Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende tafamidis til transthyretin-medieret amyloidose med kardiomyopati

Versionsnr.: 1.1

Medicinrådet

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 Baggrunden for Medicinrådets anbefaling

Baggrund for Medicinrådets anbefaling er en sammenfatning af lægemidlets værdi for patienterne, omkostninger for samfundet og en gengivelse af de vurderinger, der er grundlag for Medicinrådets anbefaling.

Anbefalingen er Medicinrådets vurdering af, om omkostningerne vedrørende brug af lægemidlet er rimelige, når man sammenligner dem med lægemidlets værdi for patienterne. I nogle tilfælde spiller sygdommens alvorlighed en særlig rolle i vurderingen.

Anbefalingen er et klinisk og økonomisk baseret råd til regionerne til brug for deres beslutning om at anvende et givet lægemiddel.

Læs eventuelt mere i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Godkendt af Medicinrådet den 21. oktober 2020
Dokumentnummer 97091
Versionsnummer 1.1

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf

Indhold

1 Anbefaling vedrørende transthyretin-medieret amyloidose med kardiomyopati

Medicinrådet anbefaler tafamidis til behandling af voksne patienter med arvelig transthyretin-medieret amyloidose med kardiomyopati, som er skrevet op til levertransplantation. Medicinrådet vurderer, at udgifterne til behandling er rimelige i forhold til den effekt, der forventes i perioden frem til levertransplantation. Anbefalingen gælder kun patienter i NYHA-klasse I og II.

Medicinrådet anbefaler ikke tafamidis til behandling af øvrige voksne patienter med arvelig og vildtype transthyretin-medieret amyloidose med kardiomyopati, fordi udgifterne til behandling er for høje i forhold til effekten. Desuden er der usikkerhed om patientpopulationens størrelse, blandt andet fordi det kan forventes, at patienterne diagnosticeres tidligere i fremtiden, samt at flere patienter vil få diagnosen. Konsekvenserne for sundhedsvæsnets samlede budget kan derfor blive uforholdsmæssigt store. Medicinrådet inddrager derfor forsigtighedsprincippet i sin beslutning. Forsigtighedsprincippet skal bl.a. sikre, at ibrugtagning af et nyt lægemiddel ikke vil indebære, at en uforholdsmæssig stor andel af sundhedsvæsenets økonomiske midler allokeres i retning af én medicinsk behandling.

2 Værdi for patienterne

Tafamidis til voksne patienter med vildtype eller arvelig transthyretin-medieret amyloidose med kardiomyopati har en moderat merværdi sammenlignet med placebo. Det betyder, at tafamidis samlet set er noget bedre for patienterne end ingen behandling. Medicinrådet har lagt vægt på, at målene med behandling med tafamidis er at forlænge livet samt at bevare livskvaliteten.

Behandling med tafamidis kan reducere sygdomsprogressionen, hvilket fører til forlænget overlevelse og forbedret livskvalitet sammenlignet med ingen behandling (”best supportive care”). Der er få ikke-alvorlige bivirkninger ved behandlingen.

Kvaliteten af de data, der er for sammenligningen af tafamidis med placebo, er moderat. Det betyder, at nye studier med lav sandsynlighed kan ændre konklusionen. Høringen har givet anledning til ændringer i lægemidlets værdi

Læs mere i Medicinrådets vurdering af klinisk værdi og den bagvedliggende protokol (bilag 4 og bilag 6).

3 Omkostninger for sundhedsvæsenet

I officielle priser vil det i gennemsnit koste ca. 2,9 mio. kr. mere at behandle én patient med vildtype transthyretin-medieret amyloidose med kardiomyopati med tafamidis end ingen behandling (”best supportive care”) med en gennemsnitlig behandlingslængde på ca. 4-5 år.

I officielle priser vil det i gennemsnit koste ca. 420.000 kr. mere at behandle én patient med arvelig transthyretin-medieret amyloidose med kardiomyopati med tafamidis end ingen behandling (”best supportive care”) med en gennemsnitlig behandlingslængde på ca. 6 måneder, frem til patienten får tilbudt levertransplantation. Hvis patienten ikke er egnet til levertransplantation, vil den officielle pris være tilsvarende til prisen for behandling af én vildtypepatient.

Med nuværende patientantal på ca. 300 og ca. 100 nye patienter pr. år med vildtype transthyretin-medieret amyloidose med kardiomyopati vil anbefalingen betyde, at de årlige budgetkonsekvenser i det 5. år vil være ca. 301 mio. kr.

Da < 1 nye patienter med arvelig transthyretin-medieret amyloidose med kardiomyopati, som samtidig er egnet til levertransplantation, forventes at kunne blive behandlet pr. år, vil anbefalingen betyde, at de årlige budgetkonsekvenser i det 5. år vil være ca. 190.000 kr.

Lægemiddelvirksomheden har dog givet en fortrolig rabat, og derfor er de reelle meromkostninger og budgetkonsekvenser lavere.

Læs mere i den sundhedsøkonomiske afrapportering (bilag 1).

4 Alvorlighed

Medicinrådet har taget højde for alvorligheden af sygdommen og symptomerne i vurderingen af tafamidis' værdi for patienterne. Medicinrådet har ikke anvendt alvorlighedsprincippet i beslutningsgrundlaget for anbefalingen af tafamidis til patienter med vildtype eller arvelig transthyretin-medieret amyloidose med kardiomyopati.

5 Anbefalingen betyder

Anbefalingen betyder, at Medicinrådet råder regionerne til at bruge tafamidis til behandling af voksne patienter med arvelig transthyretinmedieret amyloidose med kardiomyopati, som er skrevet op til levertransplantation, og som er i NYHA-funktionsklasse I og II.

Anbefalingen betyder også, at Medicinrådet ikke råder regionerne til at bruge tafamidis til behandling af øvrige voksne patienter med arvelig og vildtype transthyretin-medieret amyloidose med kardiomyopati.

6 Sagsbehandlingstid

Medicinrådet har brugt 19 uger og 1 dag på arbejdet med tafamidis til patienter med transthyretin-medieret amyloidose med kardiomyopati.

7 Kontaktinformation til Medicinrådet

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

8 Versionslog

Version	Dato	Ændring
1.0	21. oktober 2020	Godkendt af Medicinrådet.
1.1	29. oktober 2020	Præcisering i anbefalingen vedr. NYHA-funktionsklasser.

9 Bilag

1) Medicinrådets sundhedsøkonomiske afrapportering vedr. tafamidis til transthyretin-medieret amyloidose med kardiomyopati, version 1.0
2) Forhandlingsnotat fra Amgros vedr. tafamidis
3) Høringssvar fra ansøger inkl. efterfølgende dialog
4) Medicinrådets vurdering vedr. tafamidis til transthyretin-medieret amyloidose med kardiomyopati, version 1.0
5) Ansøgers endelig ansøgning inkl. teknisk dokument
6) Medicinrådets protokol for vurdering vedr. tafamidis til transthyretin-medieret amyloidose med kardiomyopati, version 1.0

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Forhandlingsnotat

Dato for behandling i Medicinrådet	21.10.2020
Leverandør	Pfizer
Lægemiddel	Tafamidis (Vyndaqel)
Ansøgt indikation	Til behandling af vildtype eller arvelig transthyretin-medieret amyloidose hos voksne patienter med kardiomyopati (ATTR-CM)

Forhandlingsresultat

Amgros har opnået følgende pris på tafamidis:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Tafamidis	61 mg	30 stk.	66.671,48	[redacted]	[redacted]

Aftalen er gældende frem til 31/10-2021 med mulighed for 6 måneders forlængelse af to omgange.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Vurdering af forhandlingsresultatet

Leverandøren har søgt om to forskellige indikationer til to forskellige patientpopulationer, forhandlingsresultatet vil derfor blive opdelt i to vurderinger.

Arvelig transthyretin-medieret amyloidose med kardiomyopati (hATTR)

Det er Amgros' vurdering, at vi har opnået en god pris i relation til en moderat klinisk merværdi. Denne vurdering baserer vi på følgende punkter:

- Leverandøren lægger vægt på, at lægemidlet har fået en **moderat klinisk** merværdi.

[redacted]

Vildtype transthyretin-medieret amyloidose med kardiomyopati (ATTRwt)

Det er Amgros' vurdering, at vi **ikke** har opnået den bedst mulige pris. Denne vurdering baserer vi på følgende punkter:

- Leverandøren lægger vægt på, at lægemidlet har fået en **moderat klinisk** merværdi.
- Tafamidis er den eneste behandling til denne indikation, og leverandøren mener det dækker et unmet need.

[redacted]

Konklusion

Amgros vurderer, at den samlede meromkostning til behandling af patienter med hATTR i 6 måneder, frem til levertransplantation er acceptabel, set i lyset af den moderate kliniske merværdi.

Amgros vurderer, at prisen på tafamidis er for høj til behandling af patienter med ATTRwt, set i lyset af den moderate kliniske merværdi.

[redacted]

Status fra andre lande

Norge og Sverige har endnu ikke færdigbehandlet tafamidis til denne indikation.

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Til Medicinrådet

Ballerup den 30. september 2020

Nedenstående er vores høringssvar til Medicinrådets vurdering af klinisk merværdi af tafamidis (Vyndaqel) til transthyretinmedieret amyloidose med kardiomyopati (ATTR-CM), modtaget d. 23. september 2020 samt udkast til Medicinrådets Sundhedsøkonomiske Afrapportering for tafamidis modtaget d. 18. september 2020.

Nedenfor vores kommentarer til disse udkast:

Klinisk merværdi af tafamidis
Vi takker Medicinrådet for en saglig, fagligt solid og velbegrundet klinisk vurdering af tafamidis til behandling af transthyretinmedieret amyloidose med kardiomyopati. Vi har ikke kommentarer til kategoriseringen 'moderat klinisk merværdi', da den er begrundet og i overensstemmelse med metodehåndbogen og dens kriterier for klassificering af klinisk merværdi.

Vi bemærker, at det både i gennemgangen for de enkelte effektmål og i konklusionen er påpeget, at for de kritiske effektmål 'overlevelse' og 'livskvalitet', er punktestimaterne næsten 3 gange større end de prædefinerede MKRF. For de vigtige effektmål er de næsten dobbelt så store som MKRF.

Vi bemærker desuden, at der i Medicinrådets metode for vurdering af absolutte effektmål er en udfordring for de studier, der primært har absolutte end points som primære outcome measures, idet disse ikke kan opnå en klassificering, der er bedre end "merværdi af ukendt størrelse". I vurderingen af tafamidis drejer det sig om effektmålene KCCQ-OS og 6MWT.

<u>NYHA-klassificering</u>
Vi bemærker, at der i vurderingen er angivet, at *'Fagudvalget undrer sig over, at ansøger ikke leverer data for patienter opdelt i NAC sygdomsstadier. Ansøger angiver, at denne inddeling ikke er defineret i studiet, og at analysen derfor ikke er lavet.'*

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I Medicinrådets protokol for vurdering af tafamidis til ATTR-CM er det angivet, at Fagudvalget ønsker at vurdere, om patienter i forskellige sygdomsstadier vil have lige stor effekt af behandling med tafamidis. Fagudvalget ønsker derfor analyser, som er opdelt på NYHA-klasser. Fagudvalget ønsker derudover analyser opdelt på National Amyloidose Center (NAC) disease-stage ud fra kombinationer af værdier af NT-ProBNP og eGFR.

Det anerkendte New York Heart Association (NYHA)-klassificeringssystem bliver anvendt til at stratificere iht. sygdomsstadie, og analysen er opdelt på baggrund af disse. 'NAC disease-staging' er et nyligt introduceret prognostisk system til inddeling i ATTR-CM sygdomsstadier baseret på data publiceret i 2018, dvs. 5 år efter initiering af det ATTR-ACT-studie, som ligger til grund for EMAs godkendelse af tafamidis til ATTR-CM. Derfor blev patienterne i ATTR-ACT-studiet ikke stratificeret iht. NAC disease-stage, der var ikke planlagt subgruppeanalyser iht. NAC disease-staging, og sådanne subgruppeanalyser er derfor ikke foretaget.

<u>Kardiologernes rolle i opsporing, diagnosticering samt valg af behandling</u>
Sidst, men ikke mindst, så vil vi gerne understrege, at kardiologerne spiller en central rolle i opsporing, diagnosticering samt valg af behandling til patienter med ATTR-CM, samt vigtigheden af at udbrede erfaringen med dette fra de ekspertcentre, der allerede findes i Danmark.

Udkast til Sundhedsøkonomiske Afrapportering for tafamidis
Vi takker Medicinrådet for et grundigt udkast til Sundhedsøkonomisk Afrapportering for tafamidis. Vi har dog identificeret en række punkter, som vi mener, vil bidrage til en mere nuanceret forståelse af de økonomiske konsekvenser ved ibrugtagning af tafamidis.

<u>Usikkerhed i forbindelse med inkrementelomkostningsanalysen af vildtype ATTR-CM</u>
I udkastet til den sundhedsøkonomiske afrapportering skriver Medicinrådet under afsnittet "Usikkerheder" i forbindelse med inkrementelomkostninger for ATTR-CM, at *'Tidshorisonten har stor betydning for begge analysers resultater (*vildtype ATTR-CM og arvelig ATTR-CM, red.*)'*. Medicinrådet skriver desuden i forbindelse med vildtype ATTR-CM: '*Sekretariatet vurderer ansøgers følsomhedsanalyser som relevante, dog vælger sekretariatet kun at præsentere et udvalg af de mest usikre parametre, hvilket drejer sig om tidshorisonten for ATTRh-patienter, den relative dosisintensitet samt enhedsomkostning for kardiovaskulære og ikke-kardiovaskulære indlæggelser'.*
Vi mener, at dette skaber uklarhed omkring usikkerheden forbundet med tidshorisonten og dermed de reelle inkrementelle omkostninger ved tafamidis.

Medicinrådet påpeger på den ene side, at tidshorisonten har stor (størst, red.) betydning for usikkerheden i forbindelse med inkrementelomkostningerne, samt at ansøgers sensitivitetsanalyser af tidshorisonten for vildtype ATTR-CM er relevante, men på den anden side forholder Medicinrådet sig ikke til denne usikkerhed i egne sensitivitetsanalyser samt ej heller ikke i diskussionen.

Medicinrådet skriver tidligere i deres afrapportering om ansøgers grundantagelse af tidshorisonten: *'Hvis tidshorisonten sættes til studiets opfølgningstid, giver dette en urealistisk kort behandlingstid med tafamidis'.* Dette retfærdiggør dog ikke, at Medicinrådet ikke har forholdt sig til en diskussion af tidshorisonten effekt på inkrementelomkostningerne for patienter med vildtype ATTR-CM.

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Vores udgangspunkt for at vælge 30 mdr. i vores grundantagelse er, at den kliniske effekt vurderes i en tidsramme på 30 mdr. Vi er bekendt med Medicinrådets metoder, der ikke foreskriver et ens tidsperspektiv for de 2 analyser, men at der for den sundhedsøkonomiske analyse oftest anmodes om et længere tidsperspektiv end i den kliniske analyse. Vi anlagde dog denne grundantagelse for at belyse overfor Medicinrådet, hvad de sammenlignelige sundhedsøkonomiske konsekvenser er for at behandle patienter med tafamidis i 30 mdr. Det gjorde vi fordi det jo netop er en analyse af effekten af 30 mdrs. behandling med tafamidis, der har medført, at Medicinrådet er nået til konklusionen om, at tafamidis giver en 'moderat klinisk merværdi'.

Vi medgav i vores analyse af inkrementelomkostninger for vildtype ATTR-CM, at tidshorisonten er en faktor, der påvirker resultatet, og medtog derfor i vores sensitivitetsanalyse to alternative tidshorisonter til de 30 mdr., for at belyse denne sensitivitet. De to sensitivitetsanalyser tog udgangspunkt i Fagudvalgets vurdering af middellevetid for 80-årige mænd (7,42 år) samt middellevetiden for patienter med vildtype ATTR-CM (5 år).

Vi anmoder derfor Medicinrådet om at forholde sig til denne usikkerhed ved inkrementelomkostningerne i den endelige beslutning om ibrugtagning af tafamidis.

<u>Sammenhængen mellem klinisk effekt og omkostningerne til behandling af vildtype ATTR-CM</u>
Som tidligere nævnt, så differentieres der i Medicinrådets metoder imellem tidshorisonten for den kliniske effekt og tidshorisonten for den sundhedsøkonomiske konsekvens.

For at illustrere konsekvensen af dette har vi ekstrapoleret effekten for vildtype ATTR-CM patienter. Anvendes en tidshorisont på hhv. 5, 10 og 15 år, og de af Medicinrådet godkendte Weibull ekstrapolationer, fremgår det af modellen, at der er en markant overlevelsesgevinst ved behandling med tafamidis vs. placebo, som er stigende over tid. Efter 5 år er mere end dobbelt så mange vildtype ATTR-CM patienter, som behandles med tafamidis i live sammenlignet med vildtype ATTR-CM patienter, der blev behandlet med placebo. Efter 10 år er forskellen i overlevelse øget, så der nu er mere end 16 gange så mange vildtype ATTR-CM patienter i live vs. placebo, mens forskellen efter knap 15 år er mere end 400 gange højere blandt vildtype ATTR-CM patienter behandlet med tafamidis vs. placebo. Det skal dog noteres at der ved 15 år er et meget lavt antal patienter behandlet med placebo tilbage i modellen.

Det er fra ovenstående evident at hvis effekten ekstrapoleres på lige fod med omkostningerne, da vil patienter behandlet med tafamidis opnå en markant større overlevelsesgevinst end ved den nuværende metode, der ikke ekstrapolere den kliniske effekt.

Vi anmoder Medicinrådet om at være opmærksom på den forskel der ligger i ikke at ekstrapolere effekt på lige for med omkostninger i den endelige beslutning om ibrugtagning af tafamidis.

<u>Usikkerhed i forbindelse med budgetkonsekvensanalysen af vildtype ATTR-CM</u>
Medicinrådets grundantagelse for budgetkonsekvensanalysen er, at samtlige vildtype ATTR-CM patienter (450 prævalente og 150 incidente) vil starte behandling med tafamidis dag 1. Medicinrådet har indikeret overfor Pfizer at '*der er risiko for at budgetkonsekvenserne er overstimeret grundet usikkerhed omkring hvor hurtigt patienterne opstartes i behandling med tafamidis´.* Medicinrådet har

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dog ikke foretaget nogen sensitivitetsanalyse af ovenstående usikkerhed i budgetkonsekvensanalysen for vildtype ATTR-CM.

Vi har i vores ansøgning inkluderet et sådant scenarie i vores ansøgning, hvor der tages højde for den usikkerhed, som Medicinrådet selv italesætter, der er ved optag af patienter. I denne analyse sker der et løbende optag af prævalente patienter over 3 måneder, samt løbende optag af incidente patienter over året. Vi lavede denne analyse på baggrund af det input vi har modtaget fra de danske eksperter, som vi har været i dialog med. Ifølge eksperterne vil det ikke være muligt at sætte 450 prævalente patienter i behandling dag 1 og ej heller at diagnosticere 150 nye patienter dag 1. I Medicinrådets udkast til vurdering af klinisk merværdi, s. 7. skriver Fagudvalget: *'for at stille den endelige diagnose ATTR-CM bør der tages en hjertebiopsi for at påvise amyloide aflejringer ved histologi'.* Denne anvisning er i overensstemmelse med de førnævnte danske eksperters antagelse om, at det ikke er muligt at sætte 150 ny diagnosticerede patienter i behandling fra dag 1.

Vores bekymring vedrørende Medicinrådets budgetkonsekvensanalyse jf. ovenstående, er om de potentielt urealistiske forventninger til optag og dermed overvurderede budgetkonsekvens kan påvirke sandsynligheden for, om tafamidis anbefales som mulig standardbehandling.

Vi anmoder derfor Medicinrådet om at være opmærksom på risikoen for at budgetkonsekvenserne er overvurderet i den endelig beslutning om ibrugtagning af tafamidis.

Vi ser frem til Medicinrådets endelige beslutning om ibrugtagning af tafamidis i oktober 2020.

På vegne af Pfizer A/S,

Mette Strand
Senior Medical Adviser

Trine Pilgaard
Senior Market Access Manager

Fra:	Ehm Andersson Galijatovic
Til:	"Pilgaard, Trine"; Strand, Mette
Cc:	Karen Kleberg Hansen; Camilla Nybo Holmberg
Emne:	Svar vedr. høringssvar til Medicinrådets vurdering af tafamidis til transthyretinmedieret amyloidose med kardiomyopati (ATTR-CM)
Dato:	6. oktober 2020 10:14:00
Vedhæftede filer:	Udkast Medicinrådets sundhedsøkonomiske afrapportering vedr. tafamidis til transthyretinmedieret amyloidose-vers. 1.0.pdf image001.png

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Kære Trine og Mette,

Tak for jeres høringssvar vedr. Medicinrådets vurdering af klinisk merværdi og udkast til sundhedsøkonomiske afrapportering for tafamidis til transthyretinmedieret amyloidose med kardiomyopati (ATTR-CM).

Jeres kommentarer til den kliniske merværdi har ikke ført til ændringer i vurderingsrapporten.

Vedr. den sundhedsøkonomiske afrapportering har vi følgende kommentarer til høringssvaret.

Usikkerhed i forbindelse med inkrementelomkostningsanalysen af vildtype ATTR-CM.

Sekretariatet anerkender at tidshorisonten har stor betydning for analysens resultat, men ikke at der er nævneværdig usikkerhed forbundet med tidshorisonten i modellen for behandling af wildtype patienter. Jf Medicinrådets metode bør tidshorisonten være så lang, at alle vigtige forskelle i omkostninger mellem alternativerne opfanges, dvs. i dette tilfælde, når alle (eller næsten alle) patienter er døde. At sætte tidshorisonten kortere vil ikke være metodisk korrekt og det er derfor heller ikke evalueret i følsomhedsanalyser eller i diskussion af resultatet. Jeres kommentar har ikke ført til ændringer i afrapporteringen.

Sammenhængen mellem klinisk effekt og omkostningerne til behandling af vildtype ATTR-CM
Tak for jeres betragtning vedr. sammenhæng mellem effekt og omkostninger. Medicinrådet er opmærksom på denne sammenhæng og udfordringen ved, at der er forskel i tidshorisont. Kommentaren har ikke ført til ændringer i afrapporteringen.

Usikkerhed i forbindelse med budgetkonsekvensanalysen af vildtype ATTR-CM
Medicinrådet medgiver, at der er risiko for at budgetkonsekvenserne har været overestimeret i det fremsendte udkast til afrapportering.
I forbindelse med vurderingen af tafamidis vurderede Medicinrådet at når den amyloidrelaterede hjerteskade er mere fremskreden, f.eks. hos patienter med vedvarende NYHA-klasse III og IV, bør der som udgangspunkt ikke opstartes behandling med tafamidis.
Med baggrund i vurderingen om ikke at behandle patienter med fremskreden sygdom (NYHA-klasse III og IV), samt jeres argumenter i høringssvaret for hvorfor det oprindelige patientantal er overestimeret, nedjusteres antallet af patienter i budgetkonsekvensanalysen. I den opdaterede analyse nedjusteres til 300 patienter i år 1 og 100 patienter per år i de efterfølgende år. Der er fortsat betydende usikkerhed omkring antallet af fremtidige patienter.

Endnu en gang tak for jeres høringssvar. Vedhæftet er den opdaterede afrapportering for tafamidis til ATTR-CM.

Mh Ehm på vegne af sekretariatets projektgruppe.

Fra: Pilgaard, Trine <Trine.Pilgaard@pfizer.com>
Sendt: 30. september 2020 20:50
Til: Ehm Andersson Galijatovic <EAG@medicinraadet.dk>
Cc: Karen Kleberg Hansen <kkh@medicinraadet.dk>; Camilla Nybo Holmberg <CNH@medicinraadet.dk>
Emne: Pfizers høringssvar på tafamidis

Kære Ehm

Som lovet sender vi hermed vores høringssvar på tafamidis.

Skulle det lede til nogle uafklarede spørgsmål er I selvfølgelig altid velkomne til at ringe eller skrive.

Bedste hilsner,
Trine

From: Ehm Andersson Galijatovic <EAG@medicinraadet.dk>
Sent: 23. september 2020 19:08
To: Pilgaard, Trine <Trine.Pilgaard@pfizer.com>
Cc: Karen Kleberg Hansen <kkh@medicinraadet.dk>; Camilla Nybo Holmberg <CNH@medicinraadet.dk>
Subject: [EXTERNAL] SV: Høring over udkast til vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for tafamidis til ATTR-CM

Kære Trine,

Sekretariatet fremsender hermed den endelige vurdering af lægemidlets værdi for tafamidis, som Medicinrådet godkendte på rådsmødet i dag (23/9-20).
Medicinrådet var enigt med fagudvalgets konklusion om lægemidlets værdi, som derfor svarer til resultatet, I tidligere har haft i høring.
Dog er tilføjet en præcisering vedr. NYHA-klasser i konklusionen.
Modelantagelserne blev ligeledes godkendt.
Vi ser frem til at modtage jeres eventuelle høringssvar inden den 30. september.

Mh Ehm

Fra: Ehm Andersson Galijatovic
Sendt: 11. september 2020 14:19
Til: 'Pilgaard, Trine' <Trine.Pilgaard@pfizer.com>
Cc: Karen Kleberg Hansen <kkh@medicinraadet.dk>; Camilla Nybo Holmberg <CNH@medicinraadet.dk>
Emne: Høring over udkast til vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for tafamidis til ATTR-CM

Kære Trine,

Sekretariatet fremsender hermed udkast til Medicinrådets vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for tafamidis.

Medicinrådet drøfter vurderingen af lægemidlets værdi og modelantagelserne for den sundhedsøkonomiske afrapportering den 23. september 2020. I får besked fra sekretariatet, hvis Rådet har ændringer til vurderingen udarbejdet af fagudvalget.

I har i alt 20 dage til at sende eventuelle bemærkninger til kategoriseringen af lægemidlets værdi og den sundhedsøkonomiske afrapportering. **Jeres frist for at indgive høringssvar er derfor den 30. september 2020.** I er selvfølgelig velkomne til at sende eventuelle bemærkninger inden denne dato. I må også gerne meddele, hvis I ikke har kommentarer til kategoriseringen.

Vurderer sekretariatet og fagudvalget, at jeres høringssvar giver anledning til at revurdere kategoriseringen af lægemidlets værdi, skal Rådet drøfte vurderingen igen. Det vil med overvejende sandsynlighed udskyde tidspunktet for Rådets drøftelse af anbefalingen.
Jeres eventuelle høringssvar indgår i det materiale, som bliver fremlagt for Medicinrådet i forbindelse med behandlingen af anbefalingen. Jeres eventuelle høringssvar bliver offentliggjort sammen med anbefalingen.

Mh Ehm

Med venlig hilsen

Ehm Andersson Galijatovic
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Cand.scient, Ph.d.
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Medicinrådet

Medicinrådets vurdering af tafamidis til behandling af transthyretinmedieret amyloidose med kardiomyopati

Versionsnr.: 1.0

Medicinrådet

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 sammenfatter vi 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.

Godkendt af Medicinrådet 23. september 2020
Dokumentnummer 89686
Versionsnummer 1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www medicinraadet.dk
Sprog: dansk
Format: pdf

Indhold

1 Medicinrådets konklusion

Medicinrådet vurderer, at tafamidis til transthyretinmedieret amyloidose med kardiomyopati giver en moderat merværdi sammenlignet med placebo.

Vurderingen er baseret på evidens af moderat kvalitet.

Den moderate merværdi gælder NYHA-klasse I og II, mens patienter med vedvarende NYHA-klasse III og IV som udgangspunkt ikke bør opstartes behandling med tafamidis.

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.

• **Samlet værdi kan ikke kategoriseres:** På grund af usikkerheder omkring effektforhold er det ikke muligt at kategorisere lægemidlets samlede værdi.

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

ACE:	*Angiotensin Converting Enzyme*
AR:	*Adverse reaction* (bivirkning)
ARR:	Absolut risiko reduction
ATTR-CM:	Transthyretinmedieret amyloidose med kardiomyopati
ATTR-PN:	Transthyretinmedieret amyloidose med polyneuropati
ATTRwt:	Vildtype transthyretinmedieret amyloidose
CI:	Konfidensinterval
DNA:	Deoxyribonucleic acid
DPD:	3,3-diphosphono-1,2-propanodicarboxylic acid
eGRF:	Estimeret glomerulær filtrationshastighed
EMA:	*European Medicines Agency*
FAC:	*Familial Amyloid Cardiomyopathy*
FAP:	*Familial Amyloid Polyneuropathy*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
hATTR:	Arvelig transthyretinmedieret amyloidose
HR:	*Hazard ratio*
ITT:	intention to treat
KCCQ-OS:	*Kansas City Cardiomyopathy Questionnaire – Overall Summary*
Leu:	Leucin
Met:	Methionin
MKRF:	Mindste klinisk relevante forskel
NAC:	National Amyloidose Center
NT-proBNP:	N-terminal pro B-type natriuretisk peptid
NYHA:	*New York Heart Association*
OR:	*Odds ratio*
OS:	*Overall survival*
RR:	Relativ risiko

3 Introduktion

Formålet med Medicinrådets vurdering af tafamidis til transthyretinmedieret amyloidose med kardiomyopati er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Pfizer A/S. Vi modtog ansøgningen den 9. juni 2020.

Det kliniske spørgsmål er:

Hvad er værdien af tafamidis sammenlignet med placebo til patienter med transthyretinmedieret amyloidose med kardiomyopati?

3.1 Transthyretinmedieret amyloidose

Transthyretin (TTR) er et transportprotein i serum og i cerebrospinalvæsken, som transporterer thyroxin (T4) og retinolbindende protein bundet til retinol (vitamin A). Ca. 95 % af transthyretin produceres i leveren, mens en mindre mængde produceres i plexus choroideus og retina.

Transthyretinmedieret amyloidose (ATTR) er en livstruende sygdom, som skyldes, at transthyretin foldes forkert og aflejres som amyloide fibriller i forskellige væv, herunder det perifere nervesystem, hjertet, mave-tarm-systemet, nyrerne, centralnervesystemet og øjnene. Oftest er der aflejring i nervevæv, hvilket fører til polyneuropati (ATTR-PN), eller hjertevæv, hvilket fører til restriktiv kardiomyopati (ATTR-CM) [1,2].

Sygdommen kan være arveligt betinget (hATTR) eller opstå spontant (kaldet vildtype (ATTRwt)).

Denne vurderingsrapport vedrører udelukkende patienter, hvor sygdommen præsenterer sig som transthyretinmedieret amyloidose med kardiomyopati (ATTR-CM), og den inkluderer både den arvelige og vildtype form af sygdommen. Patientpopulationerne og sygdomskarakteristika for den arvelige og vildtype form af ATTR-CM er forskellige i Danmark og beskrives herunder separat.

3.2 Arvelig transthyretinmedieret amyloidose (hATTR)

hATTR skyldes medfødte forandringer i det gen, som koder for dannelsen af proteinet transthyretin. Mutationer i TTR-genet fører til destabilisering af TTR-tetramerdannelsen og dermed fejl i foldningen af proteinet. De misfoldede proteiner danner tilsammen de amyloide fibriller bestående af muteret transthyretin, som aflejres primært i nervevæv og hjertevæv. Afhængig af mutationen kan de mest fremtrædende symptomer være fra nervesystemet (hATTR-PN) eller fra hjertet (hATTR-CM). Den generelle symptomdebut for den arvelige form er varierende og kan være fra 25-70 år afhængig af mutationstypen, men kan også variere indenfor samme mutation [3].

Den arvelige form for ATTR er yderst sjælden i Danmark. I alt 35 patienter fra [redacted] -mutation, og denne mutation er i disse patienter primært associeret med kardiomyopati [4]. Denne mutation, som findes [redacted] er exceptionel alvorlig. Sygdomsdebut sker i 40-50-årsalderen, og sygdommen progredierer herefter hurtigt. Patienterne udvikler svær hjertesvigt og dør efter omkring to år uden behandling. Den danske mutation har 100 % penetrans. Danske patienter med arvelig ATTR-CM og p.Leu131Met (L111M)-mutation tilbydes derfor levertransplantation for at standse sygdomsudviklingen [4]. Transplantation af en rask lever medfører, at der ikke længere produceres mutant TTR fra leveren, og aflejringen af fibriller reduceres. Levertransplantation standser oftest progression i sygdommen, men remission af symptomer er sjælden. Det er derfor væsentligt, at levertransplantation gives tidligt i sygdomsforløbet. Der er ofte ventetid på en levertransplantation, og i den venteperiode er der risiko for betydende sygdomsprogression. Uden levertransplantation har patienterne en dårlig prognose med medianlevetid på to år efter, at diagnosen er stillet. En levertransplantation er et invasivt indgreb, der i sig

selv er forbundet med en vis risiko for død og følgesygdomme af den medicin, der gives i forbindelse med transplantationen. 5-årsoverlevelsen efter transplantation er ca. 85 %, og fagudvalget vurderer, at for hovedparten af patienterne opnås derefter en overlevelse næsten svarende til normalbefolkningens. Der findes kun få andre kendte mutationer end p.Leu131Met i Danmark. Disse patienter har et klinisk forløb, der minder mere om ATTRwt, dog med sygdomsdebut omkring 65-70-årsalderen. Denne gruppe af patienter vil kun i begrænset omfang være egnede til levertransplantation.

Incidens og prævalens
Arvelig ATTR med kardiomyopati er en meget sjælden sygdom. Der kendes 35 patienter [redacted] Der findes kun få patienter med andre mutationer end p.Leu131Met. Fagudvalget estimerer, at det ikke er sandsynligt, at man vil finde flere familier med mutation i p.Leu131Met ved at indføre en mere systematisk genetisk screening af potentielle patienter. Estimatet omkring fremtidig incidens er behæftet med usikkerhed.

3.3 Ikkearvelig ATTR (ATTRwt)

Ved ATTRwt skyldes aflejringerne af amyloide fibriller, at vildtype transthyretin misfoldes. De misfoldede amyloide fibriller bestående af vildtype transthyretin aflejres primært i hjertevæv, hvilket kan føre til kardiomyopati. Sygdommen er relateret til stigende alder, men årsagen til, at nogle får sygdommen, mens andre ikke gør, er endnu ukendt. Det har længe har været kendt fra obduktionsundersøgelser, at amyloidaflejringer af transthyretin er til stede i hjertet i op til 25 % af ældre mennesker uden nødvendigvis at give symptomer på sygdom [5]. Dog anses det kliniske syndrom som en sjælden sygdom, som overvejende findes hos ældre mænd med kliniske tegn på restriktiv kardiomyopati, muligvis aortastenose og ofte med tillæg af karpaltunnelsyndrom [5]. Det er også sandsynligt, at sværhedsgraden af symptomer ved de nævnte ret almindelige lidelser kan vise sig delvist at være betinget af graden af amyloidaflejringer i hjertemusklen.

ATTRwt er karakteriseret ved en sen symptomdebut. I dansk klinisk praksis er patienterne typisk mænd omkring 80 år, men fagudvalget bemærker, at sygdommen sandsynligvis er underdiagnosticeret, og at diagnosen i nuværende praksis stilles senere, end symptomerne indtræder. Overlevelsen for patienter med ATTRwt er median ca. 5 år fra diagnose [5]. Ifølge Danmarks Statistik er den gennemsnitlige restlevetid 7,87 år for en mand på 80 år.

Incidens og prævalens
Der er ikke publiceret estimater for incidens og prævalens af ATTRwt i Danmark. EMA estimerede i 2011, at vildtype ATTR fandtes i 3 ud af 10.000 mennesker i EU [6].

Med introduktion af en ny behandlingsmulighed og lettere initial non-invasiv screening i form af 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) skintigrafi forventes en stigning i incidens og prævalens for sygdommen. Dette skyldes øget diagnostisk fokus, som forventes at føre til en øget opsporing af patienter (øget incidens) og samtidig en tidligere diagnose, hvilket fører til, at patienterne får en længere levetid med diagnosen (øget prævalens). Fagudvalget vurderer, at der er ca. 150 nye patienter om året og at der i alt er på 400-500 patienter med ATTRwt med kardiomyopati. Estimatet omkring fremtidig incidens og prævalens er dog behæftet med stor usikkerhed.

3.4 Symptomer

Indenfor både den arvelige og vildtype form af ATTR-CM medfører sygdommens progressive natur og alvorlige symptomer nedsat livskvalitet og forkortet levetid. Restriktiv kardiomyopati er kendetegnet ved hæmmet fyldning af den ene eller begge ventrikler på grund af øget stivhed og dermed en abnorm diastolisk ventrikelfunktion. Systolefunktionen er som hovedregel normal. Vægtykkelserne i ventriklerne er væsentligt

forøget [7]. Symptomerne på hjertepåvirkning inkluderer typisk åndenød, nedsat fysisk kapacitet, træthed og ødemer. Andre symptomer kan være svimmelhed, besvimelser, anginalignende smerter, arytmier og atrieflimmer.

Graden af hjertesvigtsymptomer beskrives traditionelt ud fra fire NYHA-funktionsklasser, der er baseret på patientsymptomer [8]. NYHA står for New York Heart Association. Nogle patienter med kronisk hjertesvigt lever et godt liv, særligt NYHA-funktionsgruppe I-II, hvor patienten kun oplever ingen eller få begrænsninger i normale fysiske aktiviteter. Andre patienter er betydeligt begrænset i deres fysiske aktivitet (NYHA-funktionsklasse III og IV) og oplever symptomer i hvile eller stillesiddende aktiviteter (klasse IV). Disse patienter har problemer med at klare dagligdagens gøremål. Dødeligheden blandt hjertesvigtpatienter stiger proportionelt med stigningen i NYHA-klasse. NYHA-klassifikation er ikke en præcis klassifikation, og den beror til dels på en subjektiv vurdering af symptomer.

En anden prognostisk klassifikation, som anvendes af det Nationale Amyloidose Center (NAC) i UK, er baseret på en biomarkør for hjertepåvirkning, NT-proBNP, og nyrefunktion, eGFR. Denne klassifikation kaldes *NAC-ATTR disease stage* [9]. Klasse I er defineret som plasma NT-pro-BNP $\leq$ 3000 ng/L og eGFR > 45 mL/min. Klasse III er defineret som NT-pro-BNP > 3000 ng/L og eGFR < 45 mL/min. Klasse II er restgruppen, der ikke opfylder begge kriterier i hhv. klasse I og III.

3.5 Diagnosticering

Mistanke om ATTR-CM opstår på baggrund af symptomer på hjertepåvirkning, observationer på EKG og ekkokardiografi og samtidig udelukkelse af anden årsag til disse fund. Amyloid Let-kæde (AL) amyloidose kan give samme symptombillede og kliniske fund og skal udelukkes ved blodprøver og evt. knoglemarvsundersøgelse. Ved mistanke om ATTR-CM laves evt. MR-scanning af hjertet, hvor man undersøger for amyloide aflejringer og/eller DPD skintigrafi, som er en billeddannende undersøgelse til påvisning af transthyretin hjerteamyloid. Ved yderligere bekræftelse på mistanken om ATTR-CM ud fra disse undersøgelser og for at stille den endelige diagnose ATTR-CM bør der tages en hjertebiopsi for at påvise amyloide aflejringer ved histologi. I nogle tilfælde kan amyloide aflejringer i biopsi fra andet væv, eksempelvis fedtvæv, sammen med en positiv skintigrafiundersøgelse være tilstrækkeligt til at stille diagnosen.

Diagnosen af den arvelige form kræver, i tillæg til ovenstående, en genetisk undersøgelse med fund af sygdomsforårsagende ændring (mutation) i TTR-genet.

I Danmark har den kendte mutation p.Leu131Met (L111M)-mutation 100 % penetrans, og derfor udredes disse mutationsbærende patienter ved første objektive tegn på hjertepåvirkning.

3.6 Tafamidis

Tafamidis er en specifik stabilisator af transthyretinproteinet TTR. Tafamidis virker på proteinniveau ved at binde til både muteret og vildtype TTR og stabiliserer herved TTR tetramer-formationen. Herved hæmmer det dissociationen til monomerer, som er det hastighedsbegrænsende trin i formationen af amyloide fragmenter. Derfor forventes tafamidis at kunne bremse sygdomsudviklingen [10,11].

Dosering
Til indikationen ATTR-CM er tafamidis godkendt i en dosis på 61 mg. Tafamidis administreres én gang dagligt peroralt i en blød kapsel indeholdende 61 mg tafamidis. Tafamidis kan tages med eller uden mad.

Tafamidis er også godkendt af EMA i 2011 til arvelig ATTR med polyneuropati stadie 1 i en dosis på 20 mg tafamidis meglumine.

Ansøger angiver, at 61 mg tafamidis er bioækvivalent med 80 mg tafamidis meglumin, og den godkendte dosering må derfor antages at være ~ 4 gange højere til kardiomyopati i forhold til polyneuropati.

3.7 Nuværende behandling

Tafamidis er godkendt af EMA i 2011 til hATTR med polyneuropati (hATTR-PN) stadie 1. I 2018 blev to produkter, inotersen og patisiran, godkendt af EMA til hATTR med polyneuropati stadie 1 og 2.

Der findes på nuværende tidspunkt i Danmark ingen godkendte lægemidler til behandling af patienter med ATTRwt, og ingen lægemidler med godkendt indikation til hATTR-CM. Nogle patienter med den arvelige form vil dog både have symptomer på polyneuropati og kardiomyopati, og disse patienter med mixed-fænotype kan således være kandidater til både tafamidis, patisiran og inotersen.

Behandlingen af ATTRwt-CM i Danmark har hidtil primært bestået af symptombehandling af de påvirkede organer. Den medicinske behandling af hjertesvigt hos patienter med ATTRwt-CM omfatter anvendelsen af diuretika. Andre lægemidler, som normalt er tilgængelig for hjertesvigtpatienter, såsom ACE-hæmmere, kalciumantagonister, betablokkere og digoxin, er ikke rekommanderet til patienter med ATTR-CM og bør anvendes med forsigtighed, da disse generelt ikke er veltolererede pga. hypotension [2,12]. Pacemakerbehandling kan blive nødvendig.

Patienter med den arvelige form hATTR-CM og p.Leu131Met (L111M)-mutation behandles med levertransplantation eller kombineret hjerte-levertransplantation, hvis der findes en egnet donor, og patienten vurderes at være egnet til at gennemgå denne procedure.

En andel af de danske patienter med hATTR-CM har fået kombineret hjerte- og levertransplantation (~6) eller isoleret levertransplantation (~14) ifølge Rigshospitalets transplantationsklinik. En mindre andel [redacted] af danske patienter med ATTR-CM er i behandling med tafamidis med det formål at forhindre yderligere sygdomsudvikling frem til levertransplantation og/eller udskyde tidspunktet for behovet for levertransplantation.

4 Metode

Medicinrådets protokol for vurdering af tafamidis til behandling af transthyretin amyloidose med kardiomyopati beskriver sammen med Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser, hvordan vi vil vurdere lægemidlets værdi for patienterne.

Hvad er værdien af tafamidis sammenlignet med placebo til patienter med transthyretinmedieret amyloidose med kardiomyopati?

Population
Voksne patienter med vildtype eller arvelig transthyretinmedieret amyloidose med kardiomyopati.

Intervention
Peroral tafamidis 61 mg én gang dagligt.

Komparator
Placebo.

Effektmål
Se tabel 1.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel samt indplacering i de tre effektmålsgrupper (”dødelighed” ”livskvalitet, alvorlige symptomer og bivirkninger” og ”ikkealvorlige symptomer og bivirkninger”).

Effektmål*	Vigtighed	Effektmåls-gruppe	Måleenhed	Mindste klinisk relevante forskel
Overlevelse Overall survival (OS)	Kritisk	dødelighed	Andel der overlever i 30 mdr.	Forskel på 5 %-point
Livskvalitet Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score	Kritisk	livskvalitet alvorlige symptomer og bivirkninger	Gennemsnitlig ændring fra baseline	Forskel på 5 point for KCCQ-QS
Hospitalsindlæggelser relateret til kardiovaskulær sygdom	Vigtig	livskvalitet alvorlige symptomer og bivirkninger	Gennemsnitlig ændring i antal indlæggelser pr. patient pr. år	Forskel på 15 %
6 minutters gangtest (6 Minute Walk Test, 6MWT)	Vigtig	livskvalitet alvorlige symptomer og bivirkninger	Gennemsnitlig ændring fra baseline	Forskel på 45 meter
Bivirkninger	Vigtig	livskvalitet alvorlige symptomer og bivirkninger	Andel patienter der oplever ≥ 1 bivirkning (AR)	Forskel på 15 %-point
			Kvalitativ gennemgang af bivirkninger	-

* For alle effektmål ønskes data med længst mulig opfølgningstid. Fase III-studiet har en varighed på 30 mdr., og dette er derfor den forventede opfølgningstid for alle effektmål.

Udover det kliniske spørgsmål specificerede fagudvalget i protokollen at de ønskede en argumentation for valg af dosis, en opdeling af resultater ift. dosis, sygdomsætiologi og sygdomsstadier.

5 Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt 1 fuldtekstartikel, som rapporterer resultater fra et randomiseret fase III-studie (ATTR-ACT-studiet) [11]. Ansøger inkluderer desuden resultater fra EPAR [10] i den endelige ansøgning.

Ansøger har desuden fremsendt upubliceret fortroligt data-on-file fra ATTR-ACT-studiet fra ”clinical study report” og konferenceabstracts til at belyse spørgsmålene omkring dosis og subgrupper, som efterspurgt i

protokollen under ”Andre overvejelser”. Fagudvalget vurderer, at det indsendte upublicerede data-on-file og data fra abstracts, som også delvist er refereret i EPAR, ikke bidrager med substantiel ny information, men at det derimod blot understøtter data, som er publiceret. Det upublicerede data vurderes dermed ikke at påvirke evidensgrundlaget markant og anvendes derfor ikke.

Reference (title, author, journal, year)	**Trial name**	**NCT number**
Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. Maurer MS, Schwartz JH, Gundapaneni B et al. N Engl J Med. 2018;379(11):1007-1016.	ATTR-ACT: Safety and efficacy of tafamidis in patients with transthyretin cardiomyopathy	NCT01994889

ATTR-ACT
ATTR-ACT er et multicenter, internationalt, dobbeltblindet, placebokontrolleret fase 3-studie. Patienter med ATTR-CM blev randomiseret til at modtage 80 mg tafamidis, 20 mg tafamidis eller matchende placebo peroralt en gang dagligt i et forhold på 2:1:2 i 30 måneder. Studiet inkluderede både patienter med den arvelige form af ATTR-CM (hATTR-CM) og patienter med vildtype formen (ATTRwt). I alt 24 % af patienterne havde den arvelige form med Val122Ile, Thr60Ala og Ile68Leu som de mest hyppige genetiske mutationer.

ATTR-ACT-forsøget blev designet til at evaluere effektivitet og sikkerhed ved aktiv medicinbehandling (doser 80 mg og 20 mg kombineret) vs. placebo. Det primære endepunkt var en hierarkisk vurdering af dødelighed og hyppighed af hjerte-kar-relaterede indlæggelser.

De sekundære endepunkter var dødelighed og hyppighed af hjerte-kar-relaterede indlæggelser analyseret separat samt ændring i gangfunktion ved ”6-minute-walk-test” (6MWT) og livskvalitet målt ved KCCQ.

Overordnet set er der god balance mellem de to grupper. Medianalderen er ~75 år, og omkring 90 % er mænd. Ca. 60 % er i NYHA klasse II, mens der er ~30 % i NYHA klasse III og ~10 % i NYHA klasse I.

Fagudvalget vurderer, at populationen er sammenlignelig med patienter i dansk praksis, dog bemærker fagudvalget, at den danske population hovedsageligt (> 95 %) udgøres af patienter med vildtypeformen af sygdommen, og at disse patienter er ældre (~80 år).

Fagudvalget vurderer også, at når der med tafamidis findes en behandling af sygdommen, såfremt denne bliver anbefalet, vil dette føre til en øget screening og diagnosticering af patienter, som kunne have gavn af behandling. Populationen i dansk klinisk praksis vil med øget opmærksomhed forventeligt omfatte en del patienter med andre sygdomme i hjertet som f.eks. aortastenose og samtidig amyloide aflejringer. Samtidig vil den danske population herefter formentlig også omfatte flere patienter i tidligere sygdomsstadier end dem, der er inkluderet i studiet.

De kendte danske patienter med den arvelige form af ATTR-CM er i gennemsnit yngre end patienterne i studiet, og størstedelen har en anden mutation.

Fagudvalget vurderer, at disse forskelle ikke bør have betydende indflydelse på vurderingen af tafamidis.

5.1.2 Databehandling og analyse

Nedenunder beskriver vi ansøgers datagrundlag, databehandling og analyse for hvert effektmål.

Ansøger har til det kliniske spørgsmål indsendt resultater for ITT-populationen for poolede doser af tafamidis meglumin (doser 80 mg og 20 mg kombineret) vs. placebo fra ATTR-ACT-studiet. Den godkendte dosering er 61 mg tafamidis, som er ækvivalent med 80 mg tafamidis meglumin. Ansøger har indsendt resultater fordelt på de to doser og diskuteret valg af dosis. Disse omtales under afsnittet "andre overvejelser".

Overlevelse

Overlevelse (OS) er analyseret med Cox-proportional hazard model for den relative effektforskel. I ATTR-ACT-studiet blev mortalitetsstatus (død/levende) indsamlet for alle patienter ved 30 måneder inkl. de, som ophørte behandling før tid. Denne status anvendes til at beregne forskel i absolut overlevelse ved 30 måneder.

Livskvalitet

Den gennemsnitlige ændring i livskvalitet blev målt ved Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score som anvist i Medicinrådets protokol.

Hospitalsindlæggelser relateret til kardiovaskulær sygdom

Hospitalsindlæggelser relateret til kardiovaskulær sygdom blev defineret som en akut indlæggelse, hvilket resulterede i mindst et døgns ophold) på grund af hjertesvigt, arytmi, hjerteinfarkt, slagtilfælde og andre hjerte-kar-relaterede begivenheder. Det blev ved hvert besøg undersøgt, om patienten var blevet indlagt på hospitalet siden sidste besøg, inklusive årsagen til indlæggelse. I tilfælde af behandlingsophør blev patientens primære læge og/eller kardiolog kontaktet for disse oplysninger. Forskellen mellem intervention og komparator blev beregnet som frekvens pr. år, som anvist i Medicinrådets protokol.

6 minutters gangtest

Den gennemsnitlige ændring i gangfunktion blev målt ved 6 minutters gangtest (6MWT), som anvist i Medicinrådets protokol.

Bivirkninger

Bivirkninger er opgjort som behandlingsrelaterede "treatment emergent adverse events" (TEAE) i den kvantitative analyse, hvilket svarer overens med det som er efterspurgt i Medicinrådets protokol.

5.1.3 Evidensens kvalitet

Fagudvalget har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 1).

Evidensens kvalitet er nedgraderet for inkonsistens, da der kun er ét studie.

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

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 2. Resultater for klinisk spørgsmål 1

Effektmål	Måleenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Overlevelse	Andel, der overlever i 30 mdr. (5 %-point)	Kritisk	13,5 %-point (4,26; 22,53)	Merværdi af ukendt størrelse	HR: 0,70 (0,51; 0,96)	Merværdi af ukendt størrelse	Merværdi af ukendt størrelse
Livskvalitet Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score	Gennemsnitlig ændring fra baseline (5 point)	Kritisk	13,65 (9,48; 17,83)	Merværdi af ukendt størrelse			Merværdi af ukendt størrelse
Hospitalsindlæggelser relateret til kardiovaskulær sygdom	Gennemsnitlig ændring i antal indlæggelser pr. patient pr. år (15 %)	Vigtig	-0.32 -0.44; -0.19 (-32% [-44;-19])	Merværdi af ukendt størrelse	RR: 0,68 0,56; 0,81	Moderat merværdi	Moderat merværdi
6 minutters gangtest (6 Minute Walk Test, 6MWT)	Gennemsnitlig ændring fra baseline (45 meter)	Vigtig	75,68 (57;56; 93,80)	Merværdi af ukendt størrelse			Merværdi af ukendt størrelse
Bivirkninger	Andel patienter der oplever ≥ 1 bivirkning (AR) (15 %-point)	Vigtig	-8,04 (-17,52; 1,44)	Ingen dokumenteret merværdi	RR: 0,84 (0,69; 1,03)	Ingen dokumenteret merværdi	Ingen dokumenteret merværdi
	Kvalitativ gennemgang						
Samlet kategori for lægemidlets værdi		Moderat merværdi					
Kvalitet af den samlede evidens		Moderat kvalitet					

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

Overlevelse

Som beskrevet i protokollen er effektmålet *overlevelse* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi ATTR-CM er livstruende og medfører forkortet levetid.

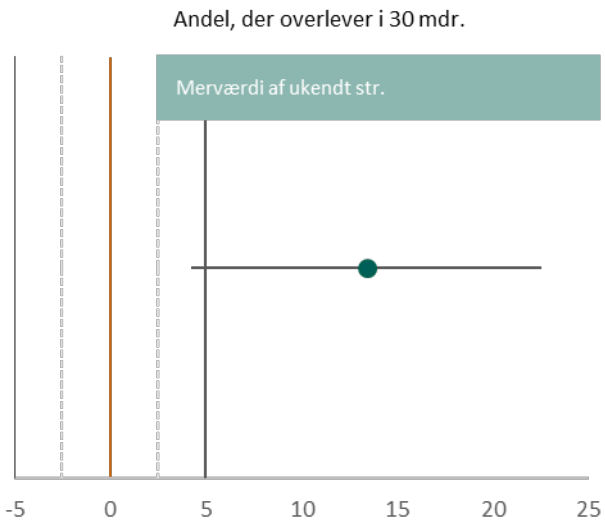
Baseret på den relative effektforskel, som fremgår af tabel 2, og som er HR: 0,70 (0,51; 0,96), har tafamidis foreløbigt en merværdi af ukendt størrelse vedr. overlevelse.

Ved behandling med tafamidis var 70,5 % af patienterne i live efter 30 måneder, mens 57,1 % var i live i placeboarmen. Dette giver en absolut forskel på 13,4 %-point [95% CI 4,26; 22,53].

Punktestimatet er næsten 3 gange større end MKRF på 5 %-point for den absolutte effektforskel og afspejler derfor en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på den klinisk relevante forskel end på 0 (ingen effekt). Derfor er den foreløbige værdi af tafamidis merværdi af ukendt størrelse vedr. overlevelse.

Fagudvalget bemærker, at Kaplan-Meier-kurverne for overlevelsen først begynder at skille sig efter 18 måneder, hvilket kan tyde på en sent indsættende effekt af behandlingen i forhold til dødelighed [11].

Den absolutte forskel er afbildet i figur 1 nedenfor.



Figur 1: Punktestimat og 95 % konfidensinterval for den absolutte forskel for overlevelse. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget vurderer, at tafamidis på aggregeret niveau har en merværdi af ukendt størrelse vedr. overlevelse, fordi både den relative og absolutte kategori er merværdi af ukendt størrelse.

For bedre at kunne vurdere resultaterne på overlevelse ønskede fagudvalget, at ansøger angav tiden fra diagnose til inklusion i studiet for de patienter, der er inkluderet i studiet.

Den gennemsnitlige tid fra diagnose til inklusion i studiet var 1,023 år (SD 1,33) for tafamidis og 1,233 år (SD 1,44) i placeboarmen.

Fagudvalget vurderer, at i dansk klinisk praksis vil behandlingen begyndes ved diagnosetidspunktet for aktiv sygdom. Fagudvalget finder dog ikke grund til at tillægge tiden mellem diagnose og inklusion på ~1 år betydning i vurderingen af tafamidis.

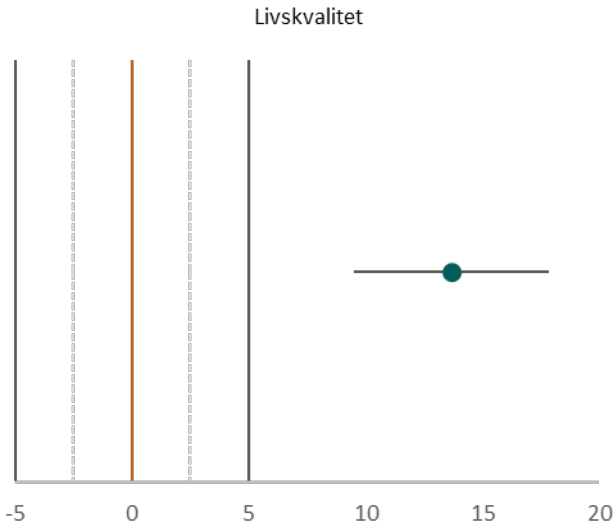
Livskvalitet

Som beskrevet i protokollen er effektmålet *livskvalitet* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi ATTR-CM påvirker patienternes daglige funktionsniveau og dermed deres livskvalitet.

Ved behandling med tafamidis var den gennemsnitlige ændring (forværring) i KCCQ-OS score -7,16 point fra baseline til 30 måneder. I placeboarmen var den tilsvarende gennemsnitlige ændring -20,81 point. Dette giver en absolut forskel på 13,65 point [95% CI 9,48; 17,83] til fordel for tafamidis.

Punktestimatet er næsten 3 gange større end MKRF på 5 point for den absolutte effektforskel og afspejler derfor en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på den klinisk relevante forskel end på 0 (ingen effekt). Derfor er den foreløbige værdi af tafamidis merværdi af ukendt størrelse vedr. livskvalitet. Hele konfidensintervallet ligger tydeligt over MKRF.

Den absolutte forskel er afbildet i figur 2 nedenfor.



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

Der kategoriseres ikke på den relative skala for kontinuerte effektmål. Tafamidis har derfor på aggregeret niveau en merværdi af ukendt størrelse for livskvalitet.

Hospitalsindlæggelser relateret til kardiovaskulær sygdom

Som beskrevet i protokollen er effektmålet hospitalsindlæggelser relateret til kardiovaskulær sygdom vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi patienter med ATTR-CM vil have en overhyppighed af indlæggelser relateret til kardiovaskulær sygdom. Hospitalsindlæggelse er et patientnært effektmål. Indlæggelse på et hospital er betydende for patientens livskvalitet, herunder sygdomsfølelse. Det

har samtidig betydning for patientens prognose, idet en indlæggelse kan medføre øget risiko for den næste indlæggelse og for død. Det er derfor relevant, om en ny behandling kan nedbringe antallet af indlæggelser i forhold til komparator. En reduktion i antal indlæggelser vil afspejle bedre tilstand, også de dage patienten ikke er indlagt.

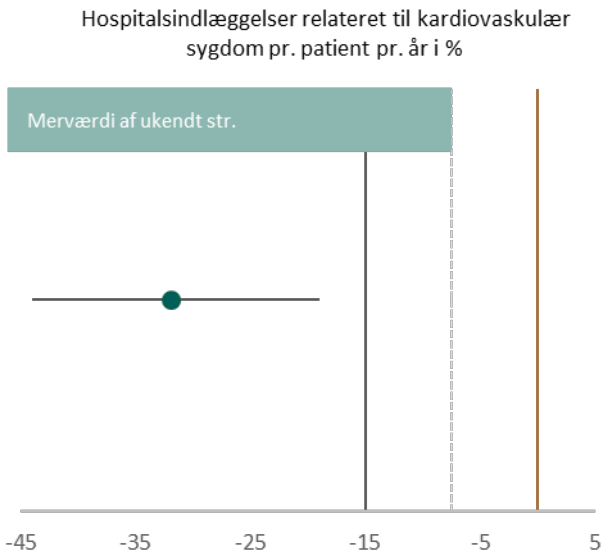
Baseret på den relative effektforskel, som fremgår af tabel 2, og som er RR: 0,68 (95 % CI 0,56; 0,81), har tafamidis foreløbigt en moderat merværdi vedr. hospitalsindlæggelser relateret til kardiovaskulær sygdom, se tabel 2.

Ved behandling med tafamidis var den absolutte frekvens af hospitalsindlæggelser relateret til kardiovaskulær sygdom 0,48 pr. patient pr. år, mens frekvensen i placeboarmen var 0,70 pr. patient pr. år.

Fagudvalget har i protokollen estimeret at den gennemsnitlige patient har ~1 hospitalsindlæggelser relateret til kardiovaskulær sygdom om året. Beregnet vha. den relative risiko og den forventede danske placebo eventrate bliver den absolutte risikoreduktion 0,32 (95 % CI 0,19; 0,44) svarende til 32 % (95 % CI 19; 44). Ved én indlæggelse pr. år pr. patient svarer en ~32 % reduktion til, at man behandler ~3 patienter i et år og undgår én indlæggelse i dette år ('numbers needed to treat' ~3).

Punktestimatet er ~2 gange større end MKRF på 15 %-point for den absolutte effektforskel og afspejler derfor en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet er tættere på den klinisk relevante forskel end på 0 (ingen effekt). Derfor er den foreløbige værdi af tafamidis merværdi af ukendt størrelse vedr. hospitalsindlæggelser relateret til kardiovaskulær sygdom. Hele konfidensintervallet ligger over MKRF.

Den absolutte forskel er afbildet i figur 3 nedenfor.



Figur 3: Punktestimat og 95 % konfidensinterval for den absolutte forskel for hospitalsindlæggelser relateret til kardiovaskulær sygdom. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget vurderer, at tafamidis på aggregeret niveau har en moderat merværdi vedr. hospitalsindlæggelser relateret til kardiovaskulær sygdom. Fagudvalget lægger vægt på, at den relative risikoreduktion giver en moderat merværdi. Samtidig er den absolutte risikoreduktion ca. dobbelt så høj som

den prædefinerede mindste klinisk relevante forskel. Hele konfidensintervaller overstiger den mindste klinisk relevante forskel. Fagudvalget vurderer derfor at den absolutte effektforskel understøtter den moderate værdi som observeres på den relative skala.

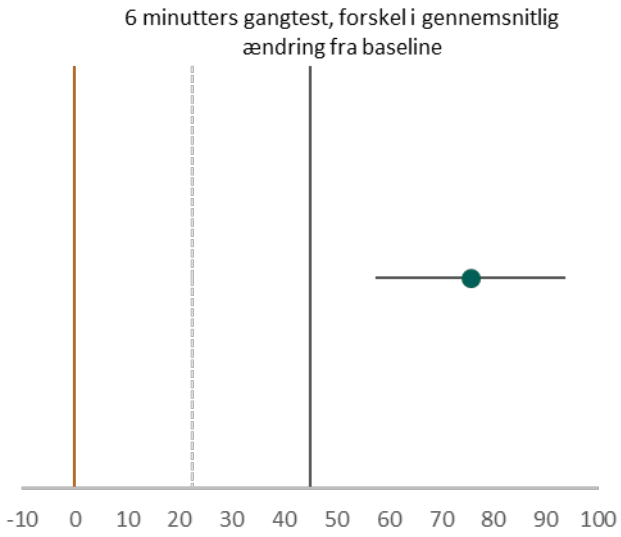
6 minutters gangtest

Som beskrevet i protokollen er effektmålet gangfunktion vurderet ved 6 minutters gangtest vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi ATTR-CM påvirker patienternes fysiske funktionsniveau og dermed deres evne til selv at klare dagligdagens gøremål som f.eks. gang til offentlig transport og indkøb.

Ved behandling med tafamidis var den gennemsnitlige ændring (forværring) i 6 minutters gangtest -54,87 meter fra baseline til 30 måneder. I placeboarmen var den tilsvarende gennemsnitlige ændring -130,55 meter. Dette giver en absolut forskel på 75,68 meter (95 % CI 57,56; 93,80) til fordel for tafamidis.

Punktestimatet er større end MKRF på 45 meter for den absolutte effektforskel og afspejler derfor en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på den klinisk relevante forskel end på 0 (ingen effekt). Derfor er den foreløbige værdi af tafamidis merværdi af ukendt størrelse vedr. 6 minutters gangtest.

Den absolutte forskel er afbildet i figur 4 nedenfor



Figur 4: Punktestimat og 95 % konfidensinterval for den absolutte forskel for 6 minutters gangtest. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Der kategoriseres ikke på den relative skala for kontinuerte effektmål. Tafamidis har derfor aggregeret en merværdi af ukendt størrelse for gangfunktion målt ved 6 minutters gangtest.

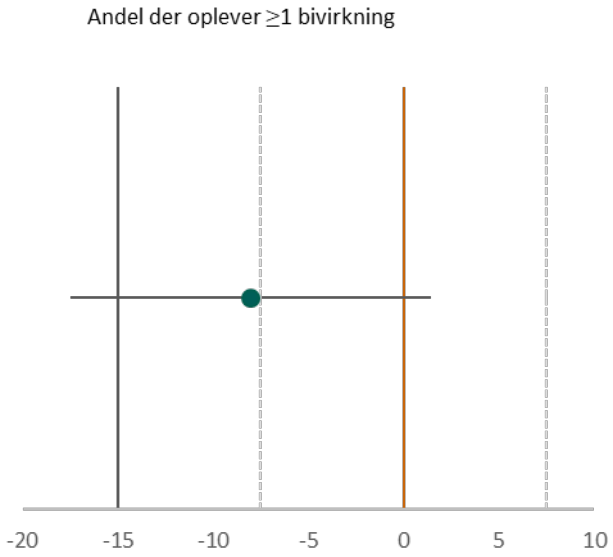
Bivirkninger

Som beskrevet i protokollen er effektmålet *bivirkninger* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi bivirkninger, som er særligt alvorlige eller generende, kan påvirke patienternes livskvalitet og mulighed for at gennemføre den medicinske behandling.

Baseret på den relative effektforskel, som fremgår af tabel 2, og som er RR: 0,84 (0,69; 1,03), har tafamidis foreløbigt ingen dokumenteret merværdi vedr. bivirkninger.

Ved behandling med tafamidis oplevede 42,8 % af patienterne ≥ 1 behandlingsrelateret TEAE, mens 50,8 % af patienterne i placeboarmen oplevede dette. Dette giver en absolut forskel på -8,04 %-point [95 % CI -17,52; 1,44].

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel (MKRF: 15 %-point). Den øvre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor har tafamidis foreløbigt ingen dokumenteret merværdi vedr. bivirkninger.



Figur 5: Punktestimat og 95 % konfidensinterval for den absolutte forskel for bivirkninger. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Kvalitativ gennemgang af bivirkninger

Sikkerhedsdata for tafamidis 61 mg er ikke tilgængelig, da denne formulering ikke blev undersøgt i det dobbeltblindede, placebokontrollerede, randomiserede fase 3-studie. Fagudvalget vurderer, at det indsendte data tyder på, at bivirkningsprofilen for tafamidis er mild og håndterbar, hvilket er i overensstemmelse med vurderingen fra EMAs EPAR. Hyppigheden af bivirkninger var ensartet og sammenlignelig hos de patienter, der blev behandlet med hhv. 80 mg tafamidis meglumin og placebo.

Følgende bivirkninger blev ifølge EMA rapporteret oftere hos patienter behandlet med 80 mg tafamidis meglumin sammenlignet med placebo: flatulens [8 patienter (4,5 %) versus 3 patienter (1,7 %)] og stigninger i leverfunktionsundersøgelser [6 patienter (3,4 %) versus 2 patienter (1,1 %)]. Behandling med tafamidis giver ikke anledning til højere behandlingsophør eller hyppigere dosisreduktion sammenlignet med placebo.

Fagudvalget bemærker, at meget sjældne bivirkninger ikke helt kan udelukkes, da det foreliggende datagrundlag består af 1 studie med 176 patienter med opfølgningstid på blot 30 måneder.

Fagudvalget vurderer, at tafamidis aggregeret har ingen dokumenteret merværdi vedr. bivirkninger. Fagudvalget lægger vægt på, at der ikke en dokumenteret en forskel i de kvantitative analyser, samt at den kvalitative gennemgang af bivirkninger viser en mild og håndterbar sikkerhedsprofil.

6 Andre overvejelser

Vedr. andre overvejelser har ansøger indsendt data fra ATTR-ACT-studiet publiceret i Maurer et al. [11], data fra EPAR [10] og upubliceret fortrolig data-on-file fra ATTR-ACT-studiet, samt data fra konferenceabstracts. Fagudvalget vurderer, at det indsendte upublicerede data-on-file og data fra abstracts, som også delvist er refereret i EPAR, ikke bidrager med substantiel ny information, men at det derimod blot understøtter data, som er publiceret. Det upublicerede data vurderes dermed ikke at påvirke evidensgrundlaget markant og anvendes derfor ikke.

6.1 Dosis 80 mg vs. 20 mg

Til indikationen hATTR med polyneuropati er den godkendte dosering 20 mg tafamidis meglumin, hvorimod den er højere til ATTR med kardiomyopati. Jf. protokollen har fagudvalget bedt ansøger redegøre for følgende: 1) valg af dosis 61 mg tafamidis (svarende til 80 mg tafamidis meglumin) fremfor en dosis bioækvivalent med 20 mg tafamidis meglumin, og 2) anvendelsen af de poolede analyser for tafamidis 20 mg og 80 mg. Fagudvalget har desuden bedt om separate analyser og opgørelser for de to anvendte doseringer og vil vurdere overensstemmelse mellem resultaterne.

Data fra ATTR-ACT viser, at der ikke er forskel på hverken klinisk effektivitet og "safety" mellem de to doser [10,11]. I EPAR findes detaljerede opgørelser over safety for de to doseringer, og begge viser en mild og håndterbar bivirkningsprofil med færre bivirkninger end placebo.

Rationalerne for valg af den højeste dosis på 80 mg tafamidis i stedet for 20 mg er: 1) den største mængde af evidens findes for tafamidis 80 mg, idet der i studiet var randomiseret 2:1:2 for hhv. 80 mg, 20 mg og placebo, og 2) analyser af biomarkøren for hjertesvigt, NT-proBNP, indikerer, at patienterne over en periode på 30 måneder opnår en mindre stigning i NT-proBNP med tafamidis 80 mg vs. 20 mg [10]. NT-proBNP er ikke medtaget i Medicinrådets vurdering af tafamidis, da det anses for et surrogat for de mere patientnære endepunkter såsom overlevelse og antal indlæggelser. Den foreslåede forskel i NT-proBNP afspejles ikke i analyserne af øvrige kliniske effektmål, hvor der ses en ensartet effekt mellem de to doser indenfor den undersøgte tidshorisont på 30 måneder.

Den nye formulering på 61 mg tafamidis er svarende til 80 mg tafamidis meglumin. Den nye formulering er ifølge ansøger lavet for "convenience", således at patienterne kun skal tage 1 kapsel pr. dag fremfor 4.

Fagudvalget vurderer, at der ikke er tilstrækkelig dokumentation for, at 80 mg tafamidis meglumine er bedre end 20 mg tafamidis meglumine på de effektmål, der indgår i vurderingen, og at evidensen for at foretrække 80 mg dosering fremfor 20 mg er baseret på data for surrogatendepunkter. Fagudvalget er imidlertid enige i betragtningen om, at der er forholdsvist mest data til at underbygge anvendelsen af dosis på 80 mg tafamidis meglumine, og at der samtidig er tilstrækkelig evidens for, at den valgte dosering på 80 mg tafamidis meglumine er effektiv med en mild sikkerhedsprofil.

6.2 Opdeling på hATTR vs. ATTRwt

Patienter med hhv. hATTR og ATTRwt har forskellige underliggende årsager til sygdommen samt markante forskelle i patientkarakteristika, herunder alder. Fagudvalget har derfor bedt om at se analyseresultater og baselinekarakteristik opgjort separat for patienter med hATTR og ATTRwt og vil vurdere disse med henblik på en eventuel differentiering af effekt.

I ATTR-ACT-studiet har ~24 % af patienterne hATTR, mens de resterende er vildtype.
Baselinekarakteristika hos patienter med den arvelige hATTR tyder på en lidt mere fremskreden sygdom end for patienter med ATTRwt-genotypen, idet at en højere andel af hATTR-patienter var i NYHA-klasse III [10]

På overlevelse ses ingen forskel i effektforhold mellem de to patientgrupper [11]. På hospitalsindlæggelser grundet kardiovaskulær sygdom ses en tydelig effekt for ATTRwt, mens effekten for hATTR ikke er signifikant og har et punktestimat, som ligger tæt på 0 (ingen forskel) i forhold til placebo [11]. Ansøger foreslår, at denne tilsyneladende forskel mellem de to grupper kan skyldes forskelle i sygdomsstadiet, idet flere med hATTR havde mere fremskreden sygdom vurderet ud fra NYHA-klasse. Dette vil blive diskuteret nærmere i næste afsnit "opdeling i sygdomsstadier".

Efter 30 måneder ses statistisk signifikante effekter i begge patientgrupper for livskvalitet og 6 minutters gangtest [10].

Fagudvalget vurderer, at begge patientpopulationer ser ud til at have effekt af behandling med tafamidis og finder ikke grund til at undlade behandling i nogle patienter på baggrund af det forelagte data. Patientpopulationen med arvelig transthyretin amyloidose er heterogen, og den danske mutation p.Leu131Met er ikke repræsenteret i studiet.

6.3 Opdeling i sygdomsstadier

I publicererede studier på tafamidis er det indikeret, at patienter i tidlige sygdomsstadier har størst gavn af behandling [12,17]. Fagudvalget ønsker derfor at vurdere, om patienter i forskellige sygdomsstadier vil have lige stor effekt af behandling med tafamidis. Fagudvalget ønsker derfor analyser, som er opdelt på NYHA-klasser. Fagudvalget ønsker herudover analyser, som er opdelt på NAC disease-stage ud fra værdier af NT-proBNP og eGFR. Fagudvalget vil vurdere data for disse opdelinger i sygdomsstadier med henblik på en eventuel differentiering af effekt. Fagudvalget vil i den forbindelse vurdere, om de to måder at inddele sygdommen på giver enslydende resultater. Fagudvalget mener, det er essentielt med en opdeling på begge disse måder, da NYHA-klassifikation er forbundet med en vis subjektivitet, mens NAC disease-stage klassificeres objektivt på baggrund af blodprøvemålinger.

Vedrørende opdeling i sygdomsstadier har ansøger indsendt data for NYHA-klasse I og II (poolet) og for NYHA-klasse III fra ATTR-ACT-studiet. ITT-populationen består af ~8 % NYHA-klasse I, ~60 % NYHA-klasse II og ~32 % NYHA-klasse III.

For effektmålet *overlevelse* ses en numerisk større effekt ved NYHA-klasse I+II vs. NYHA-klasse III. For patienter i NYHA-klasse III er punktestimatet til fordel for tafamidis, men af mindre størrelsesorden og opnår ikke statistisk signifikans [11].

For effektmålet hospitalsindlæggelser grundet kardiovaskulær sygdom ses en interaktion med NYHA-klasser, idet tafamidis med NYHA-klasse I+II mindsker frekvensen af indlæggelser, mens tafamidis ved NYHA-klasse III øger indlæggelsesfrekvensen [11]. Ansøger diskuterer, at dette fænomen kan skyldes en længere overlevelse i et mere alvorligt sygdomsstadie for patienter behandlet med tafamidis.

For patienter med NYHA-klasse I +II sås en statistisk signifikant effekt på livskvalitet fra måned 6 til 30. En statistisk signifikant behandlingseffekt blev kun observeret ved måned 18 og 30 for patienter med NYHA-klasse III. For patienter med NYHA-klasse I +II sås en statistisk signifikant effekt på 6MWT fra måned 6 til 30. En statistisk signifikant behandlingseffekt blev kun observeret ved måned 24 for patienter med NYHA-klasse III [10].

Fagudvalget bemærker, at der ikke forelagt evidens for NYHA-klasse I. For den samlede gruppe af NYHA-klasse I og II (som består af en stor overvægt af NYHA-klasse II) ses en effekt for alle effektmål. For patienter i NYHA-klasse III tyder den forelagte evidens på, at behandling med tafamidis medfører en øget frekvens af hospitalsindlæggelser. For øvrige effektmål er effekterne i NYHA-klasse III mindre overbevisende end for NYHA-klasse I+II.

Data tyder dermed på, at der er størst gavn af behandling inden NYHA-klasse III.

Fagudvalget undrer sig over, at ansøger ikke leverer data for patienter opdelt i NAC sygdomsstadier. Ansøger angiver, at denne inddeling ikke er defineret i studiet, og at analysen derfor ikke er lavet.

Fagudvalget vurderer, at effekten af tafamidis er størst i de tidligere sygdomsstadier (NYHA-klasse I+II) og bemærker, at det kan skyldes enten mangel på effekt i de senere stadier grundet fremskreden sygdom, eller at effekten er (for) sent indsættende, som observeret ved effekten på overlevelse.

6.4 Opstart og seponering

Behandling med tafamidis bør opstartes så hurtigt som muligt, efter at diagnosen er stillet og aktiv sygdom konstateret. I udredningen af patienter med symptomer på hjertepåvirkning i form af kardiomyopati skal AL amyloidose udelukkes ved blodprøver og evt. knoglemarvsundersøgelse, og mistanken om ATTR-CM skal bekræftes ved MR-scanning af hjertet, og/eller DPD skintigrafi af hjertet. For at stille den endelige diagnose, ATTR-CM, bør der tages en hjertebiopsi for at påvise amyloide aflejringer ved histologi. I nogle tilfælde kan amyloide aflejringer i biopsi fra andet væv, eksempelvis fedtvæv, sammen med en positiv skintigrafiundersøgelse være tilstrækkeligt til at stille diagnosen. Diagnosen af den arvelige form kræver, i tillæg til ovenstående, en genetisk undersøgelse med fund af sygdomsforårsagende ændring (mutation) i TTR-genet.

Fagudvalget vurderer, at når den amyloidrelaterede hjerteskade er mere fremskreden, f.eks. hos patienter med vedvarende NYHA-klasse III og IV, bør der som udgangspunkt ikke opstartes behandling med tafamidis.

Tafamidis bør seponeres ved uacceptable bivirkninger, ved levertransplantation, eller når patienten er i terminalstadiet eller har så udtalt sygdomsudvikling, at behandlingen ikke længere skønnes meningsfuld.

7 Fagudvalgets konklusion

Fagudvalget vurderer, at tafamidis giver en *moderat merværdi* sammenlignet med placebo til patienter med transthyretin amyloidose med kardiomyopati.

Fagudvalget lægger vægt på, at der ses en klinisk relevant behandlingsgevinst på alle de inkluderede effektmål, hvilket vil sige forbedret overlevelse og livskvalitet grundet en klinisk relevant reduceret sygdomsprogression indenfor studiets opfølgningstid.

Relative effektestimater: På den relative skala observeres en effektstørrelse, der giver en moderat merværdi for *hospitalsindlæggelser relateret til kardiovaskulær sygdom*, mens *overlevelse* giver merværdi af ukendt størrelse på den relative skala.

Absolutte effektestimater: Punktestimaterne for de absolutte effektforskelle vedr. de kritiske effektmål *overlevelse* og *livskvalitet* ligger næsten 3 gange over de prædefinerede MKRF. For overlevelse ligger næsten hele konfidensintervallet over MKRF og for livskvalitet ligger hele konfidensintervallet betydeligt over MKRF. Punktestimaterne med tilhørende konfidensintervaller for de absolutte forskelle vedr. de vigtige effektmål *hospitalsindlæggelser relateret til kardiovaskulær sygdom* og *gangfunktion* ligger tydeligt over de prædefinerede MKRF på de absolutte skalaer. Disse absolutte effektforskelle for *overlevelse*, *livskvalitet*, *hospitalsindlæggelser relateret til kardiovaskulær sygdom* samt *gangfunktion* er af betydelig størrelsesorden og er i overensstemmelse med en moderat merværdi. Der ses ingen betydende bivirkninger.

Samlet set vurderer fagudvalget, at effekten af tafamidis er betydelig og relevant for patienten og vurderer derfor, at tafamidis har en moderat merværdi.

Fagudvalget vurderer, at den moderate merværdi gælder NYHA-klasse I og II, og at der hos patienter med vedvarende NYHA-klasse III og IV som udgangspunkt ikke bør opstartes behandling med tafamidis.

Evidensens kvalitet er moderat og nye studier vil med lav sandsynlighed ændre konklusionen.

8 Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning, og fagudvalget har derfor ikke taget stilling til en foreløbig placering af lægemidlet.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende transthyretin amyloidose
Forvaltningslovens § 4, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg

Formand	**Indstillet af**
Redi Pecini Afdelingslæge	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Claus Holst-Hansen Overlæge	Region Nordjylland
Henrik Ølholm Vase Afdelingslæge	Region Midtjylland
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Hanne Elming Overlæge	Region Sjælland
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Johannes Jakobsen Professor	Dansk Neurologisk Selskab
Anette Torvin Møller Overlæge	Dansk Neurologisk Selskab
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Peter Ott Ledende overlæge	Dansk Selskab for Gastroenterologi og Hepatologi
Jens Michael Hertz Professor, overlæge	Dansk Selskab for Medicinsk Genetik
Astrid Juhl Terkelsen Speciallæge i Neurologi	Inviteret af formanden
Birthe Byskov Holm Patient/patientrepræsentant	Danske Patienter

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11 Versionslog

Version	Dato	Ændring
1.0	23. september 2020	Godkendt af Medicinrådet.

12 Bilag 1: Evidensens kvalitet

12.1 Cochrane, Risk of Bias

Vurdering af risiko for bias ved Cochranes RoB 2.0 assessment tool.

	Risiko for bias i randomiseringsprocessen	**Risiko for bias grundet afvigelser fra tilsigtet intervention** **(effekt af tildeling til intervention)**	**Manglende data for effektmål**	**Risiko for bias ved indsamlingen af data**	**Risiko for bias ved udvælgelse af resultater der rapporteres**	**Overordnet risiko for bias**
ATTR-ACT	lav	lav	lav	lav	lav	lav

12.2 GRADE-profil

GRADE-profil tafamidis vs. placebo (ATTR-ACT)

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	Studiedesign	Risk of bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Tafamidis	placebo	Relativ [95 % CI]	Absolut		
Overlevelse, median (måneder)												
1	Randomiseret undersøgelse	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Ikke alvorlig	Ingen	264	177	HR: 0,70 [0,51; 0,96]	13,4 % [4,26; 22,53]	⊕⊕⊕◯ MODERAT	KRITISK
Livskvalitet, gennemsnitlig ændring i Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score												
1	Randomiseret undersøgelse	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Ikke alvorlig	Ingen	170	84	-	13,65 [9,48; 17,83]	⊕⊕⊕◯ MODERAT	KRITISK
Hospitalsindlæggelser relateret til kardiovaskulær sygdom, antal indlæggelser pr. patient pr. år (%)												
1	Randomiseret undersøgelse	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Ikke alvorlig	Ingen	264	177	RR: 0,68 [0,56; 0,81]	-32 % [-44;-19]	⊕⊕⊕◯ MODERAT	VIGTIGT
Gangfunktion, , gennemsnitlig ændring i 6 minutters gangtest (m)												
1	Randomiseret undersøgelse	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Ikke alvorlig	Ingen	155	70	-	75,68 meter [57,56; 93,80]	⊕⊕⊕◯ MODERAT	VIGTIGT
Bivirkninger, andel patienter der oplever ≥ 1 bivirkning (AR) (%-point)												
1	Randomiseret undersøgelse	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Alvorlig[b]	Ingen	264	177	RR: 0,84 [0,69; 1,03]	-8,04 %-point [-17,52; 1,44]	⊕⊕◯◯ LAV	VIGTIGT
Samlet kategori: Moderat												

CI Konfidensinterval; HR Hazard ratio; RR Relativ risiko
a. Der er kun data fra ét randomiseret studie. Derfor nedgraderes ét niveau for inkonsistens.
b. Der er et bredt konfidensinterval, hvilket indikerer stor usikkerhed om estimatet. Derfor nedgraderes ét niveau for unøjagtighed.

Medicinrådet

Application for the assessment of tafamidis for treatment of transthyretin amyloid cardiomyopathy

Contents

1 Basic information

TABLE 1 CONTACT INFORMATION

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TABLE 2 OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	Vyndaqel®
Generic name	Tafamidis
Marketing authorization holder in Denmark	Pfizer, Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgium
ATC code	N07XX08
Pharmacotherapeutic group	Other nervous system drugs
Active substance(s)	Tafamidis
Pharmaceutical form(s)	Capsule
Mechanism of action	Tafamidis is a selective stabilizer of transthyretin (TTR). Tafamidis binds to the two thyroxine binding sites on the native tetrameric form of TTR, stabilizing the tetramer and preventing dissociation into monomers, the rate-limiting step in the amyloidogenic process. The inhibition of TTR tetramer dissociation forms the rationale for the use of tafamidis to slow disease progression in patients with TTR amyloid cardiomyopathy.
Dosage regimen	The recommended dose of tafamidis for patients with TTR amyloid cardiomyopathy is 61 mg taken orally once daily
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Vyndaqel is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)
Other approved therapeutic indications	Vyndaqel is indicated for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurological impairment. [ATTR-PN] The approved dose for ATTR-PN is 20 mg taken orally once daily.
Will dispensing be restricted to hospitals?	Yes

Combination therapy and/or co-medication	Not applicable
Packaging – types, sizes/number of units, and concentrations	Pack size: a pack of 30 x 1 soft capsules. Each soft capsule contains 61 mg of micronized tafamidis.
Orphan drug designation	Yes

Nomenclature, transthyretin amyloid cardiomyopathy

The disease transthyretin amyloid cardiomyopathy (ATTR-CM) can be either hereditary or wild-type ATTR-CM.

ATTR-CM can be inherited as an autosomal dominant trait caused by pathogenic mutations in the transthyretin gene (*TTR*) leading to misaggregation and deposition of variant ATTR (denoted ATTRm).

ATTR-CM can also appear as a sporadic, non-genetic disease due to misaggregation and deposition of wild-type TTR protein (denoted ATTRwt).

For convenience and readability, the abbreviations ATTRm and ATTRwt are used throughout the document to refer to the *TTR* genotype as well as the disease hereditary or wild-type ATTR-CM, respectively.

Confidential information

Confidential unpublished information is marked in [redacted] It includes figures and tables with headings in orange font. The information, including figures and tables, must be treated as confidential and not published on the Danish Medicines Council website.

2 Abbreviations

6MWT	6-minute walk test
AE	adverse event
ATTR-ACT	Tafamidis in Transthyretin Cardiomyopathy Clinical Trial
ATTR-CM	transthyretin amyloid cardiomyopathy
ATTR-PN	transthyretin amyloid polyneuropathy
ATTRm	variant (mutant) transthyretin amyloid*
ATTRwt	wild-type transthyretin amyloid*
BMI	body mass index
CHMP AR	Committee for Medicinal Products for Human Use assessment report
CI	confidence interval
Cmax,ss	maximum concentration at steady state
Cmin,ss	minimum concentration at steady state
DMC	Danish Medicines Council
EC	European Commission
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	US Food and Drug Administration
F-S Method	Finkelstein-Schoenfeld method
HF	heart failure
HR	hazard ratio
ITT	intention-to-treat
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire - Overall Summary
LS mean	least squares mean
LV	left ventricular
mBMI	modified body mass index
MCRD	minimal clinically relevant difference
NT-proBNP	N-terminal pro B-type natriuretic peptide
NAC	National Amyloidose Center
NYHA	New York Heart Association
OS	overall survival
PICO	population, intervention, comparator, outcome
RR	relative risk
RRR	relative risk ratio
SD	standard deviation
SE	standard error
TEAE	treatment-emergent adverse event
TTR	transthyretin
TTR	transthyretin gene
UTI	urinary tract infection

*For convenience and readability, the abbreviations ATTRm and ATTRwt are used throughout the document to refer to the *TTR* genotype as well as the disease hereditary or wild-type ATTR-CM, respectively.

3 Summary

Vyndaqel (tafamidis) is a specific stabilizer of transthyretin (TTR) approved by the EMA for the treatment of TTR amyloidosis in adult patients with wild-type or hereditary cardiomyopathy (ATTR-CM). By stabilizing TTR, tafamidis inhibits the dissociation of TTR tetramers into monomers, which is the rate-limiting step in the formation of TTR amyloid. The inhibition of tetramer dissociation forms the rationale for the use of tafamidis to slow disease progression in patients with ATTR-CM.

ATTR-ACT was a randomized, placebo-controlled phase 3 trial investigating the efficacy and safety of tafamidis in adult patients with ATTR-CM. Eligible patients were randomly assigned to receive 80 mg of tafamidis, 20 mg of tafamidis or matching placebo once daily in a 2:1:2 ratio for 30 months.

All-cause mortality was lower among the 264 patients who received tafamidis (80 mg tafamidis and 20 mg tafamidis pooled) as compared to the 177 patients who received placebo (hazard ratio 0.70 [95% confidence interval (CI) 0.51; 0.96], p=0.0259). This was reflected in the overall survival rate, which was 70.5% in the tafamidis group and 57.1% in the placebo group at 30 months (absolute difference 13.4% [95% CI 4.26; 22.53], p=0.0044).

Quality of life, as assessed by the Kansas City Cardiomyopathy Questionnaire - Overall Summary (KCCQ-OS) score, declined to a lower extent in the pooled tafamidis group as compared to placebo, with a least square (LS) mean change from baseline difference of 13.65 points [95% CI 9.48; 17.83] in favour of tafamidis (p<0.0001) after 30 months of treatment.

The rate of hospitalizations related to cardiovascular events was lower for patients receiving tafamidis, with 0.48 per patient per year for the tafamidis group vs 0.70 per patient per year for the placebo group (relative risk ratio 0.68 [95% CI 0.56; 0.81], p<0.0001). With an assumed control group rate of 1 cardiovascular-related hospitalization per patient per year, this corresponds to a reduction of 0.32 [0.19; 0.44] cardiovascular-related hospitalizations per patient per year in patients treated with tafamidis.

Functional capacity was assessed by the distance walked on the 6-minute walk test (6MWT). After 30 months of treatment, tafamidis reduced the decline in distance walked as compared to placebo significantly. The absolute difference in change from baseline was 75.68 metres in favour of tafamidis (p<0.0001).

The safety profiles for tafamidis and placebo were similar. The proportion of treatment-related treatment-emergent adverse events (TEAEs) was 42.8% in patients treated with tafamidis vs 50.8% in those receiving placebo, and the proportion of patients with serious treatment-related TEAEs was also lower in the tafamidis group as compared with placebo. Most treatment-related TEAEs were mild to moderate in severity.

Primary and secondary endpoints of the ATTR-ACT trial did not include analyses by dose, *TTR* genotype, or disease stage, and the trial was thus not designed to evaluate responses in these subgroups. Still, pre-specified exploratory analyses were conducted to understand the effect of the doses administered, and subgroup analyses were conducted according to *TTR* genotype (wild-type vs variant) and disease stage (NYHA class I and II vs NYHA class III).

Analyses revealed that the efficacy and safety were similar for tafamidis 80 mg and tafamidis 20 mg, albeit data for 80 mg tafamidis had more power due to the greater number of patients randomized to the tafamidis 80 mg group than the tafamidis 20 mg group. Exploratory analyses of the cardiac biomarker NT-proBNP favoured the 80 mg dose over the 20 mg dose. The increase in NT-proBNP through the study with tafamidis 80 mg was significantly lower than with 20 mg (–1170.51 pg/mL (standard error 587.31), p=0.0468).

ATTR-CM can be inherited as an autosomal dominant trait caused by pathogenic mutations in the transthyretin gene (*TTR*) with deposition of variant TTR amyloid protein (denoted ATTRm) or it can appear as a sporadic, non-genetic disease due to misaggregation and deposition of wild-type TTR amyloid protein (denoted ATTRwt). In the ATTR-ACT trial, both types of patients were included. Subgroup analyses revealed that efficacy of tafamidis in terms of all-cause mortality, KCCQ-OS and 6MWT was similar for ATTRm and ATTRwt patients. Likewise, the safety profiles were similar for the two types of patients.

Stage of disease was categorized according to New York Heart Association (NYHA) class I, II and III. NYHA class subgroup analyses indicated that patients in NYHA class I and II benefit more from tafamidis as compared to patients in NYHA class III. The higher efficacy of tafamidis in earlier disease stages emphasizes the importance of starting treatment with tafamidis as early as possible. According to the protocol for assessment of tafamidis, a stratification according to National Amyloidose Center (NAC) disease stage, combining levels of the two biomarkers NT-proBNP and estimated glomerular filtration rate (eGFR), was also requested. NAC disease staging is a prognostic staging system introduced recently based on data published in 2018, i.e. 5 years after initiation of the ATTR-ACT trial. For this reason, patients were not stratified according to NAC stage, no subgroup analyses were planned according to this disease staging system, and no subgroup analyses according to NAC disease stage have been conducted.

In conclusion, tafamidis treatment of patients with wild-type and hereditary ATTR-CM was associated with reductions in all-cause mortality and cardiovascular-related hospitalizations and reduced the decline in functional capacity and quality of life as compared with placebo. Safety data from the ATTR-ACT trial demonstrate that tafamidis once daily is well tolerated with a safety profile comparable to placebo when used for the treatment of adult patients with ATTR-CM.

Tafamidis 61 mg is the first and only drug approved and available for ATTR-CM.

4 Literature search

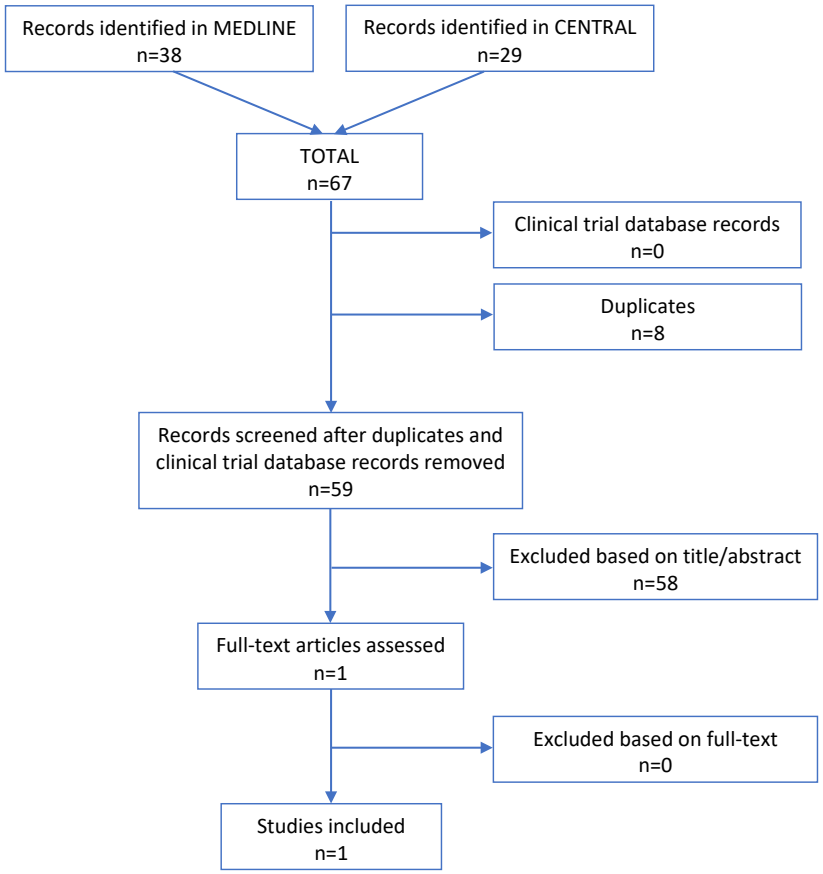
4.1 Databases and search strategy

Systemic literature searches were performed in MEDLINE via PubMed and in CENTRAL via Cochrane Library on 12 March 2020 according to the search strategies provided in the protocol for assessment of tafamidis [1]. No language or date limits were applied. The complete search strategies provided in the protocol for assessment of tafamidis are summarized in Appendix 6.1, Table 15 and Table 16. A total of 38 records were identified in MEDLINE and 29 in CENTRAL. After removal of duplicates and clinical trial database records, 59 records were left for screening. The records were screened and assessed by two researchers independently based on the PICOs (patients, intervention, comparator, outcomes) and inclusion and exclusion criteria as described in the assessment protocol for tafamidis [1].

Based on screening at the title and abstract level, all except one publication were excluded. A PRISMA flow diagram of the selection process is provided in Figure 1. No disagreements were noted between researchers during the selection process.

The included article (Maurer et al. 2018 [2]) describes the results of the phase 3 randomized clinical trial ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial), which meets all the inclusion and exclusion criteria of the search outlined in Appendix 6.1, Table 17. Relevant data were extracted into a project-specific Microsoft Excel table by one researcher and a second researcher independently checked the data extraction for accuracy and completeness. No disagreements were noted.

FIGURE 1 PRISMA FLOW DIAGRAM



4.2 Relevant studies

The relevant trial and the related publication are summarized in Table 3.

TABLE 3 RELEVANT STUDIES INCLUDED IN THE ASSESSMENT

Reference (title, author, journal, year)	**Trial name**	**NCT number**	**Dates of trial** (start and actual completion date)
Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. Maurer MS, Schwartz JH, Gundapaneni B et al. N Engl J Med. 2018;379(11):1007-1016. [2]	ATTR-ACT: Safety and efficacy of tafamidis in patients with transthyretin cardiomyopathy	NCT01994889	Dec 2013 – Feb 2018

4.3 Main characteristics of included studies

ATTR-ACT was a multicentre, international, double-blind, placebo-controlled, phase 3 trial. Eligible patients were randomly assigned to receive 80 mg of tafamidis, 20 mg of tafamidis, or matching placebo once daily in a 2:1:2 ratio for 30 months. The main characteristics for the ATTR-ACT trial is summarized in Appendix 6.2, Table 18.

ATTR-CM was a disease area with no established and recognized efficacy endpoints for evaluation. Therefore, before initiation of the trial, endpoints were discussed and agreed with authorities (FDA and EMA). The endpoints are linked to the natural history, characteristics, and clinical course of the disease.

ATTR-CM is a life-threatening and most often fatal disease and the hard endpoint 'mortality' was given priority, together with cardiovascular-related hospitalizations known to occur often in this patient group.

The ATTR-ACT trial was designed to evaluate efficacy and safety on active drug treatment (doses combined) vs placebo with focus on hierarchical assessment of efficacy on all-cause mortality, followed by frequency of cardiovascular-related hospitalizations. The endpoints were also analysed separately.

The analysis of the combined primary endpoint was supported by assessment of patient functional capacity and quality of life that both typically decline quickly as the disease progresses.

The drug tafamidis has been developed for a small patient group with a relatively rare disease. Although, the number of patients in the ATTR-ACT trial is relatively high considering the rarity of the disease, sub-group analyses will be challenging due to the low patient numbers in the different disease strata.

Given the rarity of ATTR-CM and the current lack of standardized measures for minimal clinically relevant differences for overall survival and cardiovascular-related hospitalizations, the Danish Medicines Council (DMC) is encouraged to also include the clinical perspective and evaluation when assessing the clinical value of tafamidis.

5 Clinical questions

5.1 What is the clinical added value of tafamidis as compared to placebo in patients with ATTR-CM?

Hvad er værdien af tafamidis sammenlignet med placebo til patienter med transthyretin-medieret amyloidose med kardiomyopati? [1]

Population
Adult patients with wild-type or hereditary ATTR-CM

Intervention
Tafamidis capsule, 61 mg once daily (oral administration)

In the ATTR-ACT trial, tafamidis was given in the form of tafamidis meglumine [2]. An evaluation of the free acid form of tafamidis 61 mg demonstrated that one 61 mg capsule of tafamidis free acid is bioequivalent to the 80 mg tafamidis meglumine dose (4 x 20 mg capsules) used in the ATTR-ACT trial [3].
For convenience, 80 mg tafamidis meglumine is designated as 80 mg tafamidis in the following.

Comparator
Placebo

5.1.1 Presentation of relevant studies

The ATTR-ACT trial [2] is used in the assessment of clinical question 5.1. Main characteristics of ATTR-ACT is provided in Appendix 6.2, Table 18.

5.1.2 Results per study

Results are based on the intention-to-treat (ITT) population and provided as pooled data analysis, combining the tafamidis 80 mg and tafamidis 20 mg groups into one pooled group (tafamidis) which was compared with the placebo group. This corresponds to the protocol-defined analyses forming the basis of the European Commission (EC) marketing authorization of 61 mg tafamidis for adult patients with ATTR-CM). (Available results for the individual doses are provided and discussed in Section 5.2.1.) An overview of the results for the ATTR-ACT trial is provided in Appendix 6.4, Table 19 and discussed further below.

Overall survival

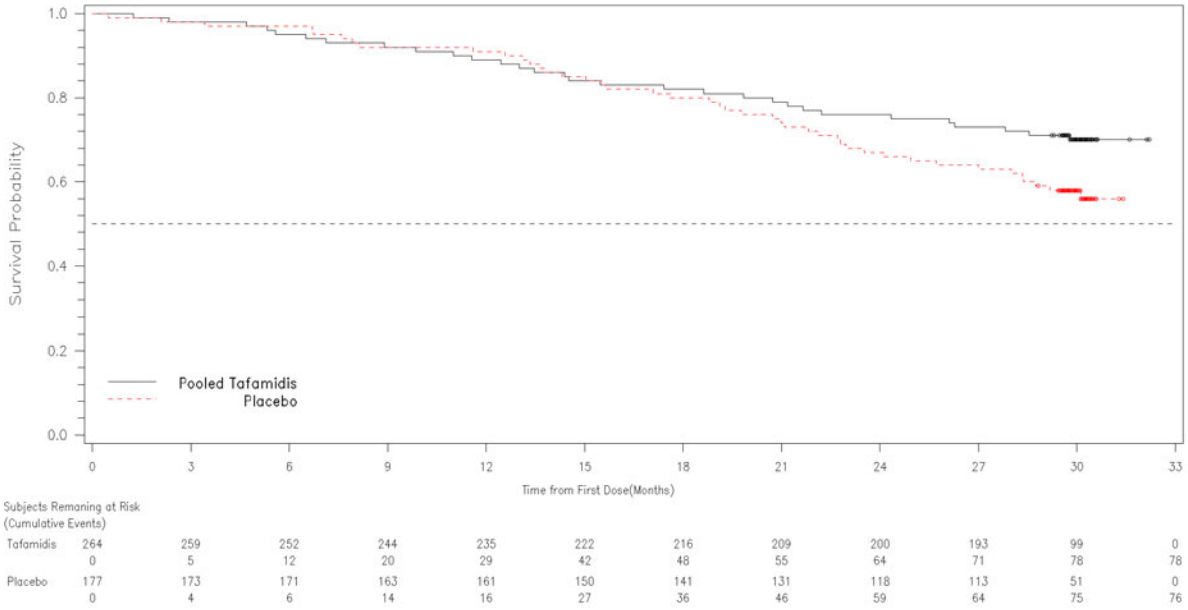
All-cause mortality was analysed using Cox proportional-hazards model with treatment and the stratification factors treated as covariates [2]. In ATTR-ACT, vital status was collected from all subjects, including all discontinuations. Therefore, mortality information for the 30 months duration of the study was available for 100% of the subjects. In the Kaplan-Meier plot and Cox regression model results, mortality information from subjects that discontinued was also included, i.e. if they died after discontinuation but prior to month 30, the death and the time of death were included. All discontinued subjects that were alive at month 30 were censored at month 30 similar to subjects who remained in the study and were alive at month 30.

All-cause mortality was lower in patients treated with tafamidis than with placebo (29.5% vs 42.9%; hazard ratio (HR) 0.70 [95% confidence interval (CI) 0.51; 0.96]), indicating a 30% reduction in the risk of death relative to the placebo group (p=0.0259) [2].

The corresponding survival rates at 30 months were 70.5% for the tafamidis group and 57.1% for the placebo group, giving an absolute treatment difference of 13.4% [95% CI 4.26; 22.53] in favour of tafamidis.

A Kaplan-Meier survival curve is shown below for illustrative purposes. The curves diverge after approximately 18 months of treatment (Figure 2).

FIGURE 2 KAPLAN-MEIER PLOT OF OVERALL SURVIVAL (ITT POPULATION)



Kaplan-Meier plot of OS in the ITT population of the ATTR-ACT trial (pooled tafamidis vs placebo). From CHMP assessment report [4].

To facilitate the evaluation of the efficacy of tafamidis in terms of overall survival, time from diagnosis to inclusion in the ATTR-ACT trial is outlined in Table 4. The difference between the time from diagnosis to inclusion in the ATTR-ACT trial was not statistically significant (p=0.1217).

TABLE 4 TIME FROM DIAGNOSIS TO INCLUSION (ITT POPULATION)

Duration since ATTR-CM diagnosis	Tafamidis (N=264)	Placebo (N=177)
Mean (SD)	1.023 (1.33)	1.233 (1.44)

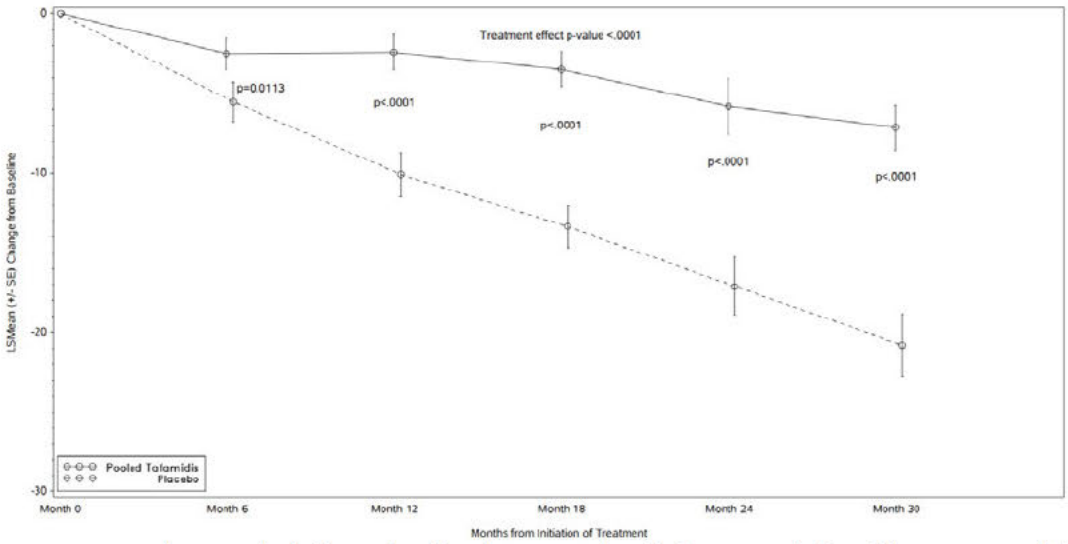
Time from diagnosis to inclusion in the ITT population of the ATTR-ACT trial. Abbreviations: ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR-CM: transthyretin amyloid cardiomyopathy; ITT: intention-to-treat; SD: standard error. From CHMP assessment report [4].

Quality of life, KCCQ-OS

Quality of life assessments included the Kansas City Cardiomyopathy Questionnaire (KCCQ), which is a validated 23-item, self-administered instrument used for quantifying physical limitations, symptoms, self-efficacy, social interference and quality of life in patients with heart failure. An overall summary score (KCCQ-OS score) can be derived from the physical limitation, symptom (frequency and severity), social limitation and quality of life domains. Scores are transformed to a range of 0-100, in which higher scores reflect better health status [5].

Treatment with tafamidis reduced the decline in KCCQ-OS score observed from baseline to 30 months as compared to placebo. The least squares (LS) mean change from baseline was -7.16 points in the tafamidis group vs -20.81 points in the placebo group, corresponding to a significant difference of 13.65 points [95% CI 9.48; 17.83], p<0.0001 in favour of tafamidis. The significant treatment difference was observed already after 6 months and remained significant through month 30 (Figure 3) [4].

FIGURE 3 KCCQ-OS SCORE CHANGE FROM BASELINE TO MONTH 30 (ITT POPULATION)



KCCQ-OS score (LS Mean (SE)) change from baseline to month 30 in the ITT population of the ATTR-ACT trial. From CHMP assessment report [4].

Cardiovascular-related hospitalizations

Cardiovascular-related hospitalization was defined as hospitalizations (a nonelective admission to an acute care setting for medical therapy resulting in at least a 24-hour stay) due to heart failure, arrhythmia, myocardial infarction, stroke, and other cardiovascular-related events. It was determined at each visit whether the patient had been hospitalized since the last visit, including the reason for hospitalization. In case of discontinuation, the subject's primary physician and/or cardiologist was contacted for this information [2, 6].

The frequency of cardiovascular-related hospitalizations was compared using a Poisson regression model, with treatment, *TTR* genotype, NYHA baseline class, treatment-by-*TTR* genotype interaction, and treatment-by-NYHA baseline class interaction terms as factors, with adjustment for duration of treatment [2].

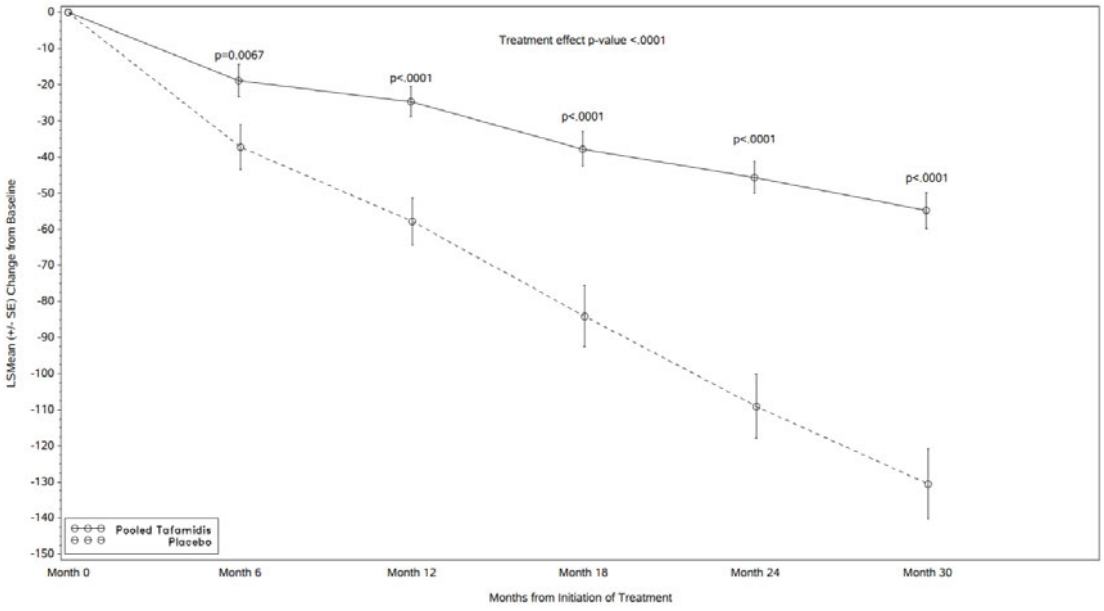
Hospitalizations related to cardiovascular events were 0.48 per patient per year in patients treated with tafamidis vs 0.70 per patient per year in the placebo group. This corresponds to a relative risk ratio of 0.68 [95% CI 0.56; 0.81], p<0.0001 [2].

Functional capacity, 6MWT

The 6-minute walk test (6MWT) is a submaximal exercise test involving the measurement of distance walked over a span of 6 minutes. It was performed indoors, along a flat, straight corridor with a hard surface. The length of the corridor should be at least 30 metres and marked every 3 metres [7].

Tafamidis reduced the decline from baseline to 30 months in distance walked during the 6MWT as compared to placebo. The LS mean change (standard error (SE)) from baseline was -54.87 metres (5.07) in the tafamidis group vs -130.55 metres (9.80) in the placebo group, corresponding to a significant difference of 75.68 metres (9.24) in favour of tafamidis (p<0.0001). The treatment difference was observed already after 6 months (p=0.0067) and remained significant trough month 30 (Figure 4) [4].

FIGURE 4 6MWT CHANGE IN DISTANCE WALKED FROM BASELINE TO MONTH 30 (ITT POPULATION)



Change from baseline in distance walked in the 6MWT (LS Means (SE)) in the ITT population of the ATTR-ACT trial. From CHMP assessment report [4].

Treatment-related TEAEs

All randomized patients who received at least one dose of study treatment were included in the safety analysis. Treatment-emergent adverse events (TEAEs), defined as those observed from the time of first dosing with study medication (at randomization) until the end of study participation (28 days after last dose of study drug) were included in the safety analysis [6].

Because all patients who were enrolled also fulfilled the three other criteria of the modified ITT analysis, this analysis was effectively also an ITT analysis [2].

One or more treatment-related TEAEs were observed in 42.8% of patients treated with tafamidis and in 50.8% of those treated with placebo [4].

Qualitative description of the safety profile of tafamidis

An overview of treatment-related TEAEs is presented in Table 5 and a short qualitative description is provided below. Further details on treatment-related TEAEs are also provided in Section 5.2.1.

TABLE 5 TREATMENT-RELATED TEAES (SAFETY POPULATION)

	Tafamidis (80 mg + 20 mg pooled)	Placebo
Subjects evaluable for adverse events	264	177
Subjects with ≥1 treatment-related TEAEs	113 (42.8%)	90 (50.8%)
Subjects with treatment-related serious TEAEs	5 (1.9%)	4 (2.3%)
Subjects with severe treatment-related TEAEs	8 (3.0%)	5 (2.8%)
Subjects discontinued treatment due to treatment-related TEAEs	1 (0.4%)	3 (1.7%)
Subjects with dose reduced due to treatment-related TEAEs	2 (0.8%)	3 (1.7%)
Subjects with temporary discontinuation due to treatment-related TEAEs	7 (2.7%)	7 (4.0%)

Treatment-related TEAEs in the safety population of the ATTR-ACT trial. Abbreviations: ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; TEAE: treatment-emergent adverse event. From CHMP assessment report [4].

Overall, safety data from the ATTR-ACT trial demonstrate that tafamidis once daily is well tolerated with a safety profile comparable to placebo when used for the treatment of adult patients with ATTR-CM. Most events were mild to moderate in severity. Furthermore, the proportion of patients with serious treatment-related TEAEs was lower in the tafamidis group as compared with placebo. Likewise, a smaller proportion of patients discontinued due to treatment-related TEAEs in the tafamidis group compared to placebo (Table 5) [4].

An overview of treatment-related TEAEs with an incidence of ≥5% is shown in Table 6. Both diarrhoea and urinary tract infection (UTI), adverse events previously reported in patients with ATTR-PN, were less common in patients who received tafamidis than in those who received placebo. The same was the case for nausea [4].

TABLE 6 SUMMARY OF TREATMENT-RELATED TEAES WITH ≥5% INCIDENCE (SAFETY POPULATION)

Treatment-related TEAEs, n (%)	Tafamidis pooled N=264	Placebo N=177
Gastrointestinal disorders	25 (9.5)	26 (14.7)
Diarrhoea	16 (6.1)	18 (10.2)
Nausea	11 (4.2)	10 (5.6)
Infections and infestations	9 (3.4)	8 (4.5)
Urinary tract infection	9 (3.4)	8 (4.5)

Summary of treatment-related TEAEs with ≥5% incidence (tafamidis pooled) in the safety population of the ATTR-ACT trial. Abbreviations: ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; TEAE: treatment-emergent adverse event. Based on data from CHMP assessment report [4].

Treatment-related serious TEAEs are shown in Table 7. Only few treatment-related serious TEAEs were registered in both the tafamidis group and the placebo group [8].

TABLE 7 SUMMARY OF TREATMENT-RELATED SERIOUS TEAES (SAFETY POPULATION)

Treatment-related serious TEAEs, n (%)	Tafamidis pooled N=264	Placebo N=177
Subjects with any serious TEAE	5 (1.9)	4 (2.3)
Cardiac disorders	0	2 (1.1)
Cardiac failure congestive	0	1 (0.6)
Ventricular fibrillation	0	1 (0.6)
Gastrointestinal disorders	2 (0.8)	0
Gastritis	1 (0.4)	0
Pancreatitis	1 (0.4)	0
General disorders and administration site conditions	0	1 (0.6)
Disease progression	0	1 (0.6)
Infections and infestations	1 (0.4)	0
Urinary tract infection	1 (0.4)	0
Investigations	1 (0.4)	0
Liver function test increased	1 (0.4)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (0.6)
Gall bladder adenocarcinoma	0	1 (0.6)
Nervous system disorders	0	1 (0.6)
Dizziness	0	1 (0.6)
Lethargy	0	1 (0.6)
Renal and urinary disorders	1 (0.4)	0
Acute kidney injury	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.6)
Dyspnoea	0	1 (0.6)

Summary of treatment-related serious TEAEs (tafamidis pooled and placebo) in the safety population of the ATTR-ACT trial. Abbreviations: ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; TEAE: treatment-emergent adverse event. The relevant Table 19 of the CHMP assessment report includes not only the intended serious TEAEs related to study treatment, but also serious TEAEs related to co-suspect concomitant medications [4]. A corrected table, including only serious TEAEs related to the study treatment has been conducted [8], and forms the basis of this table.

A summary of all-cause TEAEs is shown in Table 8. Many of the registered TEAEs were as common in patients treated with placebo as in those receiving tafamidis, or even more common in patients treated with placebo. Again, diarrhoea, nausea and UTI were less common in the tafamidis group as compared to the placebo group [2].

TABLE 8 SUMMARY OF ALL-CAUSALITY TEAES BY MEDDRA SYSTEM ORGAN CLASS AND PREFERRED TERM WITH ≥15% INCIDENCE (SAFETY POPULATION)

All-causality TEAEs, n (%)	Tafamidis pooled N=264	Placebo N=177
Blood and lymphatic system disorders	36 (13.6)	24 (13.6)
Cardiac disorders	185 (70.1)	124 (70.1)
Cardiac failure	76 (28.8)	60 (33.9)
Atrial fibrillation	51 (19.3)	33 (18.6)
Cardiac failure congestive	39 (14.8)	33 (18.6)
Congenital, familial and genetic disorders	3 (1.1)	2 (1.1)
Ear and labyrinth disorders	18 (6.8)	10 (5.6)
Endocrine disorders	22 (8.3)	16 (9.0)
Eye disorders	42 (15.9)	23 (13.0)
Gastrointestinal disorders	135 (51.1)	100 (56.5)
Diarrhoea	32 (12.1)	39 (22.0)
Constipation	40 (15.2)	30 (16.9)
Nausea	29 (11.0)	36 (20.3)
General disorders and administration site conditions	143 (54.2)	103 (58.2)
Fatigue	45 (17.0)	33 (18.6)
Oedema peripheral	47 (17.8)	31 (17.5)
Hepatobiliary disorders	25 (9.5)	15 (8.5)
Immune system disorders	6 (2.3)	3 (1.7)
Infections and infestations	165 (62.5)	109 (61.6)
Urinary tract infection	25 (9.5)	27 (15.3)
Injury, poisoning and procedural complications	107 (40.5)	66 (37.3)
Fall	70 (26.5)	41 (23.2)
Investigations	104 (39.4)	85 (48.0)
Metabolism and nutrition disorders	119 (45.1)	110 (62.1)
Fluid overload	32 (12.1)	29 (16.4)
Gout	28 (10.6)	29 (16.4)
Musculoskeletal and connective tissue disorders	129 (48.9)	85 (48.0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	29 (11.0)	13 (7.3)
Nervous system disorders	121 (45.8)	94 (53.1)
Dizziness	42 (15.9)	37 (20.9)
Product issues	7 (2.7)	5 (2.8)
Psychiatric disorders	64 (24.2)	42 (23.7)
Renal and urinary disorders	83 (31.4)	74 (41.8)
Acute kidney injury	29 (11.0)	29 (16.4)
Reproductive system and breast disorders	39 (14.8)	23 (13.0)
Respiratory, thoracic and mediastinal disorders	124 (47.0)	111 (62.7)
Dyspnoea	50 (18.9)	55 (31.1)
Pleural effusion	26 (9.8)	32 (18.1)
Cough	37 (14.0)	30 (16.9)
Skin and subcutaneous tissue disorders	76 (28.8)	51 (28.8)
Social circumstances	0	1 (0.6)
Vascular disorders	66 (25.0)	46 (26.0)

All-causality TEAEs by MedDRA system organ class and a 15% cut-off used for preferred terms. Abbreviations: TEAE: treatment-emergent adverse event. From Maurer et al. 2018 (suppl.) [2][a].

5.1.3 Comparative analyses

Comparative analyses for all outcomes of clinical question 1 are summarized in Appendix 6.5, Table 20 and provided below for each individual outcome. The analyses were conducted on the ITT population, and compared pooled tafamidis (80 mg and 20 mg) with placebo after 30 months of treatment.

ATTR-CM is a rare disease, and it should be taken into account that in cases where the patient population is relatively small, as in the ATTR-ACT trial, it must be expected that 95% CI will be broader and thus affect the categorisations. Acknowledging the very clear and consistent point estimates from this trial will be important.

Overall survival

Treatment with tafamidis was associated with a 30% reduction in all-cause mortality (HR 0.70 [95% CI 0.51; 0.96], p=0.0259), and an absolute difference with respect to overall survival of 13.4% ([95% CI 4.26; 22.53], p=0.0044) in favour of tafamidis after 30 months of treatment [2].

According to the hazard ratio and associated 95% CI and the criteria for categorization defined in the Danish Medicines Council (DMC) guideline, Table 1 [9], tafamidis provides an added clinical value of unknown size. Notably, it is very close to meeting the criteria for an added clinical value of moderate size.

Looking at the absolute treatment difference and associated 95% CI, a minimal clinically relevant difference (MCRD) of 5% as provided in the protocol [1], and the categories provided in the DMC guideline, Table 3 [9], tafamidis is placed in a category of no documented added clinical value. Again, however, tafamidis is very close to meeting the criteria for the best possible category for absolute outcomes, namely an added clinical value of unknown size, and had the MCRD been set 1% lower, the result would have met the criteria for this category. In the preliminary application, a MCRD of 2.5% was suggested based on guidance from Danish clinical specialists experienced with the treatment of ATTR-CM patients [Danish Advisory Board, March 2019]. They based this on the accepted difference used for a comparable cardiovascular disease, namely chronic heart failure.

Quality of life, KCCQ-OS

Treatment with tafamidis had a significant positive effect on quality of life, as evaluated by KCCQ-OS. After 30 months of treatment, tafamidis reduced the decline of KCCQ-OS score from baseline by 13.65 points [95% CI 9.48; 17.83] as compared to placebo (p<0.0001).

When comparing the absolute treatment difference and associated 95% CI, a MCRD of 5 points as provided in the protocol [1], and the categories provided in the DMC guideline, Table 3 [9], tafamidis is placed in the best possible category of added clinical value of unknown size. Notably, despite the limited size of the patient population, the lower limit of the 95% CI is well above the MCRD of 5 points.

Cardiovascular-related hospitalizations

Treatment with tafamidis reduced the relative risk of hospitalizations related to cardiovascular events by 32% as compared to placebo (relative risk (RR) 0.68 [95% CI 0.56; 0.81], p<0.0001). With an assumed control group rate of one cardiovascular-related hospitalization per patient per year, as provided in the protocol [1], this corresponds to an absolute reduction of 0.32 [0.19; 0.44] cardiovascular-related hospitalization per patient per year in patients treated with tafamidis, which again corresponds to a reduction of 32% [19%; 44%] relative to the stated control group rate.

According to the risk ratio and associated 95% CI and the categories provided in the DMC guideline, Table 1 [9], tafamidis provides moderate added clinical value. When comparing the absolute differences and associated 95% CI as calculated from the relative rate and the assumed control group rate, a MRCD of 15% as provided in the protocol [1], and the categories provided in the DMC guideline, Table 3 [9], tafamidis is placed in the category of added clinical value of unknown size.

Functional capacity, 6MWT

Treatment with tafamidis had a clear effect on functional capacity, as evaluated by the 6MWT. After 30 months of treatment, tafamidis reduced the decline from baseline by 75.68 metres [95% CI 57.56; 93.80] as compared to placebo ($p<0.0001$).

When combining the absolute treatment difference and associated 95% CI, a MCRD of 45 metres as provided in the protocol [1], and the categories provided in the DMC guideline, Table 3 [9], tafamidis is placed in the best possible category of added clinical value of unknown size. Again, despite the limited size of the patient population, the lower limit of the 95% CI is well above the MCRD of 45 metres.

Treatment-related TEAEs

It is noteworthy that a smaller proportion of patients treated with tafamidis experienced treatment-related TEAEs as compared to placebo. The relative risk of experiencing treatment-related TEAEs was 0.84 [95% CI 0.69; 1.03] in favour of tafamidis ($p=0.0989$). In absolute numbers, treatment with tafamidis resulted in a reduction in the proportion of patients experiencing treatment-related TEAEs of -8.04% [-17.52; 1.44] as compared to placebo ($p=0.0989$).

Regardless of whether the relative difference is compared to the DMC guideline, Table 1 [9] or the absolute difference is compared to the DMC guideline, Table 3 [9], treatment-related TEAEs for tafamidis are categorized as having no added clinical value, which, the nature of this outcome considered, must be interpreted as a positive categorization.

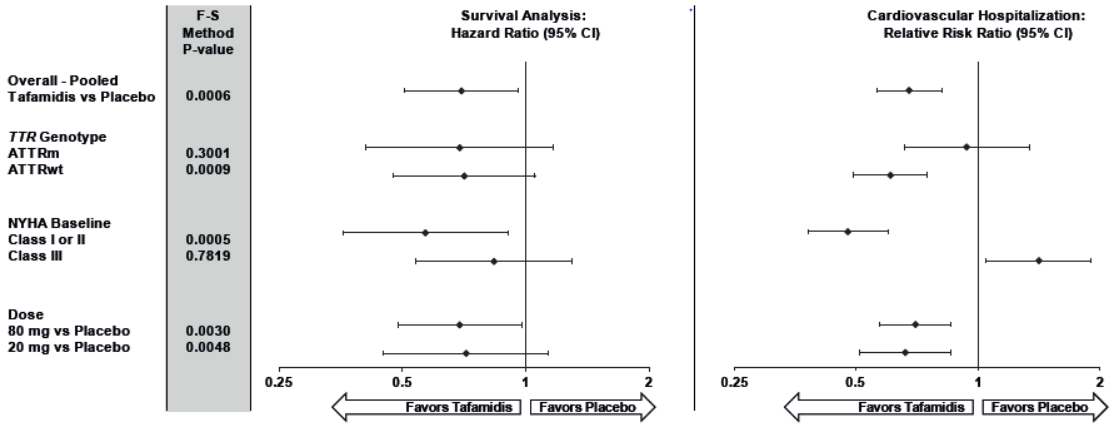
5.2 Other considerations

The design of the ATTR-ACT trial was discussed and agreed with authorities (FDA and EMA) before it was initiated. Primary and secondary endpoints of the ATTR-ACT trial did not include analyses by dose, *TTR* genotype, or disease stage, and the trial was thus not designed and powered to evaluate responses in these subgroups. Still, pre-specified exploratory analyses were conducted to understand the effect of the doses administered (80 mg and 20 mg), and subgroup analyses were conducted according to *TTR* genotype (wild-type vs variant) and disease stage (NYHA class I and II vs NYHA class III). The pooled data analyses combined with the results of the subgroup analyses have formed the base of the EC marketing authorization of tafamidis 61 mg for adult patients with ATTR-CM [4, 10].

For this application, pooled analyses form the basis of the response to clinical question 1, whereas results of subgroup analyses and considerations related to these will be provided in the following. Please note that a part of the subgroup data and analysis results have not been published and should be handled confidentially. Unpublished data (including figure and table text for confidential figures and tables) are written in [redacted]

An overview of hazard ratios for the survival analysis and relative risk ratios (RRR) for cardiovascular-related hospitalizations by *TTR* genotype, NYHA class at baseline and dose are summarized in Figure 5.

FIGURE 5 ALL-CAUSE MORTALITY HR AND FREQUENCY OF CV-RELATED HOSPITALIZATIONS RRR BY SUBGROUP



All-Cause mortality hazard ratio and frequency of cardiovascular-related hospitalization relative risk ratio by subgroup in the ITT population of the ATTR-ACT trial. From CHMP assessment report [4].

5.2.1 Dose - 80 mg vs 20 mg

The approved dose for Vyndaqel® (tafamidis) as a treatment for ATTR-CM is the once-daily 61 mg oral capsule. The tafamidis 61 mg capsule corresponds to an 80 mg tafamidis meglumine dose (4 x 20 mg capsules), which was studied in the ATTR-ACT trial, and was developed for patient convenience to enable a single capsule for daily administration. The 20 mg dose of tafamidis has been used previously in ATTR-PN clinical trials [11-13]. Although this dose was shown to stabilize the wild-type and Val122Ile TTR tetramer in most patients after 12 months of treatment [14], a greater range of tafamidis exposures has been used to assess TTR stabilization in healthy volunteers and in ATTR-CM subjects [15]. Based on the new data, it was assumed for the calculations that a 20 mg once daily tafamidis dose at steady state produces a mean molar ratio in the range of 1.2 to 3.2 from mean minimum concentration at steady state (Cmin,ss) to maximum

concentration at steady state (Cmax,ss), which is below the plateau region, whereas mean Cmin,ss to Cmax,ss following tafamidis doses of 80 mg were expected to produce tafamidis:TTR molar ratios of 3.5 to 9.6, which are approaching or on the plateau region of TTR % stabilization [2][b]. The exploration of this dose was further supported by the 2:1:2 randomization to placebo:20 mg:80 mg.

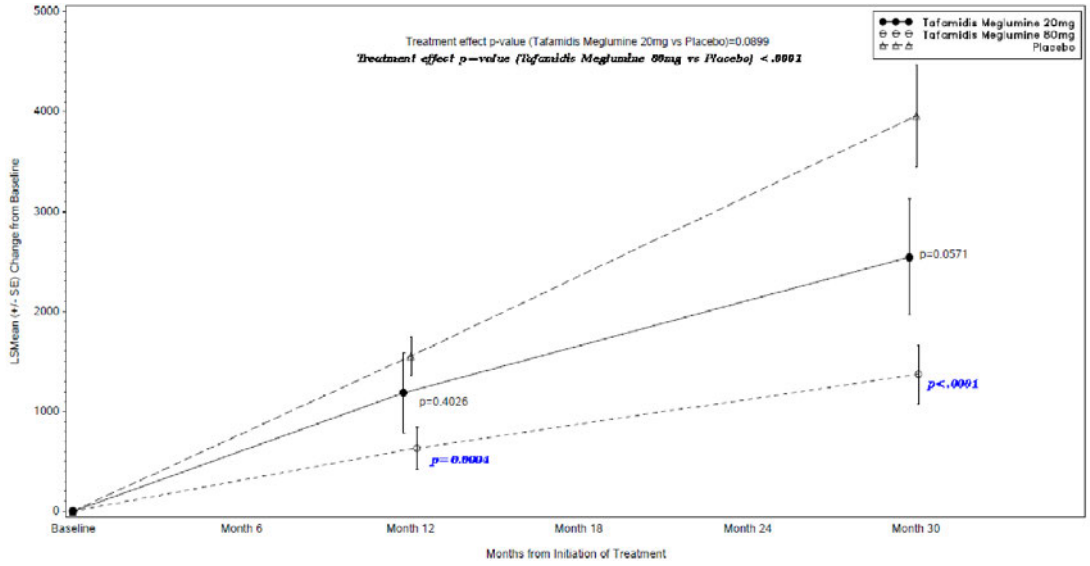
The inclusion of an 80 mg dose in the ATTR-ACT trial, which has been shown to result in near maximal TTR stabilization, permitted the exploration of a higher dose to assess efficacy and safety of adequately separated doses [4, 16].

TTR stabilization was included as an exploratory endpoint in the ATTR-ACT trial. After one month of treatment, a significantly greater proportion of patients treated with tafamidis 80 mg and 20 mg (87.8% and 82.7%, respectively) demonstrated TTR stabilization than was observed for patients in the placebo group (3.5%) (p<0.0001) [4].

In addition to TTR stabilization, measurement of the cardiac biomarker N-terminal pro B-type natriuretic peptide (NT-proBNP) was an exploratory endpoint in the ATTR-ACT trial. NT-proBNP has prognostic value for ATTR-CM patients with heart failure or left ventricular dysfunction and has been shown to be a significant predictor for mortality in an exposure-efficacy longitudinal analysis [4].

Subgroup analyses revealed that the increase in NT-proBNP from baseline to month 30 with placebo was significantly reduced with tafamidis 80 mg (LS mean (SE) (–2587.54 pg/mL (570.25); p<0.0001), while the reduction with 20 mg was not significant (–1417.02 pg/mL (743.38); p=0.0571). For 80 mg, the difference was significant already after 12 months. A significantly lower increase in NT-proBNP was also observed with tafamidis 80 mg compared with 20 mg (–1170.51 pg/mL (587.31); p=0.0468) at month 30 (Figure 6) [4].

FIGURE 6 NT-PROBNP CONCENTRATION CHANGE FROM BASELINE TO MONTH 30 BY DOSE (ITT POPULATION)



NT-proBNP concentration LS Means (SE) change from baseline to month 30 by dose (80 mg tafamidis and 20 mg tafamidis) in the ITT population of the ATTR-AT trial. P values in blue refer to tafamidis 80 mg. From CHMP assessment report [4].

Accordingly, the reason for choosing 80 mg for the treatment of patients with ATTR-CM relates to the higher efficacy of this dose in terms of NT-proBNP. Also, due to the higher number of patients in the 80 mg tafamidis dose group, the largest evidence base is available for this group. That said, as appears from Figure 5 (lower rows) and the results of the analyses shown below, data were comparable for 80 mg and 20 mg tafamidis. This goes for all endpoints requested by the DMC for this application, namely all-cause mortality, KCCQ-OS, cardiovascular-related hospitalizations, 6MWT and, not the least, treatment-related TEAEs.

Therefore, considering also that there are no clear biomarker target levels, signs, or symptoms to steer dosing and the therapy has shown benefits in terms of morbidity and mortality, it was agreed by EMA that the 80 mg dose (bioequivalent to the 61 mg dose approved for ATTR-CM) is an appropriate dose in this particular context of this severe and evolutive disease [4].

In the following section, data and analyses for each dose are provided [4]. Of notice, all the analyses comparing 80 mg tafamidis with placebo provided below lead to the same clinical value categorizations, as the analyses comparing the pooled data for tafamidis 80 mg and 20 mg to placebo.

Overall survival

Hazard ratios for all-cause mortality by dose are shown in Figure 5. [redacted]

Quality of life, KCCQ-OS

A significant treatment effect in terms of KCCQ-OS favouring the 80 mg tafamidis dose was observed as early as month 6 (p=0.0273). For the tafamidis 20 mg dose a significant treatment effect favouring tafamidis was observed at month 12 (p=0.0005). Both tafamidis 80 mg and 20 mg significantly reduced the decline in KCCQ-OS score from baseline to month 30 compared with placebo [4].

[redacted]

[redacted]

Cardiovascular-related hospitalizations

Relative risk ratios for hospitalizations related to cardiovascular events by dose are shown in Figure 5.

[redacted]

Functional capacity, 6MWT

Analyses demonstrated a significant treatment effect favouring tafamidis 80 mg and tafamidis 20 mg vs placebo in the change from baseline to month 30 in the distance walked during the 6MWT [4].

[redacted] The significant difference was observed as early as at 6 months (p=0.0240 for 80 mg tafamidis and p=0.0339 for 20 mg tafamidis) [4].

Treatment-related TEAEs

As shown in Table 9, tafamidis was similarly well tolerated across both dose groups, with a lower proportion of patients treated with 80 mg tafamidis or 20 mg tafamidis experiencing treatment-related TEAEs as compared to placebo.

TABLE 9 TREATMENT-RELATED TEAES BY DOSE AND POOLED (SAFETY POPULATION)

	Tafamidis 20 mg	Tafamidis 80 mg	Tafamidis pooled	Placebo
Subjects evaluable for treatment-related TEAEs	88	176	264	177
Subjects with ≥1 treatment-related TEAEs	34 (38.6%)	79 (44.9%)	113 (42.8%)	90 (50.8%)
Subjects with treatment-related serious TEAEs	2 (2.3%)	3 (1.7%)	5 (1.9%)	4 (2.3%)
Subjects with severe treatment-related TEAEs	3 (3.4%)	5 (2.8%)	8 (3.0%)	5 (2.8%)
Subjects discontinued treatment due to treatment-related TEAEs	0	1 (0.6%)	1 (0.4%)	3 (1.7%)
Subjects with dose reduced due to treatment-related TEAEs	0	2 (1.1%)	2 (0.8%)	3 (1.7%)
Subjects with temporary discontinuation due to treatment-related TEAEs	2 (2.3%)	5 (2.8%)	7 (2.7%)	7 (4.0%)

Treatment-related TEAEs in the safety population of the ATTR-ACT trial – presented by treatment dose. Abbreviations: ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; TEAE: treatment-emergent adverse event. From CHMP assessment report [4].

Treatment-related TEAEs such as diarrhoea and nausea were reported in a higher proportion of patients treated with tafamidis 80 mg compared to tafamidis 20 mg: 8.0% vs 2.3% for diarrhoea and 5.7% vs 1.1% for nausea. In contrast, UTI were more frequently reported with tafamidis 20 mg than with tafamidis 80 mg (5.7% vs 2.3%). Notably, both diarrhoea and UTI were less common in patients treated with tafamidis 80 mg than in patients receiving placebo. Nausea was reported similarly in patients treated with tafamidis 80 mg and in the placebo group (Table 10) [4].

TABLE 10 SUMMARY OF TREATMENT-RELATED TEAES WITH ≥5% INCIDENCE BY DOSE (SAFETY POPULATION)

Treatment-related TEAEs, n (%)	Tafamidis 20 mg N=88	Tafamidis 80 mg N=176	Placebo N=177
Gastrointestinal disorders	3 (3.4%)	22 (12.5%)	26 (14.7%)
Diarrhoea	2 (2.3%)	14 (8.0%)	18 (10.2%)
Nausea	1 (1.1%)	10 (5.7%)	10 (5.6%)
Infections and infestations	5 (5.7%)	4 (2.3%)	8 (4.5%)
Urinary tract infection	5 (5.7%)	4 (2.3%)	8 (4.5%)

Summary of treatment-related TEAEs with ≥5% incidence in the safety population of the ATTR-ACT trial – presented by dose. Abbreviations: ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; TEAE: treatment-emergent adverse event. From CHMP assessment report [4].

[redacted] Treatment-related serious TEAEs (Table 11) were very few for both tafamidis doses and for placebo [8].

TABLE 11 TREATMENT-RELATED SERIOUS TEAES BY DOSE (SAFETY POPULATION)

Treatment-related serious TEAEs, n (%)	Tafamidis 20 mg N=88	Tafamidis 80 mg N=176	Placebo N=177
Subjects with any serious TEAE	2 (2.3)	3 (1.7)	4 (2.3)
Cardiac disorders	0	0	2 (1.1)
Cardiac failure congestive	0	0	1 (0.6)
Ventricular fibrillation	0	0	1 (0.6)
Gastrointestinal disorders	1 (1.1)	1 (0.6)	0
Gastritis	1 (1.1)	0	0
Pancreatitis	0	1 (0.6)	0
General disorders and administration site conditions	0	0	1 (0.6)
Disease progression	0	0	1 (0.6)
Infections and infestations	0	1 (0.6)	0
Urinary tract infection	0	1 (0.6)	0
Investigations	0	1 (0.6)	0
Liver function test increased	0	1 (0.6)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	1 (0.6)
Gall bladder adenocarcinoma	0	0	1 (0.6)
Nervous system disorders	0	0	1 (0.6)
Dizziness	0	0	1 (0.6)
Lethargy	0	0	1 (0.6)
Renal and urinary disorders	1 (1.1)	0	0
Acute kidney injury	1 (1.1)	0	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.6)
Dyspnoea	0	0	1 (0.6)

Summary of treatment-related serious TEAEs in the safety population of the ATTR-ACT trial. Abbreviations: ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; TEAE: treatment-emergent adverse event. The relevant Table 19 of the CHMP assessment report includes not only the intended serious TEAEs related to study treatment, but also serious TEAEs related to co-suspect concomitant medications [4]. A corrected table, including only serious TEAEs related to the study treatment has been conducted [8], and forms the basis of this table.

Conclusion – 80 mg vs 20 mg

It is evident from the analyses of the endpoints requested by the DMC that the efficacy and safety of tafamidis is comparable for the 80 mg and 20 mg doses.

NT-proBNP (shown to be a significant predictor for mortality) data supports the choice of the 80 mg dose. A significantly lower increase in NT-proBNP was observed with tafamidis 80 mg compared with 20 mg (–1170.51 pg/mL (587.31), p=0.0468) at month 30 [4]. Thus, NT-proBNP data indicate that patients treated with the 80 mg dose might have better long-term prognosis, and taking into account that the safety profile is very benign for both doses - with no overall differences in AEs reported between the two doses - the benefit-risk seems to be in favour of recommending treatment with the 80 mg dose for patients with ATTR-CM.

5.2.2 *TTR* genotype – variant vs wild-type

ATTR-CM can be inherited as an autosomal dominant trait caused by pathogenic mutations in the gene *TTR* with deposition of variant TTR amyloid protein (ATTRm) or it can appear as a sporadic, non-genetic disease due to misaggregation and deposition of wild-type TTR amyloid protein (ATTRwt). Wild-type ATTR-CM was previously called senile systemic amyloidosis. In the ATTR-ACT trial, approximately one in four patients had the ATTRm genotype (Table 12) [2]. [redacted]

TABLE 12 DISTRIBUTION OF PATIENTS WITH ATTRm AND ATTRwt (ITT POPULATION)

	Tafamidis (N=264)	Placebo (N=177)
***TTR* genotype - no (%)**		
ATTRm	63 (23.9%)	43 (24.3%)
ATTRwt	201 (76.1%)	134 (75.7%)

Distribution of patients by genotype in the ITT population of the ATTR-ACT trial.
Abbreviations: ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTRm: variant transthyretin amyloid (hereditary ATTR-CM); ATTRwt: wild-type transthyretin amyloid (wild-type ATTR-CM); ITT: intention-to-treat; TTR: transthyretin. From Maurer et al. 2018 [2].

[redacted]

Quality of life, KCCQ-OS

Significant treatment effects favouring tafamidis were first observed after 12 months of treatment (p=0.0034) for ATTRm patients and after 6 months of treatment in ATTRwt patients (p=0.0412) [4].

[redacted]

Cardiovascular-related hospitalizations

Relative risk ratios for hospitalizations related to cardiovascular events by *TTR* genotype are shown in Figure 5.

[redacted]

Functional capacity, 6MWT

Significant treatment effects favouring tafamidis were first observed after 24 months of treatment for patients with ATTRm (p=0.0172) and after 6 months of treatment for patients with ATTRwt (p=0.0170) [4].

[redacted]

Treatment-related TEAEs

The impact of age, race, sex, *TTR* genotype, baseline NYHA classification, and geographic region on the incidence of TEAEs (all-causality and treatment-related), serious adverse events (AEs), AEs leading to discontinuation, and deaths was evaluated [4]. However, no differences in risk of AE s or TEAEs according to *TTR* genotype was reported.

Conclusion – ATTRm vs ATTRwt

According to the baseline characteristics, the baseline condition of patients with the ATTRm genotype is slightly worse than for patients with the ATTRwt genotype, despite their somewhat lower age. A higher proportion of ATTRm patients were in NYHA class III, which is reflected in their cardio-related parameters. Still, the efficacy of tafamidis is evident in both groups for parameters like all-cause mortality, KCCQ-OS and 6MWT. The groups differ only for hospitalizations, in that the relative risk ratio for patients with ATTRm is markedly higher for cardiovascular-related hospitalizations as compared to placebo. This is most likely closely related to their higher NYHA class, as also discussed below.

5.2.3 Stage of disease - NYHA class I and II vs class III

In the ATTR-ACT trial, NYHA classification was used to classify the extent of heart failure. Patients were classified based on their limitations during physical activity (e.g. varying degrees of shortness of breath and/or angina pain) [21]. Classes were as follows: No symptoms of heart failure (NYHA class I), mild limitations (NYHA Class II), or marked limitation (NYHA Class III). Patients with NYHA class IV (severe limitations) were excluded from the trial. The distribution of patients according to NYHA classes is summarized in Table 14.

TABLE 14 DISTRIBUTION OF PATIENTS WITH BASELINE NYHA CLASS I, II AND III (ITT POPULATION)

	Tafamidis (N=264)	Placebo (N=177)
NYHA class - no (%)		
Class I	24 (9.1%)	13 (7.3%)
Class II	162 (61.4)	101 (57.1)
Class III	78 (29.5%)	63 (35.6%)

Distribution of patients by NYHA class in the ITT population of the ATTR-ACT trial.
Abbreviations: ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ITT: intention-to-treat; NYHA: New York Heart Association. From Maurer et al. 2018 [2].

According to the protocol for assessment of tafamidis [1], a stratification according to National Amyloidose Center (NAC) disease stage, combining levels of the two biomarkers NT-proBNP and estimated glomerular filtration rate (eGFR), was also requested. NAC disease staging is a recently introduced prognostic staging system applicable to patients with both wild-type and hereditary ATTR-CM based on data published in 2018 [22], i.e. 5 years after initiation of the ATTR-ACT trial. For this reason, patients were not stratified according to NAC stage, no subgroup analyses were planned according to this disease staging system, and no subgroup analyses according to NAC disease stage have been conducted. The recognized NYHA classification was used to stratify according to disease stage.

All-cause mortality

Hazard ratios for all-cause mortality by NYHA class are shown in Figure 5. [redacted]

Quality of life, KCCQ-OS

A significant treatment effect favouring tafamidis in NYHA class I and II combined was first observed after 6 months of treatment (p=0.0100) and remained significant through month 30 [4]. [redacted] Significant treatment effects were observed for patients with NYHA class III at 18 months (p=0.0264) [4]. [redacted]

[redacted]

Cardiovascular-related hospitalizations

Relative risk ratios for hospitalizations related to cardiovascular events are shown in Figure 5. [redacted]

The observed higher rate of cardiovascular-related hospitalizations for patients in NYHA class III as compared to placebo might be attributable to a longer survival during a more severe period of disease, underscoring the importance of early diagnosis and treatment of this fatal, progressive disease. Given the progressive nature of the disease and the mechanism through which tafamidis reduces amyloidogenesis - by specifically stabilizing transthyretin tetramers - the drug is expected to have greater benefit when administered early in the disease course [2].

Functional capacity, 6MWT

Significant treatment effects favouring tafamidis were first observed after 6 months of tafamidis treatment (p=0.0013) for NYHA class I and II combined [4]. [redacted] A significant treatment effect was observed only at month 24 (p=0.0096) for patients with NYHA class III [4].

Treatment-related TEAEs

No differences were reported for treatment-related TEAEs.

Conclusion - NYHA class I and II vs NYHA class III

The subgroup analyses by disease stage indicate that patients in NYHA class I and II benefit more from tafamidis as compared to patients in NYHA class III. Still, also for patients with a very progressed stage of disease (NYHA class III), treatment with tafamidis results in improvements, both in terms of a longer survival and an improved quality of life and functional capacity. Most of all, the higher efficacy of tafamidis in earlier disease stages emphasize the disease-modifying effect of tafamidis and the importance of starting treatment as early as possible.

6 Appendices

6.1 Literature search

TABLE 15 PUBMED SEARCH

Search	Add to builder	Query	Items found	Time
#12	Add	Search **(#10 AND #11)**	38	07:10:48
#11	Add	Search **((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals [mh] NOT humans [mh]))**	4101910	07:10:34
#10	Add	Search **(#6 AND #9)**	83	07:10:01
#9	Add	Search **(#7 OR #8)**	186	07:09:51
#8	Add	Search **(tafamidis[tiab] OR vyndaqel*[tiab])**	171	07:09:43
#7	Add	Search **tafamidis[nm]**	89	07:09:32
#6	Add	Search **(#4 AND #5)**	1041	07:09:13
#5	Add	Search **(Cardiomyopathies[mh] OR cardiomyopathy[tiab] OR cardiomyopathies[tiab] OR cardiac[tiab])**	667819	07:09:03
#4	Add	Search **(#1 OR #2 OR #3)**	3160	07:08:36
#3	Add	Search **(transthyretin[tiab] AND (amyloid[tiab] OR amyloidosis[tiab]))**	2751	07:08:22
#2	Add	Search **(ATTR[tiab] OR ATTRwt[tiab] OR hATTR[tiab] OR ATTR-ACT[tiab] OR ATTRCM[tiab] OR TTR-CM[tiab])**	942	07:08:11
#1	Add	Search **Amyloidosis, Hereditary, Transthyretin-Related[nm]**	570	07:07:37

TABLE 16 CENTRAL SEARCH

−	+	#1	(tafamidis OR vyndaqel*):ti,ab,kw	Limits	82
−	+	#2	("conference abstract" OR review):pt	Limits	169664
−	+	#3	NCT*:au or abstract:ti	Limits	194121
−	+	#4	("clinicaltrials.gov" OR trialsearch):so	Limits	323244
−	+	#5	#2 or #3 or #4	Limits	500674
−	+	#6	#1 NOT #5	Limits	29
−	+	#7	Type a search term or use the S or MeSH buttons to compose	S ▾ MeSH ▾	Limits	N/A

TABLE 17 INCLUSION AND EXCLUSION CRITERIA FOR THE LITERATURE SEARCH

Inclusion criteria	Population: Adult patients with transthyretin amyloid cardiomyopathy Intervention: Tafamidis Comparator: Placebo Outcomes: OS, hospitalizations, KCCQ-OS, 6MWT, adverse events Study design: randomized clinical trial Language restrictions: None Other search limits or restrictions applied: None
Exclusion criteria	Population: Adult patients with transthyretin amyloidosis with polyneuropathy Study design: Single-arm trials

6.2 Main characteristics of included studies

TABLE 18 MAIN STUDY CHARACTERISTICS

Trial name (official title from clinicaltrials.gov)	Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy (ATTR-ACT)
NCT number	NCT01994889
Objective	To determine the efficacy, safety and tolerability of tafamidis meglumine in comparison to placebo in patients with hereditary and wild-type transthyretin amyloid cardiomyopathy.
Publications – title, author, journal, year	• Design and Rationale of the Phase 3 ATTR-ACT Clinical Trial (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) Maurer et al. Circ Heart Fail. 2017;10(6). pii: e003815. [6] • Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. Maurer et al. N Engl J Med. 2018;379(11):1007-1016. [2]
Study type and design	Phase 3, international, multicentre, placebo-controlled, double-blind, parallel-group design, randomized clinical trial. Patients were randomly assigned to receive 80 mg of tafamidis meglumine, 20 mg of tafamidis meglumine, or matching placebo once daily in a ratio of 2:1:2. Stratification was conducted according to *TTR* genotype (variant or wild-type) and baseline disease severity determined by New York Heart Association class (NYHA class I and II combined or NYHA class III). Enrolment started December 2013 and study was completed February 2018.
Follow-up time	The trial duration was 30 months (completed). On completion patients were offered enrolment in an extension study (Protocol B3461045, NCT02791230), the extension study is ongoing.
Population (inclusion and exclusion criteria)	**Inclusion criteria** 1. Men and women aged 18-90 years 2. Medical history of Heart Failure (HF) with at least 1 prior hospitalization for HF or clinical evidence of HF (without hospitalization) manifested by signs or symptoms of volume overload or elevated intracardiac pressures (e.g., elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, peripheral oedema) that required/requires treatment with a diuretic for improvement 3. Documented TTR amyloid cardiomyopathy in accordance with institutional site standard of care, which is defined as: a. Hereditary TTR amyloid cardiomyopathy defined by all of the following: • Presence of a variant *TTR* genotype associated with cardiomyopathy phenotype (e.g. a history of congestive heart failure), 1) *TTR* genotyping is required at screening unless documentation of a prior determination of a *TTR* genotype is produced, 2) Subjects with a confirmed diagnosis of hereditary (variant genotype) ATTR-CM with concurrent monoclonal gammopathy of undetermined significance (MGUS) based on serum or urine light chain determinations, should be tested in the same manner as in the case of equivocal immunohistochemistry for subjects with wild-type ATTR-CM below, • Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm

	• Presence of amyloid deposits in biopsy tissue, such as fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac (amyloid demonstrated per appropriate stain such as Congo red or Alcian blue stain). b. Wild-type TTR amyloid cardiomyopathy defined by all of the following: • Absence of variant genotype • Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm • Presence of amyloid deposits in biopsy tissue, such as fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac (amyloid demonstrated per appropriate stain such as Congo red or Alcian blue stain). • TTR precursor protein identification by immunohistochemistry, scintigraphy or mass spectrometry 4. NT-proBNP concentration ≥ 600 pg/ml 5. 6-minute walk test (6MWT) distance > 100 m **Exclusion criteria** 1. Presence of primary (light chain) amyloidosis 2. Prior liver or heart transplantation, or implanted cardiac mechanical assist device 3. New York Heart Association (NYHA) classification IV 4. Modified body mass index (mBMI) < 600 kg/m^2·g/L 5. Taking or have previously taken tafamidis 6. Requiring treatment with calcium channel blockers or digitalis 7. Renal failure requiring dialysis and/or have an estimated glomerular filtration rate (eGRF) of < 25 mL/min/1.73 m^2 8. History of sustained ventricular tachycardia or aborted ventricular fibrillation or with a history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but will not be placed 9. Heart failure that in the opinion of the investigator is based on ischemic heart disease, or uncorrected valvular disease and not primarily due to transthyretin amyloid cardiomyopathy 10. Drugs not allowed according to protocol *Primary criteria are given. Detailed inclusion and exclusion criteria can be found in Protocol Amendment 3, 24 May 2016, (page 36-39) available in New England Journal of Medicine as supplementary material to the ATTR-ACT trial data publication [2][b].*
Intervention	Tafamidis meglumine 80 mg or 20 mg, both administered in soft gel capsules once daily for 30 months. 264 patients were randomized to the pooled group that received tafamidis meglumine treatment (80 mg n=176; 20 mg n=88). 177 patients were randomized to the placebo group that received matching placebo capsules.

Baseline characteristics	Demographic and clinical characteristics of the patients at baseline*

	Tafamidis (n = 264)	Placebo (n = 177)
Men, n (%)	241 (91.3)	157 (88.7)
Age, yr		
Mean ± SD	74.5 ± 7.2	74.1 ± 6.7
Median (range)	75 (46-88)	74 (51-89)
Race/ethnicity, n (%)		
White	211 (79.9)	146 (82.5)
Black	37 (14.0)	26 (14.7)
Asian	13 (4.9)	5 (2.8)
Other	3 (1.1)	0
***TTR* genotype**, n (%)		
ATTRm	63 (23.9)	43 (24.3)
ATTRwt	201 (76.1)	134 (75.7)
Blood pressure, mmHg		
Supine		
Systolic	115.4 ± 15.4	115.1 ± 15.7
Diastolic	70.4 ± 10.3	70.2 ± 9.5
Standing		
Systolic	115.5 ± 15.5	115.9 ± 15.9
Diastolic	70.6 ± 9.9	71.0 ± 10.3
Heart rate, mean – beats per minute		
Supine	70.7 ± 12.3	69.9 ± 11.7
Standing	72.9 ± 12.9	73.8 ± 12.2
NYHA class, no (%)		
Class I	24 (9.1)	13 (7.3)
Class II	162 (61.4)	101 (57.1)
Class III	78 (29.5)	63 (35.6)
Modified BMI ‡	1058.8 ± 173.8	1066.4 ± 194.4
KCCQ-OS score, points		
Mean ± SD	67.3 ± 21.4	65.9 ± 21.7
6MWT distance, metres		
Mean ± SD	350.6 ± 121.3	353.3 ± 126.0
NT-proBNP level, pg/ml		
Median	2995.9	3161.0
Interquartile range	1751.5 – 4861.5	1864.4 – 4825.0

*Plus-minus values are means ± SD. Percentages may not total 100 because of rounding.
Abbreviations: 6MWT: 6-minute walk test; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire - Overall Summary; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association.
‡ The modified body-mass index (mBMI) is calculated as the serum albumin level in grams pr. litre multiplied by the conventional BMI (the weight in kilograms divided by the square of the height in metres).

Primary and secondary endpoints	**Primary endpoint** Hierarchical combination of 1. all-cause mortality and 2. frequency of cardiovascular-related hospitalizations (defined as a nonelective admission to an acute care setting for medical therapy for cardiovascular-related morbidity resulting in at least a 24-hour stay) **Key secondary endpoints** 1. Change from baseline to month 30 in distance walked on the 6-minute walk test (6MWT), a measure of functional capacity 2. Change from baseline to month 30 in the Kansas City Cardiomyopathy Questionnaire - Overall Summary (KCCQ-OS) score, which assesses quality of life **Secondary endpoints** 1. All-cause mortality 2. Frequency of cardiovascular-related hospitalization 3. Cardiovascular-related mortality (not published yet) 4. TTR stabilization at month 1
Method of analysis	The patients in the tafamidis 80 mg and tafamidis 20 mg groups were pooled to form a single pooled tafamidis group which was compared to placebo in all analyses. The primary analysis hierarchically assessed all-cause mortality, followed by frequency of cardiovascular-related hospitalizations with the use of the Finkelstein– Schoenfeld method [23], which is based on the principle that each patient in the clinical trial is compared with every other patient within each stratum in a pairwise manner. This method gives a higher importance to all-cause mortality. The Finkelstein-Schoenfeld method was discussed and agreed with authorities before initiation of the study. For subjects who discontinued before month 30, a vital status follow-up was conducted at month 30 to obtain their mortality status for use in the analysis. Heart transplantation, combined heart and liver transplantation, and implantation of a cardiac mechanical assist device were treated as death for the purposes of this analysis. All cause-mortality was analysed with the use of Cox proportional-hazards model, with treatment and the stratification factors treated as covariates. Patients who discontinued for transplantation (i.e. heart transplantation and combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device, were handled in the same manner as death. Frequency of cardiovascular-related hospitalizations were compared with the use of a Poisson regression model, with treatment, *TTR* genotype, (variant and wild-type), NYHA baseline class (NYHA class I and II combined vs NYHA class III), treatment-by-*TTR* genotype interaction, and treatment-by-NYHA baseline class interaction terms as factors, with adjustment for treatment duration. The key secondary endpoints were assessed with the use of a mixed-effect model, repeated-measure approach and analysis of covariance, with an unstructured covariance matrix. Centre and patient-within-centre were treated as random effects, and treatment, visit, *TTR* genotype (ATTRm vs ATTRwt), and visit-by-treatment interaction were treated as fixed effects, with the baseline value as covariate. A prespecified hierarchical testing order (6MWT, followed by the KCCQ-OS) provided multiplicity protection against type 1 error. The remaining secondary and exploratory analyses and endpoints were not adjusted for multiplicity. All analyses were pre-specified in the protocol.

Subgroup analyses	Pre-specified exploratory analyses were conducted to understand the effect of the two doses administered, as well as to explore efficacy within the subgroups based on genotype and NYHA classification.

6.3 Statistical considerations

The statistical principles used for this application followed the specifications provided in the protocol [1].

The endpoints requested by the protocol were of four types:

- binary (fractions)
- continuous outcomes
- survival data (overall mortality)
- event rates (cardiovascular-related hospitalizations)

The two treatments involved, tafamidis versus placebo, were reported using a single two-armed phase 3 trial (ATTR-ACT) comparing the treatments directly.

In general some simple pre-processing imputation was done on published data in cases where no doubt existed as to the relevant procedure: missing standard errors were derived from reported standard deviations and the number of patients, and missing proportions (including 95% CI) were derived from the number of events and patients.

For fraction outcomes, a missing risk-ratio could then be derived in every case, including a confidence interval. The incidences and 95% confidence intervals were found as exact Clopper-Pearson intervals, whereas risk differences were derived directly as Newcombe intervals

The calculations were performed on the log-transformed scale for fractions - and then transformed back in order to present estimates and confidence intervals as ratios.

For the event rate data, a standard error could be derived from published results, by treatment arm. Based on this, the rate difference with a 95% CI and an approximative test based on the normal distribution could be obtained.

Mean time-from-diagnosis-to-inclusion in the ATTR-ACT trial was obtained directly from the EPAR, by treatment arm. From this, the time difference with a 95% CI and an approximative test based on the normal distribution could again be derived.

6.4 Results per study

TABLE 19 RESULTS OF ATTR-ACT

Trial name:	ATTR-ACT: Safety and efficacy of tafamidis in patients with transthyretin cardiomyopathy									
NCT number:	NCT01994889									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/ Odds/ Risk ratio	95% CI	*P* value		
Mortality, *no of events (%)*	Tafamidis 80 mg + 20 mg pooled	264	29.5% (24.0; 35.0)				HR: 0.70	0.51–0.96	0.0259	Vital status was available and confirmed for all patients at 30 months. All-cause mortality was analysed with the use of Cox proportional hazards model, with treatment and the stratification factors treated as covariates. As reported, except 95% CI for event rates, which were calculated by us (see appendix 6.3 for statistical method).	Maurer et al. 2018, Fig 2B + p1012-1013 [2] and CHMP AR p41 [4]
	Placebo	177	42.9% (35.6; 50.2)								
Survival, *no of events at 30 months (%)*	Tafamidis 80 mg + 20 mg pooled	264	186 (70.5%)	13.4%	4.26; 22.53	0.0044				Vital status was available and confirmed for all patients at 30 months. Survival rate after 30 months as reported. Absolute difference is calculated by us (see appendix 6.3 for statistical method).	Maurer et al. 2018, Fig 2A [2]
	Placebo	177	101 (57.1%)								
KCCQ-OS score, *LS means change from baseline (points)*	Tafamidis 80 mg + 20 mg pooled	170	-7.16 (-9.93; -4.39)	13.65	9.48; 17.83	<0.0001				Change from baseline at 30 months as reported. 95% CI interval for change calculated by us. Difference in change from baseline and related 95% CI and p value as reported (see appendix 6.3 for statistical method).	Maurer et al. 2018, p1013 + Fig. 4B p1014 [2] + CHMP AR p43 [4]
	Placebo	84	-20.81 (-24.67; -16.95)								

Trial name:	ATTR-ACT: Safety and efficacy of tafamidis in patients with transthyretin cardiomyopathy										
NCT number:	NCT01994889										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/ Odds/ Risk ratio	95% CI	*P* value		
Cardiovascular-related hospitalizations, *number/patient /year*	Tafamidis 80 mg + 20 mg pooled	264	0.48 (0.42; 0.54)	-0.23	-0.33; -0.12	<0.0001	RR: 0.68	0.56; 0.81	<0.0001	Frequencies of cardiovascular-related hospitalizations were compared by use of Poisson regression model, with treatment *TTR* genotype, NYHA baseline class, treatment-by-*TTR* genotype interaction, and treatment-by-NYHA baseline class interaction terms as factors, with adjustment for treat-ment duration. As reported.	Maurer et al. 2018, Fig 2C + p1013 [2] and CHMP AR p42 [4]
	Placebo	177	0.70 (0.62; 0.80)								
6MWT, *LS means change from baseline (metres)*	Tafamidis 80 mg + 20 mg pooled	155	-54.87 (-64.80; -44.94)	75.68	57.56; 93.80	<0.0001				Change from baseline at 30 months as reported. 95% CI interval for change calculated by us (see appendix 6.3 for statistical method). Difference in change from baseline and related 95% CI and p value as reported.	Maurer et al. 2018, p1013 + Fig 4B p1014 [2] + CHMP AR p43 [4]
	Placebo	70	-130.55 (-149.75; -111.35)								
≥ 1 treatment-related TEAEs, *proportion of patients*	Tafamidis 80 mg + 20 mg pooled	264	42.8% (36.8; 48.8)	-8.04	-17.52; 1.44	0.0989	RR: 0.84	0.69; 1.03	0.0989	Proportion of patients as reported. Absolute difference, RR, 95% CIs and p values calculated by us (see appendix 6.3 for statistical method).	CHMP AR p59 [4]
	Placebo	177	50.8% (43.8; 58.2)								

6.5 Results per PICO (clinical question)

TABLE 20 RESULTS PER PICO FOR CLINICAL QUESTION 1

Results per outcome		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Overall survival	ATTR-ACT	13.4%	4.26; 22.53	0.0044	HR: 0.70	0.51; 0.96	0.0259	*Absolute difference in survival rate after 30 months and 95% CI for absolute difference calculated by us (see appendix 6.3 for statistical method). Hazard ratio for all-cause mortality (as reported) was calculated by Cox proportional hazards model, with treatment and stratification factors treated as covariates.*
KCCQ-OS score	ATTR-ACT	13.65	9.48; 17.83	<0.0001				*Difference in change from baseline and related 95% CI and p value as reported.*
Cardiovascular-related hospitalizations	ATTR-ACT	-0.32	-0.44; -0.19	<0.0001	RR: 0.68	0.56; 0.81	<0.0001	*Frequencies of cardiovascular-related hospitalizations were compared by use of Poisson regression model, with treatment, TTR genotype, NYHA baseline class, treatment-by-TTR genotype interaction, and treatment-by-NYHA baseline class interaction terms as factors, with adjustment for treatment duration. As reported. The absolute difference is calculated based on the RR and an assumed control group risk of 1 cardiovascular-related hospitalization per patient per year.*
6MWT	ATTR-ACT	75.68	57.56; 93.80	<0.0001				*Difference in change from baseline and related 95% CI and p value as reported.*
≥ 1 treatment-related TEAEs	ATTR-ACT	-8.04	-17.52; 1.44	0.0989	RR: 0.84	0.69; 1.03	0.0989	*Proportion of patients as reported. RR, 95% CIs and p values calculated by us (see appendix 6.3 for statistical method).*

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Tafamidis (Vyndaqel®) indicated for transthyretin amyloid cardiomyopathy (ATTR-CM) - cost per patient and budget impact analysis

Application to the Danish Medicines Council

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Abbreviations

ACE	angiotensin-converting enzyme
ACM	all-cause mortality
AE	treatment emergent adverse event
AIC	Akaike's information criterion
AIP	Apotekets indkøbspris (pharmacy purchasing price)
ATTR	transthyretin amyloid
ATTR-ACT	Tafamidis in Transthyretin Cardiomyopathy Clinical Trial
ATTR-CM	transthyretin amyloid cardiomyopathy
ATTR-PN	transthyretin amyloid polyneuropathy
ATTRm	variant (mutant) transthyretin amyloid*
ATTRwt	wild-type transthyretin amyloid[1]
AUP	Apotekets udsalgspris (pharmacy retail price)
BIC	Bayesian information criterion
CEA	cost-effectiveness analysis
CI	confidence interval
CM	cardiomyopathy
CU	cost-utility
CV	cardiovascular
DMC	Danish Medicines Council
EC	European Commission
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
GP	general practitioner
HF	heart failure
HTA	health technology assessment
INR	International Normalized Ratio
ITT	intention-to-treat
KM	Kaplan-Meier
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire – Overall Summary
Leu111Met	methionine-for-leucine substitution at amino acid number 111
LTx	liver transplant
LY	life year
NAC	National Amyloidose Center
NICE	National Institute for Health and Care Excellence
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
OS	overall survival
RCT	randomised controlled trial

[1] For convenience and readability, the abbreviations ATTRm and ATTRwt are used throughout the document to refer to the *TTR* genotype as well as the disease hereditary or wild-type ATTR-CM, respectively.

RDI	relative dose intensity
PSA	probabilistic sensitivity analysis
SD	standard deviation
SE	standard error
SOC	standard of care
TTR	transthyretin
TTR	transthyretin gene
UK	United Kingdom
WTP	willingness to pay

1 Background

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a rare, life-threatening disease characterised by the accumulation of amyloid fibrils composed of misfolded transthyretin (TTR) protein in the heart (1). Under normal conditions, TTR circulates as a homotetramer, composed of four identical transthyretin subunits (2). Due to genetic mutation or aging, tetramers can dissociate to monomers that misassemble and/or misfold into amyloid fibrils (3). TTR amyloid deposition and accumulation can lead to diastolic dysfunction progressing to restrictive cardiomyopathy and heart failure (HF) (4). Infiltration of the conduction system can lead to arrhythmia, such as bundle-branch block, atrioventricular block, sinoatrial disease and atrial fibrillation (1,5).

The prognosis for ATTR-CM patients is poor. ATTR-CM is a progressive, debilitating, life-threatening and ultimately fatal disease. Patients have a prognosis of 2–5 years of survival from diagnosis (4,6–10).

The disease ATTR-CM can be either hereditary or wild-type ATTR-CM. ATTR-CM can be inherited as an autosomal dominant trait caused by pathogenic mutations in the transthyretin gene (*TTR*) leading to misaggregation and deposition of variant TTR amyloid protein (denoted ATTRm). ATTR-CM can also appear as a sporadic, non-genetic disease due to misaggregation and deposition of wild-type TTR amyloid protein (denoted ATTRwt). Wild-type ATTR-CM was previously called 'senile systemic amyloidosis' (3,11). Hereditary ATTR-CM involves aggregation of primarily ATTRm while wild-type ATTR-CM only has aggregation of ATTRwt and deposits primarily in the heart (5). In the following we used the ATTRm and ATTRwt to describe the hereditary and wild-type ATTR-CM diseases, respectively.

ATTRm is very rare in Denmark (12). Penetrance and the typical age at onset depend on the specific mutation (3,13). More than 130 *TTR* mutations, known to cause hereditary TTR amyloidosis, have been identified and registered. At least 25 of these are mostly associated with ATTR-CM (2,14–16). A unique Danish mutation, Leu111Met (methionine-for-leucine substitution at amino acid number 111), of a predominantly cardiac phenotype causing ATTR-CM has been identified (17,18). Leu111Met has been traced to 35 patients in a large Danish family (12). The penetrance is 100% and carriers are typically monitored closely after the age of 35 and convert to being patients between 40 and 50 years of age (12). If left untreated, patients die within 2 years (12). Therefore, these patients are offered a liver transplant (12). Because 95% of TTR protein is produced by the liver, liver transplant has been employed in ATTRm to stop production of amyloidogenic variant TTR and thereby halt amyloid formation (19,20). Liver transplant and in some cases both liver and heart transplant (12) can therefore be a disease-modifying treatment option for ATTR-CM patients with the hereditary form of the disease (3,21).

ATTRwt is a late-onset disease caused by deposition of wild-type TTR amyloid with symptoms typically manifesting in patients ≥60 years of age (3). In Denmark, patients are typically males diagnosed at the age of approx. 80 years (12). However, ATTRwt is underdiagnosed and diagnosis is often delayed (12).

Until February 2020, there were no European Commission approved medicines for the treatment of ATTR-CM (12). Up until then, treatment of ATTR-CM has included symptom management such as diuretics for symptoms of HF (3,22). Other medical treatments that can typically help HF patients with reduced ejection fraction include ACE inhibitors, calcium antagonists, beta blockers and digoxin. However, these treatment options are contraindicated or must be administered with extreme caution in ATTR-CM patients as they can worsen the condition (1,3,12,22). Sometimes, prophylactic pacemaker placement for cardiac arrhythmias is used (12).

Tafamidis is a new medical treatment option for ATTR-CM patients. The objective of this analysis is to estimate the cost per patient and budget impact of introducing tafimidis in the treatment of hereditary and ATTRwt in Denmark.

1.1 Tafamidis and tafamidis' indication

Tafamidis is a selective stabiliser of TTR. Tafamidis binds to TTR at the thyroxine binding sites, stabilising the tetramer and slowing dissociation into monomers, the rate-limiting step in the amyloidogenic process. The inhibition of transthyretin tetramer dissociation forms the rationale for the use of tafamidis to slow disease progression in patients with TTR amyloid cardiomyopathy (5,23,24).

Since 2011, tafamidis 20 mg has been approved for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy (ATTR-PN) to delay peripheral neurologic impairment (24).

The approved dose of tafamidis for ATTR-CM is 61 mg taken orally as a soft capsule once daily. Dosing can be with or without food. The tafamidis 61 mg capsule was developed for patient convenience to enable a single capsule for daily administration.

In the ATTR-ACT trial, tafamidis was given in the form of tafamidis meglumine (5) and was administered both as a daily dose of 20 mg and of 4 x 20 mg capsules. An evaluation of the free acid form of the tafamidis 61 mg capsule demonstrated that it is bioequivalent to the 80 mg tafamidis meglumine dose (4 x 20 mg capsules) (25). For convenience, 80 mg tafamidis meglumine is referred to as "80 mg tafamidis" in the following.

In the phase 3 ATTR-ACT trial, tafamidis' safety and efficacy for the treatment of ATTR-CM was evaluated (5). The ATTR-ACT trial found that tafamidis reduced all-cause mortality by 31.2% (78 of 264 [29.5%] vs. 76 of 177 [42.9%]; hazard ratio, 0.70; 95% confidence interval (CI) 0.51 to 0.96) and rates of cardiovascular (CV)-related hospitalisations by 32.4% (0.48 per year vs. 0.70 per year; relative risk ratio, 0.68 [95% CI 0.56 to 0.81]) compared to placebo ($p < 0.001$). Tafamidis was also associated with a lower rate of decline in distance for 6-minute walk test ($p<0.001$) and a lower rate of decline in KCCQ-OS score ($p<0.001$). The incidence and types of AEs were similar in the two groups.

On 17 February 2020, the European Commission (EC) approved the following new indication for tafamidis 61 mg soft capsules:

> Tafamidis is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

Tafamidis is the first and only drug approved and available for ATTR-CM.

The Expert committee ('Fagudvalget') has asked for separate clinical analyses of the two doses included in the ATTR-ACT trial. Dose subgroup analyses revealed that the efficacy and safety were similar for tafamidis 80 mg and tafamidis 20 mg, albeit data for 80 mg tafamidis had more power due to the greater number of patients randomized to the tafamidis 80 mg group than the tafamidis 20 mg group. Exploratory analyses of the cardiac biomarker NT-proBNP favoured the 80 mg dose over the 20 mg dose. The increase in NT-proBNP through the study with tafamidis 80 mg was significantly lower than with 20 mg (-1170.51 pg/mL (standard error 587.31), p=0.0468).

For this reason and since drug costs of both 20 mg and 80 mg (4×20 mg) tafamidis is higher than the drug cost of the 61 mg tafamidis capsule, we have found it superfluous to include analysis of these two drug variants in the economic application. In the analysis presented in the following, we therefore present the costs of introducing the 61 mg tafamidis capsule for the treatment of ATTR-CM in Denmark.

Table 1 **Tafamidis 61mg**

Name	**Vyndaqel®**
Active ingredient	Tafamidis
Indication	For 61 mg soft capsules: Vyndaqel® is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).
Strengths and dosing	ATTR-CM: 61 mg capsules once daily (oral administration)
ATC-code	N07XX08
Dispensing group	BEGR - limited
Packages	30 x 61 mg soft capsules
EC date of approval	17 February 2020 (61 mg)
Storage and shelf life	2 years. Do not store above 25°C.

1.2 Tafamidis in Danish clinical setting

To gain knowledge of the characteristics of the Danish patient population and to establish the Danish clinical practice for treatment of ATTRm and ATTRwt, Pfizer hosted a Medical Advisory Board meeting in March 2019. Participants were:

- Professor Steen Hvitfeldt Poulsen (SHP) from Aarhus University Hospital,
- Professor Finn Gustafsson (FG) from Rigshospitalet,
- Professor Henning Mølgaard (HM) from Aarhus University Hospital and
- Chief physician Jens Jakob Thune (JJT) from Bispebjerg/Frederiksberg Hospital.

SHP, FG and JJT treat patients with ATTRwt and FG and HM treat patients with ATTRm. The members agreed for us to use their insight regarding prevalence, incidence, diagnosis, monitoring, and clinical practice for the application for tafamidis to the DMC. In the application, information from the meeting is referred to as "Medical Advisory Board 2019".

In order to obtain additional relevant information about clinical practice based on the specific questions raised in the protocol from the DMC, Pfizer again contacted SHP, FG and HM in March/April 2020. They have all agreed to serve as references for Danish clinical practice and have been kind to provide the needed information despite the challenges our health care system is facing with the COVID-19 pandemic. Whenever we have used input from the experts in this report, we have documented it by inserting the specific expert's initials. In a few cases, no input from the Danish clinical practice exists and Pfizer has used assumptions based on the best available evidence.

All the above is to ensure that the present analysis of the cost associated with treatment of ATTRm and ATTRwt resembles the current Danish clinical practise in the best possible way. The implication is that this application in some cases apply different assumptions than the assumptions from the protocol developed by the Expert Committee ('Fagudvalget').

1.3 Patient population

The epidemiology of ATTR-CM in Denmark is not well characterised. There are no published data on the incidence or prevalence of ATTR-CM in Denmark.

1.3.1 ATTRwt

For ATTRwt, the Expert Committee ('Fagudvalget') assesses a prevalence of 400-500 patients and an incidence of approx. 150 patients per year. However, these estimates do not provide any details of uptake or percentage of eligible patients. Pfizer has therefore asked SHP and FG to

a) quantify the expected actual patient population eligible for treatment in year 1 i.e. the share of prevalent patients eligible for treatment
b) quantify the expected share of the incident patients eligible for treatment each year and
c) quantify the expected annual uptake of treatment i.e. to assess if half-cycle correction is a correct measure to apply to the incidence rate.

SHP and FG agree with the prevalence of 400-500 patients, but have explained to Pfizer, that the current number of candidates for tafamidis is lower than this prevalence. The reason is the current low suspicion and diagnostic rate as well as the disease progression. SHP and FG assess that the number of patients who are candidates for treatment with tafamidis today is 200. SHP and FG also assess that these 200 patients will initiate treatment within 3 months after the day where tafamidis is possibly recommended as standard of care. In our base case budget impact analysis, we therefore assumed that the 200 patients will initiate tafamidis treatment within 3 months. SHP and FG agree with the incidence of 150 suggested by the Expert Committee. They add that of the 150 incident patients, approximately 20% will not be candidates for tafamidis, as they will already have progressed to NYHA class IV at the stage of diagnosis. SHP and FG therefore assess the incidence of eligible patients to be 120 (80% of 150). Therefore, our base case budget impact analysis includes 120 new incident patients per year.

In the ATTRwt budget impact analysis, we perform a sensitivity analysis in which we assume full uptake. Specifically, we assume a prevalence of treatment eligible patients of 450 patients in year 1 and an incidence of 150 patients per year.

1.3.2 ATTRm

For ATTRm, a prevalence of 35 patients with the unique Danish mutation Leu111Met is known. For this mutation, an incidence of 10 patients (carriers converting to patients) is expected in the next 10-20 years (12). The majority of the 35 known patients have already been treated with liver transplant or a combined liver and heart transplant and are no longer candidates to tafamidis treatment. Therefore only incident ATTRm patients are eligible for treatment with tafamidis. That is, 0.5-1 patient with ATTRm per year will expectedly initiate tafamidis treatment. We have used 0.5 patients in our budget impact base case analysis.

Since the patient numbers are both low and quite predictable in ATTRm, we do not perform a sensitivity analysis here.

1.4 Clinical question

The basis for the performed cost per patient and budget impact analysis is the following clinical question presented in the Danish Medicines Council's (DMC's) protocol (12):

> What is the added clinical value of treatment with tafamidis compared to placebo in adult patients with ATTR-CM?

Overall, answering this question involves preparing a cost per patient and a budget impact analysis.

We have agreed with the DMC that two seperate analyses are presented:

1. A cost per patient and a budget impact analysis for ATTRwt.
2. A cost per patient and a budget impact analysis for hereditary ATTRm.

2 Methods

The analyses forming the basis for this report are based on a Danish adaptation of a global Excel-based cost-utility (CU) model developed by Cornerstone for Pfizer Inc. The relevant details about the model functionalities and input are described in this section.

ATTRwt has until recently been considered an ultra-rare disease. However, new data suggest that this perception is primarily caused by challenges related to low suspicion of the disease and substantial under- and misdiagnosis of the disease (26–29). Available data on key patient characteristics such as health care utilisation and median life expectancy is hence sparse.

In this section, we present the assumptions for the base case analysis along with a description of the uncertainties for each of the model inputs. The detected uncertainties are also addressed in section 2.8 and 3.2 where we describe and present the results from a range of sensitivity analyses. The aim of these is to provide an overview of how the detected uncertainties affect the results.

For the Danish adaptation, we only use the cost part of the model and not the utility sheets since a cost-utility analysis is currently not required by the DMC. We have added sheets to the model to perform and present the cost per patient and budget impact analyses according to the DMC's guidelines (30).

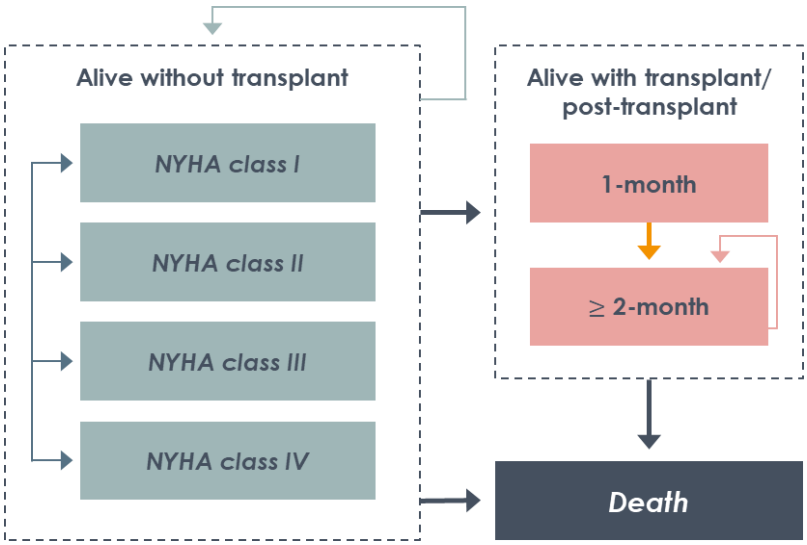
The model calculates the cost per average ATTRwt patient and ATTRm patient separately. The characteristics of the patient population in the model are aligned with characteristics of the ATTR-ACT trial population which included patients with either ATTRwt or ATTRm and a medical history of HF.

2.1 Applied model

The model is a multi-state, cohort Markov model developed in Microsoft Excel to capture all costs and outcomes associated with patients receiving tafamidis (intervention) or placebo (comparator). A model cycle of 30,44 days (average month) is used to estimate the costs. Appendix 1: Model overview provides a detailed overview of the content of the model.

The model tracks ATTR-CM-diagnosed patients according to 3 main groups of health states: 1) alive without transplant, 2) alive with transplant and 3) dead. The "alive without transplant" state is divided into the 4 New York Heart Association (NYHA) class stages and the "alive with transplant" state is divided into 1 month or ≥ 2 months following a transplant. Descriptions of the NYHA classes can be found in Table 2. Death is an absorbing health state. The model structure is shown in Figure 1 below.

Figure 1 **Model structure**



Note: The red health states are not used in this analysis.
Source: CU model.

The NYHA classification is shown in the tabel below.

Table 2 **NYHA classification grading of symptoms in chronic heart failure**

NYHA Class	Description
Class I	No symptoms and limitations in ordinary physical activity.
Class II	Slight limitation of physical activity. Ordinary physical activity results in mild symptoms such as fatigue, shortness of breath and angina.
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms.
Class IV	Severely limited. Experiences symptoms even at rest.

Source: (31).

In the protocol, the DMC has requested a number of sub-analyses including separate analyses for patients by initial National Amyloidose Center (NAC) disease stage, which is based on their levels of NT-ProBNP and eGFR (12). However, as these data are not available, it has not been possible to perform these analyses.

In the Danish adaptation of the model, we ignore the transplant states (liver and/or heart transplant) because these are not relevant for the objective of the analyses. ATTRwt patients do not undergo liver and/or heart transplant, but are currently treated only with symptomatic medical care such as diuretics. ATTRm patients in Denmark are treated with a transplant, but

since the time horizon for the base case analyses is set to 'time to transplant', which is 6 months, transplanation states are also irrelevant for this base case analyses (see also section 2.5).

The implication of the disregard of the transplant states is that "Probability of transplant (per cycle)" is set to 0.0% in the "Inputs – Transplants" sheet. This can; however, be changed if the DMC is interested in changing this assumption.

Cardiac mechanical assist device implants (pacemakers) are also disregarded in the analysis. The reason is that there is no known difference of the need for pacemakers following treatment with tafamidis compared to treatment with placebo. In the ATTR-ACT trial, very few patients (0.8% (N=2) in the tafamidis arm and 0.0% in the placebo arm) had a cardic implant (5). We know from a recent study by Ladefoged et al (32), that the prevalence of pacemakers was 30% for Danish patients with ATTRwt. The article explains that "In accordance with previous observations, a substantial number of patients had a pacemaker device implanted years before their established ATTRwt diagnosis. In this context, undiagnosed CA (cardiac amyloidosis) could be the major cause of these arrhythmias". So, even though the prevalence in Denmark is higher than in the ATTR-ACT trial, the cost will most likely not change if tafamidis is recommended. Therefore, the "probability of cardiac implant (per cycle)" is set to 0.0% in the "Inputs - Cardiac Implant" sheet.

Pfizer and the DMC discussed whether costs of screening and diagnosis should be included in the analysis. Pfizer believes that cost of screening and diagnosis is important and needed irrespectively of the introduction of medical treatment for ATTR-CM. A UK study investigating the initiation of systematic screening in the UK in 2012 found a significant improvement in median OS following early diagnosis, implying that the benefits of screening are independent of the improvements generated by new, targeted treatments (33). Therefore, costs of screening and diagnosis are not included in the analysis.

The table below illustrates the possible movements between health states. The first row (separated from the rest of the table by a dotted line and named 'Model entry') indicates the baseline health states for patients entering the model. As evident from the table no patients enter the model in NYHA IV or death health state. Besides the restrictions on the baseline health states the table shows that the model is fully flexible regarding the movements between states except for death.

Table 3 **Possible movements between health states in the model**

From / to	NYHA Class I	NYHA Class II	NYHA Class III	NYHA Class IV	Dead
Model entry	✓	✓	✓		
NYHA Class I	✓	✓	✓	✓	✓
NYHA Class II	✓	✓	✓	✓	✓
NYHA Class III	✓	✓	✓	✓	✓
NYHA Class IV	✓	✓	✓	✓	✓
Dead					✓

Source: CU model.

2.1.1 Patient flow

In the model, treatment efficacy for tafamidis or placebo is captured through health state occupancy, survival estimates and incidence of hospitalisations.

All patients start in the model as alive without transplant in one of the NYHA class health states.

Table 4 **NYHA class distribution of patients included in the ATTR-ACT trial**

NYHA Class	ATTRwt	ATTRm
Class I	9.0%	6.6%
Class II	63.3%	48.1%
Class III	27.8%	45.3%
Class IV	0.0%	0.0%

Table 4 presents the NYHA class distribution of patients included in the ATTR-ACT trial. Since tafamidis is not recommended to be initiated in patients in NYHA class IV, the ATTR-ACT trial only included patients in NYHA class I-III at baseline.

The Medical Advisory Board 2019 assesses that it is reasonable to use the above NYHA class distribution to describe the Danish patient population of both prevalent and future incident patients with ATTRm and ATTRwt.

However, the Medical Advisory Board 2019 also notes that a positive recommendation from the DMC could lead to increased diagnostic awareness of especially ATTRwt and hence a higher share of patients in NYHA class I.

This becomes important since treatment with tafamidis has proven to be more effective if initiated early (NYHA class I-II) than late during the disease. Unfortunately, the economic model does not allow changes in the baseline NYHA class distribution to assess the effect of more patients being diagnosed in NYHA class I-II. This is due to pooled efficacy data across all NYHA classes. Thus, changing the baseline distribution to include more patients in NYHA class I-II will underestimate the effect of treating patients with tafamidis.

2.1.2 Mortality

In the base case, the proportion of patients who die in each cycle from non-transplant related causes is informed by the mortality data from the Kaplan-Meier (KM) curve from the ATTR-ACT trial separately for patients with ATTRm and ATTRwt. Please note that this section does not describe the transition to death stratified by NYHA class. This information can instead be found in section 2.1.3. The focus of this section is to describe how mortality is modelled, i.e. how many patients died between cycles n and n+1 irrespective of NYHA classes.

Although data by NYHA class was collected in ATTR-ACT, modelling mortality within each NYHA class was not possible due to the small number of patients enrolled in class I and lack of patients enrolled in class IV. This limits the ability to generate robust NYHA-specific extrapolations of survival. Instead, all-cause survival was based on the subgroup- and treatment-specific OS KM curves (i.e., the OS for ATTRwt patients was used to model survival in the wildtype subgroup analysis, and the OS for ATTRm patients was used to model survival in the hereditary subgroup analysis). Data from ATTR-ACT on overall survival for the two subpopulations are unpublished "data on file". Kaplan-Meier survival curves along with relevant extrapolations are provided in

[redacted]

[redacted]

[redacted]

In addition, the model will correct trial OS for background general population mortality (see model sheet: Survival Curve Data). The OS data used in the model is adjusted using the maximum hazard of dying for background mortality vs. from the trial at each cycle, such that the risk of dying cannot be lower than that for general population at any age.

In the model, there are two options for modeling survival by treatment. We apply option 1 ("All-cause mortality from trial") because option 2 ("Country-specific all-cause mortality") is only relevant when the general population mortality is anticipated to be higher than that of ATTR-CM patients from the trial. Option 1 (and option 2) are selected in the "Inputs – Overall Survival Sheet".

Option 1 assumes that survival reflects the trial population and its baseline characteristics. Modifying the baseline age or gender distribution is not available, since it would have no effects on the trial-based all-cause mortality curve.

Extrapolation of the OS curve beyond the 30 months of follow-up from first treatment dose was required to capture the long-term benefit of treatment. Briefly, to extrapolate the KM survival curves to a lifetime horizon for the model, 7 standard parametric survival models (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma) were fitted to the individual patient data from the ATTR-ACT trial in accordance with the best practices from the NICE Technical Support Document 14 for survival analysis alongside clinical trials (34). Parameters and model fit statistics (i.e. Akaike's information criterion [AIC] and Bayesian information criterion [BIC]) were calculated for each curve type and are avaliable in [redacted].

The most appropriate curve for data extrapolation was then selected based on the following:

- The extrapolated curve must be clinically meaningful for both patient populations.
    - This implies that tails cannot extend indefinitely or plateau before reaching 0% survival.
    - Moreover we apply a restriction, where the predicted share of surviving patients cannot exceed 5% 55 years after the beginning of the analysis.
- The goodness of fit for each parametric survival function based on statistical analyses of AIC and BIC.
    - In general, the lower the AIC or BIC, the better the statistical model fits the KM data.
    - Specifically, we select the extrapolation function which minimize the sum of the AIC and BIC criteria in the placebo and the tafamidis arm.

Based on these criteria extrapolations of survival will be carried out using the Weibull survival model for patients with ATTRwt, and the Exponential survival model for patients with ATTRm.

2.1.3 Number of patients in the "Alive without transplant by NYHA class" health states

The OS data are used to determine the transitions to death; that is to say, how many patients died between cycles n and n+1. This section describes how patients alive were stratified by their NYHA class in each cycle and how dead patients are removed from NYHA classes in each cycle.

For the first 30 months of the model time horizon, the number of patients alive in a given NYHA class in cycle n was informed by the observed longitudinal data of the total intent-to-treat (ITT) population at cycle n in the ATTR-ACT trial. This approach uses the observed trial distribution, i.e. the share of patients who are alive in each NYHA class from baseline over the first 30 months of treatment, thereby allowing for consistent within-trial analysis and avoiding the need to make assumptions on how patients by NYHA class at baseline get to each NYHA class state over the 30 months. These empirical transition rates were derived under the last observation carried forward by assumption for missing NYHA class data. Moreover, since the ATTR-ACT trial used 6-month assessment time points, the distribution in each assessment was applied for 6 months so that NYHA transitions were possible at the end of each 6-month period. For example, the month 6 NYHA distribution was applied for months 6-11.

The implication of the above is that the patient distribution in each of the NYHA classes is known (e.g. patients from NYHA class I at baseline are going to be X% in NYHA class I, X% in NYHA class II, X% in NYHA class III, and X% in NYHA class IV at month 6, etc.). Combined with the OS curve (described in section 2.1.2) evaluating the proportion of patients alive vs. dead at each time point (e.g. X% of patients are still alive at month 6), it was possible to distribute the "alive" patients into each of the NYHA classes according to the observed distributions at each of the time points (month 6, 12, 18, 24 and 30) in the ATTR-ACT trial. This approach allowed us to exactly match the patient distributions to the trial (and achieve internal validity), without having to introduce assumptions on how patients get to each NYHA health state over the 30-months.

After 30 months in the model we no longer have NYHA distribution data from the ATTR-ATC trial and the number of patients in each NYHA class in cycle n+1 was instead determined in a two-step process.

Step 1 removed patients who died in cycle n. The OS curve (described in section 2.1.2) tells us the % of patients who are alive vs. dead. Instead of assuming that there was an equal risk of death across NYHA classes, the distribution of mortality by NYHA class from the trial was used. Information on the NYHA class specific mortality can be found in

[redacted]

[redacted]

[redacted]. For any cycle where the distribution of mortality led to more deaths within a particular NYHA class than the number of patients who were alive in that NYHA class, all patients were removed from that NYHA class, and the remainder would be taken out of the NYHA class with the highest number of patients

In step 2, a transition probabilities matrix was used to estimate the number of patients that would move to another NYHA class. These transition probabilities were based on transitions in the trial between months 24 and 30.

2.1.4 Time on treatment

We used monthly KM data on the proportion of total ITT patients remaining on tafamidis treatment from the ATTR-ACT trial. Patients who died, had transplants and/or cardiac mechanical assist device implantations were excluded from the trial because these events were considered discontinuation events.

Estimates were the same for the population regardless of TTR genotype or baseline NYHA class since the willingness to stay on treatment is not expected to depend on these characteristics.

Since data were only available up to 30 months, the model allows use of treatment discontinuation data that were extrapolated over a longer time horizon. Curve fit statistics for the discontinuation data along with Kaplan-Meier discontinuation curves and extrapolations are provided in [redacted].

2.2 Intervention

As outlined in the clinical question presented in the DMC's protocol, the intervention is tafamidis (61 mg daily), see section 1.1 and 1.4.

2.3 Comparator

The comparator in the analysis is placebo (see section 1.4).

For both the intervention (tafamidis) and the comparator (placebo), it was assumed that patients were also treated with diuretics (see also section 2.7.1).

2.4 Perspective of the analysis

A limited societal cost perspective is applied in the analysis. The analysis includes:

- drug costs

- hospital costs (admissions, outpatient (monitoring) costs)
- costs of AEs and end of life costs
- cross-sectional costs
- cost of patient time
- transportation costs
- patients' copayment of prescription drugs

The analysis does not include indirect costs (productivity loss).

2.5 Time horizon

In the ATTRwt analysis, we apply a time horizon of 30 months in the base case, which is the follow-up time in the ATTR-ATC trial (5). This time horizon is chosen in order to align the cost per patient and budget impact analysis presented in this report with the clinical application for tafamidis. Thereby, the incremental costs associated with a recommendation of tafamidis treatment as first-line treatment for patients with ATTRwt are directly comparable to the health gains presented in the clinical application. Moreover, the ATTR-ATC trial data constitute the best available data, and we suggest that the 30 months' time horizon should be used as the base case in a Danish setting. Application of a 30 months' time horizon implies that OS and time on treatment are based on KM data. These are real data, and in this way we avoid extrapolations and the added uncertainty of the results that comes with it.

Following the DMC guidelines for modelling the costs, the time horizon should be chosen such that all relevant costs are included in the analysis. There is no published data on median life expectancy of Danish patients with ATTRwt. International estimates show great uncertainty regarding the median survival from diagnosis. The estimates vary with study setting and they range from 26 to 67 months (4,9,10,28,29,33,35).

In the protocol, the Expert Committee assumes the average life expectancy for ATTRwt in Denmark to be the same as that of UK patients (reported in Lane et al. 2019) which is 5 years (12,33). In addition, the protocol stipulates that the average life expectancy for an 80-year old man is 87.87. In section 3.2, we therefore present results from two separate sensitivity analyses applying a time horizon of 5 and 7.87 years (rounded to 94 monthly cycles) respectively. These sensitivity analyses are made using extrapolations of the survival data from ATTR-ACT, and they are therefore subject to more uncertainty than the base case. For the analysis of ATTRm patients, we apply a time horizon of 6 months in the base case. This is based on input from HM, who has indicated that patients are likely to be assigned to treatment with tafamidis when they are placed on the waiting list for a liver transplant. According to HM, the average time from a patient is placed on the waiting list until they receive a liver transplant is 6 months (ranging from 1 to 12 months). FG has confirmed this estimate.

The DMC has in an email exchange with Pfizer indicated that they would like to see a sensitivity analysis with a longer time horizon for ATTRm than the 6 months. They assume that a delayed progression prior to transplant could cause a better foundation for transplant as well as increase

life expectancy and quality of life after transplant. However, despite Pfizer's ambition to deliver analyses as requested by the DMC, performing a sensitivity analysis of life-long treatment of tafamidis vs. placebo post-transplant is not possible for two reasons:

- Pfizer does not have an approved indication of tafamidis post-transplant (i.e. following a transplant, patients are no longer eligible to receive tafamidis)
- There is no efficacy data post-transplant. If patients in the ATTR-ACT trial received a liver transplant they were withdrawn from the study (5). Moreover, Pfizer has no knowledge of the existence of efficacy data post-transplant depending on the patients' pre transplant disease severity.

Pfizer has previously consulted the Medical Advisory Board 2019 on the potential of tafamidis for ATTRm patients in Denmark, and they have expressed the following, as written in the early application:

> *"Tafamidis will provide a treatment option for hereditary ATTR-CM patients who are not candidates for LTx (liver transplant) due to age, comorbidities, heart disease status, or other issues.*
>
> *Danish specialists are considering the potential opportunity to replace LTx with tafamidis for Leu111Met patients.*
>
> *Therefore, in the future, tafamidis might offer the opportunity to replace a LTx for new patients with hereditary ATTR-CM caused by Leu111Met mutation.*(36)"

For ATTRm patients who are not candidates for LTx, we therefore included a sensitivity analysis where we compare the total cost of life-long treatment with tafamidis vs. placebo. This analysis is subject to several limitations:

- It includes the full patient population as the model does not allow for selecting patients who are not candidates for transplant.
- The placebo group will, according to the DMCs protocol, develop serious heart failure and die after approximately 2 years without treatment. Hence, the consequence is that the sensitivity analysis compares the cost of life-long treatment with tafamidis with a group of patients who die within 2 years.

For patients who in the future might be offered the opportunity to have a transplant replaced by tafamidis, we are limited by lack of efficacy data post-transplant for the placebo group. However, a recent study accepted for publication in Value in Health, May 2020, assessed the transplant and hospital costs of Danish ATTRm patients, and found that the average transplant costs per patient were USD 270,664 and that the average hospitalisation costs per patient were USD 103,294 leading to a total of DKK 2,554,133 (37). These costs are conservative as they exclude primary care sector costs (drugs).

An overview of the sensitivity analyses is presented in section 2.8. If the DMC finds it relevant to compute the per patient cost and budget impact associated with tafamidis treatment for other

time horizons than the ones presented in this report, the time horizon can be changed in sheet 'Inputs – General'.

2.6 Discounting

In accordance with the DMC guidelines (30), costs incurring in the 2nd to 34th year after model entry are discounted by 4% per year, and costs beyond 35 years are discounted with 3% per year. The latter discount rate becomes relevant since the maximum time horizon of the model is 55 years.

2.7 Resource use and unit costs

This section includes an overview of the methodology applied to calculate drug costs, inpatient hospitalisations costs, outpatient contact costs, adverse events costs, cross-sectional costs, end of life costs and patient costs.

The resource use and unit costs can be changed in the following model sheets:

- 'Inputs – Hospitalisations'
- 'Inputs - Outpatient contacts'
- 'Inputs - Treatment Costs'
- 'Inputs - Adverse Events'
- 'Inputs – Cross sectional costs'
- 'Inputs - End of life costs'

2.7.1 Drug costs

In the model, all patients alive who have not discontinued treatment incur a drug cost. The daily cost of tafamidis is provided by Pfizer as well as the package size and the daily dosage. This enables the user to explore the costs associated with different package sizes and under various price regimes.

The model then calculates the per-cycle drug cost based on the daily cost and relative dose intensity (RDI) also denoted as the "adherence" factor. The RDI used in the base case analysis is 97.2%, which is based on the mean dose adherence of ITT patients in the pooled tafamidis arm in the ATTR-ACT trial (i.e. simple ratio between the number of doses taken versus the number of doses expected if the patient was alive and 100% compliant over the 30-month trial period).

Table 5 provides the drug formulations and unit costs for each therapy along with the calculated costs per dose and per cycle. Placebo acquisition costs were assumed to be zero (by virtue of being placebo) in the base case analysis.

Table 5 **Drug costs**

Treatment	Tafamidis	Placebo
Formulation size	61 mg	
Cost per package, AIP (DKK)	68,381.00	
Capsules per package	30	
Capsules per day	1	
Cost per daily dose (DKK)	2,279.37	0
RDI	97.20%	
Cost per RDI adjusted cycle (30,42 days) (DKK)	67,435.63*	0

Source: Pfizer.
Note: RDI is measured as the mean compliance for the pooled tafamidis patient population in ATTR-ACT.
*cost per RDI adjusted cycle is calculated as the cost per package multiplied by the RDI and adjusted to monhtly costs ((68,381*0,9720)/30)*30,44.

In addition to the above, all patients receive standard medical treatment which consists mainly of diuretics. For that reason, the model includes costs associated with diuretics as standard medical treatment for all patients (i.e. patients in the tafamidis arm and patients in the placebo arm). Specifically, we assume that all patients alive receive 120 mg of Furix® daily. These assumptions are based on assessments from SHP. The costs associated with diuretics are presented in Table 6. The table shows that the average cost of treatment with Furix® equals to DKK 27.28 per cycle (medicinpriser.dk). Of this amount, 39.65% is paid by the patient 2. This number is based on the average regional reimbursement to the Danish population above 65 from 2012 to 2016 as a share of the total revenue in the primary sector.

Due to the risk of hypotension, other medical treatment which is often used in treatment of patients with heart failure, is not recommended to patients with ATTR-CM (12). This comprises for example ACE inhibitors, calcium channel blockers, beta blockers and digoxin. We do hence not include costs associated with other types of treatments in the analysis.

[2] Calculated on the basis of sales statistics from medstat.dk.

Table 6 **Costs associated with other medical treatment**

Treatment	Cost per package (AUP, DKK)	Tablets per package	Daily dose (tablets)	Cost per Cycle (DKK)	Average copayment rate
Furix®	149.35	500	3 tablets of 40 mg	27.28	39.65%

Source: medicinpriser.dk and medstat.dk.

2.7.1.1 Treatment discontinuation

As described in section 2.1.4, time on treatment is based on data from the ATTR-ACT trial.

Approximately 20% of patients had discontinued tafamidis treatment by the end of the ATTR-ACT trial period (5). In the model, the number of patents alive was adjusted by the proportion of patients remaining on tafamidis therapy (discontinuation data from the trial) to adjust cost of therapy in any given cycle[3].

Data on discontinuation of treatment are available for the duration of the ATTR-ACT trial period of 30 months. This enables us to use the pooled discontinuation data (Kaplan-Meier estimates) from the ATTR-ACT trial in the base case analysis. Moreover, where relevant we extrapolate the discontinuation data over the relevant time horizon by using the exponential survival function. We do this because it is statistically the best fitting curve (lowest AIC and BIC values, see Appendix 2) in the sensitivity analyses presented in section 2.8.

2.7.2 Inpatient hospitalisations costs

In every model cycle, patients diagnosed with ATTRwt and ATTRm will incur a cost associated with a CV related or non-CV related inpatient hospitalisation. These costs are calculated based on the unit costs per inpatient hospitalisation and the frequency of inpatient hospitalisations (CV or non-CV related).

2.7.2.1 Unit costs of CV and non-CV related inpatient hospitalisations

This section describes the assumptions behind the unit costs per CV and non-CV related inpatient hospitalisations.

No data exist on the healthcare utilisation of Danish patients after diagnosis with ATTRm or ATTRwt. Therefore, the unit costs per CV related hospitalisation are based on knowledge from

[3] The survival and disease progression data from the trial are based on the ITT analysis, which uses outcomes for all patients allocated to tafamidis regardless of discontinuation of therapy. As such, the treatment outcomes applied in the model are maintained at the ITT levels since these already reflect the impact of treatment discontinuation.

SHP and HM's clinical experience from Aarhus University Hospital. SHP and HM have documented the findings in two studies accepted for publication in the May issue of Value in Health 2020 (37,38).

Below, Table 7 presents the case-mix of CV related inpatient hospitalisations for both ATTRwt and ATTRm along with the unit costs associated with an inpatient hospitalisation with each of the listed diagnoses. Based on these numbers, we have calculated the weighted average unit costs of a CV related inpatient hospitalisation for patients with ATTRwt and ATTRm respectively. These are presented in Table 8. In order to validate these results, we have consulted FG who supports the results by SHP and HM. FG adds that the results are conservative estimates and that patients hospitalised with a CV related event are often more expensive to treat due to the frequency and prevalence of comorbidities.

The DRG rates presented in Table 7 represent the average unit costs of treating patients within the given DRG category. Moreover, the DRG rates presented in Table 7 exclude costs of long-term hospitalisations of DKK 2,127 per day of hospitalisation beyond the DRG rate specific trim point. For that reason and due to the frequency of comorbidities and the general poor health status of this patient population, one might expect the actual treatment costs of these patients to be even higher. This is supported by a recent registry study of 176,067 Danish patients which showed that the total yearly net costs after an incidence of heart failure were EUR 11,158 (39) which is equivalent to DKK 83,342[4].

To account for the uncertainty regarding unit costs of CV related inpatient hospitalisations (i.e. a conservative estimate), we present the results from a sensitivity analysis in section 3.2 where we increase unit costs associated with a CV related inpatient hospitalisation by 50% to DKK 56,804 for ATTRwt patients and DKK 55,515 for patient with ATTRm.

[4] Using the average exchange rate from EUR to DKK in 2020 of 7.4692 from Danmarks Nationalbank.

Table 7 **Case-mix of CV related inpatient hospitalisations of patients with ATTRwt and ATTRm and associated unit costs**

Diagnosis and procedure group	Share of CV related hospitalisations		2020 DRG rate (DKK)	2020 DRG group
	ATTRwt	ATTRm		
Total	**100%**	**100%**		
Heart failure and shock	14.4%	11.5%	34,337	[DRG:05MA04]
Stable ischaemic heart disease/chest pain	2.9%	5.8%	2,697	[DRG:05MA03]
Acute myocardial infarction with ST segment elevation	1.4%	1.4%	18,493	[DRG:05MA01]
Specific angiopathy in the brain excl. common carotid arteries	0.0%	0.7%	36,280	[DRG:01MA05]
Stable ischaemic heart disease, procedure group B or C	0.0%	0.7%	12,655	[DRG:05MP39]
Stable ischaemic heart disease, procedure group A	1.4%	1.4%	75,677	[DRG:05MP40]
Cardiac insufficiency, incl. cardiac shock, procedure group C	11.5%	11.5%	75,677	[DRG:05MP40]
Cardiac insufficiency, incl. cardiac shock, procedure group B	11.5%	11.5%	52,491	[DRG:05MP41]
Cardiac insufficiency, incl. cardiac shock, procedure group A	11.5%	11.5%	30,775	[DRG:05MP42]
Other heart diseases	8.6%	8.6%	1,847	[DRG:05MA08]
Rehabilitation after cardiac event	0.7%	0.7%	21,332	[DRG:05MA14]
Other heart diseases, procedure group C	8.6%	8.6%	80,594	[DRG:05MP52]
Other heart diseases, procedure group B	8.6%	8.6%	34,010	[DRG:05MP53]
Other heart diseases, procedure group A	8.6%	8.6%	16,091	[DRG:05MP54]
Cardiac arrhythmia syncope	10.1%	10.1%	15,926	[DRG:05MA07]

Source: (37,38) and drg.dk.

Table 8 **Weighted average unit costs of CV related inpatient hospitalisations for ATTRwt and ATTRm patients**

	Weighted average cost (DKK)
ATTRwt	37,869
ATTRm	37,310

Source: (37,38) and drg.dk.

ATTRm have no non-CV related hospitalisations from the initiation of treatment until they receive a liver transplant (see section 2.7.2.2). For ATTRwt, SHP and FG have explained to Pfizer that there are no published references regarding the unit costs of non-CV related inpatient hospitalisation. The best assumption according to SHP and FG is to use the DRG rate of an

inpatient hospitalisation with pneumonia (DRG: 04MA13, DKK 37,050) since pneumonia was observed as one of the most frequent non-CV related causes of hospitalisation in the relevant population (40). As we know, the DRG rate only represents the average unit costs of the hospital associated with treating a given disease during the inpatient hospitalisation. That is, the DRG rate does not capture costs associated with subsequent outpatient contacts, visits to the general practitioner (GP) or costs associated with medical treatment and social care. A recent Danish study has estimated the costs of pneumonia to be USD 24,155 per patient in Denmark during the first 6 months after diagnosis (41). This is equivalent to DKK 164,216[5].

To account for the uncertainty regarding unit costs of non-CV related inpatient hospitalisations (i.e. a conservative estimate), we present the results from a sensitivity analysis in section 3.2 for ATTRwt, where we increase the costs associated with non-CV related inpatient hospitalisation by 50% to DKK 55,575.

In addition to the above, the costs of patient time associated with CV and non-CV related hospitalisations are based on estimates of the duration of inpatient hospitalisations from the participants of the Medical Advisory Board 2019. Specifically, they estimate the mean duration of CV related inpatient hospitalisations to be 6.76 days and 1.5 days for patients with ATTRwt and ATTRm and 9 days for non-CV related inpatient hospitalisations for ATTRwt patients. In order for the duration of CV and non-CV related hospitalisations to reflect the difference in duration across NYHA classes and between patients treated with tafamidis and patient receiving placebo, we adjust the above estimates with the relative difference in duration of hospitalisations across NYHA classes and treatment arms from the ATTR-ACT study. The duration of hospitalisations across NYHA classes and treatment arms from the ATTR-ACT study are included in [redacted]. The data is “data on file” and confidential.

2.7.2.2 Frequency of CV and non-CV related inpatient hospitalisations

Inpatient hospitalisation costs are an aggregated measure of both the unit cost per event and the frequency of the CV related and non-CV related inpatient hospitalisations. This section concerns the frequency of CV and non-CV related inpatient hospitalisations.

There are currently no data on the healthcare utilisation of Danish patients diagnosed with ATTRm and ATTRwt after diagnosis. Estimates from international studies range between 0.7 and 2.33 inpatient hospitalisations per year (5,33). To align the assumptions of the base case analysis with the characteristics of the Danish patient population, we rely on estimates from the Medical Advisory Board 2019. Specifically, we compute the frequency of CV and non-CV related hospitalisations as a weighted average of the estimates from the participants of the Medical Advisory Board 2019. As weights we use the number of patients with the relevant diagnosis that the experts are currently treating.

[5] Using the average exchange rate from USD to DKK in 2020 of 6.7984 from Danmarks Nationalbank.

Since tafamidis is not yet used as a standard of care for patients with ATTRwt and ATTRm, the knowledge of hospitalizations applies to the placebo group. For the placebo group, we estimate the number of CV and non-CV related hospitalisations to be 1.73 and 0.68 per year for patients diagnosed with ATTRwt. Similarly, we estimate that patients diagnosed with ATTRm in the placebo group have 0.33 CV related hospitalisations per year, and that patients diagnosed with ATTRm have no non-CV related hospitalisations from the initiation of treatment until they receive a liver transplant.

In order for the frequency of hospitalisations to reflect the difference in hospitalisation risk across NYHA classes and between patients treated with tafamidis and patients receiving placebo, we adjust the above estimates with the relative risk of hospitalisation across NYHA classes and treatment arms from the ATTR-ACT study.

Finally, we convert the frequencies to per cycle probabilities and apply them to all patients who were alive without a transplant in each cycle over the time horizon.

The NYHA class per cycle-specific frequencies for both CV and non-CV related inpatient hospitalisations are included in [redacted] but not listed in the main report because the data is “data on file” and confidential.

The scaled 6-months frequencies of CV and non-CV related hospitalisation, based on statements from the Medical Advisory Board 2019 meeting, as well as the 6-months frequencies of hospitalisation from the ATTR-ACT trial are available from row 120 in the ‘Inputs – Hospitalisations’ sheet.

To address the large variation in the frequency of hospitalisations reported in international studies, we present, in section 3.2, the results from a sensitivity analysis where we set the sum of CV and non-CV related hospitalisations to be 2.33 per year in the placebo arm following the estimates from Lane et al. 2019 (33). In addition to this, we present the results from a sensitivity analysis where we employ the NYHA-specific frequencies of hospitalisation from the ATTR-ACT trial, for both CV and non-CV related inpatient hospitalisations. Data on NYHA-class specific 6 months frequencies of CV and non-CV related hospitalisations are included in [redacted] but not listed in the main report because the data is “data on file” and confidential. Data from the ATTR-ACT trial used in the model show that the average number of CV and non-CV related hospitalisations are lower than what we assume in our base case analysis. The described sensitivity analyses thereby provide the span of the impact of CV and non-CV related hospitalisations based on currently available data.

2.7.3 Outpatient contact costs

Both patients diagnosed with ATTRwt and ATTRm are followed up on (monitored) regularly at the hospital. These follow-up visits are classified as outpatient contacts. Outpatient contact costs are calculated based on the unit cost per outpatient contact and the frequency of these contacts. This section presents the assumptions behind the outpatient contact costs and, in addition, the assumptions behind the patient time spent in relation to outpatient contacts.

Table 9 **Outpatient contacts assumptions for patients with ATTRwt or ATTRm**

		Outpatient contacts per year	Probability of outpatient contacts per cycle	Unit cost of outpatient contact (DKK)	Duration of outpatient contact (hours)
ATTRwt	NYHA I	1.5	11.75%	1,827 [DRG:05PR05]	1.5
	NYHA II	2	15.35%	1,827 [DRG:05PR05]	1.5
	NYHA III	2.5	18.81%	1,827 [DRG:05PR05]	1.5
	NYHA IV	3	22.12%	1,827 [DRG:05PR05]	1.5
ATTRm	NYHA I-IV	3.33	24.25%	1,827 [DRG:05PR05]	1.5

Source: Medical Advisory Board 2019, SHP and drg.dk.

Table 9 presents the assumptions regarding the frequency of follow-up outpatients contacts of patients with ATTRwt and ATTRm respectively. SHP has provided estimates for ATTRwt by NYHA class, and the Medical Advisory Board 2019 has provided estimates for the full population of ATTRm. Because most patients with ATTRm have already received a liver transplant, it is not possible to obtain NYHA class specific estimates of outpatient contacts for patients before they receive a transplant. Therefore, we assume that the frequency is the same across NYHA classes.

Furthermore, we assume that the unit cost associated with an outpatient contact at the outpatient clinic is DKK 1,827, which corresponds to the relevant DRG rate *'05PR05: Extended Cardiac investigation'*. The average patient time spent during an outpatient contact is assumed to be 1.5 hours, including 30 minutes for transportation each way and 30 minutes for the consultation.

To the best of our knowledge, Lane et al. (2019) is the only study that gives information about the frequency of outpatient contacts for patients with ATTRm and ATTRwt. Based on 364 patients with ATTRm and ATTRwt, the study finds the median number of outpatient contacts per year to be 8. In that context, the numbers presented in Table 9 should be interpreted as conservative estimates. In section 3.2, we therefore present the results from a sensitivity analysis, where the average number of outpatient contacts per years is set to 8.

2.7.4 Adverse event costs

In addition to the costs already mentioned, the base case analysis includes costs associated with the treatment of treatment-related treatment-emergent Adverse Events (AE). This section

presents the assumptions behind the AE costs and the patient time spent in relation to hospital contacts to treat the AEs.

The ATTR-ACT trial concluded that tafamidis was well tolerated with a safety profile similar to placebo in patients diagnosed with ATTR-CM (5). The study identified 3 treatment-related AEs with an incidence of ≥5% in either the 20mg arm, the 4x20 mg arm or the placebo arm of the ATTR-ACT trial: diarrhoea, urinary tract infection and nausea. As advised by SHP, these 3 AEs are treated in outpatient care with an average of 2 visits per adverse event.

Table 10 presents the risks of each AE, the DRG rates (unit costs) and how much time the patient spends getting treatment for these AEs. Note that the probability of AE can be lower than 5% since the AE is included if it had an incidence of more than 5% in just one arm.

Table 10 **Unit costs and time use associated with treatment-related adverse events (AE) with an incidence of ≥5% for patients with ATTRwt or ATTRm**

	Diarrhoea	Urinary tract infection	Nausea
Probability of AE in tafamidis	6.06%	3.41%	4.17%
Probability of AE in placebo	10.2%	4.5%	5.6%
Share of AEs requiring outpatient contact	100%	100%	100%
Number of outpatient contacts per AE	2	2	2
Unit cost of AE treated during outpatient contact	5,297 [DRG:06MA11]	1,932 [DRG:11MA98]	5,297 [DRG:06MA11]
Patient time spent per outpatient contact (hours)	1.5	1.5	1.5

Source: (40) and drg.dk.

Since AEs are most likely to occur with treatment initiation, a one-time total cost for AEs are applied during the first cycle. In contrast, costs for AE management can be applied on a per-cycle basis for the entire model analysis time horizon by selecting the “In perpetuity” option from the drop-down menu in the ‘Inputs – Adverse Events’ sheet. It is important to note, that when 'In perpetuity' is chosen in the model, the user should manually convert the risk of the relevant AEs during the trial from Table 10 (30 months) to monthly probabilities.

2.7.5 Cross-sectional costs

This section presents the assumptions behind the cross-sectional costs as well as the assumptions behind the patient time spent in relation to the cross-sectional activities.

SHP has informed us that patients are regularly seen for consultations with their GP, which is considered a cross-sectional cost. Such a consultation usually includes INR testing as well as measurement of blood pressure and blood tests. Moreover, the GP examines the patients’ disease

progression during consultation and refers the patient to the ambulatory if she finds the need for further follow-up of the patient.

Based on input from SHP, Table 11 presents the estimates of the frequency of visits to the GP for both ATTRwt and ATTRm patients in each of the 4 NYHA classes. The unit cost is based on the fee for service payments of GPs in Denmark (42). Specifically, the cost is set to DKK 267.72 per visit (standard consultation, service code: 0101, DKK 145.46) plus an added fee for service payment of an INR test (service code: 7126, DKK 122.26).

Lastly, it is assumed that the average time spent on a visit to the GP is 50 minutes. This is based on the assumption that the average duration of a GP visit is 20 minutes and that the average time spent on transportation is 15 minutes each way.

Table 11 **Unit cost and time spent on visits to GP for patients with ATTRwt or ATTRm**

	GP visits per year	GP visits per cycle	Cost per GP visit (DKK)	Duration of GP visit (minutes)
NYHA I	2	15.35%	267.72	50
NYHA II	2	15.35%	267.72	50
NYHA III	4	28.35%	267.72	50
NYHA IV	7	44.20%	267.72	50

Source: SHP and (42).

2.7.6 End-of-life costs

Patients who transition to the death health state incur a one-time cost for end of life. This cost input takes into consideration the costs for palliative care in the last month of life. Specifically, the end of life costs is set to the DRG rate for 30 days of palliative care (DRG tariff 2020 code: 05MA04 - Cost of 30 days palliative care for an HF patient) which equals DKK 64,115. End-of-life costs are applied in full to all patients who died in each model cycle as a tariff for death.

2.7.7 Patient costs

Patient costs include:

- transportation costs to GP
- transportation costs to the hospital
- patient time costs
- copayment (purchases of prescription drugs).

Transportation costs to the GP are calculated as 2 ways times 5 km/way times DKK 3.52 per km times number of visits to the GP. Transportation costs to the hospital are calculated as DKK 100 times the number of visits to the hospital. Patient time costs are calculated as the total time spent during inpatient hospitalisation, outpatient contacts and GP visits as well as transportation. The total time spent is then multiplied by a patient time unit cost per hour of DKK 179. As mentioned above, the patient copayment of prescription drugs is 39.65%.

As described in section 2.7.2, it is worth noticing that the mean duration of hospitalisations varies with both NYHA classes and treatment. This means that patients treated with tafamidis in for example NYHA class III can have a different mean duration of hospitalisations than patients treated with placebo in NYHA class III. The mean duration of hospitalisations for all NYHA classes and treatment are included in [redacted] but not listed in the main report because the data is "data on file" and confidential.

Table 12 presents the assumptions used for the basis of calculating the patient costs.

Table 12 **Patient costs assumptions: transportation unit costs, patient time unit costs and copayment of prescription drug**

	Cost
Transportation unit costs per hospital contact	DKK 100
Transportation unit cost per kilometre travelled to GP	DKK 3.52
Average distance to GP (km)	5
Patient time unit costs per hour	DKK 179
Average copayment rate of prescription drugs	39.65%

Source: (43) and statistics from medstat.dk.

Transportation costs and patient time costs are applied to both inpatient and outpatient hospital contacts, hospital contacts related to AEs and visits to the GP. Moreover, it is assumed in the base case analysis that the patient incurs a cost of DKK 179 per hour for all 24 hours during an inpatient hospital admission.

The assumptions related to patient time spent on inpatient hospitalisations, outpatient contacts, GP visits and time spent on AE management have been presented in section 2.7.2, 2.7.3, 2.7.4 and 2.7.5.

We assume that the opportunity cost of time is minimal for patients receiving palliative care in the last month of life. For that reason, the analysis does not include cost of patient time spent during end of life treatments.

2.8 Sensitivity analyses

In the following section, we summarise the identified uncertainties that may impact the estimate of the cost per patient associated with tafamidis treatment in each of the 2 base case analyses.

We have presented these uncertainties to the DMC and discussed their implications for the analyses. Should the DMC wish to perform their own sensitivity analyses, this is possible from the 'One-Way Inputs' and the 'Scenario Inputs' sheet.

2.8.1 Time horizon

As mentioned in section 2.5, the DMC assumes the average life expectancy for patients with ATTRwt in Denmark to be the same as that of UK patients (reported in Lane et al. 2019), namely 5 years (12,33). In addition, the protocol stipulates that the average life expectancy for an 80-year old man is 87.87 years. We therefore present a sensitivity analysis of 5 and 7.87 years (rounded off to 94 monthly cycles) (12).

Since we only have survival and discontinuation data from the ATTR-ACT study for the first 30 months, we extrapolate the OS curve beyond the 30 months of follow-up. Specifically, the sensitivity analyses were carried out using the Weibull parametric function to extrapolate OS. The parametric function is chosen based on the criteria outlined in section 2.1.2. In addition, discontinuation was extrapolated using the exponential function for both treatment arms.

For the analysis of the cost associated with tafamidis treatment in patients diagnosed with ATTRm, we present a sensitivity analysis where we set the time horizon to 1 and 12 months respectively. We also present a sensitivity analysis with a lifelong time horizon (55 years) in order to provide an estimate of the cost associated with tafamidis treatment in ATTRm patients who are not candidates for liver transplant. For this analysis, we extrapolate survival data using the exponential function, since this function provide the best fit in accordance to the criteria outlined in section 2.1.2. Moreover, we extrapolate discontinuation data using the exponential function.

2.8.2 No discontinuation and relative dose intensity

We present a sensitivity analysis for both ATTRwt and ATTRm where we assume no treatment discontinuation and a relative dose intensity of 1 implying no waste in order to assess the costs of tafamidis treatment with complete adherence.

2.8.3 Frequency of CV related and non-CV realted inpatient and outpatient contacts

As explained in section 2.7.2.2, we would like to investigate the impact of the frequency of CV and non-CV related hospitalisations. Therefore, we present two separate sensitivity analysis for each of the two base case scenarios. In the first sensitivity analysis, we set the average yearly

number of hospitalisations to 2.33 in the placebo arm corresponding to the findings of Lane et al. (2019) (33). We have carried out this analysis by scaling the CV and non-CV related hospitalisations such that the weighted average number of all inpatient hospitalisations (weighting with the initial NYHA class distribution of patients) equals 2.33 hospitalisations.

As a conservative estimate we present another sensitivity analysis where we base the NYHA class specific frequency of hospitalisations on what was found in the ATTR-ACT trial. Again, the NYHA class per cycle frequencies for both CV and non-CV related inpatient hospitalisations are included in [redacted] but not listed in the main report because the data is "data on file" and confidential.

Finally, as mentioned in section 2.7.3, we present the results of a sensitivity analysis where we set the frequency of outpatient contacts to 8 per year for both patients in the tafamidis and placebo arm with no variation across NYHA classes. This is in accordance with the results presented in Lane et al. (2019) (33).

2.8.4 Unit costs of CV and non-CV related inpatient hospitalisations

As explained in section 2.7.2.1, unit costs of CV and non-CV related inpatient hospitalisations are likely underestimating the real-world costs associated with these events. For this reason, we present two separate sensitivity analyses for ATTRwt where we increase the unit cost associated with CV and non-CV related hospitalisations with 50%. For ATTRm, we only present one sensitivity analysis, where we increase the unit costs associated with CV-related hospitalisations with 50%, as patients with ATTRm do not experience any non-CV related hospitalisations.

2.8.5 Patient costs

Finally, we provide four sensitivity analyses for each of the two base case scenarios that consider the uncertainty related to the patient costs.

Since we do not have data on the opportunity cost of time for this patient population and the costs associated with transportation to the GP, outpatient contacts and inpatient hospitalisations, we propose distinct sensitivity analyses.

In the first sensitivity analysis, where transportation unit costs are increased by 50%, the resulting unit cost of transportation per hospital contact is DKK 150 and the resulting unit cost per kilometre travelled to the GP is DKK 5.28. In the second sensitivity analysis, where transportation unit costs are decreased by 50%, the resulting unit cost of transportation per hospital contact is DKK 50 and the resulting unit cost per kilometre travelled to the GP is DKK 1.76. In both sensitivity analyses the value of patient time is kept at the central estimate of DKK 179.00 per hour.

In the third sensitivity analysis where the value of patient time is increased by 50% the resulting value of patient time is DKK 268.50 per hour. And in the fourth sensitivity analysis where the

value of patient time is decreased by 50%, the resulting value of patient time is DKK 89.50 per hour.

All sensitivity analyses impact the total patient costs associated with both CV and non-CV related inpatient hospitalisations, outpatient contacts, GP visits and treatment related to AEs.

2.9 Overview

In alignment with the DMC guidelines, Table 13 provides an overview of the most important elements and assumptions in this cost per patient and budget impact analysis.

Table 13 **Analysis overview**

Element	Base case
Number of analyses	1 analysis for ATTRwt 1 analysis for ATTRm
Applied model	Adaptation of the cost part of a global CU model for tafamidis
Model type	Multi-state, cohort Markov model
Intervention	Tafamidis
Comparator	Placebo
Perspective	Limited societal
Included costs	Drug costs (incl. relevant prescription drug) Hospital sector costs: admissions outpatient contacts adverse events end of life Cross sectional costs: GP visits Patient cost (excl. producitivity costs, incl. copayment for prescription drug)
Unit costs	DRG charges Fees AIP or AUP DMC unit prices (43)
Time horizon	ATTRwt analysis: 30 months ATTRm analysis: 6 months
Discount rate	4% (year 2-34), 3% (year 35-55)
Frequency of CV related hospitalisations per year for patients receiving placebo	1.73 for ATTRwt 0.33 for ATTRm
Frequency of non-CV related hospitalisations per year for patients receiving placebo	0.68 for ATTRwt 0.0 for ATTRm
OS modelling	**Base case**: Kaplan-Meier **Sensitivity analyses:** ATTRwt: Weibull ATTR-m: Exponential
Time on treatment	**Base case**: Kaplan-Meier **Sensitivity analyses:** Exponential

3 Results: Cost per patient analysis

3.1 Base case

In this section, we present the results of the two base case analysis of the cost per patient treated with tafamidis compared to placebo. The results are presented separately for patients with ATTRwt and ATTRm.

3.1.1 ATTRwt

3.1.1.1 Drug costs

Table 14 presents the costs associated with primary treatment i.e. tafamidis or placebo, cost of regional reimbursement of diuretics and other prescription drugs separately for patients in the tafamidis and the placebo treatment arm. Drug prices are pharmacy purchasing price (PPP/AIP) excl. VAT for tafamidis and pharmacy retail price excl. VAT (AUP) for diuretics.

Table 14 **Total drug costs for ATTRwt patients during the time horizon of 30 months (DKK), discounted**

	Tafamidis (DKK)	Placebo (DKK)
Primary treatment	1,575,756	0
Diuretics (regional reimbursement)	427	413
Other prescibtion drugs (regional reimbursement)	0	0
Total drug costs	**1,576,183**	**413**

Note: Cost associated with primary treatment includes costs to treatment with tafamidis or placebo.

3.1.1.2 Hospital costs

Table 15 presents the total hospital costs. The hospital costs for patients in the tafamidis arm are DKK 149,546 and DKK 221,224 for patients in the placebo arm.

Table 15 **Total hospital costs for ATTRwt patients during the time horizon of 30 months (DKK), discounted**

	Tafamidis (DKK)	Placebo (DKK)
Inpatient CV related hospitalisation costs	88,990	135,855
Inpatient non-CV related hospitalisation costs	36,901	54,777
Outpatient contacts costs	7,623	7,553
AEs costs	1,211	1,841
End of life costs	14,821	21,197
Total hospitalisation costs	**149,546**	**221,224**

The table shows that even though the survival is higher for patients in the tafamidis treatment arm, total hospital costs are still higher for patients on placebo. This is caused by the fact that treatment with placebo is associated with a higher frequency of hospitalisation and a longer duration of hospitalisations

3.1.1.3 Cross sectional costs

Table 16 presents the cross-sectional costs for patients with ATTRwt. In the analysis, cross sectional costs are limited to costs associated with visits to the GP. The total costs amount to DKK 1,351 and DKK 1,385 per patient for patients treated with tafamidis and placebo respectively.

Table 16 **Total cross-sectional costs for ATTRwt patients during the time horizon of 30 months (DKK), discounted**

	Tafamidis (DKK)	Placebo (DKK)
Cross sectional costs	1,351	1,385

3.1.1.4 Patient costs

Patient costs consist of patient time costs, transportation costs and individual copayment of prescription drugs (diuretics). Patient costs differ between the tafamidis and placebo arm due to differences in the frequency of both CV and non-CV related hospitalisations as well as the differences in the mean duration of hospitalisations between the 2 groups. Moreover, the differences in patient costs reflect differences in the risk of AEs as well as the increased survival in the tafamidis arm. Table 17 presents the patient costs. The patient costs for tafamidis are DKK 75,198 and for placebo DKK 176,492. Even though the survival is higher for patients in the

tafamidis treatment arm, patient costs are still higher for patients on placebo. This is caused by the fact that treatment with placebo is associated with a higher frequency of hospitalisation and a longer duration of hospitalisations.

Table 17 **Total patient costs for ATTRwt patients during the time horizon of 30 months (DKK), discounted**

	Tafamidis (DKK)	Placebo (DKK)
Patient time costs	73,960	175,078
Transportation costs	957	1,143
Individual copayment (prescription drugs)	280	271
Total patient costs	**75,198**	**176,492**

3.1.1.5 Total costs per patient

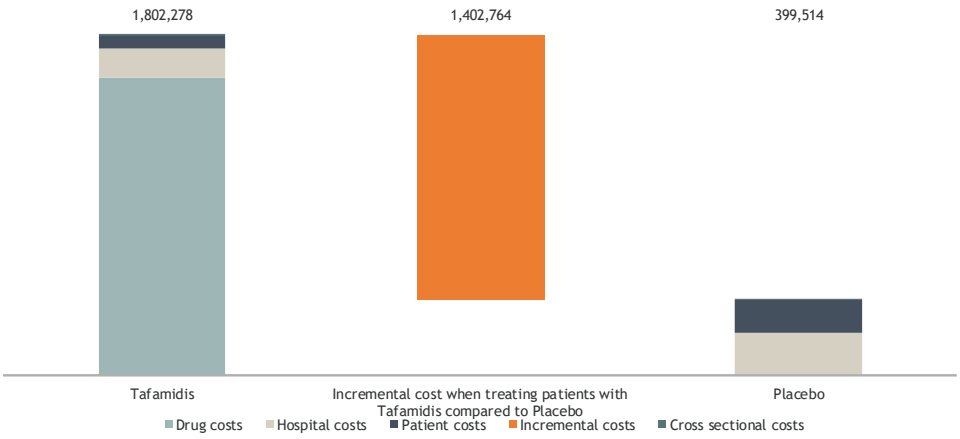
The total costs associated with treatment of ATTRwt with tafamidis or placebo are presented in Table 18.

Table 18 **Total cost per patient for ATTRwt patients during the time horizon of 30 months (DKK), discounted**

	Tafamidis (DKK)	Placebo (DKK)
Drug costs	1,576,183	413
Hospitalisation costs	149,546	221,224
Cross sectional costs	1,351	1,385
Patient costs	75,198	176,492
Total cost per patient	**1,802,278**	**399,514**

Figure 2 provides a graphical presentation of the total cost per patient in the tafamidis arm compared to the total cost per patient in the placebo arm divided into cost components. Moreover, the figure presents the incremental costs associated with treating ATTRwt patients with tafamidis.

Figure 2 **Total cost per patient (DKK) for ATTRwt patients during the time horizon of 30 months (DKK), discounted**



The incremental cost of tafamidis is 1,402,764 DKK.

3.1.2 ATTRm

3.1.2.1 Drug costs

Table 19 presents the costs associated with primary treatment i.e. tafamidis or placebo, cost of regional reimbursement of diuretics and other prescription drugs given to ATTRm patients. Drug costs are presented separately for patients in the tafamidis and the placebo treatment arm. Drug prices are pharmacy purchasing price (PPP/AIP) excl. VAT for tafamidis and pharmacy retail price excl. VAT (AUP) for diuretics.

Table 19 **Total drug costs for ATTRm patients during the time horizon of 6 months (DKK)**

	Tafamidis (DKK)	Placebo (DKK)
Primary treatment	379,340	0
Diuretics (regional reimbursement)	94	95
Other prescibtion drugs (regional reimbursement)	0	0
Total drug costs	**379,434**	**95**

Note: Cost associated with primary treatment includes costs to treatment with tafamidis or placebo.

3.1.2.2 Hospital costs

Hospital costs are presented in Table 20. The hospital costs for patients treated with tafamidis are estimated to DKK 16,057 and correspondingly DKK 15,029 for patients treated with placebo.

Table 20 **Total hospital costs for ATTRm patients during the time horizon of 6 months (DKK)**

	Tafamidis (DKK)	Placebo (DKK)
Inpatient CV related hospitalisation costs	7,966	5,847
Inpatient non-CV related hospitalisation costs	0	0
Outpatient contacts costs	2,541	2,551
AEs costs	1,211	1,845
End of life costs	4,339	4,785
Total hospitalisation costs	**16,057**	**15,029**

Note: Number are rounded.

3.1.2.3 Cross-sectional costs

Table 21 presents the cross-sectional costs associated with treatment of ATTRm patients. The total costs attributable to visits to the GP amounts to DKK 326 and DKK 327 for ATTRm patients in the tafamidis arm and in the placebo arm respectively.

Table 21 **Total cross-sectional costs for ATTRm patients during the time horizon of 6 months (DKK)**

	Tafamidis (DKK)	Placebo (DKK)
Cross-sectional costs	326	327

3.1.2.4 Patient costs

Table 22 presents the patient costs which consist of patient time costs, transportation costs and individual copayment for prescription drugs (diuretics). In total, the patient costs associated with tafamidis treatment are DKK 3,181, and DKK 1,976 for patients treated with placebo.

Table 22 **Total patient costs for ATTRm patients during the time horizon of 6 months (DKK)**

	Tafamidis (DKK)	Placebo (DKK)
Patient time costs	2,888	1,675
Transportation costs	231	239
Individual copayment (prescription drugs)	62	62
Total patient costs	**3,181**	**1,976**

3.1.2.5 Total costs per patient

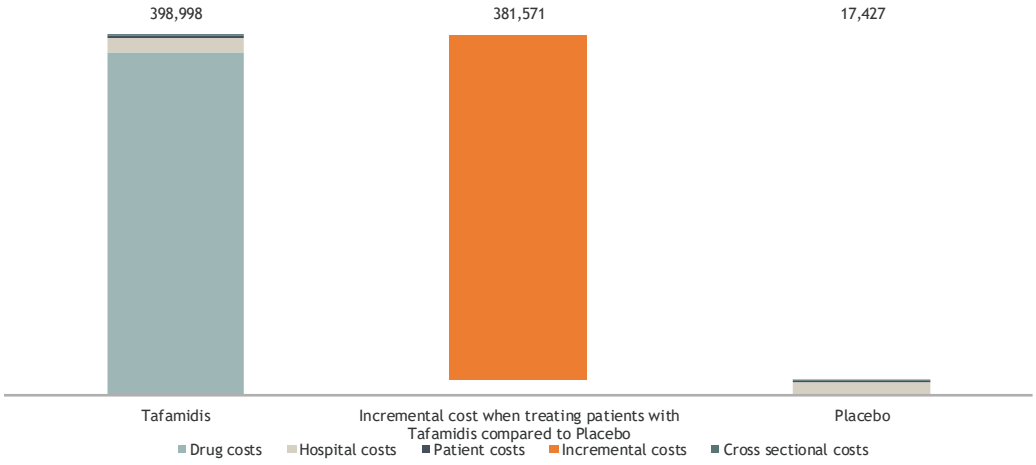
The total costs associated with treating ATTRm patients with tafamidis or placebo in 6 months are presented in Table 23.

Table 23 **Total cost per patient for ATTRm patients during the time horizon of 6 months (DKK)**

	Tafamidis (DKK)	Placebo (DKK)
Drug costs	379,443	95
Hospitalisation costs	16,057	15,029
Cross sectional costs	326	327
Patient costs	3,181	1,976
Total cost per patient	**398,998**	**17,427**

Figure 3 provides a graphical presentation of the total cost per patient in the tafamidis arm compared to the total cost per patient in the placebo arm divided into cost components. Moreover, the figure presents the incremental costs associated with treating ATTRm patients with tafamidis.

Figure 3 **Total cost per patient (DKK) for ATTRm patients during the time horizon of 6 months (DKK)**



The incremental cost of tafamidis is 381,571 DKK.

3.2 Sensitivity analyses

This section presents the results from the sensitivity analysis described in section 2.8.

3.2.1 ATTRwt

The results of the sensitivity analyses for the ATTRwt patients are presented in Table 24. From the table it is evident that most sensitivity analyses result in differences close to the base case difference of DKK 1,402,764.

The frequency of inpatient hospitalisations, outpatient contacts, relative dose intensity, elimination of discontinuation and patient costs associated with time use and transportation all have limited impact on the total cost per patient.

In contrary, the time horizon of the analysis affects the results. Extending the time horizon of the treatment increases the incremental cost per patient associated with tafamidis treatment in patients with ATTRwt. It is important to note that extending the time horizon of the treatment naturally implies extending the efficacy gains in terms of life years gained and the utility gains of the patients, which is not included in these cost analyses.

Table 24 **Sensitivity analysis (DKK)**

	Tafamidis (DKK)	Placebo (DKK)	Difference (DKK)
Base case	**1,802,278**	**399,514**	**1,402,764**
Time horizon: 5 years	2,827,059	618,164	2,208,894
Time horizon: 7.87 year	3,334,765	685,128	2,649,637
Relative dose intensity, 100%	1,847,670	399,514	1,448,156
No discontinuation	1,974,745	399,514	1,575,231
Frequency of inpatient hospitalisations (CV and non-CV related) per year set to 2.33	1,796,359	388,889	1,407,470
Frequency of inpatient hospitalisations (CV and non-CV related) per year following ATTR-ACT	1,745,197	293,861	1,451,326
Frequency of outpatient contacts per year set to 8	1,820,812	417,220	1,403,592
Unit costs per CV related hospitalisation (increased with 50%)	1,846,773	467,442	1,379,331
Unit costs per non-CV related hospitalisation (increased with 50%)	1,820,729	426,903	1,393,826
Unit cost of patient time (increased with 50%)	1,839,258	487,053	1,352,205
Unit cost of patient time (reduced with 50%)	1,765,298	311,975	1,453,323
Transportation costs (increased with 50%)	1,802,757	400,086	1,402,671
Transportation costs (reduced with 50%)	1,801,799	398,742	1,402,857

3.2.2 ATTRm

The results of the sensitivity analyses for the ATTRm patients are presented in Table 25. Similarly, to what was the case for the sensitivity analyses for patients with ATTRwt, the incremental costs of treatment with tafamidis are close to the results from the base case of DKK 381,571.

We can conclude that the frequency of inpatient hospitalisations, outpatient contacts, relative dose intensity, elimination of discontinuation and patient costs associated with time use and transportation have limited impact on the total cost per patient.

The parameter with the largest impact on the incremental costs is the time horizon of the analysis. As expected, extending the time horizon of the treatment increases also the incremental cost per patient. Extending the time horizon of the treatment naturally would extend the efficacy gains in terms of life years and the utility gains of the patients, which is not accounted for in these cost analyses. This is especially the case for the sensitivity analysis where we set the time horizon to be lifelong (55 years). Based on the protocol received by the DMC, patients with the Danish Leu11Met mutation will develop serious heart failure and die after approximately 2 years if not

treated. In this scenario, the costs associated with tafamidis treatment reflects large gains in efficacy, which is not covered in this analysis.

Table 25 **Sensitivity analysis (DKK)**

	Tafamidis (DKK)	Placebo (DKK)	Difference (DKK)
Base case	**398,998**	**17,427**	**381,571**
Time horizon: 1 month	70,973	3,847	67,126
Time horizon: 12 months	735,331	32,892	702,439
Time horizon: Lifelong (55 years)	2,717,224	108,286	2,608,937
Relative dose intensity, 100%	409,926	17,427	392,499
No discontinuation	406,378	17,427	388,951
Frequency of inpatient hospitalisations (CV and non-CV related) per year set to 2.33	449,809	54,411	395,398
Frequency of inpatient hospitalisations (CV and non-CV related) per year following ATTR-ACT	444,558	49,125	395,433
Frequency of outpatient contacts per year set to 8	402,071	20,512	381,559
Unit costs per CV related hospitalisation (increased with 50%)	402,981	20,351	382,630
Unit cost of patient time (increased with 50%)	400,442	18,265	382,178
Unit cost of patient time (reduced with 50%)	397,501	16,536	380,965
Transportation costs (increased with 50%)	399,114	17,547	381,567
Transportation costs (reduced with 50%)	398,883	17,308	381,575

4 Results: Budget impact analysis

4.1 Budget impact: Real-world scenario

The budget impact analysis follows the methodology stipulated by the DMC and does not include patient costs and discounting. The base case analysis follows a "real-world" scenario informed by the protocol and Danish experts' assessments on incidence and prevalence.

4.1.1 ATTRwt

The DMC estimates the prevalence of ATTRwt patients as of March 2020 to be between 400 and 500. Moreover, they estimate that 150 new patients will be diagnosed each year (12). The DMC does not indicate anything about the percentage of patients who are candidates for treatment or speed of uptake, and Pfizer has therefore collected this information from Danish experts.

Based on assessments from SHP and FG as explained in section 1.3.1, we assume that 200 patients are candidates for treatment and that they will initiate treatment within 3 months. Moreover, we assume an annual incidence of 120 patients (80% of 150) implying all eligible patients take up treatment if tafamidis is recommended.

Table 26 presents the population estimates used in the budget impact analysis. Patient numbers can be changed in the 'Budget Impact' sheet in the model.

Table 26 **Population estimates of ATTRwt patients used in budget impact model**

Population estimates	
Prevalence (candidates for treatment), 2020	200
Yearly incidence	120
Time to uptake of treatment for prevalent population (months)	3

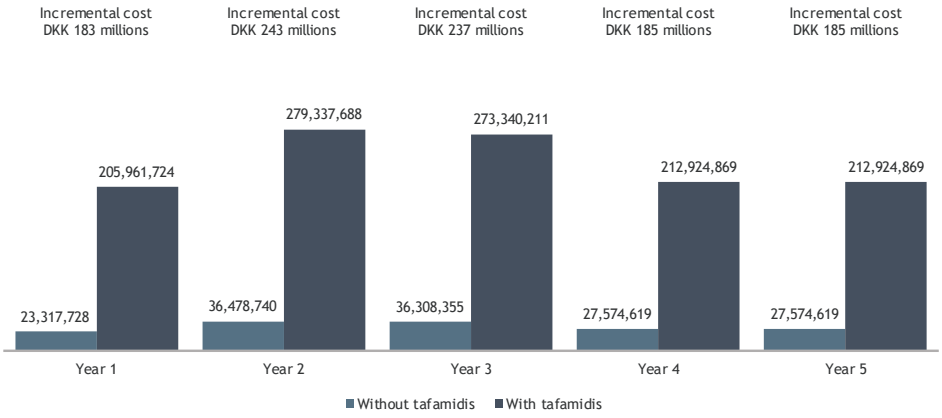
SHP and FG have informed us that incident patients are – naturally – not all diagnosed the first day of the year, but that they are diagnosed evenly across the year. We therefore assume that the uptake of treatment among these patients are uniformly distributed across the year. This implies that we assume that 10 patients initiate treatment with tafamidis each month. Moreover, we assume that the patient distribution follows the survival curve from the total cost analysis. Table 27 presents the patient flow of the real-world budget impact analysis in patient years from year 1-5.

Table 27 **Patient flow in budget impact analysis for ATTRwt patients, patient years per year**

	Year 1	Year 2	Year 3	Year 4	Year 5
Placebo	243	349	337	262	262
Tafamidis	245	354	355	271	271

Figure 4 shows the budget impact in the first 5 years with and without a positive recommendation for tafamidis. The budget impact in the first year is an incremental cost of DKK 182,643,996.

Figure 4 **Budget impact results for ATTRwt patients: Real world scenario 1-5 years (DKK), not discounted**



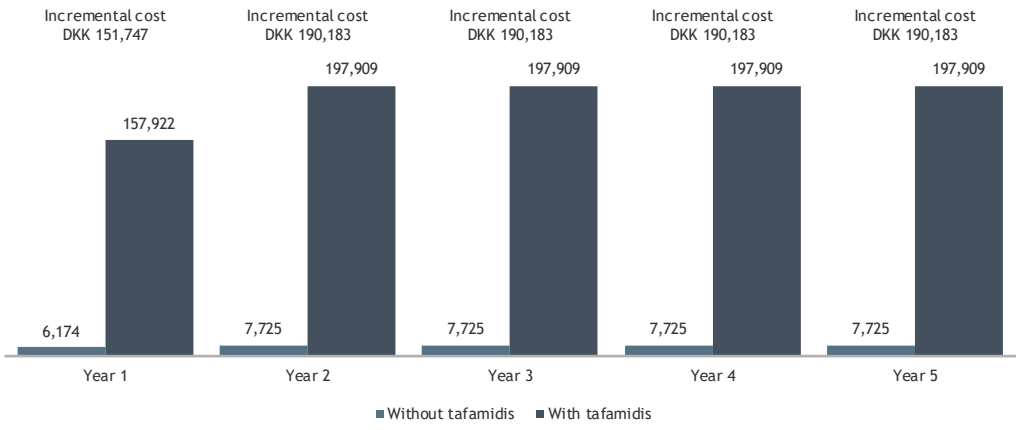
4.1.2 ATTRm

As mentioned in section 1.3.2, a prevalence of 35 ATTRm patients with the unique Danish mutation Leu111Met is known. For this mutation, an incidence of 10 patients (carriers converting to patients) is expected in the next 10-20 years (12) and only the incident patients are eligible for treatment with tafamidis. That is, approx. ½-1 patient per year will expectedly initiate tafamidis treatment. Therefore, the results from the budget impact analysis presented below reflect an assumed prevalence of 0 patients and a incidence of 0.5 patients per year.

Again, we assume that all eligible patients take up treatment if tafamidis is recommended and that patient uptake is distributed uniformly across the year. Moreover, we assume that the patient distribution follows the survival curve from the total cost analysis.

Figure 5 shows the budget impact in the first 5 years with and without a positive recommendation for tafamidis. The budget impact in the first year is an incremental cost of DKK 151,747.

Figure 5 **Budget impact results for ATTRm patients: Real world scenario 1-5 years (DKK), not discounted**



There is limited uncertainty concerning the expected number of future ATTRm patients. Therefore, this section of the report only includes the above results from the base case scenario for ATTRm patients.

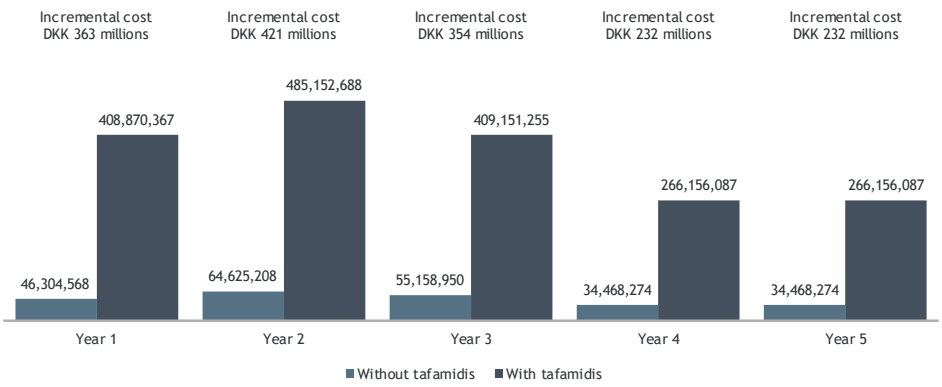
4.2 Budget impact: Scenario with full uptake of treatment

As mentioned, the DMC estimates the prevalence of ATTRwt patients as of March 2020 to be between 400 and 500. Moreover, they expect that 150 new patients will be diagnosed each year (12). As also referred to in the early application, the Medical Advisory Board 2019 estimates the Danish prevalence to be 440 patients with ATTRwt in Denmark. The Advisory Board estimated that it would take 5 years to reach a diagnostic awareness among cardiologist leading to this prevalence.

However, to identify the impact on public finances if the DMC assumptions are applied, Figure 6 presents the budget impact assuming full uptake. Specifically, we assume a prevalence of

treatment eligible patients of 450 patients (enrolled in treatment during the first 3 months after recommendation) and a yearly incidence of 150 patients, as specified in the protocol from the DMC (12). It is seen from the figure that the impact on public finances increases to DKK 363 mill. in the first year after the recommendation.

Figure 6 **Budget impact results for ATTRwt patients: Full uptake scenario 1-5 years (DKK), not discounted**

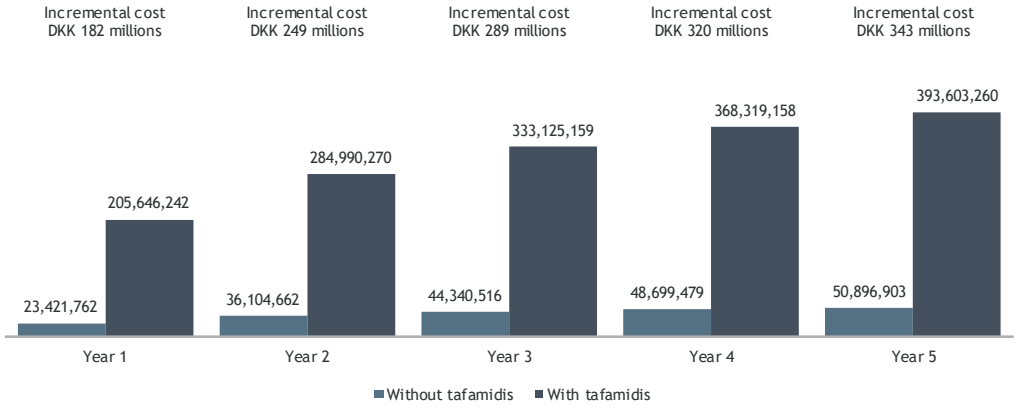


4.3 Budget impact: 5 year time horizon

In addition to the real-world budget impact analysis presented above, Figure 7 presents the results from a budget impact analysis for patients with ATTRwt, where the time horizon of treatment is set to 5 year. Thereby, the results presented in the figure below are equivalent to the budget impact with a lifelong time horizon for ATTRwt patients.

As with the sensitivity analyses presented in section 2.8, we have extrapolated efficacy data using the Weibull parametric function. Moreover, we have extrapolated discontinuation using the exponential model.

Figure 7 **Budget impact results for ATTRwt patients: 5 year time horizon 1-5 years (DKK), not discounted**



5 Discussion

The analyses presented in this report show that tafamidis presents a total added cost per patient of DKK 1,402,764 for ATTRwt and DKK 381,571 for ATTRm.

Comprehensive sensitivity analyses have been performed. They show that the results (i.e. cost per patient and budget impact) are especially sensitive to changes in time horizon and the number of ATTRwt patients. What further challenges the results of this analysis, which is not accounted for in the sensitivity analyses, is the lack of inclusion of costs caused by delays in diagnosis and cost of misdiagnoses and mistreatment prior to diagnosis.

A UK register-based study estimated that 42% of patients wait >4 years to get a proper diagnosis (33). As referred to previously, a Danish study of costs of ATTRwt accepted for publication in Value in Health May 2020 has assessed the costs of ATTRwt in Denmark and concludes that cost of hospitalisation pre-diagnosis amounts to USD 17,906 (DKK 122,298) per patient. This is a conservative estimate because it only includes costs 3 years prior to diagnosis even though costs are also present in previous years (38).

Furthermore, we have not included the costs of patients who are mis- or undiagnosed (with for example spinal stenosis or carpal tunnel syndrome) and the costs of investigations and treatments associated with misdiagnosis prior to proper diagnosis. A Danish registry study has recently quantified the frequency of misdiagnosis and mistreatment and concludes that 60% of patients with ATTRwt receive more than 2 misdiagnoses before they get a correct diagnosis (32). This article also refers to some simple but not costly measures in order to increase suspicion and thereby the diagnostic rate of patients with ATTRwt.

According to the Medical Advisory Board 2019, diagnostic awareness will most likely increase with the positive recommendation of tafamidis. Thereby, patients will to a larger extent be diagnosed earlier which will result in a higher share of patients in NYHA class I and II. This again will lead to a delayed progression and thereby better overall survival and quality of life for patients. It will also most likely decrease and possibly diminish the costs the healthcare system has today when it comes to delays in diagnoses, misdiagnoses and unnecessary treatments.

For ATTRm patients, the results for the base case analysis are robust. However, for the sensitivity analysis that applies a longer time horizon, uncertainty is presented by the lack of data on efficacy and costs after transplant. As referred to previously, a recent Danish study of the cost of ATTRm accepted for publication in the May issue of Value in Health 2020 has assessed the total lifetime costs of ATTRm and finds that the average lifetime hospital cost (excluding diagnosis) per patient is DKK 2,554,133 (37).

6 Conclusion

The ATTR-ACT trial shows that tafamidis treatment of patients with wild-type and ATTRm reduces all-cause mortality and CV related hospitalisations, reduces the decline in functional capacity and increases quality of life. Tafamidis once daily is well tolerated with a safety profile comparable to placebo when used for the treatment of adult patients.

The analyses presented in this report show that tafamidis is associated with a total added cost per patient of DKK 1,420,764 for ATTRwt patients and DKK 381,571 for ATTRm patients. The analyses are based on data from the ATTR-ACT trial as well as additional input from Danish clinical experts regarding the Danish incidence and prevalence, and Danish clinical practice in the field of ATTR-CM.

The results are limited by a general lack of data because ATTR-CM is not routinely diagnosed and treated today. The results are also conservative since they exclude costs of treatment prior to diagnosis and costs of misdiagnosis and mistreatments.

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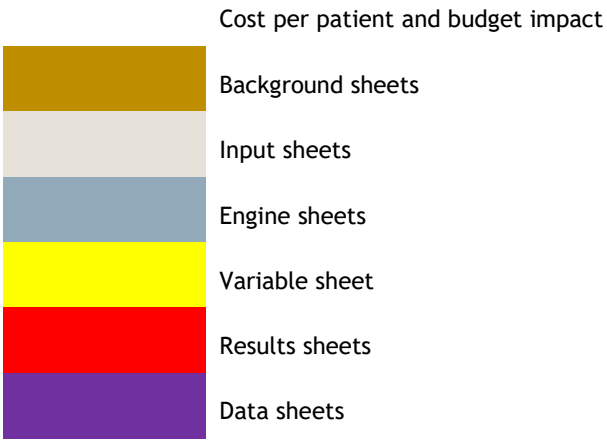
Appendix 1: Model overview

The cost-utility model was built and tested in Microsoft Excel 2016 and is 32-bit and 64-bit compatible. Visual Basic for Applications (VBA) macros and forms were employed to facilitate ease-of-use and to automate the running of probabilistic analyses.

The model includes the following color-coded worksheets:



- **Cost per patient and budget impact sheets**
    - **Cost per patient:** Contains the results from the base case analysis and groups the costs into the four relevant categories. Moreover, the sheet contains a graphical presentation of the total per patient costs both with and without patient costs.
    - **Budget impact:** Presents the 5-year budget impact of the base case analysis, where costs are grouped into relevant categories. Moreover, the sheet graphically presents the budget impact for each year up until 5 years after the approval of tafamidis.
- **Background sheets**
    - **Cover**: Contains the title and last revised date of the cost utility model.
    - **Instructions**: Displays simplified instructions on how to use and navigate the model.
    - **Model Design**: Shows the model diagram and a brief description of the model structure.

- **Input sheets**
    - **General**: Contains general input for the analysis (such as perspective, treatment names, currency, time horizon and discounting) and population (including number of patients in the cohort, 'total population' versus subgroup selection and NYHA class distributions for the 'total population').
    - **Overall Survival:** Contains input for selecting the type of mortality (all-cause or CV related) and the parametric survival function of choice used for extrapolating the tafamidis and placebo arms. If the 'total population' is being evaluated in the analysis, the curves for the NYHA class I/II and NYHA class III subgroups are displayed on the same screen with the same extrapolation functions by treatment arm used in both subgroups.
    - **Hospitalisations:** Contains input for the per-cycle probabilities and unit costs of CV or non-CV related hospitalisations by treatment arm.
    - **Outpatient Contacts:** Contains input for the per-cycle probabilities and unit costs of outpatient hospital contacts related to patient follow-up.
    - **Treatment Costs:** Contains input for drug acquisition costs by treatment arm, including cost per day, RDI and assumption for extrapolation of tafamidis discontinuation. Moreover, the sheet contains input of cost per cycle for diuretics and other prescription drugs.
    - **Adverse Events:** Contains input for the type of AEs, cost to manage AEs and the probability of AEs by treatment arms.
    - **Transplants:** Contains input for per-cycle probability of receiving cardiac transplant (by NYHA class) and death due to transplant. Also contains inputs for per-cycle transplant costs and utilities.
    - **Cardiac Implant:** Contains input for per-cycle probability of receiving cardiac mechanical assists device (by treatment arm). Also contains input for implant costs.
    - **Background Management:** Contains input for per-cycle costs of background management or other resource use costs by NYHA class.
    - **End of life costs:** Contains an input for end of life costs.
    - **Indirect costs:** Contains input for per-cycle indirect costs by treatment arm and by NYHA class.
    - **Utilities:** Contains input for per-cycle health state utilities by treatment arm and by NYHA class.
    - **One-Way Inputs:** Contains input to run the one-way sensitivity analysis.

- **Scenario Inputs:** Contains input to run the multi-way scenario analysis for the selected ‘subgroup’. This worksheet is hidden if the ‘total population’ option is selected.
- **Scenario Inputs - Total:** Contains input for the NYHA class I/II and NYHA class III subgroups to run the multi-way scenario analysis for the ‘total population’.
- **PSA Inputs:** Contains input to run the probabilistic sensitivity analysis.
- **Cohort Inputs:** Contains input for running a multi-cohort scenario analysis, including the number of future incident cohorts to run and the NYHA class distribution of each incident cohort. The analysis will use the current model settings for all other inputs. This worksheet is only available with the ‘total population’ option.

- **Results sheets**
  - **Results – Base Case:** Provides results from the reference case analysis for the selected ‘subgroup’. This worksheet is hidden if the ‘total population’ option is selected.
  - **Budget Impact:** Provides the results for the 5-year budget impact of the base case analysis.
  - **Results – Total Analysis:** Provides weighted results from the reference case analysis for the ‘total population’. This worksheet is hidden if the ‘subgroups’ option is selected.
  - **One-way results – ICER:** Displays results in terms of the cost per QALY ratio from the one-way sensitivity analysis for the selected ‘subgroup’. This worksheet is hidden if the ‘total population’ option is selected.
  - **One-way results – ICER Total:** Displays weighted results in terms of the cost per QALY ratio from the one-way sensitivity analysis for the ‘total population’. This worksheet is hidden if the ‘subgroups’ option is selected.
  - **One-way results – Costs:** Displays results in terms of the incremental costs from the one-way sensitivity analysis for the selected ‘subgroup’. This worksheet is hidden if the ‘total population’ option is selected.
  - **One-way results – Costs Total:** Displays weighted results in terms of the incremental costs from the one-way sensitivity analysis for the ‘total population’. This worksheet is hidden if the ‘subgroups’ option is selected.
  - **One-way results – QALYs:** Displays results in terms of the incremental QALYs gained from the one-way sensitivity analysis for the selected ‘subgroup’. This worksheet is hidden if the ‘total population’ option is selected.

- **One-way results – QALYs Total:** Displays weighted results in terms of the incremental QALYs gained from the one-way sensitivity analysis for the 'total population'. This worksheet is hidden if the 'subgroups' option is selected.
- **Scenario Results:** Displays results from the multi-way scenario analysis for the selected 'subgroup'. This worksheet is hidden if the 'total population' option is selected.
- **Scenario Results Total:** Displays weighted results from the multi-way scenario analysis for the 'total population'. This worksheet is hidden if the 'subgroups' option is selected.
- **PSA Results:** Displays results from the PSA for the selected 'subgroup'. This worksheet is hidden if the 'total population' option is selected.
- **PSA Results Total:** Displays weighted results from the PSA for the 'total population'. This worksheet is hidden if the 'subgroups' option is selected.
- **Cohort Results:** Displays weighted results from the multi-cohort scenario analysis. This worksheet is only available with the 'total population' option.

- **Engine sheets**
  - **Vyndaqel:** Contains the trace sheet calculations for the tafamidis arm.
  - **Budget Impact (Vyndaqel):** Contains the trace sheet calculations for the budget impact results for the tafamidis arm.
  - **Placebo:** Contains the trace sheet calculations for the placebo arm.
  - **Budget Impact (Placebo):** Contains the trace sheet calculations for the budget impact results for the tafamidis arm.
- **Variable sheet**: Variable names used throughout the model are listed in this sheet.
- **Data sheets**
  - **Survival curve data:** Contains survival curve extrapolations of all-cause mortality data.
  - **Drug cost decrease:** Stores the per-cycle costs of tafamidis used in the drug cost calculations over time.
  - **Discontinuation:** Contains time to treatment discontinuation data of tafamidis, such as the AIC and BIC statistics and a graphical illustration of the selected extrapolation function used in the drug cost calculations.
  - **Shift tables:** Contains cross-sectional patient distribution data by NYHA health state.

- **Life tables:** Contains life tables and calculations for determining all-cause mortality using CV related survival data from ATTR-ACT trial and non-CV survival data from country-specific life tables.
- **Mortality by NYHA:** Contains the distribution of deaths by NYHA class by treatment arm as reported in the ATTR-ACT trial.
- **Transition probabilities:** Contains transition probability data used to inform patient distributions by NYHA class post 30 months.
- **Survival curve additional data:** Contains the AIC and BIC statistics for trial-derived all-cause mortality and CV mortality extrapolation.

Additionally, there are several sheets that store the output from running the one-way sensitivity, multi-way scenario, probabilistic and multicohort analyses macros. The outputs are used to inform the displayed weighted results for the 'total population'. These sheets are always hidden but can be unhidden for full transparency if needed.

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Medicinrådet

Medicinrådets protokol for vurdering af tafamidis til behandling af transthyretin-medieret amyloidose med kardiomyopati

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om protokollen

Protokollen er grundlaget for Medicinrådets vurdering af et nyt lægemiddel. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i den endelige ansøgning, og som Medicinrådet skal basere sin vurdering på.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	6. marts 2020
Ikrafttrædelsesdato	6. marts 2020
Dokumentnummer	72952
Versionsnummer	1.0

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 6. marts 2020

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Vyndaqel®
Generisk navn	Tafamidis
Firma	Pfizer
ATC-kode	N07XX08
Virkningsmekanisme	Tafamidis er en specifik stabilisator af transthyretin
Administration/dosis	Peroral 61 mg én gang daglig
Godkendt EMA-indikation	Til behandling af vildtype eller arvelig transthyretin-medieret amyloidose hos voksne patienter med kardiomyopati (ATTR-CM)

2 Forkortelser

ATTRwt:	Vildtype transthyretinmedieret amyloidose
ACE:	*Angiotensin Converting Enzyme*
ATTR-CM:	transthyretinmedieret amyloidose med kardiomyopati
ATTR-PN:	transthyretinmedieret amyloidose med polyneuropati
AR:	*adverse reaction* (bivirkning)
ARR:	absolut risiko reduktion
CI:	Konfidensinterval
DNA:	*Deoxyribonucleic acid*
DPD:	3,3-diphosphono-1,2-propanodicarboxylic acid
eGRF:	Estimeret glomerulær filtrationshastighed
EMA:	*European Medicines Agency*
FAC:	*Familial Amyloid Cardiomyopathy*
FAP:	*Familial Amyloid Polyneuropathy*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
hATTR:	Arvelig transthyretinmedieret amyloidose
HR:	*Hazard ratio*
ITT:	*intention-to-treat*
KCCQ-OS:	*Kansas City Cardiomyopathy Questionnaire – Overall Summary*
Leu:	Leucine
Met:	Methionine
MKRF:	Mindste klinisk relevante forskel
NAC:	*National Amyloidose Center*
NT-proBNP:	N-terminal pro B-type natriuretisk peptid
NYHA :	New York Heart Association
OR:	*Odds ratio*
OS:	O*verall Survival*
RR:	Relativ risiko

SMD:	*Standardized Mean Difference*
TTR:	Transthyretin
Val:	Valine
6MWT:	6 minutters gangtest

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af tafamidis som mulig standardbehandling af patienter med transthyretin amyloidose med kardiomyopati. I protokollen angives en definition af population(er), komparator(er) og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende tafamidis modtaget den 4. december 2019.

Protokollen danner grundlag for den endelige ansøgning for vurdering af tafamidis sammenlignet med gældende dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem tafamidis og komparator af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

4 Baggrund

Transthyretin (TTR) er et transportprotein i serum og i cerebrospinalvæsken, som transporterer thyroxin (T4) og retinolbindende protein bundet til retinol (vitamin A). Ca. 95 % af transthyretin produceres i leveren, mens en mindre mængde produceres i plexus choroideus og retina.

Transthyretinmedieret amyloidose (ATTR) er en livstruende sygdom, som skyldes, at transthyretin foldes forkert og aflejres som amyloide fibriller i forskellige væv, herunder det perifere nervesystem, hjertet, mave-tarm-systemet, nyrerne, centralnervesystemet og øjnene. Oftest er der aflejring i nervevæv, hvilket fører til polyneuropati (ATTR-PN), eller hjertevæv, hvilket fører til restriktiv kardiomyopati (ATTR-CM) [1,2].

Sygdommen kan være arveligt betinget (hATTR) eller opstå spontant (kaldet vildtype (ATTRwt)).

Denne protokol vedrører udelukkende patienter, hvor sygdommen præsenterer sig som transthyretin-medieret amyloidose med kardiomyopati (ATTR-CM), og den inkluderer både den arvelige og vildtype form af sygdommen. Patientpopulationerne og sygdomskarakteristika for den arvelige og vildtype form af ATTR-CM er forskellige i Danmark og beskrives herunder separat.

4.1 Arvelig transthyretin amyloidose (hATTR)

hATTR skyldes medfødte forandringer i det gen, som koder for dannelsen af proteinet transthyretin. Mutationer i TTR-genet fører til destabilisering af TTR-tetramerdannelsen og dermed fejl i foldningen af proteinet. De misfoldede proteiner danner tilsammen de amyloide fibriller bestående af muteret transthyretin, som aflejres primært i nervevæv og hjertevæv. Afhængig af mutationen kan de mest fremtrædende symptomer være fra nervesystemet (hATTR-PN) eller fra hjertet (hATTR-CM). Den generelle symptomdebut for den arvelige form er varierende og kan være fra 25-70 år afhængig af mutationstypen, men kan også variere indenfor samme mutation [3].

Den arvelige form for ATTR er yderst sjælden i Danmark. I alt 35 patienter fra [redacted] mutation, og denne mutation er i disse patienter primært associeret med kardiomyopati [4]. Denne mutation, som findes [redacted] er exceptionel alvorlig. Sygdomsdebut sker i 40-50-års alderen, og sygdommen progredierer herefter hurtigt. Patienterne udvikler svær hjertesvigt og dør efter omkring to år uden behandling. Den danske mutation har 100 % penetrans. Danske patienter med arvelig ATTR-CM og p.Leu131Met (L111M)-mutation tilbydes derfor levertransplantation for at standse sygdomsudviklingen [4]. Transplantation af en rask lever medfører, at der ikke længere produceres mutant TTR fra leveren, og aflejringen af fibriller reduceres. Levertransplantation standser oftest progression i sygdommen, men remission af symptomer er sjælden. Det er derfor væsentligt, at levertransplantation gives

tidligt i sygdomsforløbet. Der er ofte ventetid på en levertransplantation, og i den venteperiode er der risiko for betydende sygdomsprogression. Uden levertransplantation har patienterne en dårlig prognose med medianlevetid på to år efter, at diagnosen er stillet. En levertransplantation er et invasivt indgreb, der i sig selv er forbundet med en vis risiko for død og følgesygdomme af den medicin, der gives i forbindelse med transplantationen. 5-årsoverlevelsen efter transplantation er ca. 85 %, og fagudvalget vurderer, at for hovedparten af patienterne opnås derefter en overlevelse næsten svarende til normalbefolkningens.

Incidens og prævalens

Arvelig ATTR med kardiomyopati er en meget sjælden sygdom. Der kendes 35 patienter [redacted]. Fagudvalget estimerer, at det ikke er sandsynligt, at man vil finde flere familier med hATTR-CM ved at indføre en mere systematisk genetisk screening af potentielle patienter. Estimatet omkring fremtidig incidens er behæftet med usikkerhed.

4.2 Ikkearvelig ATTR (ATTRwt)

Ved ATTRwt skyldes aflejringerne af amyloide fibriller at vildtype transthyretin misfoldes. De misfoldede amyloide fibriller bestående af vildtype transthyretin aflejres primært i hjertevæv (ATTRwt-CM). Sygdommen er relateret til stigende alder, men årsagen til at nogle får sygdommen, mens andre ikke gør, er endnu ukendt. Det har længe har været kendt fra obduktionsundersøgelser, at amyloidaflejringer af transthyretin er til stede i hjertet i op til 25 % af ældre mennesker uden nødvendigvis at give symptomer på sygdom [5]. Dog anses det kliniske syndrom som en sjælden sygdom, som overvejende findes hos ældre mænd med kliniske tegn på restriktiv kardiomyopati, muligvis aortastenose og ofte med tillæg af karpaltunnelsyndrom [5].

ATTRwt er karakteriseret ved en sen symptomdebut. I dansk klinisk praksis er patienterne typisk mænd omkring 80 år, men fagudvalget bemærker, at sygdommen sandsynligvis er underdiagnosticeret, og at diagnosen i nuværende praksis stilles senere, end symptomerne indtræder. Overlevelsen for patienter med ATTRwt er median ca. 5 år fra diagnose [5]. Ifølge Danmarks Statistik er den gennemsnitlige restlevetid 7,87 år for en mand på 80 år.

Incidens og prævalens

Der er ikke publiceret estimater for incidens og prævalens af ATTRwt-CM i Danmark. EMA estimerede i 2011, at vildtype ATTR fandtes i 3 ud af 10.000 mennesker i EU [6].

Med introduktion af en ny behandlingsmulighed og lettere initial non-invasiv screening i form af 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) skintigrafi forventes en stigning i incidens og prævalens for sygdommen. Dette skyldes øget diagnostisk fokus, som forventes at føre til en øget opsporing af patienter (øget incidens) og samtidig en tidligere diagnose, hvilket fører til, at patienterne får en længere levetid med diagnosen (øget prævalens). Fagudvalget vurderer, at incidensen er ca. 150 om året og med prævalens på ATTRwt-CM på 400-500 patienter. Estimatet omkring fremtidig incidens og prævalens er dog behæftet med stor usikkerhed.

4.3 Symptomer

Indenfor både den arvelige og vildtype form af ATTR-CM medfører sygdommens progressive natur og alvorlige symptomer nedsat livskvalitet og forkortet levetid. Restriktiv kardiomyopati er kendetegnet ved hæmmet fyldning af den ene eller begge ventrikler på grund af øget stivhed og dermed en abnorm diastolisk

ventrikelfunktion. Systolefunktionen og myokardiets tykkelse er som hovedregel normale. Vægtykkelserne i ventriklerne er væsentligt forøget [7]. Symptomerne på hjertepåvirkning inkluderer typisk åndenød, nedsat fysisk kapacitet, træthed og ødemer. Andre symptomer kan være svimmelhed, besvimelser, anginalignende smerter, arytmier og atrieflimmer.

Graden af hjertesvigtsymptomer beskrives traditionelt ud fra fire NYHA-funktionsklasser, der er baseret på patientsymptomer [8]. NYHA står for New York Heart Association. Nogle patienter med kronisk hjertesvigt lever et godt liv, særligt NYHA-funktionsgruppe I-II, hvor patienten kun oplever ingen eller få begrænsninger i normale fysiske aktiviteter. Andre patienter er betydeligt begrænset i deres fysiske aktivitet (NYHA-funktionsklasse III og IV) og oplever symptomer i hvile eller stillesiddende aktiviteter (klasse IV). Disse patienter har problemer med at klare dagligdagens gøremål. Dødeligheden blandt hjertesvigtpatienter stiger proportionelt med stigningen i NYHA-klasse. NYHA-klassifikation er ikke en præcis klassifikation, og den beror til dels på en subjektiv vurdering af symptomer.

En anden prognostisk klassifikation, som anvendes af det Nationale Amyloidose Center (NAC) i UK, er baseret på en biomarkør for hjertepåvirkning, NT-proBNP, og nyrefunktion, eGFR. Denne klassifikation kaldes *NAC-ATTR disease stage* [9]. Klasse I er defineret som plasma NT-pro-BNP $\leq$ 3000 ng/L og eGFR > 45 mL/min. Klasse III er defineret som NT-pro-BNP > 3000 ng/L og eGFR < 45 mL/min. Klasse II er restgruppen, der ikke opfylder begge kriterier i hhv. klasse I og III.

4.4 Diagnosticering

Mistanke om ATTR-CM opstår på baggrund af symptomer på hjertepåvirkning, observationer på EKG og ekkokardiografi og samtidig udelukkelse af anden årsag til disse fund. AL amyloidose kan give samme symptombillede og kliniske fund og skal udelukkes ved blodprøver og evt. knoglemarvsundersøgelse. Ved mistanke om ATTR-CM laves evt. MR-scanning af hjertet, hvor man undersøger for amyloide aflejringer og/eller DPD skintigrafi, som er en billeddannende undersøgelse til påvisning af transthyretin hjerteamyloid. Light-Chain (AL) amyloidose, også kaldet primær amyloidose, skal udelukkes ved blodprøver. Ved yderligere bekræftelse på mistanken om ATTR-CM ud fra disse undersøgelser og for at stille den endelige diagnose ATTR-CM bør der tages en hjertebiopsi for at påvise amyloide aflejringer ved histologi. I nogle tilfælde kan amyloide aflejringer i biopsi fra andet væv, eksempelvis fedtvæv, sammen med en positiv skintigrafiundersøgelse være tilstrækkeligt til at stille diagnosen.

Diagnosen af den arvelige form kræver, i tillæg til ovenstående, en genetisk undersøgelse med fund af sygdomsforårsagende ændring (mutation) i TTR-genet.

I Danmark har den kendte mutation p.Leu131Met (L111M)-mutation 100 % penetrans, og derfor udredes disse mutationsbærende patienter ved første objektive tegn på hjertepåvirkning.

4.5 Nuværende behandling

Tafamidis er godkendt af EMA i 2011 til hATTR med polyneuropati (hATTR-PN) stadie 1. I 2018 blev to produkter, inotersen og patisiran, godkendt af EMA til hATTR med polyneuropati stadie 1 og 2.

Der findes på nuværende tidspunkt i Danmark ingen godkendte lægemidler til behandling af patienter med ATTRwt og ingen lægemidler med godkendt indikation til ATTR-CM, hverken den arvelige form eller vildtype. Nogle patienter med den arvelige form hATTR vil både have symptomer på polyneuropati og kardiomyopati og kan således også være kandidater til patisiran og inotersen.

Behandlingen af ATTRwt-CM i Danmark har hidtil primært bestået af symptombehandling af de påvirkede organer. Den medicinske behandling af hjertesvigt hos patienter med ATTRwt-CM omfatter anvendelsen af diuretika. Andre lægemidler, som normalt er tilgængelig for hjertesvigtpatienter, såsom ACE-hæmmere,

kalciumantagonister, betablokkere og digoxin, er ikke rekommanderet til patienter med ATTR-CM og bør anvendes med forsigtighed, da disse generelt ikke er veltolererede pga. hypotension [2,10]. Pacemakerbehandling kan blive nødvendig.

Patienter med den arvelige form hATTR-CM og p.Leu131Met (L111M)-mutation behandles med levertransplantation eller kombineret hjerte-levertransplantation, hvis der findes en egnet donor, og patienten vurderes at være egnet til at gennemgå denne procedure.

En andel af de danske patienter med hATTR-CM har fået kombineret hjerte- og levertransplantation (~6) eller isoleret levertransplantation (~14) ifølge Rigshospitalets transplantationsklinik. En mindre andel [redacted] af danske patienter med ATTR-CM er i behandling med tafamidis med det formål at forhindre yderligere sygdomsudvikling frem til levertransplantation og/eller udskyde tidspunktet for behovet for levertransplantation.

4.6 Tafamidis

Tafamidis er en specifik stabilisator af transthyretinproteinet TTR. Tafamidis virker på proteinniveau ved at binde til både muteret og vildtype TTR og stabiliserer herved TTR tetramer-formationen. Herved hæmmer det dissociationen til monomerer, som er det hastighedsbegrænsende trin i formationen af amyloide fragmenter. Derfor forventes tafamidis at kunne bremse sygdomsudviklingen [11,12].

Dosering

Til indikationen ATTR-CM er tafamidis godkendt i en dosis på 61 mg. Tafamidis administreres én gang dagligt peroralt i en blød kapsel indeholdende 61 mg tafamidis. Tafamidis kan tages med eller uden mad.

Tafamidis er også godkendt af EMA i 2011 til arvelig ATTR med polyneuropati stadie 1 i en dosis på 20 mg tafamidis meglumine.

Ansøger angiver, at 61 mg tafamidis er bioækvivalent med 80 mg tafamidis meglumine, og den godkendte dosering må derfor antages at være ~ 4 gange højere til kardiomyopati i forhold til polyneuropati.

5 Kliniske spørgsmål

5.1 Klinisk spørgsmål 1

Hvad er værdien af tafamidis sammenlignet med placebo til patienter med transthyretin-medieret amyloidose med kardiomyopati?

Population
Voksne patienter med vildtype eller arvelig transthyretin-medieret amyloidose med kardiomyopati.

Intervention
Peroral tafamidis 61 mg én gang dagligt.

Komparator
Placebo.

Effektmål
Se tabel 1.

5.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, den mindste klinisk relevante forskel og effektmålsgruppe. For alle effektmål ønskes både absolutte og relative værdier, inkl punktestimater og tilhørende konfidensintervaller, jf. ansøgningsskemaet. For de relative værdier vurderes den kliniske relevans (værdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets håndbog. De relative effektestimater skal angives i relativ risiko (RR) eller hazard ratio (HR). Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel samt indplacering i de tre effektmålsgrupper (”dødelighed” ”livskvalitet, alvorlige symptomer og bivirkninger” og ”ikkealvorlige symptomer og bivirkninger”).

Effektmål*	**Vigtighed**	**Effektmåls-gruppe**	**Måleenhed**	**Mindste klinisk relevante forskel**
Overlevelse Overall survival (OS)	Kritisk	dødelighed	Andel der overlever i 30 mdr.	Forskel på 5 %-point
Livskvalitet Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score	Kritisk	livskvalitet alvorlige symptomer og bivirkninger	Gennemsnitlig ændring fra baseline	Forskel på 5 point for KCCQ-QS
Hospitalsindlæggelser relateret til kardiovaskulær sygdom	Vigtig	livskvalitet alvorlige symptomer og bivirkninger	Gennemsnitlig ændring i antal indlæggelser pr. patient pr. år	Forskel på 15 %
6 minutters gangtest (6 Minute Walk Test, 6MWT)	Vigtig	livskvalitet alvorlige symptomer og bivirkninger	Gennemsnitlig ændring fra baseline	Forskel på 45 meter
Bivirkninger	Vigtig	livskvalitet alvorlige symptomer og bivirkninger	Andel patienter der oplever ≥ 1 bivirkning (AR)	Forskel på 15 %-point
			Kvalitativ gennemgang af bivirkninger	-

* For alle effektmål ønskes data med længst mulig opfølgningstid. Fase III-studiet har en varighed på 30 mdr., og dette er derfor den forventede opfølgningstid for alle effektmål.

Kritiske effektmål

Overlevelse
Overlevelse er et kritisk effektmål, da ATTR-CM er livstruende og medfører forkortet levetid. Fagudvalget ønsker at vurdere effektmålet på baggrund af en hazard ratio for dødelighed og en overlevelsesrate. Fase III-studiet ATTR-ACT har en opfølgningstid på 30 måneder [12], og det vurderes at være en relevant tidshorisont for måling af overlevelsesraten. Fagudvalget vurderer, at i dansk klinisk praksis er ca. 60 % i live efter 30 måneder. Fagudvalget vurderer, at den mindste klinisk relevante forskel er 5 %-point, svarende til at 20 flere patienter er i live efter 30 måneder i en population på 400 patienter. Dette svarer til, at der ved 30 måneder er 260 i live ved behandling med tafamidis vs. 240 uden behandling med tafamidis.

For bedre at kunne vurdere resultaterne på overlevelse ønsker fagudvalget, at ansøger angiver tiden fra diagnose til inklusion i studiet for de patienter, der er inkluderet i studiet.

Livskvalitet
ATTR-CM er en sygdom, der påvirker patienternes livskvalitet, og det er derfor et kritisk effektmål. Inden for kardiomyopati anvendes ofte måleværktøjet Kansas City Cardiomyopathy Questionnaire til måling af livskvalitet. Kansas City Cardiomyopathy Questionnaire (KCCQ) er et valideret måleværktøj for patienter med kronisk hjertesvigt. Værktøjet indeholder 23 elementer, der kvantificerer fysisk funktion, symptomer (hyppighed, sværhedsgrad og nylige ændringer), social funktion og livskvalitet [13] Skalaen går fra 0-100 hvor en lavere værdi betyder dårligere livskvalitet. Fagudvalget vurderer, at dette måleredskab vil være passende til at vurdere livskvalitet for patienter med ATTR-CM. For en gruppe af hjertesvigtpatienter er en gennemsnitlig forskel på 5 point i KCCQ-Overall Summary (KCCQ-OS)-score vist at være den mindste klinisk relevante ændring [14]. Fagudvalget vurderer, at denne forskel kan anses for at være repræsentativ for patienter med ATTR-CM.

Vigtige effektmål

Hospitalsindlæggelser relateret til kardiovaskulære sygdom
Patienter med ATTR-CM vil have en overhyppighed af indlæggelser relateret til kardiovaskulær sygdom. Hospitalsindlæggelse er et patientnært effektmål. Indlæggelse på et hospital er betydende for patientens livskvalitet, herunder sygdomsfølelse. Det har samtidig betydning for patientens prognose, idet en indlæggelse kan medføre øget risiko for den næste indlæggelse og for død. Det er derfor relevant, om en ny behandling kan nedbringe antallet af indlæggelser i forhold til komparator. En reduktion i antal indlæggelser vil afspejle bedre tilstand også de dage patienten ikke er indlagt. Fagudvalget vurderer, at det er relevant se på alle kardiovaskulære årsager til indlæggelser, herunder hjertesvigt, arytmier, akut koronart syndrom, apopleksi og operationer (herunder indsættelser af pacemaker). I et observationelt studie fra UK National Amyloidosis Centre blev patienter i gennemsnit indlagt 2 gange pr. år [5]. I det foreliggende studie på tafamidis er det årlige gennemsnit noget lavere med 0,7 indlæggelser pr. år [12]. Fagudvalget vurderer, at danske patienter med ATTRwt-CM i gennemsnit indlægges en gang pr. år. Dette estimat er baseret på, at vi i Danmark i stigende grad diagnosticerer patienterne tidligere i sygdomsforløbet.

Fagudvalget vil vurdere gennemsnitlige antal årlige indlæggelser relateret til kardiovaskulær sygdom. Ud fra ovenstående beskrivelse og estimat vurderer fagudvalget, at det er klinisk relevant, hvis man kan nedbringe antallet af indlæggelser med 15 %. Ved én indlæggelse pr. år pr. patient svarer en 15 % reduktion til, at man behandler ~7 patienter i et år og undgår én indlæggelse ('numbers needed to treat' ~7). Da tafamidis ikke stopper sygdommen, men blot reducerer progressionshastigheden, må patienterne på den lange bane dog forvente at blive indlagt lige så mange gange.

6-minutters gangtest
Patienternes fysiske funktionalitet falder, mens sygdommen ATTR-CM skrider frem, hvilket påvirker deres evne til selv at klare dagligdagens gøremål som f.eks. gang til offentlig transport og indkøb.

6-minutters gangtest (6MWT) er en udbredt test og et standardiseret mål for funktionel træningskapacitet, som er anvendelig til patienter med hjertesvigt og til patienter med andre hjertesygdomme og lungesygdomme [15]. Fagudvalget er fortrolige med testen og anvender den i klinikken.

En systematisk oversigtsartikel fra 2012 konkluderede, at den mindste klinisk relevante forskel for 6MWT for kroniske hjertesvigtpatienter var omkring 45 meter [16]. Fagudvalget vurderer på den baggrund, at den mindste klinisk relevante forskel mellem grupperne på den gennemsnitlige ændring fra baseline er 45 meter.

Bivirkninger
Fagudvalget ønsker at vurdere risikoen for bivirkninger ved behandling med tafamidis.

Der ønskes en opgørelse over andelen af patienter, der oplever en eller flere bivirkninger (adverse reactions – AR). Den mindste klinisk relevante forskel i andel, der oplever bivirkninger, vurderes at være 15 %-point.

Fagudvalget ønsker herudover kvalitativt at vurdere håndterbarhed, alvorlighed og tyngde af bivirkningsprofilen for tafamidis baseret på studiedata og EMAs produktresumé.

6 Litteratursøgning

Vurderingen af klinisk værdi baseres som udgangspunkt på data fra peer-reviewed publicerede fuldtekstartikler og data fra EMAs EPAR – public assessment report(s). Data skal derudover stemme overens med protokollens beskrivelser.

Sekretariatet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere peer-reviewede publicerede fuldtekstartikler, hvor tafamidis er sammenlignet direkte med placebo.

Virksomheden skal søge efter studier, der kan anvendes til en direkte sammenligning af tafamidis og placebo. Til det formål har sekretariatet udarbejdet søgestrenge, som skal anvendes i MEDLINE (via PubMed) og CENTRAL (via Cochrane Library). Søgestrengene kan ses herunder. Derudover skal EMAs European public assessment reports (EPAR) konsulteres for det aktuelle lægemiddel.

MEDLINE (via PubMed) https://www.ncbi.nlm.nih.gov/pubmed/advanced

#1	Amyloidosis, Hereditary, Transthyretin-Related[nm]	Søgetermer for population
#2	ATTR[tiab] OR ATTRwt[tiab] OR hATTR[tiab] OR ATTR-ACT[tiab] OR ATTR-CM[tiab] OR TTR-CM[tiab]	
#3	transthyretin[tiab] AND (amyloid[tiab] OR amyloidosis[tiab])	
#4	#1 OR #2 OR #3	
#5	Cardiomyopathies[mh] OR cardiomyopathy[tiab] OR cardiomyopathies[tiab] OR cardiac[tiab]	
#6	#4 AND #5	
#7	tafamidis[nm]	Søgetermer for interventionen
#8	tafamidis[tiab] OR vyndaqel*[tiab]	
#9	#7 OR #8	
#10	#6 AND #9	Kombination af population og intervention
#11	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh]	RCT-filter

	OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals [mh] NOT humans [mh])	
#12	#10 AND #11	Endelig søgning

CENTRAL (via Cochrane Library) https://www.cochranelibrary.com/advanced-search/search-manager

#1	(tafamidis OR vyndaqel*):ti,ab,kw	Søgetermer for intervention
#2	("conference abstract" OR review):pt	Ikke relevante publikationstyper
#3	NCT*:au or abstract:ti	
#4	("clinicaltrials.gov" OR trialsearch):so	
#5	#2 or #3 or #4	
#6	#1 NOT #5	Endelig søgning

Kriterier for udvælgelse af litteratur
Virksomheden skal først ekskludere artikler på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Inklusions- og eksklusionskriterier: andre studiedesign end RCT ekskluderes, studier med andre populationer end de valgte ekskluderes, studier, som ikke rapporterer mindst et af de kritiske eller vigtige effektmål, ekskluderes.

7 Databehandling og analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention to treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser, specielt i forhold til præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængelig for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (ORR, SAE, behandlingsstop pga. bivirkninger og ikkealvorlige bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i

Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risikoreduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end ét sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

8 Andre overvejelser

Dosis 80 mg vs. 20 mg

Til indikationen hATTR med polyneuropati er den godkendte dosering 20 mg tafamidis meglumine, hvorimod den er højere til ATTR med kardiomyopati. Ansøger bedes redegøre for valg af dosis 61 mg tafamidis (svarende til 80 mg tafamidis meglumine) fremfor en dosis bioækvivalent med 20 mg tafamidis meglumine til denne indikation. Ansøger bedes desuden redegøre for anvendelsen af de poolede analyser for tafamidis 20 mg og 80 mg.

Fagudvalget ønsker separate analyser for de to anvendte doseringer og vil vurdere overensstemmelse mellem resultaterne. Fagudvalget ønsker bivirkninger opgjort for de to doseringer separat.

Opdeling på hATTR vs. ATTRwt

Patienter med hhv. hATTR og ATTRwt har forskellige underliggende årsager til sygdommen samt markante forskelle i patientkarakteristika, herunder alder. Fagudvalget ønsker derfor at se analyseresultater og baselinekarakteristik opgjort separat for patienter med hATTR og ATTRwt. Fagudvalget vil vurdere disse data med henblik på en eventuel differentiering af effekt.

Opdeling i sygdomsstadier

I publicererede studier på tafamidis er det indikeret, at patienter i tidlige sygdomsstadier har størst gavn af behandling [12,17].

Fagudvalget ønsker derfor at vurdere, om patienter i forskellige sygdomsstadier vil have lige stor effekt af behandling med tafamidis. Fagudvalget ønsker derfor analyser, som er opdelt på NYHA-klasser.

Fagudvalget ønsker herudover analyser, som er opdelt på NAC disease-stage ud fra værdier af NT-ProBNP og eGFR.

Fagudvalget vil vurdere data for disse opdelinger i sygdomsstadier med henblik på en eventuel differentiering af effekt. Fagudvalget vil i den forbindelse vurdere, om de to måder at inddele sygdommen på giver enslydende resultater. Fagudvalget mener, det er essentielt med en opdeling på begge disse måder, da NYHA-klassifikation er forbundet med en vis subjektivitet, mens NAC disease-stage klassificeres objektivt på baggrund af blodprøvemålinger.

Opstart og seponering

Fagudvalget vil formulere forslag til kriterier for opstart, monitorering af effekt og seponering af tafamidis i vurderingsrapporten.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende transthyretin amyloidose

Forvaltningslovens § 4, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg

Formand	**Indstillet af**
Redi Pecini Afdelingslæge	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Claus Holst-Hansen Overlæge	Region Nordjylland
Henrik Ølholm Vase Afdelingslæge	Region Midtjylland
Martin Busk Overlæge	Region Syddanmark
Hanne Elming Overlæge	Region Sjælland
Kasper Rossing Overlæge	Region Hovedstaden
Hilde Omestad Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Claus Stage Speciallæge	Dansk Selskab for Klinisk Farmakologi
Anette Torvin Møller Overlæge	Dansk Neurologisk Selskab
Søren Fanø Overlæge	Dansk Cardiologisk Selskab
Peter Ott Ledende overlæge	Dansk Selskab for Gastroenterologi og Hepatologi
Jens Michael Hertz Professor, overlæge	Dansk Selskab for Medicinsk Genetik
Astrid Juhl Terkelsen Speciallæge i Neurologi	Inviteret af formanden
Karen Rudolf Forsknings- og udviklingsterapeut, ambulatorieleder	Inviteret af formanden
Birthe Byskov Holm Patient/patientrepræsentant	Danske Patienter

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Bettina Fabricius Christensen (informationsspecialist)
Annemette Anker Nielsen (teamleder)

Tidligere medarbejdere, der har bidraget til arbejdet:

Heidi Møller Johnsen (projektdeltager)

11 Versionslog

Version	Dato	Ændring
1.0	6. marts 2020	Godkendt af Medicinrådet.