Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende nintedanib til behandling af systemisk sklerodermi-associeret interstitiel lungesygdom

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. nintedanib til SSc-ILS, version 1.0
2. Forhandlingsnotat fra Amgros vedr. nintedanib
3. Medicinrådets vurdering vedr. nintedanib til behandling af systemisk sklerodermi-associeret interstitiel lungesygdom, version 1.0
4. Ansøgers endelige ansøgning
5. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
6. Medicinrådets protokol for vurdering vedr. nintedanib til behandling af systemisk sklerodermi-associeret interstitiel lungesygdom, version 1.0

Ansøger har ikke indsendt høringssvar i sagen.

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Nintedanib

Systemisk sklerodermi-associeret interstitiel lungesygdom

Version 1.0

Om Medicinrådet

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

Dokumentets formål

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

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

Dokumentoplysninger	
Godkendelsesdato	23. februar 2022
Dokumentnummer	131889
Versionsnummer	1.0

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 24. februar 2022

Indholdsfortegnelse

1. Begreber og forkortelser

PF-ILS	Interstitiel lungesygdom med progredierende fibrose
SSc-ILS	Systemisk sklerodermi-associeret interstitiel lungesygdom

2. Konklusion

Medicinrådet vurderer, at nintedanib til patienter med systemisk sklerodermi-associeret interstitiel lungesygdom (SSc-ILS) ikke kan kategoriseres efter Medicinrådets metoder sammenlignet med placebo. Det skyldes, at studiepopulationen i det underliggende SENSCIS-studie [1] afviger væsentligt fra populationen defineret i det kliniske spørgsmål, idet en stor del af patienterne ikke har modtaget immunmodulerende behandling eller opfylder bestemte progressionskriterier oplistet i afsnit 3.3 i vurderingsrapporten. Dermed vil størstedelen af studiepopulationen ikke betragtes som kandidater til antifibrotisk behandling i dansk klinisk praksis, og en sundhedsøkonomisk model, der tager udgangspunkt i data fra SENSCIS-studiet [1], vil ikke være meningsfuld, da effekten afhænger af patientpopulationen.

3. Referencer

1. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease. https://doi.org/101056/NEJMoa1903076. 2019;380(26):2518–28.

4. Versionslog

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

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01.02.2022

MGK/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.02.2021
Leverandør	Boehringer Ingelheim
Lægemiddel	Nintedanib
Ansøgt indikation	- Interstitiel lungesygdom med progredierende fibrose - Systemisk sklerodermi-associeret interstiel lungesygdom

Forhandlingsresultat

[redacted]

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/dosis	Form	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Rabatprocent ift. AIP
Nintedanib	100 mg	Bløde kapsler	60 stk.	14.368,99	[redacted]	[redacted]
Nintedanib	150 mg	Bløde kapsler	60 stk.	17.029,24	[redacted]	[redacted]

[redacted]

Status fra andre lande

Norge: Nintedanib er for nuværende under vurdering i Norge.

England: Nintedanib er anbefalet som en mulighed for behandling af kronisk progressiv fibroserende interstitielle lungesygdomme (PF-ILD) hos voksne.

"*Nintedanib is recommended, within its marketing authorisation, as an option for treating chronic progressive fibrosing interstitial lung diseases (PF-ILD) in adults.*
Current treatment for PF-ILD often starts with immunosuppressants, which may or may not be continued when nintedanib is offered.

The clinical trial evidence suggests that nintedanib slows the decline of lung function compared with placebo. But, there are uncertainties in the evidence: it is unclear if nintedanib helps people to live longer, and the trial reflects how nintedanib would be used in the NHS in some but not all people with PF-ILD.

Because follow up was short in the trial for nintedanib in PF-ILD, the economic model uses longer follow-up data from nintedanib trials in idiopathic pulmonary fibrosis, a related condition that progresses in a similar way. This allows better modelling of nintedanib's long-term effect on life expectancy. The cost-effectiveness estimates are likely to be within what NICE considers an acceptable use of NHS resources. So, nintedanib is recommended."[1]

[1] https://www.nice.org.uk/guidance/ta747/chapter/1-Recommendations

Medicinrådet

Medicinrådets vurdering vedrørende nintedanib til behandling af systemisk sklerodermi-associeret interstitiel lungesygdom

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om vurderingsrapporten

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

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

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

Dokumentoplysninger	
Godkendelsesdato	26. januar 2022
Dokumentnummer	131767
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet vurderer, at nintedanib har en samlet værdi, der ikke kan kategoriseres efter Medicinrådets metoder sammenlignet med placebo til patienter med systemisk sklerodermi-associeret interstitiel lungesygdom (SSc-ILS).

Det skyldes, at studiepopulationen i det underliggende studie afviger væsentligt fra populationen defineret i det kliniske spørgsmål, fordi en stor del af patienterne ikke har modtaget immunmodulerende behandling eller opfylder de progressionskriterier, der vil være relevante i dansk klinisk praksis.

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Udgivet af Medicinrådet, 27. januar 2022

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

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

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

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

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

2. Begreber og forkortelser

AE	Uønsket hændelse (*Adverse Event*)
CI:	Konfidensinterval
DL_{CO}	Diffusionskapacitet
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EPAR:	*European Public Assessment Report*
FGFR	Fibroblast vækstfaktorreceptor (*Fibroblast Growth Factor Receptor*)
FVC	Forceret vitalkapacitet (*Forced Vital Capacity*)
FDA:	*The Food and Drug Administration*
FINOSE:	Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HRCT	Højopløsnings-CT-scanning
ILS	Interstitiel lungesygdom
IPF	Idiopatisk pulmonal (lunge) fibrose
IQWIG:	*The Institute for Quality and Efficiency in Healthcare*
ITT:	*Intention-to-treat*
K-BILD	*King's Brief Interstitial Lung Disease*
MKRF:	Mindste klinisk relevante forskel
OS:	Samlet overlevelse (*Overall Survival*)
PDGFR	Trombocytderiverede vækstfaktorreceptor (*Platelet-Derived Growth Factor Receptor*)
PF-ILS	Interstitiel lungesygdom med progredierende fibrose
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*
RCT:	Randomiseret kontrolleret studie (*Randomised Controlled Trial*)
SAE:	Alvorlig uønsket hændelse (*Serious Adverse Event*)
SGRQ:	*St George´s Respiratory Questionnaire*
SSc:	Systemisk sklerodermi
SSc-ILS	Systemisk sklerodermi-associeret interstitiel lungesygdom
VEGFR	Vaskulær endotelial vækstfaktorreceptor (*Vascular Endothelial Growth Factor Receptor*)

3. Introduktion

Formålet med Medicinrådets vurdering af nintedanib til systemisk sklerodermi-associeret interstitiel lungesygdom (SSc-ILS) er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Boehringer Ingelheim. Medicinrådet modtog ansøgningen den 26. maj 2021.

Det kliniske spørgsmål er:

Hvilken værdi har nintedanib sammenlignet med placebo for patienter med systemisk sklerodermi-associeret interstitiel lungesygdom?

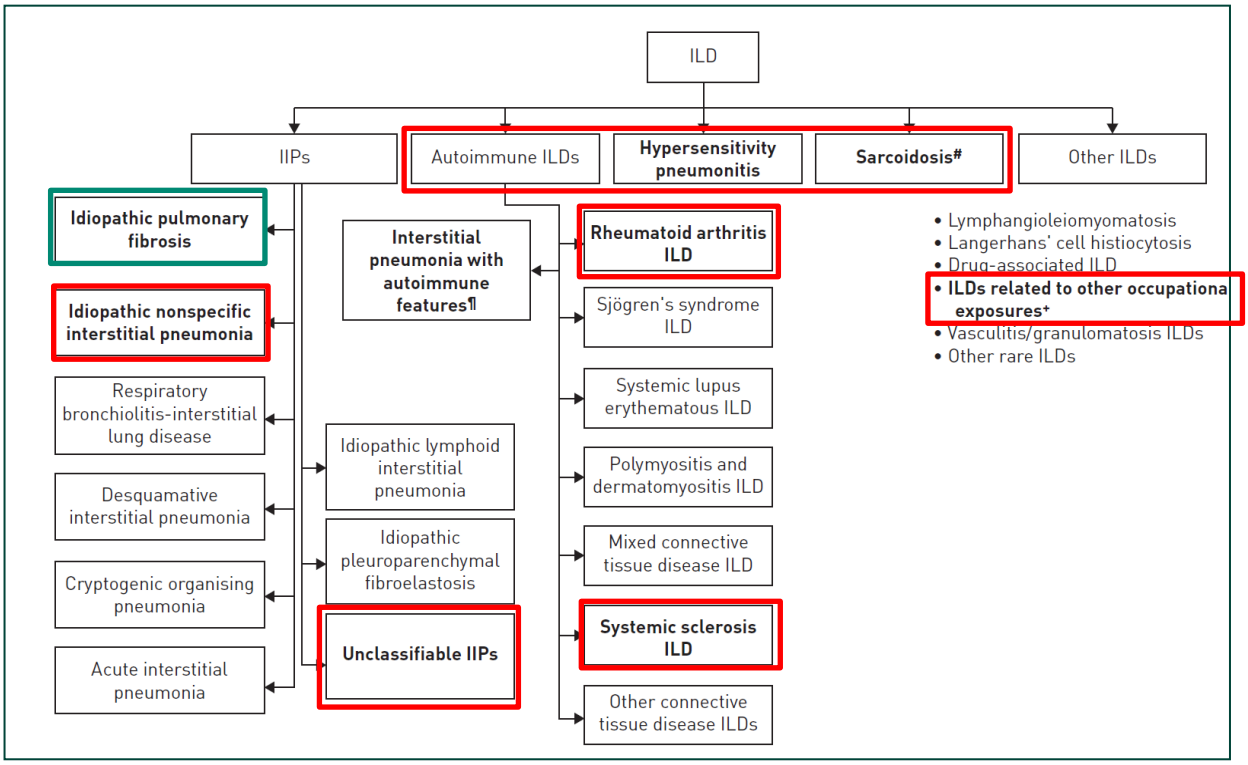
3.1 Systemisk sklerodermi-associeret interstitiel lungesygdom

Systemisk sklerodermi (SSc) er en sjælden, kronisk, autoimmun sygdom, hvor øget inflammation og bindevævsdannelse (fibrose) fører til stivhed og dysfunktion af kroppens væv. Sygdommen er kendetegnet ved stivhed i huden, primært i fingre, hænder og ansigt. Hos nogle patienter dannes der også bindevæv i de indre organer, f.eks. i fordøjelseskanalen, lungerne, hjertet og nyrerne. Årsagen til sygdommen er ikke kendt, men er associeret med både miljømæssige og arvelige faktorer. Patienter med SSc diagnosticeres oftest ved 30-40-årsalderen, og flere kvinder end mænd får stillet diagnosen [1,2].

Interstitielle lungesygdomme (ILS) er en blandet gruppe af sygdomme karakteriseret ved inflammation og/eller fibrosedannelse i lungerne (alveoler, bindevæv, små bronkier og kar) [3–5]. Omkring 40-50 % af SSc-patienter udvikler ILS [1,6] som følge af skader på endotel- og/eller epitelceller, aktivering af koagulations- og inflammationssignaler, som fører til fibrosedannelse i lungerne [7]. Lungefibrosen medfører stivhed i lungevævet og nedsat alveolar funktion. Jo mere fibrose, der opstår i lungerne, jo mere bliver lungefunktionen påvirket. Sygdommen diagnosticeres typisk ved lungefunktionsmålinger, hvor patienter med SSc-ILS typisk har en nedsat forceret vitalkapacitet (*forced vital capacity* (FVC)) og diffusionskapacitet (DL_{CO}), som falder gradvist over årene [7–10]. Dertil foretages højopløsnings-CT-scanning (HRCT) af thorax, som typisk viser interstitielle forandringer, der afspejler inflammation og fibrose [7–10].

Der findes mange typer af ILS (se oversigt i figur 1), hvoraf en af de mest undersøgte er idiopatisk pulmonal fibrose (IPF), som er kendetegnet ved irreversibel udvikling af progredierende lungefibrose [11–13]. Andre undertyper af ILS kan også medføre progredierende lungefibrose, selvom de ikke kan kategoriseres som værende IPF. Disse bliver samlet kaldt for PF-ILS, og SSc-ILS er én af disse.

Figur 1. Oversigt over forskellige undertyper af ILS, som kan medføre PF-ILS, inklusiv SSc-ILS



Figuren viser, hvilke undertyper af ILS (*interstitiel lung disease*; ILD) ud over IPF (idiopatisk pulmonal fibrose; fremhævet med grøn) der kan udvikle progredierende fibrose (PF-ILS). Disse er fremhævet med rød. En af disse undertyper er systemisk sklerodermi-associeret ILS.

SSc-ILS-patienter har øget dødelighed i forhold til baggrundsbefolkningen [6]. SSc-ILS påvirker desuden patienternes livskvalitet i høj grad [14] og er den ledende dødsårsag hos SSc-patienter [15–17]. 35 % af dødsfaldene blandt SSc-patienter skyldes udvikling af lungefibrose [17]. SSc-ILS-patienter har en 5- og 10-årsoverlevelse på hhv. 85,9 % og 71,7 % [18]. Et studie, som fulgte SSc-ILS-patienter efter diagnose (median opfølgningstid på 155 måneder), viste, at 52 % af patienterne døde inden for dette tidsrum [19]. Sygdomsforløbet varierer meget fra patient til patient [20,21], hvor et mere aggressivt sygdomsforløb, som involverer de indre organer, er associeret med en højere dødelighed [10]. Dette ses overvejende hos patienter med diffus kutan SSc, hvor arvævsdannelsen foregår mere udbredt i kroppens organer og fører til dysfunktionelt væv. Limiteret kutan SSc er en anden form, karakteriseret ved mere lokaliseret arvævsdannelse og stivhed i huden på hænder/underarme med bedre prognose og lavere risiko for interstitiel lungesygdom [10].

Incidens af SSc-ILS

Incidensen af ILS er svær at vurdere. Der foreligger et nationalt register over ILS i Danmark, men det indeholder primært data over patienter med IPF og kun i begrænset grad SSc-ILS-patienter. En retrospektiv opgørelse fra 2013 fandt en incidens af ILS i Danmark på 4,1 pr. 100.000 [22]. Der er mistanke om en betydelig underdiagnosticering af ILS, som følge af at sygdommene er sjældne og kan være svære at diagnosticere. Incidensen har været stigende gennem det sidste årti [23], hvilket kan skyldes flere faktorer, blandt andet indførelsen af antifibrotisk behandling og udvikling af

retningslinjer på området, som har ført til en øget bevidsthed og viden om ILS blandt læger generelt. Samtidig er der sket en øgning i antallet af CT-scanninger, som involverer thorax, som kan rejse mistanke om ILS. Incidensen af SSc-ILS baseret på et nyt norsk studie er ca. 10 tilfælde/million/år [6]. Fagudvalget skønner på den baggrund, at ca. 20-30 nye patienter årligt med SSc-ILS i progression potentielt kan være kandidater til behandling med nintedanib. Fagudvalget bemærker desuden, at en eventuel anbefaling af nintedanib kan føre til flere diagnosticerede patienter, blandt andet pga. den øgede opmærksomhed.

3.2 Nintedanib (Ofev)

Nintedanib (med handelsnavnet Ofev i Danmark) er en lavmolekylær tyrosinkinasehæmmer med affinitet til en række celleoverfladereceptorer, inkl. trombocytderiverede vækstfaktorreceptor (PDGFR) α og β, fibroblast vækstfaktorreceptor (FGFR) 1-3 og vaskulær endotelial vækstfaktorreceptor (VEGFR) 1-3. Ved binding til PDGFR og FGFR blokeres receptorernes intracellulære signalveje, som er med til at stimulere proliferation, migration og differentiering af lungefibroblaster. Dette forhindrer videre udvikling af lungefibrosen [24]. Denne mekanisme anses for at være en fælles sygdomsmekanisme ved de fibrosedannende interstitielle lungesygdomme. Det er derfor biologisk plausibelt, at nintedanib også vil være effektivt ved andre fibrosedannende lungesygdomme end IPF.

Nintedanib fik følgende indikation i 2015 som *orphan drug* hos det Europæiske Lægemiddelagentur (EMA):

> *Ofev er indiceret til behandling af idiopatisk lungefibrose (IPF) hos voksne.*

Behandling med nintedanib er livsforlængende ved IPF og gives indtil forekomsten af uacceptabel toksicitet eller død.

Denne vurdering af nintedanib omhandler følgende indikationsudvidelse, som blev givet hos EMA i 2020:

> *Ofev er indiceret til behandling af systemisk sklerodermi-associeret interstitiel lungesygdom (SSc-ILS) hos voksne.*

Den anbefalede dosis er 150 mg blød kapsel nintedanib to gange dagligt med ca. 12 timers mellemrum. Dosis kan sænkes til 100 mg to gange dagligt til patienter, der ikke tolererer en dosis på 150 mg to gange dagligt.

Ud over SSc-ILS har nintedanib samtidig fået følgende indikationsudvidelse i 2020 hos EMA til interstitiel lungesygdom med progredierende fibrose (PF-ILS):

> *Ofev er også indiceret til behandling af andre kroniske fibroserende interstitielle lungesygdomme (ILS) med en progressiv fænotype (PF-ILS) hos voksne.*

Ved markedsføringstilladelsen af de to indikationsudvidelser mistede nintedanib sin status som *orphan drug*.

Begge indikationsudvidelser, PF-ILS og SSc-ILS, vurderes samtidig hos Medicinrådet.

3.3 Nuværende behandling

Dødeligheden af SSc-ILS korrelerer i høj grad med reduktionen i lungefunktion (fald i forceret vitalkapacitet (FVC)) som følge af progression af lungefibrosen. Jo mere lungefibrose på HRCT-scanning eller højere FVC-faldhastighed, jo højere risiko for at dø [6,17,19,21,25–28]. Behandlingsmålet er derfor bremsning af sygdomsudvikling med henblik på uforandret status eller reduceret progressionshastighed.

Udredning af SSc-ILS
Den diagnostiske proces for IPF og andre fibrotiske lungesygdomme (herunder SSc-ILS) følger i hovedtræk den diagnostiske algoritme, som er anbefalet i internationale retningslinjer for udredning af IPF [29,30].

Patienter henvist med fibrotisk lungesygdom på HRCT-scanning gennemgås grundigt i forhold til, om der kan påvises en underliggende udløsende årsag som f.eks. indånding af skadelige stoffer i miljø/arbejdsplads, medicinbivirkning eller en underliggende reumatologisk sygdom (herunder sklerodermi), se figur 1. Hvis der ikke kan identificeres en udløsende årsag, betegnes sygdommen som idiopatisk og afgrænser mulighederne til en mindre række tilstande, hvoraf IPF er den hyppigste. HRCT-scanningen kan påvise fibrotiske forandringer med varierende grad af inflammation og ud fra mønsteret give vigtige informationer om den mulige underliggende sygdom, men er ofte ikke tilstrækkelig i sig selv. Hos ca. 20 % af patienterne er det nødvendigt at supplere med bronkoskopi med BAL (bronkoalveolær lavage) og evt. lungebiopsi.

Hvis der i udredningen er mistanke om underliggende reumatologisk sygdom, vurderes patienten af en reumatolog. Har patienten eksisterende eller nykonstateret sklerodermi, og det er foreneligt med den kliniske vurdering (inkl. HRCT), stilles diagnosen sklerodermi-associeret interstitiel lungesygdom. Patienter med SSc-ILS er i modsætning til IPF-patienter betydeligt yngre med lang restlevetid. Ca. en tredjedel af SSc-ILS-patienterne dør pga. udvikling af lungefibrose, med en 10-års overlevelse på omkring 60-70 %.

Den indledende udredning ved mistanke om ILS kan finde sted på alle lungemedicinske afdelinger. Ved mistanke om fibrotisk ILS eller behov for *second opinion* henvises patienter til yderlige udredning ved en af de højtspecialiserede lungemedicinske afdelinger i Danmark (Odense Universitetshospital, Aarhus Universitetshospital, Herlev-Gentofte Hospital og Rigshospitalet). Diagnosen stilles på multidisciplinær konference (MDT) med et tværfagligt team af læger med ekspertise inden for lungemedicin, thorax-radiologi, reumatologi, kardiologi og patologi [31,32], som alle er specialiseret inden for interstitielle lungesygdomme. De tre højtspecialiserede centre anvender MDT i forbindelse med udredning og behandling af ILS i henhold til internationale og nationale

guidelines. Behandling med antifibrotisk medicin varetages alene af de tre højtspecialiserede ILS-centre [3].

Behandling af SSc-ILS
Behandling af ILS-patienter med progredierende lungefibrose, herunder SSc-ILS, tilrettelægges ved en multidisciplinær tilgang, da der er flere mulige differentialdiagnoser. Derfor tilrettelægges behandlingen individuelt for den enkelte patient, baseret på om deres sygdom primært er drevet af inflammation eller lungefibrose. Langt fleste SSc-ILS-patienter vil modtage immunmodulerende behandling i førstelinje, hvor der indtil nu har været national konsensus om, at patienterne responderer bedst på cyclophosphamid eller mycophenolatmofetil [3], hvilket baseres på de to randomiserede kliniske studier Scleroderma Lung Studies I og II [33,34]. Mycophenolatmofetil foretrækkes oftest af hensyn til en bedre bivirkningsprofil og ligeværdig effekt. Derudover modtager enkelte patienter biologiske lægemidler, f.eks. rituximab [35] eller tocilizumab (interleukin-6-hæmmer) [36]. Typisk startes behandling til de patienter, som har høj risiko for progression [37]. Ingen af de nævnte lægemidler har SSc-ILS som indikation, men har været anvendt uden for indikation (*off-label*) i Danmark som førstelinjebehandling over en længere årrække. Behandling fortsættes indtil sygdomsprogression, hvilket monitoreres ud fra ændring i patientens symptomer, serielle lungefunktionsmålinger, evt. suppleret med gangtest og HRCT-scanning [13].

Fagudvalget understreger, at ved progression af lungefibrose på førstelinjebehandling med immunmodulerende lægemidler eller udvikling af uacceptable bivirkninger modtager danske SSc-ILS-patienter i dag ikke yderligere behandling pga. manglende godkendte behandlingsmuligheder. Selvom patienterne er relativt unge og i den erhvervsdygtige alder, er de desværre ofte ikke kandidater til lungetransplantation pga. de systemiske manifestationer af SSc. Ca. hver femte patient med SSc vil dø af lungefibrose [15]. Her vurderer fagudvalget, at antifibrotisk behandling med nintedanib, som er det første lægemiddel, der er regulatorisk godkendt til indikationen SSc-ILS, og som specifikt er rettet mod fibrosedannelsen, potentielt kan finde anvendelse. Fagudvalget vurderer, at nintedanib primært vil blive anvendt i tillæg til patientens immunmodulerende behandling. Denne placering i behandlingsalgoritmen er i overensstemmelse med nylige anbefalinger fra en international ILS-ekspertgruppe vedrørende antifibrotisk behandling til ILS-patienter med progredierende lungefibrose (PF-ILS), herunder SSc-ILS [13,29,38]. Fagudvalget vurderer, at SSc-ILS-patienter, der er kandidater til behandling med nintedanib, skal opfylde følgende kriterier:

- Nedsat lungefunktion og fibrose på HRCT (FVC > 40 % af forventet normalværdi, DLco 30-79 % af forventet normalværd og > 10 % fibrose på HRCT), og som ved ekspertvurdering er i risiko for progression. Derudover skal patienterne:
    - have progredieret på behandling med mycophenolat eller ikke tåle behandling med mycophenolat
    - eller
    - i udvalgte tilfælde ved primært fibrotiske forandringer på HRCT kan opstart uden forudgående mycophenolat besluttes og efter vurdering på MDT-konference.

Når alle medicinske behandlingsmuligheder er udtømt, kan en minoritet af højt selekterede patienter undergå lungetransplantation.

Ifølge fagudvalget vil de fleste SSc-ILS-patienter modtage immunmodulerende behandling i første linje, da deres sygdom primært er drevet af inflammation. Først ved progression på disse lægemidler vil antifibrotisk behandling blive overvejet, jf. det kliniske spørgsmål i Medicinrådets protokol for vurdering vedrørende nintedanib til behandling af SSc-ILS [39]. For en mindre gruppe af patienter, ca. 10 %, vurderer fagudvalget dog, at sygdommen primært er drevet af fibrotisk udvikling, hvorfor det vil være oplagt, at nintedanib vil blive indplaceret som førstelinjebehandling, hvis lægemidlet anbefales ved MDT-konference-beslutning/-notat.

Fagudvalget gør opmærksom på, at EMA-indikationen ikke stiller krav om forudgående behandling.

4. Metode

Medicinrådets protokol for vurdering vedrørende nintedanib til behandling af systemisk sklerodermi-associeret interstitiel lungesygdom [39] beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, *version 2.*6, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

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

Ansøgningen baserer sig på de 2 artikler, der er angivet i protokollen. Begge artikler er baseret på det kliniske studie SENSCIS [40,41]. Derudover indgår yderligere to artikler i ansøgningen, som også er baseret på SENSCIS: én subgruppeanalyse på patienter, der modtog/ikke modtog mycophenolat ved baseline [42], og en opgørelse over bivirkninger og dosisreduktioner [43]. Desuden indgår EMAs *European Public Assessment Report* (EPAR) og produktresuméet for nintedanib [24,44].

SENSCIS

Dette er et randomiseret, dobbeltblindet fase III-studie, der undersøgte effekten og sikkerheden af nintedanib sammenlignet med placebo hos patienter med systemisk sklerodermi-associeret interstitiel lungesygdom. Patienterne skulle opfylde *the American*

College of Rheumatology og *European League Against Rheumatism*-kriterierne for systemisk sklerodermi med deres første non-Raynaud's-symptom, maksimalt 7 år før screening. Patienter, som modtog prednisone (≤ 10 mg pr. dag), en stabil dosis mycophenolat eller methotrexat i minimum 6 måneder før randomisering, måtte godt deltage. Ligeledes kunne ekstra behandling[1] opstartes hos patienter, der oplevede klinisk signifikant forværring af deres sygdom i løbet af studiets forløb. Patienterne skulle opfylde følgende kriterier:

- ≥ 10 % fibrose i lungerne, som fremgår på en HRCT-scanning
- FVC ≥ 40 % af forventet normalværdi[2]
- DLco ≥ 30-89 % af forventet normalværdi.

Patienterne blev randomiseret 1:1 til nintedanib (n = 288), 150 mg to gange dagligt, eller placebo (n = 288). Randomiseringen var stratificeret efter tilstedeværelsen af anti-topoisomerase 1 antistof, som har været associeret med fald i FVC hos patienter med tidlig systemisk sklerodermi. Studiets opfølgningstid var 52 uger, hvor primære effektanalyser blev foretaget. Resultater efter 52 ugers opfølgning er rapporteret i Distler et al. [41]. Patienterne kunne derefter fortsætte på den behandling, de blev randomiseret til, i yderlige 48 uger, dvs. maks. 100 uger i alt. Data efter 100 ugers opfølgning er rapporteret i nintedanibs EPAR for SSc-ILS [44]. Patienter, der fuldførte studiet *on-treatment* og mødte op til en opfølgende kontrol 28 dage efter sidste behandling, kunne deltage i et ekstensionsstudie, hvor alle patienter modtog nintedanib. Der foreligger ikke data herfra endnu. I tilfælde af bivirkninger kunne patienter dosisreduceres til 100 mg to gange dagligt eller kortvarigt stoppe med behandlingen.

Studiets primære effektmål var den årlige FVC-faldhastighed, vurderet over 52 uger. Sekundære effektmål af relevans for vurderingen, jf. protokollen [39], var den absolutte ændring fra baseline i *St George´s Respiratory Questionnaire* (SGRQ)-spørgeskemaet ved uge 52, tiden til død over 52 ugers opfølgningstid, og sikkerhed/bivirkninger.

Alle analyser blev foretaget på patienter, der modtog mindst én studiedosis.

En præspecificeret subgruppeanalyse på patienter, der modtog/ikke modtog mycophenolat ved baseline er blevet publiceret med 52 ugers data i Highland et al. [42].

[1] Dette inkluderede mycophenolatmofetil, mycophenolat sodium, methotrexate, azathioprin, cyclophosphamid, cyclosporin A, prednison > 10 mg/dag, hydroxychloroquin, colchicin, D-penicillamin, sulfasalazin, rituximab, tocilizumab, abatacept, leflunomide, tacrolimus og andre nylige anti-reumatiske behandlinger ligesom tofacitinib og potassium para-aminobenzoat.

[2] FVC afhænger af patientens etnicitet, alder, køn og højde. % af forventet FVC er derfor korrigeret for disse faktorer.

Tabel 1. Oversigt over publikationer

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention vs. komparator
Distler et al. 2019 [41] Highland et al. 2021 – subgruppeanalyse [42] Distler et al. 2017 [40] Seibold et al. 2020 [43] EPAR [44]	SENSCIS	NCT02597933	Patienter med SSc-ILS, som opfylder bestemte lungefibrosekriterier	Nintedanib vs. placebo

Tabel 2. Baselinekarakteristika i SENSCIS-studiet*

	***Intention-to-treat* (ITT)**	
	Nintedanib 150 mg (n = 288)	**Placebo (n = 288)**
Kvinder, antal (%)	221 (76,7)	212 (73,6)
Alder, år	54,6±11,8	53,4±12,6
Lungefibrose på HRCT, %	36,8±21,8	35,2±20,7
FVC		
– Gennemsnit værdi i ml	2459±736	2541±816
– % af forventet normalværdi	72,4±16,8	72,7±16,6
DLco - % af forventet normalværdi	52,9±15,1	53,2±15,1
Andel af patienter med diffus kutan SSc, antal (%)	153 (53,1)	146 (50,7)
Anti-topoisomerase 1 antistof-positiv, antal (%)	173 (60,1)	177 (61,5)
Livskvalitet ved SGRQ score	40,7±20,2	39,4±20,9
Medicinsk behandling, antal (%)		
– Mycophenolat	139 (48,3)	140 (48,6)
– Methotrexat	23 (8,0)	15 (5,2)

*Alle værdier er opgjort som gennemsnit ± SD, medmindre andet er specificeret. NA = *not available*.

Overordnet er der ikke er nogen betydende forskelle i baselinekarakteristika mellem de to studiearme for den samlede studiepopulation (ITT). Der er tale om en heterogen gruppe af patienter, hvor nogle patienter har et mildt, mens andre har et svært sygdomsforløb. SENSCIS-studiet inkluderede patienter, uafhængigt om der var dokumenteret sygdomsprogression, eller om patienterne tidligere havde modtaget immunmodulerende behandling. Fagudvalget bemærker, at studiepopulationen dermed afviger væsentligt fra den danske patientpopulation, der er beskrevet i det kliniske spørgsmål, jf. protokollen, da en stor del af patienterne ikke har modtaget immunmodulerende behandling eller opfylder progressionskriterierne, jf. afsnit 3.3. Dermed ville den samlede studiepopulation ikke betragtes som kandidater til antifibrotisk behandling i dansk klinisk praksis. Forskellen i patientpopulationerne ses bl.a. ved, at kun omkring 50 % af patienterne i SENSCIS-studiet har diffus kutan SSc, hvorimod der i dansk klinisk praksis vil være en overvægt af patienter med diffus kutan SSc, som er kandidater til nintedanib, da disse patienter har betydelig fibrosedannelse. Dertil kommer, at ca. halvdelen af patienterne i SENSCIS-studiet er i stabiliserende immunmodulerende behandling med mycophenolat ved studiestart. Der er publiceret en præspecificeret subgruppeanalyse for denne subpopulation [42]. En væsentlig del af subgruppen vil pga. mycophenolat-behandling forventeligt være patienter med et mere stabilt sygdomsforløb. Dermed afviger gruppen væsentligt fra den kliniske population i fraværet af progressionskriteriet, beskrevet i afsnit 3.3, og er ikke egnet til at svare på det kliniske spørgsmål.

Fagudvalget vurderer, at de nævnte forskelle vil betyde, at effekten af nintedanib fra SENSCIS-studiet formentlig er underestimeret i forhold til den forventede effekt hos SSc-ILS-patienter, der vil være kandidater til nintedanib i dansk klinisk praksis. Det skyldes, at den danske patientgruppe, som opfylder progressionskriterierne i afsnit 3.3, har en sygdom drevet af lungefibrose og dermed kan forventes at få størst mulig gavn af en antifibrotisk behandling.

5.1.2 Databehandling og analyse

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

Jf. afsnit 5.1.1 afviger studiepopulationen fra SENSCIS-studiet væsentligt fra populationen defineret i det kliniske spørgsmål. Fagudvalget ønsker alligevel at gennemgå de tilgængelige studiedata, da SENSCIS-studiet er det første kliniske studie, der undersøger effekten af antifibrotisk behandling hos SSc-ILS-patienter.

Det er data på ITT-populationen indsendt af ansøger, der vil blive gennemgået i rapporten her.

For samtlige effektmål har ansøger foretaget en direkte sammenligning af nintedanib og placebo med data fra SENSCIS-studiet. Ansøger har leveret data for ITT-populationen for alle effektmål efter 100 ugers opfølgningstid [44], med undtagelse af effektmålet *Lungefunktion – årlig FVC-faldhastighed* og *Livskvalitet,* som er opgjort efter 52 ugers opfølgningstid [41]. Gennemsnitlig behandlingslængde ved 100 uger var 14,5 og 15,7

måneder i hhv. nintedanib- og placeboarmen og 10,5 og 11,4 måneder i hhv. nintedanib- og placeboarmen ved 52 uger [44].

Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

Derudover ønsker Medicinrådet at fremhæve følgende:

- Da effektmålet ***Lungefunktion – årlig FVC-faldhastighed*** og *Livskvalitet* er kontinuerte effektmål, foreligger der kun data på de absolutte effektforskelle.
- Der foreligger data efter 52 ugers (studiets primære endepunkt) og 100 ugers (eksplorativ analyse) opfølgningstid for effektmålet ***Lungefunktion – årlig FVC-faldhastighed***, hvor fagudvalget primært vil lægge vægt på 52 ugers data. Studiedesignet gør, at alle *study completers* ikke er fulgt i 100 uger ved 100 ugers *data cut-off,* i og med 100 uger defineres med udgangspunkt i, hvornår den sidst randomiserede deltager har være behandlet og fulgt op i 52 uger. Der er dermed usikkerhed forbundet med dataopgørelsen ved 100 uger sammenlignet med 52 uger, hvilket var det tidspunkt, hvor studiets primære endepunkt blev opgjort.
- Ansøger har indsendt livskvalitetsdata fra SGRQ-spørgeskemaet frem for K-BILD, som var specificeret i protokollen, da der ikke foreligger data på K-BILD fra SENSCIS-studiet. Fagudvalget accepterer at benytte dette livskvalitetsværktøj, da det er beskrevet i protokollen som et muligt alternativ til K-BILD.

5.1.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for det kliniske spørgsmål. Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 3. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 4).

Der er udarbejdet én GRADE-profil for det kliniske spørgsmål. Evidensen er nedgraderet på baggrund af inkonsistens (kun ét studie), indirekthed (studiepopulationen afviger fra populationen i det kliniske spørgsmål) og unøjagtighed (konfidensintervallet for effektmålene *Dødelighed-median overlevelse* og *Alvorlige uønskede hændelser* indeholder en beslutningsgrænse).

Evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj 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 3. Resultater for klinisk spørgsmål 1: nintedanib sammenlignet med placebo til patienter med SSc-ILS

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Dødelighed	Median overlevelse (6 mdr.)	Kritisk	Median ikke nået	Kan ikke kategoriseres	HR 1,16 (0,47; 2,84)	Kan ikke kategoriseres	Kan ikke kategoriseres
	Lungefunktion – årlig FVC-faldhastighed (25 ml/år)		40,95 ml/år (2,88; 79,01)	Ingen dokumenteret merværdi	Kan ikke estimeres*	Kan ikke kategoriseres	
Livskvalitet	Gennemsnitlig forværring i SGRQ-spørgeskemaet, fra baseline (4 point)	Kritisk	1,69 point (-0,73; 4,12)	Ingen dokumenteret merværdi	Kan ikke estimeres*	Kan ikke kategoriseres	Kan ikke kategoriseres
Bivirkninger	Andel patienter, der oplever mindst én alvorlig uønsket hændelse (5 %-point)	Vigtig	3 %-point (-4,0; 11,0)	Kan ikke kategoriseres	RR 1,11 (0,86; 1,44)	Kan ikke kategoriseres	Kan ikke kategoriseres
	Andel patienter, der oplever behandlingsophør grundet uønskede hændelser (5 %-point)		7 %-point (2,0; 13)**	Kan ikke kategoriseres	RR 1,72 (1,12; 2,64)	Negativ værdi	
	Kvalitativ gennemgang af bivirkningsprofilen		Se nedenfor				
Konklusion							
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres						
Kvalitet af den samlede evidens	Meget lav						

MKRF = Mindste klinisk relevante forskel, CI = Konfidensinterval, HR = Hazard Ratio, RR = Relativ risiko.
*Det er ikke muligt at regne en relativ risiko for effektmål opgjort på en kontinuerlig skala.
**Fagudvalget bemærker, at den absolutte effektforskel er statistisk signifikant (CI inkluderer ikke 0) og klinisk relevant, da den er større end MKRF. Men på baggrund af Medicinrådets metoder, der tager udgangspunkt i MKRF, kan den foreløbige værdi dog ikke kategoriseres.

Dødelighed

Som beskrevet i protokollen er effektmålet *Dødelighed* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi SSc-ILS er en uhelbredelig, dødelig sygdom, som har en median overlevelse (OS) på omkring 155 måneder (range 9-180) efter diagnosen [19], og hvor behandlingsmålet er at bremse sygdomsprogressionen med henblik på stabilisering og dermed forlænget overlevelse.

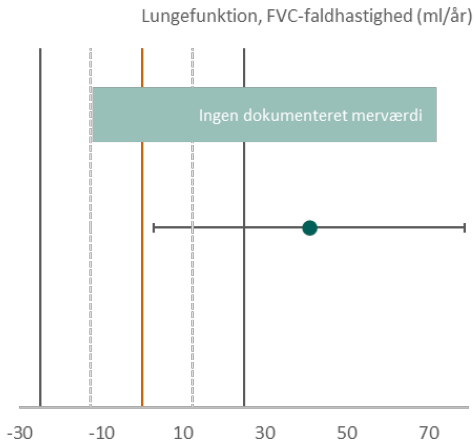
Median overlevelse

På grund af få hændelser er median overlevelse ikke nået gennem studiets opfølgningstid for nogen af armene, og den absolutte effektforskel for *Dødelighed, Median overlevelse* kan derfor ikke kategoriseres efter Medicinrådets metoder. Tages dog 2 års (100 ugers) dødelighed med i betragtning, fandtes 10 ud af 288 patienter (3,5 %) døde i nintedanib-armen sammenlignet med 9 ud af 288 patienter (3,1 %) i placeboarmen, med en statistisk ikke-signifikant hazard ratio på 1,16 (0,47; 2,84).

Fagudvalget bemærker, at hændelsesraten for dødelighed er, som det kan forventes for studiepopulationen i SENSCIS-studiet. Samlet set vurderer fagudvalget, at det tilgængelige OS-data er sparsomt grundet få hændelser, og dermed er en kategorisering af nintedanibs værdi for effektmålet *Dødelighed,* baseret alene på median overlevelse, ikke meningsfuld. Som beskrevet i protokollen vil fagudvalget inddrage lungefunktionseffektmålet FVC-faldhastighed, hvis OS-data er for umodne til at blive anvendt i kategoriseringen [39]. Der foreligger omfattende dokumentation for, at fald i FVC korrelerer med dødelighed ved SSc-ILS, se bilag 1.

Lungefunktion målt ved årlig FVC-faldhastighed

Patienter, som modtog nintedanib, oplevede et gennemsnitligt fald i FVC på 52,4 ml/år, mens patienter i placeboarmen oplevede et gennemsnitligt fald på 93,3 ml/år efter 52 ugers opfølgning [41]. Således er den absolutte effektforskel 40,95 ml/år, dvs. at patienter, som modtager nintedanib, bibeholder mere lungefunktion end patienter, som ikke modtager nintedanib. Den absolutte forskel er vist i figur 2 nedenfor.



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

Punktestimatet for den absolutte effektforskel på 40,95 ml/år (2,88; 79,01) afspejler en klinisk relevant effektforskel, da det ligger over mindste klinisk relevante effektforskel på 25 ml/år. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel, og den øvre grænse for konfidensintervallet indikerer en positiv forskel. Derfor har nintedanib, baseret på den absolutte effektforskel, foreløbigt ingen dokumenteret merværdi jf. Medicinrådets metoder vedr. effektmålet *Lungefunktion – årlig FVC-faldhastighed*.

Da FVC-faldhastighed er et kontinuert effektmål, og der ikke foreligger tilgængelige data præsenteret som andel patienter med et prædefineret fald over en bestemt frekvens, kan den relative effektforskel ikke udregnes. Baseret på den relative effektforskel kan den foreløbige værdi af nintedanib vedr. effektmålet *Lungefunktion – årlig FVC-faldhastighed* derfor ikke kategoriseres efter Medicinrådets metoder.

Fagudvalget noterer sig, at efter 100 ugers opfølgning ligger den absolutte effektforskel på 23,71 ml/år (5,77; 53,18) [44], hvilket er mindre end efter 52 ugers opfølgning. Fagudvalget understreger, at klinisk erfaring med nintedanib fra IPF viser, at effekten af nintedanib bibeholdes over tid. En mulig forklaring på, at effektforskellen falder over tid i SENSCIS-studier, kan være, at flere patienter i placeboarmen er blevet behandlet med anden *rescue*-behandling, hvilket kan medføre en mindre effektforskel på det senere opfølgningstidspunkt.

Fagudvalget har inddraget resultater fra mycophenolat-subgruppen for at perspektivere den observerede effekt. Subgruppeanalysen viser, at patienter, der ikke modtager mycophenolat ved baseline, har større effekt af nintedanib (absolut effektforskel på 55,4 ml/år) end patienter, der modtager mycophenolat ved baseline (absolut effektforskel på 26,3 ml/år) [42]. Fagudvalget vurderer, at dette kan skyldes, at den sidstnævnte gruppe er i stabiliserende behandling og ikke har behov for yderligere behandling. Subgruppeanalysen understreger vigtigheden af at vurdere, hvilken type behandling den

enkelte patient vil have størst gavn af, og understøtter, at patienter, som ikke modtager mycophenolat, kan have gavn af behandling med nintedanib i modsætning til patienter i stabiliserende behandling med mycophenolat.

Fagudvalgets samlede konklusion vedr. effektmålet *Dødelighed*

Fagudvalget vurderer, at nintedanib aggregeret har en merværdi, der **ikke kan kategoriseres** vedr. effektmålet *Dødelighed*. Det skyldes, at studiepopulationen i SENSCIS-studiet afviger væsentligt fra den danske patientpopulation, der er beskrevet i det kliniske spørgsmål, jf. protokollen, da en stor del af patienterne ikke har modtaget immunmodulerende behandling eller opfylder progressionskriterierne (se afsnit 5.1.1).

Fagudvalget har gennemgået data fra SENSCIS-studiet (se tabel 3), da det er det første kliniske studie, der undersøger effekten af antifibrotisk behandling hos SSc-ILS-patienter. Her kan fagudvalget ikke udtale sig sikkert om nintedanibs effekt på samlet overlevelse grundet få hændelser inden for studiets opfølgningstid, hvor der dog på 2-års opfølgning ikke kunne påvises en statistisk effekt. Data for fald i FVC, som, jf. bilag 1, korrelerer med dødelighed ved SSc-ILS, i ITT-populationen efter 52 ugers opfølgning viser, at behandling med nintedanib er forbundet med en klinisk relevant effekt (absolut effektforskel på -40,95 ml/år) sammenlignet med placebo, men at den absolutte effektforskel kategoriseres som ingen dokumenteret merværdi, jf. Medicinrådets metoder. Ved opfølgningstid på 100 uger var punktestimatet for den absolutte effektforskel (23,71 ml/år) ikke klinisk relevant. Fagudvalget mener dog, at det faktum, at flere patienter i placeboarmen modtager anden *rescue*-behandling i løbet af studiet, kan bidrage til, at effekten af nintedanib undervurderes ved længere opfølgningstid. Derfor mener fagudvalget, at resultaterne ved 52 ugers opfølgningstid indikerer, at nintedanib har bedre effekt end placebo.

Fagudvalget understreger, at behandling med nintedanib samlet set giver et mindre fald i FVC sammenlignet med ingen behandling, hvilket på længere sigt kan betyde, at patientens sygdom progredierer langsommere. I dag findes ingen behandlingstilbud til SSc-ILS-patienter, som progredierer trods standard immunmodulerende behandling.

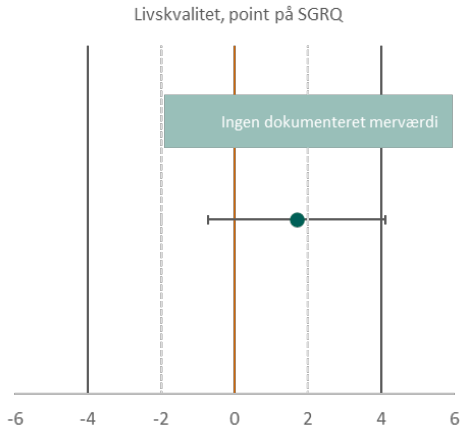
Studiepopulationen i SENSCIS-studiet består af en heterogen gruppe af SSc-ILS-patienter, hvor kun nogle af patienterne vil være kandidater til antifibrotisk behandling i dansk klinisk praksis. Subgruppeanalysen i studiet understøtter f.eks., at patienter, som ikke modtog mycophenolat, har større effekt af behandling med nintedanib sammenlignet med patienter, som modtog mycophenolat. Endvidere viser en post hoc-analyse fra INBUILD-studiet, hvor nintedanib blev undersøgt hos patienter med interstitiel lungesygdom med progredierende fibrose (PF-ILS), at effekten af nintedanib gælder for hver enkelt sygdomsgruppe, inkl. dem med autoimmun ILS, som SSc-ILS er en del af. 26 % af patienterne i INBUILD-studiet havde autoimmun ILS og 5,9 % af patienterne havde SSc-ILS. Den absolutte effektforskel for fald i FVC var hhv. 104 ml/år (21,1; 186,9) og 122,8 ml /år (-57,2; 302,8) i de to grupper [45]. Ifølge fagudvalget er patienternes baselinekarakteristika i INBUILD-studiet på mange måder mere betegnende end SENSCIS-studiet for den danske patientpopulation med SSc-ILS, som er kandidater til nintedanib. Patienterne i INBUILD-studiet karakteriseres af progressiv lungefibrose på trods af standardbehandling. Det er derfor fagudvalgets forventning på baggrund af

dokumentationen i INBUILD-studiet, at SSc-ILS patienter, som opfylder progressionskriterierne i afsnit 3.3, ville have større gavn af behandling med nintedanib, end der ses i SENSCIS-studiet.

Livskvalitet

Som beskrevet i protokollen er effektmålet *Livskvalitet* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det er et patientrelevant effektmål, som påvirkes i væsentlig grad af sygdomsprogressionen ved SSc-ILS [46–50]. Da nintedanibs virkningsmekanisme potentielt bremser sygdomsprogressionen, er der en formodning om, at nintedanib kan bremse faldet i patienternes livskvalitet eller i bedste fald stabilisere patienternes livskvalitet. Fagudvalget ønskede effektmålet opgjort med K-BILD-spørgeskemaet, som er et sygdomsspecifikt spørgeskema til patienter med ILS. Ansøger har indsendt livskvalitetsdata fra SGRQ-spørgeskemaet frem for K-BILD, da der ikke foreligger data på K-BILD fra SENSCIS-studiet.

Patienter, som modtog nintedanib, oplevede en forbedring i overordnet livskvalitet på 0,81 point på SGRQ-spørgeskemaet hen over de 52 ugers opfølgningstid. Patienter, som modtog placebo, oplevede derimod et fald på 0,88 point. Dermed er den absolutte effektforskel på 1,69 point, og der var således ingen påvist forskel. Den absolutte forskel er vist i figur 3 nedenfor.



Figur 3. Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet, målt med SGRQ-værktøjet. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Punktestimatet for den absolutte effektforskel på 1,69 point (-0,73; 4,12) afspejler ikke en klinisk relevant effektforskel, da det ligger under mindste klinisk relevante effektforskel på 4 point. Dertil er den nedre grænse for konfidensintervallet tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel, og den øvre grænse for konfidensintervallet indikerer en positiv forskel, som passerer MKRF. Derfor har nintedanib, baseret på den absolutte effektforskel, foreløbigt ingen dokumenteret merværdi jf. Medicinrådets metoder vedr. *Livskvalitet*.

Data på livskvalitet blev opgjort på en kontinuert skala, og der foreligger ikke data for den relative effektforskel (f.eks. andel patienter med > 4 points ændring). Derfor har nintedanib, baseret på den relative effektforskel, foreløbigt en værdi, som ikke kan kategoriseres vedr. *Livskvalitet*.

Fagudvalget vurderer, at nintedanib aggregeret har en merværdi, der **ikke kan kategoriseres** vedr. effektmålet *Livskvalitet*, da patientpopulationen i SENSCIS-studiet afviger væsentligt fra populationen i det kliniske spørgsmål.

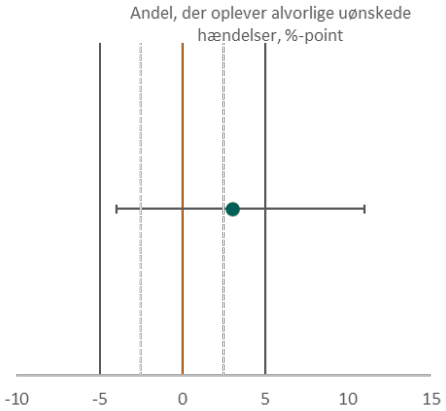
Data på ITT-populationen i SENSCIS-studiet viser, at den absolutte effektforskel er mindre end MKRF. Data tyder på, at 52 ugers behandling med nintedanib hverken er forbundet med en klinisk relevant forbedring eller forværring af patienternes livskvalitet.

Bivirkninger

Som beskrevet i protokollen er effektmålet *Bivirkninger* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi de både er generende for patienterne og kan forårsage pauser i behandlingen, hvilket kan forværre sygdommen. Fagudvalget ønskede effektmålet opgjort som tre delmål: andel patienter, som oplever minimum én alvorlig uønsket hændelse, behandlingsophør grundet uønskede hændelser og en kvalitativ gennemgang af nintedanibs bivirkningsprofil.

Alvorlige uønskede hændelser (*serious adverse event* (SAE))

Efter 100 ugers opfølgning oplevede 88 ud af 288 patienter (30,6 %), som modtog nintedanib, mindst én alvorlig uønsket hændelse (SAE), hvilket var tilfældet for 79 ud af 288 patienter (27,4 %), som modtog placebo. Den absolutte effektforskel er beregnet til 3 %-point. Den absolutte forskel er vist i figur 4 nedenfor.



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

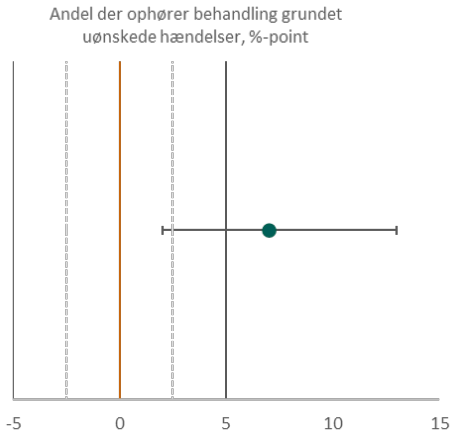
Punktestimatet for den absolutte effektforskel på 3 %-point (-4,0; 11,0) afspejler ikke en klinisk relevant effektforskel, da det ligger under mindste klinisk relevante effektforskel på 5 %-point. Den nedre grænse for konfidensintervallet ligger dog tættere på 0 (ingen

effektforskel) end på en negativ klinisk relevant forskel, og samtidig rummer konfidensintervallet muligheden for, at nintedanib har en klinisk negativ eller ingen værdi. Derfor kan den foreløbige værdi af nintedanib, baseret på den absolutte effektforskel vedr. delmålet *Andel patienter, der oplever alvorlige uønskede hændelser,* ikke kan kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, som er opgjort som en relativ risiko på 1,11 (0,86; 1,44) (fremgår af tabel 3), har nintedanib foreløbigt en værdi, der ikke kan kategoriseres vedr. delmålet *Andel patienter, der oplever alvorlige uønskede hændelser*.

Behandlingsophør grundet uønskede hændelser

Efter 100 ugers opfølgning ophørte 50 ud af 288 patienter (17,4 %) behandlingen grundet uønskede hændelser i nintedanib-armen, hvilket var tilfældet for 29 ud af 288 patienter (10,1 %) i placeboarmen. Den absolutte effektforskel er beregnet til 7 %-point. Den absolutte forskel er vist i figur 5 nedenfor.



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

Fagudvalget har i protokollen defineret MKRF til 5 %-point. Punktestimatet for den absolutte effektforskel på 7 %-point (2; 13) afspejler en negativ klinisk relevant effektforskel og en statistisk set signifikant effektforskel. Den nedre grænse for konfidensintervallet ligger dog lidt tættere på 0 (der svarer til ingen effektforskel) end på den mindste klinisk relevante forskel, og samtidig rummer konfidensintervallet muligheden for, at nintedanib har en klinisk negativ eller ingen værdi. Derfor kan den foreløbige værdi af nintedanib, baseret på den absolutte effektforskel vedr. delmålet *Andel patienter, der ophører behandling grundet uønskede hændelser,* ikke kan kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, som er opgjort som en relativ risiko på 1,72 (1,12; 2,64) (fremgår af tabel 3), har nintedanib foreløbigt en negativ værdi vedr. delmålet *Andel patienter, der ophører behandling grundet uønskede hændelser*.

Gennemgang af bivirkningsprofil

Gennemgangen af nintedanibs bivirkningsprofil tager udgangspunkt i EMAs produktresumé [24] og EPAR for SSc-ILS [44]. Fagudvalget har primært benyttet produktresuméet, da det indeholder en samlet gennemgang af bivirkninger for alle nintedanibs indikationer.

De hyppigst indberettede bivirkninger forbundet med nintedanib er diarré, kvalme og opkastning, mavesmerter, nedsat appetit, vægttab og forhøjede leverenzymer (se tabel 4 i bilag 1), som kan imødegås ved medicinsk behandling, dosisreduktioner eller behandlingspauser. Fagudvalget fremhæver, at patienter med systemisk sklerodermi døjer med gastrointestinale symptomer pga. af deres underliggende sygdom, som kan indvirke på både ophør, dosisreduktion og behandlingspauser. Nogle af bivirkningerne bliver fremhævet i nintedanibs produktresumé ift. særlige advarsler og forsigtighedsregler vedr. brug af nintedanib. Efter markedsføring af nintedanib er der blevet rapporteret om alvorlige tilfælde af diarré, som har ført til dehydrering og elektrolytforstyrrelser. Ligeledes er der observeret tilfælde af lægemiddelinduceret leverskade under behandling med nintedanib (hændelsesrate på 0,3 % i SENSCIS-studiet, jf. tabel 7 i bilag 1), herunder svær leverskade med dødelig udgang. Behandling med nintedanib anbefales ikke til patienter med moderat (*Child Pugh B*) og svært (*Child Pugh C*) nedsat leverfunktion. Ligeledes anbefales tæt kontrol af patienter med øget risiko for forhøjede leverenzymer. Øvrige bivirkninger, som fremhæves i nintedanibs produktresumé, er nedsat nyrefunktion, øget risiko for blødning, gastrointestinal perforation og iskæmisk colitis. For yderlige information henvises til nintedanibs produktresumé. På grund af risiko for fosterskader skal fertile kvinder rådes til at undgå at blive gravide, mens de er i behandling med nintedanib, samt bruge meget sikker kontraception [24].

Bivirkningerne rapporteret i SENSCIS-studiet var i henhold med nintedanibs kendte bivirkningsprofil (se tabel 5-7 i bilag 1) [44].

Behandling med nintedanib i SENSCIS-studiet var forbundet med markant flere dosisreduktioner (40,6 vs. 4,5 % i placeboarmen) og behandlingspauser (37,8 vs. 11,5 % i placeboarmen) sammenlignet med placebo. 34 % af patienterne i nintedanib-armen havde en permanent dosisreduktion sammenlignet med 3,5 % af patienterne i placeboarmen. En subgruppeanalyse på baggrund af dosisreduktion i SENSCIS-studiet har dog vist, at en reduceret dosis af nintedanib ikke er forbundet med en lavere effekt på FVC-faldhastighed [51].

Fagudvalgets samlede konklusion vedr. effektmålet *Bivirkninger*

Baseret på ovenstående gennemgang af effektmålets tre deleffektmål vurderer fagudvalget, at nintedanib aggregeret har en merværdi, der **ikke kan kategoriseres** vedr. effektmålet bivirkninger sammenlignet med placebo, da patientpopulationen i SENSCIS-studiet afviger væsentligt fra populationen i det kliniske spørgsmål.

Fagudvalget understreger, at bivirkningerne rapporteret i SENSCIS-studiet er i henhold med nintedanibs kendte bivirkningsprofil. Behandling med nintedanib er forbundet med flere alvorlige uønskede hændelser og behandlingsophør end placebo, hvilket er forventeligt i en sammenligning af en aktiv behandling – med betydelige og kendte

bivirkninger – med ingen behandling. I den forbindelse fremhæver fagudvalget, at frekvensen er sammenlignelig med den, som er rapporteret i INPULSIS-studierne for IPF-patienter [52]. Nintedanib giver mange bivirkninger i mave-tarm-kanalen, hvilket resulterer i flere dosisreduktioner og øget behov for supplerende behandling i form af lægemidler mod diarré og kvalme/opkastning. Bivirkningerne, der opstår ved behandling med nintedanib hos patienter med SSc-ILS, er velkendte for nintedanib og som rutinemæssigt behandles i klinisk praksis med dosis ændring eller medicinskift, omend de er generende for patienterne. Derudover finder fagudvalget det relevant, at behandling med nintedanib samlet set ikke påvirker livskvaliteten.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at nintedanib til patienter med systemisk sklerodermi-associeret interstitiel lungesygdom giver en merværdi, der **ikke kan kategoriseres** sammenlignet med placebo, da studiepopulationen i SENSCIS-studiet afviger væsentligt fra populationen i det kliniske spørgsmål, fordi en stor del af patienterne ikke har modtaget immunmodulerende behandling eller opfylder progressionskriterierne.

Den direkte sammenligning af nintedanib mod placebo i SENSCIS-studiet kan ikke dokumentere, at behandling med nintedanib er forbundet med en klinisk relevant effekt for ITT-populationen ift. fald i FVC eller livskvalitet. Fagudvalget vurderer, at studiet indikerer, at nintedanib reducerer faldet i FVC, men effekten ikke er klinisk relevant. Behandling med nintedanib er forbundet med flere bivirkninger, hvilket fagudvalget vurderer er forventeligt, da nintedanib sammenlignes med placebo. Bivirkningerne er dog velkendte for nintedanib og som rutinemæssigt behandles i klinisk praksis med dosis ændring eller medicinskift, omend de er generende for patienterne. Hvad angår livskvalitet, finder fagudvalget det relevant, at nintedanib ikke påvirker livskvaliteten negativt.

Fagudvalget fremhæver, at SENSCIS-studiet er det første kliniske studie, der undersøger effekten af antifibrotisk behandling hos SSc-ILS-patienter. Den beskedne effekt i SENSCIS-studiet kan være forårsaget af studiets inklusionskriterier. Der var ikke krav om, at patienterne opfyldte kriterierne defineret i afsnit 3.3, og som i dansk klinisk praksis skal være opfyldt, for at SSc-ILS-patienter kan komme i betragtning til antifibrotisk behandling. Det er fagudvalget kliniske vurdering, at effekten af nintedanib sandsynligvis ville være klinisk relevant for de danske SSc-ILS-patienter, som opfylder kriterierne i afsnit 3.3. Disse patienter har en særlig dårlig prognose, og der findes i dag ikke nogen god behandlingsmulighed. Fagudvalget mener desuden, at behandling ved progression understøttes af resultaterne fra INBUILD-studiet, som undersøgte effekten af nintedanib hos PF-ILS-patienter (SSc-ILS udgør en subtype af PF-ILS), og hvor patienterne skulle leve op til de progressionskriterier, som benyttes i dansk klinisk praksis. I INBUILD-studiet blev der påvist en markant effekt på fald i FVC [53], som ifølge en post hoc-analyse gjaldt for alle subgrupper, inkl. dem med autoimmun ILS og SSc-ILS (absolut effektforskel for fald i FVC på hhv. 104 ml/år (21,1; 186,9) og 122,8 ml /år (-57,2; 302,8) [45].

6. Andre overvejelser

Fagudvalget ønskede i protokollen at få belyst, om en reduceret dosis påvirker effekten af nintedanib. Dette er beskrevet i afsnit 5.1.4 – gennemgang af bivirkningsprofil.

Fagudvalget ønskede ligeledes en redegørelse af sammenligneligheden mellem studiepopulationen i SENSCIS-studiet og populationen defineret i det kliniske spørgsmål samt argumenter for betydningen af eventuelle afvigelser. Dette bliver adresseret i afsnit 5.1.1 og i fagudvalgets samlede konklusion.

Relation til Medicinrådets vurdering af nintedanib til patienter med PF-ILS

Fagudvalget gør opmærksom på, at der også udarbejdes en vurdering vedr. nintedanibs effekt hos patienter med PF-ILS. Som beskrevet ovenfor udgør SSc-ILS en subtype af PF-ILS. Grundet forskelle i inklusionskriterier i de respektive studier for patienter med SSc-ILS (SENSCIS-studiet) og patienter med PF-ILS (INBUILD-studiet) understreger fagudvalget, at patienternes baselinekarakteristika i INBUILD-studiet på mange måder er mere betegnende for den danske patientpopulation med SSc-ILS, som er kandidater til nintedanib. Fagudvalgets vurdering i denne vurderingsrapport skal derfor sættes i relation til fagudvalgets vurdering af nintedanib til PF-ILS.

Opstarts- og stopkriterier

Fagudvalget foreslår, at nintedanib kan tilbydes til patienter, som opfylder én af nedenstående progressionskriterier inden for de sidste 24 måneder. Derudover skal patienterne have progression af lungefibrose på førstelinjebehandling med mycophenolat eller udvikling af uacceptable bivirkninger ved behandling med mycophenolat.

Progressionskriterier inden for de sidste 24 måneder på trods af standardbehandling:

- relativt fald i FVC $\geq$ 10 % af forventet normalværdi
- relativt fald i FVC $\geq$ 5-< 10 % af forventet normalværdi samtidig med forværring af respiratoriske symptomer eller forværret fibrose på HRCT
- forværring af respiratoriske symptomer samtidig med forværret fibrose på HRCT.

I udvalgte tilfælde ved primært fibrotiske forandringer på HRCT kan opstart uden forudgående mycophenolat besluttes efter vurdering på MDT-konference.

Fagudvalget foreslår, at behandling bør stoppes:

- ved lungetransplantation
- ved kronisk lungesvigt (behov for døgn-ilttilskud) og dårlig performansstatus 3 eller 4
- ved et FVC-fald på samlet set > 10 % i løbet af et år (målt ved 3 uafhængige målinger), trods stabilt indtag af nintedanib.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning fra hverken Medicinrådet eller RADS.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lungeemfysem og lungefibrose

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

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Jon Torgny Rostrup Wilke *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Jasmina Huremovic *Overlæge*	Region Nordjylland
Pernille Hauschildt *Ledende overlæge*	Region Midtjylland
Sofie Lock Johansson *Afdelingslæge*	Region Syddanmark
Christian Niels Meyer *Overlæge*	Region Sjælland
Kristine Jensen* *Afdelingslæge*	Region Hovedstaden
Peter Kjeldgaard *Overlæge*	Dansk Lungemedicinsk Selskab
Torkell Ellingsen *Specialeansvarlig overlæge, klinisk professor*	Dansk Reumatologisk Selskab
Allan Mikael Schrøder *Farmaceut, specialist i sygehusfarmaci*	Dansk Selskab for Sygehusapoteksledelse
Thomas Øhlenschlæger *Læge*	Dansk Selskab for Klinisk Farmakologi
Linda Marie Sevelsted Møller* *Læge*	Dansk Selskab for Gastroenterologi og Hepatologi
Finn Wulff *Patient/patientrepræsentant*	Danske Patienter
Heinrich Andreasen *Patient/patientrepræsentant*	Danske Patienter
Saher Burhan Shaker *Overlæge*	Inviteret af formanden

*Har ikke deltaget i vurderingen af nintedanib til PF-ILS eller SSc-ILS.

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10. Versionslog

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

11. Bilag

Bilag 1: Sammenhæng mellem fald i FVC og dødelighed – evidens fra IPF og SSc-ILS

Ifølge fagudvalget er det en generel opfattelse blandt specialister i ILS, at faldende FVC hos patienter med fibrotisk lungesygdom, ligesom ved IPF, er en robust indikator for sygdomsprogression og forværret prognose. FVC betegner det volumen luft, man kan tømme ud af lungerne ved en forceret eksspiration, efter at man har taget en fuld inspiration. Ved dannelse af arvæv sker der pga. de elastiske egenskaber en skrumpning af lungerne. Derfor ser man ved sygdomsprogression, at den mængde luft, man kan eksspirere (FVC), falder. HRCT-scanninger fra patienter med progredierende arvævssygdom illustrerer på samme måde tydeligt, hvordan lungerne skrumper over tid. Tabet i FVC ved fibrotisk lungesygdom er irreversibelt og kumulerer over tid ved sygdomsprogression. Raske individer har en FVC, som typisk ligger > 80 % af forventet normalværdi, og i klinisk praksis ses sjældent fibrosepatienter med FVC under 40 %, da de typisk vil være døde pga. af deres sygdoms sværhedsgrad. Når lungefibrose progredierer, ser man især tiltagende åndenød med tendens til iltmangel og begrænsninger i fysisk kapacitet. I slutstadiet af sygdommen er patienten ofte bundet til kørestol eller seng og med behov for et højt ilttilskud. Ved opfølgning af patienter med interstitielle lungesygdomme er den kliniske praksis generelt at monitorere med måling af FVC og diffusionskonstant (DLco). Et fald i FVC anvendes som en indikator for sygdomsprogression og er den mest reproducerbare parameter sammenlignet med DLco.

Ifølge fagudvalget er fald i FVC ved IPF generelt accepteret som mål for sygdomsprogression og er det primære endemål, som hyppigst har været anvendt i studier på området. I det følgende er FVC angivet som en procentdel af den forventede værdi hos raske. Et fald i FVC er vist at være et robust mål for en forværret prognose, hvor et fald mellem 5-10 % over 6-12 måneder er associeret med en øget mortalitet. Tabel 4 viser en oversigt over nogle af de publikationer, hvor fald i FVC er blevet korreleret med dødelighed; jo højere faldhastighed, jo større risiko for at dø.

Tabel 4. Risikoen for død er blevet korreleret med fald i FVC i række publikationer

Kilde	Fald i FVC	Risiko for død	Uddybbning
Paterniti et al. [54]	≥ 10 - 15 % vs. FVC < 5 %	HR på 2,2 (95 % CI 1,1-4,4)	Gennemgang af seks kliniske studier med nintedanib og pirfenidon til behandling af IPF
	≥ 15 % vs. FVC < 5 %	HR på 6,1 (95 % CI 3,1-11,8)	
du Bois et al. [55]	Absolut fald på 5-10 %	HR på 2,14 (95 % CI 1,43-3,20)	Gennemgang af to kliniske studier med IFN-γ1b til behandling af IPF
	Absolut fald på ≥ 10 %	HR på 4,78 (95 % CI 3,12-7,33)	
Brown et al. [56]	INBUILD: relativt fald på > 10 % (48,9 % af patienterne)	HR på 3,64 (95 % CI 1,29-10,28)	Risikoen for død hos patienter med > 10 % relativt fald i FVC på et år i INBUILD (PF-ILS)- og INPULSIS (IPF)-studierne
	INPULSIS: relativt fald på > 10 % (48,7 % af patienterne)	HR på 3,95 (95 % CI 1,87-8,33)	
Richeldi et al. [57]	Relativt fald på ≥ 5 %	2-års risiko: HR på 1,85 (0,82 to 4,17)	Studiet undersøgte, hvor god prædiktor fald i FVC var for 2-års transplantationsfri overlevelse samt dødelighed hos patienter med IPF fra to kohorter
	Relativt fald på ≥ 10 %	2-års risiko: HR på 1,85 (0,82 to 4,17)	
	Relativt fald på ≥ 15 %	2-års risiko: HR på 2,86 (0,77 to 10,61)	
Zappala et al. [58]	Relativt fald 5-10 % ved 6 mdr. vs. stabil sygdom	HR på 2,34 (95 % CI 1,19-4,60)	Kohorte-studie, som undersøgte, hvor god prædiktor fald i FVC var for overlevelse hos patienter med IPF
	Relativt fald > 10 % ved 6 mdr. vs. stabil sygdom	HR på 2,80 (95 % CI 1,54-5,06)	

I 2015 anerkendte det amerikanske *Food and Drug Administration* (FDA) på baggrund af seks kliniske studier med nintedanib og pirfenidon til behandling af IPF, at fald i FVC er et klinisk relevant effektmål på grund af dens korrelation med dødelighed [59]. FDA's hovedargumenter var:

- Da IPF resulterer i progressiv forværring i lungefunktionen, er det logisk at monitorere en lungefunktionsparameter ligesom FVC, som vil blive påvirket af progressionen.
- På baggrund af de seks studier med enten nintedanib eller pirfenidon, sås der en korrelation mellem fald i FVC og mortalitet, se tabel 5. I fem af studierne var faldet i

FVC signifikant lavere hos patienter, der modtog antifibrotisk behandling sammenlignet med placebo. Ingen af studierne havde styrke til at vise statistisk signifikant reduktion i mortalitet, men alle viste en numerisk forbedret overlevelse med en HR < 1.

- I det ene studie, hvor der ikke kunne dokumenteres forskel i FVC-fald mellem pirfenidon og placebo, sås der heller ikke en numerisk forbedret overlevelse.

Tabel 5. Fald i FVC og risiko for død i seks studier hos IPF-patienter, hvor antifibrotisk behandling sammenlignes med placebo [59]

Studie	Absolut forskel i fald i FVC i ml (95 % CI)	Antal dødsfald (%)		HR for tid til død (95 % CI)
		Studiemedicin	Placebo	
CAPACITY 004 (pirfenidon) [60]	157 (3; 311) til fordel for pirfenidon	14 (8,0)	20 (11,5)	0,65 (0,33 ; 1,29)
CAPACITY 006 (pirfenidon) [60]	-6 (-178; 167) til fordel for placebo	18 (10,5)	17 (9,8)	1,07 (0,55 ; 2,08)
ASCEND (pirfenidon) [61]	193 (96; 289) til fordel for pirfenidon	12 (4,3)	21 (7,6)	0,57 (0,28 ; 1,16)
TOMORROW (nintedanib) [62]	131 (27; 235) til fordel for nintedanib	7 (8,1)	9 (10,3)	0,73 (0,27; 1,98)
INPULSIS-1 (nintedanib) [52]	125 (78; 173) til fordel for nintedanib	13 (4,2)	13 (6,4)	0,63 (0,29; 1,36)
INPULSIS-2 (nintedanib) [52]	94 (45; 143) til fordel for nintedanib	22 (6,7)	20 (9,1)	0,74 (0,40; 1,35)

Adskillige analyser har vist, at hos patienter med SSc-ILS korrelerer fald i FVC med lungefibroseprogression og dødelighed [6,17,19,21,25–28]. Et systemisk review, som inkluderede 27 studier, viste, at lav alder, lavere FVC og lavere DLco var associeret med mortalitet, selvom korrelationen med FVC ikke var helt konsistent [63]. En retrospektiv analyse af data fra 156 patienter med SSc-ILS viste, at FVC % af forventet normalværdi ved baseline var associeret med 1-års mortalitet [27]. Ligeledes har en analyse af data fra EUSTAR-databasen vist, at FVC < 80 % forventet ved baseline var en uafhængig risikofaktor for mortalitet med en HR på 1,64 (95 % CI 1,11-2,44) [17]. Et studie fra 2017 har ligeledes understøttet korrelationen mellem FVC og mortalitet, hvor HR for FVC ≥ 10 % af forventet var 1,84 (95 % CI 1,14-2,97) og 2,36 (95 % CI 1,35-4,14) for FVC ≥ 15 % af

forventet [19]. I et retrospektivt canadisk studie med 171 SSc-ILS-patienter blev patienterne kategoriseret i tre prognostiske grupper på baggrund af overlevelse efter diagnose. Patienter med den korteste overlevelse (≤ 4 år, årligt fald i FVC % af forventet var -4,1 (-7,92;-0,28)) havde en højere årlig FVC-faldhastighed end patienter med længere overlevelse (≥ 8 år, årligt fald i FVC % af forventet var -0,94 (-1,46;-0,42)) [64].

Bilag 2: Oversigter over bivirkninger fra nintedanibs produktresumé samt EPAR for SSc-ILS

Tabel 6. Oversigt over bivirkninger for de tre godkendte indikationer i henhold til MedDRA-systemorganklasse (SOC) efter hyppighedskategori. Tabel fra nintedanibs produktresumé.

	Hyppighed		
Systemorganklasse foretrukken term	Idiopatisk lungefibrose	Andre kroniske fibroserende ILS med en progressiv fænotype	Systemisk sklerodermi-associeret interstitiel lungesygdom
Blod og lymfesystem			
Trombocytopeni	Ikke almindelig	Ikke almindelig	Ikke almindelig
Metabolisme og ernæring			
Vægttab	Almindelig	Almindelig	Almindelig
Nedsat appetit	Almindelig	Meget almindelig	Almindelig
Dehydrering	Ikke almindelig	Ikke almindelig	Ikke kendt
Hjerte			
Myokardieinfarkt	Ikke almindelig	Ikke almindelig	Ikke kendt
Vaskelære sygdomme			
Blødning (se pkt. 4.4)	Almindelig	Almindelig	Almindelig
Hypertension	Ikke almindelig	Almindelig	Almindelig
Aneurismer og arterielle dissektioner	Ikke kendt	Ikke kendt	Ikke kendt
Mave-tarm-kanalen			
Diarré	Meget almindelig	Meget almindelig	Meget almindelig
Kvalme	Meget almindelig	Meget almindelig	Meget almindelig
Abdominalsmerter	Meget almindelig	Meget almindelig	Meget almindelig
Opkastning	Almindelig	Meget almindelig	Meget almindelig
Pancreatitis	Ikke almindelig	Ikke almindelig	Ikke kendt
Colitis	Ikke almindelig	Ikke almindelig	Ikke almindelig
Lever og galdeveje			
Leverskade forårsaget af lægemidlet	Ikke almindelig	Almindelig	Ikke almindelig
Forhøjede leverenzymer	Meget almindelig	Meget almindelig	Meget almindelig
Forhøjet alaninaminotransferase (ALAT)	Almindelig	Meget almindelig	Almindelig
Forhøjet aspartataminotransferase (ASAT)	Almindelig	Almindelig	Almindelig
Forhøjet gamma-glutamyltransferase (GGT)	Almindelig	Almindelig	Almindelig
Hyperbilirubinæmi	Ikke almindelig	Ikke almindelig	Ikke kendt
Forhøjet basisk fosfatase (ALKP) i blodet	Ikke almindelig	Almindelig	Almindelig
Hud og subkutane væv			
Udslæt	Almindelig	Almindelig	Ikke almindelig
Pruritus	Ikke almindelig	Ikke almindelig	Ikke almindelig
Alopeci	Ikke almindelig	Ikke almindelig	Ikke kendt
Nyrer og urinveje			
Nyresvigt (se pkt. 4.4)	Ikke kendt	Ikke almindelig	Ikke almindelig
Nervesystemet			
Hovedpine	Almindelig	Almindelig	Almindelig

Meget almindelig (≥ 1/10), almindelig (≥ 1/100 til < 1/10), ikke almindelig (≥ 1/1.000 til < 1/100), sjælden (≥ 1/10.000 til < 1/1.000), meget sjælden (< 1/10.000), ikke kendt (kan ikke estimeres ud fra forhåndenværende data).

Tabel 7. Oversigt over bivirkninger rapporteret i > 5 % af patienterne i SENSCIS-studiet. Tabel fra nintedanibs EPAR for SSc-ILS.

Adverse events reported for more than 5% of patients over 52 weeks in either treatment group on the PT level in trial 1199.214 - TS

MedDRA system organ class Preferred term	Placebo		Nintedanib 150 mg bid	
	N	%	N	%
Number of patients	288	100.0	288	100.0
Total with any AE	276	95.8	283	98.3
Gastrointestinal disorders	164	56.9	254	88.2
Diarrhoea	91	31.6	218	75.7
Nausea	39	13.5	91	31.6
Vomiting	30	10.4	71	24.7
Abdominal pain	21	7.3	33	11.5
Abdominal pain upper	13	4.5	20	6.9
Gastrooesophageal reflux disease	22	7.6	12	4.2
Infections and infestations	183	63.5	180	62.5
Nasopharyngitis	49	17.0	36	12.5
Upper respiratory tract infection	35	12.2	33	11.5
Urinary tract infection	23	8.0	24	8.3
Bronchitis	24	8.3	16	5.6
Influenza	15	5.2	12	4.2
Respiratory tract infection	15	5.2	5	1.7
Respiratory, thoracic and mediastinal disorders	111	38.5	101	35.1
Cough	52	18.1	34	11.8
Dyspnoea	25	8.7	21	7.3
Musculoskeletal and connective tissue disorders	87	30.2	100	34.7
Arthralgia	19	6.6	17	5.9
Back pain	12	4.2	16	5.6
Skin and subcutaneous tissue disorders	94	32.6	96	33.3
Skin ulcer	50	17.4	53	18.4
Investigations	48	16.7	86	29.9
Weight decreased	12	4.2	34	11.8
Alanine aminotransferase increased	3	1.0	21	7.3
Gamma-glutamyltransferase increased	4	1.4	17	5.9
Aspartate aminotransferase increased	1	0.3	15	5.2
General disorders and administration site conditions	72	25.0	77	26.7
Fatigue	20	6.9	31	10.8
Pyrexia	13	4.5	17	5.9
Nervous system disorders	59	20.5	60	20.8
Headache	24	8.3	27	9.4
Dizziness	12	4.2	17	5.9
Metabolism and nutrition disorders	22	7.6	44	15.3
Decreased appetite	12	4.2	27	9.4

Note: SOCs are tabulated only if they include individual PTs reported at a frequency of >5% in either treatment group.
Source data: [c22686034, Table 15.3.1.1.1: 2]

Tabel 8. Oversigt over bivirkninger fra mave-tarm-kanalen i SENSCIS-studiet. Tabel fra nintedanibs EPAR for SSc-ILS.

Gastrointestinal and metabolic adverse events over 52 weeks - TS

Organ system Safety topic	Placebo		Nintedanib 150 mg bid	
	N	%	N	%
Number of patients	288	100.0	288	100.0
Gastrointestinal AEs				
Diarrhoea (PT)	91	31.6	218	75.7
Nausea (PT)	39	13.5	91	31.6
Vomiting (PT)	30	10.4	71	24.7
Abdominal pain[1] (HLT gastrointestinal and abdominal pains [excl. oral and throat])	32	11.1	53	18.4
Pancreatitis (SMQ acute pancreatitis [narrow])	0	0.0	1	0.3
Gastrointestinal perforation (SMQ gastrointestinal perforation [narrow])	1	0.3	0	0.0
Metabolic AEs				
Decreased appetite (PT)	12	4.2	27	9.4
Decreased weight (PTs weight decreased and abnormal loss of weight)	13	4.5	34	11.8

[1] Includes PTs abdominal pain, abdominal pain upper, abdominal pain lower, and oesophageal pain

Tabel 9. Oversigt over hepatobiliære og laboratoriske lever bivirkninger i SENSCIS-studiet. Tabel fra nintedanibs EPAR for SSc-ILS.

Hepatobiliary and liver laboratory adverse events over 52 weeks - TS

Organ system Safety topic *Subcategory* Preferred term	Placebo		Nintedanib 150 mg bid	
	N	%	N	%
Number of patients	288	100.0	288	100.0
Hepatobiliary AEs				
Hepatic disorders combined	14	4.9	50	17.4
SMQ drug-related hepatic disorders – comprehensive search (narrow)	14	4.9	49	17.0
SMQ liver-related investigations, signs and symptoms (broad)	9	3.1	40	13.9
SMQ cholestasis and jaundice of hepatic origin (narrow)	1	0.3	1	0.3
SMQ hepatitis, non-infectious (narrow)	0	0.0	1	0.3
Hepatic failure (SMQ hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions [narrow])	3	1.0	11	3.8
Liver disorder	0	0.0	6	2.1
Liver injury	0	0.0	2	0.7
Drug-induced liver injury	1	0.3	1	0.3
Hepatic steatosis	2	0.7	1	0.3
Hepatocellular injury	0	0.0	1	0.3
Liver laboratory AEs				
Hepatic enzymes increased	9	3.1	38	13.2
Alanine aminotransferase increased	3	1.0	21	7.3
Gamma-glutamyl-transferase increased	4	1.4	17	5.9
Aspartate aminotransferase increased	1	0.3	15	5.2
Hepatic enzyme increased	4	1.4	8	2.8
Blood alkaline phosphatase increased	1	0.3	5	1.7
Transaminases increased	1	0.3	3	1.0
Hepatic function abnormal	0	0.0	1	0.3

Source data: Table 15.3.1.1.1: 5

Bilag 3: Cochrane – risiko for bias

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

Tabel 10. Vurdering af risiko for bias Highland et al., 2021, SENSCIS, NCT02597933

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Randomisering foretaget med en interaktiv responsteknologi. Randomiseringen var stratificeret efter tilstedeværelsen af anti-topoisomerase 1 antistof. Patienterne blev randomiseret 1:1 til nintedanib, 150 mg to gange dagligt, eller placebo.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet, placebokontrolleret studie, hvor både investigator, deltagere og alle, der deltog i udførelsen eller analysen af studiet, var blindede indtil efter *database lock*.
Manglende data for effektmål	**Lav**	Alle analyser blev foretaget på patienter, der modtog mindst én studiedosis. Der foreligger data på de effektmål, der er beskrevet i studieprotokollen.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet, placebokontrolleret studie.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der foreligger data på de effektmål, der er beskrevet i studieprotokollen, og der er ingen indikation om selektiv rapportering.
Overordnet risiko for bias	**Lav**	Den overordnede risiko for bias er lav, da alle domæner har lav risiko for bias.

Bilag 4: GRADE

Klinisk spørgsmål 1 – nintedanib sammenlignet med placebo til behandling af patienter med SSc-ILS

Tabel 11. GRADE evidensprofil for klinisk spørgsmål 1

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Nintedanib	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Median overlevelse, 100 uger												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ingen	-	-	HR 1,16 (0,47; 2,84)	-	⨁◯◯◯ MEGET LAV	KRITISK
Fald i FVC, 52 uger												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Ingen	Ingen	52,4 ml/år	93,3 ml/år	-	40,95 ml/år (2,88; 79,01)	⨁⨁◯◯ LAV	KRITISK
Livskvalitet målt ved SGQR, 52 uger												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Ingen	Ingen	0,81 point	-0,88 point	-	1,69 point (-0,73; 4,12)	⨁⨁◯◯ LAV	KRITISK
Alvorlige bivirkninger, 100 uger												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ingen	88/288	79/288	RR 1,11 (0,86; 1,44)	3 %-point (-4,0; 11,0)	⨁◯◯◯ MEGET LAV	VIGTIG

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	**Studie-design**	**Risiko for bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**Nintedanib**	**Placebo**	**Relativ (95 % CI)**	**Absolut (95 % CI)**	**Sikkerhed**	**Vigtighed**
Ophør grundet uønskede hændelser, 100 uger												
1	RCT	Ingen	Alvorlig[a]	Alvorlig[b]	Ingen	Ingen	50/288	29/288	RR 1,72 (1,12; 2,64)	7 %-point (2,0; 13)	⨁⨁◯◯ LAV	VIGTIG
Kvalitet af den samlede evidens MEGET LAV[d]												

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

[b] Studiepopulationen afviger fra populationen i det kliniske spørgsmål, da en stor del af patienterne i studiet ikke har modtaget immunmodulerende behandling eller opfylder progressionskriterierne, jf. afsnit 3.3.

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

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

Application for the assessment of Ofev® (nintedanib) in adults for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD)

Boehringer Ingelheim Danmark A/S
Strødamvej 52
DK-2100 København Ø

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1. Basic information

Table 1 Contact information

Contact information	
Name	**Jens Holt**
Title	Market Access Manager
Area of responsibility	Primary contact
Phone number	+45 22 72 48 73
E-mail	jens.holt@boehringer-ingelheim.com

Table 2 Overview of the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Ofev®
Generic name	Nintedanib
Marketing authorization holder in Denmark	Boehringer Ingelheim International GmbH, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany
ATC code	L01XE31 – L01EX09
Pharmacotherapeutic group	Antineoplastic agents, protein kinase inhibitors
Active substance(s)	Nintedanib
Pharmaceutical form(s)	Soft capsules for oral administration
Mechanism of action	Nintedanib is a small molecule tyrosine kinase inhibitor targeting the platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and Vascular Endothelial Growth Factor receptor (VEGFR) 1-3. In addition, nintedanib inhibits Lck (lymphocyte-specific tyrosine-protein kinase), Lyn (tyrosine-protein kinase lyn),Src (proto-oncogene tyrosine-protein kinase src), and CSF1R (colony stimulating factor 1 receptor) kinases. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signalling cascades, involved in the pathogenesis of fibrosis. [1]
Dosage regimen	The recommended dose in all indications is 150 mg nintedanib twice daily administered approximately 12 hours apart. The 100 mg twice daily dose is only recommended to be used temporarily in patients who do not tolerate the 150 mg twice daily dose.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Ofev is indicated in adults for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).

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Overview of the pharmaceutical	
Other approved therapeutic indications	Ofev is indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF). Ofev is also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.
Will dispensing be restricted to hospitals?	Yes, BEGR
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Ofev 100 mg soft capsules/ Ofev 150 mg soft capsules is available in the following pack-size: - 60 x 1 soft capsules in aluminium/aluminium perforated unit dose blisters
Orphan drug designation	No

2. Abbrevations

Table 3 Abbreviations

Abbreviation	Term
ACR	American College of Rheumatology
ADR	Adverse Drug Reaction
AE	Adverse event
DLCo	Carbon Monoxide Diffusion Capacity
DMC	Danish Medicines Council (Medicinrådet)
EPAR	European Public Assessment Report
EULAR	European League Against Rheumatism
EUSTAR	European Scleroderma Trials and Research Group
FVC	Forced Vital Capacity
HR	Hazard Ratio
HRCT	High Resolution Computed Tomography
QoL	Quality of Life
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
MedDRA	Medical Dictionary for Regulatory Affairs
mRSS	Modified Rodnan Skin Score
PF-ILD	Progressive Fibrosing Interstitial Lung Disease
RD	Risk Difference
RR	Risk Ratio
SD	Standard Deviation

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SGRQ	Saint George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SSc	Systemic Sclerosis
SSc-ILD	Systemic Sclerosis – Interstitial Lung Disease

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3. Summary

On 17. April 2020 the European Commission approved Ofev (nintedanib) as the first and only medicinal product for the treatment of Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD) in adults – this indication is the subject for the present application.

Ofev® was initially approved by the European Commission in 2015 for the treatment of Idiopathic Pulmonary Fibrosis (IPF) in adults. On 13. July 2020 the European Commission approved Ofev as the first medicinal product for the treatment of other chronic fibrosing interstitial lung diseases with a progressive phenotype (PF-ILD) in adults. This indication is subject to a separate application to the Danish Medicines Council (DMC).

In SSc-ILD nintedanib was investigated in one placebo-controlled pivotal phase III study – the SENSCIS study. SENSCIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis) was a phase III, multicentre, prospective, randomised (1:1), double-blind, placebo-controlled study with objective of assessing the efficacy and safety of nintedanib 150 mg twice daily compared with placebo in patients who had SSc with an onset of the first non-Raynaud's symptom within the past 7 years, a high-resolution computed tomographic (HRCT) scan that showed fibrosis affecting at least 10% of the lungs and an Forced Vital Capacity (FVC) that was at least 40% of the predicted value and a diffusion capacity of the lung for carbon monoxide (DLCO) (corrected for haemoglobin) that was 30 to 89% of the predicted value.

In the DMC protocol the patient population described had to have shown progression of pulmonary disease on baseline treatment. However, this was not a predefined inclusion criterion into the INBUILD study, and data were not collected.

The primary end point was the annual rate of decline in FVC (millilitres per year), assessed over a 52-week period and analysed with a random coefficient regression model. Key secondary end points were absolute changes from baseline in the modified Rodnan skin score (mRSS) and the total score on the St. George's Respiratory Questionnaire (SGRQ) at week 52. Assessments of the primary endpoint, key secondary endpoints, and adverse events (AE) in subgroups by use of mycophenolate at baseline were prespecified in the statistical analysis plan. Assessment of the other endpoints in subgroups by use of mycophenolate at baseline was post hoc.

The population included in the SENSCIS study is not fully in line with the patient population defined in the DMC protocol for this application (documented disease progression despite 3-6 months of treatment with immunomodulatory medication) as the study was designed to document the efficacy and safety of nintedanib in a broader SSc-ILD population, regardless of baseline mycophenolate and progression of disease. The implications of the difference in population for the interpretation of data from the SENSCIS study are described in the application.

To provide a full perspective of the efficacy and safety of nintedanib in SSc-ILD, data for both the overall population and the subgroups receiving mycophenolate or not at baseline is presented is the application.

The number of deaths in the study was low in both treatment groups which is why no difference in median survival could be shown.

In the mycophenolate subgroup, the reduction in the annual rate of the decline of FVC was -40.2 [95% Confidence Interval (CI): -79.1, -1.3) ml per year in the nintedanib group (n=138) and −66.5 (95% CI: -104.3, -28.7) ml per year in the placebo group (n=140) with between-group difference of 26.3 ml (95% CI: -27.9, 80.6; (interaction) p=0.347). [2]

In the overall population, analysing on treatment patients only, nintedanib demonstrated a significant improvement in the adjusted rate of decline in the FVC over the whole trial (week 100), of -55.1 [95%CI: -79.2, -31.0] ml per year in the nintedanib group (n=287) and −94.0 [95% CI: -117.0, -71.0] ml per year in the placebo group (n=288) with between-group difference of 38.85 ml (95% CI: 5.56, 72.14; p=0.022).[3]

The difference in effect between nintedanib and placebo in the measure for quality of life (SGRQ) was not statistically significant, neither in the overall population nor in the mycophenolate subgroup. [4]

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In the mycophenolate subgroup, one or more serious adverse events (SAE) was experienced at 52 weeks by 36/139 (25.9%) patients in the nintedanib group and 22/140 (15.7%) patients in the placebo group, a Risk Difference (RD) of 0.10 [95% CI 0.01, 0.20; p=0.039]. [2] In the overall population the incidence of SAEs was similar between nintedanib and placebo as 88/288 (30.6%) patients in the nintedanib group and 79/288 (27.4%) patients in the placebo group had experienced one or more SAEs at week 100 [RD: 0.03; 95% CI -0.04, 0.11; p=0.441]. [3]

In the mycophenolate subgroup, at 52 weeks 15/139 (10.8%) patients in the nintedanib group and 9/140 (6.4%) patients in the placebo group had experienced treatment discontinuation due to AEs [RD:0.04; 95% CI: -0.02, 0.11; p=0.230]. [2] In the overall population, at week 100 50/288 (17.4%) patients in the nintedanib group and 29/288 (10.1%) patients in the placebo group had experienced treatment discontinuation due to AEs [RD: 0.07; 95% CI: 0.02, 0.13; p=0.013]. [3]

The qualitative review of the safety profile of nintedanib in patients with SSc-ILD confirmed the well-known and manageable safety profile from use in IPF since 2015. No new signals were identified in the SENSCIS study.

Ofev® (nintedanib) is the first approved treatment option for patients with SSc-ILD and has documented effect on pulmonary function by reducing the annual rate of decline of FVC and a well-known and manageable safety profile.

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4. Literature search

As per the instruction in the DMC protocol no literature search has been conducted.[5] The application is based on the pivotal phase III study SENSCIS. [4]

4.1 Relevant studies

Table 1 Relevant studies included in the assessment.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Distler O, Highland KB, Gahlemann M, et al.; SENSCIS Trial. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease N Engl J Med. 2019 Jun 27;380(26):2518-2528[4] *Highland KB, Distler O, Kuwana M, et al.* Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. Lancet Respir Med. 2021 Jan;9(1):96-106.[2] *Distler O, Brown KK, Distler JHW, et al.*; SENSCIS™ trial investigators. Design of a randomised, placebo-controlled clinical trial of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SENSCIS™). Clin Exp Rheumatol. 2017 Sep-Oct;35 Suppl 106(4):75-81. [Design publication][6] *Seibold JR, Maher TM, Highland KB, et al.*; SENSCIS trial investigators. Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSCIS trial. Ann Rheum Dis. 2020 Nov;79(11):1478-1484.[7]	*SENSCIS*	*NCT02597933*	*NOV 2015 – NOV 2018*	1

*when multiple clinical questions are defined in the protocol

In addition, the current Summary of Product Characteristics (SmPC) for nintedanib and the following European Public Assessment Reports (EPAR) for nintedanib has been reviewed and information included, if applicable. [1, 3, 8, 9]

- Assessment report EMA/315975/2020. Procedure No. EMEA/H/C/003821/II/0027 (the PF indication/INBUILD study)[9]
- Assessment report EMA/155527/2020. Procedure No. EMEA/H/C/003821/II/0026 (the SSc-indication/SENSCIS study)[3]
- Assessment report EMA/76777/2015. Procedure No. EMEA/H/C/003821/0000 (the IPF indication/INPULSIS studies)[8]

4.2 Main characteristics of included studies

The clinical development program for nintedanib in SSc-ILD consists of one phase III study – the SENSCIS study which is briefly described below and in detail in Table 9 on p. 23. [2, 4]

SENSCIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis) was phase III, multicentre, prospective, randomised (1:1), double-blind, placebo-controlled study with objective of assess the efficacy and safety of nintedanib 150 mg twice daily compared with placebo in patients who had SSc with an onset of the first non-Raynaud's symptom within the past 7 years, an HRCT scan that showed fibrosis affecting at least 10% of the lungs and an FVC that was at least 40% of the predicted value and a diffusion capacity of DLCO (corrected for haemoglobin) that was 30 to 89% of the predicted value. [4]

The DMC has defined the patient population in scope as SSc-ILD patients, who are progressing on first line treatment with immunomodulatory medications. [5]

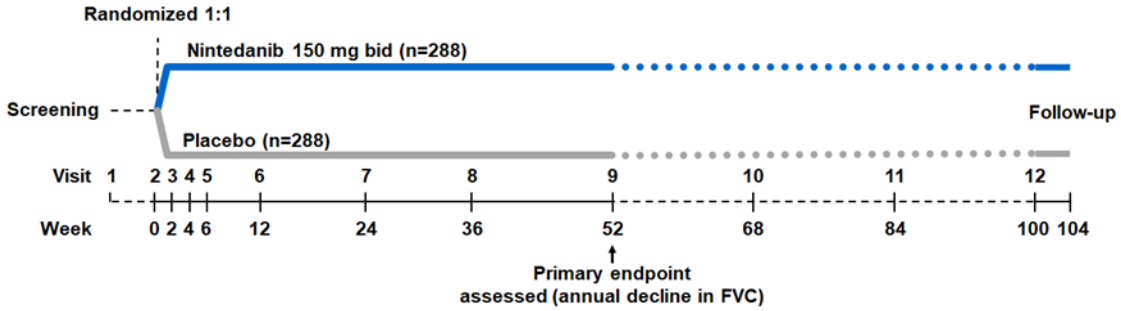
The inclusion criteria for the SENSCIS study allowed for patients with SSc-ILD to be included regardless of documented progression or not, and regardless of prior immunomodulatory treatment. [10] Thus, data for the subgroup progressing on first line treatment with immunomodulatory drugs in general are not reported in the SENSCIS study. However, patients on stable therapy with either mycophenolate or methotrexate for at least 6 months prior to Visit 2 were allowed into the study and should stay stable on this background therapy for at least 6 months after randomization.[10]

The implications of the difference in patient definition between the DMC definition and the patient population in the SENSCIS study are explained in section 5.2.2 on p. 18.

Patients were randomised 1:1 to receive treatment or placebo with additional stratification by anti-topoisomerase antibodies (ATA) status (positive or negative) which is associated with disease progression.

Screening took place at Visit 1 followed by randomisation at Visit 2, with a maximum of 12 weeks between visits. Beginning at Visit 2, patients took oral nintedanib 150 mg or placebo twice daily for up to 100 weeks and had visits to assess efficacy and safety on pre-specified days (Figure 1).

Figure 1 Patient visit schedule - the SENSCIS SSc-ILD study



As shown in Figure 2, the design of the trial meant that in practice, treatment duration beyond 52 weeks varied at the individual patient level.

The main treatment efficacy analysis was performed at 52 weeks (primary endpoint), however treatment continued until one of the following timepoints was reached:

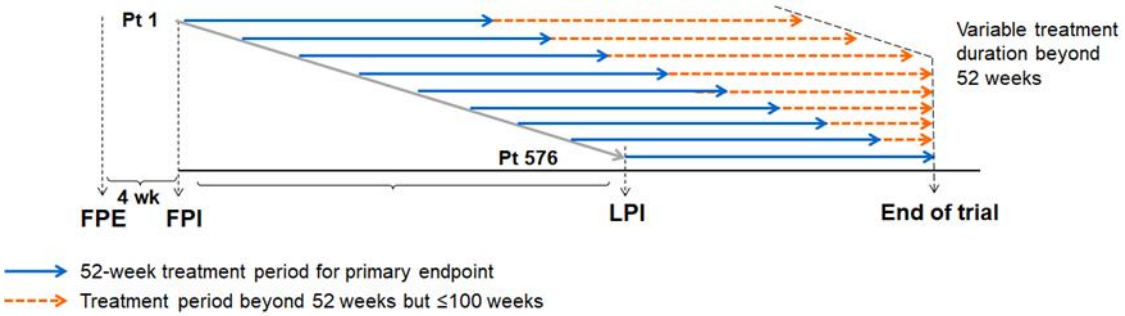
- Patient reached 100 weeks of treatment
- The last patient randomised in the trial completed 52 weeks of treatment
- A final follow-up assessment was completed 28 days after the last treatment dose, marking the end of the trial for each patient.

Data collected beyond 52 weeks were used in exploratory analyses of efficacy and safety.

Analysis (52 week) on the full study population is reported in Distler et al. [4] Data for the overall population for the week 100 analysis has been reported in the EPAR. [3]

However, data for the mycophenolate subgroup has only been reported for the 52-week cut-off, except for the mortality outcome, where data are available for the 100 week analysis.[2]

Figure 2 Patient level study design – the SENSCIS SSc-ILD study



Dose reduction of nintedanib to 100mg twice daily or interruption for up to 4 to 8 weeks (in case AE were considered drug related or not drug related, respectively) was available during the trial as a management strategy for patients with AEs.

The primary end point was the annual rate of decline in FVC (millilitres per year), assessed over a 52-week period and analysed with a random coefficient regression model. Key secondary end points were absolute changes from baseline in the mRSS and the total score on the SGRQ at week 52. [4]

The main points of the methodology for the subgroup analysis were as follows:

Assessments of the primary endpoint, key secondary endpoints, and AEs in subgroups by use of mycophenolate at baseline were prespecified in the statistical analysis plan (before database lock and unmasking). Assessment of the other endpoints listed above in subgroups by use of mycophenolate at baseline was post hoc. The proportion of patients who died was analysed over the entire trial period. Safety was assessed based on AEs reported, irrespective of causality, over 52 weeks. [2]

The analysis was performed by using a random coefficient regression model (with random slopes and intercepts) including anti-topoisomerase I anti body status (positive, negative), age, height, sex, and baseline FVC (mL) as covariates and terms for baseline-by-time, treatment-by-subgroup and treatment-by-subgroup-by-time interactions. For further details on the statistical methodology, please refer to the section on subgroup analysis in Table 9 (p. 23). [2]

5. Clinical question

5.1 What is the value of nintedanib compared to placebo in patients with systemic sclerosis associated interstitial lung disease?

5.1.1 Presentation of relevant studies

The pivotal study SENSCIS is briefly described in section 4.2 above and in detail in Table 9 on p. 23.

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Results for the group of patients receiving mycophenolate at baseline is reported in Highland et al. [2] Results for the overall population consisting of patients receiving and not receiving mycophenolate are described in the main publication by Distler et al. [4]

In the SENSCIS study, between Nov 30**,** 2015, and Oct 31, 2017, 819 patients were screened and 580 were randomly assigned to either nintedanib (290) or placebo (290). 576 patients received at least one dose of nintedanib (288) or placebo (288). [2, 4]

At baseline, 139 (48%) participants in the nintedanib group and 140 (49%) in the placebo group were taking mycophenolate (268 [47%] mycophenolate mofetil, 11 [2%] mycophenolate sodium). [2, 4]

The median dose of mycophenolate used at baseline was 2000 mg (minimum 500, maximum 2600) in the nintedanib group, and 2000 mg (minimum 200, maximum 4000) in the placebo group). Mean age and sex distributions were similar across subgroups. [2]

The proportion of participants with diffuse cutaneous SSc was higher among those who were taking mycophenolate at baseline than in those not taking mycophenolate at baseline. Also, mean mRSS was higher and mean FVC % predicted was lower in those taking mycophenolate at baseline than in those not taking mycophenolate at baseline. [2]

Of the participants who were taking mycophenolate at baseline, 131 (94%) of 139 in the nintedanib group and 136 (97%) of 140 in the placebo group were still taking mycophenolate at week 52. [2]

Baseline demographics for the overall population are shown in Table 10 (p. 25) as reported by Distler et al, and for the subgroup receiving mycophenolate in Table 11 (p. 27) as reported by Highland et al. [2, 4]

5.1.2 Results per study

The results presented in the DMC result table (Table 12 (p. 30)) are based on the mycophenolate subgroup as described in Highland et al. For comparison, the data the overall population have been included in Table 13 (p. 33). In addition, the data also for the non-mycophenolate group have been briefly described the narrative section below to show that the results are similar across the two groups.

Mortality – median survival

In the mycophenolate subgroup 4/139 (2.9%) in the nintedanib group and 2/140 (1.4%) in the placebo group had died at the week 100 database lock [HR 1.99; 95% CI 0.36, 10.96]. [2]

In the overall population 10/288 (3.5%) patients in the nintedanib group and 9/288 (3.1%) patients in the placebo group (HR: 1.16; 95% CI: 0.47, 2.84; p=0.7535) had died at the week 100 database lock. [3, 4]

Lung function as measured by annual rate of decline in FVC

In the mycophenolate subgroup, the adjusted rate of decline of FVC over the 52-week period (the primary endpoint) was -40.2 [95% CI: -79.1, -1.3] ml per year in the nintedanib group (n=138) and −66.5 [-104.3, -28.7] ml per year in the placebo group (n=140) with between-group difference of 26.3 ml (95% CI: -27.9, 80.6; (interaction) p=0.347]. [2]

In comparison the difference in the subgroup not treated with mycophenolate was 55.4 [2.3, 108.5] ml per year. [2]

In the overall population, the adjusted rate of decline of FVC over the 52-week period was -52.4 [95% CI:-79.6, -25.2) ml per year in the nintedanib group (n=287) and −93.3 [95% CI: -120.0, -66.7] ml per year in the placebo group (n=288) with between-group difference of 40.95 ml [95% CI: 2.88 to 79.01; p=0.0350]. [3]

The annual rate of decline of FVC over the whole trial (100 weeks) in the originally planned analysis in the overall population, including post treatment data, was -62.3 [95% CI: -83.3, -41.2) mL/year in the nintedanib group and -86.0 [95% CI: -106.6, -65.3] mL/year in the placebo group, with the estimated treatment difference of 23.71 mL/year [95% CI:

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- 5.77, 53.18]. [3, 11] However as this analysis included patients who discontinued treatment, it is considered a very conservative estimate of the effect of nintedanib.

Therefore, a post hoc analysis including only data for patients on-treatment was conducted, [3] in which the annual rate of decline in FVC over the whole trial was -55.1 (95% CI: -79.2, -31.0] mL/year in the nintedanib group and -94.0 [95% CI: -117.0, -71.0] mL/year in the placebo group, resulting in a treatment difference of 38.85 mL/year [95% CI: 5.56 to 72.14; p=0.022] These data have been included in the results table (Table 13) in the present application. [3, 11]

Quality of life – Mean worsening in SGRQ questionnaire from baseline

The DMC has requested data from the King's Brief Interstitial Lung Disease (K-BILD) questionnaire. The K-BILD questionnaire was however not used in the SENSCIS study. Data from the SGRQ questionnaire are presented instead as described as an alternative in the DMC protocol.

In the mycophenolate subgroup, the adjusted absolute change from baseline in SGRQ total score at week 52 was 0.7 [95% CI: -1.8, 3.2] points in the nintedanib group (n=137) and -0.9 [95% CI: -3.3, 1.6] points in the placebo group (n=138) with between-group difference of 1.6 [95% CI: -1.9, 5.0; (interaction) p=0.382) points. [2]

In comparison the difference in the subgroup not treated with mycophenolate was 1.8 [-1.6, 5.2] points. [2]

In the overall population, the adjusted absolute change from baseline in SGRQ total score at week 52 was 0.81 [95% CI: -0.92, 2.55] points in the nintedanib group (n=282) and -0.88 [95% CI: -2.58, 0.82) points in the placebo group (n=283) with between-group difference of 1.69 [95% CI: -0.73, 4.12; p=0.1711). [3, 4]

Adverse events – Proportion of patients experiencing at least one serious adverse event

In the mycophenolate subgroup, at 52 weeks 36/139 (25.9%) patients in the nintedanib group and 22/140 (15.7%) patients in the placebo group had experienced one or more SAEs with a Risk Difference of 0.10 [95% CI: 0.01, 0.20; p=0.039], and a Risk Ratio of 1.65 [95% CI: 1.02 to 2.65; (interaction) p=0.039]. [2]

The data should be assessed in the context of the frequency of SAEs in the SENSCIS study in the non-mycophenolate group, which was 33/149 (22.1%) for patients receiving nintedanib and 40/148 (27.0%) in the non-mycophenolate group receiving placebo, a difference of 4.9 %-point in favour of nintedanib. [2]

It is well-known that mycophenolate is associated with gastrointestinal AEs.[12] It must be taken into consideration that the patients recruited into the SENSCIS study mycophenolate subgroup had been receiving mycophenolate at a stable dose for at least 6 month and thus had shown to be able to tolerate mycophenolate for an extended period of time. [2, 7]

Published data for later database locks for the mycophenolate subgroup have not been identified.

In the overall population the incidence of SAEs was similar between nintedanib and placebo. At week 100, 88/288 (30.6%) patients in the nintedanib group and 79/288 (27.4%) patients in the placebo group had experienced one or more SAEs [RD: 0.03; 95% CI: -0.04, 0.11; p=0.441] with a Risk Ratio of 1.11 [95% CI: 0.86, 1.44; p=0.436].[3]

Adverse events – Proportion of patients experiencing treatment discontinuation due to adverse event

In the mycophenolate subgroup, at 52 weeks 15/139 (10.8%) patients in the nintedanib group and 9/140 (6.4%) patients in the placebo group had experienced treatment discontinuation due to AEs [RD 0.04; 95% CI: - 0.02, 0.11; p=0.230] with a Risk Ratio of 1.68 [95% CI: 0.76 to 3.71; (interaction) p=0.201].[2]

Data for later database locks for the mycophenolate subgroup have not been reported.

In the overall population, at week 100, 50/288 (17.4%) patients in the nintedanib group and 29/288 (10.1%) patients in the placebo group had experienced treatment discontinuation due to AEs [RD of 0.07; 95% CI: 0.02, 0.13; p=0.013) with a Risk Ratio of 1.72 (95% CI: 1.12, 2.64; p= 0.013]. [3]

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Adverse drug reactions – Qualitative review of the adverse event profile

The DMC has requested information on adverse drug reactions (ADR) based on the SmPC. However, the SmPC does not distinguish ADRs based on use of mycophenolate or not, why the overall ADR profile across the indications for nintedanib has been described. Supplementary data for AEs from the Highland publication on subgroups has been included in this section for completion of the information.

Overall ADR profile

Sourced from the SmPC, Table 4 provides a summary of the ADRs by indication and by MedDRA System Organ Class (SOC) and frequency category using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). [1]

Table 4 Adverse Drug Reactions for nintedanib

System Organ Class preferred term	Frequency Idiopathic pulmonary fibrosis	Other chronic fibrosing ILDs with a progressive phenotype	Systemic sclerosis associated interstitial lung disease
Blood and lymphatic system disorders			
Thrombocytopenia	Uncommon	Uncommon	Uncommon
Metabolism and nutrition disorders			
Weight decreased	Common	Common	Common
Decreased appetite	Common	Very common	Common
Dehydration	Uncommon	Uncommon	Not known
Cardiac disorders			
Myocardial infarction	Uncommon	Uncommon	Not known
Vascular disorders			
Bleeding	Common	Common	Common
Hypertension	Uncommon	Common	Common
Aneurysms and artery dissections	Not known	Not known	Not known
Gastrointestinal disorder			
Diarrhoea	Very common	Very common	Very common
Nausea	Very common	Very common	Very common
Abdominal pain	Very common	Very common	Very common
Vomiting	Common	Very common	Very common
Pancreatitis	Uncommon	Uncommon	Not known
Colitis	Uncommon	Uncommon	Uncommon
Hepatobiliary disorders			
Drug induced liver injury	Uncommon	Common	Uncommon
Hepatic enzyme increased	Very common	Very common	Very common
Alanine aminotransferase (ALT) increased	Common	Very common	Common
Aspartate aminotransferase (AST) increased	Common	Common	Common
Gamma glutamyl transferase (GGT) increased	Common	Common	Common
Hyperbilirubinemia	Uncommon	Uncommon	Not known
Blood alkaline phosphatase (ALKP) increased	Uncommon	Common	Common
Skin and subcutaneous tissue disorders			
Rash	Common	Common	Uncommon
Pruritus	Uncommon	Uncommon	Uncommon
Alopeci	Uncommon	Uncommon	Not known
Renal and urinary disorders			

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Renal failure	Not known	Uncommon	Uncommon
Nervous system disorders			
Headache	Common	Common	Common
Ref.: [1]			

Dose adjustment and or dose interruption of nintedanib can in many cases mitigate the severity and duration of ADRs, which is described in section 4.2 of the SmPC. In addition to symptomatic treatment if applicable, the management of ADRs to nintedanib could include dose reduction and temporary interruption until the specific ADR has resolved to levels that allow continuation of therapy. Nintedanib treatment may be resumed at the full dose (150 mg twice daily) or a reduced dose (100 mg twice daily). If a patient does not tolerate 100 mg twice daily, treatment with nintedanib should be discontinued. If diarrhoea, nausea and/or vomiting persist despite appropriate supportive care (including anti-emetic therapy), dose reduction or treatment interruption may be required. The treatment may be resumed at a reduced dose (100 mg twice daily) or at the full dose (150 mg twice daily). In case of persisting severe diarrhoea, nausea and/or vomiting despite symptomatic treatment, therapy with nintedanib should be discontinued. [1]

In case of interruptions due to aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3x upper limit of normal (ULN), once transaminases have returned to baseline values, treatment with Nintedanib may be reintroduced at a reduced dose (100 mg twice daily) which may be increased to the full dose (150 mg twice daily). [1]

In clinical trials, diarrhoea was the most frequent gastro-intestinal event reported. In most patients, the event was of mild to moderate intensity. More than two thirds of patients experiencing diarrhoea reported its first onset already during the first three months of treatment. In most patients, the events were managed by anti-diarrhoeal therapy, dose reduction or treatment interruption. [1] An overview of the reported diarrhoea events in the clinical trials is listed in Table 5

Table 5 Diarrhoea reported as adverse events

	INPULSIS (IPF)		INBUILD (PF-ILD)		SENSCIS (SSc-ILD)	
	Placebo	**Nintedanib**	**Placebo**	**Nintedanib**	**Placebo**	**Nintedanib**
Diarrhoea	18.4%	62.4%	23.9%	66.9%	31.6%	75.7%
Severe diarrhoea	0.5%	3.3%	0.9%	2.4%	1.0%	4.2%
Diarrhoea leading to nintedanib dose reduction	0%	10.7%	0.9%	16.0%	1.0%	22.2%
Diarrhoea leading to nintedanib discontinuation	0.2%	4.4%	0.3%	5.7%	0.3%	6.9%
Ref.: [1]						

Hepatic enzyme increased

In the INPULSIS trials, liver enzyme elevations were reported in 13.6% versus 2.6% of patients treated with nintedanib and placebo, respectively. In the INBUILD trial, liver enzyme elevations were reported in 22.6% versus 5.7% of patients treated with nintedanib and placebo, respectively. In the SENSCIS trial, liver enzyme elevations were reported in 13.2% versus 3.1% of patients treated with nintedanib and placebo, respectively. Elevations of liver enzymes were reversible and not associated with clinically manifest liver disease. [1]

Bleeding

In clinical trials, the frequency of patients who experienced bleeding was slightly higher in patients treated with nintedanib or comparable between the treatment arms (nintedanib 10.3% versus placebo 7.8% for INPULSIS; nintedanib 11.1% versus placebo 12.7% for INBUILD; nintedanib 11.1% versus placebo 8.3% for SENSCIS). Non-serious epistaxis was the most frequent bleeding event reported. Serious bleeding events occurred with low frequencies in the 2 treatment groups (nintedanib 1.3% versus placebo 1.4% for INPULSIS; nintedanib 0.9% versus placebo 1.5% for INBUILD; nintedanib 1.4% versus placebo 0.7% for SENSCIS). [1]

General comments

As nintedanib has been on the market for IPF since 2015 the documentation of post marketing safety experience is robust. In addition, open label, long term safety data for nintedanib in IPF and in SSc-ILD are available in Crestani et al, Allanore et al, and Lasky et al, respectively. [20-22]

In the EPAR the CHMP noted that overall, the safety findings of this trial were consistent with the known safety profile of nintedanib in IPF. Furthermore, there was consistency in the safety findings for the 52-weeks data and the whole trial data.[3]

Safety profile by subgroup treatment at baseline

Safety data based on reporting of AEs for the subgroup treated with mycophenolate is available in Highland et al (Table 6). [2]

Table 6 Adverse events in subgroups by use of mycophenolate at baseline

	Patients taking mycophenolate at baseline		Patients not taking mycophenolate at baseline	
	Nintedanib (n=139)	Placebo (n=140)	Nintedanib (n=149)	Placebo (n=148)
Any AE*	136 (98%)	135 (96%)	147 (99%)	141 (95%)
Most frequent AEs†				
Diarrhoea	106 (76%)	48 (34%)	112 (75%)	43 (29%)
Nausea	43 (31%)	23 (16%)	48 (32%)	16 (11%)
Skin ulcer	22 (16%)	23 (16%)	31 (21%)	27 (18%)
Vomiting	32 (23%)	17 (12%)	39 (26%)	13 (9%)
Cough	20 (14%)	33 (24%)	14 (9%)	19 (13%)
Nasopharyngitis	10 (7%)	22 (16%)	26 (17%)	27 (18%)
Upper respiratory tract infection	19 (14%)	25 (18%)	14 (9%)	10 (7%)
Abdominal pain	14 (10%)	6 (4%)	19 (13%)	15 (10%)
Fatigue	19 (14%)	14 (10%)	12 (8%)	6 (4%)
Headache	16 (12%)	15 (11%)	11 (7%)	9 (6%)
Urinary tract infection	16 (12%)	11 (8%)	8 (5%)	12 (8%)
Weight decreased	10 (7%)	4 (3%)	24 (16%)	8 (5%)
Decreased appetite	14 (10%)	10 (7%)	13 (9%)	2 (1%)
Severe AE	28 (20%)	18 (13%)	24 (16%)	18 (12%)
Serious AE	36 (26%)	22 (16%)	33 (22%)	40 (27%)
Fatal AE	3 (2%)	2 (1%)	2 (1%)	2 (1%)
AE leading to treatment discontinuation	15 (11%)	9 (6%)	31 (21%)	16 (11%)

Data are n (%) of patients with at least one such adverse event. *Adverse events reported over 52 weeks (or until 28 days after last study drug intake for patients who discontinued study drug before week 52). †Adverse events that were reported in >10% of participants in any of these subgroups are shown.

Ref.: [2]

5.1.3 Comparative analyses

The comparison is based solely on data from the SENSCIS study why no further comparative analysis is presented.

5.2 Other considerations

5.2.1 Dose reduction

Question from the DMC:

The recommended dose of nintedanib is 150 mg twice daily, which can be reduced to 100 mg twice daily for patients who do not tolerate the recommended dose.

The applicant is asked to provide information about the frequency of patients expected to have the dose reduced to 100 mg twice daily. In addition, the applicant is asked to clarify if the reduced dose influences the efficacy of nintedanib. [5]

Reply from the applicant:

Overall, the pattern of dose reduction from 150 mg to 100 mg ranging from approximately 26 to 40 percent of the patients is well documented from data from the three pivotal programs in IPF, PF-ILD and SSc-ILD.[4, 15] [16] Data for subgroups experiencing dose reduction and dose interruption in the SENSCIS (SSc-ILD) and INPULSIS (IPF) are presented below. Subgroup data for the INBUILD study in PF-ILD have not yet been published.

In the phase III pivotal study for SSc-ILD (SENSCIS) the number of patients with at least one dose reduction was 117/288 (40.6%) in the nintedanib group and 13/288 (4.5%) in the placebo group.[3]

The incidence of AEs leading to a permanent dose reduction was higher in the nintedanib group than in the placebo group (nintedanib: 34.0%; placebo: 3.5%).[3]

The mean duration of exposure was 8.17 (SD 4.44) months to the nintedanib 150 mg dose, and 11.11 (SD 2.72) for the placebo dose. The mean duration of exposure was 5.09 (SD 3.30) months to the nintedanib 100 mg dose, and 3.79 (SD 3.51) for the placebo dose. [3]

The exposure throughout the whole trial was 14.51 (SD 6.67) months equal to 349.0 patient years for nintedanib and 15.70 (SD 5.67) months equal to 377.5 patient years for the placebo group. [3]

A subgroup analysis based on dose reductions in the SENSCIS study was presented as an abstract at the World Congress of Systemic Sclerosis 2020. In patients with SSc-ILD Mayes et al found that the estimated annual rate of decline in FVC was similar in nintedanib-treated patients irrespective of whether they had dose adjustments to manage AEs (Table 7). [17]

Table 7 Effect of dose reduction/interruption - the SENSCIS SSc-ILD study

Treatment group	Adjusted mean (SE) annual rate of decline in FVC (mL/year)
Placebo overall (n=288)	-93.3 (13.5)
Nintedanib overall (n=288)	-52.4 (13.8)
Dose reduction of nintedanib (n=117)	-39.7 (21.4)
Treatment interruption of nintedanib(n=109)	-60.9 (22.0)
Dose reduction and/or treatment interruption of nintedanib (n=139)	-47.1 (19.7)
Dose intensity ≤90% of nintedanib (n=105)	-44.3 (22.7)

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Ref.: [17]	

The selection of the 150 mg dose for the initial indication (IPF) for nintedanib was based on the results of the phase II trial in IPF.[18]

The efficacy and safety of this dosing was confirmed in the phase III IPF study, INPULSIS.[15]

A post hoc analysis by Maher et al of the effect of dose reduction/interruptions on the efficacy of nintedanib in patients with IPF in the INPULSIS study was published as an abstract. [19]

This post hoc analysis of data from the INPULSIS trials showed that decline in FVC was similar in patients treated with nintedanib irrespective of whether they had dose reductions and/or treatment interruptions. [19]

Table 8 Change from baseline in FVC (ml) at week 52 by dose subgroups - the INPULSIS IPF study

	Nintedanib		Placebo	
	N	Mean (SD) change in FVC (ml)	N	Mean (SD) change in FVC (ml)
All patients	519	-89 (264)	345	-203 (293)
Patients who did not have a dose reduction or treatment interruption	340	-90 (265)	309	-200 (292)
Patients who took 150 mg bid as last dose and had ≥1 dose reduction and/or treatment interruption	56	-118 (251)	31	-203 (273)
Patients who took 100 mg bid as last dose after ≥1 dose reduction and/or treatment interruption	123	-74 (269)	5	-391 (422)
[15, 19]				

In summary the subgroup analyses from the IPF population in INPULSIS and the SSc-ILD population in SENSCIS did not identify any clinically significant differences in the efficacy between subgroups with dose reductions and interruption.

5.2.2 The study population in the SENSCIS study

Question from the DMC:

Referring to the clinical question, the DMC Expert Committee requests data for SSc-ILD patients, who are progressing on first line treatment with immunomodulatory medications.
The applicant is therefore requested to explain the comparability between the study population in the SENSCIS study and the population defined in the clinical question and provide an argumentation for the consequences of any differences.

Reply from the applicant:

The inclusion and exclusion criteria as well as the baseline demographics for the patient population in the SENSCIS study are shown in detail in Table 9.

The inclusion criteria allowed for patients with SSc-ILD to be included regardless of documented progression or not. Thus, data for the subgroup progressing on first line treatment with immunomodulatory drugs are not reported in the SENSCIS study.

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Exclusion criteria related to prior/current medication were:

- Previous treatment with nintedanib or pirfenidone.
- Other investigational therapy received within 1 month or 6 half-lives (whichever was greater) prior to screening Visit (Visit 1).
- Treatment with
    - Prednisone >10 mg/day or equivalent received within 2 weeks prior Visit 2,
    - Azathioprine, hydroxychloroquine, colchicine, D-penicillamine, sulfasalazine, received within 8 weeks prior Visit 2,
    - Cyclophosphamide, rituximab, tocilizumab, abatacept, leflunomide, tacrolimus, newer anti-arthritic treatments like tofacitinib and ciclosporine A, potassium paraaminobenzoate , received within 6 months prior Visit 2.
- Unstable background therapy with either mycophenolate or methotrexate (combined therapy of both not allowed).

However, patients on stable therapy with either mycophenolate or methotrexate for 6 months prior to Visit 2 were allowed into the study and should stay stable on this background therapy for at least 6 months after randomization.[10]

The reasoning for this approach is explained in detail below.

Most patients with SSc-ILD experience a slow decline in lung function; however, there are patients who experience a rapid loss of lung function following the onset of disease.[20] A post-hoc analysis of observational data in EUSTAR database found that among patients whose overall FVC course was defined as improved or stable (a decline in FVC or increase in FVC of <5% predicted), 47% experienced one or more 12-month intervals in which their FVC declined by ≥5% during their 5-year follow-up period.[21] Ultimately, SSc-ILD has a variable clinical course with unpredictable rates of disease progression. [21]

Patients with slowly progressing disease are susceptible to abrupt lung function decline. [21] A 2020 European consensus statement recommends that all SSc-ILD patients should be routinely assessed every 3–6 months.[22]

SSc-ILD patients who are at risk of such progression, require early therapeutic intervention and close clinical monitoring to help preserve lung function.[23] However, there are currently no valid tools or biomarkers available to predict which SSc-ILD patients are at risk of ILD progression. [23] Analysis of a UK primary care database for over 2,000 pulmonary fibrosis patients found that in the 10 years prior to diagnosis, lower respiratory-related healthcare resource use progressively increased.[24] This suggests that there are missed opportunities for both early identification and early treatment of patients to prevent progression and preserve lung function. [24]

As ILD is the leading cause of death in SSc and adversely affects quality of life (QoL), [23] early treatment has the potential to increase survival, improve QoL and reduce healthcare costs associated with disease progression.

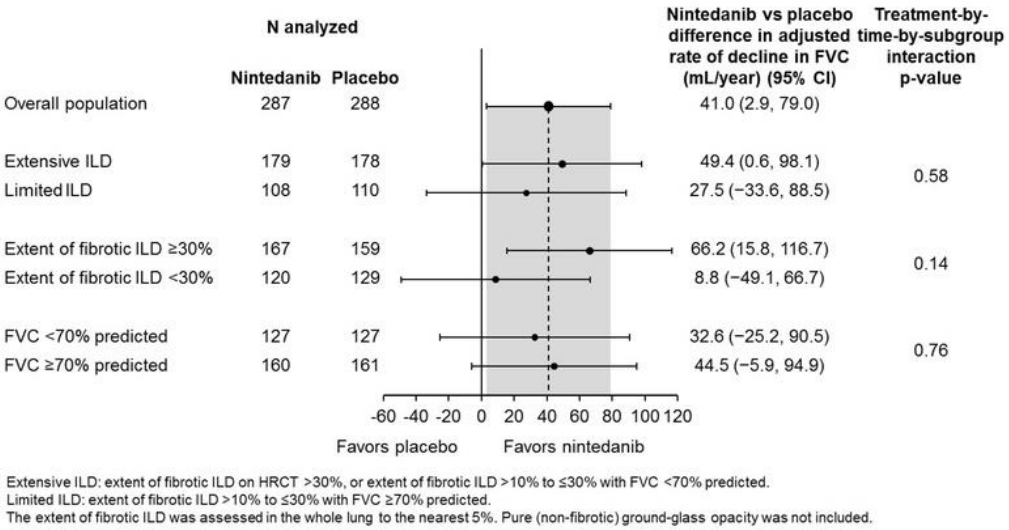
Nintedanib is an antifibrotic that inhibits the fundamental processes of progressive lung fibrosis and has proven efficacy in IPF as well as PF-ILD.[4, 16]

In the SENSCIS trial, nintedanib significantly reduced the annual rate of decline in FVC in SSc-ILD patients over 52 weeks. [4] The absolute treatment effect of 41 mL/year by nintedanib is clinically meaningful as it reflects the slowing of disease progression in a condition that mainly affects patients of working age[3, 25], who may benefit from the cumulative treatment effect over a long period of time.

An analysis of the annual rate of decline in FVC (mL/year) and the proportion of patients with an absolute decline in FVC >5% predicted over 52 weeks in patients with “extensive ILD” (extent of fibrotic ILD on HRCT >30%, or extent of fibrotic ILD >10% to ≤30% with FVC <70% predicted) and “limited ILD” (extent of fibrotic ILD on HRCT <30%, or extent of fibrotic ILD >10% to ≤30% with FVC ≥70% predicted) at baseline in SENSCIS™ was carried out.[26]

Results concluded that the effect of nintedanib versus placebo on the annual rate of FVC decline was numerically greater in patients with extensive ILD compared to limited ILD, but statistical testing did not indicate a heterogenous treatment effect between subgroups (Figure 3). [26]

Figure 3 The effect of nintedanib versus placebo on the annual rate of FVC decline (extensive versus limited ILD)



ILD, interstitial lung disease; FVC, forced vital capacity; CI, confidence interval.

Declines in FVC of >5% predicted have been associated with reduced survival in IPF and other fibrosing ILDs.[27] In both subgroups, smaller proportions of patients treated with nintedanib than placebo had an absolute decline in FVC >5% predicted at week 52 (extensive ILD: 21.2% versus 27.0%; limited ILD: 19.4% versus 30.9%).[26] The presented results are in line with the beneficial effects nintedanib has demonstrated in IPF patients with minimally impaired lung function at baseline.[28]

Therefore, initiation of nintedanib treatment at an earlier disease stage in SSc-ILD patients, may help to preserve lung function before it is lost irredeemably, as demonstrated in IPF.

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7. Appendices

7.1 Literature search

As per the DMC protocol no literature search has been performed.[5]

7.2 Main characteristics of included studies

Table 9 Main study characteristics for the SENSCIS SSc-ILD study

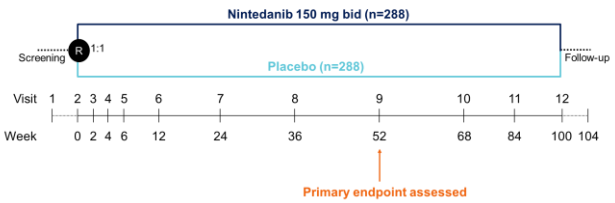
Main study characteristics - SENSCIS	
Trial name[4]	SENSCIS
NCT number[4]	NCT02597933
Objective[4]	The purpose of the trial was to assess the efficacy and safety of nintedanib 150 mg bid in patients with SSc-ILD, compared with placebo.
Publications – title, author, journal, year	*Distler O, Highland KB, Gahlemann M, et al.*; SENSCIS Trial Investigators. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. N Engl J Med. 2019 Jun 27;380(26):2518-2528. [Results publication] [4] *Distler O, Brown KK, Distler JHW, et al.*; SENSCIS™ trial investigators. Design of a randomised, placebo-controlled clinical trial of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SENSCIS™). Clin Exp Rheumatol. 2017 Sep-Oct;35 Suppl 106(4):75-81. [Design publication][6] *Seibold JR, Maher TM, Highland KB, et al*.; SENSCIS trial investigators. Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSCIS trial. Ann Rheum Dis. 2020 Nov;79(11):1478-1484.[7] *Highland KB, Distler O, Kuwana M, et al.* SENSCIS trial investigators. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. Lancet Respir Med. 2021 Jan;9(1):96-106. [2] *Maher TM, Mayes MD, Kreuter M, et al*. SENSCIS Trial Investigators. Effect of Nintedanib on Lung Function in Patients With Systemic Sclerosis-Associated Interstitial Lung Disease: Further Analyses of a Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis Rheumatol. 2020 Nov 3. doi: 10.1002/art.41576. Epub ahead of print. PMID: 33142016.[29]
Study type and design	Phase III, randomized, double-blind, parallel, placebo-controlled. [4] 

	Figure 4 Study design – the SENSCIS SSc-ILD study
Follow-up time	Primary efficacy evaluation was done at week 52. [4] Blinded, placebo-controlled treatment was maintained (up to a maximum of 100 weeks). Data for 52 weeks have been published. [4] Data for 100 weeks are available in the EPAR, but not yet formally published.
Population (inclusion and exclusion criteria)	Inclusion criteria: • Age >= 18 years • 2013 ACR/EULAR classification criteria for SSc fulfilled • SSc disease onset (defined by first non-Raynaud symptom) within 7 years • SSc related Interstitial Lung Disease confirmed by HRCT; Extent of fibrotic disease in the lung >= 10% • FVC >= 40% of predicted normal • DLCO 30% to 89% of predicted normal Exclusion criteria: • AST, ALT >1.5 x ULN • Bilirubin >1.5 x ULN • Creatinine clearance <30 mL/min • Airway obstruction (pre-bronchodilator FEV1/FVC <0.7) • Other clinically significant pulmonary abnormalities • Significant PH • Cardiovascular diseases • More than 3 digital fingertip ulcers or a history of severe digital necrosis requiring hospitalization or severe other ulcers • Bleeding risk (such as predisposition to bleeding, fibrinolysis, full-dose anticoagulation, high dose antiplatelet therapy, history of haemorrhagic central nervous system (CNS) event within last year • international normalised ratio (INR) >2, prolongation of prothrombin time (PT) and partial thromboplastin time (PTT) by >1.5 x ULN) • History of thrombotic event within last year • Clinical signs of malabsorption or needing parenteral nutrition • Previous treatment with nintedanib or pirfenidone • Treatment with prednisone >10 mg/day, azathioprine, hydroxychloroquine, colchicine, D-penicillamine, sulfasalazine, cyclophosphamide, rituximab, tocilizumab, abatacept, leflunomide, tacrolimus, newer anti-arthritic treatments like tofacitinib and ciclosporine A, potassium para-aminobenzoate. Patients who were receiving prednisone at a dose of up to 10 mg per day or mycophenolate or methotrexate at a stable dose for at least 6 months before randomization (or both therapies) could participate in the trial • Unstable background therapy with either mycophenolate or methotrexate • Previous or planned hematopoietic stem cell transplantation

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

- Patients with underlying chronic liver disease (Child Pugh A, B, C hepatic impairment)

Patients with a history of Scleroderma Renal Crisis</td></tr>
<tr><td>Intervention[4]</td><td>Nintedanib 150 mg orally twice daily (N=288).
Placebo for nintedanib (N=288)</td></tr>
<tr><td>Baseline characteristics[4]</td><td>

Table 10 Baseline demographics - the SENSCIS SSc-ILD study (overall population)

<table>
<tr><th colspan="3">Baseline Characteristics – overall population.*</th></tr>
<tr><th>Characteristic</th><th>Nintedanib (N = 288)</th><th>Placebo (N = 288)</th></tr>
<tr><td>Female sex — no. (%)</td><td>221 (76.7)</td><td>212 (73.6)</td></tr>
<tr><td>Age — years</td><td>54.6±11.8</td><td>53.4±12.6</td></tr>
<tr><td>Diffuse cutaneous systemic sclerosis — no. (%)</td><td>153 (53.1)</td><td>146 (50.7)</td></tr>
<tr><td>Years since the onset of the first non-Raynaud’s symptom</td><td></td><td></td></tr>
<tr><td>Median</td><td>3.4</td><td>3.5</td></tr>
<tr><td>Range</td><td>0.3 to 7.1</td><td>0.4 to 7.2</td></tr>
<tr><td>Extent of fibrosis of the lungs on high-resolution CT — %</td><td>36.8±21.8</td><td>35.2±20.7</td></tr>
<tr><td>FVC — ml</td><td>2459±736</td><td>2541±816</td></tr>
<tr><td>FVC — % of predicted value</td><td>72.4±16.8</td><td>72.7±16.6</td></tr>
<tr><td>DLCO — % of predicted value†</td><td>52.9±15.1</td><td>53.2±15.1</td></tr>
<tr><td>Anti-topoisomerase antibody positive — no. (%)‡</td><td>173 (60.1)</td><td>177 (61.5)</td></tr>
<tr><td>Modified Rodnan skin score§</td><td>11.3±9.2</td><td>10.9±8.8</td></tr>
<tr><td>Patients with diffuse cutaneous systemic sclerosis</td><td>17.0±8.7</td><td>16.3±8.9</td></tr>
<tr><td>Patients with limited cutaneous systemic sclerosis</td><td>4.9±4.2</td><td>5.4±4.1</td></tr>
<tr><td>Total score on the SGRQ¶</td><td>40.7±20.2</td><td>39.4±20.9</td></tr>
<tr><td>Score on the HAQ-DI‖</td><td>0.65±0.70</td><td>0.55±0.58</td></tr>
<tr><td>Scaled score on the FACIT-Dyspnoea questionnaire**</td><td>47.01±9.64</td><td>45.67±9.90</td></tr>
<tr><td>Receiving mycophenolate — no. (%)</td><td>139 (48.3)</td><td>140 (48.6)</td></tr>
<tr><td>Receiving methotrexate — no. (%)</td><td>23 (8.0)</td><td>15 (5.2)</td></tr>
</table>

* Plus–minus values are means ±SD. Data on some variables were not available for all patients. A larger table of baseline characteristics is included in section G in the Supplementary Appendix. CT denotes computed</td></tr>
</table>

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	tomography, DLCO diffusion capacity of the lungs for carbon monoxide, FACIT Functional Assessment of Chronic Illness Therapy, FVC forced vital capacity, HAQ-DI Health Assessment Questionnaire–Disability Index, and SGRQ St. George's Respiratory Questionnaire. † The DLCO value was corrected for the haemoglobin level. DLCO values were available for 285 patients in the nintedanib group and 284 patients in the placebo group. ‡ Historical information on antitopoisomerase antibody status was used, or, if this information was not available to the trial sites, it was provided by a central laboratory. § The modified Rodnan skin score is used to evaluate a patient's skin thickness through palpation of 17 areas; scores range from 0 to 3 for each area (to give a maximum score of 51), with higher scores indicating worse skin fibrosis. Scores were available for 288 patients in the nintedanib group and 286 patients in the placebo group. Among the patients with diffuse cutaneous systemic sclerosis, scores were available for 153 of those in the nintedanib group and for 144 of those in the placebo group. Among the patients with limited cutaneous systemic sclerosis, scores were available for 135 of those in nintedanib group and for 142 of those in placebo group. ¶Total scores on the SGRQ range from 0 to 100, with higher scores indicating worse health-related quality of life. Scores were available for 282 patients in the nintedanib group and 283 patients in the placebo group. ‖ Scores on the HAQ-DI range from 0 to 3, with higher scores indicating worse disability. Scores were available for 283 patients in the nintedanib group and 281 patients in the placebo group. ** Scaled scores on the FACIT-Dyspnea questionnaire range from 27.7 to 75.9, with higher scores indicating worse.

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Table 11 Baseline demographics – the SENSCIS SSc-ILD study (mycophenolate-sub-group)

	Patients taking mycophenolate at baseline		Patients not taking mycophenolate at baseline	
	Nintedanib (n=139	Placebo (n=140)	Nintedanib (n=149)	Placebo (n=148)
Sex				
Female	102 (73%)	101 (72%)	119 (80%)	111 (75%)
Male	37 (27%)	39 (28%)	30 (20%)	37 (25%)
Age, years	52·6 (12·0)	51·5 (11·9)	56·5 (11·3)	55·1 (13·0)
Body-mass index, kg/m²	26·9 (5·0)	26·2 (5·5)	25·1 (4·5)	25·4 (4·8)
Race*				
White	112 (81%)	108 (77%)	89 (60%)	78 (53%)
Asian	9 (6%)	19 (14%)	53 (36%)	62 (42%)
Black or African-	14 (10%)	9 (6%)	6 (4%)	7 (5%)
American, American Indian, Alaska, Native, Native Hawaiian, or other Pacific Islander	3 (2%)	2 (1%)	0	1 (1%)
Region				
Europe	64 (46%)	58 (41%)	76 (51%)	68 (46%)
USA and Canada	57 (41%)	57 (41%)	12 (8%)	16 (11%)
Asia	7 (5%)	12 (9%)	52 (35%)	59 (40%)
Rest of world	11 (8%)	13 (9%)	9 (6%)	5 (3%)
Diffuse cutaneous SSc	79 (57%)	74 (53%)	74 (50%)	72 (49%)
Years since onset of first non-Raynaud's symptom	3·4 (0·9–6·9)	3·5 (1·0–7·0)	3·4 (0·3–7·1)	3·3 (0·4–7·2)
Extent of fibrotic ILD on high-resolution CT, %	37·9 (22·4)	35·8 (20·9)	35·8 (21·2)	34·7 (20·6)
FVC				
mL	2496 (724)	2581 (813)	2423 (748)	2503 (819)
% predicted	70·4 (15·6)	71·1 (16·5)	74·2 (17·7)	74·2 (16·6)
Diffusing capacity of the lung for carbon monoxide, % predicted†	50·8 (13·7)	52·6 (14·6)	54·8 (16·1)	53·8 (15·5)
Anti-topoisomerase I antibody positive	88 (63%)	84 (60%)	89 (60%)	89 (60%)
mRSS	12·5 (9·4)	11·3 (8·3)	10·3 (8·9)	10·5 (9·2)
SGRQ total score	43·9 (20·3)	41·1 (19·8)	38·0 (19·7)	37·8 (21·9)
C-reactive protein, mg/L‡	4·9 (5·9)	8·5 (25·3)	6·8 (15·3)	5·2 (7·7)
Platelets, 10^{-9} per L§	277 (79)	283 (77)	267 (77)	260 (73)

Primary and secondary endpoints[4, 30]

Primary endpoint

- Annual rate of decline in FVC in mL [Time Frame: 52 weeks], analysed with a random-coefficient regression model
  Spirometry was performed at weeks 2, 4, 6, 12, 24, and 52.

Key Secondary endpoints

- Absolute change from baseline in SGRQ total score [Time Frame: 52 weeks]
- Absolute change from baseline in the mRSS [Time Frame: 52 weeks]

	Other secondary • Time to all-cause mortality [Time Frame: 52 weeks] • Absolute change from baseline in FACIT dyspnoea score [Time Frame: 52 weeks] • Annual rate of decline in FVC in percent predicted [Time Frame: 52 weeks] • Absolute change from baseline in FVC in mL [Time Frame: 52 weeks] • Relative change from baseline (%) of mRSS [Time Frame: 52 weeks] • Absolute change from baseline in DLCO in percent predicted [Time Frame: 52 weeks] • Absolute change from baseline in digital ulcer net burden (defined as the number of new digital ulcers (DUs) plus the number of DUs that have been verified at any earlier assessment during the trial) [Time Frame: 52 weeks] Absolute change from baseline in SHAQ total score [Time Frame: 52 weeks]
Method of analysis[4]	All analyses were conducted in the patients who received at least one dose of the trial drug or placebo. The primary end point was analysed with the use of a random-coefficient regression model (with random slopes and intercepts) that included effects of treatment, anti-topoisomerase I antibody status (positive or negative), age, height, sex, baseline FVC (measured in millilitres), time, and treatment-by-time and baseline-by-time interactions. The slope of the decline in FVC was calculated for every patient, and the average was compared between trial groups. The analysis was based on all measurements taken over a 52-week period, including those from patients who discontinued the trial drug or placebo. The model allowed for missing data, with the assumption that the data were missing at random. The primary and secondary end points were tested under a hierarchical test strategy that protected the type I error as described in the Supplementary Appendix of the publication. Significance tests were two-sided, with an alpha value of 0.05. The 95% confidence intervals for the end points that were not covered by the hierarchical testing procedure were not adjusted for multiplicity. Descriptive statistics are presented for safety data.
Subgroup analyses [2]	The results of analyses in subgroups of participants by use of mycophenolate (mofetil or sodium) at baseline are reported. All analyses were done in participants who received at least one dose of study drug. The annual rate of decline in FVC (mL per year) in the subgroups was analysed using a random coefficient regression model (with random slopes and intercepts) including anti-topoisomerase I anti body status (positive, negative),

	age, height, sex, and baseline FVC (mL) as covariates and terms for baseline-by-time, treatment-by-subgroup and treatment-by-subgroup-by-time interactions. Time was defined as duration since the first intake of study drug and was used as a continuous variable in this analysis. The analysis was based on all measurements taken within the first 52 weeks of the study, including those from participants who discontinued study drug. The model allowed for missing data, assuming they were missing at random. Changes from baseline in mRSS and SGRQ total score at week 52 in the subgroups was analysed using a restricted maximum likelihood-based repeated measures approach. The analyses included fixed categorical effects of anti-topoisomerase I antibody status (positive, negative), visit, and treatment-by subgroup- by-visit interaction, and fixed continuous effect of baseline by visit. A least squares mean estimate statement, with appropriate contrasts, was used to do an F test of heterogeneity between the subgroups. Thus, the interaction p value was an indicator of the potential heterogeneity in the treatment effect of nintedanib versus placebo between the subgroups. In the analysis of categorical changes in FVC (% predicted or mL) at week 52, data from participants with missing values at week 52 were imputed using a worst-value-carried-forward approach; we assumed that missing FVC data at week 52 were missing at random because most patients (42 of 78) who had missing FVC data at week 52 had non-missing FVC data until week 36 or after week 52. Statistical analyses of other endpoints are described in the appendix (p 6) in the Highland et al publication. Adverse events are presented by subgroup using descriptive statistics.

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7.3 Results per study – SENSCIS

Table 12 Results of the SENSCIS SSc- ILD study – mycophenolate subgroup

Please note that the data in this table are for the **subgroup** of patients receiving mycophenolate at baseline.

Results of the SENSCIS SSc-ILD study – mycophenolate subgroup											
Trial name:	*SENSCIS*										
NCT number:	NCT02597933										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median survival (W100)	Nintedanib	139	4 (2.9%)	NA*	NA*	NA*	1.99	0.36 to 10.96	0.438 (interaction p-value)†	The HR and CI are based on Cox's regression model with treatment as covariate, stratified by ATA status. * Median not estimable as median survival is a time to event endpoint.	Highland, p. 104.[2] † calculated by BI
	Placebo	140	2 (1.4%)								

Results of the SENSCIS SSc-ILD study – mycophenolate subgroup										
FVC, annual rate of decline (ml) (Week 52)	Nintedanib	138	-40.2 (-79.1 to -1.3) †	26.3	-27.9 to 80.6	0.347 (interaction p-value) †	NA	NA	NA	The absolute difference in effect is estimated by means of a subgroup analysis to investigate the heterogeneity of the treatment effect on the slope across the subgroup baseline mycophenolate use vs. no baseline mycophenolate use. A random slope and intercept model with fixed effects for ATA status, gender, baseline FVC (mL), age and height as well as the baseline-by-time, treatment-by-subgroup and treatment-by-subgroup-by-time interactions is used. Random effect was included for patient specific intercept and time. P-value for the absolute difference is calculated according to the method described in Altman and Bland (2011)[31].	Highland, table 2. [2] † calculated by BI
	Placebo	140	-66.5 (-104.3 to -28.7) †							
QoL-Mean change from baseline (SGRQ) (points) (52 weeks)	Nintedanib	137	0.7 (-1.8 to 3.2) †	1.6	-1.9 to 5.0	0.382 (interaction p-value) †	NA	NA	NA	The absolute difference in effect is estimated by means of a subgroup analysis to investigate the heterogeneity of the treatment effect across the subgroup baseline mycophenolate use vs. no baseline mycophenolate use. A Mixed Model for Repeated Measures (MMRM), with fixed effects for ATA status, visit, baseline SGRQ total score and treatment-by-subgroup-by-visit and baseline-by-visit interactions. P-value for the absolute difference is calculated according to the method described in Altman and Bland (2011) [31].	Highland, table 2. [2] † calculated by BI
	Placebo	138	-0.9 (-3.3 to 1.6) †							

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Results of the SENSCIS SSc-ILD study – mycophenolate subgroup										
SAE Proportion of patients experiencing ≥1 SAE (week 52)	Nintedanib	139	36 (25.9%)	Risk Difference: 0.10†	0.01 to 0.20†	0.039†	Risk Ratio: 1.65†	1.02 to 1.65†	0.039 (interaction p-value) †	Risk ratio with CI are estimated by Cochran-Mantel-Haenszel method. Risk difference with CI are estimated by the method described in Greenland and Robins (1985)[32]. Treatment by subgroup interaction p-value for homogeneity of the odds ratio, based on the Breslow-Day test. P-values for risk difference and risk ratio are calculated according to the method described in Altman and Bland (2011) [31].	Highland, table 3. [2] † calculated by BI
	Placebo	140	22 (15.7%)							
Discontinuation due to AE (Week 52)	Nintedanib	139	15 (10.8%)	Risk Difference: 0.04†	-0.02 to 0.11†	0.230†	1.68†	0.76 to 3.71†	0.201 (interaction p-value) †	Risk ratio with CI are estimated by Cochran-Mantel-Haenszel method. Risk difference with CI are estimated by the method described in Greenland and Robins (1985) [32]. Treatment by subgroup interaction p-value for homogeneity of the odds ratio, based on the Breslow-Day test. P-values for risk difference and risk ratio are calculated according to the method described in Altman and Bland (2011) [31].	Highland, table 3. [2] † calculated by BI
	Placebo	140	9 (6.4%)							

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Table 13 Results of the SENSCIS SSc-ILD study – overall population

Please note that the data in this table are for the **overall** population regardless of treatment at baseline.

Results of the SENSCIS SSc-ILD study –overall population											
Trial name:	*SENSCIS*										
NCT number:	NCT02597933										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median survival (Week 100)	Nintedanib	288	10 (3.5%)	Median not estimable as less than 50% of the patients died			1.16	0.47 to 2.84	0.7535†	The HR, CI and p-value are based on Cox's regression model with treatment as covariate, stratified by ATA status	Distler, p. 2526, col. 2.[4] † calculated by BI
	Placebo	288	9 (3.1%)								

Results of the SENSCIS SSc-ILD study –overall population											
FVC, annual rate of decline (ml) (Week 100) **On treatment population only**	Nintedanib	287	-55.1 (-79.2 to -31.0)†	38.85	5.56 to 72.14	0.022†	NA	NA	NA	The absolute difference in effect is estimated using a random slope and intercept model with fixed effects for treatment, ATA status, gender, time, baseline FVC (mL), age and height as well as the treatment-by-time and baseline-by-time interactions. Random effect was included for patient specific intercept and time. P-value for the absolute difference is calculated according to the method described in Altman and Bland (2011) [31].	EPAR, p. 54. [3] † calculated by BI
	Placebo	288	-94.0 (-117.0 to -71.0)†								
QoL-Mean worsening from baseline (SGRQ) (points) (52 weeks)	Nintedanib	282	0.81 (-0.92 to 2.55)†	1.69	-0.73 to 4.12	0.1711†	NA	NA	NA	The absolute difference in effect is estimated using a Mixed Model for Repeated Measures (MMRM), with fixed effects for baseline SGRQ total score, ATA status, visit, treatment-by-visit interaction and baseline-by-visit interaction.	Distler, table 2. [4] † calculated by BI
	Placebo	283	-0.88 (-2.58 to 0.82)†								
SAE Proportion of patients experiencing ≥1 SAE (week 100)	Nintedanib	288	88 (30.6%)	Risk Difference: 0.03†	-0.04 to 0.11†	0.441†	Risk Ratio: 1.11†	0.86 to 1.44†	0.436†	Risk ratio with CI is estimated by Cochran-Mantel-Haenszel method. Risk difference with CI is estimated by the method described in Greenland and Robins (1985) [32]. p-values for risk difference and risk ratio are calculated according to the method described in Altman and Bland (2011) [31].	EPAR, table 36 (p. 77). [3] † calculated by BI
	Placebo	288	79 (27.4%)								

Results of the SENSCIS SSc-ILD study –overall population									
Discontinuation due to AE (Week 100)	Nintedanib	288	50 (17.4%)	Risk Difference: 0.07†	0.02 to 0.13†	0.013†	Risk Ratio: 1.72†	1.12 to 2.64†	0.013†	Risk ratio with CI is estimated by Cochran-Mantel-Haenszel method. Risk difference with CI is estimated by the method described in Greenland and Robins (1985) [32]. p-values for risk difference and risk ratio are calculated according to the method described in Altman and Bland (2011) [31].	EPAR, table 36 (p. 77). [3] † calculated by BI
	Placebo	288	29 (10.1%)								

7.4 Results per PICO

As the application is based on data from one study only, please refer to the Results per study tables for results per outcome.

Table 14 Results per PICO

Table A4 Results referring to <clinical question x>								
Results per outcome:	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
	Not applicable							

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Cost per patient and budget impact analysis of nintedanib (Ofev®) for the treatment of systemic sclerosis-associated interstitial lung disease

Application to the Danish Medicines Council

26 May 2021

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Text marked with yellow and survival curves are strictly confidential and should be deleted before publication.

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List of abbreviations

AE	Adverse event
AIC	Akaike's information criterion
ATP	Adenosine triphosphate
BIC	Bayesian information criterion
CSF1R	Colony-stimulating factor 1 receptor
CTGF	Connective tissue growth factor
CU	Cost-utility
CYC	Cyclophosphamide
DLCO	Diffusing capacity of the lung for carbon monoxide
DMC	Danish Medicines Council
EUSTAR	European Scleroderma Trial and Research group
FGFR	Fibroblast growth factor receptor
FVC	Forced vital capacity
FVC%pred	Forced vital capacity percentage of predicted
HRCT	High-resolution computed tomography
HRQoL	Health-related quality of life
ICU	Intensive care unit
IFN	Interferon
IL	Interleukin
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
IPS	Individual patient simulation
MMF	Mycophenolate mofetil
mRSS	Modified Rodnan skin score
MTX	Methotrexate
OS	Overall survival
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PF-ILD	Progressive Fibrosing ILD
SmPC	Summary of product characteristics
SoC	Standard of care
SSc	Systemic scleroderma
TGF-ß	Transforming growth factor- ß
Th	T-helper
ToT	Time on treatment
TLR	Toll-like-receptors
VBA	Visual basic application
VEGFR	Vascular endothelial growth

1 Background

Systemic sclerosis (SSc) is a rare, chronic autoimmune disease where inflammation and connective tissue (fibrosis) cause rigidity and dysfunction of the body tissues. SSc is characterised by rigidity of the skin, primarily in the fingers, hands and the face. In some patients, connective tissue is also formed in the internal organs such as the gastrointestinal tract, lungs, heart and kidneys. SSc patients are often diagnosed at the age of 30-40, and more women than men are diagnosed (1,2).

Interstitial lung diseases (ILD) are a heterogenous group of rare lung diseases characterised by inflammation and/or fibrosis in the lung tissue (alveoli, connective tissue, small bronchi and vessels) (3–5). 40-50% of SSc patients develop ILD due to damage on endothelial cells and/or epithelial cells activated by coagulation and inflammation signals, which leads to formation of fibrosis in the lungs (6). The fibrosis causes rigidity of the lung tissue and decreased alveolar functioning, and the more fibrosis the more the lung function is affected. The diagnosis is done with lung functioning measurements where SSc-ILD patients typically show decreased forced vital capacity (FVC) and diffusion capacity (DLCO) that further decrease throughout the years (6–9). High resolution computed tomography (HRCT) scans of thorax are performed and typically show interstitial changes due to inflammation and fibrosis (6–9).

Many different types of ILD exists, and idiopathic pulmonary fibrosis (IPF) is the most examined. IPF is characterised by irreversible progressing lung fibrosis (10–12). Other types of ILDs can also lead to progressing lung fibrosis and are termed progressive fibrosing ILD (PF-ILD). SSc-ILD is one of these, and the other types are presented in Figure 1.

The diagnosis of ILD is complex and done by an inter-disciplinary team of physicians specialised in pulmonary medicine, thorax-radiology, rheumatology and pathology (13,14). Establishing the presence and classifying the type of ILD require various examinations such as a thorough description of the medical history, lung functioning assessment, thorax x-ray, HRCT scans and in some cases echocardiography and lung biopsy. The initial assessment of ILD takes place at the Danish pulmonary medical units and treatment is managed by the highly specialised ILD centres in Denmark (Odense University hospital, Aarhus University Hospital, Herlev-Gentofte Hospital and Rigshospitalet) (3).

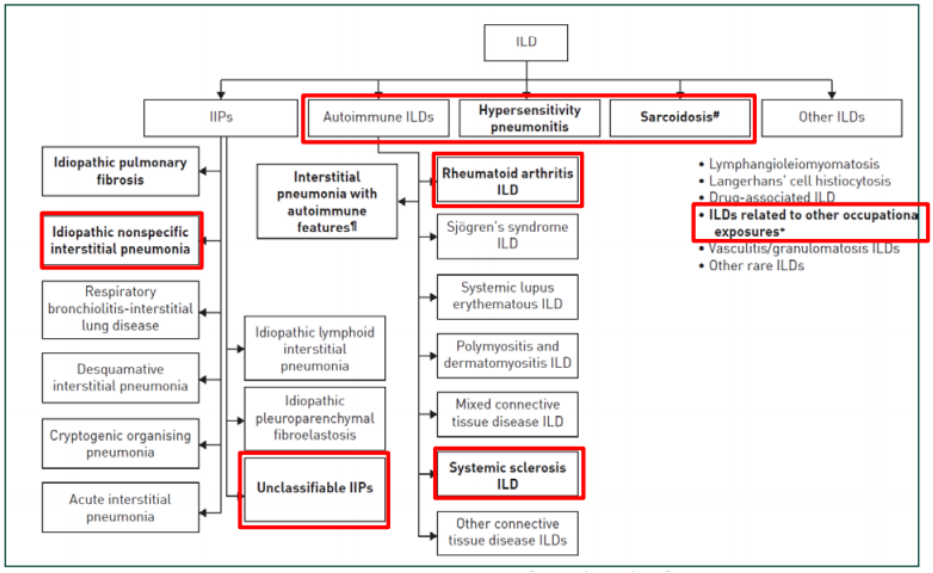

Figure 1: The figure shows the different types of ILD. The types that can develop progressing fibrosis are marked with red. Source: (15)

Current treatment options

SSc-ILD patients have an increased mortality compared to the general Danish population (16). Moreover, SSc-ILD highly affects patients' quality of life, and ILD is the leading cause of death in SSc patients (17–19). 35% of deaths in SSc patients are caused by the development of lung fibrosis and the 5-year and 10-year survival are 85.0% and 71.7%, respectively. Patients have very individual disease courses and more aggressive courses with involvement of internal organs are associated with a higher mortality (9,20,21). The mortality of SSc-ILD is highly correlated with the reduction in lung function due to progression of the lung fibrosis. The more fibrosis on the HRCT scan or the higher the rate of FVC decrease, the higher risk of death (16,17,19,21–25).

Due to the above mentioned, the treatment goal is to slow disease progression. Nintedanib is the first drug with a regulatory approval for the SSc-ILD indication. Until recently, there has been nationally consensus regarding SSc-ILD patients responding best to immunomodulating treatment with cyclophosphamide or mycophenolate mofetil (3). Mycophenolate mofetil is often preferred due to the more favourable safety profile and equal effect. None of these drugs have an indication for SSc-ILD and are used off-label as first line treatment. Treatment is continued until progression and monitored based on the patient's symptoms, lung function and sometimes supplemented with walk-tests and HRCT scans (12). When patients run out of medical treatment options, a minority of highly selected patients can undergo a lung transplantation. If patients progress from first line treatments, no other medical options are available today and the expert committee states that this could be the place for nintedanib in the treatment algorithm. The EMA indication of nintedanib does not require previous treatment.

The expert committee in the Danish Medicines Council (DMC) estimates that approximately 30-50 new patients with progressing SSc-ILD potentially could be candidates for nintedanib each year.

1.1 Nintedanib (Ofev®)

Nintedanib is a small molecule that inhibits tyrosine kinase receptors, platelet-derived growth factor receptor (PDGFR) α and ß, fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor (VEGFR) 1-3. In addition, nintedanib inhibits lymphocyte-specific tyrosine-protein kinase (Lck), tyrosine-protein kinase (lyn), proto-oncogene tyrosine-protein kinase, and colony-stimulating factor 1 receptor (CSF1R) kinases. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding components of these kinases, and blocks the intracellular signalling cascades, which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling in ILD. (26)

The recommended dose of nintedanib is 150 mg orally twice daily (300 mg per day). If the 150 mg twice daily dose is not tolerated, the dose can be reduced to 100 mg twice daily. According to the summary of product characteristics (SmPC) on nintedanib, the management of adverse events can include temporary dose interruptions or dose reductions. (26). Information about nintedanib is provided in Table 1.

Table 1 **Nintedanib**

Name	Ofev®
Active ingredient	Nintedanib
Indication*	Nintedanib is indicated for the treatment of SSc-ILD in adult patients.
Strengths	150 mg capsules 100 mg capsules
Dosing	150 mg capsules orally twice daily (300 mg per day)
ATC code	L01XE31
Packages	60 x 150 mg capsules 60 x 100 mg capsules
EC date of approval	17 April 2020

*Nintedanib is also indicated for the treatment of IPF and PF-ILD.
Abbreviations: EC: European commission.
Source: (26)

1.2 Clinical questions

The Danish Medicines Council (DMC) protocol for assessing nintedanib for the treatment of SSc-ILD lists the following clinical question:

What is the value of nintedanib compared to placebo for patients with SSc-ILD?

2 Methods: cost per patient analysis

The purpose of the cost per patient analysis was to estimate the incremental cost of treating SSc-ILD patients with nintedanib compared to the current standard treatment practice at Danish hospitals. To estimate the cost per patient and answer the clinical question, we adapted a global cost-utility (CU) model of nintedanib to a Danish clinical setting. The global CU model was developed by the consultancy Bresmed for Boehringer Ingelheim.

The adaption of the global CU model to a Danish clinical setting only involves the cost elements in the model. The model elements related to health-related quality of life (HRQoL) are not adjusted, as they are not applied in the health economic analysis.

To inform the cost per patient analysis, we used data from the SENSCIS trial and other relevant external literature. We also interviewed Danish clinical experts. The interviewed Danish clinical experts were Jesper Rømhild Davidsen from the research unit for interstitial lung diseases of Southern Denmark and Odense University Hospital and Elisabeth Bendstrup from the Department of Respiratory Diseases and Allergy at Aarhus University Hospital. Both clinical experts are highly experienced in treating patients with different types of ILDs. The experts were interviewed by phone and agreed to be cited in the current analysis.

The SENSCIS trial was a randomised, double-blinded, placebo-controlled trial investigating the efficacy and safety of nintedanib in patients with SSc-ILD. The SENSCIS trial included adult patients who had SSc according to the classification criteria of the American College of Rheumatism, with an onset of the first non-Raynaud's symptom within seven years before screening. Patients had to have fibrosis affecting at least 10% of the lungs, as confirmed by an expert radiologist on HRCT scans. Patients were required to have an forced vital capacity (FVC) that was at least 40% of the predicted value and a diffusion capacity of the lung for carbon monoxide (DLCO) (corrected for haemoglobin) that was 30-89% of the predicted value (27). Baseline characteristics of patients included in the trial are presented in Table 2. The primary endpoint was the annual rate of decline in FVC (millilitres per year) assessed over a 52-week period. The endpoint was analysed with a mixed effects regression model.

Table 2 **Baseline characteristics of patients in the SENSCIS trial**

Characteristics	Nintedanib	Placebo	Overall
Number of patients	288	288	576
Age – mean (SD)	54.59 (11.78)	53.36 (12.59)	53.98 (12.19)
Sex			
Female – no. (%)	221 (76.7)	212 (73.6)	433 (75.2)
Male – no. (%)	67 (23.3)	76 (26.4)	143 (24.8)
Methotrexate background therapy			
No – no. (%)	265 (92.0)	273 (94.8)	538 (93.4)
Yes – no. (%)	23 (8.0)	15 (5.2)	38 (6.6)
Mycophenolate mofetil background therapy			
No – no. (%)	149 (51.7)	148 (51.4)	297 (51.6)
Yes – no. (%)	139 (48.3)	140 (48.6)	279 (48.4)
SSCGR1			
Diffuse cutaneous SSc – no. (%)	153 (53.1)	146 (50.7)	299 (51.9)
Limited cutaneous SSc – no. (%)	135 (46.9)	142 (49.3)	277 (48.1)
ATASTAT			
Negative – no. (%)	115 (39.9)	111 (38.5)	226 (39.2)
Positive - no. (%)	173 (60.1)	177 (61.5)	350 (60.8)
TSTIDIA – mean (SD)	2.67 (1.71)	2.58 (1.77)	2.63 (1.74)
TSNRSYM – mean (SD)	3.48 (1.62)	3.50 (1.78)	3.49 (1.70)
FVC – mean (SD)	72.38 (16.79)	72.67 (16.60)	72.53 (16.68)
mRSS – mean (SD)	11.33 (9.18)	10.91 (8.81)	11.12 (8.99)

Source: the SENSCIS trial (27)
Abbreviations: SD: standard deviation, SSCGR1: systemic sclerosis subgroup, ATASTAT: Anti-topoisomerase status, TSTIDIA: time since disease onset, TSNRSYM: Time since non-raynaud symptom onset, FVC: forced vital capacity, mRSS: modified rodnan skin score.

The applied model is an individual patient simulation (IPS) model and coded in visual basic for applications (VBA) to allow a rapid simulation of a large number of patients. VBA is used to complete all model calculations. Model controls and inputs (except for a few cells) feed through to the "parameters" Excel sheet where they are extracted and go into the VBA. A detailed description of the VBA codes used to run the model is provided in Section 2.1. Model results for an individual patient are then pasted out from the VBA at the end of each model run and into one of the patient-flow sheets (Nin_PLoutput or SoC_PLoutput) with each row representing a cycle.

2.1 Description of the VBA processes in the model

The VBA can be found in the Developer Tab in Excel. The code and macros used to run the model are located within the map called "Modules" and starts with "PLS". A detailed description of the

code and VBA process are provided in the following. We have updated the most relevant VBA modules with a description of the specific VBA process in the separate VBA modules.

In the module “PLS_2_DECLARE_PARAMETERS”, global variables are defined. Global parameters are variables used throughout the model across different VBA modules. Most of the variables in the model are global variables with a few exceptions. User defined functions are located within the “PLS_1_DECLARE_FUNCTIONS” module. User defined functions are grouped in the following categories: 1) sampling from probability distributions, 2) convenience functions to reduce the amount of repeated code (and improving simulation speed), and 3) aesthetic functions used to simplify the model or generate specific outputs.

The VBA contains four large modules that assemble each model process in turn, required to complete a model run for each type of analysis. Four analyses are included:

- deterministic: PLS_01_RUN_DETERMINISTIC;
- probabilistic: PLS_02_RUN_PROBABILISTIC;
- one-way-sensitivity analysis: PLS_03_RUN_OWSA; and
- scenario analysis: PLS_04_RUN_SCENARIOS.

The probabilistic analysis will not be presented, because it is not performed in the current analysis.

Preparation of the model

Code for preparation of the model is found in the VBA modules “PLS_3_MODEL_PREP” and “PLS_4_EXCEL_EXTRACTION”. The “PLS_3_MODEL_PREP” module contains code that clears the “PL_output” sheets for results from the previous run, so a new simulation can be run. “PLS_4_EXCEL_EXTRACTION” module contains code to bring all data sources from the Excel sheets into the VBA, based on the selected controls in the “control” Excel sheet. Code used to populate the model with data from Excel is located in the subroutine (sub) “populate_model” in VBA. When the model is populated, the two above-mentioned modules also complete the sampling of random numbers required in any stage throughout the model. This is described in the following.

Random numbers

Random numbers in the model are values between 0 and 1. Random numbers are used in the model for the three things listed below. For reason 1 and 2, the sampling of random numbers can happen with the option to “fix the seed”. If it is chosen to “fix seeds”, the model will use the same random numbers each time the model is run and produce the same results. This is important because the different analyses will use the same set of random numbers for each patient cohort. This means that any difference in results every time the model is run is either due to probabilistic sampling or changing of model settings. The same random numbers are also used in both treatment arms to apply the same patient profiles to the two treatment arms in the model. Random numbers are used in the model for the following:

1. To sample patient profiles
   Random numbers are used to sample patients in the model from patient profiles in the SENSCIS trial. The random numbers are used to randomly sample a row from the table containing baseline characteristics in the "Baseline characteristics" Excel sheet. The random numbers for this purpose are stored in the code "Rand_1order". Rand_1order is referred to in VBA as 2d array meaning that the array has 2 dimensions (number of baseline characteristic parameters and number of patients simulated). The sampling of patient profiles is described below.

2. To use in the patient flow
   Several of the calculations in the patient flow Excel sheet require random numbers, often with a different random number in each cycle. An example of how the random numbers are used in the model is the calculation of whether a patient dies or survives in a cycle. In this example, the selected parametric model is used to calculate the probability of death in every cycle. An individual patient is run through the model and a random number is sampled for that patient in a specific cycle. If the random number is smaller than the probability of death, the patient dies. If the random number is larger than the probability, the patient survives and continues to the next cycle.

3. To sample probabilistically from parameter distributions
   For each parameter in the model, a random number is used to sample from its chosen distribution in the PSA. This will not be described further, because the current analysis does not include a PSA.

Sampling of patient profiles and baseline characteristics

Code used to sample patients can be found in the "PLS_6_SIM_PATIENTS" VBA module. The approach to sampling patients can be referred to as non-parametric sampling with replacement. It involves randomly sampling individual patient profiles from the SENSCIS trial and applying their baseline characteristics in the model. In this way, the covariance structure of different parameters is maintained in the model, and no assumptions regarding data distributions is required in the model (non-parametric). "With replacement" means that in the VBA, patient profiles are sampled with replacement from the patient profiles given in the "summary baseline characteristics (trial)" table in the "Baseline characteristics" Excel sheet. If data is missing, the whole patient profile is excluded. The excluded profiles can also be seen in the "Baseline characteristics" Excel sheet in the model. Due to the small number of missing observations, it was deemed appropriate to exclude patient profiles if data was missing. The VBA subroutine "Simulate_patients_baseline" samples the patient profiles with replacement. The same patient profiles are applied in both treatment arms (the same patient is looped through both treatment arms). This is acceptable because the SENSCIS trial was well-balanced across the treatment arms. This is done outside the treatment loop in the model to apply the same patients to both treatment arms. 500 patients are simulated in the model. A convergence analysis was performed to test stability. Figure 2 shows that already with a couple of hundred iterations, the model produced stable results with very little variance in the mean simulated incremental cost. 500 simulations were chosen to maintain efficacy of the model and avoid long simulation time. The number of simulations is a flexible parameter in the model and can be changed by the user. Summary of the baseline characteristics of the sampled patients can be seen in Table 11.

Selection of treatment-specific parameters and sampling of parameter values

This process is inside the treatment loop, meaning that patients are assigned to a treatment arm when this loop occurs. The process is first completed for one treatment arm and then repeated for the next arm. The code for sampling and selecting model parameters can be found in the "PLS_5_SAMPLE_DIST" VBA module and stored in the subroutine "Apply_treatment_params". The following variable names are used throughout the model to reduce the number of variables needed and ensure transparency of the model code. Variable types function like a selective directing system resulting in a single _LIVE version to be used in all model calculations. The variable names used are:

- _nin_= for all variable types below, naming of treatment-specific parameters for nintedanib
- _SoC_= for all variable types below, naming of treatment specific parameters for SoC
- _DET= Deterministic variables used in the model. These can be assigned based on the model controls selected and the current treatment arm.
- _SE= Measure of variance (standard error) used to sample from parameter distributions. These can be assigned based on the model controls selected and the current treatment arm.
- _cov= Deterministic variables used in the model. Used for multivariate parameters and synonymous with _DET used for univariate parameters.
- _vcov= Measure of variance used to sample multivariate model parameters. Synonymous with _SE used for univariate parameters.
- _PSA= Array of sampled model parameters values with the number of rows equal to the number of parameters (1 for univariate, >1 for multivariate) and number of columns equal to either number of patients for parameters associated with first order uncertainty or number of PSA iterations for second order uncertainty.
- _LIVE= Live value are those used in the patient flow Excel sheet. These select _DET values for deterministic runs and a column of the _PSA array for each PSA iteration for probabilistic runs.

Running the model

The patient flow in the model can be found in the "PLS_7_PATIENT_FLOW" VBA module. When the random numbers, patient baseline characteristics, and model parameters are generated, the model can be run. The main engine of the model is in the subroutine "patient_flow". The "Patient_flow" subroutine consists of two nested loops: a cycle number loop within a patient number loop. Each column in the "PL_output" Excel sheets (that is calculated for each patient in the model and cleared when a new run is about to start) is in the VBA module "PLS_7_PATIENT_FLOW" labelled with a heading and a corresponding number, referring to the column in the "PL_output" Excel sheets to which it refers. In the patient number loop, once a patient has died or the maximum time horizon is reached, the totals for the patient are calculated by summing each relevant column in the "PL_output" sheets with the function "sum_PL_output_column". Patient totals are then stored in one row per patient in the "Cohort_output" Excel sheet.

Calculation of cohort totals

The calculation of cohort totals can be found in the "PLS_8_PRODUCE_RESULTS" VBA module. When the desired number of patients are completed (500 in the current analysis), the cohort results are pasted into the output sheets and cohort averages are calculated. The averages are calculated by summing columns in the "cohort_output" Excel sheets, where one row represents one patient, and dividing it with the number of simulated patients.

When the model has completed for both treatment arms, the subroutine "FinishUp" pastes all final model results into the output Excel sheets and creates the output data used to populate the figures for FVC%pred, mRSS, OS and ToT. Some code is sorted into the module "PLS_8_VALIDATION" and used to record patient-level FVC%pred and mRSS. When this is done, the model is complete, and results should be available.

The sensitivity analyses in the model are performed the same way as the base case analysis with different parameter values. The performed sensitivity analyses are described under section 2.10.

2.2 Applied model

The health economic model used to answer the clinical question is an individual patient simulation model (microsimulation model). An overview of the model structure is provided in Figure 3. The model estimates costs and effects of nintedanib plus standard of care (SoC) compared to SoC alone over a patient's lifetime (set to 35 years in the base case).

An individual patient simulation model models outcomes for individual patients one at a time, and calculates the average across a sufficiently large number of simulated patients (28). The rationale for an individual patient simulation model is based on the nature of SSc-ILD. SSc-ILD has a complex and uncertain treatment pathway and includes multiple health outcomes that characterise various forms of disease progression and patient heterogeneity. Individual patient simulation models allow individual patient pathways to be modelled and capture the

heterogeneity in the SSc-ILD patient population (29). These models also allow health outcomes to be modelled as continuous variables instead of specifying categories to define mutually exclusive health states as in a Markov model. Future health outcomes can be predicted based on patient history in these models, and non-linear relationships between patient characteristics and model outcomes can be modelled more flexibly.

An individual patient simulation model samples patient profiles and simulates outcomes for the sampled patients. The sampling of patient profiles and simulation of outcomes for each patient in the current model are based on VBA coding, thoroughly described in section 2.1.

Patient profiles in the model are sampled two times: at baseline and when patients enter the model (i.e. when they enter the treatment loop), as illustrated in Figure 3. Each individual patient's FVC%pred (and modified Rodnan Skin Score (mRSS)) are predicted using regression analyses. The model estimates costs, discontinuation events and death events based on current FVC%pred and mRSS score, evaluated in every one-month cycle in the model. Death can occur in any cycle and is based on the patient's current disease outcome.

Figure 3 is an illustration of the patient flow in the model. As mentioned, patients in the model are sampled with replacement from the patient profiles in the SENSCIS trial at baseline and when they enter the model. When possible, model inputs were informed by analyses of patient-level data from the SENSCIS trial.

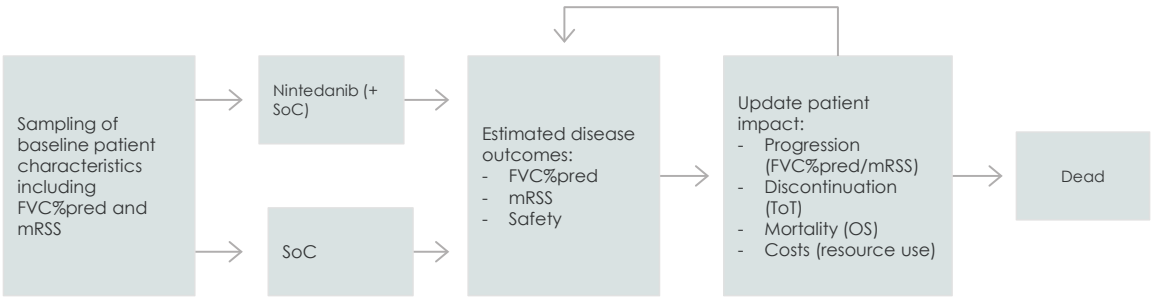

Figure 2: Overview of the model structure in the current analysis.

2.2.1 Possible events in the model

The model is primarily driven by the following health outcomes:

- FVC%pred;
- mRSS; and
- time on treatment (ToT).

Both FVC%pred and mRSS over time were predicted using linear mixed effects regression models fitted to SENSCIS patient-level data up until 52 weeks. Linear mixed effects regression models are regression models that allow both fixed and random effects (30). FVC%pred was considered most relevant compared to mRSS, due to the strength of evidence linking FVC%pred to mortality

and FVC%pred being the key driver of the model. MRSS was excluded in the base case but can be included in the model. The exclusion of mRSS was based on the scarcity of data linking mRSS to mortality and the fact that the SENSCIS trial showed no impact of treatment on mRSS score.

If patients discontinue treatment with nintedanib, several options are available to model the maintenance of treatment effect on outcomes in the model. In the case where the treatment effect of nintedanib stops, efficacy was informed by the placebo arm in the SENSCIS trial, representing what could be expected had the patient not received nintedanib (the counterfactual).

Forced vital capacity percentage of predicted (FVC%pred)

FVC is a measure of lung function. FVC%pred measures lung function as a percentage of the normalised FVC predicted value, adjusted for age, gender and height. FVC%pred was modelled as a continuous outcome with values predicted for individual patients each cycle in each treatment arm. The impact of FVC%pred on HRQoL and the resource use in ILDs are well documented, especially in IPF, which has many similarities to SSc-ILD (22,31,32). FVC%pred has been shown to have a significant impact on mortality in SSc-ILD patients (22).

Changes in FVC%pred over time are predicted with linear mixed effects regression models fitted to data from the intervention and comparator arm in the SENSCIS trial (27). A constant rate of change in FVC%pred was assumed in the prediction of FVC over time in the model. The model provides an option to use “fixes” to ensure that the predicted FVC%pred values are reasonable by applying a maximum and minimum FVC%pred value (maximum value of 120% and minimum value of 40%). Patients were assumed to die if their FVC%pred falls below 40%. Data from the 52-week follow-up period in the SENSCIS trial was used. The rationale for restricting data to 52 weeks and not using the maximum follow-up (100 weeks) was a differential dropout of younger patients with lower FVC%pred values in the placebo arm after 52 weeks. This would potentially bias the results after 52 weeks for those patients. The impact of the differentiated dropout in the placebo arm is shown in Figure 4.

The linear mixed effects regression models used to predict FVC%pred changes over time were chosen because these models make it possible to use fixed effects for the included covariates (including a covariate for treatment arm) and both a random intercept and random slope. The random intercept captured individual patient heterogeneity. The random slope was included to capture the varying relationship between FVC%pred and time for individual patients and to account for the heterogeneity in the rate of disease progression. The selection of covariates was based on a stepwise backwards selection approach using a 95% confidence threshold with a p-value cut-off of 0.05. A backward stepwise regression is an approach that begins with a full (saturated) model and at each step gradually eliminates variables from the regression model to find a reduced model that best explains the data. The process starts with all explanatory variables and select variables based on statistical significance. In addition, variables which were known to be prognostic of FVC%pred were included irrespective of statistical significance. The approach was supplemented by literature to include covariates that were previously suggested predictive of FVC%pred in the literature, regardless of statistical significance (33). The final equation describing the final regression were the following:

$$FVC_{it} = \alpha_{i1} + \beta_0 + \beta_1 * YEAR_t + \beta_2 * Placebo_i + \beta_3 * FVCBase_i + \beta_4 * MMFBase_i + \beta_5 * DLCOBase_i + \beta_6 * mRSSBase_i + \beta_7 * AGE_i + \beta_8 * SEX + \beta_9 * TSTDIA + \beta_{10} * (Placebo_i * AnalysisYear) + \beta_{11} * (MMFLY * AnalysisYear) + \beta_{12} * (DLCHOHBBL * AnalysisYear) + \alpha_{i2} * AnalysisYear$$

$$FVC_{it} = \alpha_{i1} + 0.677 - 4.269 * YEAR_t - 0.257 * Placebo_i + 0.978 * FVCBase_i + 0.116 * MMFBase_i + 0.009 * DLCOBase_i - 0.057 * mRSSBase_i + 0.017 * AGE_i - 0.117 * MALE + 0.023 * TSTDIA_i - 1.270 * (Placebo_i * AnalysisYear_t) + 1.390 * (MMFBase_i * AnalysisYear_t) + 0.042 * (DLCHOBase_i * AnalysisYear_y) + \alpha_{i2} * AnalysisYear$$

The final fitted models for FVC%pred are shown below. Figure 5 shows observed versus predicted (stippled) curves for the trial period (52 weeks). Figure 6 shows the predicted values beyond the 52 weeks. Fixed effects and random effects coefficients and variance covariance matrices are provided in Table 29 and Table 30 in the appendix.

An adjustment factor was applied in the model, allowing adjustment of the overall rate of FVC decline (which was constant in the base case). The adjustment factor is a multiplier that can be applied to the coefficient for time (in years) within the regression model fitted to the observed SENSCIS FVC%pred data. Applying a multiplier >1 results in an increase in the rate of decline, while a multiplier <1 results in a decrease of the FVC decline rate. The multiplier can be found in the "Efficacy" Excel sheet. However, results using this adjustment factor should be interpreted with caution, as the implementation of a multiplier means that the covariance structure of the fitted regression model cannot be retained. In the base case, the multiplier was set to 1, which means that no adjustment factor was implemented.

shows the simulated FVC%pred for the average of the patient cohort over a time horizon of 35 years. The FVC%pred of patients who died were assumed to be 0. shows that FVC%pred values decline over a patient's lifetime, with a more rapid decline within the first 10 years.

[redacted]

2.2.2 Mortality

Overall survival (OS) data from the SENSCIS trial were immature due to the short follow-up period relative to the life expectancy of patients with SSc-ILD (see [redacted]). Only nine deaths in the placebo arm and 10 deaths in the nintedanib arm were observed. Based on this, external data demonstrating a surrogacy relationship between decline in FVC%pred (and/or mRSS) and increased mortality risk was used to model OS. This was appropriate due to the surrogacy relationship between FVC%pred and mortality, which is well documented (34).

Two options for modelling OS are available in the model, both based on external published long-term observational data. The options are: Sobanski et al. 2018 and Goh et al. 2008 (23,33). Sobanski et al. 2018 was used in the base case.

In both options, OS was adjusted for the general Danish population mortality. This was applied so that the probability of death in any cycle due to SSc-ILD could not be lower than the probability of death in the general Danish population.

Estimating mortality with data from Sobanski et al. 2018 (EUSTAR)

Sobanski et al. 2018 investigated the impact of short-term changes in health outcomes on the mortality risk over 12 months and presents observational data from 693 adult SSc-ILD patients from the European Scleroderma Trials and Resource (EUSTAR) database. Patients were enrolled in the study if they meet the 1980 American College of Rheumatology (ACR) or 2013 ACR/EULAR criteria for SSc, with signs of lung fibrosis on X-ray and/or HRCT scans and/or an available date of ILD diagnosis, with ≥1 follow-up visit within 12 months after the first visit with ILD diagnosis. 12-month absolute changes in lung function including FVC%pred and predicted diffusing capacity of carbon monoxide (DLCO%pred), changes in the mRSS and occurrence of digital ulcer (DU) were assessed for associations with overall survival. The EUSTAR data were used to link FVC%pred and mRSS to the mortality risk. Cox proportional hazard models were fitted to the available EUSTAR data and analysed with univariable and multivariable models. Two predictive covariates for mortality were identified in the analysis:

- decline in FVC%pred of >10%; and
- composite outcome of decline in FVC of >10% or increase in mRSS of >5 points and >25%.

The hazard ratios from the univariable and multivariable models performed in Sobanski et al. 2018 are presented in Table 3.

Table 3 **Hazard ratios associated with decline in FVC%pred (and/or mRSS)**

	Univariate analysis				Multivariate analysis*			
	HR	95% CI LB	95% CI UB	P-value	HR	95% CI LB	95% CI UB	P-value
	FVC % predicted change							
Increase or no decline	Reference				Reference			
Decline >0-10%	1.1	0.58	2.1	0.761	1.3	0.6	2.84	0.511
Decline >10%	3.06	1.59	5.88	0.001	3.81	1.67	8.66	0.001
	Composite FVC or mRSS change							
Increased or stable FVC or decline in FVC <10% and decreased or stable mRSS or increased in mRSS of <5 points or <25%	Reference				Reference			
Decline in FVC of >10% or increase in mRSS of >5 points and >25%	1.99	1.13	3.52	0.018	2.82	1.43	5.56	0.003

*Models adjusted for age, gender, tobacco use and immunosuppressive therapy.
Abbreviations: CI: confidence interval, FVC: forced vital capacity, FVC%pred: percentage predicted forced vital capacity, HR: hazard ratio, LB: lower bound, mRSS: modified Rodnan skin score, SSc-ILD: systemic sclerosis-associated interstitial lung disease, UB: upper bound.

Figure 9 shows the Kaplan Meier (KM) curves from Sobanski et al. 2018 (33). To determine a baseline mortality rate, parametric survival models were fitted to pseudo-patient-level data, which were generated by applying an algorithm outlined by Guyot et al. 2012 (35) to the digitised reference curve (blue curve) in Figure 9.

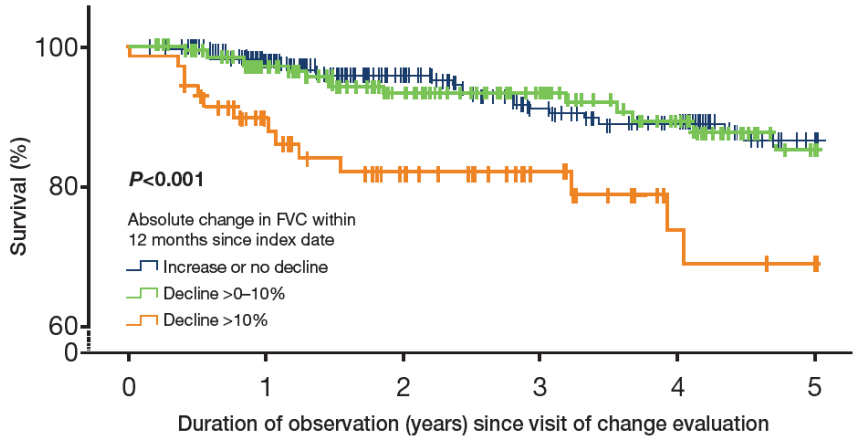

Figure 3: Absolute change in FVC%pred within 12 months since index date from Sobanski et al. 2018, EUSTAR data. The blue curve is the reference curve to which the Guyot algorithm is applied to generate the KM curve in Figure 10.

The generated the KM curve for stable disease seen in [redacted] and parametric models was then fitted to the KM curve as shown in the figure.

[redacted]

Sobanski et al. 2018: Choice of parametric model with the best fit for OS

In the base case, the baseline mortality rate was determined by fitting the standard parametric models to the reference KM curve for stable disease from Sobanski et al. 2018. When patients met the disease progression threshold (stated in Table 3), their mortality rate was adjusted by applying the corresponding hazard ratio from Table 3. Thus, it was assumed that the proportional hazard assumption holds. The choice of the parametric model with the best fit was based on statistical criteria (Akaike's information criterion and Bayesian information criterion (AIC/BIC)) where the smallest AIC and BIC values indicated the best-fit parametric model, visual inspection of the curves and the clinical plausibility of the curves (in consultation with the Danish clinical experts). The AIC and BIC values of the parametric models are presented in Table 4.

Table 4 **AIC and BIC values for OS in Sobanski et al. 2018**

Parametric model	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Note: the Weibull model did not converge and is not reported.

The exponential model had the lowest AIC and BIC values. However, the Danish clinical experts informed that the median survival of SSc-ILD patients is approximately 11 to 14 years. When visually inspecting the parametric curves in [redacted], all parametric curves had a median survival above the median survival stated by the Danish clinical experts. The exponential model was dismissed as the best fit, due to the high percentage of the cohort still being alive after extrapolating OS over the total time horizon. Instead, the parametric Gompertz model was used to determine the baseline mortality rate from Sobanski et al. 2018 in the base case. The Gompertz model was chosen, even though it had high AIC and BIC values compared to the other models, because it was assumed to be the model that came closest to the median survival stated by the Danish clinical experts. Furthermore, the AIC and BIC values were very close for all parametric models; therefore, we found it appropriate to choose the model based on visual inspection and statements from the Danish clinical experts. The model is flexible for the user to select other parametric models.

Extrapolation of OS with Sobanski et al. 2018 data and chosen parametric model

The model includes the options to use the HRs in Table 3 for either FVC%pred alone or a composite of FVC%pred and mRSS to adjust the mortality risk. FVC%pred alone was chosen in the base case but both options use the same reference curve, namely the FVC%pred alone reference curve in Figure 9. The selected HR was applied to patients in the model where the identified

decline occurred. An example of how the values in Table 3 are used in the model is provided here: If a patient had a decline of 8% in FVC%pred and a multivariate model type was chosen, the mortality risk estimated by fitting parametric models to the reference curve would be adjusted with a HR of 1.3. In the model, two options for adjusting mortality were available (i.e., adjusting the mortality risk when and if it was adjusted):

- Option 1: At 12 months only. In this option, the increased mortality risk was applied if the required decline in FVC%pred or mRSS occurred in the first 12 months. This option is included to be aligned with analyses from Sobanski et al. 2018 (33). This is a conservative estimate, because this means that further decline after 12 months would not result in an increased mortality risk.
- Option 2: At any time. If the decline in either FVC%pred or mRSS occurred at any time, the increase in mortality risk was applied after the occurrence of the decline.

Examples of the two options are provided here. The examples are based on the mortality risk for FVC%pred alone: If a patient's FVC%pred declined by 10% 18 months after entering the model, then in option 1, no increase in mortality risk would be assumed. In option 2, a 10% decline after 18 months would result in an increased mortality risk post 18 months and until death. Option 2 was selected in the base case.

[redacted] shows the final OS curve fitted with a Gompertz parametric model (PSM) and adjusted for FVC (and mRSS if that is included) by applying the selected HR to the parametric curve. Furthermore, [redacted] shows the survival curve for the general Danish population and the survival curve adjusted for general population mortality. As mentioned, the Danish clinical experts informed that the median survival of SSc-ILD patients in Denmark is approximately 11 to 14 years, which is consistent with the green curve in [redacted] (PSM curve adjusted for FVC/mRSS (HR applied to selected PSM)).

shows the simulated extrapolated OS curve for the average of the cohort over the total time horizon. shows a small benefit in OS of nintedanib due to the improved FVC%pred, because FVC%pred is indirectly linked to OS via the surrogacy relationship modeled with Sobanski et al. 2018 (33). The simulated median OS in both arms is presented in Table 5.

Table 5 **Simulated median OS in the nintedanib arm and placebo arm**

Median Survival	
Median OS nintedanib (years)	
Median OS BSC (years)	
Incremental benefit of nintedanib	

[redacted]

2.2.3 Time on treatment (ToT)

In the SENSCIS trial, patients received either nintedanib plus SoC or SoC alone. Patients could discontinue treatment at the discretion of the physician due to safety concerns or clinical deteriorations. ToT was measured as the time from treatment initiation to permanent treatment discontinuation. ToT data from the maximum follow-up period in the SENSCIS trial are shown in [redacted]. Analyses of ToT were adjusted to censor death events to avoid double counting when modelling OS and ToT separately.

[redacted]

[redacted]

Parametric models were fitted to ToT data (ToT KM curves) and incorporated in the model to extrapolate ToT data beyond the SENSCIS trial. Parametric models were fitted both with a single parametric model where a covariate for treatment arm was included and as two separate parametric models, one for each treatment arm. The parametric models with the two options are displayed in [redacted] and [redacted]. The ToT curves include events due to treatment discontinuation only, i.e., they do not include death events, as mentioned above. The option to model ToT with a single parametric model with treatment as a covariate was chosen in the base case.

Choice of parametric model with the best fit to ToT data

To determine which parametric model provided the best fit for extrapolating ToT data, AIC and BIC values were compared and the curves were visually inspected. The AIC and BIC values of the separate models and the single model (treatment as a covariate) are presented in Table 6 and Table 7, respectively. Low AIC and BIC values are indicative of a good statistical fit.

The AIC and BIC values in Table 7 indicate that the parametric model with the best statistical fit was the log-normal model. However, when visually inspecting the log-normal parametric model in [redacted], the extrapolation of ToT with this parametric model was assumed to be clinically implausible. This was due to the curve not approximating towards 0 and the high percentage of the cohort remaining in treatment after 20 years. Based on this, ToT was extrapolated with an exponential parametric model, because this curve was assumed to be the best-fit for the ToT data. Even though the exponential model was associated with the highest AIC and BIC values, the curve was chosen because it was assumed to be the most clinically plausible, as it was the only ToT curve that approximated 0. The model is flexible for the user to choose other parametric models to extrapolate ToT. Parametric models were fitted to data from the maximum follow-up period in the SENSCIS trial (100 weeks).

Table 6 **The AIC and BIC values for parametric models fitted to ToT data with two separate models, one for each treatment arm**

Parametric model	AIC	BIC
	Nintedanib (separate models)	
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
	SoC (separate models)	
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Table 7 **AIC and BIC values for parametric models fitted to ToT data using a single model with treatment as a covariate (the base case)**

	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

The simulated extrapolated ToT curves for nintedanib can be seen in [redacted]. As mentioned, the ToT curves in [redacted] and [redacted] include discontinuation events due to treatment discontinuation only. Simulated ToT curves in [redacted] capture discontinuation events due to both discontinuation and death. It is important to note that the parametric models and the KM curves in [redacted] are presented at the cohort level. To apply survival curves to a microsimulation, the probability of an event, e.g. a discontinuation event in each cycle, must be derived, and a random number determines whether the event occurs or not. The generation of random numbers are described under 2.1.

[redacted]

The model assumes that patients entering the model while receiving background therapy remain on such therapy, i.e. they cannot discontinue MMF and MTX. It is also important to note that, given the immature time to treatment discontinuation data collected in the SENSCIS trial, the long-term treatment duration is uncertain.

A range of scenarios can be investigated by applying certain stopping rules in the model and these are described in the following.

Assumptions regarding treatment stopping rules in the model

Stopping rules can be applied to the nintedanib treatment arm in the model. The stopping rule results in patients discontinuing nintedanib and move to SoC. Four options are available in the model for applying a stopping rule:

1) no stopping rule is applied (base case);
2) the stopping rule is based on the maximum treatment duration;
3) the stopping rule is based on clinical events; or
4) the stopping rule is based on both the maximum treatment duration and clinical events.

In the following, a description of each option is provided. It should be noted that the stopping rules are not mutually exclusive, which means that in all cases where a stopping rule is applied in the model, the stopping rule is added to how discontinuation is modelled when no stopping rule is applied.

No stopping rule is applied

This option was applied in the base case. Patients discontinue treatment due to death or a discontinuation event. Death is based on OS as outlined under "Mortality" in section 2.2.2, and discontinuation events are based on parametric models fitted to SENSCIS data as described under "Time on treatment" in section 2.2.3.

Based on maximum treatment duration

An arbitrary maximum treatment duration may be specified for nintedanib. When this stopping rule is applied, a patient that reaches the maximum treatment duration while still receiving nintedanib will discontinue nintedanib treatment.

Stopping rule based on clinical events

Can be applied based on worsening in FVC%pred alone, mRSS alone, or a combination of the two. The user may specify the level of worsening in each outcome that will lead to discontinuation. Worsening of the disease is assessed on a 12-month basis, meaning that if in any 12 months the specified level of disease worsening in the outcome is reached, the patient will discontinue.

Based on both maximum treatment duration and clinical events

Discontinuation will occur based on which of the two is observed first.

Maintenance of treatment effect

The SENSCIS trial demonstrated an improvement in FVC%pred in patients treated with nintedanib. It is uncertain how FVC%pred responds to treatment discontinuation; thus, several options for modeling the maintenance of treatment effect after discontinuing treatment with nintedanib were included in the model. The options are the following:

- the treatment effect stops when treatment is discontinued (base case);
- the treatment effect continues indefinitely; or
- the treatment effect continues for an arbitrary period of time, which should be defined by the user.

In the case where treatment effect is maintained, modelling of the health outcomes described under section 2.2.1 is informed by analyses of relevance for the treatment initially received. If treatment effect is stopped in the nintedanib arm, health outcomes are informed by using the counterfactual case, i.e. representing the case where nintedanib is not used. The counterfactual here refers to the health outcomes observed while receiving SoC alone. An example of how FVC%pred is calculated for nintedanib in a given cycle where the treatment effect is not maintained and the counterfactual is used is provided in the equation below:

$$FVC\%pred_t = FVC\%pred_{t-1} + \Delta counterfactual\ FVC\%pred_{t,t-1}$$

Adverse events

AEs were included in the model if they met the following criteria:

- AEs with a significant impact on costs;
- AEs with an incidence of ≥5 %; or
- AEs with an incident difference greater than 1.5 between the two treatment arms.

The criteria provide a framework for ensuring that the impact of the most important AEs is captured in the model. AEs from the SENSCIS trial meeting the criteria outlined above were gastrointestinal disorders (diarrhoea, nausea and vomiting) and severe infections and infestations, which were included in the analysis. Table 8 shows a full overview of the AEs observed in the SENSCIS trial. The Danish clinical experts were consulted regarding the AEs associated with nintedanib treatment who agreed on the included AEs. Furthermore, the clinical experts disclosed that patients treated with nintedanib are monitored for increases in liver enzymes, which consists of a blood sample approximately three times per year. The blood sample was assumed to be taken at one of the GP visits, and a unit cost of 50.11 DKK was applied (36).

Data on the frequency of AEs from the SENSCIS trial were used to calculate a rate using the mean exposure of nintedanib and SoC. Rates were converted to monthly probabilities using the formula listed below. AEs were only applied in the model while patients were on initial treatment. Safety of subsequent therapies was not included in the model due to the uncertainties about what subsequent therapies consist of.

$$Cycle\ probability = 1 - EXP(-rate * \left(\frac{cycle\ length}{duration\ of\ 1\ year}\right))$$

Table 8 **The AEs observed in the SENSCIS trial**

	Nintedanib, N=288 (%)	Placebo, N=288 (%)
Any adverse event	283 (98.3)	276 (95.8)
Most common adverse event*		
Diarrhoea	218 (75.7)	91 (31.6)
Nausea	91 (31.6)	39 (13.5)
Skin ulcers	53 (18.4)	50 (17.4)
Vomiting	71 (24.7)	30 (10.4)
Coughing	34 (11.8)	52 (18.1)
Nasopharyngitis	36 (12.5)	49 (17.0)
Upper respiratory tract infection	33 (11.5)	35 (12.2)
Abdominal pain	33 (11.5)	21 (7.3)
Fatigue	31 (10.8)	20 (6.9)
Weight decrease	34 (11.8)	12 (4.2)
Severe adverse events**	52 (18.1)	36 (12.5)
Serious adverse events***	69 (24.0)	62 (21.5)
Fatal adverse events	5 (1.7)	4 (1.4)
Adverse events leading to discontinuation of intervention	46 (16.0)	25 (8.7)

*AEs reported over 52 weeks plus a 28-day post-treatment period, coded according to the preferred terms in the Medical Dictionary of Regulatory Activities. Data are shown for the patients who had at least one such adverse event
**A severe adverse event was defined as an event that was incapacitating or that caused an inability to work or perform usual activities
***Serious adverse events were defined as an event that resulted in death, was life-threatening, resulted in hospitalisation or prolongation of hospitalisation, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed to be serious for any other reason.
Source: (27)

Table 9 **Information on adverse events included in the model**

	Nintedanib			Placebo		
	Patients	Rate (N/patient years on treatment)	Cycle probability	Patients	Rate (N/patient years on treatment)	Cycle probability
Serious gastrointestinal disorders	22	0.09	0.01	6	0.02	0.00
Severe infections and infestations	19	0.08	0.01	10	0.04	0.00

Source: The SENSCIS trial.
Abbreviations: AE: adverse events.

2.3 Intervention

The intervention in the model is nintedanib 150 mg orally twice daily (300 mg per day). According to the SmPC on nintedanib, some patients do not tolerate the 150 mg twice daily dose and can receive 100 mg twice daily (200 mg per day) instead (26). Dose reductions, dose interruptions and dose re-escalations were permitted in the model, and the following options are available in the model:

- No adjustments: No adjustment of the drug cost of nintedanib. Patients will receive the full dose of 150 mg nintedanib orally twice daily. The drug costs are applied each cycle.
- Relative dose intensity (RDI) adjustment: The total cost per cycle is adjusted using the RDI reported in the SENSCIS trial (RDI adjustment factor=0.9034).
- Dose reductions only: The cycle probability of dose reductions is applied in the model, based on SENSCIS data. If the adjustment is applied, patients receive 100 mg nintedanib twice daily until the maximum time horizon is reached or the patient dies. In some cases where a reduction occurs, the dose is re-escalated to 150 mg twice daily. If the patient re-escalates the nintedanib dose, it was assumed that the dose reduction lasts for one cycle.
- Dose interruptions only: Patients can experience an interruption in their treatment. The duration of the interruption comes from the SENSCIS trial and was assumed not to exceed one cycle.
- Both dose reduction and dose interruption: In this adjustment, it was assumed that patients experiencing any dose reductions could also interrupt nintedanib treatment. The assumptions are the same as mentioned above for reductions and interruptions (base case).

In the base case, the option to include both dose reductions and interruptions was chosen. Information used to calculate the cycle probability of dose reductions and dose interruptions came from the SENSCIS trial and can be seen in Table 10.

Table 10 **Number of dose reductions and interruptions observed in the SENSCIS trial and the respective rates and cycle probabilities**

	Observed events	Rate *(N/Patient years on treatment)*	Cycle probability
Dose reduction	130	0.51	4.3%
Dose interruption	182	0.72	6.0%

Source: the clinical study report on the SENSCIS trial.

The SENSCIS trial allowed nintedanib to be given in combination with background therapy with either MTX or MMF if patients were stable for six months prior to receiving nintedanib. Add-on medications were also allowed in the case of clinical SSc deteriorations but results from the trial showed that use of add-on medication was rare and did not differ between treatment arms. Consequently, add-on medications were not included in the economic model.

2.4 Comparator

In the base case, the comparator is off-label standard of care (SoC). SoC includes background therapies with the off-label drugs mycophenolate mofetil (MMF) and methotrexate (MTX) as permitted in the SENSCIS trial. Concurrent use of low dose glucocorticoid steroids was also allowed. Placebo was outlined as comparator in the DMC protocol on nintedanib.

Administration and recommended dose of SoC

The administration and dose of the off-label drugs MMF and MTX as SoC treatment were based on the SENSCIS trial (27). Patients who received MTX or MMF at a stable dose for at least six months were included in the SENSCIS trial. In the placebo arm, 48.6% of patients received MMF and 5.2% received MTX. In the nintedanib arm, 48.3% received MMF and 8% received MTX (27).

Mycophenolate mofetil and methotrexate

The dose of MMF in SSc-ILD is 1,500 mg orally twice daily (37). The dose of MTX is 15 mg orally per week (38). We assumed that patients would not discontinue SoC when they discontinued nintedanib.

2.5 Patient population in the model

The model samples patient profiles directly from the SENSCIS trial data. This approach can be referred to as non-parametric sampling with replacement and involves randomly sampling individual patients included in the SENSCIS trial and applying their baseline characteristics to the model. This approach ensured that the covariance structure of the different parameters was maintained and not required to make any assumptions regarding the distribution of data due to

the individual sampling. If data was missing for a parameter in a patient profile, the whole patient profile was excluded. This was assumed to be appropriate due to the small number of cases of missing data. The same baseline characteristics were applied to both treatment arms because patient characteristics were well balanced between the two treatment arms in the SENSCIS trial. Baseline characteristics of the patient population included in the SENSCIS trial are presented in Table 2, and the baseline characteristics of the modelled/simulated patient population can be seen in Table 11.

Table 11 **Baseline characteristics of modelled (simulated) patients**

Characteristics	Overall
Number of patients	500
Age – mean (SD)	53.89 (12.13)
Sex	
Female – no. (%)	379 (75.8)
Male – no. (%)	121 (24.2)
Methotrexate background therapy	
No – no. (%)	459 (91.8)
Yes – no. (%)	41 (8.2)
Mycophenolate mofetil background therapy	
No – no (%)	267 (53.4)
Yes – no. (%)	233 (46.6)
SSCGR1	
Diffuse cutaneous SSc – no. (%)	260 (52)
Limited cutaneous SSc – no. (%)	240 (48)
ATASTAT	
Negative – no. (%)	214 (42.8)
Positive - no. (%)	286 (57.2)
TSTIDIA – mean (SD)	2.58 (1.72)
TSNRSYM – mean (SD)	3.41 (1.73)
FVC – mean (SD)	72.81 (16.42)
mRSS – mean (SD)	11.28 (8.84)

Abbreviations: SD: standard deviation, SSCGR1: systemic sclerosis subgroup, ATASTAT: Anti-topoisomerase status, TSTIDIA: time since disease onset, TSNRSYM: Time since non-raynaud symptom onset, FVC: forced vital capacity, mRSS: modified rodnan skin score.

2.6 Applied perspective

The analysis has a limited societal perspective in accordance with guidelines from the DMC (39).

2.7 Time horizon and cycle length

The analysis has a lifetime time horizon, which was set to 35 years. A lifetime time horizon of 35 years was assumed appropriate, since the mean age of modelled patients was 53.98 years. The cycle length was one month, consistent with the intervals between efficacy evaluations in the SENSCIS trial. Moreover, shorter cycle lengths would have increased the model run time and resulted in a greater computational burden.

2.8 Discounting

Costs incurred from year 1 to year 35 are discounted by 3.5% each year in accordance with the discounting rates presented by the Danish Ministry of Finances (40).

2.9 Resource use and unit costs

The overall cost categories included in the cost per patient analysis of nintedanib were drug costs, hospital costs, AE costs, cross-sectional costs, end of life costs and patient and transportation costs. Hospital costs consisted of costs of admissions and outpatient visits, and cross-sectional costs included GP visits and physiotherapy visits. The primary source for the resource utilisation was patient-level data from the SENSCIS trial.

A minority of highly selected patients can receive a lung transplant if they meet specific criteria. However, lung transplants were not included in the model, because we have no data on the survival or resource utilisation of patients who have undergone lung transplantation. SSc-ILD patients can undergo various procedures to control and monitor their disease while receiving treatment and when they do not receive treatment. The costs of such procedures have a minimal impact on the total cost of a SSc-ILD patient, and no data on the utilisation of such procedures among SSc-ILD patients exist. Therefore, we did not include such costs in the model. An option for the user to define per cycle probabilities and unit costs of incurring these procedure costs are incorporated in the model.

2.9.1 Drug costs

The drug costs included in the model were drug cost of nintedanib, MMF and MTX (SoC), because it was allowed in the SENSCIS trial to administer nintedanib in combination with MMF and MTX if patients were stable for six months prior to nintedanib treatment. No drug costs were included in subsequent treatment lines when patients discontinue treatment with nintedanib, because no treatment alternatives in subsequent lines exists for SSc-ILD patients. All drugs included in the analysis are administrated orally; therefore, no administration costs were included in the model.

Nintedanib drug cost

Nintedanib comes in capsules with two strengths: 100 mg and 150 mg with 60 capsules per package. The 150 mg formulation was used in the base case. The drug costs were based on the pharmacy purchasing prices (PPP) and obtained from www.medicinpriser.dk (March 2021). Drug information and applied PPPs are presented in Table 12.

Drug costs of background treatments (SoC)

As mentioned, patients with SSc will receive MTX and MMF as background treatments. MTX exists in several formulations. However, 2.5 mg with 100 tablets per package was chosen due to the lowest PPP. MMF exists in two formulations: 250 mg and 500 mg, with 150 and 300 capsules per package, respectively. The 250 mg formulation with 300 capsules per package was chosen due to the lowest PPP. Drug information and applied PPPs are presented in Table 12.

Table 12 **Information and PPP on drugs included in the analysis**

Treatment	Strength (mg)	Package size	PPP (DKK)
Nintedanib	100 mg	60 capsules	14,737
Nintedanib	150 mg	60 capsules	17,466
MTX	2.5 mg	100 tablets	50
MMF	250 mg	300 capsules	537

Source: www.medicinpriser.dk (March 2021).

2.9.2 Hospital costs

The hospital resource use was grouped into 10-point FVC%pred groups, because changes in FVC%pred are what drives the model. A cycle probability for incurring each resource in each FVC%pred group was derived from patient-level data from the SENSCIS trial. The cost associated with a resource in each FVC%pred group is calculated as illustrated in Figure 17.

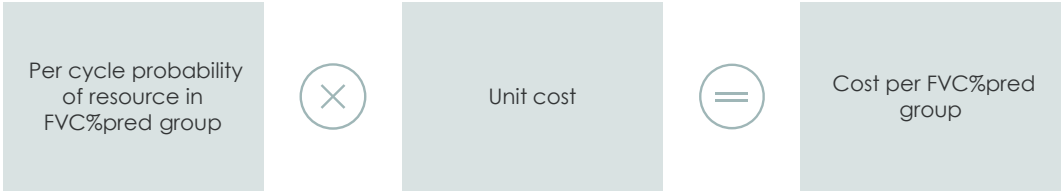

Figure 4: Illustration of how the costs of the hospital resources in each FVC%pred group are calculated based on the per cycle probability of incurring the resource and the unit cost

Admissions

The cost of an admission was based on patient-level data from the SENSCIS trial and included all-cause healthcare resource utilisation of patients in the SENSCIS trial, meaning that it was not limited to the resource use associated with SSc-ILD.

The cost of an admission was synthesised based on the following:

- percentage of admissions associated with intensive care unit (ICU) stays: 3.5%, SE 1.4%;
- percentage of admissions associated with mechanic ventilation: 0.39%, SE 0.4%;
- percentage of admissions not associated with the two above-mentioned: 96.1%;
- percentage of admissions associated with emergency room (ER) stays: 2.8%, SE 1.0%; and
- percentage of admissions associated with ambulance use: 6.7%, SE 1.6%.

The unit cost of each resource included in the admission cost and the source/assumption used for the estimation are presented in Table 13.

Table 13 **Unit costs, assumptions and sources used to estimate the cost of an admission**

Resource	Unit cost (DKK)	Source/assumption
Normal admission	41,260	Based on the DRG tariff 2021 04MA17 (Interstitial lung disease) with 6 contact days because the average duration of an admission in the patient-level data from the SENSCIS trial was 6.76 days
ICU stay	257,220	The unit cost for staying at the ICU was based on the DRG tariff 2021 26MP11 (intensive group I: simple organ failure in one or two organs).
ER stay	41,260	The unit cost for an ER overnight stay was based on the DRG tariff 2021 04MA17 (interstitial lung disease) with 2 contact days.
Ambulance use	1,514	The unit cost for ambulance use was based on a unit cost reported in a publication from "Akutteam Odense" (41).
Mechanic ventilation	51,463	Based on the DRG tariff 2021 04MP04 (Non-invasive ventilation treatment due to respiratory diseases) with 6 contact days

In the estimation of the cost of an admission, it was assumed that ICU stays and mechanical ventilation were part of the admission, while ER overnight stays and ambulance use were separate to the admission. Figure 18 illustrates how the total cost of an admission was calculated with the percentages listed above, unit costs from Table 13 and the per cycle probabilities of incurring the admission cost in each FVC%pred group given in Table 14. Per cycle probabilities were calculated based in the admission rates per month in the SENSCIS trial and the formula for calculating probabilities based on rates presented in Fleurence et al. 2007 (42). Rates were calculated based on the time spent within each FVC%pred group and already capture observations where resources were used multiple times within a given cycle.

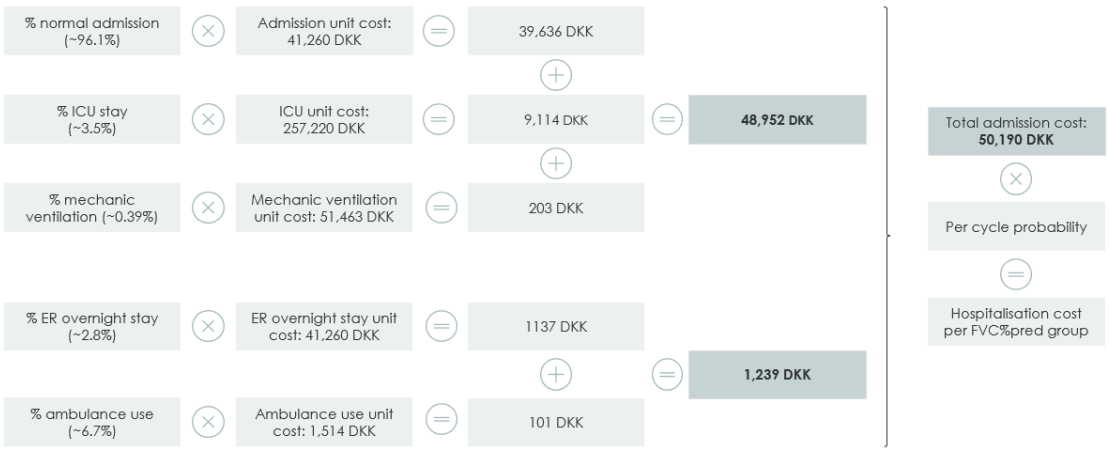

Figure 5: Illustration of how the cost of an admission was estimated. The 96.1% normal admission was estimated by subtracting the percentage of admissions associated with ICU stay (3.5%) and mechanic ventilation (0.39%) from 100%. The approximation signs were inserted to show that the percentages have many decimals.

Table 14 **Per cycle probability of incurring the cost of an admission in each FVC%pred group**

FVC%pred group	Per cycle probability
>110	[redacted]
100-110	[redacted]
90-100	[redacted]
80-90	[redacted]
70-80	[redacted]
60-70	[redacted]
50-60	[redacted]
<50	[redacted]

Source: patient-level data from the SENSCIS trial (27).

Emergency room visits

Beside the ER stays associated with admissions mentioned above, SSc-ILD patients can visit the ER without it being associated with an admission. The unit cost used to estimate the cost of an ER visit was based on the DRG tariff "04MA98" of 1,732 DKK, which was a combination of DJ849 – interstitial lung disease and BWST2A – multidisciplinary acute arrival of non-traumatic patient. Based on patient-level data from the SENSCIS trial, 6.7% of ER visits were associated with ambulance use. The unit cost used to estimate the cost of ambulance transportation was based on a publication from Akutteam Odense (41), where a unit cost per ambulance drive of 1,514 DKK was stated. The cycle probabilities of visiting the ER in each FVC%pred group can be seen in

Table 15. Per cycle probabilities were calculated based in the ER visit rates per month in the SENSCIS trial and the formula for calculating probabilities based on rates presented in Fleurence et al. 2007 (42). Rates were calculated based on the time spent within each FVC%pred group and already capture observations where resources were used multiple times within a given cycle.

Table 15 **Per cycle probability of an ER visit in each FVC%pred group**

FVC%pred group	Per cycle probability
>110	[redacted]
100-110	[redacted]
90-80	[redacted]
80-90	[redacted]
70-80	[redacted]
60-70	[redacted]
50-60	[redacted]
<50	[redacted]

Source: patient-level data from the SENSCIS trial (27).

Outpatient visits (ambulatory visits)

Based on data from the SENSCIS trial, SSc-ILD patients also incur specialist and nurse contacts. In Danish clinical practice, ILD patients are followed at the pulmonary outpatient clinic, and it was assumed that the specialist and nurse contacts were incurred during their visits to the outpatient clinic (43). The interviewed Danish clinical experts informed us that patients visit the outpatient clinic approximately two to four times per year, and a per cycle probability of an outpatient visit of 22.12% was applied regardless of FVC%pred group. A unit cost of 1,732 DKK was applied based in the DRG tariff 2021 "04MA98" because this was the generated tariff when combining the diagnosis DJ849 – interstitial lung disease and various ambulatory procedures.

Oxygen therapy

In the model, patients would receive oxygen supplementation if their FVC%pred fell below 80%. Patients with FVC%pred >80% were assumed to be in relatively good health and not in need of oxygen therapy. The unit cost of oxygen therapy was based on the DRG tariff "04MA98" of 1,732 DKK and was applied as a one-off cost if the FVC%pred fell below 80%. The DRG tariff was the result of combining DJ849 – interstitial lung disease and BGXA5 – oxygen therapy.

2.9.3 Cross-sectional costs

The cross-sectional costs included in the model were estimated based on patient-level data from the SENSCIS trial. The resource use consisted of visits to the GP and physiotherapy visits. The unit cost for physiotherapy was derived from the DMC catalogue for unit costs and the unit cost for a GP visit was based on the official agreed GP fees from 2021 (36). The unit costs are presented in

Table 16 and per cycle probabilities of a GP visit and physiotherapy in each FVC%pred group are presented in Table 17. Per cycle probabilities were calculated based in the GP visit and physiotherapy rates per month in the SENSCIS trial and the formula for calculating probabilities based on rates presented in Fleurence et al. 2007 (42). Rates were calculated based on the time spent within each FVC%pred group and already capture observations where resources were used multiple times within a given cycle.

Table 16 **Unit cost of a visit of the GP and one hour of physiotherapy**

Resource	Unit costs (DKK)	Source
GP	146.25 DKK	DMC catalogue for unit costs and current official agreed GP fees (36,44)
Physiotherapy	512 DKK per hour	

Table 17 **Per cycle probability of incurring GP visits and physiotherapy in each FVC%pred group**

FVC%pred group	GP visit	Physiotherapy
>110	[redacted]	[redacted]
100-110	[redacted]	[redacted]
90-100	[redacted]	[redacted]
80-90	[redacted]	[redacted]
70-80	[redacted]	[redacted]
60-70	[redacted]	[redacted]
50-60	[redacted]	[redacted]
<50	[redacted]	[redacted]

Source: patient-level data from the SENSCIS trial (27).

2.9.4 Adverse events costs

AEs from the SENSICS trial were included in the model. AEs were included if they meet the following criteria: 1) had a significant impact on outcomes (i.e. were severe or serious), 2) had an incidence ≥5%, and 3) had an incidence of 1.5 times greater between the two arms. The AEs that met the above-mentioned criteria and were included in the analysis were serious gastrointestinal disorders and severe infections and infestations (all AEs from the SENSCIS trial can be seen in Table 8). When patients experienced an AE that met the criteria, we assumed they would incur an outpatient visit to receive treatment. To estimate the cost associated with treating AEs at the outpatient clinic, we applied the DRG tariff "04MA98" of 1,732 DKK. The tariff was chosen based on information from the consulted clinical experts. They informed that treatment of gastrointestinal disorders such as diarrhea typically consists of pharmacologic

symptom relieving treatment (e.g. Imodium treatment). When combining the diagnosis "Other interstitial lung disease DJ848" with the procedure "Treatment with medicine for diarrhea BIHA80" in interactive DRG, the 04MA98 tariff was formed. Other gastrointestinal disorders such as decreased appetite and decreased weight are managed with dietary supplements and abdominal pain is managed with pain-relieving drugs. Moreover, the clinical experts informed that the management of gastrointestinal and infectious adverse events primarily will be at the outpatient clinic. The probabilities of experiencing the included AEs are presented in Table 9.

2.9.5 End of life costs

An end of life cost was included and assumed to be incurred when patients reached the end of their life. The rationale was that individuals incur additional costs shortly before death. The cost was applied in the last year of a patient's life and was estimated with the DRG tariff 2021 "04MA17" of 41,260 DKK. The DRG tariff was a combination of DJ849 – interstitial lung disease and BXBA – specialised palliative action and we assumed an arbitrary number of admission days of 30 contact days.

2.9.6 Patient and transportation costs

Patient costs and transportation costs were included in the analysis in accordance with the guidelines from the DMC (45). To estimate patient time associated with nintedanib and SoC treatment, an hourly cost of 179 DKK was applied. To estimate the transportation cost associated with nintedanib and SoC treatment, an average distance of 28 kilometers per hospital visit was assumed, in line with DMC guidelines (46). The DMC recommend using a cost of 3.52 DKK per kilometer and a transportation cost of 100 DKK per hospital visit was applied in the model. An average of 30 minutes of patient time each way to the hospital was assumed, summarising to one hour of patient transportation time per visit. Patient and transportation costs were assumed to be incurred when patients had to travel to the hospital, to the outpatient clinic and for cross-sectional visits. No patient or transportation costs were assumed to be associated with administration of nintedanib or placebo.

Patient-level data from the SENSCIS trial showed that the average duration of an admission was [redacted], which was applied as the patient time spend on admissions. No transportation costs were included for admissions or overnight stays at the ER. The patient time spent on an ER overnight stay and an ER visit was assumed to be one day and five hours, respectively. Outpatient and cross-sectional visits (GP and physiotherapy visits) were assumed to last for 30 minutes per visit. Outpatient visits associated with AEs were assumed to take 60 minutes. All visits were associated with 60 minutes of transportation time. All inputs are flexible and can be changed by the user. The time assumed spent by patients on the various resources described above are summarised in Table 18.

Table 18 **Patient and transportation time spent on the various resources described above**

	Patient time	Transportation time	Total time utilisation
Admission	[redacted]	-	[redacted]
ER overnight stay	1 day	-	1 day
ER visit	5 hours	60 minutes	6 hours
Outpatient visit	30 minutes	60 minutes	1.5 hours
GP visit	30 minutes	60 minutes	1.5 hours
Physiotherapist visit	30 minutes	60 minutes	1.5 hours
Outpatient visits associated with treating AEs	1 hour	60 minutes	2 hours

Source: assumptions and SENSCIS patient-level data.

2.10 Sensitivity analyses

To assess the uncertainties associated with the assumptions and parameter values applied in the cost per patient analysis, we conducted various one-way sensitivity analyses, presented in Table 20, with the alternative scenarios/values and values applied in the base case. Some of the sensitivity analyses required a deeper explanation and are described in the following.

Mortality with Goh et al. 2008

Estimating survival based on Goh et al. 2008 was assessed in a sensitivity analysis. Goh et al. 2008 included 330 patients referred to the Royal Brompton Hospital in London, UK, who met the criteria for SSc and had evidence of ILD on HRCT (23). The analysis in Goh et al. 2008 defined two levels of disease: limited and extensive disease. A significant increase in the mortality rate for patients with extensive disease compared to patients with limited disease was observed, which is shown in Figure 19 along with the approach to disease categorisation.

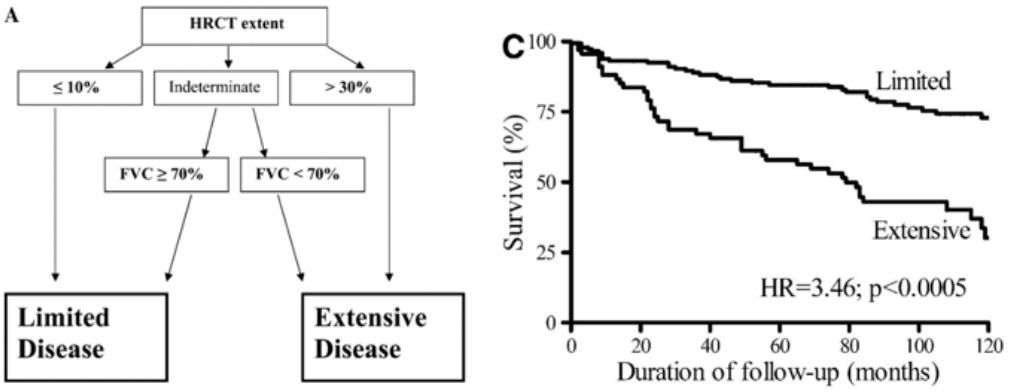

Figure 6: Mortality associated with limited and extensive disease from Goh et al. 2008 and an overview of the disease categorisation (23)

KM curves for limited disease were digitised, and the standard parametric models were fitted to the data from Goh et al. 2008 (see [redacted]). This was used to determine the baseline mortality risk when using Goh et al. 2008 to model OS. The hazard ratio shown in Figure 19 of 3.46 was applied to patients who either entered the model with extensive disease or who transitioned to extensive disease following a worsening of their FVC%pred score. A limitation to this approach was that HRCT was only assessed at baseline in the SENSCIS trial, which was used to determine the disease extent. Based on this, it was assumed that HRCT scores remained constant throughout the model time horizon. This means that patients transitioned to extensive disease based on their change in FVC%pred. This was assumed acceptable because there is a correlation between FVC%pred and HRCT scores.

[redacted]

When patients progressed from limited disease to extensive disease, their mortality risk was adjusted using the HR in Figure 19. As mentioned above, disease status was categorised with HRCT data, which was only reported at baseline in the SENSCIS trial and was therefore assumed to be constant throughout the model time horizon. Based on this, patients transitioned to extensive disease based on their deterioration in FVC%pred. This approach assumed that the proportional hazard assumption holds for Goh et al. 2008.

The standard parametric models were also fitted to data from Goh et al. 2008 to model OS. The choice of the model with the best-fit was done the same way as described under the estimation with Sobanski et al. 2018. The AIC and BIC values for the six standard parametric models fitted to Goh et al. 2008 KM curve for limited disease are presented in Table 19.

Table 19 **AIC and BIC values for the six standard parametric models fitted to Goh et al. 2008 limited disease KM curve**

	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Table 19 shows that the exponential parametric model had the lowest AIC and BIC values. The curves in [redacted] were visually inspected based on the statement on the median survival of SSc-ILD patients by the Danish clinical experts, the exponential model was chosen as the best-fit model. The model is flexible for the user to select other parametric models. [redacted] shows the extrapolated OS curve with the selected PSM adjusted for FVC/mRSS and applied HR (green curve).

[redacted]

Modified Rodnan skin score (mRSS)

Changes in mRSS was a secondary endpoint in the SENSCIS trial. MRSS consists of an evaluation of the patient's skin thickness rated by clinical palpation using a 0-3 scale (0= normal skin, 1 = mild thickness, 2 = moderate thickness, and 3= severe thickness). 17 anatomic areas of the body are scored, including: face, anterior chest, abdomen, (right and left separately) fingers, forearms, upper arms, thighs, lower legs, and dorsum of hands and feet. These individual values are added together, and the sum is defined as the total skin score (maximum 51).

MRSS was excluded from the base case because it does not affect the resource utilisation or mortality. However, the model includes an option where the mortality risk can be a function of a combined endpoint of FVC%pred and mRSS, which was included in a sensitivity analysis.

MRSS was modelled as a continuous outcome with values predicted for individual patients at each cycle for each treatment arm. The same approach used for modelling FVC%pred was used to model mRSS. Linear mixed effects models were fitted to SENSCIS trial data up to 52 weeks. The SENSCIS trial did not show any significant impact on the mRSS score of patients treated with nintedanib compared to placebo, as shown in [redacted]. Thus, a covariate for treatment arm was not included in the linear mixed effects regression models fitted to mRSS in the model. This means that no difference in mRSS score between nintedanib and SoC was assumed. The mRSS curves from the SENSCIS trial and predicted curves can be seen in [redacted] and [redacted].

[redacted]

[redacted]

As mentioned, a covariate for treatment arm was not included, due to the limited difference in mRSS score between the two treatment arms. The difference in mRSS values between the two arms illustrated in [redacted] and [redacted] is due to baseline characteristics imbalances between patients in the nintedanib arm and patients in the SoC arm in the SENSCIS trial. Predictions for mRSS in the model were based on the patient profiles sampled from the SENSCIS trial and since the model applies the same patient profiles in both treatment arms, this difference is not apparent in the model.

Parametric extrapolation of OS and ToT

Sensitivity analyses investigating the impact on the result of the base case when using other parametric models to extrapolate OS and ToT were conducted. This was done in accordance with Latimer et al. 2013, who state that a thorough justification of the choice of parametric model should be supplemented with testing other parametric models in a sensitivity analysis (47).

Table 20 **Overview of the sensitivity analyses conducted on assumptions and parameters in the cost per patient analysis**

Parameter	Base case analysis	Sensitivity analysis
Time horizon	35 years	10 years
Stopping rules	None applied	Two stopping rules could be applied: 1) maximum treatment duration of two years and 2) treatment stop due to 10% decline in FVC%pred.
Modelling of OS based on FVC%pred	Sobanski et al. 2018	Goh et al. 2008
Inclusion of mRSS	Not included	Included
Nintedanib dose adjustment	Both dose reductions and interruptions included	No dose adjustment
FVC%pred <40%	Results in death	Removal of assumption of death when the FVC%pred falls below 40%
OS parametric model	Gompertz	Exponential, generalised gamma, log-normal and log-logistic
ToT parametric model	Exponential	Gompertz, generalised gamma, log-normal, log-logistic and Weibull
ToT modelling	Single model (treatment as covariate)	Separate models (one for each treatment arm)
Maintenance of treatment effect	Treatment effect stops at discontinuation	Treatment effect continues indefinitely

2.11 Overview of base case settings in the model

The table below provides an overview of the base case settings in the model. The table also provides an overview of alternative options that can be applied in the model.

Table 21 **Overview of the base case settings in the model and alternative options. Many of the settings in the table can be changed in the "Controls" sheet in the Excel model**

	Base case	Alternative settings
Cost per patient analysis		
Number of simulated patients	500	Flexible. But it should be noted that increasing the number will increase the simulation time
Time horizon	35 years	Flexible (maximum 35 years)
Cycle length	1 month	None
Discounting	Year 1-35: 3.5% Year 36-50: 2.5%	Flexible
Population	SSc-ILD patients (ITT from the SENSCIS trial)	None
Included costs	Drug costs Hospital costs Cross-sectional costs End of life costs Patient and transportation costs	None, but cost inputs can be changed
Procedure costs	No	Yes. Included in sensitivity analysis
Subsequent treatments	No	None
OS data source	Sobanski et al. 2018	Goh et al. 2008
OS parametric model	Gompertz	Flexible to choose between the parametric models
Sobanski et al. 2018 model type	Multivariate	Univariate
Sobanski et al. 2018 model outcomes	FVC%pred alone	Composite FVC%pred and mRSS
Mortality timing adjustment	Anytime in the model	At 12 months only
FVC-regression model	Linear mixed effects model with EUSTAR covariates	No alternatives
FVC%pred capping	Maximum value: 120% Minimum value: 40%	Maximum cap fully flexible in model. Minimum value: patients assumed to die at FVC%pred <40, but also flexible in model.
Include mRSS	No	Inclusion of mRSS is flexible in model. Setting must be aligned with choice of outcome linked to OS
ToT parametric model	Exponential	Choice of parametric distribution flexible in model. Option for separate or covariate adjusted models
Maintenance of treatment effect	Treatment effect stops at discontinuation	Treatment duration continues indefinitely, or treatment effect is set to an arbitrary duration.
Nintedanib dose adjustment	Both dose reductions and interruptions included	Option to include relative dose intensity (RDI) adjustment or reductions/interruptions, separately and in combination
Nintedanib stopping rule	None	Based on maximum treatment duration, based on clinical events (FVC, mRSS), based on both maximum treatment duration and clinical events

3 Results: Cost per patient analysis

In the following, we present the result of the cost per patient analysis. The results of the analysis can be found in the "Deterministic results" sheet in the Excel model.

3.1 Results of the base case analysis

In the cost per patient analysis, we estimated an incremental cost of treating SSc-ILD patients with nintedanib plus SoC compared to SoC alone of 647,845 DKK over a lifetime time horizon. An overview of the total costs in each cost category included in the analysis is provided in Table 22.

Table 22 **Results of the cost per patient analysis of nintedanib plus SoC and SoC alone over a lifetime (35 years), with discounted costs (DKK)**

	Nintedanib + SoC	SoC	Incremental
Drug costs	734,181	97,156	637,025
Hospital costs	244,191	235,857	8,334
Cross-sectional costs	1,645	1,073	573
AE costs	1,021	897	124
End of life costs	28,000	28,813	-812
Patient and transportation costs	70,6184	68,017	2,601
In total	1,079,656	431,811	647,845

3.2 Results of the sensitivity analyses

Results of the one-way sensitivity analyses are presented in Table 23. The table presents the incremental costs of nintedanib compared to placebo in the respective sensitivity analyses, which can be compared with the incremental cost of nintedanib from the base case analysis, as this is also stated in the table.

Table 23 **Overview of the results of each sensitivity analysis**

Sensitivity analysis		Incremental cost (DKK)
Base case		**647,845**
Time horizon of 10 years		610,810
Stopping rule: maximum treatment duration of two years		312,693
Stopping rule: treatment stop due to 10% decline in FVC%pred		635,852
Modelling of OS based on FVC%pred from Goh et al. 2008		537,917
No nintedanib dose adjustment		744,024
Removal of assumption of death when the FVC%pred falls below 40%		705,098
OS extrapolation		
Exponential	651,006	
Generalised gamma	648,477	
Log-normal	651,189	
Log-logistic	655,911	
ToT extrapolation		
Gompertz	1,184,792	
Generalised gamma	1,008,342	
Log-normal	923,622	
Log-logistic	838,116	
Weibull	769,208	
ToT modelling with separate models (one for each treatment arm)		647,845
Maintenance of treatment effect: Treatment effect continues indefinitely.		659,342

4 Methods: Budget impact analysis

The purpose of the budget impact analysis was to estimate the impact of recommending nintedanib as standard treatment of SSc-ILD at Danish hospitals. The budget impact is estimated per year in the first five years after the recommendation of nintedanib to SSc-ILD patients. The budget impact analysis compares the cost to the Danish regions in the scenario where nintedanib is recommended as possible standard treatment and the scenario where nintedanib is not recommended as possible standard treatment of SSc-ILD. The total budget impact per year is the difference between the two scenarios. The budget impact was based on the cost per patient analysis, but patient and transportation costs were excluded, and costs were not discounted.

The methodology in the budget impact analysis was to multiply the estimated cost per patient of nintedanib and placebo in the first five years with the number of patients who are candidates for treatment each year stated by the DMC protocol.

4.1 Patient numbers

According to the expert committee, 30 to 50 new patients with progressing SSc-ILD are potentially candidates for treatment with nintedanib each year and no separation of prevalence and incidence is made. Therefore, we calculated the budget impact of nintedanib assuming 30 new patients each year in the budget impact. The number of new patients treated with nintedanib and placebo (SoC) per year with a recommendation is presented in Table 24. Table 25 shows that all new patients will receive SoC if nintedanib is not recommended. The model is flexible for the user to specify other numbers of potential candidates to nintedanib treatment each year in the budget impact analysis.

It should be noted that mortality is accounted for in the budget impact analysis because the patient numbers in year 1-5 are multiplied by the cost per patient in year 1-5 where the mortality each year is reflected.

Table 24 **Number of new patients treated with nintedanib and SoC each year in the budget impact analysis if nintedanib is recommended**

	Year 1	Year 2	Year 3	Year 4	Year 5
Nintedanib	30	+30	+30	+30	+30
SoC	0	0	0	0	0

Table 25 **Number of new patients treated with nintedanib and SoC each year in the budget impact analysis if nintedanib is not recommended**

	Year 1	Year 2	Year 3	Year 4	Year 5
Nintedanib	0	0	0	0	0
SoC	30	+30	+30	+30	+30

4.2 Sensitivity analyses on the budget impact analysis

We conducted sensitivity analyses on the budget impact analysis where we reduced and increased the number of new patients each year with 50%. In the sensitivity analysis with a reduction of 50%, 15 new patients were potentially candidates to treatment each year. In the sensitivity analysis with an increase of 50%, 45 new patients were potentially candidates to treatment each year. The sensitivity analysis with a reduced patient number reflects that not all potential candidates may be referred and treated. The sensitivity analysis with the increased patient number reflect that more patients could in fact be referred and treated each year.

5 Results: Budget impact analysis

In the following, we present the results of the budget impact analysis in the first five years with and without a recommendation of nintedanib. Results of the budget impact analysis can be found in the "Budget impact" Excel sheet in the model.

The budget impact of recommending nintedanib as standard treatment of SSc-ILD in Denmark is 5,3 mil DKK the first year and 15,9 mil DKK in year 5. The budget impact of nintedanib compared to SoC in each year in the budget impact analysis can be seen in Table 26.

Table 26 **The budget impact in DKK each year if nintedanib is recommended and if nintedanib is not recommended. Costs are undiscounted and rounded in millions.**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	6,6	11,8	15,9	19,2	21,8
Without recommendation	1,3	2,6	3,8	4,9	5,9
Budget impact	**5,3**	**9,2**	**12,1**	**14,3**	**15,9**

5.1 Results of the sensitivity analyses on the budget impact analysis

If the number of new patients who are potentially candidates for treatment is reduced to 15 patients each year, the budget impact in year 5 changes from 15,9 mill DKK to 8,0 mill DKK. Results of the sensitivity analysis with a reduction in the number of new patients each year are presented in Table 27.

If the number of new patients who are potentially candidates for treatment is increased to 45 patients each year, the budget impact in year 5 changes from 15,9 mill DKK to 23,8 mill DKK. Results of the sensitivity analysis with an increase in the number of new patients each year are presented in Table 28.

Table 27 **Result of the sensitivity analysis with 15 new patients each year if nintedanib is recommended and if nintedanib is not recommended. Costs are undiscounted and rounded in millions.**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	3,3	5,9	8,0	9,6	10,9
Without recommendation	0,6	1,3	1,9	2,4	2,9
Budget impact	**2,7**	**4,6**	**6,1**	**7,2**	**8,0**

Table 28 **Result of the sensitivity analysis with 45 new patients each year if nintedanib is recommended and if nintedanib is not recommended. Costs are undiscounted and rounded in millions.**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	9,9	17,7	23,9	28,8	32,6
Without recommendation	1,9	3,8	5,6	7,3	8,8
Budget impact	**8,0**	**13,9**	**18,3**	**21,5**	**23,8**

6 Discussion

In the cost per patient analysis, an incremental cost of treating SSc-ILD patients with nintedanib compared to placebo was estimated to be 647,845 DKK over a time horizon of 35 years. Not surprisingly, nintedanib is associated with higher costs compared to SoC, especially since nintedanib extends SSc-ILD patients' lives and SoC consists of the relatively low-cost generic immunosuppressants MMF and MTX.

We chose a microsimulation approach which functions by predicting health outcomes including FVC%pred (and mRSS) at monthly cycles. Both health outcomes are volatile and variable measures, characterised by large degrees of individual patient heterogeneity and variable rates of disease progression. Linear mixed effects regression models were fitted to the available SENSCIS data. The limited follow-up of the SENSCIS trial, relative to the life expectancy of SSc-ILD patients, is a significant limitation and makes extrapolation of outcomes for the lifetime of patients challenging. In addition, linear models may be considered inflexible when dealing with outcomes characterised by variable rates of decline. While data would only be available to inform the SoC arm, more mature data could improve the clinical plausibility of long-term extrapolations.

A separate issue related to the limited follow-up of the SENSCIS trial was modelling of overall survival. As using available SENSCIS data was not feasible, published data linking improved FVC%pred and mRSS score with reduced mortality were used. The value case of nintedanib is largely reliant on demonstrating that the benefit in terms of prevented or slowed decline of FVC%pred results in patients living longer. A key limitation of the current published literature is that a threshold of a decline of 10% is used to predict change in mortality risk. Consequently, any change below this threshold has no impact.

The performed sensitivity analyses revealed that the result of the cost per patient analysis is sensitive to changes in the parametric model chosen to extrapolate ToT data as selecting any of the other parametric models increased the incremental cost of nintedanib. Furthermore, the result also changed when applying a stopping rule which resulted in the maximum treatment duration of nintedanib in the model to be two years. Other parameters the result is sensitive to are when no dose adjustments of nintedanib is applied and when removing the assumption of death when the FVC%pred falls below 40%.

A key area of uncertainty of the economic model was the lack of mature overall survival data available from either completed randomised controlled trials or the available published literature. Data from Sobanski et al. used in the base case followed patients for up to 5 years, yet more than 60% of patients remained alive. Goh et al. followed up patients for 10 years, yet even up to 25% of patients with extensive disease remained alive. Simulated model results are comparable with the published sources. However, as shown, the assumption that patients die at FVC%pred <40% causes overall survival estimates to be reduced significantly. This could be due to a lack of clinical plausibility associated with a linear decline in FVC%pred.

If nintedanib is recommended by the DMC, it will be the first treatment alternative to be recommended for patients with SSc-ILD. Our analysis shows that nintedanib can prolong SSc-ILD patients' survival at an acceptable cost per patient of 647,845 DKK over a time horizon of 35 years and a limited budget impact in 1-5 years.

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8 Appendix

Table 29 **FVC % predicted regression model treatment as a covariate: fixed effects**

Covariate	Coefficient	Variance covariance matrix												
(Intercept)	0.677	0.954	-0.175	-0.049	-0.003	-0.064	-0.003	-0.005	-0.007	-0.033	-0.019	0.021	0.029	0.003
analysis_year	-4.269	-0.175	1.170	0.021	0.000	0.028	0.003	0.000	0.000	0.000	0.000	-0.139	-0.190	-0.017
TRT01P Placebo	-0.257	-0.049	0.021	0.082	0.000	-0.001	0.000	0.000	0.000	-0.003	0.001	-0.043	0.001	0.000
fvc_base	0.978	-0.003	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
MMFFLY	0.116	-0.064	0.028	-0.001	0.000	0.086	0.000	0.000	0.000	-0.007	-0.004	0.000	-0.043	0.000
DLCOHBBL	0.009	-0.003	0.003	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.000
mrss_base	-0.057	-0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AGE	0.017	-0.007	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SEXM	-0.117	-0.033	0.000	-0.003	0.000	-0.007	0.001	0.000	0.000	0.104	0.002	0.000	0.000	0.000
TSTIDIA	0.023	-0.019	0.000	0.001	0.000	-0.004	0.000	0.000	0.000	0.002	0.007	0.000	0.000	0.000
analysis_year :TRT01P Placebo	-1.270	0.021	-0.139	-0.043	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.289	-0.003	0.000
analysis_year :MMFFLY	1.390	0.029	-0.190	0.001	0.000	-0.043	0.000	0.000	0.000	0.000	0.000	-0.003	0.292	0.001
analysis_year :DLCOHBBL	0.042	0.003	-0.017	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000

Table 30 **FVC%pred linear mixed effects model coefficients – random effects for final fitted models**

Covariate	Coefficients	Variance covariance matrix	
Intercept	0	8.5293	-1.7548
Analysis_year	0	-1.7548	27.1298

Table 31 **mRSS regression model - treatment as a covariate: fixed effects**

Covariate	Coefficient	Variance covariance matrix											
(Intercept)	0.893614	0.6960301	-0.447932	-0.004541	-0.00966	-0.061999	-0.054531	-0.040708	-0.01985	-0.009583	0.003521	0.006707	0.048461	0.031962
analysis_year	-1.093852	-0.447931	1.281624	0.003566	0.006713	0.048499	-0.000023	0.032258	-0.00169	-0.000175	-0.010439	-0.019200	-0.133891	-0.089353
mrss_base	0.899349	-0.004541	0.003566	0.000314	3.85E-05	-0.000241	-0.000381	-0.00049	-5.2E-05	-0.000189	-0.000225	-0.000025	0.000307	0.000424
AGE	-0.018724	-0.009664	0.006712	0.000038	0.000164	0.000527	0.000300	0.000408	-0.00016	-0.000033	-0.000025	-0.000114	-0.000367	-0.000333
MMFFLY	0.2920719	-0.061998	0.048499	-0.000241	0.000527	0.096759	0.001519	-0.008433	-0.006833	-0.003578	0.000310	-0.000368	-0.066406	0.005042
ATASTATPOSITIVE	0.5792973	-0.054531	-2.36E-05	-0.000381	0.000301	0.001520	0.074775	-0.000998	0.006202	-0.001753	0.000052	-0.000008	-0.000315	-0.000004
synovitisY	-0.5456342	-0.040785	0.032258	-0.000492	0.000408	-0.008429	-0.000976	0.126435	0.006578	-0.001546	0.000432	-0.000326	0.005241	-0.008839
SEXM	0.2449404	-0.019854	-0.001686	-0.000051	-0.000016	-0.006826	0.006201	0.006578	0.093103	0.001239	0.000014	0.000027	0.000232	0.000394
TSTIDIA	0.0622844	-0.009583	-0.000176	-0.000189	-3.4E-05	-0.003579	-0.001753	-0.00155	0.001239	0.006250	-0.000005	0.000003	0.000030	0.000022
analysis_year:mrss_base	-0.1971891	0.003521	-0.010439	-0.000253	-2.5E-05	0.000311	0.000052	0.000432	0.000014	-0.000005	0.000638	0.000078	-0.000781	-0.001227
analysis_year:AGE	0.0366995	0.006707	-0.019200	-0.000025	-0.000011	-0.000368	-0.000008	-0.000033	2.71E-05	0.000003	0.000077	0.000028	0.000949	0.000891
analysis_year:MMFFLY	-1.1257453	0.048461	-0.133891	0.000307	-0.000037	-0.066406	-0.000315	0.005241	0.000232	0.000030	-0.000781	0.000949	0.189833	-0.016279
analysis_year:synovitisY	1.2272416	0.031962	-0.089353	0.000424	-0.000033	0.005043	-0.000004	-0.008839	0.000395	0.000221	-0.001272	0.000891	-0.016279	0.255401

Medicinrådet

Medicinrådets protokol for vurdering vedrørende nintedanib til behandling af systemisk sklerose-associeret interstitiel lungesygdom

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet sammenligner med, og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

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

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1. Begreber og forkortelser

AE	Uønsket hændelse (*Adverse event*)
DL_{CO}	Diffusionskapacitet
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EPAR:	*European Public Assessment Report*
EUnetHTA:	*European Network for Health Technology Assessment*
FGFR	Fibroblast vækstfaktorreceptor (*Fibroblast Growth Factor Receptor*)
FVC	Forceret vitalkapacitet (*Forced Vital Capacity*)
FDA:	*The Food and Drug Administration*
FINOSE:	Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HRCT	Højopløsnings-CT-scanning
HTA:	Medicinsk teknologivurdering (*Health Technology Assessment)*
ILS	Interstitiel lungesygdom
IPF	Idiopatisk pulmonal (lunge) fibrose
IQWIG:	*The Institute for Quality and Efficiency in Healthcare*
ITT:	*Intention-to-treat*
K-BILD	*King's Brief Interstitial Lung Disease*
MKRF:	Mindste klinisk relevante forskel
NICE:	*The National Institute for Health and Care Excellence*
PDGFR	Trombocytderiverede vækstfaktorreceptor (*Platelet-Derived Growth Factor Receptor*)
PF-ILS	Interstitiel lungesygdom med progredierende fibrose
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*
SMD:	*Standardized Mean Difference*
SGRQ:	*St George´s Respiratory Questionnaire*
SSc	Systemisk sklerodermi

SSc-ILS	Systemisk sklerose-associeret interstitiel lungesygdom
VEGFR	Vaskulær endotelial vækstfaktorreceptor (*Vascular Endothelial Growth Factor Receptor*)

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Boehringer Ingelheim, som ønsker, at Medicinrådet vurderer nintedanib til systemisk sklerose-associeret interstitiel lungesygdom (SSc-ILS). Medicinrådet modtog den foreløbige ansøgning den 21. februar 2020.

2.1 Systemisk sklerose-associeret interstitiel lungesygdom

Systemisk sklerodermi (SSc) er en sjælden, kronisk, autoimmun sygdom, hvor øget inflammation og bindevævsdannelse (fibrose) fører til stivhed og dysfunktion af kroppens væv. Sygdommen er kendetegnet ved stivhed i huden, primært i fingre, hænder og ansigt. Hos nogle patienter dannes der også bindevæv i de indre organer, fx i fordøjelseskanalen, lungerne, hjertet og nyrerne. Årsagen til sygdommen er ikke kendt, men er associeret med både miljømæssige og arvelige faktorer. Patienter med SSc diagnosticeres oftest ved 30-40-årsalderen, og flere kvinder end mænd får stillet diagnosen [1,2].

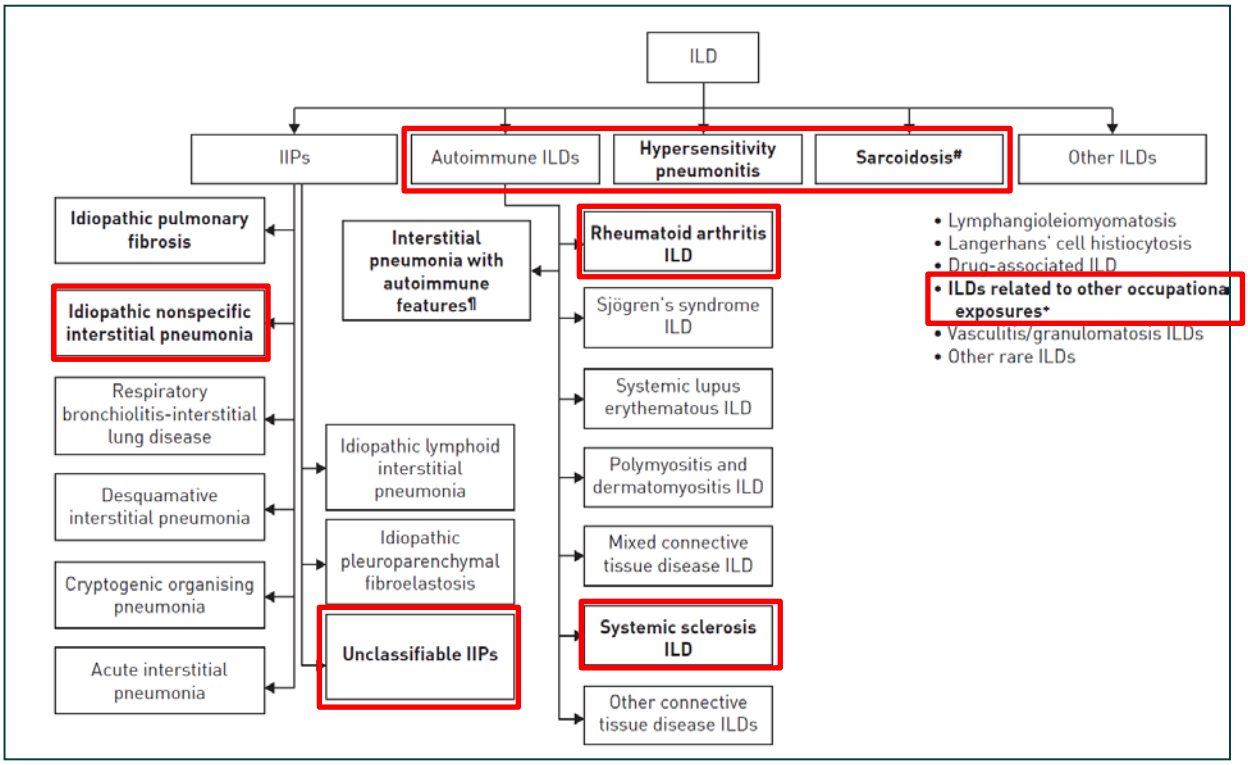
Interstitielle lungesygdomme (ILS) er en blandet gruppe af sygdomme karakteriseret ved inflammation og/eller fibrosedannelse i lungerne (alveoler, bindevæv, små bronkier og kar) [3–5]. Omkring 40-50 % af SSc-patienter udvikler ILS [1,6] som følge af skader på endotel- og/eller epitelceller aktivering af koagulations- og inflammationssignaler, som fører til fibrosedannelse i lungerne [7]. Lungefibrosen medfører stivhed i lungevævet og nedsat alveolar funktion. Jo mere fibrose, der opstår i lungerne, jo mere bliver lungefunktionen påvirket. Sygdommen diagnosticeres typisk ved lungefunktionsmålinger, hvor patienter med SSc-ILS typisk har en nedsat forceret vitalkapacitet (*forced vital capacity* (FVC)) og diffusionskapacitet (DL_{CO}), som falder gradvist over årene [7–10]. Dertil foretages højopløsnings-CT-skanning (HRCT) af thorax, som typisk viser interstitielle forandringer, der afspejler inflammation og fibrose [7–10].

Der findes mange typer af ILS, se oversigt i figur 1, hvoraf en af de mest undersøgte er idiopatisk pulmonal fibrose (IPF), som er kendetegnet ved irreversibel udvikling af progredierende lungefibrose [11–13]. Andre undertyper af ILS kan også medføre progredierende lungefibrose, selvom de ikke kan kategoriseres som værende IPF. Disse bliver samlet kaldt for PF-ILS, og SSc-ILS er én af disse.

Diagnosen af ILS er kompleks og bliver foretaget af et tværfagligt team af læger med ekspertise inden for lungemedicin, thorax-radiologi, reumatologi og patologi [14,15]. Udredning af ILS kræver en del undersøgelser, både for at påvise tilstedeværelsen af ILS samt for at klassificere, hvilken type ILS patienten har. Disse inkluderer blandt andet grundig anamneseoptag, lungefunktionsundersøgelse, røntgen af thorax, HRCT-skanning og i visse tilfælde ekkokardiografi og lungebiopsi. Den indledende udredning ved mistanke om ILS kan finde sted på alle lungemedicinske afdelinger. Ved mistanke om fibrotisk ILS eller behov for *second opinion* henvises patienter til yderlige udredning ved en af de højtspecialiserede lungemedicinske afdelinger i Danmark (Odense Universitetshospital, Aarhus Universitetshospital, Herlev-Gentofte Hospital og

Rigshospitalet). Behandling med antifibrotisk medicin varetages alene af de tre højt specialiserede ILS-centre [3].

Figur 1. Oversigt over forskellige undertyper af ILS, som kan medføre PF-ILS



De undertyper udover IPF, der kan udvikle progredierende fibrose (PF-ILS), er fremhævet.

SSc-ILS patienter har øget dødelighed i forhold til baggrundsbefolkningen [6]. SSc-ILS påvirker desuden patienternes livskvalitet i høj grad [16] og er den ledende dødsårsag hos SSc-patienter [17–19]. 35 % af dødsfald blandt SSc-patienter skyldes udvikling af lungefibrose [19]. SSc-ILS patienter har en 5- og 10-årsoverlevelse på hhv. 85,9 % og 71,7 % [20]. Et studie, som fulgte SSc-ILS-patienter efter diagnose (median opfølgningstid på 155 måneder), viste, at 52 % af patienterne døde inden for dette tidsrum [21]. Sygdomsforløbet varierer meget fra patient til patient [22,23], hvor et mere aggressivt sygdomsforløb, som involverer de indre organer, er associeret med en højere dødelighed [10].

Incidensen af ILS er svær at vurdere. Der foreligger et nationalt register over ILS i Danmark, men det indeholder primært data over patienter med IPF og kun i begrænset grad SSc-ILS-patienter. En retrospektiv opgørelse fra 2013 fandt en incidens af ILS i Danmark på 4,1 pr. 100.000 [24]. Der er mistanke om en betydelig underdiagnosticering af ILS som følge af, at sygdommene er sjældne og kan være svære at diagnosticere. Incidensen har været stigende gennem det sidste årti [25], hvilket kan skyldes flere faktorer, blandt andet indførelsen af antifibrotisk behandling og udvikling af retningslinjer på området, som har ført til en øget bevidsthed og viden om ILS blandt læger generelt. Samtidig er der sket en øgning i antallet af CT-skanninger, som involverer

thorax, som kan rejse mistanke om ILS. Incidensen af SSc-ILS baseret på et nyt norsk studie er ca. 10 tilfælde/million/år [6]. Fagudvalget skønner på den baggrund, at ca. 30-50 nye patienter årligt med SSc-ILS i progression potentielt kan være kandidater til behandling med nintedanib. Fagudvalget bemærker desuden, at en eventuel anbefaling af nintedanib kan føre til flere diagnosticerede patienter, blandt andet pga. den øgede opmærksomhed.

2.2 Nintedanib

Nintedanib er en lavmolekylær tyrosinkinasehæmmer med affinitet til en række celleoverfladereceptorer, inkl. trombocytderiverede vækstfaktorreceptor (PDGFR) α og β, fibroblast vækstfaktorreceptor (FGFR) 1-3 og vaskulær endotelial vækstfaktorreceptor (VEGFR) 1-3. Ved binding til PDGFR og FGFR blokeres receptorernes intracellulære signalveje, som er med til at stimulere proliferation, migration og differentiering af lungefibroblaster. Dette forhindrer videre udvikling af lungefibrosen [26].

Nintedanib fik følgende indikation i 2015, som orphan drug, hos det Europæiske Lægemiddelagentur (EMA):

> *Ofev er indiceret til behandling af idiopatisk lungefibrose (IPF) hos voksne.*

Behandling med nintedanib er livsforlængende ved IPF og gives indtil forekomsten af uacceptabel toksicitet eller død.

Denne vurdering af nintedanib omhandler følgende indikationsudvidelse, som blev givet hos EMA i 2020:

> *Ofev er indiceret til behandling af systemisk sklerodermi-associeret interstitiel lungesygdom (SSc-ILS) hos voksne.*

Den anbefalede dosis er 150 mg blød kapsel nintedanib to gange dagligt med ca. 12 timers mellemrum. Dosis kan sænkes til 100 mg to gange dagligt til patienter, der ikke tolererer en dosis på 150 mg to gange dagligt.

Udover SSc-ILS har nintedanib samtidig fået følgende indikationsudvidelse i 2020 hos EMA til interstitiel lungesygdom med progredierende fibrose (PF-ILS):

> *Ofev er også indiceret til behandling af andre kroniske fibroserende interstitielle lungesygdomme (ILS)med en progressiv fænotype hos voksne.*

Ved markedsføringstilladelsen af de to indikationsudvidelser mistede nintedanib sin status som orphan drug.

Begge indikationsudvidelser, PF-ILS og SSc-ILS, vurderes samtidig hos Medicinrådet.

2.3 Nuværende behandling

Dødeligheden af SSc-ILS korrelerer i høj grad med reduktionen i lungefunktion som følge af progression af lungefibrosen. Jo mere lungefibrose på HRCT-skanning eller højere FVC-faldhastighed, jo højere risiko for at dø [6,19,21,23,27–30]. Behandlingsmålet er derfor bremsning af sygdomsudvikling med henblik på uforandret status eller reduceret progressionshastighed.

Nintedanib er det første lægemiddel, som er regulatorisk godkendt til indikationen SSc-ILS, og som specifikt er rettet mod fibrosedannelsen. Der har indtil nu været national konsensus om, at SSc-ILS-patienter responderer bedst på immunmodulerende behandling med cyclophosphamid eller mycophenolat mofetil [3], hvilket baseres på de to randomiserede kliniske studier Scleroderma Lung Studies I og II [31,32]. Mycophenolat mofetil foretrækkes oftest af hensyn til en bedre bivirkningsprofil og ligeværdig effekt. Derudover modtager enkelte patienter biologiske lægemidler, fx rituximab [33] eller tocilizumab (interleukin-6 hæmmer) [34]. Typisk startes behandling til de patienter, som har høj risiko for progression [35]. Ingen af de nævnte lægemidler har SSc-ILS som indikation, men har været anvendt uden for indikation (off-label) i Danmark som førstelinjebehandling over en længere årrække. Behandling fortsættes indtil sygdomsprogression, hvilket monitoreres ud fra ændring i patientens symptomer, serielle lungefunktionsmålinger, evt. suppleret med gangtest, og HRCT-skanning [13].

Når alle medicinske behandlingsmuligheder er udtømt, kan en minoritet af højt selekterede patienter undergå lungetransplantation.

Fagudvalget understreger, at ved progression på førstelinjebehandling med immunmodulerende lægemidler eller udvikling af uacceptable bivirkninger modtager danske SSc-ILS-patienter i dag ikke yderligere behandling pga. manglende godkendte behandlingsmuligheder. Her vurderer fagudvalget, at antifibrotisk behandling med nintedanib potentielt kan finde anvendelse. Denne placering i behandlingsalgoritmen er i overensstemmelse med nylige anbefalinger fra en international ILS-ekspertgruppe vedrørende antifibrotisk behandling til ILS-patienter med progredierende lungefibrose, herunder SSc-ILS [13,36,37]. Fagudvalget gør opmærksom på, at EMA-indikationen ikke stiller krav om forudgående behandling.

3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, Medicinrådet undersøger (interventionen), af den behandling, Medicinrådet sammenligner med (komparator(er)), og af effektmålene.

Patientkarakteristika
I SENSCIS-studiet, som undersøgte antifibrotisk behandling i form af nintedanib til SSc-ILS, skulle patienterne opfylde bestemte kriterier for at deltage i studiet [38]. Fagudvalget tilslutter sig disse kriterier og mener, at SSc-ILS-patienter, som a) progredierer over 3-6 måneder til trods for førstelinjebehandling med

immunmodulerende medicin (typisk mycophenolat mofetil), og som b) opfylder de følgende kriterier, er kandidater til antifibrotisk behandling med nintedanib:

- ≥ 10 % fibrose i lungerne, som fremgår på en HRCT-skanning
- FVC ≥ 40 % af forventet
- DLco ≥ 30-89 % af forventet.

3.1 Klinisk spørgsmål 1

Hvilken værdi har nintedanib sammenlignet med placebo for patienter med systemisk sklerose-associeret lungesygdom?

Population
Voksne patienter med SSc-ILS, der progredierer ved førstelinjebehandling med immunmodulerende lægemidler[*]. Patienterne skal opfylde kriterierne oplistet i afsnit 2.3.

Intervention
Nintedanib, 150 mg to gange dagligt

Komparator
Placebo

Effektmål
De valgte effektmål fremgår af tabel 1.

3.2 Effektmål

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

[*]Patienter, der har svigtet efter førstelinjebehandling i 3-6 måneder eller har kontraindikationer til immunmodulerende behandling.

Tabel 1. Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Dødelighed	Kritisk	Dødelighed	Median overlevelse	12 måneder
	Kritisk[1]	Livskvalitet, alvorlige symptomer og bivirkninger	Lungefunktion målt ved årlig FVC-faldhastighed	25 mL/år
Livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig forværring i King's Brief Interstitial Lung Disease (K-BILD) spørgeskemaet, fra baseline	2,7 point
Bivirkninger	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever mindst én alvorlig uønsket hændelse (*serious adverse event (SAE)*)	5 %-point
			Andel patienter, der oplever behandlingsophør grundet uønskede hændelser	5 %-point
			Kvalitativ gennemgang af bivirkningsprofilen	

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
**Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.
[1]Det er sandsynligt, at der endnu ikke foreligger modne OS-data, som kan benyttes til at kategorisere effekten af nintedanib. Effekmålet lungefunktion målt ved årlig FVC-faldhastighed er et surrogatmål for dødelighed og vil kun blive benyttet, hvis der ikke kan benyttes OS-data.

3.2.1 Kritiske effektmål

Dødelighed

SSc-ILS er en uhelbredelig, dødelig sygdom, som rammer i 30-40-årsalderen og har en median overlevelse på omkring 155 måneder (range 9-180) [21]. Behandlingsmålet er at bremse videre sygdomsprogression med henblik på stabilisering og dermed forlænget overlevelse. Derfor er dødelighed et kritisk effektmål ved vurderingen af nintedanibs værdi til patienter med SSc-ILS.

Behandling med nintedanib er livsforlængende ved IPF og bremser hastigheden for udvikling af lungefibrosen. Hos SSc-ILS-patienter kan lægemidlet forventes at have en tilsvarende effekt og kan dermed teoretisk påvirke dødeligheden. Fagudvalget er klar over, at effekten af behandling med nintedanib på dødeligheden hos SSc-ILS-patienter vil kræve en længere opfølgning, end der er tilgængelig i de kliniske studier. Det forventes derfor ikke, at der inden for den nærmeste tid vil foreligge modne data fra kliniske studier, der kan dokumentere, at behandling med nintedanib reducerer dødeligheden. Derudover er nintedanib-studierne ikke designet til at vise en effekt på dødelighed [38,39]. Fagudvalget vurderer trods disse forhold, at det væsentligste mål med behandling af SSc-ILS er at nedsætte risikoen for tidlig død og behov for lungetransplantation.

Fagudvalget ønsker effektmålet opgjort som median overlevelse og vurderer, at en forbedring på 12 måneder er klinisk relevant. Fagudvalget har ved fastsættelsen af den mindste klinisk relevante forskel taget udgangspunkt i SSc-ILS-patienternes prognose.

Lungefunktion
Da nintedanib-studierne ikke er designet til at vise en effekt på dødelighed, vurderer fagudvalget, at det er relevant at definere et effektmål med en veldokumenteret korrelation til dødelighed (et surrogatmål), som kan benyttes, hvis OS-data ikke er tilgængelige eller fx for umodne til at blive anvendt i kategoriseringen af nintedanibs kliniske merværdi. I den sammenhæng betragter fagudvalget lungefunktionseffektmålet FVC-faldhastighed som et validt effektmål med en veldokumenteret korrelation til dødelighed, jf. nedenstående evidens. På baggrund af det vurderer fagudvalget, at lungefunktion er et kritisk effektmål ved vurderingen af nintedanibs værdi til patienter med SSc-ILS.

Fald i FVC bliver ofte anvendt som et primært effektmål i randomiserede studier vedr. lungefibrose, da det er veldokumenteret, at fald i FVC korrelerer med ILS-sygdomsprogression og dødelighed. I 2015 anerkendte det amerikanske Food and Drug Administration (FDA) på baggrund af seks kliniske studier med nintedanib og pirfenidon i IPF, at fald i FVC er et klinisk relevant effektmål på grund af dens korrelation med dødelighed [40]. Paterniti et al. kom frem til samme konklusion efter gennemgang af samme seks studier; jo højere FVC-faldhastigheden er, jo højere er risikoen for at dø[†] [41]. Ligeledes viste INPULSIS-studiet, hvor nintedanib blev undersøgt hos IPF-patienter, at patienter, der havde højere fald i FVC, var i højere risiko for at dø [42]. Adskillige analyser har vist, at det samme gør sig gældende for patienter med SSc-ILS, hvor fald i FVC korrelerer med lungefibroseprogression og dødelighed [6,19,21,23,27–30].

Fagudvalget ønsker effektmålet opgjort som forskel i årlig FVC-faldhastighed, målt som ml/år, og vurderer, at en forskel på 25 ml/år er klinisk relevant. Fagudvalget har ved fastsættelsen af den mindste klinisk relevante forskel taget udgangspunkt i, at FVC falder 15-25 ml/år hos lungeraske [43], og omkring 90 ml/år hos SSc-ILS-patienter [38]. Således vurderer fagudvalget, at en forskel på 25 ml/år vil være af klinisk betydning, set i lyset af FVC-faldhastigheden hos SSc-ILS-patienter.

Livskvalitet
Livskvalitet er et patientrelevant effektmål, som påvirkes i væsentlig grad af sygdomsprogressionen ved SSc-ILS [16], dvs. at patienterne vil opleve et kontinuerligt fald i livskvalitet, efterhånden som deres sygdom skrider frem. Da nintedanibs virkningsmekanisme potentielt bremser sygdomsprogressionen, er der en formodning om, at nintedanib kan bremse faldet i patienternes livskvalitet eller i bedste fald

[†] HR på 2,2 (95 % CI, 1,1–4,4) for patienter med faldhastighed ≥ 10 - 15 % og HR på 6,1 (95 % CI, 3,1–11,8) for patienter med faldhastighed ≥ 15 %, begge to sammenlignet med FVC < 5 % af forventet.

stabilisere patienternes livskvalitet. Fagudvalget betragter derfor livskvalitet som et kritisk effektmål i vurderingen af nintedanibs værdi til patienter med SSc-ILS.

Fagudvalget ønsker effektmålet opgjort med *King´s Brief Interstitial Lung Disease* (K-BILD)-spørgeskemaet, som er et sygdomsspecifikt spørgeskema til patienter med ILS. K-BILD-spørgeskemaet består af 15 elementer inden for 3 domæner; åndenød og aktiviteter, psykiske faktorer og symptomer fra brystkassen. Patienternes livskvalitet kan scores på en skala fra 0-100 i spørgeskemaet, hvor højere score repræsenterer bedre livskvalitet [44,45]. Et dansk studie har defineret, at en forværring på 2,7 point fra baseline er klinisk relevant [46]. Jf. forventningen om, at patienternes livskvalitet vil forværres uden behandling, vurderer fagudvalget, at det er klinisk relevant at undgå yderlige forværring i patienternes livskvalitet. Fagudvalget tilslutter sig dermed den ovenstående definition af MKRF og vurderer, at den mindste klinisk relevante forskel er 2,7 point i gennemsnitlig forværring i K-BILD-spørgeskemaet fra baseline. Estimatet begrænses af, at det tager udgangspunkt i en population af patienter med IPF. Der findes ikke studier, som vurderer mindste klinisk relevante forskel i K-BILD-score specifikt for patienter med sklerodermi, og fagudvalget vurderer, at resultatet fra det danske studie under disse forhold er ekstrapolerbart.

Hvis der ikke foreligger data fra K-BILD, foretrækker fagudvalget data fra *St George´s Respiratory Questionnaire* (SGRQ). En undersøgelse har vist, at den mindste klinisk relevante forskel i SGRQ er ca. 4 point [47].

3.2.2 Vigtige effektmål

Bivirkninger
Fagudvalget vægter effektmålet bivirkninger som vigtigt i vurderingen af nintedanibs værdi til patienter med SSc-ILS, fordi de både er generende for patienterne og kan forårsage pauser i behandlingen, hvilket kan forværre sygdommen.

Alvorlige bivirkninger
For randomiserede studier er forskellen i andelen af patienter, som oplever uønskede hændelser (serious adverse event (SAE) eller adverse event (AE)) i interventionsgruppen sammenlignet med komparatorgruppen, den andel af patienter, som må formodes at opleve bivirkninger. Fagudvalget ønsker effektmålet opgjort som andel patienter, der oplever mindst én alvorlig uønsket hændelse (SAE). Fagudvalget vurderer, at den mindste klinisk relevante forskel er 5 %-point.

Behandlingsophør grundet uønskede hændelser
Udover alvorlige bivirkninger betragter fagudvalget det som relevant at inddrage andel patienter, der ophører med behandling grundet uønskede hændelser, i vurderingen af effektmålet bivirkninger. Fagudvalget vurderer ligeledes her, at den mindste klinisk relevante forskel er 5 %-point.

Gennemgang af bivirkningsprofil

Fagudvalget ønsker en gennemgang af nintedanibs bivirkningsprofil for at vurdere bivirkningernes type, håndtérbarhed og reversibilitet. Ansøger bedes derfor levere bivirkningsdata fra lægemidlets produktresumé.

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Herudover kan data fra the Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (fx NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Hvis disse data er tilstrækkelige til at kunne vurdere lægemidlet, vil Medicinrådet som hovedregel ikke anvende andre data[‡]. Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data, der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets kriteriepapir.

Klinisk spørgsmål 1

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der findes et studie, SENSCIS-studiet, hvor nintedanib er sammenlignet direkte med placebo. Studiet er rapporteret i følgende publikationer:

- Distler O et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. N Engl J Med. 2019 Jun 27;380(26):2518-2528 [38]
- Distler O et al. Design of a randomised, placebo-controlled clinical trial of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SENSCIS). Clinical and experimental rheumatology. 2017;35 Suppl 106(4):75-81 [48]

Det er tilstrækkeligt datagrundlag til at besvare det kliniske spørgsmål. Ansøger skal derfor ikke søge efter yderligere data, men skal konsultere EMAs EPAR for det aktuelle lægemiddel.

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

5. Den endelige ansøgning

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (fx intention-to-treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jf. appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'-modeller og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.
- Narrative analyser.
- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier, og vurdér, hvorvidt resultaterne er sammenlignelige.

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

Sundhedsøkonomiske analyser
En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men er en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, fx behandlingslængde eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.
- Udfør følsomhedsanalyser, som belyser, hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

6. Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

Dosisreduktion
Den anbefalede dosis af nintedanib er 150 mg to gange dagligt, som kan reduceres til 100 mg to gange dagligt for patienter, der ikke tolererer den anbefalede dosis. Ansøger bedes bidrage med information om frekvens af patienter, der forventes at blive reduceret til 100 mg to gange dagligt. Derudover bedes ansøger belyse, om den reducerede dosis påvirker effekten af nintedanib.

Studiepopulationen i SENSCIS-studiet
Jf. det kliniske spørgsmål ønsker fagudvalget data på SSc-ILS-patienter, der progredierer på førstelinjebehandling med immunmodulerende lægemidler. Ansøger bedes redegøre for sammenligneligheden mellem studiepopulationen i SENSCIS-studiet og populationen defineret i det kliniske spørgsmål samt argumentere for betydningen af eventuelle afvigelser.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning fra Medicinrådet.

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende lungeemfysem og lungefibrose

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Jon Torgny Rostrup Wilke *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Jasmina Huremovic *Overlæge*	Region Nordjylland
Pernille Hauschildt *Ledende overlæge*	Region Midtjylland
Sofie Lock Johansson *Afdelingslæge*	Region Syddanmark
Christian Niels Meyer *Overlæge*	Region Sjælland
Helene Priemé* *Overlæge, lektor*	Region Hovedstaden
Peter Kjeldgaard *Overlæge*	Dansk Lungemedicinsk Selskab
Torkell Ellingsen *Specialeansvarlig overlæge, klinisk professor*	Dansk Reumatologisk Selskab
Allan Mikael Schrøder *Farmaceut, specialist i sygehusfarmaci*	Dansk Selskab for Sygehusapoteksledelse
Thomas Øhlenschlæger *Læge*	Dansk Selskab for Klinisk Farmakologi
Linda Marie Sevelsted Møller* *Læge*	Dansk Selskab for Gastroenterologi og Hepatologi
Finn Wulff Patient/patientrepræsentant	Danske Patienter

Sammensætning af fagudvalg	
Heinrich Andreasen Patient/patientrepræsentant	Danske Patienter

*Har ikke deltaget i vurderingen af nintedanib til SSc-ILS eller PF-ILS.

Medicinrådets sekretariat

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11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	25. januar 2021	Godkendt af Medicinrådet