib

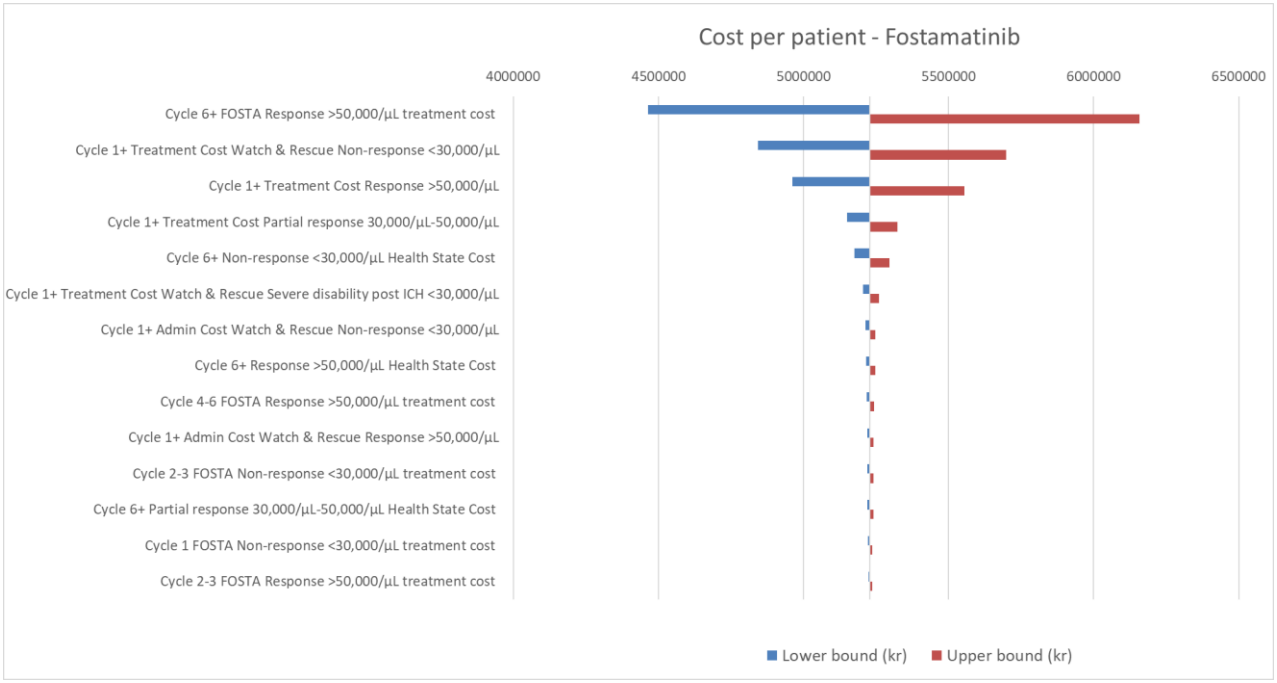
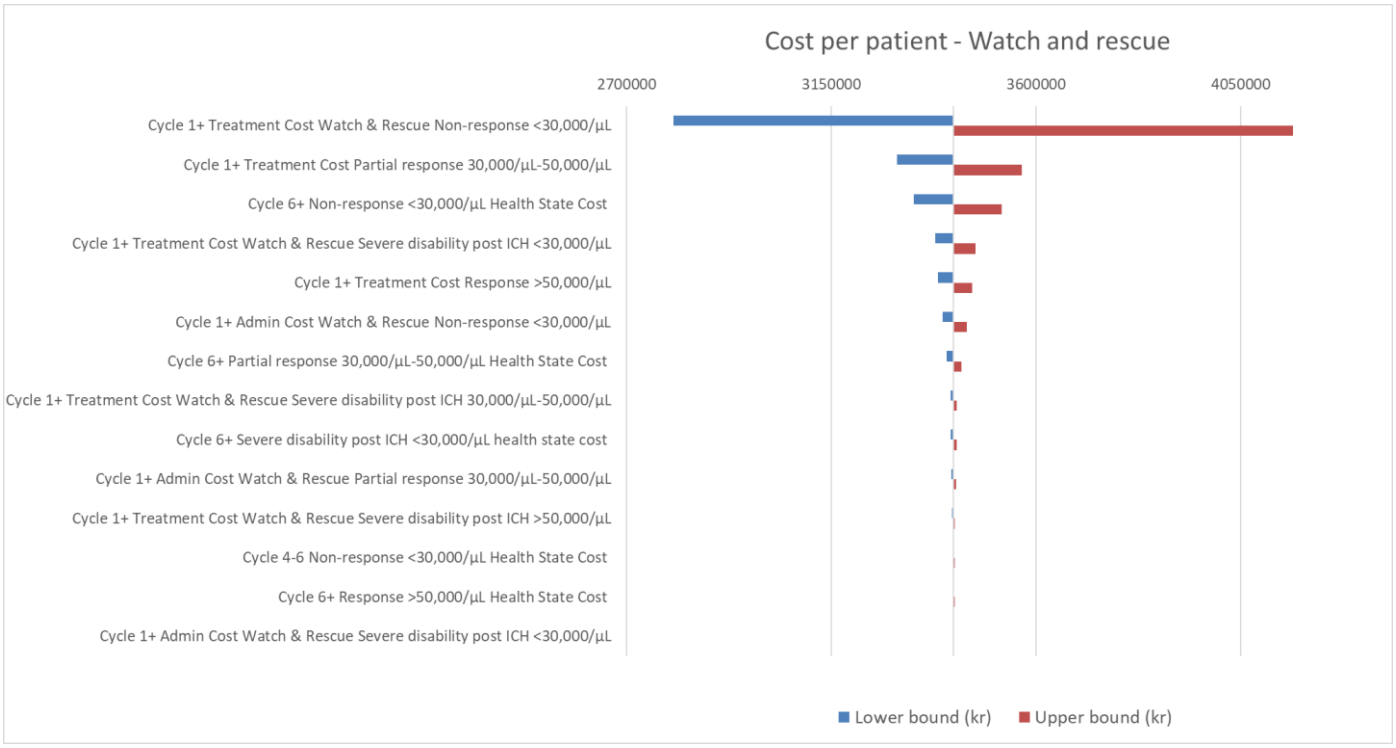


Figure 7. Tornado diagram – Cost per patient for watch and rescue



As mentioned above, the model appears to be robust regarding changes.

7 Discussion and conclusions

The objective of this health economic analysis was to evaluate the per-patient cost and budget impact compared to 'watch and rescue' for patients with cITP over a lifetime horizon (40 years) from a Danish perspective. Watch and rescue encompassed several treatment options including IVIg and methylprednisolone. Key model inputs were sourced from the pivotal trials FIT1 and FIT2.

According to the base case results of the model, fostamatinib is associated with a cost-per-patient of DKK 5,209,648 when considering a lifetime horizon. This translates into a budget impact of DKK 2,641,128 compared to watch and rescue at year five after introduction of fostamatinib.

Scenario analyses have shown that the results are relatively stable towards changes of the analysis settings.

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9 Appendix

9.1 Life tables

Table 46. Life table – Denmark

Age	Probability of death at age x (per 100 000) (Ungraduated), qx	
	Men	Women
0 years	0.00347	0.00268
1 year	0.00028	0.00007
2 years	0.00016	0.00003
3 years	0.00012	0.00007
4 years	0.00007	0.0001
5 years	0.00007	0.00014
6 years	0.00007	0.00004
7 years	0.00006	0.0001
8 years	0.00003	0.00007
9 years	0.00003	0
10 years	0.00006	0.00003
11 years	0.00011	0
12 years	0.00012	0.00009
13 years	0	0
14 years	0.00017	0.00006
15 years	0.00009	0.00018
16 years	0.00029	0.00015
17 years	0.00023	0.00006
18 years	0.00034	0.00012
19 years	0.0003	0.00026

20 years	0.00038	0.00023
21 years	0.00032	0.00014
22 years	0.00039	0.00016
23 years	0.00058	0.00013
24 years	0.00053	0.00023
25 years	0.00065	0.00022
26 years	0.00042	0.00015
27 years	0.00053	0.00018
28 years	0.00056	0.00013
29 years	0.00045	0.00034
30 years	0.00054	0.00016
31 years	0.00051	0.00022
32 years	0.00033	0.00041
33 years	0.00059	0.00021
34 years	0.00067	0.00024
35 years	0.00075	0.00041
36 years	0.00099	0.00032
37 years	0.00082	0.00031
38 years	0.00074	0.00065
39 years	0.00096	0.00041
40 years	0.00063	0.00069
41 years	0.00093	0.00042
42 years	0.0011	0.00054
43 years	0.00125	0.00058
44 years	0.00157	0.00083
45 years	0.00177	0.001
46 years	0.00184	0.00093

47 years	0.00191	0.00109
48 years	0.00242	0.00142
49 years	0.00252	0.00147
50 years	0.00315	0.00136
51 years	0.00352	0.00165
52 years	0.00329	0.0021
53 years	0.00361	0.0027
54 years	0.00407	0.00279
55 years	0.00505	0.00254
56 years	0.00487	0.00303
57 years	0.00535	0.00371
58 years	0.00624	0.00364
59 years	0.00734	0.0053
60 years	0.00812	0.0053
61 years	0.00924	0.00621
62 years	0.00959	0.00604
63 years	0.01064	0.00712
64 years	0.01282	0.00788
65 years	0.01361	0.00814
66 years	0.01531	0.01042
67 years	0.01699	0.00951
68 years	0.01835	0.01147
69 years	0.02007	0.0124
70 years	0.01965	0.01238
71 years	0.0218	0.01284
72 years	0.02296	0.01428
73 years	0.02653	0.01709

74 years	0.02823	0.01929
75 years	0.03516	0.02311
76 years	0.03557	0.02395
77 years	0.03804	0.02672
78 years	0.04167	0.02893
79 years	0.0491	0.03285
80 years	0.053	0.03837
81 years	0.05833	0.04183
82 years	0.07139	0.04668
83 years	0.0761	0.05885
84 years	0.08819	0.06306
85 years	0.09688	0.07139
86 years	0.11066	0.08227
87 years	0.1279	0.0923
88 years	0.14679	0.10559
89 years	0.16051	0.11195
90 years	0.18276	0.13644
91 years	0.19784	0.14757
92 years	0.21978	0.1694
93 years	0.23389	0.17571
94 years	0.25429	0.20629
95 years	0.27271	0.21823
96 years	0.30141	0.23845
97 years	0.35231	0.25509
98 years	0.39796	0.30897
99 years	0.37803	0.32367

9.2 Transition matrices

9.2.1 Fostamatinib

Table 47. Fostamatinib transition matrix for Baseline to Week 4

Health State	Non-response <30k/µL	Partial response 30k/µL-50k/µL	Response >50k/µL	Severe disability post ICH <30k/µL	Severe disability post ICH 30k/µL-50k/µL	Severe disability post ICH >50k/µL
Non-response <30k/µL	68%	18.9%	13.3%	0.1%	0.0%	0.0%
Partial response 30k/µL-50k/µL	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%
Response >50k/µL	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%
Severe disability post ICH <30k/µL	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%
Severe disability post ICH 30k/µL-50k/µL	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%
Severe disability post ICH >50k/µL	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%

Table 48. Fostamatinib transition matrix for Week 5 to Week 12

Health State	Non-response <30k/µL	Partial response 30k/µL-50k/µL	Response >50k/µL	Severe disability post ICH <30k/µL	Severe disability post ICH 30k/µL-50k/µL	Severe disability post ICH >50k/µL
Non-response <30k/µL	70.0%	17.7%	12.2%	0.1%	0.0%	0.0%
Partial response 30k/µL-50k/µL	28.1%	33.3%	38.6%	0.0%	0.0%	0.0%
Response >50k/µL	0.0%	27.4%	72.6%	0.0%	0.0%	0.0%
Severe disability post ICH <30k/µL	0.0%	0.0%	0.0%	70.1%	17.7%	12.2%

Severe disability post ICH 30k/µL-50k/µL	0.0%	0.0%	0.0%	28.1%	33.3%	38.7%
Severe disability post ICH >50k/µL	0.0%	0.0%	0.0%	0.0%	27.4%	72.6%

Table 49. Fostamatinib transition matrix for Week 13 to Week 24

Health State	Non-response <30k/µL	Partial response 30k/µL-50k/µL	Response >50k/µL	Severe disability post ICH <30k/µL	Severe disability post ICH 30k/µL-50k/µL	Severe disability post ICH >50k/µL
Non-response <30k/µL	70.7%	29.2%	0.0%	0.1%	0.0%	0.0%
Partial response 30k/µL-50k/µL	33.3%	33.3%	33.3%	0.0%	0.0%	0.0%
Response >50k/µL	4.6%	4.6%	90.7%	0.0%	0.0%	0.0%
Severe disability post ICH <30k/µL	0.0%	0.0%	0.0%	70.8%	29.2%	0.0%
Severe disability post ICH 30k/µL-50k/µL	0.0%	0.0%	0.0%	33.3%	33.3%	33.3%
Severe disability post ICH >50k/µL	0.0%	0.0%	0.0%	4.6%	4.6%	90.7%

Table 50. Fostamatinib transition matrix for extrapolation beyond week 24

Health State	Non-response <30k/µL	Partial response 30k/µL-50k/µL	Response >50k/µL	Severe disability post ICH <30k/µL	Severe disability post ICH 30k/µL-50k/µL	Severe disability post ICH >50k/µL
Non-response <30k/µL	69.98%	23.63%	6.28%	0.08%	0.03%	0.01%
Partial response 30k/µL-50k/µL	26.01%	44.41%	29.54%	0.01%	0.01%	0.02%

Response >50k/µL	0.00%	0.00%	100.00%	0.00%	0.00%	0.00%
Severe disability post ICH <30k/µL	0.00%	0.00%	0.00%	75.42%	20.51%	4.07%
Severe disability post ICH 30k/µL-50k/µL	0.00%	0.00%	0.00%	26.02%	44.42%	29.55%
Severe disability post ICH >50k/µL	0.00%	0.00%	0.00%	0.00%	0.00%	100.00%

9.2.2 Watch and rescue

Table 51. 'Watch and rescue' transition matrix for Baseline to Week 4

	Non-response <30k/µL	Partial response 30k/µL-50k/µL	Response >50k/µL	Severe disability post ICH <30k/µL	Severe disability post ICH 30k/µL-50k/µL	Severe disability post ICH >50k/µL
Non-response <30k/µL	76.1%	23.8%	0.0%	0.1%	0.0%	0.0%
Partial response 30k/µL-50k/µL	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%
Response >50k/µL	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%
Severe disability post ICH <30k/µL	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%
Severe disability post ICH 30k/µL-50k/µL	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%

Severe disability post ICH >50k/µL	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%

Table 52. 'Watch and rescue' transition matrix for Week 5 to Week 16

	Non-response <30k/µL	**Partial response 30k/µL-50k/µL**	**Response >50k/µL**	**Severe disability post ICH <30k/µL**	**Severe disability post ICH 30k/µL-50k/µL**	**Severe disability post ICH >50k/µL**
Non-response <30k/µL	82.1%	12.0%	5.9%	0.1%	0.0%	0.0%
Partial response 30k/µL-50k/µL	45.9%	45.9%	8.2%	0.0%	0.0%	0.0%
Response >50k/µL	45.9%	45.9%	8.2%	0.0%	0.0%	0.0%
Severe disability post ICH <30k/µL	0.0%	0.0%	0.0%	82.2%	12.0%	5.9%
Severe disability post ICH 30k/µL-50k/µL	0.0%	0.0%	0.0%	45.9%	45.9%	8.2%
Severe disability post ICH >50k/µL	0.0%	0.0%	0.0%	45.9%	45.9%	8.2%

Table 53. 'Watch and rescue' transition matrix for Week 17 to Week 24

	Non-response <30,000/µL	Partial response 30,000/µL-50,000/µL	Response >50,000/µL	Severe disability post ICH <30,000/µL	Severe disability post ICH 30,000/µL-50,000/µL	Severe disability post ICH >50,000/µL
Non-response <30,000/µL	82.1%	12.0%	5.9%	0.1%	0.0%	0.0%
Partial response 30,000/µL-50,000/µL	45.9%	45.9%	8.2%	0.0%	0.0%	0.0%
Response >50,000/µL	38.7%	16.8%	44.5%	0.0%	0.0%	0.0%
Severe disability post ICH <30,000/µL	0.0%	0.0%	0.0%	82.2%	12.0%	5.9%
Severe disability post ICH 30,000/µL-50,000/µL	0.0%	0.0%	0.0%	45.9%	45.9%	8.2%
Severe disability post ICH >50,000/µL	0.0%	0.0%	0.0%	38.7%	16.8%	44.5%

Table 54. 'Watch and rescue' transition matrix for extrapolation

	Non-response <30,000/µL	Partial response 30,000/µL-50,000/µL	Response >50,000/µL	Severe disability post ICH <30,000/µL	Severe disability post ICH 30,000/µL-50,000/µL	Severe disability post ICH >50,000/µL
Non-response <30,000/µL	81.1%	13.9%	4.9%	0.1%	0.0%	0.0%

Partial response 30,000/µL-50,000/µL	38.2%	54.9%	6.8%	0.0%	0.0%	0.0%
Response >50,000/µL	34.6%	23.7%	41.7%	0.0%	0.0%	0.0%
Severe disability post ICH <30,000/µL	0.0%	0.0%	0.0%	85.1%	10.0%	4.9%
Severe disability post ICH 30,000/µL-50,000/µL	0.0%	0.0%	0.0%	38.3%	54.9%	6.8%
Severe disability post ICH >50,000/µL	0.0%	0.0%	0.0%	34.6%	23.7%	41.7%

Medicinrådet

Medicinrådets protokol for vurdering vedrørende fostamatinib 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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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:	Thrombopoietin-receptor agonist

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2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Instituto Grifols S.A., som ønsker, at Medicinrådet vurderer fostamatinib til patienter med kronisk immun trombocytopeni, som er refraktære over for andre behandlinger. Medicinrådet modtog den foreløbige ansøgning den 11. december 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 blodplademangel. 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]. De fleste af disse vil være tilstrækkeligt hjulpet af de nuværende behandlinger, og fagudvalget vurderer, at der er ca. 10 patienter, som ikke vil have gavn af de nuværende behandlinger, og som dermed er kandidater til behandling med fostamatinib. Derudover skønner fagudvalget, at der vil være 1-5 nye patienter om året.

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 Fostamatinib

Fostamatinib er et en milt-tyrosinkinase (SYK) inhibitor, der modvirker nedbrydelsen af blodplader gennem den aktive metabolit, R406. R406 reducerer den antistof-medierede destruktion af trombocytter, ved at hæmme signaleringen hos B-cellereceptorer og Fc-aktiverende receptorer.

Fostamatinib er i det europæiske lægemiddelagentur godkendt til patienter ≥ 18 år med kronisk ITP, der er refraktære over for andre behandlinger.

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 vurderer, at fostamatinib bør anvendes efter behandlinger med glukokortikoider, evt. rituximab og TPO-RA'er på linje med de immunsuppressive behandlinger.

Fostamatinib indtages oralt som tabletter à 100 mg eller 150 mg to gange dagligt. Lægemidlet doseres, så den laveste dosis for at opnå et trombocyttal på > 50 x 10^9 pr. liter anvendes. Den rekommanderede dosis er 100 mg to gange dagligt. Dosis kan øges til 150 mg ved uge 4 baseret på trombocyttal og tolerabilitet.
Behandlingen seponeres efter 12 ugers behandling, hvis trombocyttallet ikke er steget til et tilstrækkeligt niveau [10]. Behandling med fostamatinib forventes at fortsætte, så længe der er tilstrækkelig effekt.

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.
Fagudvalget har stillet to kliniske spørgsmål. Dels vurderer fagudvalget, at fostamatinib er et relevant behandlingsalternativ til immunsuppressive behandlinger. Da alle immunsuppressive behandlinger anvendes off-label, og der er tale om en behandling meget sent i behandlingsforløbet, er det også relevant at sammenligne med placebo.

3.1 Klinisk spørgsmål 1

Hvilken værdi har fostamatinib sammenlignet med placebo for patienter med primær kronisk behandlingsrefraktær ITP?

Population
Patienter ≥ 18 år med primær kronisk ITP, som ikke har effekt af andre behandlinger.

Intervention
Fostamatinib 100 mg to gange dagligt. Kan efter 4 uger opjusteres til 150 mg dagligt.

Komparator

Placebo (ingen behandling).

Effektmål
De valgte effektmål fremgår af tabel 1.

3.2 Klinisk spørgsmål 2

Hvilken værdi har fostamatinib sammenlignet med immunsuppressive behandlinger såsom dapson, danazol, mycophenolate mofetil, azathioprin eller ciclosporin for patienter med primær kronisk ITP?

Population
Patienter ≥ 18 år med primær kronisk ITP, som ikke har effekt af andre behandlinger.

Intervention
Fostamatinib 100 mg to gange dagligt. Kan efter 4 uger opjusteres til 150 mg dagligt.

Komparator
I dansk klinisk praksis anvendes de immunsuppressive behandlinger på dette behandlingstrin. For at belyse effekten af interventionen op mod gældende klinisk praksis er de derfor valgt som komparatorer i dette kliniske spørgsmål, selvom de anvendes off-label. Valget af behandlingerne listet nedenfor afhænger i klinikken af erfaring og en helhedsvurdering af den enkelte patient. Derfor er der ikke én behandling, som er foretrukket frem for en anden.
De relevante komparatorer er derfor en af følgende:

- Danazol, 200 mg to til tre gange dagligt
- Dapson, 75-100 mg dagligt
- Mycophenolat mofetil, op til 1 g to gange dagligt
- Azathioprin, 100-150 mg dagligt
- Ciclosporin, 2-3 mg/kg/dag fordelt på 2 doser.

Ansøger bør foretage en sammenligning med mindst én af komparatorerne og vælge komparator ud fra, hvor der er det bedste datagrundlag, baseret på en vurdering af studiestørrelse og -design, sammenlignelighed med dansk klinisk praksis, sammenlignelige studiepopulationer, ønskede effektmål mv.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.3 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

Tabel 1. Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Forskel i gennemsnitlig ændring fra baseline målt ved SF-36	8 point
			Andel, der opnår en stigning på ≥ 8 point	5 %-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 med blodpladetal ≥ 30 x 10^9/L	10 %-point
Bivirkninger	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Andel, der ophører behandling pga. uønskede hændelser	10 %-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.

3.3.1 Kritiske effektmål

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. 5-års risikoen for hospitalisering som følge af intrakranielle blødninger er 1,4 % blandt patienter med kronisk ITP. Derudover er den estimerede 5-års risiko for hospitalisering som følge af blødning (andre end intrakraniel blødning) 3,6 % [2]. Alvorlige blødninger er alvorligt for patienten, men altså sjældent forekommende, og derfor fastsætter fagudvalget den mindste kliniske relevante forskel til 1 %-point. Fagudvalget ønsker effektmålet opgjort med længst mulig opfølgningstid.

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. Fordi det er en behandling sent i behandlingsforløbet, betragter fagudvalget en forskel på 5 %-point som en mindste klinisk relevant forskel.

3.3.2 Vigtige effektmål

Mindre blødninger
Fagudvalget finder det relevant at vurdere effektmålet *mindre blødninger* defineret i overensstemmelse CTCAE eller *WHO Bleeding Scale*. Definitionen 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 at blive i behandlingen. Med de immunsuppressive behandlinger oplever omkring 20-70 % tilbagefald under behandling [11]. På den baggrund vurderer fagudvalget, at den mindste klinisk relevante forskel er 10 %-point.

Andel af patienter med blodpladetal ≥ 30 x 10^9/L
Blodpladetallet er et surrogat for patientens blødningsrisiko og af mindre betydning i sig selv 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 fostamatinib 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* ≥ 30 x 10^9/L, opgjort efter 6 måneders behandling uden behov for supplerende medicin. Da behandling med fostamatinib vil ligge sent i behandlingsrækkefølgen, og man deraf vil kunne forvente, at patienterne har et lavt blodpladetal, finder fagudvalget et blodpladetal ≥ 30 x 10^9/L som et acceptabelt niveau. Omkring 40-70 % opnår respons med de immunsuppressive behandlinger, som anvendes i dag [11]. Derfor vurderer fagudvalget den mindste kliniske relevante forskel til at 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 fostamatinib og immunsuppressive behandlinger 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, der ophører behandling på grund af uønskede hændelser med længst mulig opfølgningstid. Baseret på studiedata ophører ca. 15 % med nuværende behandling [11]. De potentielle kandidater til fostamatinib og immunsuppressiva vil have afprøvet mange behandlinger, som ikke længere har effekt, og fagudvalget vurderer på den baggrund, at der er en høj tolerance over for uønskede hændelser. Fagudvalget vurderer derfor, at en forskel på 10 %-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 opmærksom på andelen, som får diarré og blodtrykforhøjelse.

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

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der findes to studier, hvor fostamatinib er sammenlignet direkte med placebo.

- FIT1 (NCT02076399)
- FIT2 (NCT02076412)

Det er ikke tilstrækkeligt datagrundlag til en komplet besvarelse af de kliniske spørgsmål, da der mangler data for komparatorerne i klinisk spørgsmål 2.

Ansøger skal derfor undersøge, om der findes andre studier, som indeholder/beskriver de angivne mangler. Søgestrengene fremgår af bilag 1.

Ansøger skal på baggrund af studierne foretage en indirekte sammenligning for at besvare de dele af de kliniske spørgsmål, som den direkte sammenligning ikke kan besvare.

Ansøger skal derudover konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er).

Virksomheden 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

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

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.

Særlige forhold i denne protokol

- Ansøger bedes undersøge muligheden for at gennemføre en netværksmetaanalyse til besvarelse af klinisk spørgsmål 2.

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 Behandlingsvarighed

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

7.2 Risiko for pneumokokinfektioner

Milten er et vigtigt forsvar mod pneumokokinfektion. Fagudvalget kan dog ikke vurdere, om virkningsmekanismen af fostamatinib ved hæmning af SYK påvirker denne funktion af milten. Fagudvalget ønsker derfor, at ansøger beskriver risikoen for pneumokokinfektioner.

7.3 Betydning af splenektomi

Fagudvalget ønsker, at ansøger beskriver, hvordan effekten af fostamatinib er påvirket hos splenektomerede patienter.

7.4 Supplerende behandling

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

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 autoimmune[tiab] OR immune[tiab]) AND thrombocytop*[tiab])	
#3	#1 OR #2	Samlet søgning for populationen
#4	fostamatinib[nm]	Søgetermer for interventionen
#5	fostamatinib[tiab] OR Tavalisse*[tiab] OR Tavlesse*[tiab] OR R-788[tiab] OR R788[tiab]	
#6	Azathioprine[mh] OR Danazol[mh] OR Dapsone[mh] OR Mycophenolic Acid[mh] OR Cyclosporine[mh]	Søgetermer for komparator
#7	azathioprine[tiab] OR danazol[tiab] OR dapsone[tiab] OR mycophenolic acid[tiab] OR mycophenolate[tiab] OR cyclosporine[tiab]	
#8	#4 OR #5 OR #6 OR #7	Intervention + komparator
#9	child*[ti] OR pediatric[ti] OR paediatric[ti]	Eksklusion af studier i børn
#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 NOT (#9 OR #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 autoimmune or immune) near thrombocytop*):ti,ab	
#5	#1 or #2 or #3 or #4	Samlet søgning for populationen
#6	(fostamatinib or Tavalisse* or Tavlesse* or R-788 or R788):ti,ab,kw	Søgetermer for interventionen
#7	(azathioprine or danazol or dapsone or mycophenolic next acid or mycophenolate or cyclosporine):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