Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende nintedanib til behandling af interstitiel lungesygdom med progredierende fibrose

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. nintedanib, version 1.0
2. Forhandlingsnotat fra Amgros vedr. nintedanib
3. Medicinrådets vurdering vedr. nintedanib til behandling af interstitiel lungesygdom med progredierende lungefibrose, 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 interstitiel lungesygdom med progredierende lungefibrose, version 1.0

Ansøger har ikke indsendt høringssvar i sagen.

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Nintedanib

Interstitiel lungesygdom med progredierende fibrose

Version 1.0

Om Medicinrådet

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

Dokumentets formål

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

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

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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
BSC	*Best supportive care*
DBL-1	*Database-lock 1*
DBL-2	*Database-lock 2*
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
FCV	Forceret vital kapacitet
IPF	Idiopatisk pulmonal fibrose
HRCT	Højopløsnings-CT-scanning
OS	Samlet overlevelse *(overall survival)*
PF-ILS	Interstitiel lungesygdom med progredierende fibrose
SAIP	Sygehusapotekernes indkøbspris
TTFAE	Tid til første akutte exacerbation *(time to first acute exacerbation)*
TTD	Tid til behandlingsophør *(time to treatment discontinuation)*

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for nintedanib ca. [redacted] DKK pr. patient sammenlignet med *best supportive care* (BSC). Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 576.000 DKK pr. patient.

De inkrementelle omkostninger er hovedsageligt drevet af lægemiddelomkostninger for nintedanib.

Fagudvalget vurderede, at OS-kurven for nintedanib sandsynligvis ville befinde sig mellem de kurver, som var blevet ekstrapoleret med hhv. den log-logistiske funktion og Weibull-funktionen. I Medicinrådets hovedanalyse blev Weibull-funktionen anvendt. De inkrementelle resultater reduceres med ca. [redacted] DKK, når den log-logistiske funktion anvendes til ekstrapolering af OS-kurven for både nintedanib og BSC. Når TTD-data ekstrapoleres med andre parametriske funktioner, end funktionen der er anvendt i hovedanalysen, øges de inkrementelle omkostninger med ca. [redacted] kr. patient. Såfremt der antages at være ens effekt mellem nintedanib og komparator, bliver de inkrementelle resultater ca. [redacted] kr. pr. patient.

Jf. vurderingsrapporten har fagudvalget foreslået en række stopkriterier for behandling med nintedanib. På baggrund af dette har Medicinrådet anvendt et stopkriterie i den økonomiske models hovedanalyse svarende til FVC-fald > 10 % over 1 år. Medicinrådet har også udført en følsomhedsanalyse hvor dette stopkriterie udelades. Den viser, at antagelsen om dette stopkriterie ikke er af betydning for analysens resultat. Det har ikke været muligt at inkorporere samtlige af fagudvalgets foreslåede stopkriterier direkte i modellen, herunder at behandling med nintedanib stoppes, såfremt patienten ikke ønsker behandling mere. Et stopkriterie som dette forventes dog at være opfanget i *time to treatment discontinuation*(TTD)-data fra INBUILD-studiet.

En væsentlig usikkerhed i modellen er den anvendte dosis. I modellen er anvendt en simpel tilgang vedr. dosis, hvor en konstant andel vil blive dosisreduceret baseret på fagudvalgets erfaring med nintedanib til patienter med idiopatisk pulmonal fibrose (IPF). Det er dog usikkert, om det samme er tilfældet for patienter med PF-ILS.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af nintedanib som mulig standardbehandling vil være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 36,4 mio. DKK i det femte år.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af nintedanib som mulig standardbehandling på danske hospitaler til interstitiel lungesygdom med progredierende fibrose (PF-ILS).

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

3.1 Patientpopulation

Interstitielle lungesygdomme (ILS) er en heterogen gruppe af lungesygdomme, hvor det mest almindelige symptom er åndenød (dyspnø). Årsagen til ILS er forskellig og kan både skyldes miljøpåvirkning, underliggende autoimmun sygdom eller ukendte årsager. ILS kan udvikles som følge af inflammation med efterfølgende fibrosedannelse (arvævsdannelse) eller alene ved fibrose [1–3]. Der findes mange typer af ILS, hvoraf en af de mest undersøgte er idiopatisk pulmonal fibrose (IPF). IPF er kendetegnet ved irreversibel udvikling af progredierende lungefibrose med et radiologisk-patologisk mønster kaldet *usual interstitial pneumonia* (UIP), som diagnosticeres ved enten HRCT-scanning eller histologisk på lungevævsbiopsi [4–6].

Ud over IPF kan andre undertyper af ILS også medføre progredierende lungefibrose, selvom de ikke kan kategoriseres som værende IPF. Disse bliver samlet kaldt for PF-ILS. PF-ILS er en heterogen gruppe af sygdomme med varierende grad af lungefibrose og inflammation, som medfører gradvis forværring af respiratoriske symptomer, nedsat lungefunktion og tiltagende fibrose på HRCT-scanning [6–8]. De patogenetiske mekanismer, det kliniske sygdomsbillede og patienternes prognose er på mange måder sammenlignelig mellem PF-ILS og IPF [9–12].

Det skønnes, at ca. 60-80 nye patienter med PF-ILS årligt potentielt kan være kandidater til behandling med nintedanib.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

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

Klinisk spørgsmål 1:

Hvilken værdi har nintedanib sammenlignet med placebo for patienter med interstitiel lungesygdom med progredierende fibrose?

4. Vurdering af den sundhedsøkonomiske analyse

Ansøger har indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for nintedanib sammenlignet med *best supportive care* (BSC). Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

Sammenligningen med BSC er lavet på baggrund af data fra det randomiserede fase III-studie INBUILD [13]. I INBUILD-studiet blev nintedanib sammenlignet med placebo hos patienter med PF-ILS, hvor > 10 % af patienternes lungevolumen var påvirket af fibrose, påvist ved højopløsnings-CT-scanning (HRCT). Det primære endepunkt i INBUILD var den årlige faldhastighed i forceret vital kapacitet (FVC), vurderet over 52 uger. INBUILD-studiet består af to dele: del A, som varede 52 uger, og del B, som fortsatte efter uge 52, og indtil alle patienter var færdige med studiets del A. I del B var patienterne fortsat randomiseret til blindet behandling med enten placebo eller nintedanib. Ansøger har udarbejdet post-hoc-analyser af data på patientniveau for samlet overlevelse (OS), tid til første akutte eksacerbation (TTFAE) og tid til behandlingsophør (TTD). I den sundhedsøkonomiske sammenligning med BSC anvendes studiets primære effektmål – årlig FVC-faldhastighed – og det antages, at placebo er en proxy for BSC.

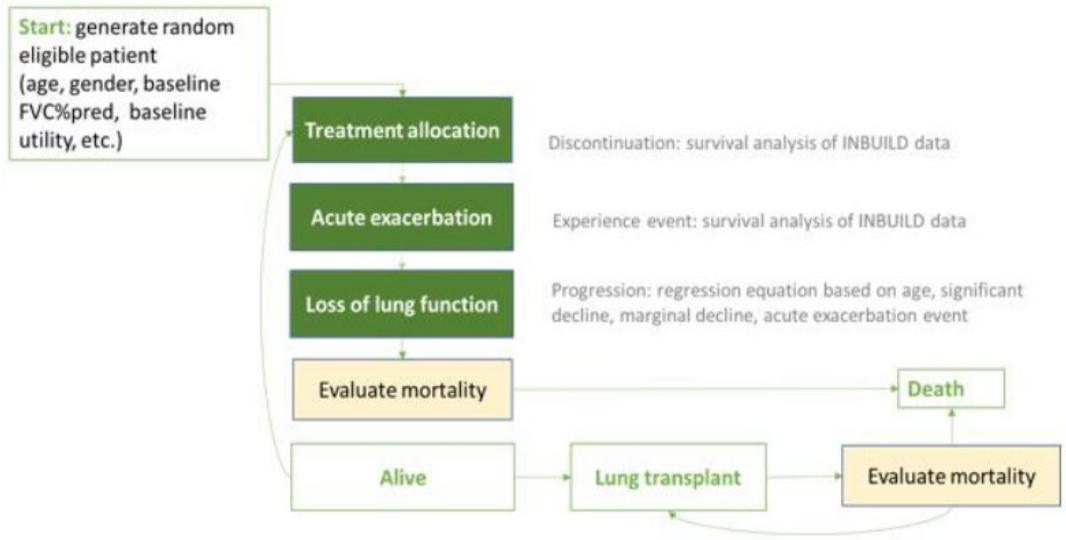
Ansøger har i udarbejdelsen af sammenligningen konsulteret to danske kliniske eksperter: Jesper Rømhild Davidsen, Syddansk Center for Interstitielle Sygdomme, Odense Universitetshospital, og Elisabeth Bendstrup, Afdeling for Respiratoriske Sygdomme og Allergi, Aarhus Universitetshospital.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en individbaseret simuleringsmodel til at estimere omkostningerne forbundet med behandlingen med nintedanib og BSC. I individbaserede simuleringsmodeller modelleres et individuelt patientforløb for hver enkelt patient, hvorefter der tages et gennemsnit af både effekt og omkostninger, estimeret på tværs af et tilstrækkeligt antal patienter. Dette afviger fra de ofte anvendte kohortemodeller, hvor effekt og omkostninger bliver modelleret som en kohorte, dvs. gennemsnitsestimat i kohortemodeller. Ansøger anvender en individbaseret simuleringsmodel fremfor en kohortemodel for at opfange den heterogenitet og kompleksitet, der er blandt PF-ILS-patienters sygdomsprofiler. Ansøgers model er illustreret i Figur 1.

Ansøger modellerer 500 individuelle patientforløb. Hver patient trækkes med tilbagelægning tilfældigt fra patientpopulationen i INBUILD-studiet. På denne måde opretholdes randomiseringen fra INBUILD-studiet. Ansøger har anvendt et *fixed seed*-nummer til at udvælge patienter, hvilket betyder, at de samme 500 patienter bliver trukket, hver gang

modellen bliver simuleret. Men ansøger har også inkluderet muligheden for at anvende et ikke-*fixed seed*-nummer, så forskellige patienter trækkes hver gang.



Figur 1. Strukturen i den sundhedsøkonomiske model

Ved hver simulering genereres en tilfældig patient ud fra baselinekarakteristika fra INBUILD-studiet, herunder alder, køn m.v., hvorefter patienterne allokeres til behandling med enten nintedanib eller BSC. Til at afspejle sygdomsforløbet for patienterne med PF-ILS har ansøger bygget modellen, så patienterne kan opleve forskellige typer af hændelser i løbet af simuleringen. Disse hændelser er opsummeret i Tabel 1, hvori det ligeledes fremgår, hvilke datainputs og metoder der er anvendt til at modellere hændelserne, samt hvilke antagelser ansøger har gjort sig vedr. hver hændelse.

Tabel 1. Mulige events, som patienterne kan opleve i modellen

Event	Datainputs og metode	Antagelser i ansøgers hovedanalyse
Akut eksacerbation	Overlevelsesanalyse af TTFAE-data fra INBUILD-studiet	• En akut eksacerbation medfører et permanent fald i % af forventet FVC-normalværdi (fremadrettet nævnt som FVC-%), hvilket betyder, at patienterne ikke kan returnere til deres respektive præ-eksacerbations FVC-niveauer. • Patienterne kan kun opleve én akut eksacerbation[1] (i modellen er det muligt at vælge op til tre eksacerbationer). • Sandsynligheden for at opleve en akut eksacerbation er konstant og dermed ikke afhængig af tidligere tilfælde af akutte eksacerbationer.

Event	Datainputs og metode	Antagelser i ansøgers hovedanalyse
Sygdomsprogression (fald i lungefunktion angivet som FVC-%)	Regressionsanalyse (*linear mixed-effect*), hvor regressionskoefficienterne for tab af lungefunktion er baseret på data fra del A af INBUILD. Regressionsanalysen anvendes til at prædikere patienternes fald i % af forventet FVC-normalværdi.	• I modellen defineres progression i FVC-% som et fald på 10 procentpoint fra baselineværdien. • Hvis patienten oplever fald i FVC-%, kan patienten ikke opnå en helbredstilstand med bedre/højere FVC %-niveau og dermed forbedret lungefunktion igen.
Behandlingsophør	Overlevelsesanalyse af TTD-data fra INBUILD-studiet	-
Mortalitet	Overlevelsesanalyse af OS-data fra INBUILD-studiet	I modellen kan patienterne dø ad to veje: • På ethvert tidspunkt baseret på OS-data. • Ved progression til FVC-% ≤ 40 %, idet dette niveau vurderes at være et uholdbart lungefunktionsniveau.
Lungetransplantation	*Eventet er ikke inkluderet i ansøgers hovedanalyse.*	En engangsomkostning for lungetransplantation blev inkluderet i simuleringen, hvis patienten oplevede sygdomsprogression (fald i lungefunktion) og var under 65 år.

[1] Antagelsen er baseret på, at de kliniske eksperter, som ansøger har konsulteret, vurderer, at akutte eksacerbationer er meget sjældne ved patienter med interstitielle lungesygdomme.

Ansøger modellerer FVC-% som en kontinueret variabel, som varierer over tid, og hver patient vil have en unik udvikling af FVC-%, da forløbet afhænger af den initiale patientkarakteristik. Ansøger estimerer det forventede fald i FVC-% over tid ved at fitte en *linear mixed effect*-regression til data fra INBUILD-studiet. Ansøger er startet med en *saturated*-model og har efterfølgende iterativt elimineret insignifikante led, hvilket resulterer i forskellige modeller. Ansøgers endelige model er præsenteret nedenfor. Ansøger har valgt en *linear mixed*-regression, da det tillader *fixed effects* for kovariater, der ikke varierer over tid såsom behandling med nintedanib, køn og etnicitet, men tillader samtidig heterogenitet mellem patienternes FVC-%-progression ved at inkludere *random effects.* Ansøger antager dermed, at FVC-%-progression er konstant over tid. De regressioner, som ansøger har anvendt til at beskrive fald i FVC-%, er for hhv. BSC og nintedanib defineret som:

$$FVC_{it} = \beta_0 + \beta_1 * FVCBase_i + \beta_2 * AGE_i + \beta_3 * PGGR1Marginal_i + \beta_4 * PGGR1Worsening_i + \beta_5 * AcuteExacerbation_{it} + \beta_6 * (AGE_i * AnalysisYear_t) + \beta_7 * (PGGR1Marginal_i) * AnalysisYear_t) + \beta_8 * (PGGR1Worsening_i * AnalysisYear_t)$$

$$FVC_{it} = \beta_0 + \beta_1 * FVCBase_i + \beta_2 * AGE_i + \beta_3 * AcuteExacerbation_{it} + \beta_4 * (AGE_o * AnalysisYear_t)$$

FVCBase: baseline FVC-værdi, AGE: alder, PGGR1Marginal: marginalt fald i FVC-% (≥ 5 - < 10%) kombineret med forværring af respiratoriske symptomer eller stigende omfang af fibrotiske forandringer ved billededannelse af brystet, PGGR1Worsening: klinisk signifikant fald i FVC-% (≥ 10 %), AcuteExacerbation: akut exacerbation, AnalysisYear: år i analysen.

Med denne regression estimerer ansøger progression i FVC-% for hver af de 500 patienter, der simuleres i modellen.

Medicinrådets vurdering af ansøgers model
Medicinrådet accepterer ansøgers anvendelse af en individbaseret simuleringsmodel til at estimere omkostningerne forbundet med nintedanib og BSC. Medicinrådet vurderer, at antallet af simuleringer (500) er tilstrækkeligt til at udjævne stokastiske usikkerheder.

Fagudvalget vurderer, at ansøgers antagelser for hændelserne, jf. Tabel 1, overordnet er rimelige. Vedr. akutte eksacerbationer påpeger fagudvalget, at PF-ILS-patienter godt kan opleve mere end én akut eksacerbation, men at antagelsen om én akut eksacerbation pr. patient er rimelig, da sandsynligheden for, at en patient oplever flere i deres levetid, er meget lav. Endvidere vurderer fagudvalget umiddelbart, at sandsynligheden for en akut eksacerbation er højere for patienter, der tidligere har oplevet en akut eksacerbation, end hvis patienten oplevede hændelsen for første gang. Fagudvalget kan dog ikke kvantitativt præcisere dette nærmere, og grundet den lave sandsynlighed for første akutte eksacerbation (og endnu lavere sandsynlighed for to eller flere eksacerbationer) accepterer fagudvalget antagelsen.

Medicinrådet vurderer ligesom ansøger, at progression i FVC-% både afhænger af individuelle patientkarakteristika, og at progression i FVC-% kan være heterogent. Derfor vurderer Medicinrådet også, at en *mixed linear*-regression estimeret baseret på INBUILD-studiet kan være rimelig til at beskrive progression i FVC-%.

Medicinrådet accepterer ansøgers tilgang vedr. ansøgers model.

4.1.2 Antagelser vedr. ekstrapolering af forløbsdata

Ansøger har for både nintedanib og BSC ekstrapoleret Kaplan-Meier (KM) data for OS, TTFAE og TTD fra INBUILD-studiet. Dette er nødvendigt, da opfølgningen i INBUILD er kortere end den anvendte tidshorisont i analysen. Ekstrapoleringerne er udført på data fra del A og varierende mængder af data fra del B af INBUILD-studiet.

Forud for modelleringen af de ekstrapolerede overlevelseskurver har ansøger – vha. statistiske analyser og visuel inspektion af log-kumulative plots – vurderet, hvorvidt antagelsen om proportionale hazards (PH) for OS, TTFAE og TTD var overholdt mellem de to behandlingsarme. Testene for PH-antagelsen blev udarbejdet på basis af data fra *database-lock 2* (DBL-2, data fra studiets del B). Testene viser, at der ikke er statistisk evidens for, at PH-antagelsen er brudt for OS og TTFAE, men at PH-antagelsen muligvis er brudt for TTD. Ved visuel inspektion krydser behandlingsarmenes kurver for OS og TTD, mens de ikke krydser for TTFAE. Idet antagelsen om PH ikke med overbevisende dokumentation

er overholdt for alle effektmål, har ansøger valgt at modellere separate kurver for hhv. nintedanib og BSC for at opnå metodisk konsistens på tværs af analysen.

Samlet overlevelse (OS)

Baseret på en statistisk og klinisk vurdering af de tilgængelige kurver har ansøger valgt at ekstrapolere OS-data med en Weibull-funktion for både nintedanib og placebo, se Figur 2 og Figur 3.

Figur 2. Ekstrapolerede kurver af OS-data for nintedanib

Figur 3. Ekstrapolerede kurver af OS-data for BSC

Fra et isoleret statistisk perspektiv er AIC- og BIC-værdierne for nintedanib lavest ved anvendelse af hhv. Gompertz- og den eksponentielle funktion. Ansøger pointerer dog, at de

statistiske værdier for alle funktionerne på nær én ligger så tæt på hinanden, at det ikke er tilstrækkeligt at basere valget af funktion på disse. På baggrund af dette har ansøger bl.a. også gjort brug af eksterne langtidsdata fra studiet INPULSIS-ON til at validere plausibiliteten af de ekstrapolerede kurver. INPULSIS-ON er et opfølgende studie af INPULSIS, hvori effekten og sikkerheden af nintedanib blev sammenlignet med placebo hos IPF-patienter. Hvis patienterne gennemførte en 52 ugers behandlingsperiode, blev de efterfølgende tilbudt at modtage *open-label*-behandling med nintedanib i INPULSIS-ON-studiet.

Ansøger har kombineret data fra INPULSIS og INPULSIS-ON til ét datasæt/én kurve og sammenholdt denne kurve med de ekstrapolerede OS-kurver for nintedanib, se Figur 4.

Figur 4. Ekstrapolerede OS-kurver for nintedanib og det kombinerede datasæt fra INPULSIS og INPULSIS-ON (rød kurve). Den lange hale af IPF-kurven skyldes censurering af en mindre gruppe af patienter. [redacted].

På baggrund af visuel inspektion af Figur 4 vurderer ansøger, at kurverne for Weibull-funktionen og den log-logistiske funktion passer bedst på det observerede IPF-data, mens de øvrige funktioner synes enten at over- eller underestimere OS. Ansøger påpeger, at den bagvedliggende hazard-antagelse for Weibull-funktionen stemmer overens med, at patienternes risiko for at dø stiger over tid. De danske eksperter, som ansøger har konsulteret, vurderede, at de mest klinisk plausible kurver var Weibull, Gompertz og den generaliserede gamma-kurve.

Ansøger anvender Weibull-funktionen til at ekstrapolere OS-data for nintedanib og placebo i hovedanalysen og udarbejder en følsomhedsanalyse, hvor den log-logistiske funktion anvendes.

Tid til akut eksacerbation (TTFAE)

Ansøger har valgt at ekstrapolere TTFAE-data med den eksponentielle funktion for både nintedanib og placebo, se Figur 5 og Figur 6.

Figur 5. Ekstrapolerede kurver af TTFAE-data for nintedanib

Figur 6. Ekstrapolerede kurver af TTFAE-data for BSC

De eksperter, som ansøger har konsulteret, vurderer ved visuel inspektion, at den log-normale kurve og den generaliserede gamma-kurve er mest klinisk og biologisk plausibel.

Det understreges dog af de kliniske eksperter, at det er svært at udpege den mest plausible kurve, idet akutte eksacerbationer er meget sjældne blandt PF-ILS-patienter, hvorfor der er mangel på evidens til at understøtte kurvernes forløb. Ansøger har derfor valgt den kurve, der har det bedste statistiske fit på det observerede TTFAE-data fra INBULD.

Tid til behandlingsophør (TTD)
Ansøger har valgt at ekstrapolere TTD-data med en eksponentiel funktion for nintedanib, se Figur 7.

Figur 7. Ekstrapolerede kurver af TTD-data for nintedanib

Ansøger påpeger, at den log-normale funktion har de laveste AIC- og BIC-værdier, men at kurven ved visuel inspektion ikke nærmer sig 0, hvorfor denne funktion ikke anvendes i ansøgers hovedanalyse. Ansøger påpeger, at IPF-data fra INPULSIS- og INPULSIS-on-studierne viser, at patienterne modtog nintedanib (mediant) i 44,7 måneder, svarende til 3,7 år. Baseret på dette vurderer ansøger, at den eksponentielle funktion genererer den mest klinisk plausible ekstrapolerede TTFAE-kurve, på trods af at denne kurve har de højeste AIC- og BIC-værdier. Eksperterne, som ansøger har konsulteret, vurderer, at den eksponentielle kurve med en median TTD på ca. 4 år er den mest klinisk plausible kurve.

Medicinrådets vurdering af ansøgers modelantagelser vedr. ekstrapolering af forløbsdata
Fagudvalget vurderer, at de ekstrapolerede OS-kurver med Weibull-funktionen umiddelbart er realistiske for forløbet med både nintedanib og BSC, men fremhæver på samme tid den generelle usikkerhed ved at ekstrapolere forløbsdata, idet data er sparsomt. Baseret på fagudvalgets erfaring med patientgruppen burde OS-kurven for BSC sandsynligvis befinde sig mellem de to OS-kurver, der er ekstrapoleret med hhv. Weibull-funktionen og den log-logistiske funktion, se Figur 3. Fagudvalget foreslår, at der udarbejdes en følsomhedsanalyse, hvor den log-logistiske funktion anvendes til at ekstrapolere OS-KM-data fra INBUILD-studiet for både nintedanib og BSC.

Vedr. ekstrapolering af TTFAE-data for både nintedanib og BSC vurderer fagudvalget, at risikoen for en akut eksacerbation stiger med tiden, hvorfor hazard-funktionen også vil være stigende. Dette er ikke foreneligt med ekstrapolering med den eksponentielle funktion, hvorfor fagudvalget vurderer, at det observerede TTFAE-data bør ekstrapoleres med Weibull-funktionen.

Fagudvalget påpeger, at patienterne i dansk klinisk praksis stopper i behandling med nintedanib grundet komorbiditet og bivirkninger, og at en konstant hazard-funktion kan være rimelig til at beskrive disse forhold. Fagudvalget understreger, at denne antagelse er baseret på klinisk erfaring og ikke på baggrund af tilgængeligt data. Idet den bagvedliggende hazard-antagelse for den eksponentielle-funktion er i overensstemmelse med fagudvalgets vurdering, anvendes denne funktion i Medicinrådets hovedanalyse.

De simulerede mediane estimater for tid i behandling og tid til hhv. første akutte eksacerbation og død fremgår af Tabel 2. I tabellen ses det, at tiden til død er kortere end tiden til at opleve en akut eksacerbation. Dette skyldes, at en akut eksacerbation er en sjælden hændelse, hvorfor en del patienter vil dø uden at opleve en eksacerbation.

Tabel 2. Simuleret median tid til hhv. behandlingsophør, første akutte eksacerbation og død

Behandling	Behandlingsvarighed [år]	TTFAE [år]	OS [år]
Nintedanib	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]

*Tid til første akutte eksacerbation (TTFAE), samlet overlevelse (OS).

De gennemsnitlige estimater for behandlingsvarigheden og hhv. tid til første akutte eksacerbation og død fremgår af Tabel 3.

Tabel 3. Gennemsnitlig tid i behandling, tid til første akutte eksacerbation og samlet overlevelse

Behandling	Behandlingsvarighed [år]	TTFAE [år]	OS [år]
Nintedanib	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]

*Tid til første akutte eksacerbation (TTFAE), samlet overlevelse (OS).

Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser, men vælger at ekstrapolere TTFAE-data med Weibull-funktionen.

4.1.3 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 25 år og en cykluslængde på 30 dage. Ansøger har ikke anvendt *half-cycle correction*.

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

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet accepterer ansøgers valgte tidshorisont.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af nintedanib sammenlignet med BSC. Ansøger har inkluderet lægemiddelomkostninger, kommunale omkostninger, hospitalsomkostninger, terminalomkostninger og patientomkostninger.

Ansøger har ikke inkluderet omkostninger forbundet med efterfølgende behandling, idet der i øjeblikket ikke findes nogen alternativer for efterfølgende behandlingslinjer. Endvidere har ansøger ikke inkluderet omkostninger associeret med lungetransplantationer, idet ansøger ikke er i besiddelse af data vedr. mortalitet, progression og ressourceforbrug forbundet med de patienter, der har modtaget en lungetransplantation. Ansøger har dog modelleret muligheden for, at omkostningerne forbundet med lungetransplantationer kan inkluderes i modellen.

Ansøger har anvendt en post-hoc-analyse af INBUILD-studiet til at estimere ressourceforbruget samt konsulteret danske kliniske eksperter.

4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP) for nintedanib. Ansøger har ikke inkluderet lægemiddelomkostninger forbundet med BSC. Doseringen af nintedanib, som er anvendt i ansøgers hovedanalyse, er hentet i det respektive produktresumé (SPC) og stemmer overnes med lægemiddeldosis i Medicinrådets protokol.

- Nintedanib: 150 mg blød kapsel to gange dagligt.

Ansøger antager, at der ikke vil være dosisreduktion eller dosisafbrydelse med nintedanib, idet det i SPC'et for nintedanib står nævnt, at disse dosisforhold kun er relevante ved håndtering af bivirkninger såsom diarre, opkast og/eller kvalme, der fortsat opstår på trods af særskilt behandling. Ansøger vurderer, at det er acceptabelt at antage, at dette ikke var tilfældet i INBUILD-studiet, hvor sværhedsgraden af disse bivirkninger var af mild til moderat grad.

I modellen er det muligt at tilvælge, at en andel af patienterne modtager en reduceret dosis af nintedanib (100 mg) to gange dagligt.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 4.

Tabel 4. Anvendte lægemiddelpriser, SAIP (januar 2022)

Lægemiddel	Styrke	Mg/dosis	Pakningsstørrelse	Pris [DKK]	Kilde
Nintedanib	150 mg	150 mg	60 stk.	[redacted]	Amgros
	100 mg	100 mg	60 stk.	[redacted]	Amgros

Fagudvalget vurderer ud fra erfaring med nintedanib, at ca. 50 % af patienterne vil blive dosisreduceret til 100 mg to gange om dagen, hvorfor dette justeres i Medicinrådets hovedanalyse. Derudover foreslår fagudvalget, at behandlingen med nintedanib bør stoppes jf. de definerede stopkriterier i vurderingsrapporten. På baggrund af dette vælger Medicinrådet i hovedanalysen at anvende et stopkriterie for behandling med nintedanib på FVC-fald > 10 % over 1 år.

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger, men vælger i hovedanalysen at antage, at 50 % af patienterne dosisreduceres med nintedanib, og at anvende et stopkriterie for behandling med nintedanib på FVC-fald > 10 % over 1 år.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Ansøger har ikke inkluderet omkostninger til administration af lægemidler.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger.

Monitoreringsomkostninger

Ansøger har inkluderet omkostninger til monitorering og antager, at patienterne bliver monitoreret tre gange om året på hospitalet – uanset FVC % – og takserer disse besøg med en DRG-takst for et ambulant besøg. De kliniske eksperter, som ansøger har konsulteret, vurderer, at patienterne er i ambulatoriet ca. tre gange årligt. Foruden monitoreringsbesøgene antager ansøger, at patienterne vil blive behandlet i ambulatoriet, hvis de måtte opleve en akut eksacerbation. Denne monitoreringsomkostning takseres ligeledes med en DRG-takst for ambulant besøg. Desuden har ansøger inkluderet omkostninger til løbende monitorering hos egen læge og omkostninger til fysioterapi og ergoterapi. Ansøger antager, at frekvenserne vedr. besøg hos egen læge, fysioterapeut og ergoterapeut ikke direkte afhænger af behandling og FVC-%. Ansøger takserer omkostninger til egen læge jf. overenskomst for almen praktiserende læger, mens ansøger anvender Medicinrådets værdisætning af enhedsomkostninger til at taksere omkostninger ved fysioterapeut og ergoterapeut. Ansøger antager, at monitorering hos egen læge for patienter i behandling med nintedanib inkluderer monitorering af leverenzymer i form af en blodprøve, og takserer denne med 50,11 DKK.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
Fagudvalget vurderer, at patienterne vil blive monitoreret på hospitalet hyppigere de første 6 måneder, hvorefter fagudvalget forventer, at patienterne vil blive monitoreret

hver 3. måned. For at undgå unødvendig kompleksitet antages det, at patienter monitoreres hver 3. måned fra start. For de øvrige monitoreringsomkostninger vurderer Medicinrådet, at de er rimelige. Medicinrådet vurderer, at omkostninger til egen læge, fysioterapeut og ergoterapeut vil blive afholdt kommunalt.

De anvendte sandsynligheder for ambulant besøg og besøg hos hhv. praktiserende læge, fysioterapeut og ergoterapeut, jf. FVC-%-grupperne, fremgår af Tabel 5.

Tabel 5. Sandsynligheder for ambulant besøg og besøg hos praktiserende læge, fysioterapeut og ergoterapeut

FVC-%-gruppe	Ambulant monitorering		Egen læge		Fysioterapeut		Ergoterapeut	
	Cyklussandsynlighed [%]	Takst [DKK]	Cyklussandsynlighed [%]	Takst [DKK]	Årlig sandsynlighed [%]	Takst [DKK]	Årlig sandsynlighed [%]	Takst [DKK]
> 110	[redacted]	1.732	[redacted]	146,25	[redacted]	512	[redacted]	508
100-110	[redacted]	1.732	[redacted]	146,25	[redacted]	512	[redacted]	508
90-100	[redacted]	1.732	[redacted]	146,25	[redacted]	512	[redacted]	508
80-90	[redacted]	1.732	[redacted]	146,25	[redacted]	512	[redacted]	508
70-80	[redacted]	1.732	[redacted]	146,25	[redacted]	512	[redacted]	508
60-70	[redacted]	1.732	[redacted]	146,25	[redacted]	512	[redacted]	508
50-60	[redacted]	1.732	[redacted]	146,25	[redacted]	512	[redacted]	508
< 50	[redacted]	1.732	[redacted]	146,25	[redacted]	512	[redacted]	508

*Medicinrådet bemærker, at ovenstående sandsynligheder muligvis ikke afspejler et realistisk billede af det reelle ressourceforbrug i dansk klinisk praksis, idet det jf. vurderingsrapporten vurderes at fald i FVC er tæt korreleret med død. Såfremt ressourceforbruget skulle afspejle denne kliniske vurdering af korrelationen mellem FVC og dødelighed, vurderes det at cyklussandsynligheden for ressourceforbruget burde være højere for de patienter, der har en lav FVC-%. Idet INBUILD-studiet er det eneste data for ressourceforbruget, som efter sekretariatets kendskab er til rådighed, vælger Medicinrådet at acceptere tilgangen.

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger, men justerer det ambulante monitoreringsbesøg til hver 3. måned.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med bivirkninger associeret med både nintedanib og BSC, hvis følgende kriterier var opfyldt vedr. bivirkningen: 1) incidens > 10 % i én behandlingsarm, 2) behandlingsrelateret, og 3) incidens i behandlingsarmen var minimum 1,5 gange højere end i kontrolarmen. For nintedanib og BSC har ansøger benyttet de rapporterede bivirkningsrater fra INBUILD-studiet. I den økonomiske sammenligning antager ansøger, at bivirkningsfrekvenserne for placebo kan anvendes som proxy til at estimere bivirkningsomkostningerne forbundet med BSC.

Ansøger har udregnet cyklussandsynligheder for at opleve de respektive bivirkninger baseret på antal patienter i hver behandlingsarm og de observerede events af hver bivirkning fra INBUILD-studiet.

Ressourcerne brugt i forbindelse med de forskellige bivirkninger har ansøger baseret på et besøg hos praktiserende læge, jf. Medicinrådets *Katalog for værdisætning af enheds-omkostninger*.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger
Fagudvalget vurderer, at det ordinerende ambulatorium varetager håndtering af bivirkninger, hvorfor sekretariatet justerer denne omkostning til værende en generel DRG-takst (04MA98). Denne ændring vurderes at have minimal betydning for analysens inkrementelle resultat.

Medicinrådet accepterer ansøgers tilgang til estimering af bivirkningsomkostninger. Bivirkningsfrekvenser og anvendte takster kan ses i Tabel 6.

Tabel 6. Rapporterede bivirkningsfrekvenser fra INBUILD-studiet og cyklussandsynligheder ved behandling med nintedanib og BSC samt enhedsomkostninger for bivirkningerne

	Nintedanib		BSC			
	Frekvens (INBUILD) [%]	Cyklussand-synlighed [%]	Frekvens (IN-BUILD) [%]	Cyklussand-synlighed [%]	DRG-kode	Takst [DKK]
Diarré	59,0	7,1	17,8	1,6	04MA98	1.732
Kvalme	23,8	2,2	5,7	0,5	04MA98	1.732
Opkast	12,3	1,1	2,1	0,2	04MA98	1.732
Øget ala-nin-ami-notransfe-rase	10,8	0,9	2,4	0,2	-	0
Nedsat ap-petit	11,1	1,0	3,0	0,3	04MA98	1.732

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men ændrer enhedsomkostningen for håndtering af bivirkninger til en generel DRG-takst.

Øvrige hospitalsomkostninger

Ansøger har yderligere inkluderet omkostninger i forbindelse med indlæggelse og besøg på akutmodtagelsen. Ansøger anvender frekvenserne for indlægger og besøg på akutmodtagelsen fra INBUILD-studiet. Ansøger antager, at disse afhænger af FVC-% og ikke direkte af behandling, og vælger derfor at stratificere frekvenserne afhængigt af FVC-%. Disse frekvenser bliver omregnet til en månedlig sandsynlighed for indlæggelse eller besøg på akutmodtagelsen. Ansøger takserer omkostningerne til indlæggelser som et vægtet gennemsnit af omkostningerne ved en generel 10-dages indlæggelse (DRG 2021 04MA17), intensiv indlæggelse (DRG 2021 26MP11), mekanisk ventilation (DRG 2021 04MP04), 2-dages indlæggelse på akutmodtagelse (DRG 2021 04MA17) samt omkostningerne til ambulancekørsel, hvilket giver en omkostning på 57.281 DKK. Ansøger takserer

omkostninger til et besøg på akutmodtagelsen med omkostningerne for et ambulant besøg (DRG 2021 04MA98) og for ambulancekørsel [14]. Desuden har ansøger inkluderet omkostninger til iltbehandling baseret på en DRG-takst (DRG 2021 04MP04) kombineret med antagelser om et prædefineret antal kontaktdage (54 dage) og gennemsnitligt timeantal, hvori patienterne modtager oxygenbehandling. Slutteligt har ansøger inkluderet terminalomkostninger og takseret disse med en DRG-takst (DRG 2021 04MA17), men ansøger har ikke redegjort for, hvad disse indeholder.

Medicinrådets vurdering af ansøgers antagelser vedr. øvrige hospitalsomkostninger
Medicinrådet accepterer ansøgers tilgang til estimering af omkostninger forbundet med indlæggelse og ambulante besøg, men accepterer ikke tilgangen til at estimere omkostningerne forbundet med terminal pleje, idet ansøger ikke tilstrækkeligt har dokumenteret det konkrete ressourceforbrug i dansk kontekst, som DRG-taksten dækker over. Endvidere accepterer Medicinrådet ikke ansøgers tilgang vedr. estimering af omkostninger forbundet med oxygenterapi. Det skyldes, at det ikke er metodisk acceptabelt at manipulere med DRG-takster ved at omdanne disse til f.eks. timeomkostninger.

De årlige sandsynligheder for indlæggelse og besøg på akutmodtagelsen pr. FVC-%-gruppe samt enhedsomkostningerne fremgår af Tabel 7.

Tabel 7. Cyklussandsynligheder for hhv. indlæggelse og besøg på akutmodtagelse, jf. INBUILD-studiet*

FVC-%-gruppe	Indlæggelse		Akutmodtagelse	
	Cyklussandsynlighed [%]	Takst [DKK]	Cyklussandsynlighed [%]	Takst [DKK]
> 110	[redacted]	57.281	[redacted]	2.039
100-110	[redacted]	57.281	[redacted]	2.039
90-100	[redacted]	57.281	[redacted]	2.039
80-90	[redacted]	57.281	[redacted]	2.039
70-80	[redacted]	57.281	[redacted]	2.039
60-70	[redacted]	57.281	[redacted]	2.039
50-60	[redacted]	57.281	[redacted]	2.039
< 50	[redacted]	57.281	[redacted]	2.039

*Medicinrådet bemærker, at ovenstående sandsynligheder muligvis ikke afspejler et realistisk billede af det reelle ressourceforbrug i dansk klinisk praksis, idet det jf. vurderingsrapporten vurderes at fald i FVC er tæt korreleret med død. Såfremt ressourceforbruget skulle afspejle denne kliniske vurdering af korrelationen mellem FVC og dødelighed, vurderes det at cyklussandsynligheden for ressourceforbruget burde være højere for de patienter, der har en lav FVC-%. Idet INBUILD-studiet er det eneste data for ressourceforbruget, som efter sekretariatets kendskab er til rådighed, vælger Medicinrådet at acceptere tilgangen.

Medicinrådet accepterer ansøgers tilgang vedr. øvrige hospitalsomkostninger, men ekskluderer omkostninger forbundet med iltbehandling og terminalomkostninger.

4.2.3 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrations- og monitoreringsbesøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og

transporttid. Ansøger antager, at der ikke er patientomkostninger forbundet med administration af nintedanib og BSC. Endvidere antager ansøger, at patienterne ved en indlæggelse i gennemsnit er indlagt i [redacted] Dette estimat er baseret på data fra IN-BUILD-studiet.

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 3,52 DKK pr. km, jf. Medicinrådet *Katalog for værdisætning af enhedsomkostninger.*

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Fagudvalget vurderer, at den gennemsnitlige tid for en indlæggelse nærmere er 8-9 dage i dansk klinisk praksis, hvorfor dette justeres i Medicinrådets hovedanalyse til gennemsnitligt 8,5 dage. De anvendte estimater i Medicinrådets hovedanalyse fremgår af Tabel 8.

Tabel 8. Estimat af effektiv patienttid

	Patienttid	Transporttid [minutter]
Indlæggelse	8,5 dage	-
Akutmodtagelse – overnatning	1 døgn	-
Akutmodtagelse – besøg	5 timer	60
Ambulant besøg	30 minutter	60
Ambulant besøg grundet eksacerbation	60 minutter	60
Besøg ved praktiserende læge	30 minutter	60
Fysioterapi	30 minutter	60
Ergoterapi	30 minutter	60
Besøg på ambulatorie grundet bivirkninger	30 minutter	60

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostninger, men ændrer den gennemsnitlige indlæggelsesperiode til 8,5 dage.

4.3 Følsomhedsanalyser

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

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges, se Tabel 9.

Tabel 9. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Tidshorisont	Tidshorisonten ændres til 10 år.
Lungetransplantation	Omkostninger forbundet med lungetransplantationer inkluderes i analysen ved anvendelse af DRG-taksten 26MP07, svarende til 817.016 kr. (engangsomkostning).
Funktion til ekstrapolering af OS-data	Den log-logistiske funktion anvendes.
Funktion til ekstrapolering af TTFAE-data	Gompertz, Weibull og den log-logistiske funktion anvendes.
Funktion til ekstrapolering af TTD-data	Weibull, den log-normale og den log-logistiske funktion anvendes.
Modellering af progression	Anvendelse af en generel model.
Sandsynligheder for at opleve eksacerbation, progression, behandlingsophør, mortalitet og bivirkninger varieres	Sandsynlighederne ændres til 95 %-konfidensintervallet (laveste og højeste værdi) af alle parameterværdier, som er inkluderet i ansøgers hovedanalyse.
Dosisreduktion	30 % af patienterne modtager nintedanib som reduceret dosis (100 mg to gange dagligt).
Antal akutte eksacerbationer	Antallet ændres til tre akutte eksacerbationer.
Stopregel for behandling med nintedanib	Patienterne stopper med at modtage behandling med nintedanib, hvis de oplever et 10 procentpoints fald i FVC-% over 6 måneder. Når patienterne ophører i behandling med nintedanib, vil de modtage BSC.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser

Medicinrådet præsenterer en scenarioanalyse, hvor det observerede OS-data for hhv. nintedanib og BSC ekstrapoleres med den log-logistiske funktion og en følsomhedsanalyse, hvor antallet af akutte eksacerbationer justeres. Medicinrådet præsenterer endvidere følsomhedsanalyser, hvor funktionerne til ekstrapolering af TTD-data justeres.

I Medicinrådets hovedanalyse antages et stopkriterie for behandling med nintedanib svarende til FVC fald > 10 % over 1 år. Betydningen for resultaterne ved at udelade stopkriteriet fra analysen undersøges i en følsomhedsanalyse. Medicinrådet præsenterer ikke ansøgers følsomhedsanalyser vedr. lungetransplantationsomkostninger og dosisreduktion.

Medicinrådet vælger at præsentere udvalgte af ansøgers følsomhedsanalyser.

4.4 Opsummering af basisantagelser

I Tabel 10 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 10. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	25 år	25 år
Diskonteringsrate	3,5 % pr. anno	3,5 % pr. anno
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Terminale omkostninger Bivirkningsomkostninger Patient- og transportomkostninger	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Patient- og transportomkostninger
Nintedanib-dosering	150 mg to gange om dagen	150 mg to gange om dagen
Nintedanib dosisreduktion	0 % af populationen	50 % af populationen
Parametriske funktioner for TTD		
Nintedanib:	Eksponentiel	Eksponentiel
Parametriske funktioner for TTFAE		
Intervention:	Eksponentiel	Weibull
Komparator:	Eksponentiel	Weibull
Parametriske funktioner for OS		
Intervention:	Weibull	Weibull
Komparator:	Weibull	Weibull
Inkludering af spild	Nej	Nej

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af Tabel 9.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 576.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 11.

Tabel 11. Resultatet af Medicinrådets hovedanalyse ved sammenligning med BSC, DKK, diskonterede tal

	Nintedanib	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	112.819	75.991	36.828
Kommunale omkostninger	1.193	433	760
Bivirkningsomkostninger	7.226	1.478	5.747
Patientomkostninger	7.048	3.962	3.085
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 12.

Tabel 12. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Stopkriterie udelades	[redacted]
Ingen behandlingseffekt af nintedanib	[redacted]
Ekstrapolering af TTD-data	

Scenarie	Inkrementelle omkostninger
- Weibull	[redacted]
- Log-logistisk	[redacted]
Ekstrapolering af OS-data med den log-logistiske funktion	[redacted]
Ændring i antal akutte eksacerbationer	[redacted]
Fuld dosis nintedanib	[redacted]

6. Budgetkonsekvenser

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

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

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

6.1 Estimat af patientantal og markedsandel

Ansøger har antaget, at der vil være ca. 70 patienter om året, der ved anbefaling vil være kandidater til behandling med nintedanib. Ansøgers estimat er baseret på protokollen [15], hvori fagudvalget har skønnet, at ca. 60-80 nye patienter med PF-ILS årligt potentielt kan være kandidater til behandling med nintedanib. Ansøger antager et markedsoptag for nintedanib på 100 % fra år 1 og de efterfølgende fire år frem, hvis lægemidlet anbefales af Medicinrådet.

Ansøger har udarbejdet følsomhedsanalyser, hvor patientantallet varieres til at være hhv. 35 og 105, for at afspejle scenarier, hvor hhv. ikke alle kandiderende patienter vil modtage nintedanib, og hvor flere patienter end de 70 patienter vil modtage behandling med nintedanib.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Idet ansøgers estimat er i overensstemmelse med protokollen, vurderer Medicinrådet, at de anvendte patientantal i analysen er rimelige. Fagudvalget pointerer dog, at patientantallet fra protokollen er et konservativt bud, og at en eventuel anbefaling af nintedanib kan føre til flere diagnosticerede patienter pga. øget opmærksomhed om sygdommen. På baggrund af dette præsenterer Medicinrådet ansøgers følsomhedsanalyse, hvor patientantallet justeres til værende 105 patienter om året.

Vedr. markedsoptaget vurderer fagudvalget, at et realistisk markedsoptag ved en anbefaling vil være 90 % fra år 1-5, idet nogle patienter sandsynligvis vil fravælge behandlingen.

Tabel 13. Medicinrådets estimat af antal nye patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Nintedanib	63	63	63	63	63
BSC	7	7	7	7	7
			Anbefales ikke		
Nintedanib	0	0	0	0	0
BSC	70	70	70	70	70

Medicinrådet accepterer ansøgers antagelser vedrørende patientantal, men vælger at justere markedsoptaget for nintedanib fra 100 % til 90 % i år 1-5.

6.2 Medicinrådets budgetkonsekvensanalyse

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

- reduceret markedsoptaget af nintedanib ved en anbefaling fra 100 % til 90 %.

Medicinrådet estimerer, at anvendelse af nintedanib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 14.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 36,4 mio. DKK i år 5.

Tabel 14. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

6.2.1 Resultat af følsomhedsanalyse for budgetkonsekvensanalyse

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser, men med ændret patientantal til 105 patienter, vil omkostninger i år 5 være ca. [redacted] DKK, se Tabel 15.

Tabel 15. Medicinrådets følsomhedsanalyse af totale budgetkonsekvenser med ændret patientantal til 105 patienter, mio. DKK, ikke-diskonterede tal

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

7. Diskussion

Behandling med nintedanib er forbundet med inkrementelle omkostninger på ca. [redacted] DKK pr. patient sammenlignet med behandling med BSC. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for nintedanib.

Fagudvalget vurderede, at OS-kurven for nintedanib sandsynligvis ville befinde sig mellem de kurver, som var blevet ekstrapoleret med hhv. den log-logistiske funktion og Weibull-funktionen. I Medicinrådets hovedanalyse blev Weibull-funktionen anvendt. De inkrementelle resultater reduceres med ca. [redacted] DKK, når den log-logistiske funktion anvendes til ekstrapolering af OS-kurven for både nintedanib og BSC. Når TTD-data ekstrapoleres med andre parametriske funktioner, end funktionen der er anvendt i hovedanalysen, øges de inkrementelle omkostninger med ca. [redacted] kr. patient. Såfremt der antages at være ens effekt mellem nintedanib og komparator, bliver de inkrementelle resultater ca. [redacted] kr. pr. patient.

Jf. vurderingsrapporten har fagudvalget foreslået en række stopkriterier for behandling med nintedanib. På baggrund af dette har Medicinrådet anvendt et stopkriterie i den økonomiske models hovedanalyse svarende til FVC-fald > 10 % over 1 år. Medicinrådet har også udført en følsomhedsanalyse hvor dette stopkriterie udelades. Den viser, at antagelsen om dette stopkriterie ikke er af betydning for analysens resultat. Det har ikke været muligt at inkorporere samtlige af fagudvalgets foreslåede stopkriterier direkte i modellen, herunder at behandling med nintedanib stoppes, såfremt patienten ikke ønsker behandling mere. Et stopkriterie som dette forventes dog at være opfanget i *time to treatment discontinuation*(TTD)-data fra INBUILD-studiet.

En anden væsentlig usikkerhed i modellen er den anvendte dosis. I modellen er anvendt en simpel tilgang vedr. dosis, hvor en konstant andel vil blive dosisreduceret baseret på

fagudvalgets erfaring med nintedanib til patienter med idiopatisk pulmonal fibrose (IPF). Det er dog usikkert, om det samme er tilfældet for patienter med PF-ILS.

Ansøger har primært estimeret ressourceforbruget baseret på en post-hoc-analyse af data fra INBUILD-studiet. Ansøger antager i denne sammenhæng, at INBUILD-studiet kan anvendes som en valid kilde for ressourceforbruget, idet post-hoc-analysen er baseret på patientniveaudata på PF-ILS-patienterne, som indgik i studiet. Der er dog usikkerheder forbundet med denne tilgang til estimering af de forbrugte ressourcer, idet det må antages, at ressourceforbruget kan variere mellem de 15 lande, som INBUILD-studiet blev udarbejdet i [13], sammenlignet med dansk klinisk praksis. Det har ikke været muligt for sekretariatet i samarbejde med fagudvalget at validere samtlige af de antagelser og sandsynligheder, der er præsenteret i indeværende afrapportering. Sammenlignet med lægemiddelomkostningerne for nintedanib har de øvrige omkostningsgrupper kun mindre betydning for de totale inkrementelle resultater. På trods af dette bør de omkostningsgrupper, som er baseret på post-hoc-analysen af INBUILD-data, tolkes med usikkerhed in mente.

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9. Versionslog

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

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 25 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 16.

Tabel 16. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Nintedanib	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	136.837	92.109	44.728
Tværsektorielle omkostninger	1.194	433	762
Bivirkningsomkostninger	661	125	486
Patientomkostninger	8.097	4.664	3.433
Terminale omkostninger	31.850	37.164	- 5.314
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

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

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af nintedanib vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 17.

Tabel 17. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

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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 interstitiel lungesygdom med progredierende fibrose

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	131765
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet vurderer, at nintedanib har en merværdi af ukendt størrelse sammenlignet med placebo til patienter med interstitiel lungesygdom med progredierende lungefibrose (PF-ILS).

Data viser, at nintedanib reducerer faldet i det kritiske effektmål forceret vitalkapacitet (FVC, som afspejler lungefunktion) hos PF-ILS-patienter med en dårlig prognose. Studiets opfølgningstid var for kort til at dokumentere bedre livskvalitet eller overlevelse ved behandling med nintedanib. Derudover viser data, at de rapporterede bivirkninger er velkendte for nintedanib og rutinemæssigt bliver behandlet i klinisk praksis med dosisændring eller medicinskift.

Sprog: dansk
Format: pdf
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*

FDA: *The Food and Drug Administration*

FGFR: Fibroblast vækstfaktorreceptor (*Fibroblast Growth Factor Receptor*)

FVC: Forceret vitalkapacitet (*Forced Vital Capacity*)

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

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*)

SMD: *Standardized Mean Difference*

SSc-ILS: Systemisk sklerodermi-associeret interstitiel lungesygdom

UIP: *Usual Interstitial Pneumonia*

VEGFR: Vaskulær endotelial vækstfaktorreceptor (*Vascular Endothelial Growth Factor*)

3. Introduktion

Formålet med Medicinrådets vurdering af nintedanib til interstitiel lungesygdom (ILS) med progredierende fibrose (PF-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:

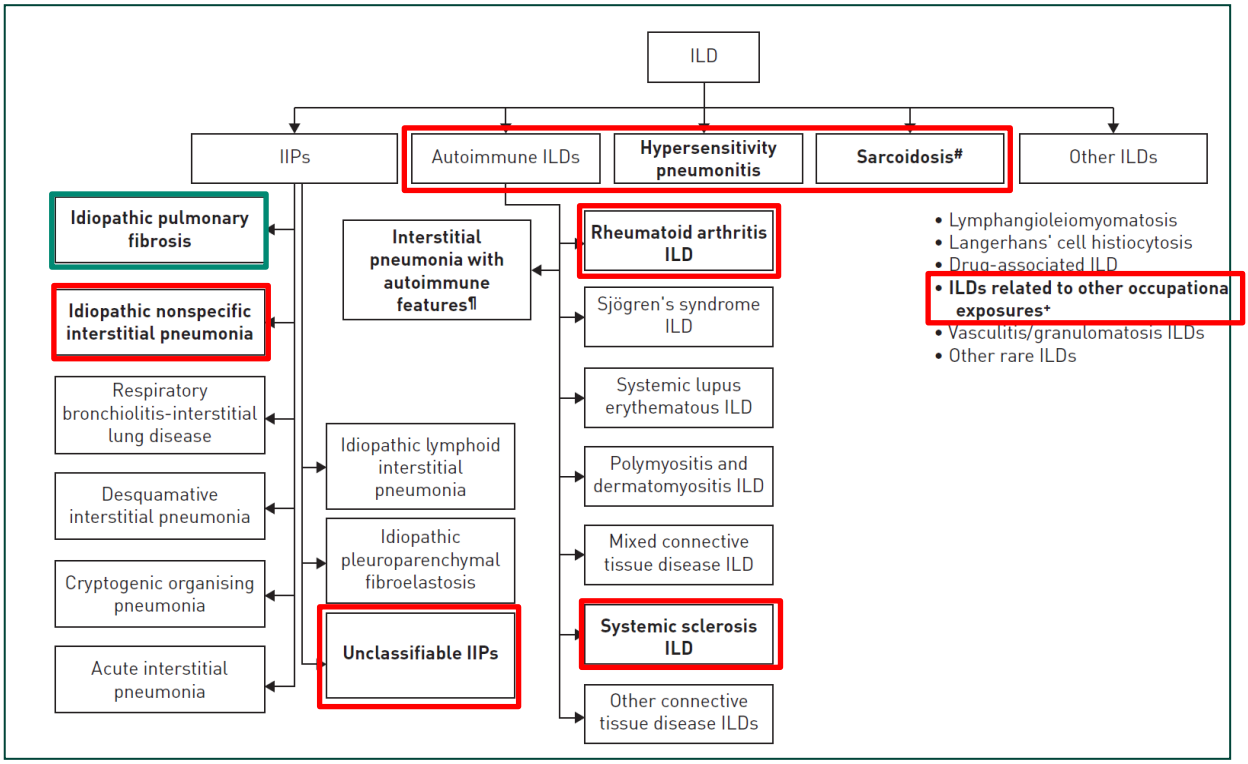
Hvilken værdi har nintedanib sammenlignet med placebo for patienter med interstitiel lungesygdom med progredierende fibrose?

3.1 Interstitiel lungesygdom med progredierende fibrose

Interstitielle lungesygdomme (ILS) er en heterogen gruppe af lungesygdomme, hvor det mest almindelige symptom er åndenød (dyspnø). Årsagen til ILS er forskellig og kan både skyldes miljøpåvirkning, underliggende autoimmun sygdom eller ukendte årsager. ILS kan udvikles som følge af inflammation med efterfølgende fibrosedannelse (arvævsdannelse) eller alene ved fibrose [1–3]. Lungefibrose er en kronisk sygdom, som kan ramme alle dele af lungevævet. Lungefibrose opstår, når celler i bindevævet, som kaldes fibroblaster, aktiveres til at udskille øget mængde af ekstracellulært materiale, som medfører stivhed i lungevævet og nedsat alveolar funktion. Jo mere fibrose, der opstår i lungerne, jo mere bliver lungefunktionen påvirket [4].

Der findes mange typer ILS (se oversigt i figur 1), hvoraf en af de mest undersøgte er idiopatisk pulmonal fibrose (IPF). IPF er kendetegnet ved irreversibel udvikling af progredierende lungefibrose med et radiologisk-patologisk mønster kaldet *usual interstitial pneumonia* (UIP), som diagnosticeres ved enten højopløsnings-CT-scanning (HRCT) eller histologisk ved lungevævsbiopsi [5–7]. Sygdommen optræder kun hos voksne, oftest over 50 år, og med en overvægt af mænd og rygere/eksrygere. IPF er forbundet med nedsat lungefunktion, dyspnø med gradvis forværring, forværret livskvalitet og dårlig prognose, hvor den gennemsnitlige overlevelse er på 3-5 år efter diagnose. Nogle patienter med IPF kan være stabile i en årrække, mens andre oplever hurtig progression over få måneder [5–8].

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



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

ILS med progredierende lungefibrose (PF-ILS)

Ud over IPF kan andre undertyper af ILS også medføre progredierende lungefibrose, selvom de ikke kan kategoriseres som værende IPF, se figur 1. Disse bliver samlet kaldt for PF-ILS. PF-ILS er en heterogen gruppe af sygdomme med varierende grad af lungefibrose og inflammation, som medfører gradvis forværring af respiratoriske symptomer, nedsat lungefunktion og tiltagende fibrose på HRCT-scanning [7,9–11]. I slutstadiet er der kun en lille gruppe af højt-selekterede patienter, som kan tilbydes lungetransplantation, ofte pga. alder. De patogenetiske mekanismer, det kliniske sygdomsbillede og patienternes prognose er på mange måder sammenlignelig mellem PF-ILS og IPF [11–14]. PF-ILS er dermed ligeledes forbundet med forværret livskvalitet og tidlig død trods behandling [7,9,10]. Nye data fra Storbritannien viser, at patienter med PF-ILS har øget mortalitet i forhold til stabile patienter, defineret ud fra kriterierne i INBUILD-studiet, som undersøgte effekten og sikkerheden af nintedanib ved PF-ILS (se afsnit 5). Mortalitet ved PF-ILS var sammenlignelig med IPF (HR 1,06; 95% CI 0,84–1,35; P = 0,6) og mere end 3 gange så høj som stabile patienter (HR 3,32; 95% CI 2,53–4,37; P ≤ 0,001) [15].

Omkring 2/3 dele af PF-ILS-patienterne har et UIP-mønster på HRCT-scanning eller histologi, mens øvrige patienter har andre fibrotiske mønstre på HRCT-scanning [16]. På grund af sygdommens progressive karakter oplever PF-ILS-patienter en væsentligt højere symptombyrde sammenlignet med øvrige ILS-patienter [9], som påvirker patienternes

livskvalitet og daglige aktivitetsniveau [17–21]. Patienternes prognose er afhængig af omfanget af fibrosen, om UIP-mønster er til stede, hvor hurtigt deres lungefunktion falder og af frekvensen af akutte eksacerbationer (dvs. akutte kliniske forværringer af patientens respiratoriske symptomer, som kræver behandling med prednisolon og/eller antibiotika eller hospitalsindlæggelse).

Incidens af PF-ILS
Incidensen af ILS, herunder PF-ILS, er svær at vurdere. Der foreligger et nationalt register over ILS i Danmark, men det indeholder overvejende patienter med IPF. 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, 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 stigning i antallet af CT-scanninger, som involverer thorax, som kan rejse mistanke om ILS. Fagudvalget skønner, at ca. 60-80 nye patienter med PF-ILS årligt potentielt kan være kandidater til behandling med nintedanib. Fagudvalget understreger, at dette er et konservativt bud. 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 af nintedanib til PDGFR og FGFR blokeres receptorernes intracellulære signalveje, som er med til at stimulere proliferation, migration og differentiering af lungefibroblaster, hvilket bremser 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 ved IPF er livsforlængende og gives indtil forekomsten af uacceptable bivirkninger eller død.

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

> *Ofev er også indiceret til behandling af andre kroniske fibroserende interstitielle lungesygdomme (ILS) med en progressiv fænotype (PF-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 PF-ILS har nintedanib samtidig fået følgende indikationsudvidelse i 2020 hos EMA til systemisk sklerodermi-associeret ILS (SSc-ILS):

> *Ofev er indiceret til behandling af systemisk sklerodermi-associeret interstitiel lungesygdom (SSc-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 PF-ILS korrelerer i høj grad med reduktionen i lungefunktion (fald i forceret vitalkapacitet (FVC), se definition i bilag 1) som følge af progression af lungefibrosen [7,9,10,12]. Behandlingsmålet er derfor bremsning af sygdomsudvikling med henblik på uforandret status eller reduceret progressionshastighed.

Udredning af PF-ILS
Den diagnostiske proces for IPF og andre fibrotiske lungesygdomme (herunder de forskellige sygdomme ved PF-ILS) følger i hovedtræk den diagnostiske algoritme, som er anbefalet i internationale retningslinjer for udredning af IPF [8,11].

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.

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 [13,25], 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 [1].

Behandling af PF-ILS

IPF er arketypen på en fibrotisk lungesygdom, som adskiller sig fra mange andre interstitielle lungesygdomme ved, at der ikke er betydelig inflammation. Behandlingen begrænses derfor primært til antifibrotisk medicin (nintedanib eller pirfenidon). Ved andre interstitielle lungesygdomme, tilrettelægges behandlingen individuelt for den enkelte patient, baseret på om deres sygdom primært er drevet af inflammation eller lungefibrose. Da PF-ILS er en heterogen gruppe af forskellige sygdomme, rettes nuværende behandlingsmuligheder mod den underliggende sygdomsårsag. Der er generelt sparsom evidens for behandling af de enkelte sygdomme med kun få randomiserede kliniske studier (*randomized clinical trial* (RCT)). Evidensen er ofte baseret på retrospektive studier, case-series og klinisk erfaring [7]. Behandlingen kan derfor variere imellem de enkelte ILS-centre, men følger generelt accepterede behandlingsprincipper. Hvis der identificeres en udløsende årsag, forsøges den elimineret. De enkelte sygdomme har varierende grader af inflammation og fibrosedannelse.

De fleste patienter har en inflammatorisk komponent og behandles med immunmodulerende lægemidler som førstelinjebehandling for at dæmpe den skadelige inflammatoriske proces. Disse omfatter blandt andet glukokortikoid, azathioprin, methotrexat, mycophenolatmofetil og cyclophosphamid [7]. Derudover anvendes i visse situationer biologiske lægemidler, f.eks. TNF-hæmmere, rituximab, abatacept eller interleukin-6-hæmmer [26–29]. Ingen af de nævnte lægemidler har PF-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 lungefunktionsmåling, evt. suppleret med gangtest og HRCT-scanning [7].

Fagudvalget understreger, at ved progression af lungefibrose på førstelinjebehandling med immunmodulerende lægemidler eller udvikling af uacceptable bivirkninger modtager danske PF-ILS-patienter i dag ikke yderlige behandling pga. manglende godkendte behandlingsmuligheder. Her vurderer fagudvalget, at antifibrotisk behandling med nintedanib, som er det første lægemiddel, der er regulatorisk godkendt til indikationen PF-ILS, og som specifikt er rettet mod fibrosedannelsen, potentielt kan finde anvendelse. Denne placering i behandlingsalgoritmen er i overensstemmelse med nylige anbefalinger fra en international ILS-ekspertgruppe vedrørende antifibrotisk behandling til PF-ILS-patienter [7,11]. Patienterne skal opfylde én af progressionskriterierne, jf. Medicinrådets protokol for vurdering vedrørende nintedanib til behandling af PF-ILS [30]. Se afsnit 6 for foreslåede start- og stopkriterier ved behandling med nintedanib.

Fagudvalget vurderer, at denne behandlingssekvens vil være gældende for flertallet af patienterne, da deres sygdom primært er drevet af inflammation i starten, hvorfor immunmodulerende behandling vil være mest effektiv som førstelinjebehandling. For en mindre gruppe af patienter 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.

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

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

4. Metode

Medicinrådets protokol for vurdering vedrørende nintedanib til behandling af interstitiel lungesygdom med progredierende fibrose [30] 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 INBUILD [16,31]. Desuden indgår EMAs *European Public Assessment Report* (EPAR) og produktresumé for nintedanib [24,32]. I ansøgningen indgår desuden en tredje artikel tillige baseret på INBUILD, som fokuserer på effekten af nintedanib i 5 subpopulationer baseret på subtype af ILS [33]. Fagudvalget vurderer ikke, at det er relevant at vurdere effekten af nintedanib ift. disse subtyper af PF-ILS, hvorfor disse resultater ikke vil blive benyttet i vurderingsrapporten.

INBUILD

Dette er et randomiseret, dobbeltblindet fase III-studie, der undersøgte effekten og sikkerheden af nintedanib sammenlignet med placebo hos patienter med interstitiel lungesygdom med progredierende fibrose, hvor > 10 % af deres lungevolumen var påvirket af fibrose, påvist ved HRCT. Patienterne skulle opfylde bestemte progressionskriterier for lungefibrose inden for de sidste 24 måneder på trods af standardbehandling med andre lægemidler end nintedanib og pirfenidon. Patienter, der modtog azathioprin, ciclosporin, mycophenolatmofetil, tacrolimus eller glukokortikoider (> 20 mg/dag) 4 uger inden uge 0 (visit 2), cyclophosphamid 8 uger inden uge 0 eller rituximab 6 måneder inden uge 0, blev ekskluderet fra studiet. Behandling med disse lægemidler kunne opstartes efter 6 måneders behandling i INBUILD-studiet, hvis den behandlende læge fandt det nødvendigt. Derudover skulle patienterne have en FVC, som

var minimum 45 % af forventet normalværdi[1], og en diffusionskapacitet for carbon monoxide (DLco) på 30-80 % af forventet normalværdi. Progressionskriterierne var:

- Relativt fald i FVC ≥ 10 % af forventet normalværdi
- Relativt fald i FVC ≥ 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.

Patienterne blev randomiseret 1:1 til nintedanib (n = 332), 150 mg to gange dagligt, eller placebo (n = 331). Randomiseringen var stratificeret efter patienternes fibrotiske mønster på HRCT (UIP-lignende mønster eller andre fibrotiske mønstre). Studiet var inddelt i to dele: del A, som kørte over de første 52 uger, og del B, hvor patienterne fortsatte på deres randomiserede behandling, indtil alle patienter var færdige med del A af studiet. Efterfølgende kunne alle patienterne modtage nintedanib i et ublindet ekstensionsstudie. I tilfælde af bivirkninger kunne patienter dosisreduceres til 100 mg to gange dagligt.

Studiets primære effektmål var den årlige FVC-faldhastighed, vurderet over 52 uger. Sekundære effektmål af relevans for vurderingen, jf. protokollen [30], var den absolutte ændring fra baseline i *King´s Brief Interstitial Lung Disease* (K-BILD)-spørgeskemaet ved uge 52, tiden til første akutte eksacerbation eller død over 52 ugers opfølgningstid og sikkerhed/bivirkninger.

Alle analyser blev foretaget på patienter, der modtog mindst én studiedosis. Det primære effektmål (fald i FVC) og sikkerhed/bivirkninger blev analyseret i den samlede population, i subpopulationen af patienter med UIP-lignende mønster og i subpopulationen af patienter med andre fibrotiske mønstre. Sekundære effektmål blev vurderet i den samlede population og i subpopulationen af patienter med UIP-lignende mønster.

Tabel 1. Oversigt over publikationer

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention vs. komparator
Flaherty et al. 2019 [16] Flaherty et al. 2017 [31] EPAR [32]	INBUILD	NCT02999178	Patienter med PF-ILS, som opfylder bestemte kriterier for deres progredierende fibrose	Nintedanib vs. placebo

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

Tabel 2. Baselinekarakteristika*

	Nintedanib 150 mg (n = 332)	Placebo (n = 331)
Mænd, antal (%)	179 (53,9)	177 (53,5)
Alder, år	65,2±9,7	66,3±9,8
Tidligere eller nuværende ryger, antal (%)	169 (50,9)	169 (51,1)
UIP-lignende mønster på HRTC, antal (%)	206 (62,0)	206 (62,2)
Progressionskriterier inden for de sidste 24 måneder, antal (%):		
– Relativt fald i FVC ≥ 10 % af forventet	160 (48,2)	172 (52,0)
– Relativt fald i FVC ≥ 5 - < 10 % af forventet samtidig med forværring af respiratoriske symptomer eller forværret fibrose på HRCT	110 (33,1)	97 (29,3)
– Forværring af respiratoriske symptomer samtidig med forværret fibrose på HRCT	62 (18,7)	61 (18,4)
FVC		
– Gennemsnit værdi i ml	2340±740	2321±728
– % af forventet normalværdi	68,7±16,0	69,3±15,2
DLco		
– Gennemsnit værdi i mmol/min/kPa	3,5±1,2	3,7±1,3
– % af forventet normalværdi	44,4±11,9	47,9±15,0
K-BILD score	52,5±11,0	52,3±9,8
Øvrig medicinsk behandling **ved studiets start**, antal (%)		
– Biologisk DMARDs**	14 (4,2)	17 (5,1)
– Glukokortikoider	3 (0,9)	5 (1,5)
– Immunmodulerende behandling af ILS§	3 (0,9)	4 (1,2)
– Ikke-biologisk DMARDs†	35 (10,5)	42 (12,7)
Øvrig medicinsk behandling, som **blev påbegyndt under studiet**, antal (%)		
– Biologisk DMARDs**	2 (0,6)	2 (0,6)
– Glukokortikoider	33 (9,9)	57 (17,2)
– Immunmodulerende behandling af ILS§	9 (2,7)	21 (6,3)
– Ikke-biologisk DMARDs†	7 (2,1)	19 (5,7)

*Alle værdier er opgjort som gennemsnit ± SD, medmindre andet er specificeret.**Bl.a. rituximab, abatacept, denosumab og tocilizumab. § Bl.a. mycophenolatmofetil, azathioprin, cyclophosphamid, ciclosporin og rituximab. † Bl.a. hydroxychloroquin, methotrexat, mycophenolatmofetil, leflunomid, sulfasalazin og azathioprin. DMARD: *Disease Modifying Anti Rheumatic Drug.*

Overordnet er der ikke nogen betydende forskelle i baselinekarakteristika mellem de to studiearme. Dog påbegyndte patienter i placeboarmen flere medicinske behandlinger under studiet sammenlignet med nintedanib-armen, bl.a. lægemidler, som var eksklusionskriterier i ugerne op til randomiseringen. Dette kan reflektere, at flere patienter progredierer i placeboarmen sammenlignet med interventionsarmen. Fagudvalget formoder, at det af etiske årsager var nødvendigt at tillade behandling under studiet med nogle af de lægemidler, som var en del af eksklusionskriterierne.

Fagudvalget vurderer ud fra baselinekarakteristika, at studiepopulationen består af patienter med en progressiv fibrotisk sygdom, som er sammenlignelig med IPF. Dette baseres på, at patienterne har udbredt fibrosedannelse og har et betydeligt (større) fald i FVC på 52 uger. Bl.a. har 2/3 dele af patienterne et UIP-lignende fibrosemønster på HRCT, som er kendetegnende for IPF, og knap halvdelen af patienterne har et relativt fald i FVC $\geq$ 10 % af forventet normalværdi på 52 uger. Til gengæld afviger studiepopulationen fra populationen i det kliniske spørgsmål, jf. protokollen [30], idet relativt få patienter har modtaget immunmodulerende behandling i ugerne op til studiestart. Ifølge INBUILD-inklusionskriterierne skulle patienterne opfylde bestemte progressionskriterier for lungefibrose inden for de sidste 24 måneder på trods af standardbehandling. Studiet har ikke opgjort, hvad standardbehandling dækkede over, men fagudvalget forventer, at der var tale om lavdosis glukokortikoider. Betydningen heraf ift. effekten af nintedanib er uvis, men fagudvalget vurderer, at det kan medføre en mindre overestimering af effekten, da patienter, der ikke har modtaget immunmodulerende lægemidler forud for randomiseringen, kan forventes at have større effekt af en aktiv behandling end patienter, der er progredieret på deres førstelinjebehandling. Dertil er der risiko for, at effekten af nintedanib underestimeres, da patienter i placeboarmen modtog flere medicinske behandlinger under studiet, hvilket kan medvirke til et mindre registreret fald i FVC.

Overordnet vurderer fagudvalget, at patientpopulationen i INBUILD er velegnet til at besvare det kliniske spørgsmål, da patienterne karakteriseres af progressiv lungefibrose, som på mange måder er sammenlignelig med IPF, hvilket indikerer, at patienterne er kandidater til antifibrotisk behandling ifølge dansk klinisk praksis for IPF-behandling.

5.1.2 Databehandling og analyse

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

For samtlige effektmål har ansøger foretaget en direkte sammenligning af nintedanib og placebo med data fra INBUILD-studiet. Ansøger har indsendt data for alle effektmål, dog benyttes der forskellige opfølgningstidspunkter.

For effektmålene *Dødelighed (*målt ved effektmålet *Lungefunktion – årlig FVC-faldhastighed)* og *Livskvalitet* er data opgjort efter 52 ugers opfølgningstid. Dvs. at alle patienter er blevet fulgt 52 uger efter første dosis. Dette opfølgningstidspunkt benævnes *del A*. Median behandlingslængde i denne opgørelse var 12,2 måneder i både nintedanib- og placeboarmen.

For de øvrige effektmål *Dødelighed (*målt ved *Median overlevelse), Akut eksacerbationsrate* og *Bivirkninger* er data opgjort med længere opfølgningstid, hvilket benævnes *del B.* I denne opgørelse er alle patienter fulgt, indtil den sidste rekrutterede patient har været fulgt 52 uger efter første dosis. Median behandlingslængde i denne opgørelse var 17,4 måneder i både nintedanib- og placeboarmen. Desuden er til supplerende sammenligning anført data for 52 ugers dødelighed.

Fagudvalget vurderer, at det er meningsfuldt, at data med længst mulig opfølgningstid ligger til grund for vurderingen. Dog har fagudvalget i protokollen defineret, at lungefunktion skal opgøres som årlig FVC-faldhastighed. Derfor benyttes data fra del A til *Lungefunktion – årlig FVC-faldhastighed*. For effektmålet *Livskvalitet* er det eneste tilgængelige data ligeledes fra del A. Data fra del B (med længst opfølgningstidspunkt) benyttes for *Median overlevelse, Akut eksacerbationsrate* og *Bivirkninger*.

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, som dermed ligger til grund for kategoriseringen.

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) og unøjagtighed (konfidensintervallet for effektmålet *Dødelighed, Median overlevelse* indeholder en beslutningsgrænse).

Evidensens kvalitet er lav, hvilket betyder, at nye studier med moderat 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 PF-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 0,78 (0,50; 1,21)	Kan ikke kategoriseres	Merværdi af ukendt størrelse
	Lungefunktion – årlig FVC-faldhastighed (50 ml/år)		107,0 ml/år (65,4; 148,5)	Merværdi af ukendt størrelse	Kan ikke estimeres*	Kan ikke kategoriseres	
Livskvalitet	Gennemsnitlig forværring i K-BILD-spørgeskemaet, fra baseline (2,7 point)	Kritisk	1,34 point (-0,31; 2,98)	Ingen dokumenteret merværdi	Kan ikke estimeres*	Kan ikke kategoriseres	Ingen dokumenteret merværdi
Akut eksacerbationsrate	Andel patienter, der oplever mindst én akut eksacerbation pr. år (20 %-point)	Kritisk	Kan ikke estimeres	Kan ikke kategoriseres	HR 0,63 (0,37; 1,07)	Ingen dokumenteret merværdi	Ingen dokumenteret merværdi
Bivirkninger	Andel patienter, der oplever mindst én alvorlig uønsket hændelse (5 %-point)	Vigtig	-5 %-point (-13; 0,2)	Ingen dokumenteret merværdi	RR 0,89 (0,76; 1,05)	Ingen dokumenteret merværdi	
	Andel patienter, der oplever behandlingsophør grundet uønskede hændelser (5 %-point)		7 %-point (2; 13)**	Kan ikke kategoriseres	RR 1,52 (1,09; 2,11)	Negativ værdi	Ingen dokumenteret merværdi
	Kvalitativ gennemgang af bivirkningsprofilen		Se nedenfor				

Konklusion	
Samlet kategori for lægemidlets værdi	Merværdi af ukendt størrelse
Kvalitet af den samlede evidens	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 PF-ILS er en uhelbredelig, dødelig sygdom, hvor den gennemsnitlige overlevelse (OS) er på 3-5 år efter diagnosen [7,9,10,12], og hvor behandlingsmålet er at bremse sygdomsprogressionen med henblik på stabilisering og dermed forlænget overlevelse.

Median overlevelse

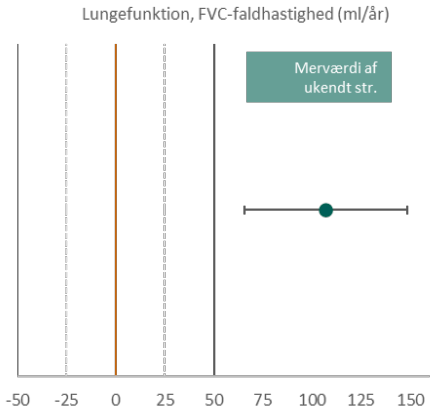
På grund af få hændelser er median overlevelse ikke nået gennem studiets opfølgningstid for nogen af armene, og den absolutte effektforskel for *Dødelighed, Median overlevelse* kan derfor ikke kategoriseres efter Medicinrådets metoder. Under studiets opfølgningstid (17,4 måneder) døde 36 ud af 332 patienter (10,8 %) i nintedanib-armen sammenlignet med 45 ud af 331 patienter (13,6 %) i placeboarmen efter 52 ugers opfølgningstid, med en statistisk set ikke-signifikant hazard ratio på 0,78 (0,5; 1,21).

Fagudvalget bemærker, at hændelsesraten for dødelighed er, hvad man kan forvente for studiepopulationen i INBUILD-studiet. Efter en opfølgningstid på 17,4 måneder er der numerisk bedre overlevelse hos patienter i behandling med nintedanib, men forskellen er ikke statistisk signifikant. INBUILD-studiet var ikke designet til at påvise en forskel i mortalitet. Udføres der styrkeberegning baseret på studieresultaterne, kan man se, at selv med mere end 1.200 deltagere i hver arm vil styrken for at detektere en signifikant 2-års mortalitetsforskel kun være omkring 80 %.

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 [30]. Der foreligger omfattende evidens for korrelationen mellem fald i FVC og dødelighed ved IPF, se bilag 1. På grund af de kliniske og patofysiologiske ligheder, der er mellem PF-ILS og IPF, formoder fagudvalget, at den sammenhæng, der er dokumenteret mellem fald i FVC og dødelighed ved IPF, også er repræsentativ for PF-ILS.

Lungefunktion målt ved årlig FVC-faldhastighed

Patienter, som modtog nintedanib, oplevede et gennemsnitligt fald i FVC på 80,8 ml/år, mens patienter i placeboarmen oplevede et gennemsnitligt fald på 187,8 ml/år. Således er den absolutte effektforskel 107 ml/år, dvs. at patienter, som modtog nintedanib, bibeholdt mere lungefunktion end patienter, som ikke modtog nintedanib. Den absolutte forskel er vist i figur 2 nedenfor.



Figur 2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for *Dødelighed, Lungefunktion målt ved årlig 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 107 ml/år (65,4; 148,5) afspejler en klinisk relevant effektforskel, da det ligger over mindste klinisk relevante effektforskel på 50 ml/år. Den nedre grænse for konfidensintervallet er over den mindste klinisk relevante forskel. Derfor har nintedanib, baseret på den absolutte effektforskel, foreløbigt en merværdi af ukendt størrelse 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.

Fagudvalgets samlede konklusion vedr. effektmålet *Dødelighed*

Fagudvalget vurderer, at nintedanib aggregeret har en **merværdi af ukendt størrelse** vedr. effektmålet *Dødelighed*.

Fagudvalget baserer konklusionen vedr. effektmålet *Dødelighed* på data for fald i FVC fra INBUILD-studiet, da fagudvalget ikke kan udtale sig sikkert om nintedanibs effekt på median overlevelse. Det er på grund af de få hændelser inden for studiets opfølgningstid, hvor der ikke kunne påvises en statistisk signifikant effekt. Til gengæld foreligger der data på fald i FVC, som er en fysiologisk parameter, der korrelerer med dødelighed hos IPF. Det er fagudvalgets vurdering, baseret på flere studier fra forskellige centre, jf. bilag 1, at fald i FVC er stærkt korreleret til død hos patienter med lungefibrose, uanset den underliggende diagnose.

INBUILD-studiet viser, at PF-ILS-patienter på nintedanib-behandling oplever et markant langsommere fald i FVC sammenlignet med patienter, der ikke modtager behandling (absolut effektforskel på 107,0 ml/år). Ifølge fagudvalget er der tale om en stor værdi for

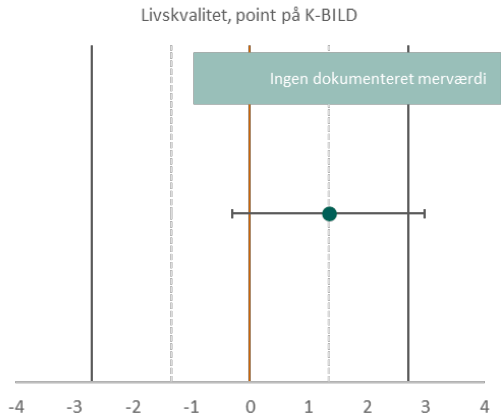
patienterne, fordi et langsommere årligt fald i FVC alt andet lige korrelerer med mindre vejrtrækningsbesvær, bedre livskvalitet og bedre performance ved 6-minutters gangtest.

Fagudvalget understreger, at INBUILD-studiet bekræfter den generelle forventning til, at nintedanib er en effektiv behandling ved fibrotiske lungesygdomme uanset årsag. Den dokumenterede reduktion i årligt fald i FVC på 107 ml er tilsvarende den dokumenterede effekt af nintedanib ved IPF, som var på 111 ml [34]. En opgørelse fra det danske PF-BIO-kohorte efter op til 4-års opfølgning har vist, at behandling med nintedanib hos danske IPF-patienter er forbundet med længere overlevelse (HR 0,50 (95 % CI 0,26-0,96) [35]. En post hoc-analyse fra INBUILD, som undersøgte effekten på subgruppeniveau i forskellige sygdomsgrupper, inkl. dem med autoimmun ILS og SSc-ILS, viste, at effekten af nintedanib gælder for hver enkelt sygdomsgruppe [36]. Dette underbygger yderligere, at der er en generel antifibrotisk effekt af nintedanib ved fibrotiske lungesygdomme.

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 PF-ILS [17–21]. 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.

Patienter, som modtog nintedanib, oplevede en forbedring i overordnet livskvalitet på 0,55 point på K-BILD-spørgeskemaet hen over de 52 ugers opfølgningstid. Patienter, som modtog placebo, oplevede derimod et fald på 0,79 point. Dermed er den absolutte effektforskel på 1,34 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. 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 specificeret, at MKRF er 2,7 point. Punktestimatet for den absolutte effektforskel på 1,34 point (-0,31; 2,98) afspejler dermed ikke en klinisk relevant effektforskel. 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 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 > 2,7 points forværring). Derfor har nintedanib, baseret på den relative effektforskel, foreløbigt en værdi, som ikke kan kategoriseres vedr. *Livskvalitet*.

Fagudvalget vurderer, at nintedanib aggregeret har **ingen dokumenteret merværdi** vedr. *Livskvalitet*, fordi den absolutte effektforskel er statistisk set ikke-signifikant (dog med en klar positiv tendens) og er mindre end MKRF. Data fra INBUILD-studiet tyder på, at 52 ugers behandling med nintedanib hverken er forbundet med en klinisk relevant forbedring eller forværring af patienternes livskvalitet. Fagudvalget bemærker, at resultaterne er sammenlignelige med den effekt på livskvalitet, der er blevet rapporteret i IPF-studierne. Her er effekten af nintedanib på livskvalitet (målt ved livskvalitetsværktøjet SGRQ (St George's Respiratory Questionnaire)) blevet undersøgt i en poolet analyse af TOMORROW- og INPULSIS-studierne, hvor der blev fundet signifikant forbedring med en effektforskel på 2,05, som ligeledes ikke overstiger MKRF [34].

Akut eksacerbationsrate
Som beskrevet i protokollen er effektmålet *akut eksacerbationsrate* kritisk for vurderingen af lægemidlets værdi for patienterne. En akut eksacerbation er en akut klinisk forværring af patientens respiratoriske symptomer og livskvalitet og kræver ofte hospitalsindlæggelse. Svære tilfælde af akutte eksacerbationer er potentielt en livstruende tilstand [37]. På grund af alvorligheden af hændelsen betragter fagudvalget akut eksacerbationsrate som et kritisk effektmål. Fagudvalget ønskede effektmålet opgjort som andel patienter, der oplever mindst én akut eksacerbation pr. år.

Da effektmålet er opgjort som et *time-to-event*, som påvirkes af opfølgningstiden og censureringer, er der usikkerhed forbundet ved at sammenligne resultaterne i hver arm, og den absolutte effektforskel kan ikke estimeres. Den foreløbige værdi af nintedanib vedr. *Akut eksacerbationsrate* kan dermed ikke kategoriseres efter Medicinrådets metoder med den angivne MKRF på 20 %.

Sammenlagt lægger fagudvalget ikke stor vægt på hændelsesraten i hver arm, og kategoriseringen vil dermed tage udgangspunkt i den relative effektforskel.

6,9 % af patienter, som modtog nintedanib, og 10,6 % af patienter, som modtog komparator, oplevede en akut eksacerbation (median behandlingslængde/opfølgningstid 17,4 måneder). Baseret på denne relative effektforskel, som er opgjort som en hazard ratio på 0,63 (0,37; 1,07) (fremgår af tabel 3), har nintedanib foreløbigt ingen dokumenteret merværdi vedr. *Akut eksacerbationsrate.*

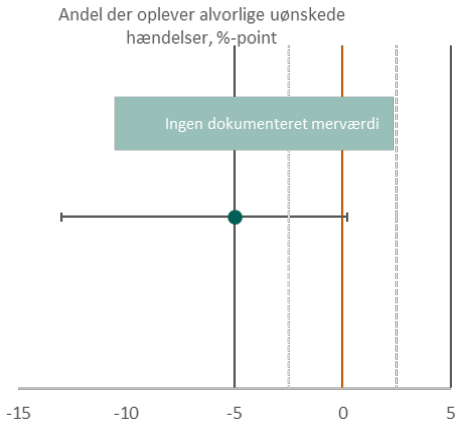
Fagudvalget vurderer, at nintedanib aggregeret har **ingen dokumenteret merværdi** vedr. *Akut eksacerbationsrate*, da den relative effektforskel ikke viser en statistisk effekt af nintedanib.

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, der oplever minimum én alvorlig uønsket hændelse, behandlingsophør grundet uønskede hændelser og en kvalitativ gennemgang af nintedanibs bivirkningsprofil.

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

147 ud af 332 patienter (44,3 %), som modtog nintedanib, oplevede mindst én alvorlig uønsket hændelse, hvilket var tilfældet for 165 ud af 331 patienter (49,5 %), som modtog placebo. Den absolutte effektforskel var beregnet til -5 %-point. Den absolutte forskel er vist i figur 4 nedenfor.



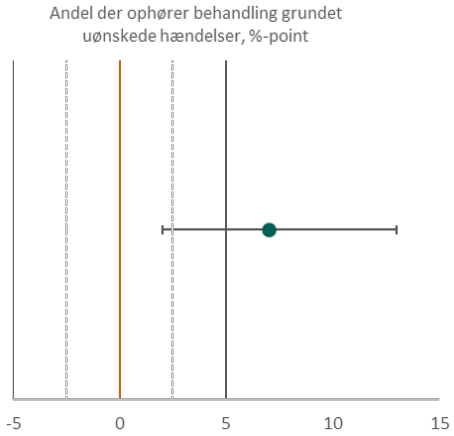
Figur 4. Punktestimat og 95 % konfidensinterval for den absolutte forskel for *Andel patienter, der oplever alvorlige uønskede hændelser*. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget har i protokollen defineret MKRF til 5 %-point. Punktestimatet for den absolutte effektforskel på -5 %-point (-13; 0,2) afspejler dog akkurat en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet passerer netop 0 (ingen effekt), og den nedre grænse på konfidensintervallet indikerer en potentiel klinisk positiv, men statistisk set ikke-signifikant forskel. Derfor har nintedanib, baseret på den absolutte effektforskel, foreløbigt ingen dokumenteret merværdi vedr. delmålet *Andel patienter, der oplever alvorlige uønskede hændelser.*

Baseret på den relative effektforskel, som er opgjort som en relativ risiko på 0,89 (0,76; 1,05) (fremgår af tabel 3), har nintedanib foreløbigt ingen dokumenteret merværdi vedr. *Andel patienter, der oplever alvorlige uønskede hændelser*.

Behandlingsophør grundet uønskede hændelser

73 ud af 332 patienter (22 %), som modtog nintedanib, ophørte behandling grundet uønskede hændelser, hvilket var tilfældet for 48 ud af 331 patienter (14,5 %), som modtog placebo. 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 *Andel patienter, der ophører behandling 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 dermed en negativ klinisk relevant 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 1,52 (1,09; 2,11) (fremgår af tabel 3), har nintedanib foreløbigt en negativ værdi vedr. *Andel patienter, der ophører behandling grundet uønskede hændelser*.

Det, at placeboarmen har modtaget flere medicinske behandlinger under studiet, jf. baselinekarakteristika, end nintedanib, har ifølge fagudvalget formentlig bidraget til, at der ikke ses et større frafald i placeboarmen.

Gennemgang af bivirkningsprofil

Gennemgangen af nintedanibs bivirkningsprofil tager udgangspunkt i EMAs produktresumé [24] samt EPAR for PF-ILS [38]. 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. Nogle af disse bivirkninger bliver ligeledes 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 1,8 % i INBUILD-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 INBUILD-studiet var i henhold med nintedanibs kendte bivirkningsprofil (se tabel 5-7 i bilag 2) [32].

Behandling med nintedanib i INBUILD-studiet var forbundet med markant flere dosisreduktioner (33,7 vs. 5,4 % i placeboarmen) og behandlingspauser (33,1 vs. 10,3 % i placeboarmen) sammenlignet med placebo [38]. Subgruppeanalyse fra INPULSIS- og SENSCIS-studierne for hhv. patienter med IPF og SSc-ILS viser, at en reduceret dosis af nintedanib ikke er forbundet med lavere effekt på FVC-faldhastighed [39,40]. En nylig opgørelse af danske IPF-patienter i behandling med nintedanib har ligeledes vist, at patienter, der modtog en reduceret dosis, havde bedre overlevelse end patienter på fuld dosis (HR 0,18 (95 % CI 0,07-0,52)) [35]. Disse resultater skal dog tages med forbehold pga. få patienter i behandling med fuld dosis nintedanib.

Fagudvalgets samlede konklusion vedr. effektmålet *Bivirkninger*

Baseret på ovenstående gennemgang af effektmålets tre delmål vurderer fagudvalget, at nintedanib aggregeret har **ingen dokumenteret merværdi** vedr. effektmålet bivirkninger sammenlignet med placebo. I den samlede vurdering har fagudvalget lagt vægt på, at bivirkningerne rapporteret i INBUILD-studiet er i henhold med nintedanibs kendte bivirkningsprofil. Behandling med nintedanib er forbundet med flere behandlingsophør grundet uønskede hændelser end placebo, hvilket er forventeligt i en sammenligning af en aktiv behandling – med betydelige og kendte bivirkninger – med ingen behandling. Til gengæld var der ingen signifikant forskel mellem nintedanib og placebo i delmålet *Andel patienter, der oplever alvorlige uønskede hændelser*. Nintedanib giver mange bivirkninger fra mave-tarm-kanalen, som ofte resulterer i dosisreduktioner og supplerende behandling i form af lægemidler mod diarré og kvalme/opkast. Fagudvalget bemærker, at bivirkningerne, der opstår ved behandling med nintedanib hos patienter med PF-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 negativt.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at nintedanib til patienter med interstitiel lungesygdom med progredierende fibrose giver en **merværdi af ukendt størrelse** sammenlignet med placebo.

I den samlede vurdering har fagudvalget lagt vægt på, at nintedanib medvirker til at reducere fald i FVC hos PF-ILS-patienter med en dårlig prognose. Den absolutte effektforskel på 107 ml/år mellem nintedanib og placebo kategoriseres foreløbigt som en merværdi af ukendt størrelse efter Medicinrådets metoder. Ifølge fagudvalget er der tale om en potentiel stor værdi for patienterne, fordi et langsommere årligt fald i FVC korrelerer med mindre vejrtrækningsbesvær, bedre livskvalitet, bedre performance ved 6-minutters gangtest og mortalitet.

Nintedanib medførte ingen dokumenteret merværdi på livskvalitet og akut eksacerbationsrate. Fagudvalget finder dette er forventet, da disse effektmål kræver studier med længere opfølgningstid end 1-1,5 år. Dertil finder fagudvalget det væsentligt at understrege, at selvom effekten på livskvalitet vil påvirkes positivt ved en klinisk effekt af nintedanib, kan den potentielt blive modvirket af en negativ påvirkning grundet bivirkninger. Derudover bemærker fagudvalget, at resultaterne på livskvalitet er sammenlignelige med den effekt, som er rapporteret ved de kliniske studier af nintedanib hos IPF [34].

Fagudvalget har ikke lagt stor vægt på bivirkningerne, der er blevet rapporteret i INBUILD-studiet, da de er velkendte for nintedanib og rutinemæssigt bliver behandlet i klinisk praksis med dosisændring eller medicinskift, omend de er generende for patienterne. Derudover finder fagudvalget det relevant, at behandling med nintedanib samlet set ikke påvirker livskvaliteten negativt.

I en samlet vægtning finder fagudvalget, at selvom der ikke kan dokumenteres effekt på de kritiske effektmål livskvalitet, regelret mortalitet og akut eksacerbationsrate, har nintedanib potentielt en stor værdi for patienterne pga. det dokumenterede årlige fald i FVC, hvilket bekræfter den generelle forventning til, at nintedanib er en effektiv behandling ved fibrotiske lungesygdomme uanset årsag. Reduktionen i årligt FVC-fald på 107 ml ved PF-ILS er tilsvarende den dokumenterede effekt af nintedanib ved IPF, som var på 111 ml [34]. Derfor vurderer fagudvalget, at nintedanib har en samlet merværdi af ukendt størrelse.

Ifølge fagudvalget giver stabiliserende behandling med nintedanib en kumulativ gevinst i form af mindre FVC-tab og vil derved give større behandlingseffekt ved længere tids behandling. Dermed er det også fagudvalgets forventning, at der ved længere patientopfølgning vil kunne ses signifikant forskel i livskvalitet, hospitalisering og mortalitet. F.eks. viser data på danske IPF-patienter, at behandling med nintedanib er forbundet med længere overlevelse (HR 0,50 (95 % CI 0,26-0,96) [35]. En reduktion af patientgruppens morbiditet gennem stabiliserende antifibrotisk behandling må ligeledes

forventes at give en positiv værdi på sundhedsudgifter, f.eks. til pleje, indlæggelser og tabte arbejdsår.

Konklusionen på alt ovenstående er, at PF-ILS kan sidestilles med IPF mht. prognose, FVC-fald og effekt af nintedanib på FVC. INBUILD havde ikke styrke til at påvise den reduktion af mortaliteten, som er vist ved observationsstudier og poolede studier af IPF. Med samme effekt af nintedanib på FVC-fald ved IPF og PF-ILS er der også en klar forventning om en tilsvarende reduktion i mortaliteten.

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 INBUILD-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.

Jf. studiebeskrivelsen kunne alle patienterne modtage nintedanib i et ublindet ekstensionsstudie. Fagudvalget har ikke kendskab til, at der foreligger en publikation fra ekstensionsstudiet, men understreger vigtigheden af dette for at belyse langtidseffekten af nintedanib.

Fagudvalget foreslår, at hvis ibrugtagning af nintedanib bliver anbefalet, bør der indsamles data i Den danske nationale ILS-database, ligesom det er tilfældet ved IPF.

Opstarts- og stopkriterier

Fagudvalget foreslår, at nintedanib kan tilbydes til patienter, som opfylder én af nedenstående progressionskriterier inden for de sidste 24 måneder, hvilket er i henhold til inklusionskriterierne i INBUILD-studiet. Derudover skal patienterne have progression af lungefibrose på førstelinjebehandling med immunmodulerende lægemidler eller udvikling af uacceptable bivirkninger.

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.

For en selekteret mindre gruppe af patienter med progressiv fibrose, som har overvejende fibrotisk sygdom uden betydelig inflammation bedømt på HRCT +/- patologi, er det oplagt, at nintedanib kan anvendes som førstelinjebehandling.

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

Da PF-ILS er en sjælden sygdom, foreligger der begrænset evidens på området, i modsætning til IPF. På grund af de kliniske og patofysiologiske ligheder, der er mellem PF-ILS og IPF, formoder fagudvalget, at den sammenhæng, der er dokumenteret mellem fald i FVC og dødelighed ved IPF, også er repræsentativ for PF-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. [37]	≥ 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. [41]	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. [12]	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. [42]	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. [43]	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 pga. korrelationen med dødelighed [44]. FDAs 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 [44]

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) [45]	157 (3; 311) til fordel for pirfenidon	14 (8,0)	20 (11,5)	0,65 (0,33 ; 1,29)
CAPACITY 006 (pirfenidon) [45]	-6 (-178; 167) til fordel for placebo	18 (10,5)	17 (9,8)	1,07 (0,55 ; 2,08)
ASCEND (pirfenidon) [46]	193 (96; 289) til fordel for pirfenidon	12 (4,3)	21 (7,6)	0,57 (0,28 ; 1,16)
TOMORROW (nintedanib) [47]	131 (27; 235) til fordel for nintedanib	7 (8,1)	9 (10,3)	0,73 (0,27; 1,98)
INPULSIS-1 (nintedanib) [48]	125 (78; 173) til fordel for nintedanib	13 (4,2)	13 (6,4)	0,63 (0,29; 1,36)
INPULSIS-2 (nintedanib) [48]	94 (45; 143) til fordel for nintedanib	22 (6,7)	20 (9,1)	0,74 (0,40; 1,35)

En række registerstudier og post hoc-analyser af randomiserede kliniske studier har entydigt vist, at behandling af IPF med pirfenidon eller nintedanib er associeret med reduceret mortalitet, se tabel 6.

Tabel 6. Antifibrotisk behandling er forbundet med lavere dødelighed

Kilde	Behandling	Risiko for død	Uddybbning
Jo et al. [49]	Antifibrotisk behandling vs. ingen antifibrotisk behandling (n= 146, nintedanib eller pirfenidon)	HR på 0,38 (95 % CI 0,24-0,59)	Australsk IPF registerstudie med op til 4 års opfølgning, der undersøgte patienternes egenskaber og effekten af demografi, fysiologiske parametre og specifikke behandlinger på dødelighed
	Multivariat analyse med justering for forskelle i alder, køn, rygning, BMI og baseline FVC	HR på 0,56 (95 % CI 0,34-0,92)	
Dempsey et al. [50]	Antifibrotisk behandling vs. ingen antifibrotisk behandling (n= 1.255, nintedanib eller pirfenidon), risiko for død efter 2-års behandling	HR på 0,77 (95 % CI 0,62-0,98)	Stort registerstudie fra en forsikringsdatabase i USA, der undersøgte effekten af antifibrotisk behandling hos IPF-patienter
	Antifibrotisk behandling vs. ingen antifibrotisk behandling (n= 1.255, nintedanib eller pirfenidon), risiko for indlæggelse efter 2-års behandling	HR på 0,70 (95 % CI 0,61-0,80)	
Guenther et al. [51]	Antifibrotisk behandling (83 % pirfenidon og 17 % nintedanib) vs. anden behandling	Median overlevelse 123,1 mdr. hos patienter i antifibrotisk behandling vs. 68,3 mdr. hos patienter i anden form for behandling	Artikel, der beskriver egenskaber af 525 IPF-patienter i det europæiske register (eurIPFreg) med opfølgning op til 7 år
Leuschner et al. [52]	Antifibrotisk behandling (n= 568 hvor 35 % modtog nintedanib) vs. ingen antifibrotisk behandling	HR på 0,74 (95 % CI, 0,60-0,90)	Karakterisering af IPF-patienter fra det tyske INSIGHTS-IPF-register med opfølgning op til 4 år
Richeldi et al. [34]	Nintedanib (n = 723) vs. placebo (n = 508)	HR på 0,70 (95 % CI 0,46-1,08) Absolut forskel i fald i FVC 110,9 ml/år (-112,4 ml/år i nintedanibarmen vs. -223,3 ml/år i placeboarmen)	Post hoc-analyse med poolede data fra INPULSIS og TOMORROW, der undersøgte effekten af nintedanib vs. placebo ved IPF
Lancaster et al. [53]	Nintedanib (n = 1.126) vs. placebo (n = 565). Median behandlingstid med nintedanib var 28 mdr.	Nintedanib: middeloverlevelse 11,6 år (95 % CI 9,6-14,1) og median overlevelse 8,5 år Placebo: middeloverlevelse 3,7 år (95 % CI 2,5-5,4) og median overlevelse 3,3 år	Artikel, der undersøgte sikkerheden af nintedanib til IPF fra seks kliniske studier. Effekten af nintedanib på overlevelse blev undersøgt via ekstrapolering af overlevelsesdata.

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

Tabel 7. 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 8. Oversigt over bivirkninger rapporteret i > 5 % af patienterne i INBUILD-studiet. Tabel fra nintedanibs EPAR for PF-ILS.

AEs reported for more than 5% of patients in either treatment group on the PT level over the whole trial (Part A+B) up to DBL1 – TS Overall population

MedDRA system organ class Preferred term	Placebo			Nintedanib 150 mg bid		
	N	%	Rate/100 pt-yrs	N	%	Rate/100 pt-yrs
Number of patients	331	100.0		332	100.0	
Patients with any AE	306	92.4	313.00	325	97.9	698.56
Gastrointestinal disorders	157	47.4	53.02	275	82.8	238.02
Diarrhoea	84	25.4	22.65	232	69.9	130.96
Nausea	33	10.0	7.56	100	30.1	30.84
Vomiting	17	5.1	3.72	63	19.0	17.03
Abdominal pain	9	2.7	1.93	34	10.2	8.42
Abdominal pain upper	7	2.1	1.50	32	9.6	7.91
Constipation	31	9.4	6.92	25	7.5	6.00
Infections and infestations	209	63.1	78.95	202	60.8	80.73
Nasopharyngitis	48	14.5	11.38	53	16.0	13.62
Bronchitis	57	17.2	13.68	46	13.9	11.64
Pneumonia	29	8.8	6.37	33	9.9	7.74
Upper respiratory tract infection	22	6.6	4.86	26	7.8	6.28
Urinary tract infection	19	5.7	4.13	22	6.6	5.22
Respiratory tract infection	15	4.5	3.27	20	6.0	4.74
Respiratory, thoracic and mediastinal disorders	172	52.0	52.35	149	44.9	48.03
Dyspnoea	54	16.3	12.53	48	14.5	11.95
Cough	50	15.1	11.80	37	11.1	9.11
Interstitial lung disease	52	15.7	11.78	24	7.2	5.60
Investigations	59	17.8	14.17	123	37.0	39.49
Alanine aminotransferase increased	12	3.6	2.60	48	14.5	12.15
Weight decreased	12	3.6	2.59	43	13.0	10.84
Aspartate aminotransferase increased	12	3.6	2.60	43	13.0	10.80
Gamma-glutamyltransferase increased	7	2.1	1.49	22	6.6	5.22
General disorders and administration site conditions	105	31.7	27.76	91	27.4	25.86
Fatigue	21	6.3	4.66	34	10.2	8.42
Asthenia	12	3.6	2.60	18	5.4	4.27
Pyrexia	18	5.4	3.93	17	5.1	3.99
Oedema peripheral	20	6.0	4.43	15	4.5	3.52
Musculoskeletal and connective tissue disorders	101	30.5	27.27	89	26.8	24.81
Back pain	24	7.3	5.31	23	6.9	5.45
Arthralgia	24	7.3	5.30	13	3.9	3.03
Nervous system disorders	68	20.5	16.75	78	23.5	21.48
Headache	26	7.9	5.84	38	11.4	9.56
Dizziness	13	3.9	2.83	18	5.4	4.23
Metabolism and nutrition disorders	49	14.8	11.29	77	23.2	21.16
Decreased appetite	21	6.3	4.62	53	16.0	13.71
Skin and subcutaneous tissue disorders	53	16.0	12.61	68	20.5	18.10
Pruritus	18	5.4	3.93	9	2.7	2.09
Hepatobiliary disorders	11	3.3	2.37	38	11.4	9.28
Hepatic function abnormal	3	0.9	0.64	19	5.7	4.51
Psychiatric disorders	35	10.6	7.73	36	10.8	8.75
Insomnia	17	5.1	3.65	15	4.5	3.50

Source data: [c26471552, Table 15.3.1.2.2.1: 2]

Tabel 9. Oversigt over diarré-bivirkninger i INBUILD-studiet. Tabel fra nintedanibs EPAR for PF-ILS.

Summary of AE diarrhoea with additional information collection over 52 weeks – TS
Overall population

		Placebo		Nintedanib 150 mg bid	
		N	%	N	%
Patients with a diarrhoea AE with additional information collection		79	100.0	221	100.0
CTCAE Grade	1	64	81.0	147	66.5
	2	10	12.7	51	23.1
	3	5	6.3	23	10.4
	4	0	0	0	0
	5	0	0	0	0
Drug-related	Yes	59	74.7	195	88.2
	No	20	25.3	26	11.8
Outcome	Recovered	64	81.0	151	68.3
	Not yet recovered[1]	13	16.5	70	31.7
	Recovered with sequelae	0	0	0	0
	Fatal	0	0	0	0
	Unknown	2	2.5	0	0
Clinical consequences	Permanent discontinuation	1	1.3	19	8.6
	Permanent dose reduction	3	3.8	47	21.3
	Neither of the above	75	94.9	155	70.1
Patients with serious diarrhoea AE		0	0	2	0.9
	Requires or prolongs hospitalisation	0	0	2	0.9

For patients with several episodes, worst intensity, relationship, outcome, and clinical consequence during the on-treatment period are displayed.
[1] Patient not yet returned to previous health status, is still followed up for the AE.

Source data: [c26471552, Table 15.3.1.1.3.1.1: 1]

Tabel 10. Oversigt over hepatobiliære og laboratoriske leverbivirkninger i INBUILD-studiet. Tabel fra nintedanibs EPAR for PF-ILS.

AEs and SAEs by hepatobiliary and liver laboratory safety topic over 52 weeks – TS
Overall population

Safety topic / *Subcategory*		Placebo		Nintedanib 150 mg bid	
		N	%	N	%
Number of patients		331	100.0	332	100.0
Hepatobiliary AEs	**Patients with**				
Drug-induced liver injury[1]	any AE	0	0	6	1.8
	SAE	0	0	6	1.8
Hepatic disorders combined[2]	any AE	25	7.6	91	27.4
	SAE	4	1.2	14	4.2
Drug-related hepatic disorders[3]	any AE	24	7.3	91	27.4
	SAE	4	1.2	14	4.2
Liver-related investigations, signs and symptoms[3]	any AE	21	6.3	80	24.1
	SAE	2	0.6	4	1.2
Cholestasis and jaundice of hepatic origin[3]	any AE	0	0	7	2.1
	SAE	0	0	6	1.8
Hepatitis, non-infectious[3]	any AE	0	0	0	0
	SAE	0	0	0	0
Hepatic failure[3]	any AE	4	1.2	17	5.1
	SAE	2	0.6	10	3.0
Liver laboratory AEs	**Patients with**				
Hepatic enzyme increased[2]	any AE	19	5.7	75	22.6
	SAE	2	0.6	4	1.2
Alanine aminotransferase increased[4]	any AE	12	3.6	43	13.0
	SAE	1	0.3	2	0.6
Aspartate aminotransferase increased[4]	any AE	12	3.6	38	11.4
	SAE	1	0.3	2	0.6
Gamma-glutamyltransferase increased[4]	any AE	7	2.1	19	5.7
	SAE	1	0.3	0	0
Blood alkaline phosphatase increased[4]	any AE	1	0.3	7	2.1
	SAE	0	0	0	0
Hyperbilirubinaemia[2]	any AE	0	0	2	0.6
	SAE	0	0	0	0

[1] MedDRA PT, subset of 'hepatic disorders combined', 'drug-related hepatic disorders', 'cholestasis and jaundice of hepatic origin', and 'hepatic failure'
[2] Grouping of MedDRA PTs [c26471552, Appendix 16.2.7, Listing 3.1]
[3] Grouping of MedDRA PTs, subset of 'hepatic disorders combined' [c26471552, Appendix 16.2.7, Listing 3.1]
[4] Grouping of MedDRA PTs, subset of 'hepatic enzyme increased' [c26471552, Appendix 16.2.7, Listing 3.1]

Source data: [c26471552, Tables 15.3.1.1.2.1: 11 and 15.3.1.1.2.1: 12]

Bilag 3: Cochrane – risiko for bias

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

Tabel 11. Vurdering af risiko for bias Flaherty et al., 2019, INBUILD, NCT02999178

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Randomisering foretaget med en interaktiv responsteknologi. Randomiseringen var stratificeret efter patienternes fibrotiske mønster på HRCT (UIP-lignende mønster eller andre fibrotiske mønstre). 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. Det primære effektmål (fald i FVC) og sikkerhed/bivirkninger blev analyseret i den samlede population, i subpopulationen af patienter med UIP-lignende mønster og i subpopulationen af patienter med andre fibrotiske mønstre. Sekundære effektmål blev vurderet i den samlede population og i subpopulationen af patienter med UIP-lignende mønster. 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 PF-ILS

Tabel 12. 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												
1	RCT	Ingen	Alvorlig[a]	Ingen	Alvorlig[b]	Ingen	-	-	HR: 0,78 (0,50; 1,21)	-	⊕⊕◯◯ LAV	KRITISK
Fald i FVC, 52 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	80,8 ml/år	187,8 ml/år	-	107,0 ml/år (65,4; 148,5)	⊕⊕⊕◯ MODERAT	KRITISK
Livskvalitet målt ved K-BILD, 52 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	0,55 point	-0,79 point	-	1,34 point (-0,31; 2,98)	⊕⊕⊕◯ MODERAT	KRITISK
Akut eksacerbationsrate, 52 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	-	-	HR 0,63 (0,37; 1,07)	-	⊕⊕⊕◯ MODERAT	KRITISK

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**
Alvorlige bivirkninger, 52 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	147/332	165/331	RR 0,89 (0,76; 1,05)	-5 %-point (-13; 0,2)	⨁⨁⨁◯ MODERAT	VIGTIG
Ophør grundet uønskede hændelser, 52 uger												
1	RCT	Ingen	Alvorlig[a]	Ingen	Ingen	Ingen	73/332	48/331	RR 1,52 (1,09; 2,11)	7 %-point (2; 13)	⨁⨁⨁◯ MODERAT	VIGTIG
Kvalitet af den samlede evidens	LAV[c]											

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

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

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

Medicinrådet

Application for the assessment of Ofev® (nintedanib) in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (PF-ILD)

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

Contents

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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. [1]
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, (EMA))	Ofev is also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype. [1]
Other approved therapeutic indications	Ofev is indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF). [1] Ofev is indicated in adults for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD). [1]

Overview of the pharmaceutical	
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 are available in the following pack-size: - 60 x 1 soft capsules in aluminium/aluminium perforated unit dose blisters
Orphan drug designation	No

2. Abbreviations

Table 3 Abbreviations

Abbreviation	Term
ADR	Adverse Drug Reaction
AE	Adverse event
BI	Boehringer Ingelheim
BID	Twice daily
CI	Confidence interval
DBL1	Data base lock 1
DBL2	Data base lock 2
DLCo	Carbon Monoxide Diffusion Capacity
DMC	Danish Medicines Council (Medicinrådet)
EC	European Commission
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FVC	Forced Vital Capacity
HR	Hazard ratio
HRCT	High Resolution Computed Tomography
ICH	International Council For Harmonisation
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
K-BILD	King's Brief Interstitial Lung Disease questionnaire
MedDRA	Medical Dictionary for Regulatory Affairs
PF-ILD	Progressive fibrosing Interstitial Lung Disease
QoL	Quality of Life
RD	Risk Difference
RR	Risk Ratio
SAE	Serious Adverse Event
SD	Standard deviation
SE	Standard error
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SSc-ILD	Systemic Sclerosis – Interstitial Lung Disease
UIP	Usual Interstitial Pneumonia

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3. Summary

On 13. July 2020 the European Commission (EC) approved Ofev® (nintedanib) as the first medicinal product for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (PF-ILD) in adults - this indication is the subject for the present application.

Ofev was initially approved by the EC in 2015 for the treatment of Idiopathic Pulmonary Fibrosis (IPF) in adults. On 17. April 2020 the EC approved Ofev as the first and only medicinal product for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD) in adults. The SSc-ILD indication is subject to a separate application to the Danish Medicines Council (DMC).

Nintedanib was investigated in one placebo-controlled pivotal phase III study – the INBUILD® study. INBUILD (Efficacy and Safety of Nintedanib in Patients With Progressive Fibrosing Interstitial Lung Disease) was a phase III, multicentre, prospective, randomised (1:1), double-blind, placebo-controlled study with objective of investigating the efficacy and safety of nintedanib 150 mg twice daily over 52 weeks in patients with PF-ILD defined as patients who present with interstitial lung disease within the 24 months before screening, despite standard treatment with an agent other than nintedanib or pirfenidone: a relative decline in the FVC of at least 10% of the predicted value, a relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms or an increased extent of fibrosis on high-resolution CT, or worsening of respiratory symptoms and an increased extent of fibrosis. Patients were stratified based on the presence of Usual Interstitial Pneumonia (UIP)-like pattern on high resolution CT (HRCT) or not. [2]

The primary endpoint was annual rate of decline in Forced Vital Capacity (FVC) (measured in millilitres per year) and key secondary endpoints were the absolute change from baseline in the total score on the King's Brief Interstitial Lung Disease (K-BILD) questionnaire at week 52, the time until the first acute exacerbation of ILD or death over the 52-week period, and the time until death over the 52-week period. [2] Data were also analysed for the entire study period (Database Lock 2 (DBL2)) until the last patient had reached 52 weeks of treatment. Data for 52 weeks is presented for the annual rate of decline of FVC and the mean change in K-BILD score, while data for DBL2 are presented for median survival, acute exacerbations, proportion of patients experiencing ≥1 SAE, and proportion of patients discontinued due to an AE.[3]

The population included in the INBUILD 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 allowed for documented disease progression within 24 months prior to inclusion into the study. The implications of the difference in population for the interpretation of data from the INBUILD study are described in the application.

At DBL2 36/332 (10.8%) of patients in the nintedanib group and 45/331 (13.6%) in the placebo group had died with a hazard ratio (HR) of 0.78 [95% Confidence Interval (CI): 0.50, 1.21; p=0.259). [3] The study was not powered to show a statistically significant difference between the treatment groups. However, the combined key secondary endpoint of time to first acute ILD exacerbations or death was statistically significant in favour of nintedanib at DBL2. [3]

At 52 weeks, the adjusted rate of decline in the FVC (used as a surrogate endpoint for mortality) over the 52-week period (the primary endpoint) was −80.8 ml per year in the nintedanib group and −187.8 ml per year in the placebo group (between-group difference, 107.0 ml; 95% CI: 65.4, 148.5; P<0.0001). [2, 4]

At 52 weeks, the mean change in K-BILD Quality of Life (QoL) score from placebo was 0.55 in the nintedanib group compared to -0.79 points in the placebo group, an absolute difference of 1.34 (95% CI: -0.31, 2.98; p-value 0.1115) point. [2, 4]

At DBL2 23/332 (6.9%) patients in the nintedanib group and 35/331 (10.6%) patients in the placebo group had experienced an acute exacerbation with a HR of 0.63 [95% CI: 0.37, 1.07; p=0.868]. [3]

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At DBL2 147/332 (44.3%) of patients in the nintedanib group and 164/331 (49.5%) of patients in the placebo group had experienced one or more serious adverse events (SAE), a Risk Difference (RD) of -0.05 [95% CI: -0.13, 0.02; p=0.158]. [3]

At DBL2 73/332 (22.0%) patients in the nintedanib group and 48/331 (14.5%) patients in the placebo group had discontinued due to an AE [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 PF-ILD confirmed the well-known and manageable safety profile from use in IPF since 2015. No new signals were identified in the INBUILD study. [2]

Ofev (nintedanib) is the first approved treatment option for patients with PF-ILD and has documented effect on pulmonary function (FVC) with a well-known and manageable safety profile.

4. Literature search

As per the instruction in the DMC protocol no literature search has been conducted. The application is based on the pivotal phase III study INBUILD.

4.1 Relevant studies

Table 4 Relevant studies included in the application

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Flaherty KR, Wells AU, Cottin V, et al. N Engl J Med. 2019 Oct 31;381(18):1718-1727. [2]				
Wells AU, et al. Lancet Respir Med. 2020 May;8(5):453-460. [5]	INBUILD	NCT02999178	JAN 2017 – AUG 2019	1
Flaherty KR, et al. European Respiratory Journal Sep 2020, 56 (suppl 64) 4578. [6]				

In addition, the assessment report from IQWiG, the 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, 4, 7, 8]

- Assessment report EMA/315975/2020. Procedure No. EMEA/H/C/003821/II/0027 (the PF indication/INBUILD study)[4]
- Assessment report EMA/155527/2020. Procedure No. EMEA/H/C/003821/II/0026 (the SSc-indication/SENSCIS study)[7]
- Assessment report EMA/76777/2015. Procedure No. EMEA/H/C/003821/0000 (the IPF indication/INPULSIS studies)[8]

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4.2 Main characteristics of included studies

The clinical development program for nintedanib in PF-ILD consists of one phase III study – the INBUILD study which is briefly described below and in detail in Table 10 on p. 22. [2]

INBUILD® (Efficacy and Safety of Nintedanib in Patients With Progressive Fibrosing Interstitial Lung Disease) was a phase III, multicentre, prospective, randomised (1:1), double-blind, placebo-controlled study with objective of investigating the efficacy and safety of nintedanib 150 mg twice daily over 52 weeks in patients with PF-ILD meeting one or more of the following inclusion criteria: interstitial lung disease within the 24 months before screening, despite standard treatment with an agent other than nintedanib or pirfenidone: a relative decline in the FVC of at least 10% of the predicted value, a relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms or an increased extent of fibrosis on high-resolution CT, or worsening of respiratory symptoms and an increased extent of fibrosis. At the time of enrollment, patients were required to have an FVC of at least 45% of the predicted value and a diffusing capacity of the lung for carbon monoxide (corrected for hemoglobin) of 30 to less than 80% of the predicted value. [2]

The primary endpoint was the annual rate of decline in FVC (measured in millilitres per year) and key secondary endpoints were the absolute change from baseline in the total score on the K-BILD questionnaire at week 52, the time until the first acute exacerbation of ILD or death over the 52-week period, and the time until death over the 52-week period. Data were analysed for both the overall population and for the group of patients having Usual Interstitial Pneumonia (UIP) like pattern on HRCT. [2] As the analysis of the group of patients having UIP-like pattern on HRCT did not differ from the results for the overall population, only results for the overall population are presented in this application.

The DMC defined outcomes includes acute exacerbations. Acute exacerbations separately were not included in the study protocol as a prespecified outcome but were recorded as adverse events (AE). For details see the results per study section on acute exacerbations on p. 11.[9]

In the INBUILD study the main outcome related to exacerbations was the key secondary composite endpoint of time to first acute ILD exacerbation or death over 52 weeks with the purpose of assessing the effect of nintedanib on the core efficacy parameters in these respiratory diseases. In addition, the time to progression or death was assessed as a composite endpoint. [2, 9]

Key secondary endpoint

- Time to first acute ILD exacerbation or death over 52 weeks
- Time to death over 52 weeks

Other secondary endpoint

- Time to progression (defined as a ≥ 10% absolute decline in FVC % predicted) or death over 52 weeks

The above were also further assessed as predefined endpoints over the whole trial (parts A + B). [9]

In the INBUILD study acute exacerbation was defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality with all of the following: [9]

- Previous or concurrent diagnosis of ILD
- Acute worsening or development of dyspnoea typically less than one month duration
- Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with fibrosing ILD
- Deterioration not fully explained by cardiac failure or fluid overload

The use of composite endpoints was based on the following reasoning. Combining two or more study outcomes typically results in an increase in the incidence rates of the composite endpoint and improves the ability to detect

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differences in the endpoint. Such pooling of study outcomes will result in a higher event rate and increased statistical precision allowing for study design with fewer patients and shorter duration. [10, 11]

The International Council for Harmonisation (ICH) Harmonised Guideline E9 (R1) on Estimands And Sensitivity Analysis In Clinical Trials describes circumstances in which the application of a composite endpoint may be relevant as described in the following. [12]

Composite variable strategies can be viewed as implementing the intention-to-treat principle in some cases where the original measurement of the variable might not exist or might not be meaningful, but where the intercurrent event itself meaningfully describes the patient's outcome, such as when the patient dies. [12]

Terminal events, such as death, are perhaps the most salient examples of the need for the composite strategy. If a treatment saves lives, its effect on various measures in surviving patients may be of interest, but it would be inappropriate to say that the summary measure of interest was only the average value of some numerical measure in survivors. The outcome of interest is survival along with the numerical measures. For example, progression-free survival in oncology trials measures the treatment effect on a combination of the growth of the tumour and survival. [12]

The EMA Guideline on multiplicity issues in clinical trials (EMA/CHMP/44762/2017) describes that a composite endpoint must make sense from a clinical perspective. For any component that is included in the composite, it is usually appropriate that any additional component reflecting a worse clinical event is also included. For example, if it is agreed that hospitalisation is an acceptable component in a composite endpoint, it would be usual to also include components for more adverse clinical outcomes that are relevant to the clinical setting (*e.g.,* non-fatal myocardial infarction and stroke) and death. Excluding such events, with an argument that no beneficial effect can be expected or that these will be captured in the safety assessment or focussing on specific types of events (for example disease-related mortality in preference to all-cause mortality) introduces difficulties for analysis and interpretation that should be approached carefully. In this event, the primary composite should always be presented and interpreted alongside a secondary analysis in which no important clinical outcomes are excluded. [10]

The selection of acute exacerbation and death as a composite endpoint is thus based on the fact that acute exacerbations are associated with very high morbidity and mortality.[13]

While the impact of acute exacerbations in PF-ILD has not previously been studied, Collard et al conducted a systematic review of the available knowledge in acute exacerbations in IPF, in which the profound prognostic implications of an acute exacerbation of IPF are described. [13]

The available data suggest that up to 46% of deaths in IPF are preceded by an acute exacerbation [14-16], and the median survival of patients with IPF who experience an acute exacerbation is approximately 3 to 4 months. [17, 18] [13]

Brown et al. used data from the INBUILD and INPULSIS trials to investigate the natural history of progressive fibrosing interstitial lung diseases (ILDs). Subjects in the two INPULSIS trials had a clinical diagnosis of idiopathic pulmonary fibrosis (IPF) while subjects in the INBUILD trial had a progressive fibrosing ILD other than IPF and met protocol-defined criteria for ILD progression despite management. Using data from the placebo groups the rate of decline in forced vital capacity (FVC) (mL/year) and mortality over 52 weeks in the INBUILD trial as compared with pooled data from the INPULSIS trials. The adjusted mean annual rate of decline in FVC in the INBUILD trial (n=331) was similar to that observed in the INPULSIS trials (n=423) (-192.9 mL/year and -221.0 mL/year, respectively; nominal p-value=0.19). The proportion of subjects who had a relative decline in FVC >10% predicted at week 52 was 48.9% in the INBUILD trial and 48.7% in the INPULSIS trials, and the proportion who died over 52 weeks was 5.1% in the INBUILD trial and 7.8% in the INPULSIS trials. A relative decline in FVC >10% predicted was associated with an increased risk of death in the INBUILD trial (hazard ratio 3.64) and the INPULSIS trials (hazard ratio 3.95).

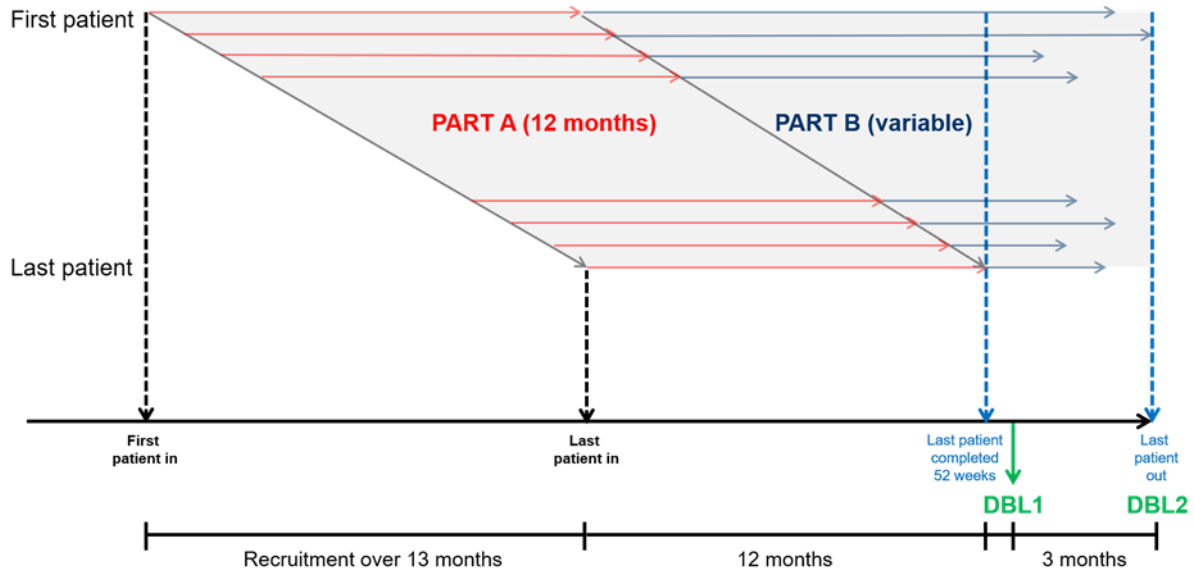
These findings indicate that patients with fibrosing ILDs other than IPF, who are progressing despite management, have a subsequent clinical course similar to patients with untreated IPF, with a high risk of further ILD progression and early mortality.[19]

As the composite endpoints of acute exacerbations and death as well as FVC worsening and death respectively rank higher than acute exacerbations alone in the endpoint hierarchy in the INBUILD study [9], data for these endpoints have been included in the narrative description of exacerbations on p. 12.

The timing of follow-up for the primary analysis was 52 weeks (Part A). Patients were followed in Part B until the last patient completed the 52-week visit. [3, 4]

Data from Part A are referred to as 52-week data, while data for Part A + B is referred to as DBL1 and data for follow-up until Last Patient Out is referred to as DBL2.

Figure 1 Data base locks – the INBUILD PF-ILD study



The patient population and outcomes defined in the INBUILD study protocol are not fully consistent with the population and outcomes defined by in DMC protocol. The main difference concerning the definition of the population is described in the section on other considerations (section 5.1.4 (p. 16)).

5. Clinical questions

5.1 Clinical question #1 What is the value of nintedanib as compared to placebo for patients with interstitial lung disease with progressive fibrosing interstitial lung disease?

5.1.1 Presentation of relevant studies

The pivotal study, INBUILD, is briefly described in section 4.2 above and in detail in Table 10 on p. 22. [2]

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5.1.2 Results per study

The results for the INBUILD study can be found in Table 12 on p. 28.

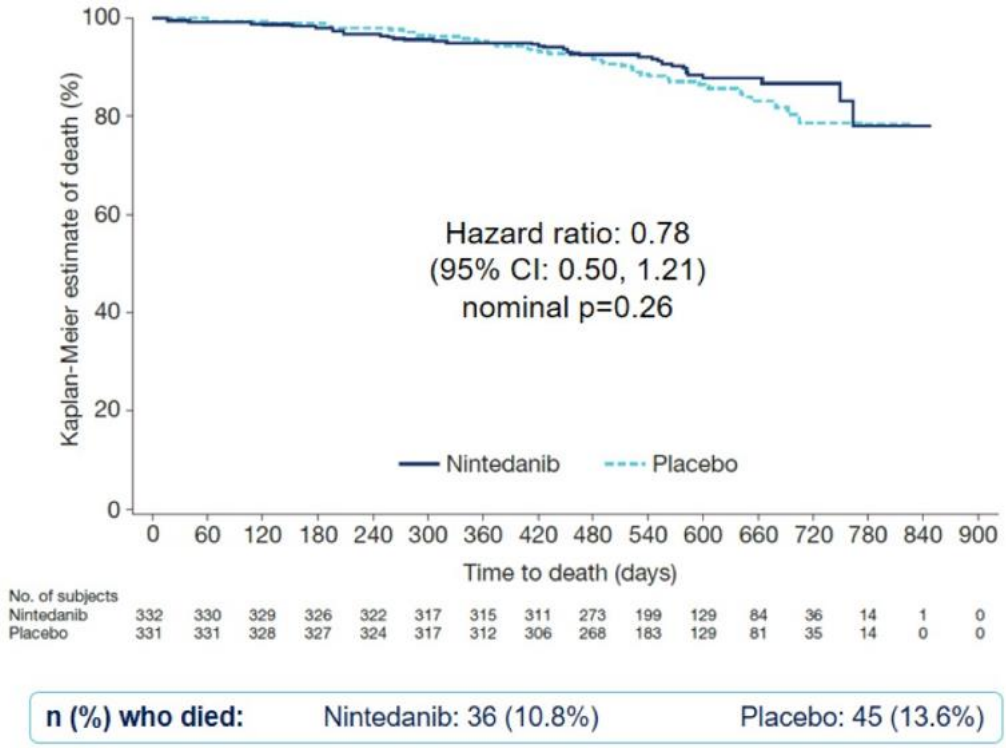
Data are shown for the overall population as the treatment effect between subgroups according to the imaging pattern (UIP vs non-UIP) was consistent. [2]

Mortality – median survival

In the INBUILD study mortality was assessed as a predefined secondary endpoint: Time to death over 52 weeks.

Time to death over the whole trial period was longer in the nintedanib group than in the placebo group corresponding to a risk reduction of 22% (HR: 0.78; 95% CI: 0.50, 1.21; nominal p=0.259, Figure 2). [1, 3, 6] Kaplan-Meier curves for time to death started separating after 480 days (approximately 68 weeks; Figure 2). [1, 3, 6]

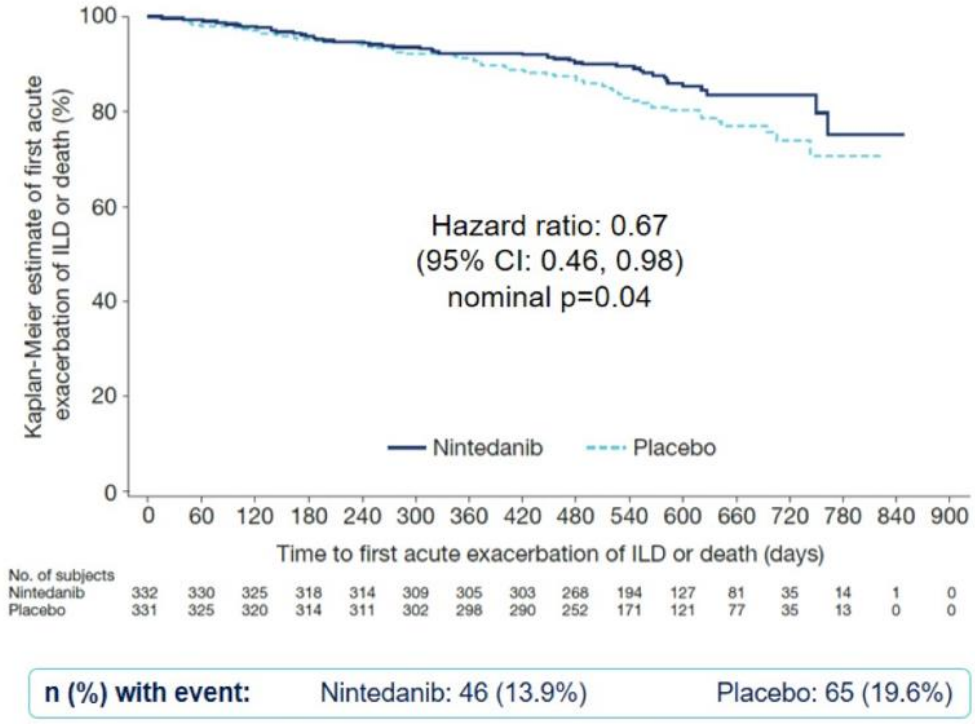
Figure 2 Kaplan-Meier plot of time to death over the whole trial (DBL2; overall population)



While the analysis for overall mortality at DBL 2 is not statistically significant, data for the predefined further efficacy endpoint related to death (time to first acute ILD exacerbation or death over the whole trial) (DBL2), show a statistically significant difference in favour of nintedanib compared to placebo. [6]

In the overall population, a lower proportion of patients treated with nintedanib had an event of first acute ILD exacerbation or death than patients in the placebo group over the whole trial period (13.9% versus 19.6%; HR: 0.67; 95% CI: 0.46, 0.98; nominal p=0.039, Figure 3). [3]

Figure 3 Kaplan Meier plot of time to first acute ILD exacerbation or death over the whole trial period (DBL2; Overall population)



FVC – annual rate annual rate of decline

The primary efficacy endpoint was the annual rate of decline in FVC (expressed in mL over 52 weeks). In the overall population, the adjusted rate of decline in the FVC over the 52-week period (the primary end point) was −80.8 ml per year in the nintedanib group and −187.8 ml per year in the placebo group [between-group difference, 107.0 ml; 95% CI: 65.4, 148.5; P<0.0001]. [2, 4]

Data for later database locks have not been reported.

Quality of life – Mean change in King's Brief Interstitial Lung Disease (K-BILD) from baseline

QoL assessed by absolute change from baseline in K-BILD total score at week 52 was a main secondary endpoint in the INBUILD study. No statistically significant difference between the nintedanib and placebo groups was identified. [2]

At week 52, the adjusted mean absolute change from baseline in the total score on the K-BILD questionnaire (3 domains: measuring breathlessness and activities, psychological factors, and chest symptoms) was 0.55 [95% CI: -0.62, 1.72] points in the nintedanib group and −0.79 [95% CI: -1.94, 0.37] points in the placebo group (between-group difference: 1.34 points; 95% CI: −0.31, 2.98; p=0.1115) in the overall population. [2, 4]

Acute exacerbation rate – proportion of patients experiencing at least one exacerbation per year

The main outcome related to exacerbations was the main secondary endpoint of time to first acute ILD exacerbation or death over 52 weeks. Acute exacerbations separately were not included in the study protocol as a prespecified outcome but was recorded as AEs. Analysis of acute exacerbations at week 52 and at DBL2 was performed.

At DBL2 23/332 (6.9%) patients in the nintedanib group and 35/331 (10.6%) patients in the placebo group had experienced an acute exacerbation [HR: 0.63; 95% CI: 0.37, 1.07; p=0.0868]. [3]

As noted above, the data for the combined endpoints of acute exacerbations and death at DBL2 showed a nominal, statistically significant benefit of nintedanib as compared to placebo in reducing the number of the combined outcome of acute exacerbations and death. [3, 6] For details see the section on mortality on p. 11.

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

At DBL2 147/332 (44.3%) patients in the nintedanib group and 164/331 (49.5%) patients in the placebo group had experienced one or more SAE with a Risk Difference of -0.05 [95% CI: -0.13, 0.002; p=0.193] and a Risk Ratio of 0.89 (95% CI: 0.76, 1.05; p=0.158].[3]

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

At DBL2 73/332 (22.0%) patients in the nintedanib group and 48/331 (14.5%) patients in the placebo group had discontinued due to an AE with a Risk Difference of 0.07 [95% CI: 0.02, 0.13; p=0.013] and a Relative Risk of 1.52 [95% CI: 1.09, 2.11; p=0.013].[3]

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Adverse drug reactions – Qualitative review of the adverse event profile

Sourced from the SmPC, Table 5 provides a summary of the adverse drug reactions (ADRs) 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 5 Adverse Drug Reactions

System Organ Class preferred term	**Idiopathic pulmonary fibrosis**	**Frequency 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			
Renal failure	Not known	Uncommon	Uncommon
Nervous system disorders			
Headache	Common	Common	Common
Ref.: [1]			

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Dose adjustment 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 6.

Table 6 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

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As nintedanib has been on the market 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 in general, the AEs reported for more than 5% of patients in the nintedanib group over 52 weeks are consistent with the known ADRs of the authorised product. Of the AEs reported for ≤5% of patients in either treatment group, frequencies were more than 2% higher in the nintedanib group compared with the placebo group for acute respiratory failure (3% vs. 0.6%). [4]

In general, investigator-defined drug-related AEs reported for more than 1.5% of patients over 52 weeks in the nintedanib group over 52 weeks is consistent with the known ADRs of the authorised product, except for epistaxis with a frequency of 0.9% in the placebo group versus 1.8% in the nintedanib group. [4]

The overall AE profile over the whole trial up to DBL1 was generally in line with the overall AE profile over 52 weeks. [4]

Of note, ILD as an AE was reported with less frequency in the nintedanib group compared with the placebo (4.8% vs. 11.8%) along with the symptomatic AEs of cough (9.9% vs 13.3%) and dyspnoea (10.8% vs 13.3%).[4]

5.1.3 Comparative analyses

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

5.1.4 Other considerations

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.[23]

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.[2, 24, 25]

Data for the efficacy in subgroups with dose reductions and interruptions for the INBUILD study have not yet been published.

However, based on data from the phase II dose ranging study, the phase III INPULSIS study in IPF and the phase III SENSCIS study in SSc-ILD as described below, the efficacy in the PF-ILD population is expected not to be clinically significantly different between the different disease entities with dose reduction/interruption.

Dose reduction/interruption pattern in PF-ILD – the INBUILD study

In the phase III pivotal study for nintedanib in PF-ILD (INBUILD), the number of patients with at least one dose reduction was 112/331 (33.7%) in the nintedanib group and 18/332 (5.4%) in the placebo group. In both treatment groups, investigator-defined drug-related AEs were the main reason for dose reduction (nintedanib: 87.3% of dose reductions, placebo: 70.0%) and treatment interruptions (nintedanib: 71.3% of interruptions, placebo: 48.8%).[4]

Exposure to investigational treatment was overall comparable between the treatment groups.

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The median (range) duration of exposure in the main part (52 week) of the study was 12.2 (0.0, 12.2) months in the nintedanib group and 12.2 (0.3, 12.2) months in the placebo group, while it in the overall study (DBL2) was 17.4 [0.0, 27.7] and 17.4 [0.3, 26.6] month for the nintedanib and placebo groups respectively. [3, 4]

The mean (SD) dose intensity was slightly lower in the nintedanib group (nintedanib: 92.54% (11.87), placebo: 98.59% (5.43)), which was due to a higher number of patients with dose reductions or treatment interruptions in the nintedanib group. [4]

Dose reduction/interruption pattern in IPF – the INPULSIS study

The selection of the 150 mg dose for the first indication IPF for nintedanib was based on the results of the phase II trial in patients with IPF.[26]

The efficacy and safety of this dosing was confirmed in the phase III IPF study, INPULSIS.[24]

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.[27]

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 (Table 7). [27]

Table 7 Change from baseline in FVC (ml) at week 52 by dose subgroups - the INPULSIS IPF study

Patient group	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)
Bid – twice daily. Ref.: [24, 27]				

Dose reduction/interruption pattern in SSc-ILD – the SENSCIS study

A similar patten was seen in the phase III pivotal study for SSc-ILD (SENSCIS), where 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. [7]

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%). [7]

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. [7]

The exposure throughout the whole trial was 14.51 (SD 6.67) equal to 349.0 patient years for nintedanib and 15.70 (SD 5.67) equal to 377.5 patient years for the placebo group. [7]

A subgroup analysis based on dose reductions in the SENSCIS study was presented as an oral presentation 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 8). [28]

Table 8 Effect of dose reduction/interruption - the SENSCIS SSc-ILD study

Patient 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 (nintedanib) (n=117)	-39.7 (21.4)
Treatment interruption (nintedanib) (n=109)	-60.9 (22.0)
Dose reduction and/or treatment interruption (nintedanib) (n=139)	-47.1 (19.7)
Dose intensity ≤90% (nintedanib) (n=105)	-44.3 (22.7)
Ref.: [28]	

In summary the subgroup analysis 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. A similar pattern is expected to be seen in the PF-ILD population in the INBUILD study.

The study population in the INBUILD study

Question from the DMC:

Referring to the clinical question, the DMC Expert Committee requests data for PF-ILD patients, who are progressing on first line treatment with immunomodulatory medications. It is unclear if this is the case for the study population in the INBUILD study.
The applicant is therefore requested to explain the comparability between the study population in the INBUILD 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 criteria for the patient population in INBUILD have been described in detail in Table 10. In the context of comparability with the population defined by the DMC, the following inclusion criteria are to be highlighted:

Patients with physician diagnosed ILD who fulfil at least one of the following criteria for PF-ILD within 24 months of screening visit (Visit 1) despite treatment with off-label medications used in clinical practice to treat ILD, as assessed by the investigator (refer to Exclusion Criteria):[2]

- Clinically significant decline in FVC % predicted based on a relative decline of >=10%
- Marginal decline in FVC % predicted based on a relative decline of >=5-<10% combined with worsening of respiratory symptoms
- Marginal decline in FVC % predicted based on a relative decline of >=5-<10% combined with increasing extent of fibrotic changes on chest imaging
- Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging

These inclusion criteria are consistent with the criteria defined in the DMC protocol.

The assessment of progression of ILD was determined at study visit 1 (screening visit). While the inclusion/exclusion criteria in the INBUILD protocol allowed for progression during the last 24 months, the patients were still receiving

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their current treatment with off-label medications used in clinical practice to treat ILD at the screening visit. Only if the patient met the inclusion criteria for progression was the patient included into the study. [2]

Patient who at the screening visit (Visit 1) were being treated with excluded medications/dosages entered a wash out period as shown below to ensure that the INBUILD study actually compared nintedanib to placebo in patients who had progressed on standard non-approved medication without the confounder of continued treatment with nonapproved medication, when they entered the study at the randomization visit (visit 2). [2]

Prohibited medications at randomization and the required wash out period prior to randomization is shown in Table 9. [2]

Table 9 Medication washout period prior to randomization – the INBUILD PF-ILD study

Medication	Washout period
Azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil, oral corticosteroids >20mg/day	4 weeks prior to visit 2
Rituximab	6 months prior to visit 2
Cyclophosphamide	8 weeks prior to visit 2
Investigational drugs	4 weeks or 6 half-lives (whichever is longer) prior to visit 1
Ref.: [2, 9]	

The patient population in the INBUILD study thus consists of patients who despite treatment with off-label medications used in clinical practice to treat ILD were assessed to have progressed at the time of the screening visit for the INBUILD study.

Therefore, no difference between the population defined by the DMC and the patient population in the INBUILD study with regard to safety and efficacy of nintedanib is expected.

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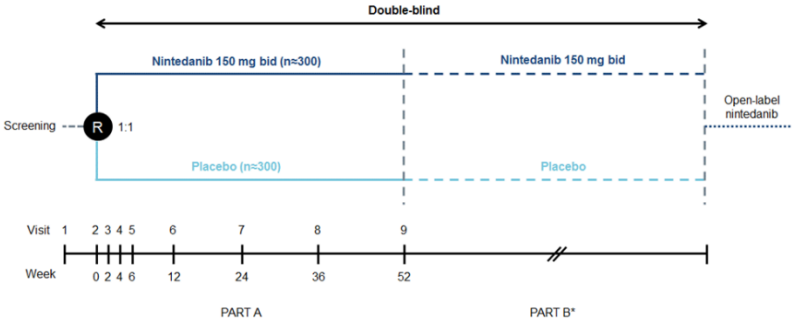
7. Appendices

7.1 Literature search

As per the DMC protocol no literature search has been performed. [23]

7.2 Main characteristics of included studies

Table 10 Main study characteristics for the INBUILD PF-ILD study

Main study characteristics – the INBUILD PF-ILD study	
Trial name[2]	INBUILD
NCT number[2]	NCT02999178
Objective[2]	To investigate the efficacy and safety of nintedanib over 52 weeks in patients with progressive fibrosing Interstitial Lung Disease defined as patients who present with features of diffuse fibrosing lung disease of >10% extent on HRCT and whose lung function and respiratory symptoms or chest imaging have worsened (see criteria below) despite treatment with off-label medications used in clinical practice to treat ILD.
Publications – title, author, journal, year	Flaherty KR, Wells AU, Cottin V, et al. INBUILD Trial Investigators. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med. 2019 Oct 31;381(18):1718-1727. [2] Wells AU, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med. 2020 May;8(5):453-460. doi: 10.1016/S2213-2600(20)30036-9. Epub 2020 Mar 5. PMID: 32145830.[5] [Abstract] Flaherty KR, et al. Effects of nintedanib on progression of ILD in patients with fibrosing ILDs and a progressive phenotype: further analyses of the INBUILD trial. European Respiratory Journal Sep 2020, 56 (suppl 64) 4578; DOI: 10.1183/13993003.congress-2020.4578 [6] Flaherty KR et al. Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. BMJ Open Respir Res. 2017 Sep 17;4(1):e000212. [29]
Study type and design[2]	Phase III, multicentre, prospective, randomised, double-blind, placebo-controlled study.  *Figure 4 Study design – the INBUILD PF-ILD study*

Main study characteristics – the INBUILD PF-ILD study	
Follow-up time	The timing of follow-up for the primary analysis was 52 weeks (Part A). Patients were followed in Part B until the last patient completed the 52-week visit, leading to a mean duration of exposure before first database lock (DBL1) of 15.0 (±6.8) months in the nintedanib-group and 16.2 (±5.5) months in the placebo group (making a time to event analysis possible) and 15.6 (±7.2) and 16.8 (±5.8) up to DBL2.[3, 4] Data from Part A are referred to as 52 week data, while data for Part A + B is referred to as DBL2 or the "whole trial".
Population (inclusion/exclusion criteria)	Inclusion criteria: Written Informed Consent consistent with International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP) and local laws signed prior to entry into the study (and prior to any study procedure including shipment of HRCT to reviewer). Male or female patients aged >= 18 years at Visit 1. Patients with physician diagnosed Interstitial Lung Disease (ILD) who fulfil at least one of the following criteria for progressive fibrosing Interstitial Lung Disease within 24 months of screening visit (Visit 1) despite treatment with off-label medications used in clinical practice to treat ILD, as assessed by the investigator (refer to Exclusion Criteria): • Clinically significant decline in Forced Vital Capacity (FVC) % predicted based on a relative decline of >=10% • Marginal decline in FVC % predicted based on a relative decline of >=5-<10% combined with worsening of respiratory symptoms • Marginal decline in FVC % predicted based on a relative decline of >=5-<10% combined with increasing extent of fibrotic changes on chest imaging • Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging [Note: Changes attributable to comorbidities e.g. infection, heart failure must be excluded. Off-label medications used in the clinical practice to treat ILD include but are not limited to corticosteroid, azathioprine, mycophenolate mofetil, n-acetylcysteine (NAC), rituximab, cyclophosphamide, cyclosporine, tacrolimus]. Fibrosing lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent of >10%, performed within 12 months of Visit 1 as confirmed by central readers. For patients with underlying Connective Tissue Disease (CTD): stable CTD as defined by no initiation of new therapy or withdrawal of therapy for CTD within 6 weeks prior to Visit 1. Carbon Monoxide Diffusion Capacity (DLCO) corrected for Haemoglobin (Hb) [visit 1] ≥ 30% and <80% predicted of normal at Visit 2 FVC >= 45% predicted at Visit 2 Exclusion criteria: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) > 1.5 x Upper Limit of Normal (ULN) at Visit 1 or Bilirubin > 1.5 x ULN at Visit 1 Creatinine clearance <30 mL/min calculated by Cockcroft-Gault formula at Visit 1.

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Main study characteristics – the INBUILD PF-ILD study	
	Patients with underlying chronic liver disease (Child Pugh A, B or C hepatic impairment). 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). Use of any of the following medications for the treatment of Interstitial Lung Disease (ILD): azathioprine (AZA), cyclosporine, mycophenolate mofetil, tacrolimus, oral corticosteroids (OCS) >20mg/day and the combination of OCS+AZA+NAC within 4 weeks of Visit 2, cyclophosphamide within 8 weeks of Visit 2, rituximab within 6 months of Visit 2. Note: Patients whose Rheumatoid Arthritis (RA)/Connective Tissue Disease (CTD) is managed by these medications should not be considered for participation in the current study unless change in RA/CTD medication is medically indicated (see Inclusion Criteria) Diagnosis of Idiopathic Pulmonary Fibrosis (IPF) based on American Thoracic Society (ATS)/ European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) 2011 Guidelines. Significant Pulmonary Arterial Hypertension (PAH) defined by any of the following: • Previous clinical or echocardiographic evidence of significant right heart failure • History of right heart catheterization showing a cardiac index <= 2 l/min/m² • PAH requiring parenteral therapy with epoprostenol/treprostinil • Primary obstructive airway physiology (pre-bronchodilator FEV1/FVC < 0.7 at Visit 1). • In the opinion of the Investigator, other clinically significant pulmonary abnormalities. Major extrapulmonary physiological restriction (e.g. chest wall abnormality, large pleural effusion) Cardiovascular diseases, any of the following: • Severe hypertension, uncontrolled under treatment (≥160/100 mmHg), within 6 months of Visit 1 • Myocardial infarction within 6 months of Visit 1 • Unstable cardiac angina within 6 months of Visit 1 Bleeding risk, any of the following: • Known genetic predisposition to bleeding. • Patients who require ◦ Fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin) ◦ High dose antiplatelet therapy. [Note: Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U. s.c. per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy) are not prohibited].

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Main study characteristics – the INBUILD PF-ILD study	
	• History of haemorrhagic central nervous system (CNS) event within 12 months of Visit 1. • Any of the following within 3 months of Visit 1: ◦ Haemoptysis or haematuria ◦ Active gastro-intestinal (GI) bleeding or GI - ulcers ◦ Major injury or surgery (Investigators judgment). • Coagulation parameters: International normalized ratio (INR) >2, prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT) by >1.5 x ULN at Visit 1. History of thrombotic event (including stroke and transient ischemic attack) within 12 months of Visit 1. Known hypersensitivity to the trial medication or its components (i.e. soya lecithin) Patients with peanut allergy. Other disease that may interfere with testing procedures or in the judgment of the Investigator may interfere with trial participation or may put the patient at risk when participating in this trial. Life expectancy for disease other than ILD < 2.5 years (Investigator assessment). Planned major surgical procedures. Women who are pregnant, nursing, or who plan to become pregnant while in the trial. Women of childbearing potential* not willing or able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly as well as one barrier method for 28 days prior to and 3 months after nintedanib administration. A list of contraception methods meeting these criteria is provided in the patient information. In the opinion of the Investigator, active alcohol or drug abuse. Patients not able to understand or follow trial procedures including completion of self-administered questionnaires without help. *A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Intervention	Nintedanib 150 mg orally twice daily (N=332) Placebo for nintedanib orally twice daily (N=331)
Baseline characteristics	*Table 11 Baseline characteristics – the INBUILD PF-ILD study*

Characteristics of the Overall Population at Baseline.* [2]

	Nintedanib	**Placebo**
Characteristic	(N = 332)	(N = 331)
Male sex — no. (%)	179 (53.9)	177 (53.5)
Age — years	65.2±9.7	66.3±9.8
Former or current smoker — no. (%)	169 (50.9)	169 (51.1)
UIP-like fibrotic pattern on high-resolution CT — no. (%)	206 (62.0)	206 (62.2)

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Main study characteristics – the INBUILD PF-ILD study		
Criteria for disease progression in previous 24 months — no. (%)		
Relative decline in FVC of ≥10% of predicted value	160 (48.2)	172 (52.0)
Relative decline in FVC of 5% to <10% of predicted value plus worsening of respiratory symptoms or increased extent of fibrosis on high-resolution CT.	110 (33.1)	97 (29.3)
Worsening of respiratory symptoms and increased extent of fibrosis on high-resolution CT.	62 (18.7)	61 (18.4)
FVC		
Mean value — ml	2340±740	2321±728
Percent of predicted value	68.7±16.0	69.3±15.2
Diffusing capacity for carbon monoxide†		
Mean value — mmol/min/kPa	3.5±1.2	3.7±1.3
Percent of predicted value	44.4±11.9	47.9±15.0
Total score on K-BILD questionnaire‡	52.5±11.0	52.3±9.8

* Plus – minus values are means ±SD. FVC denotes forced vital capacity, and UIP usual interstitial pneumonia.
† The values for diffusing capacity for carbon monoxide were corrected for the hemoglobin level.
‡ Scores on the King's Brief Interstitial Lung Disease (K-BILD) questionnaire range from 0 to 100, with higher scores representing better health status.

Primary and secondary endpoints	Primary Outcome Measures : Annual rate of decline in Forced Vital Capacity (measured in millilitres per year) [Time Frame: 52 weeks] Secondary Outcome Measures: Absolute change from baseline in King's Brief Interstitial Lung Disease Questionnaire (K-BILD) total score at week 52 [Time Frame: 52 weeks] Time to first acute ILD exacerbation or death over 52 weeks [Time Frame: 52 weeks] Time to death over 52 weeks [Time Frame: 52 weeks] Time to death due to respiratory cause over 52 weeks [Time Frame: 52 weeks] Time to progression (defined as a equal or more than 10 percent absolute decline in Forced Vital Capacity (FVC) percent predicted) or death over 52 weeks [Time Frame: 52 weeks] Proportion of patients with a relative decline from baseline in Forced Vital Capacity (FVC) percent predicted of more than 10 percent at week 52 [Time Frame: 52 weeks] Proportion of patients with a relative decline from baseline in Forced Vital Capacity (FVC) percent predicted of more than 5 percent at week 52 [Time Frame: 52 weeks] Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms dyspnoea domain score at week 52 [Time Frame: 52 weeks]

Main study characteristics – the INBUILD PF-ILD study	
	Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms cough domain score at week 52 [Time Frame: 52 weeks]
Method of analysis	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	The primary analysis provided data on the overall population and the population with Usual Interstitial Pneumonia (UIP) on high resolution CT-scan.

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7.3 Results per study

Table 12 Results of the INBUILD PF-ILD study

Results of the INBUILD PF-ILD study											
Trial name:	INBUILD										
NCT number:	NCT02999178										
				Estimated absolute difference in effect			Estimated relative difference in effect			Methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median survival n (%) (DBL2)	Nintedanib	332	36 (10.8%)	Median not estimable as <50% of patients died*			HR:0.78	0.50 to 1.21	0.259	The HR and CI are based on a Cox's regression model with terms for treatment and stratified by HRCT pattern. The p-value is based on a stratified log-rank test, stratified by HRCT pattern. *Mortality was defined as time-to-event endpoint. Median thus not estimable.	IQWiG, table 13 (p. 23).[3]
	Placebo	331	45 (13.6%)								
FVC, annual rate of decline, mL/per year (52 weeks)	Nintedanib	332	-80.8 (-110.4 to -51.2)†	107.0	65.4 to 148.5	P<0.0001	NA	NA	NA	The absolute difference in effect is estimated using a random slope and intercept model with fixed effects for treatment, HRCT pattern, time, baseline FVC (mL) as well as the treatment-by-time and baseline-by-time interactions. Random effect was included for patient specific intercept and time.	Flaherty 2019, table 2.[2] P-value from EPAR, table 31 (p. 60) [4]
	Placebo	331	-187.8 (-216.9 to -158,6)†								

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Results of the INBUILD PF-ILD study										
QoL (K-BILD) Mean change from baseline) (points),(52 weeks)	Nintedanib	332	0.55 (-0.62 to 1.72)†	1.34	-0.31 to 2.98	0.1115	NA	NA	NA	The absolute difference in effect is estimated using a Mixed Model for Repeated Measures (MMRM), with fixed effects for baseline K-BILD value, HRCT pattern, visit, treatment-by-visit interaction and baseline-by-visit interaction.	EPAR, table 31 (p. 60) [4]
	Placebo	330	-0.79 (-1.94 to 0.37)†								
Acute exacerbations Proportion of patients experiencing ≥1/year (n(%)) (DBL 2)	Nintedanib	332	23 (6.9%)	NA*	NA*	NA*	HR 0.63	0.37 to 1.07	0.0868	The HR and CI are based on a Cox's regression model with terms for treatment and stratified by HRCT pattern. The p-value is based on a stratified log-rank test, stratified by HRCT pattern. *Acute exacerbations were defined as time-to-event endpoint. Data thus not estimable.	IQWiG, table 13 (p.23). [3]
	Placebo	331	35 (10.6%)								
SAE, proportion of patients experiencing ≥ 1 (n(%)) (DBL 2)	Nintedanib	332	147 (44.3%)	Risk Difference: - 0.05†	-0.13 to 0.02†	0.193†	Risk Ratio: 0.89†	0.76 to 1.05†	0.158†	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) [30]. P-values for risk difference and risk ratio are calculated according to the method described in Altman and Bland (2011) [31].	IQWiG, table 25 (p.58). [3]
	Placebo	331	164 (49.5%)								
Discontinuations due to AEs (n(%)) (DBL2)	Nintedanib	332	73 (22.0%)	Risk Difference: 0.07†	0.02 to 0.13†	0.013†	Risk Ratio: 1.52†	1.09 to 2.11†	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) [30]. P-values for risk difference and risk ratio are calculated according to the method described in Altman and Bland (2011) [31].	IQWiG, table 15 (p.25). [3]
	Placebo	331	48 (14.5%)								
†Calculated by Boehringer Ingelheim											

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 13 Results per PICO

Table A4 Results referring to the clinical question								
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 interstitial lung disease with a progressive fibrosing phenotype

Application to the Danish Medicines Council

18 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
BSC	Best supportive care
CSF1R	Colony-stimulating factor 1 receptor
CU	Cost-utility
DLCO	Diffusing capacity of the lung for carbon monoxide
DMC	Danish Medicines Council
ER	Emergency room
FE	Fixed effects
FGFR	Fibroblast growth factor receptor
FVC	Forced vital capacity
FVC%pred	Forced vital capacity percentage of predicted
GI	Gastrointestinal
GP	General practitioner
HRCT	High resolution computed tomography
HRQoL	Health-related quality of life
ICU	Intensive care unit
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
KM	Kaplan Meier
OS	Overall survival
PDGFR	Platelet-derived growth factor receptor
PF	Progressive fibrosing
PF-ILD	Progressive fibrosing interstitial lung disease
PPP	Pharmacy purchasing price
QoL	Quality of life
SmPC	Summary of product characteristics
SSc-ILD	Systemic sclerosis interstitial lung disease
TSTIDIA	Time since trial initial diagnosis
TTD	Time to discontinuation
TTFAE	Time to first acute exacerbation
UIP	Usual-interstitial pneumonia
VEGFR	Vascular endothelial growth

1 Background

Interstitial lung diseases (ILD) are a heterogeneous group of rare lung diseases where the most common symptom is dyspnoea. ILD can develop due to inflammation with subsequent formation of fibrosis (scar tissue) or due to fibrosis alone (1–3). Lung fibrosis is a chronic condition that can affect all parts of the lung tissue. Lung fibrosis develops when fibroblasts in the connective tissue are activated to segregate an increased amount of extracellular material, causing rigidity of the lung tissue and decreased alveolar function. As the fibrosis develops in the lungs, the lung function becomes increasingly affected (4).

The diagnosis of ILD is complex and done by an inter-disciplinary team of physicians specialised in pulmonary medicine, thorax-radiology, rheumatology, cardiology and pathology (5,6). Establishing the presence and classifying the type of ILD requires various examinations such as a thorough description of the medical history, lung functioning assessment, thorax x-rays, high-resolution computed tomography (HRCT) scans and sometimes echocardiography and lung biopsy. The initial assessments for ILD take place at the Danish pulmonary medical units, while the treatment is managed at highly specialised ILD centres (Odense University hospital, Aarhus University Hospital, Herlev-Gentofte Hospital and Rigshospitalet) (3).

Many different types of ILD exist. Idiopathic pulmonary fibrosis (IPF) is the most well-known and characterised by irreversible development of progressing lung fibrosis with a radiologic-pathologic pattern called usual interstitial pneumonia (UIP), diagnosed with either HRCT scans or histologically with a lung biopsy (7–9).

ILD with progressive lung fibrosis (PF-ILD)

Aside from IPF, other types of ILD develop progressive lung fibrosis and are called PF-ILD. These are presented in Figure 1. PF-ILD is a heterogenous group of diseases with varying degrees of lung fibrosis and inflammation. This causes a gradual worsening of the respiratory symptoms, decreasing lung functioning and progressing fibrosis on HRCT scans (9–12). IPF and PF-ILD are comparable in many ways (e.g. the pathological mechanisms, clinical picture and prognosis), and PF-ILD is also associated with deteriorated quality-of-life (QoL) and premature death despite treatment (5,9–14). Approximately 2/3 of ILD patients have an UIP-like pattern on either HRCT-scans or histological tests while the rest have other patterns (15). Due to the progressive nature of PF-ILD patients experience a substantially higher symptom burden compared to other ILD patients, which highly affects their QoL and everyday life (10,16–20). The prognosis of PF-ILD depends on the extent of fibrosis, the presence of a UIP-like pattern, the rate of deterioration of lung function and the frequency of acute exacerbations (acute deteriorations of the respiratory symptoms that require medical treatment or hospitalisation).

The expert committee in the Danish Medicines Council (DMC) estimates that approximately 60-80 new PF-ILD patients potentially could be candidates to treatment with nintedanib.

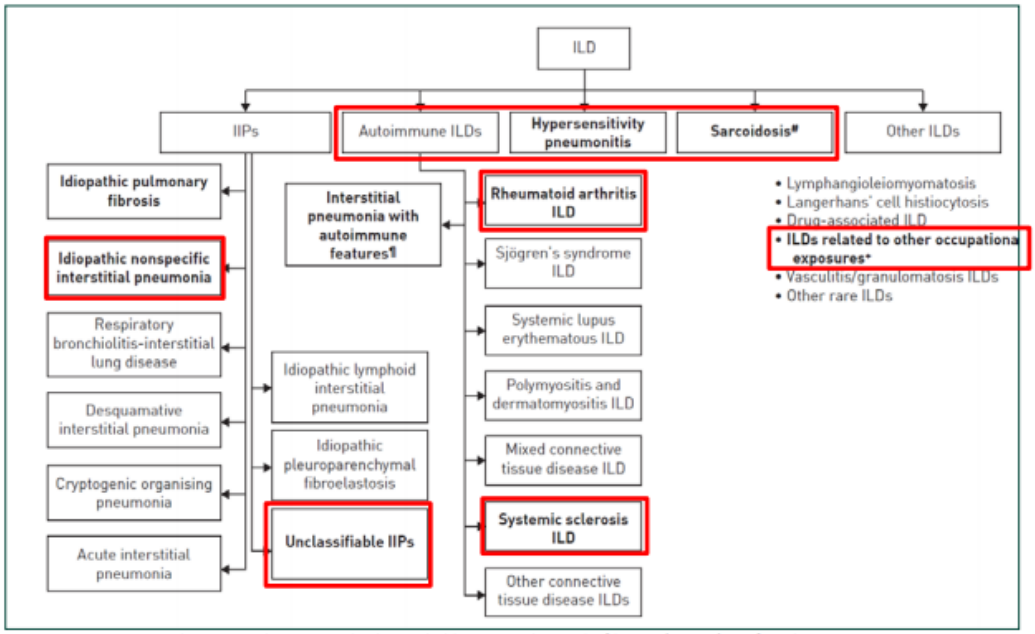

Figure 1: The figure shows the different types of ILD. The types that can develop progressing fibrosis are marked with red. Source: (21).

Current treatment options

The mortality associated with PF-ILD is correlated with reduction in lung functioning (measured with forced vital capacity (FVC)) caused by progression of the lung fibrosis (9–11,13). Therefore, the treatment goal is to slow disease progression. Nintedanib is the first drug with regulatory approval for the PF-ILD indication.

As mentioned, PF-ILD is a heterogenous group of diseases; therefore, the current treatment options target the underlying cause of disease. To supress the damaging inflammatory process, immunomodulating drugs such as glucocorticoid, azathioprine, methotrexate, mycophenolate mofetil and cyclophosphamide are used as first-line treatments (9). None of these drugs have an indication for PF-ILD and are used off-label. Treatment is continued until progression and monitored based on the patient's symptoms, lung functioning and sometimes supplemented with walk tests and HRCT scans. 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 (9,12). The EMA indication of nintedanib does not require previous treatment.

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.

Nintedanib is administrated orally with 150 mg twice daily (a daily dose of 300 mg). 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 (22).

Table 1 **Nintedanib**

Name	Ofev®
Active ingredient	Nintedanib
Indications	Nintedanib is indicated for the treatment of PF-ILD in adult patients Nintedanib is also indicated for the treatment of adult patients with IPF and systemic sclerosis associated ILD (SSc-ILD)
Dosing	150 mg capsules orally twice daily (300 mg per day)
ATC code	L01XE31
Packages and strengths	60 x 150 mg capsules 60 x 100 mg capsules
EC-decision date	13 July 2020

Abbreviations: EC: European commission.
Source: (22).

1.2 Clinical question

The cost per patient analysis and budget impact analysis of nintedanib for the treatment of PF-ILD are based on the clinical question outlined by the DMC:

What is the value of nintedanib compared to placebo in patients with PF-ILD?

2 Methods: Cost per patient analysis

The purpose of the cost per patient analysis was to estimate the incremental cost of treating PF-ILD patients with nintedanib compared to placebo.

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 and the DMC guidelines. The global CU model is developed by the consultancy Symmetron 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) measurements are not adjusted, as they are not applied in the cost per patient analysis.

To inform the cost per patient analysis, the INBUILD trial was used and clinical experts were consulted. The model was informed primarily by a post-hoc analysis of individual patient-level data from the INBUILD trial. The INBUILD trial is a randomised, international, prospective, double-blind, placebo-controlled trial evaluating the efficacy and safety of nintedanib. The trial consisted of two parts: part A, which lasted 52 weeks, and part B, which included patients who continued the randomised and blinded treatment with either nintedanib or placebo beyond the 52 weeks. The primary endpoint was the annual rate of decline in FVC. (15)

The patient population in the INBUILD trial had features of fibrosing lung disease affecting more than 10% of the lung volume on HRCT scans. Moreover, patients were required to meet at least one of the following criteria for progression of ILD despite standard treatment with an agent other than nintedanib or pirfenidone within 24 months before screening:

1. a relative decline in the FVC of at least 10% of the predicted value;
2. a relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms or an increased extent of fibrosis on HRCT scans; or
3. worsening of respiratory symptoms and an increased extent of fibrosis on HRCT.

At the time of enrolment in the trial, patients were required to have a FVC of at least 45% of the predicted value and a diffusing capacity of the lung for carbon monoxide (corrected for hemoglobin) ranging from 30% to less than 80% of the predicted value. Characteristics of the overall population at baseline are presented in Table 2.

Table 2 **Baseline characteristics of overall population***

Characteristics	Nintedanib (N=332)	Placebo (N=331)
Male sex – no. (%)	179 (53.9)	177 (53.5)
Age in years	65.2 ± 9.7	66.3 ± 9.8
Former or current smoker – no. (%)	169 (50.9)	169 (51.1)
UIP-like fibrotic pattern on high-resolution CT — no. (%)	206 (62.0)	206 (62.2)
Criteria for disease progression in previous 24 mo. — no. (%)		
Relative decline in FVC of ≥10% of predicted value	160 (48.2)	172 (52.0)
Relative decline in FVC of 5% to ≥10% of predicted value plus worsening of respiratory symptoms or increased extent of fibrosis on high-resolution CT	110 (33.1)	97 (29.3)
Worsening of respiratory symptoms and increased extent of fibrosis on high-resolution CT	62 (18.7)	61 (18.4)
FVC		
Mean value – ml	2340 ± 740	2321 ± 728
% of predicted value	68.7 ± 16.0	69.3 ± 15.2
Diffusing capacity for carbon monoxide**		
Mean value – mmol/min/kPa	3.5 ± 1.2	3.7 ± 1.3
% of predicted value	44.4 ± 11.9	47.9 ± 15.0
Total score on K-BILD questionnaire***	52.5 ± 11.0	52.3 ± 9.8

*Plus-minus values are means ±SD.
**The values for diffusing capacity for carbon monoxide were corrected for the hemoglobin level.
*** Scores on the King's Brief Interstitial Lung Disease (K-BILD) questionnaire range from 0 to 100, with higher scores rep- resenting better health status.
Source: The INBUILD trial (15)
Abbreviations: FVC: forced vital capacity, UIP: usal interstitial pneumonia, K-BILD: Kings Brief Interstitial Lung Disease

The interviewed Danish clinical experts were Jesper Rømhild Davidsen from the Research unit for interstitial lung diseases of Southern Denmark (part of Odense University Hospital) and Elisabeth Bendstrup from the Department of Respiratory Diseases and Allergy at Aarhus University Hospital. Both consulted 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 health economic model applied in the current analysis was an individual patient simulation model build with VBA-coding. In the following, a description of the procedure executed in the three key VBA modules in the model is presented.

2.1 VBA programming in the Excel model

Module: CHEBS_Functions

The observable characteristics of the 500 simulated patients are based on the distributions of the patient characteristics from the INBUILD clinical trial (15). These are presented in the sheet 'Patient'. In the model, we assume that the characteristics of the simulated patients follow a multivariate normal distribution. In the sheet 'Seeding', you will find the percentile of the multivariate normal distribution for each dimension of observable characteristics for each patient.

Currently, Excel does not have a built-in function that can draw numbers from a combination of percentiles in a multivariate normal distribution. For that reason, it was necessary to manually program this function as a public function called 'MULTINORMINV'. The programming of the inverse multivariate normal distribution relies on a Cholesky decomposition, which is a widely used solution to this issue.

Module: FirstOrder

After simulating the patient characteristics, the course of disease and patient outcomes are generated in the 'ModelEngine' sheet. The VBA module 'FirstOrder' carries out the following process:

1. It loops over the 500 simulated patients in the 'ModelEngine' sheet.
   This implies that the module pastes each of the 500 simulated patients into the 'ModelEngine' sheet to generate the patient-level outcomes.

2. It pastes the per patient results into the 'FirstOrderResults' sheet.
   After generating the outcomes for the individual patient, the 'FirstOrderModule' pastes the patient-level outcomes from the 'ModelEngine' sheet into the 'FirstOrderResults' sheet.

3. It pastes the per patient results into the 'BIM' sheets.
   Similar to the process above, the 'FirstOrder' module pastes the yearly patient-level results into the 'BIMyr1' to 'BIMyr5' sheets. This process is necessary in order to generate the budget impact results.

Module: OWSA

The inputs applied in the model are summarised in the 'MiscInputs' sheet.
For the majority of the inputs, the following four values are indicated as potential inputs to the model:

1. deterministic;
2. low/LLCI;
3. high/LLCI; and
4. probabilistic *(not used in the current version of the model).*

The column ‘U’ indicates which of the four input values is to be used in the executed analysis. The ‘OWSA’ module generates an upper and lower estimate of the incremental cost of treatment with nintedanib based on changes in the assumptions in a range of predefined inputs.

It does so by separately changing the ‘number’ in Column U in the input table to first “2” (thereby replacing the deterministic parameter assumption with the ‘low/LLCI’ parameter value) and afterwards “3” (replacing the deterministic parameter assumption with the ‘High/HLCI’ parameter value).

Following each change in parameter value, the module executes the analysis and pastes the results into the ‘Tornado_BackEnd’ sheet.

The module repeats this procedure for all parameters included in the OWSA analysis.

2.2 Applied model

The health economic model informing the cost per patient analysis was designed to accommodate as much of the available evidence as possible and accurately reflect the condition of patients with PF-ILD. The applied model is an individual patient simulation model, and the overall structure of the model is presented in Figure 3. Individual patient simulation models display outcomes for individual patients one at a time, and estimate the average across a sufficiently large number of patients (23). An individual patient simulation model was chosen because it was considered more flexible for modelling PF-ILD compared to a cohort model. The flexibility is due to allowing the unique course of each individual patient to be followed in the model, thus accounting for the variabilities in the profiles of PF-ILD patients. Furthermore, the impact on disease progression by the PF-ILD disease history can be included in the model. An individual patient simulation model more accurately reflects the heterogeneity and complexity of PF-ILD by allowing outcomes in the model to be linked to previous events.

The current individual patient simulation model simulates decline in lung function and incidence of first acute exacerbation over a lifetime (25 years in the base case). The model generates patients based on the patient baseline characteristics in the INBUILD trial and the model runs 500 simulations, i.e., the model generates 500 individual patient simulations. Stability test on 1000 simulations showed that results stabilised before 500 simulations were attained, which is presented graphicly in terms of costs in Figure 2. To ensure speed computation, the lower number of 500 simulations were chosen.

[redacted]

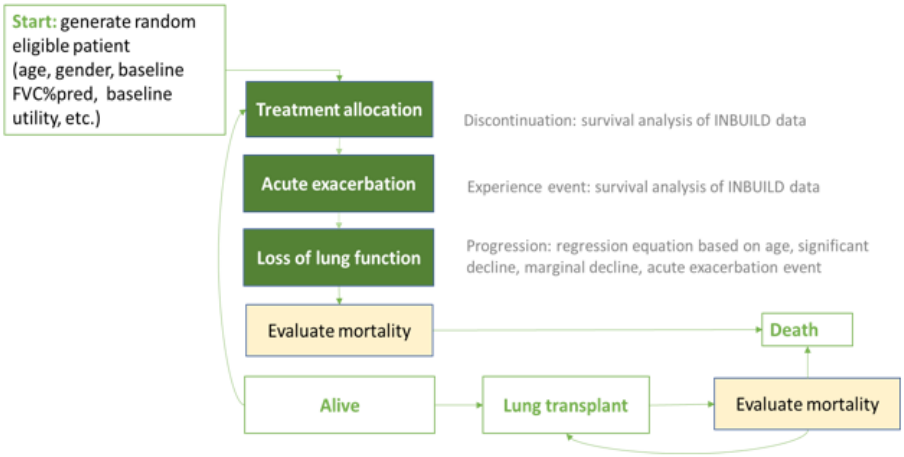

Figure 2: Structure of the health economic model (individual patient simulation model). The figure illustrates the different possible events captured by the model.

Half-cycle correction was not implemented in the base case analysis due to the short cycle length of 30 days. An option to include half-cycle correction to all outcomes is available in the model.

As mentioned, post-hoc analyses of individual patient-level data from the INBUILD trial were conducted and used to inform the model. The post-hoc analyses were completed for treatment efficacy data of overall survival (OS), time to first acute exacerbation (TTFAE) and time to treatment discontinuation (TTD) at database lock (DBL) 1. Extrapolation of overall survival, TTFAE and TTD was also based on data up to DBL 1, where 52-week data on the last randomised patient had been collected (part A of the trial). Not all patients were enrolled in the trial concurrently, meaning by the time the last randomised patient had completed part A, other

randomised patients had been enrolled for longer than 52 weeks, and therefore had begun part B of the trial. As such, the extrapolation was based on data from part A and varying amounts of data from part B of the trial. An illustration of the trial design is presented in Figure 4.

[redacted]

2.2.1 Possible events in the model

The model captures five types of events: mortality (overall survival, OS), acute exacerbations, decline of lung function (progression based on FVC percentage of predicted, FVC%pred), treatment discontinuation and lung transplant (not included in the base case). OS, TTFAE and TTD were extrapolated beyond the INBUILD follow-up period (52 weeks) with parametric survival analysis of the 52-week INBUILD data. Decline of lung function was measured with FVC%pred for each simulated patient and was calculated using coefficients from a regression analysis which considers different predictors that influence the decline of lung function. The coefficients of the regression for loss of lung function (FVC% predicted) were not based on DBL1 data, but on the 52-week data (part A) of all the randomised patients in the trial. The rationale for this was that since the primary endpoint of lung function decline was 52 weeks, it was decided that the endpoint analyses would be based on data through 52 weeks.

FVC%pred was the main factor of disease progression in the model. FVC%pred can be used to reflect a patient's absolute disease state adjusted for age, gender and height. Acute ILD exacerbations were also included in the model. The model was designed to simulate PF-ILD patients' outcomes based on their lung function measured with FVC%pred combined with whether they experienced an acute ILD exacerbation and whether they were on nintedanib or on best supportive care (BSC), which was the comparator in the model.

Acute exacerbations are included in the model because they are dramatic and singular events that are often fatal and a huge cause of morbidity and mortality in PF-ILD patients. In the INBUILD trial, an acute exacerbation was defined in line with the categorisation of acute

exacerbations of IPF in the latest international working group report (24). The definition was: an acute, clinically significant respiratory deterioration characterised by evidence of new, widespread alveolar abnormality meeting all the following criteria: acute worsening or development of dyspnoea (typically of <1 month duration), CT with new bilateral ground-glass opacity or consolidation superimposed on a background pattern consistent with fibrosing ILD, and deterioration not fully explained by cardiac failure or fluid overload. (15)

It was assumed that once progressed to a lower FVC%pred, the patient could not go back to health states with improved/higher FVC%pred values and thereby improved lung function. Progression in FVC%pred was defined as the date when ≥10% absolute decline in FVC%pred compared to baseline occurred for the first time. Acute exacerbations are assumed to result in a permanent drop in FVC%pred, meaning that the FVC%pred value of a patient cannot return to the pre-exacerbation level.

Death can occur in two ways in the model: 1) at any time and from any health state, based on survival analysis of clinical trial data, and 2) when a patient's FVC%pred decreases to ≤40%, because this was considered to be an unsustainable level of lung function. The possible events in the model and the data source informing the occurrence of the events are provided in Table 3.

Table 3 **Events and inputs in the model**

Events	Inputs
Mortality	· Survival analysis of time to death · Progression to FVC%pred ≤40 %
Acute exacerbation	· Survival analysis of time to first acute ILD exacerbation
Disease progression	· Regression analysis of time to progression of FVC%pred (progression is defined as a 10%-point decline form baseline)
Treatment discontinuation	· Survival analysis of time to discontinuation

Source: The INBUILD trial (15)

Parametric extrapolation was done for OS, TTFAE and TTD. The parametric models were applied for the full duration of the model, which means that the time in which clinical trial data was available was also included. This was done to allow a more robust representation of uncertainty from the trial results. Six different standard parametric models (exponential, Gompertz, generalised gamma, log-normal, log-logistic, and Weibull) were explored for modelling mortality, TTD and TTFAE.

The goodness of fit of the parametric models to data was assessed based on the following criteria:

- statistical criteria (Akaike and Bayesian information criterion, AIC/BIC) (the smallest AIC and BIC values indicated the best-fit parametric model);
- visual inspection in relation to evidence from the IPF literature when possible (IPF due to lack of PF-ILD literature); and
- clinical plausibility assessed by consulting interviewed clinical expert

Assessing proportional hazards

For a general model to be used, it was necessary for the proportional hazards (PH) assumption to be true. If this assumption is violated, then independent survival models should be used (25). In the health economic model, the PH assumption did not hold for all of the survival models. Therefore, independent survival models were used for all relevant outcomes to be consistent across the model. The PH assumption tests were conducted on the DBL2 dataset.

We conducted some analyses to formally test whether the PH assumption held for OS, TTD and TTFAE. The analysis results were as follows:

- OS: There was no conclusive evidence against the PH assumption for this outcome (test p-value: 0.3081; Cox regression model interaction terms also not significant);
- TTD: There was evidence against the PH assumption (test p-value: 0.0017; Cox regression interaction term p-values <0.05);
- TTFAE: There was no conclusive evidence against the PH assumption for this outcome (test p-value: 0.707; Cox regression model interaction terms also not significant).

Graphical assessments of the log-cumulative hazard plots were also conducted. The treatment arms cross in both the OS (Figure 5) and TTD (Figure 6) plots assuming that the PH assumption is violated. For TTFAE (Figure 7), the treatment arms do not cross and remain relatively parallel and seems to hold.

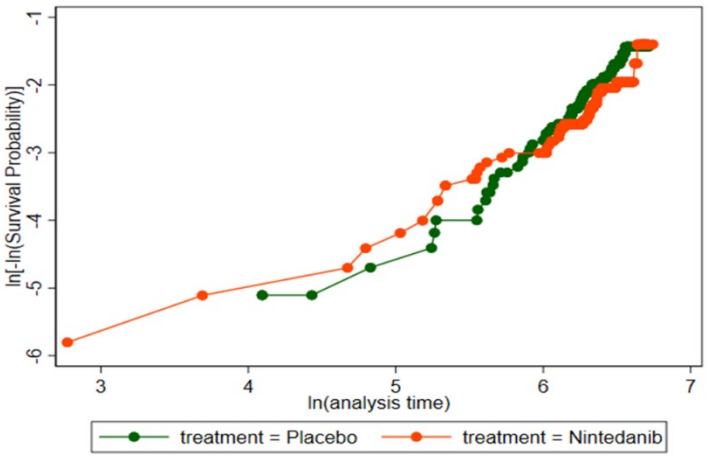

Figure 3: OS log-cumulative hazard plot.

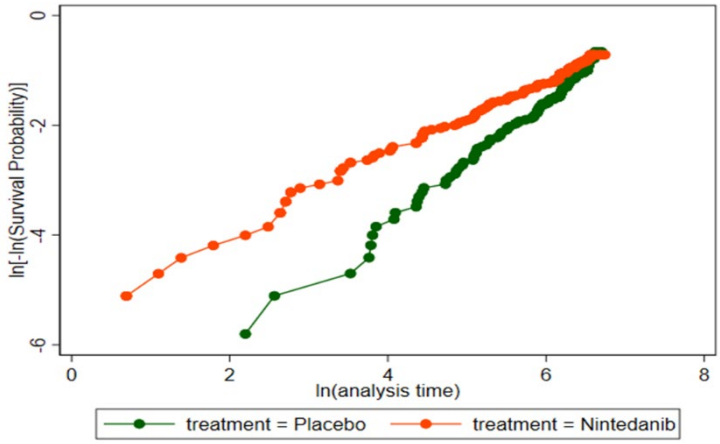

Figure 4: TTD log-cumulative hazard plot.

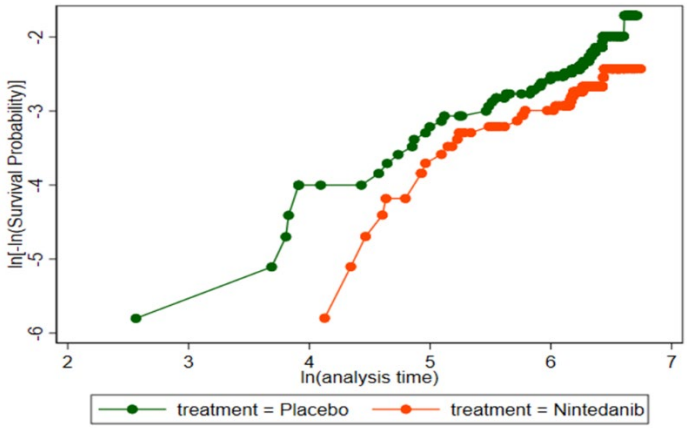

Figure 5: TTFAE log-cumulative hazard plot.

2.2.2 Modelling of overall survival (OS)

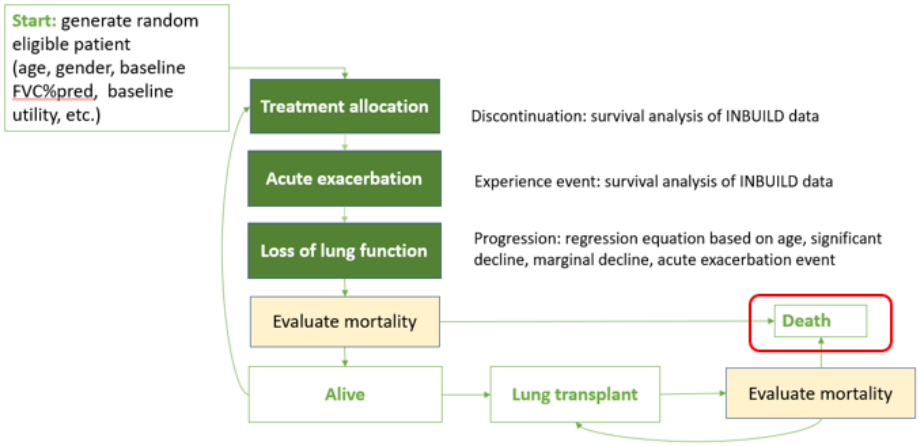

Figure 6: The structure of the model and OS

Parametric extrapolation of OS

Parametric model extrapolation with data from the INBUILD trial was used to derive OS data for nintedanib and placebo. The estimated AIC and BIC values of the six parametric models for OS are presented in Table 4.

Table 4 **AIC and BIC values for OS with the standard six parametric models**

Model	Exponential	Gompertz	Generalised Gamma	Log-logistic	Log-normal	Weibull
			Nintedanib			
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Placebo			
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Table 4 shows that for nintedanib, the parametric model with the lowest AIC value is the Gompertz model, while the exponential model has the lowest BIC value. However, most models (beside the generalised gamma model) fell within two to three points from the model with the lowest value beside the BIC value of the log-normal model, which fell almost five points from the model with the lowest value (exponential). Since the models had similar AIC and BIC values, the

model with the best fit for extrapolating OS in the nintedanib arm needed to be assessed with other criteria as well.

There is limited long-term data on PF-ILD that can be used to assess the external validity of the extrapolation with the parametric models and therefore, we used long-term IPF data for this. This was assumed acceptable, as the rate of decline in FVC over 52 weeks in the placebo arm of the INBUILD trial was consistent with the decline observed in the pooled placebo results from the IPF INPULSIS trials. Additionally, INBUILD safety findings were consistent with those seen in the SENSCIS trial and INPULSIS clinical trials in SSc-ILD and IPF, respectively. These findings are considered supportive of the concept of a progressive phenotype across multiple ILDs, following a similar disease behaviour as IPF. Therefore, in the absence of long-term PF-ILD data, IPF data was considered an acceptable alternative to validate the OS analysis for PF-ILD.

A combined IPF trial dataset with the INPULSIS-ON trial (the long-term follow-up to the INPULSIS IPF trials) provided just over eight years of data for IPF patients treated with nintedanib. These data were used to visually assess the standard parametric models in Table 4.

Extrapolated OS curves with the six standard parametric models

[redacted] and [redacted] show the extrapolation of OS with the six standard parametric models with placebo and nintedanib, respectively. The coefficients for the parametric models for nintedanib and placebo can be found in the appendix in Table 43 and Table 44, and the variance-covariance matrices corresponding to each placebo and nintedanib parametric model for OS are also available in the appendix (Table 45 and Table 46).

[redacted]

The nintedanib Kaplan-Meier (KM) curve from a pooled IPF trial dataset (including INPULSIS and the long-term follow-up (INPULSIS-ON trial)), was plotted over the INBUILD extrapolated survival curves from [redacted] to visually assess the best-fitting curves. The IPF KM curve is the red curve presented in [redacted].

[redacted]

Figure 11 shows that the exponential, Gompertz, generalised gamma and log-normal distributions seem to either overestimate or underestimate survival in the nintedanib arm and will therefore not be considered for generation of results (best fit for OS). Figure 11 also shows that the external IPF KM curve follows the extrapolated parametric Weibull and log-logistic curves very well up to around year six where the IPF KM curve reaches a plateau. The last recorded death in the pooled dataset was at approximately 5.7 years. After this timepoint, 49 patients remained in the trials, all of whom were later censored. The long tail seen in the IPF KM curve is therefore due to the censoring of a small number of patients remaining in the pooled trial dataset after 5.7 years (26). Figure 12 and Figure 13 compare the fit of the remaining parametric models (log-logistic and Weibull) to the KM curves from the INBUILD clinical trial for placebo and nintedanib, respectively.

[redacted]

The median survival of the modelled extrapolations ranges from [redacted] years for the placebo arm and [redacted] years for the nintedanib arm. In the nintedanib arm, the Weibull model reports the lowest median survival time, while the log-logistic models estimate the highest value. In the placebo arm, the two models estimate the same median survival (see Table 5). [redacted] shows the extrapolation of OS in the two treatment arms with the log-logistic and Weibull models.

Table 5 **Median survival time after extrapolation**

Treatment arm	Parametric model	Median survival time
Placebo	Log-logistic	[redacted]
	Weibull	[redacted]
Nintedanib	Log-logistic	[redacted]
	Weibull	[redacted]

[redacted]

We presented the extrapolated curves in [redacted] and [redacted] to the clinical experts and asked them to point out the curve they regarded as being most clinical plausible. One clinical expert pointed at the Weibull curve and the other expert pointed at the Gompertz curve or the generalised gamma curve but mentioned that the Weibull curve could also be the most clinical plausible for some patients.

When visually inspecting the curves in [redacted], assessing the AIC and BIC values reported in Table 4, and considering the statements from the clinical experts regarding the clinical plausibility of the curves, a Weibull parametric model was selected for extrapolating OS in both arms in the base case. The Weibull model allows the underlying hazard to increase or decrease proportionally with time. This makes the Weibull model good for extrapolating OS in PF-ILD patients, as these patients' risk of dying increases as time passes. The model allows the user to select another parametric model if needed (remember to run the simulation). Sensitivity analyses will be presented with extrapolation of OS with a log-logistic parametric model. The extrapolated OS curves for nintedanib and placebo are presented in [redacted].

In Table 6, the simulated median OS in the nintedanib and placebo arms is presented.

Table 6 **Simulated median OS in the nintedanib and placebo (BSC) arms**

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

2.2.3 Modelling of time to first acute exacerbation (TTFAE)

Time to first acute ILD exacerbation is included in the model and the event is presented in Figure 16.

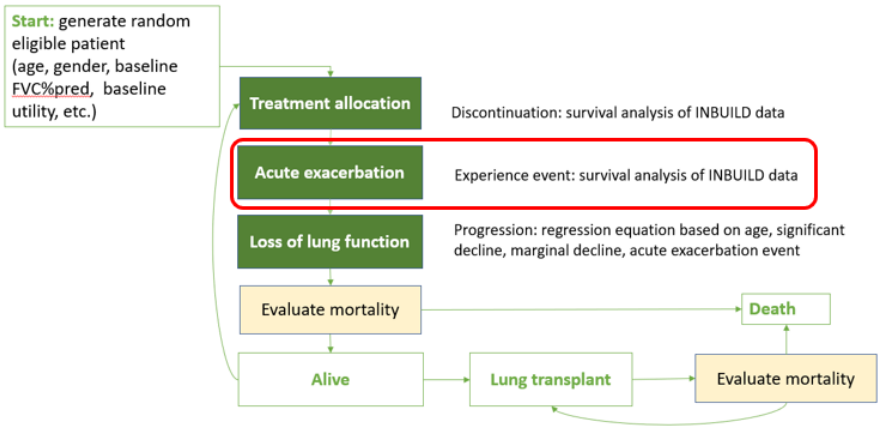

Figure 7: Acute exacerbations in the model structure

In the INBUILD trial, TTFAE over 52 weeks was a secondary endpoint, and the definition of an acute ILD exacerbation is presented in section 2.2.1. TTFAE was also extrapolated beyond the INBUILD trial period with parametric models. The AIC and BIC values for the six standard parametric models are presented in Table 7, and the coefficients for the parametric models can be seen in the appendix in Table 45 and Table 46.

Table 7 **AIC and BIC values for acute exacerbations with the standard six parametric models**

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

The extrapolated curves and the KM curves from the INBUILD trial of TTFAE with nintedanib and placebo are presented in [redacted] and [redacted], respectively.

We consulted the clinical experts on the clinical and biological plausibility of the extrapolated parametric TTFAE curves. One informed that acute exacerbations are very rare among PF-ILD patients and that it was very difficult to point towards one of the curves but chose the Log-

normal curve. The other clinical expert chose the generalised gamma curve. The experts pointed out, that PF-ILD is a very heterogenic disease where lack of evidence makes it difficult to point towards a curve. The exponential parametric model had the lowest AIC and BIC values, and in [redacted], the exponential parametric model is visually fitted to the KM curves of TTFAE from the INBUILD trial, which shows that the exponential model fit the KM curves very well. Based on the statistical test with AIC and BIC values, the contradictory statements from the clinical experts a[redacted]

[redacted]

In the base case, it was assumed that a patient could experience one acute exacerbation, but the model allows a maximum of three acute exacerbations. The choice of one acute exacerbation in the base case was based on the interviews with Danish clinical experts, who informed us that acute exacerbations are rare events in ILD patients. Acute exacerbations were generated independently, which means that once a patient experienced one acute exacerbation it did not change their probability of experiencing a subsequent acute exacerbation. This also points towards the exponential parametric model as the best fit for TTFAE, because the exponential model assumes a constant hazard.

TTFAE was used to simulate time to first, second and third acute exacerbation because acute exacerbations were rare in the INBUILD trial; there would likely not have been enough patients experiencing a second or third acute exacerbation to produce reasonable model estimates. The inverse of the exponential cumulative distribution function using the TTFAE data was used to estimate the cycle when the patient experienced the first, second and third acute exacerbation, where each function provided the time until the next (or first) event. The patient would experience the event only if alive in that cycle.

[redacted]

Table 8 shows the median time to TTFAE in the nintedanib arm and in the placebo arm.

Table 8 **Simulated median TTFAE in the nintedanib and placebo (BSC) arms**

Median TTFAE nintedanib (years)	
Median TTFAE BSC (years)	
Incremental benefit	

2.2.4 Modelling of loss of lung functioning

Figure 21 shows how loss of lung functioning is modelled in the model structure.

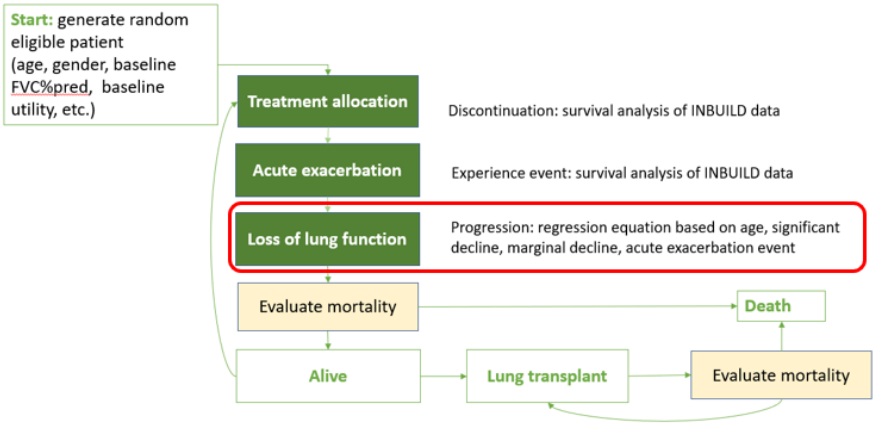

Figure 8: Model structure with the modelling of loss of lung functioning

A regression analysis to predict patient FVC%pred was conducted based on a post-hoc analysis of INBUILD trial patient-level data. Lung function decline was explored using both independent and general models. Independent models consider the trial arms separately and the general model analyses them together by considering the relative differences between the two arms. Coefficients from the independent models can be found in Table 9 and Table 10 and were used in the base case analysis. Coefficients for the general model are reported in appendix in Table 49 and used in a sensitivity analysis.

Table 9 **Independent model for placebo, linear mixed-effects estimates (FVC%pred first 52 weeks)**

Term	Estimate	SE	Statistic	DF	P-value
			(t-test)		
(Intercept)	1.979	1.654	1.196	321.761	0.232
fvc_base	0.976	0.014	68.7	324.781	0
AGE	-0.015	0.021	-0.698	323.888	0.486
PGGR1_marginal	0.333	0.507	0.656	330.044	0.513
PGGR1_worsening	-0.032	0.595	-0.053	325.752	0.958
acute_ild_exacerbation1	-6.946	1.424	-4.878	1779.34	0
AGE:analysis_year	-0.102	0.008	-12.401	264.101	0
PGGR1_marginal:analysis_year	2.148	0.922	2.329	265.155	0.021
PGGR1_worsening:analysis_year	2.421	1.063	2.277	256.464	0.024

Abbreviations: BL: Baseline; DF: degrees of freedom; FVC%pred: forced vital capacity percent predicted; ILD: interstitial lung disease; PGGR1: grouped criteria for progressive interstitial lung disease; SE: Standard error.

Table 10 **Independent model for nintedanib, linear mixed-effects estimates (FVC%pred first 52 weeks)**

Term	Estimate	SE	Statistic	DF	P-value
			(t-test)		
(Intercept)	-0.179	1.574	-0.114	323.889	0.909
fvc_base	0.993	0.013	75.147	324.217	0
AGE	0.007	0.022	0.34	325.216	0.734
acute_ild_exacerbation1	-4.028	1.535	-2.625	1822.064	0.009
AGE:analysis_year	-0.038	0.007	-5.338	285.131	0

Abbreviations: BL: Baseline; DF: degrees of freedom; FVC%pred: forced vital capacity percent predicted; ILD: interstitial lung disease; SE: Standard error.

The parameters included in the lung function decline model were selected using backwards stepwise regression. The backward stepwise regression was 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 data. Lung function decline (FVC % predicted) was modelled using a linear mixed-effect regression analysis to control for repeated measurements and to identify risk factors associated with change in FVC % predicted over the observation period. Treatment, risk factors (HRCT pattern, baseline FVC % predicted, age, sex, race, criteria for progressive ILD, methotrexate use at baseline, time since diagnosis, underlying ILD diagnosis) and time-dependent predictor (ongoing acute ILD exacerbation) were fixed effects in all models. Time dependent variable, acute ILD exacerbation, was derived as a factor variable having value 1 if a patient had an ongoing acute ILD exacerbation (PF-ILD) at the time of EQ-5D measurement otherwise 0. Interaction effects between time and all fixed factors were checked by including product terms in the models. All models included random intercept and slope, and an unstructured correlation matrix was used. Risk factors considered by expert opinion were included as fixed factors in the multivariable analysis. All multivariable analyses were preceded by estimation of correlation between risk factors. Variable selection was done via stepwise backwards selection with a p-value cut-off of 0.05. The final model included treatment, risk factors (HRCT pattern, baseline FVC%pred, age, sex, race, criteria for progressive ILD, time since diagnosis, underlying ILD diagnosis) and a time-dependent predictor (ongoing acute ILD exacerbation) as fixed effects (FE). Ongoing acute ILD exacerbations were not found to be significant in the backwards stepwise regression, possibly due to the small number of events that occurred in the INBUILD trial. However, acute exacerbations were thought to be strongly linked to lung function decline, thus this variable was included in the model. The model also included interaction effects between time and fixed factors if they were found to be significant in the backwards stepwise regression. The final equations describing the final regressions were the following:

Placebo

$$FVC_{it} = \beta_0 + \beta_1 * FVCBase_i + \beta_2 * AGE_i + \beta_3 * PGGR1Marginal_i + \beta_4 * PGGR1Worsening_i + \beta_5 * AcuteExacerbation_{it} + \beta_6 * (AGE_i * AnalysisYear_t) + \beta_7 * (PGGR1Marginal_i * AnalysisYear_t) + \beta_8 * (PGGR1Worsening_i * AnalysisYear_t)$$

$$FVC_{it} = 1.979 + 0.976 * FVCBase_i - 0.015 * AGE_i + 0.333 * PGGR1Marginal_i - 0.032 * PPGR1Worsening_i - 6.946 * AcuteExacerbation_{it} - 0.102 * (AGE_i * AnalysisYear_t) + 2.148 * (PGGR1Marginal_i * AnalysisYear_t) + 2.421 * (PGGR1Worsening_i * AnalysisYear_t)$$

Nintedanib

$$FVC_{it} = \beta_0 + \beta_1 * FVCBase_i + \beta_2 * AGE_i + \beta_3 * AcuteExacerbation_{it} + \beta_4 * (AGE_i * AnalysisYear_t)$$

$$FVC_{it} = -0.174 + 0.993 * FVCBase_i + 0.007 * AGE_i - 4.028 * AcuteExacerbation_{it} - 0.038 * (AGE_i * AnalysisYear_t)$$

As previously mentioned, progression was defined as the date when ≥10% of absolute decline in FVC%pred compared to baseline occurred for the first time. In the model, this was represented by a binary variable that indicated whether a patient has progressed in a certain cycle. If a patient was marked as progressed in a cycle, they would be marked as such in subsequent cycles as well. The covariance matrices for the FE covariates are reported in the appendix in Table 50, Table 51 and Table 52.

Validity of model projections for FVC%pred

Individual patient FVC%pred values were simulated by sampling from the fixed, random, and residual components at each time point based on patient-level data. Simulated distributions of FVC%pred for both arms closely match the clinical observations in the trial as seen in Figure 22 and Figure 23 (27).

[redacted]

[redacted]

2.2.5 Modelling of treatment discontinuation (TTD)

Although most AEs were of mild or moderate severity, the nature of the AE is likely to influence treatment tolerability and persistence. It is reported that up to DBL 1, approximately 34% of patients discontinued treatment with nintedanib in the INBUILD trial (Part A + Part B, post-hoc analysis of INBUILD data). TTD is relevant to the event presented in Figure 24 below (shown in red).

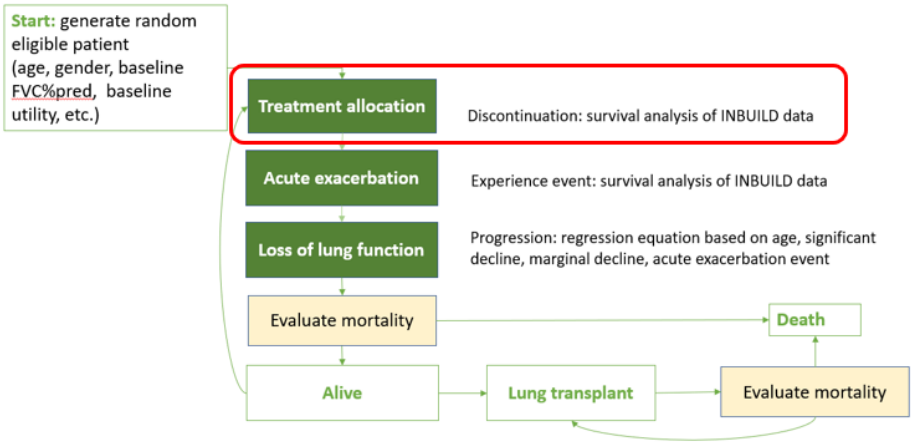

Figure 9: Treatment discontinuation in the model structure

Like OS and TTFAE, the six standard parametric models were considered for modelling TTD. The AIC and BIC values for the six standard parametric models are presented in Table 11, and the coefficients are presented in the appendix in Table 53.

Table 11 **AIC and BIC values for TTD with the six standard parametric models**

	Exponential	Generalised Gamma	Log-logistic	Log-normal	Gompertz	Weibull
			Nintedanib			
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Placebo			
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

In the nintedanib arm, the log-normal model was the one with the lowest AIC and BIC values. However, when visually inspecting the log-normal curve in [redacted], the log-normal curve did not approach 0 and was disregarded as the best-fit. IPF data from the INPULSIS and INPULSIS-on trials showed a median exposure time of nintedanib of 44.7 months (3.7 years). Based on this, the parametric model assumed to be the most clinically plausible was the exponential model, even though this model had the highest AIC and BIC values compared to the other parametric models. The exponential model was plotted with the KM TTD curve for nintedanib from the INBUILD trial in [redacted] and showed a good fit to the KM curve. To determine if the exponential TTD curve is also the most clinical meaningful curve, we consulted the Danish clinical experts who informed that the exponential curve with a median TTD of approximately four years is the most clinical plausible curve. Thus, the exponential model was chosen to extrapolate TTD in the base case. The simulated median time to TTD was [redacted] years in the nintedanib arm. [redacted] shows the modelled TTD curve for nintedanib.

2.2.6 Modelling of lung transplant (not included in the base case)

Patients could undergo a lung transplant if they progressed and met a certain age threshold. As previously mentioned, in the INBUILD trial, progression was defined as the date when a 10% absolute decline of FVC%pred compared to baseline occurred for the first time. Lung transplant is an optional model feature and is relevant to the event presented in Figure 29.

Please note that once a patient was assessed to be eligible for a lung transplant, PF-ILD related costs were interrupted. However, in the absence of patient survival data following a lung transplant, the patient was assumed to follow the ILD mortality rather than general population mortality, as it was assumed that a patient who has had a lung transplant is not as healthy as one of the general population.

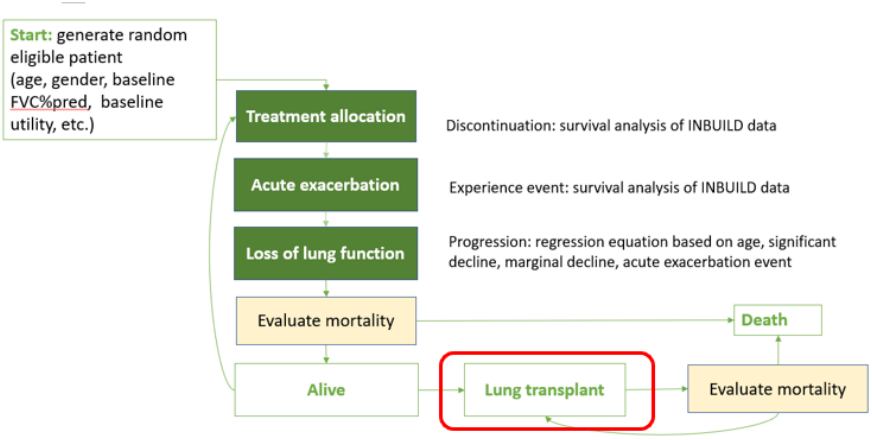

Figure 10: Lung transplant in the model structure

2.2.7 Modelling of adverse events (AEs) and tolerability

AEs associated with nintedanib and placebo were obtained from the INBUILD clinical trial report. A set of criteria were developed to select AEs for the economic analysis based on their severity and incidence. The criteria were:

- an AE had to be common, i.e. incidence of >10% in either treatment arm;
- an AE had to be treatment-related/treatment-emergent; and
- incidence in the treatment arm had to be at least 1.5 times higher than in the control arm.

Based on the above criteria, the selected AEs for both arms of the model are presented in Table 12.

Table 12 **Adverse events in nintedanib and placebo arms**

Adverse event	Nintedanib N (%)	Placebo N (%)
Patients	332 (100.0)	331 (100.0)
Patients with drug-related AEs	262 (78.9)	126 (38.1)
GI events		
Diarrhoea	196 (59.0)	59 (17.8)
Nausea	79 (23.8)	19 (5.7)
Vomiting	41 (12.3)	7 (2.1)
Investigations		
Alanine aminotransferase increased	36 (10.8)	8 (2.4)
Metabolism and nutrition disorders		
Decreased appetite	37 (11.1)	10 (3.0)

Source: INBUILD clinical trial report.
Abbreviations: GI: gastrointestinal.

The AEs reported in Table 12 were reported for part A of the INBUILD trial (the 52 weeks) and represent the investigator defined drug-related AEs (15). The full AE list can be found in the appendix in Table 54. The per cycle probability of experiencing the selected AEs was calculated and presented in Table 13. The per cycle probability was calculated based on the number of patients in each treatment arm (332 and 331 in the nintedanib and placebo arm, respectively) and the number of observed events of diarrhoea, nausea, vomiting, alanine aminotransferase increased and decreased appetite, respectively.

Table 13 **Per cycle probability of selected AEs in the nintedanib and placebo arm**

	Nintedanib	Placebo
GI events		
Diarrhoea	0.0709	0.0160
Nausea	0.0221	0.0048
Vomiting	0.0108	0.0017
Investigations		
Alanine aminotransferase increased	0.0094	0.0020
Metabolism and nutrition disorders		
Decreased appetite	0.0096	0.0025

2.3 Intervention

The intervention in the model was nintedanib 150 mg orally twice daily (300 mg per day). According to the SmPC, some patients do not tolerate the 150 mg twice daily dose and can receive 100 mg twice daily (200 mg per day) instead. It is not established which patients receive the 100 mg twice daily dose; therefore, all patients received 300 mg in the base case. We conducted a sensitivity analysis assessing the impact on the cost per patient if a proportion of patients receive the 100 mg twice daily dose.

2.4 Comparator

The comparator in the model was best supportive care (BSC). In the current analysis, BSC was assumed to be presented by the control arm in the INBUILD trial, which is placebo (15). Placebo is also the comparator outlined by the expert committee in the protocol on nintedanib.

2.5 Patient population in the model

When the model started the simulation, a random patient was generated based on the following baseline characteristics:

- age;
- gender;
- FVC%pred;
- UIP-like pattern;
- marginal decline in FVC%pred (≥5-<10%) combined with worsening of respiratory symptoms or increasing extent of fibrotic changes on chest imaging (PGGR1_marginal);
- clinically significant decline in FVC%pred (≥10%) (PGGR1_worsening); and
- time since trial initial diagnosis (TSTIDIA).

These baseline characteristics (except gender) were selected because they were significant in at least one regression analysis used to inform the model. Gender was included as an additional characteristic, as it was believed to be a characteristic of clinical interest (28). Mean and standard deviations of the total simulated population baseline characteristics are presented in Table 14. Correlation between covariates was maintained with a variance-covariance matrix to ensure that the characteristics of the generated patients in the model were aligned with those observed in the INBUILD trial. The variance-covariance matrix is provided in Table 15. A maximum age of 100 was assumed in the model, which means that if a patient reaches an age of 100 years, he or she dies. The user can override this assumption in the model. The baseline characteristics from the INBUILD trial are presented in Table 16.

Table 14 **Baseline characteristics of simulated model population based on INBUILD trial data**

Parameter	Pooled data	Nintedanib arm	Placebo arm
Age, mean (SD)	65.75 (9.77)	65.25 (9.71)	66.26 (9.81)
Sex, n (%)			
Male	356 (53.7)	179 (53.9)	177 (53.5)
Female	307 (46.3)	153 (46.1)	154 (46.5)
FVC%pred (SD)	68.99 (15.62)	68.70 (16.04)	69.27 (15.21)
UIP, n (%)	412 (62.1)	206 (62.0)	206 (62.2)
PGGR1_marginal, n (%)	207 (31.2)	110 (33.1)	97 (29.3)
PGGR1_worsening, n (%)	123 (18.6)	62 (18.7)	61 (18.4)
TSTIDIA (SD)	3.77 (3.75)	3.65 (3.80)	3.90 (3.69)

Abbreviations: FVC%pred: forced vital capacity I of predicted; PGGR1: grouped criteria for progressive interstitial lung disease; TSTDIA: time since diagnosis; UIP: usual interstitial pneumonia.

Table 15 **Variance-covariance matrix of overall population baseline characteristics based on INBUILD trial data**

	Age	Sex	FVC%pred	UIP	PGGR1_marginal	PGGR1_worsening	TSTIDIA
Age	95.659	0.488	18.53	1.385	-0.101	-0.435	-1.837
Sex	0.488	0.249	0.249	0.038	0.011	0.007	-0.194
FVC%pred	18.53	0.249	243.623	0.998	0.831	0.614	-1.107
Utility	0.118	0.009	0.379	0.011	0.002	0.001	-0.046
UIP	1.385	0.038	0.998	0.235	0.023	-0.009	-0.025
PGGR1_marginal	-0.101	0.011	0.831	0.023	0.216	-0.058	-0.063
PGGR1_worsening	-0.435	0.007	0.614	-0.009	-0.058	0.15	0.024
TSTIDIA	-1.837	-0.194	-1.107	-0.025	-0.063	0.024	14.05

Abbreviations: FVC%pred: forced vital calpercent predicted; PGGR1: grouped criteria for progressive interstitial lung disease; TSTDIA: time since diagnosis; UIP: usual interstitial pneumonia.

Table 16 **Baseline characteristics of the overall patient population in the INBUILD trial***

Characteristics	Nintedanib (N=332)	Placebo (N=331)
Male sex – no. (%)	179 (53.9)	177 (53.5)
Age – years	65.2 ± 9.7	66.3 ± 9.8
Former or current smoker – no. (%)	169 (50.9)	169 (51.1)
UIP-like fibrotic pattern on HRCT – no. (%)	206 (62.0)	206 (62.2)
Criteria for disease progression in previous 24 months – no. (%)		
Relative decline in FVC of ≥10% of predicted value	160 (48.2)	172 (52.0)
Relative decline in FVC of 5% to <10% of predicted value plus worsening of respiratory symptoms or increased extent of fibrosis on NRCT	110 (33.1)	97 (29.3)
Worsening of respiratory symptoms and increased extent of fibrosis on high-resolution CT	62 (18.7)	61 (18.4)
FVC		–
Mean value - ml	2340 ± 740	2321 ± 728
Percent of predicted value	68.7 ± 16.0	69.3 ± 15.2
Diffusing capacity for carbon monoxide**		
Mean value – mmol/min/kPa	3.5 ± 1.2	3.7 ± 1.3
Percent of predicted value	44.4 ± 11.9	47.9 ± 15.0
Total score on K-BILD questionnaire***	52.5 ± 11.0	52.3 ± 9.8

*Plus–minus values are means±SD. FVC denotes forced vital capacity, and UIP usual interstitial pneumonia
** The values for diffusing capacity for carbon monoxide were corrected for the hemoglobin level.
*** Scores on the King's Brief Interstitial Lung Disease (K-BILD) questionnaire range from 0 to 100, with higher scores representing better health status

Source: (15)

2.6 Applied perspective

The analysis has a limited societal perspective in accordance with the DMC guidelines (29).

2.7 Time horizon and cycle length

The analysis has a lifetime time horizon, which was set to 25 years in the base case. A lifetime time horizon was chosen because PF-ILD is a chronic disease that affect patients' survival. The time horizon of 25 years was considered long enough to capture patients' lifetime, as the mean age of patients in the model was 65.75 years and due to the mortality risk associated with PF-ILD. Simulation tests in the model also showed, that most patients in the model died before

reaching 20 years after baseline and a longer time horizon than 25 years was assumed unnecessary. The model is flexible enough to define a time horizon between 1 and 25 years.

The cycle length was set to 30 days, chosen to match the nintedanib pack size usage. The cycle length of 30 days means that patients were evaluated over a 30-day period.

2.8 Discounting

Costs incurred after year 1 in the analysis were discounted with 3.5% each year in accordance with the discounting rate presented by the Danish Ministry of Finance (30).

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 the of costs of hospitalisations, emergency room (ER) visits, ambulance use, lung transplantations (not in base case) and outpatient visits. Cross-sectional costs included general practitioner (GP) visits, physiotherapy visits and occupational therapy. The above-mentioned resource use was primarily informed by a post-hoc analysis of the INBUILD trial, and some assumptions were based on interviews with Danish clinical experts. We assumed that the post-hoc analysis of the INBUILD trial was a valid information source regarding the resource use, since the post-hoc analysis was conducted on patient-level data on PF-ILD patients included in the INBUILD trial.

2.9.1 Drug costs

The drug costs included in the model were the drug cost of nintedanib. No drug costs were assumed for BSC because it reflects the control arm in the INBUILD trial, which was placebo. Moreover, the INBUILD trial included patients that were progressed on first line treatments and therefore, we found it acceptable not to include any drug costs in the BSC arm. No drug costs were included for subsequent treatment lines when patients discontinue nintedanib, because no treatment alternatives in subsequent lines exists.

Nintedanib exists in two formulations: 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 (February 2021).

In the base case, no dose reductions or interruptions were applied because the SmPC on nintedanib states that dose reductions and interruptions are only relevant to manage AEs related to nintedanib treatment such as diarrhoea, nausea and/or vomiting that persist despite appropriate supportive care (e.g. anti-emetics) (22). We find it acceptable to assume that this was not the case in the INBUILD trial, where the severity of these AEs was all mild to moderate.

However, the model is flexible for the user to specify a proportion of patients to be treated with the 100 mg twice daily dose.

Table 17 **Drug information**

Treatment	Strength (mg)	Package size	PPP (DKK)
Nintedanib 150 mg	150 mg	60 capsules	17,465.89
Nintedanib 100 mg	100 mg	60 capsules	14,737.45

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

2.9.2 Hospital costs

The hospital costs were estimated based on a post-hoc analysis of individual patient data from the INBUILD trial. The resource use at hospitals included in the model were the following:

- hospitalisation costs, which consisted of the percentage of hospitalisations associated with intensive care unit (ICU) stays, percentage of hospitalisations associated with ER overnight stays and percentage of hospitalisations associated with ambulance use;
- ER visits, which consisted of the percentage ER visits associated with ambulance use;
- outpatient visits, which included specialist and nurse contacts and management of acute exacerbations; and
- oxygen use.

The resource use was grouped into 10-point FVC%pred groups, and the resource use inputs at DBL 1 was used together with the number of months that patients spend in each FVC%pred group to calculate a probability per cycle of incurring the various resources. In some cases, the probability per cycle is presented as an annual probability in the following, due to very small per cycle probabilities. The resource use at DBL 1 and the number of months in each FVC%pred group can be found in the appendix in Table 55 and Table 56. The estimation of the costs per FVC%pred group was done as illustrated in Figure 30.

Figure 11: The diagram used to analyse the healthcare resource use

Estimation of the cost associated with hospitalisation

The estimation of the cost of a hospitalisation was complex and based on the following:

- proportion of hospitalisations associated with an ICU stay: 5.8% (SE 1.3%);

- proportion of hospitalisations associated with mechanical ventilation: 1.6% (SE 0.7%);
- proportion of hospitalisation not associated with the two above-mentioned: 92.6%;
- proportion of hospitalisations associated with an ER overnight stay: 7.4% (SE 1.5%); and
- proportion of hospitalisations associated with ambulance use: 20.3% (SE 2.2%).

The values above were derived from the post-hoc analysis of the INBUILD trial and are per patient values and all-cause (i.e., not just PF-ILD related). Table 18 presents the unit costs, assumptions and sources used to estimate the cost of a hospitalisation.

Table 18 **Unit costs, assumptions and sources used to estimate the cost of a hospitalisation**

Resource use	Unit cost (DKK)	Assumption and source
Normal hospitalisation	41,260	Based on the DRG tariff 2021 04MA17 (Interstitial lung disease) with 10 contact days (the average duration of a hospitalisation in the patient-level data from the INBUILD trial was 10.54 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)
Mechanical ventilation	51,463	Based on the DRG tariff 2021 04MP04 (Non-invasive ventilation treatment due to respiratory diseases) with 10 contact days (the average duration of a hospitalisation in the patient-level data from the INBUILD trial was 10.54 days)
ER overnight 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" (31)

Sources: interactive DRG, the INBUILD trial and "Akutteam Odense"

In the estimation of a total hospitalisation cost, it was assumed that ICU stays and mechanical ventilation were part of a patient's hospitalisation, while ER overnight stays and ambulance use were separate from the hospitalisation. Figure 31 illustrates how the total cost of a hospitalisation was estimated with the information on proportions listed above, unit costs from Table 18 and the probabilities listed in Table 19. The per cycle total hospitalisation cost in each FVC%pred group was estimated by multiplying the 57,281 DKK from Figure 31 with the cycle probability of incurring the cost in the respective FVC%pred group.

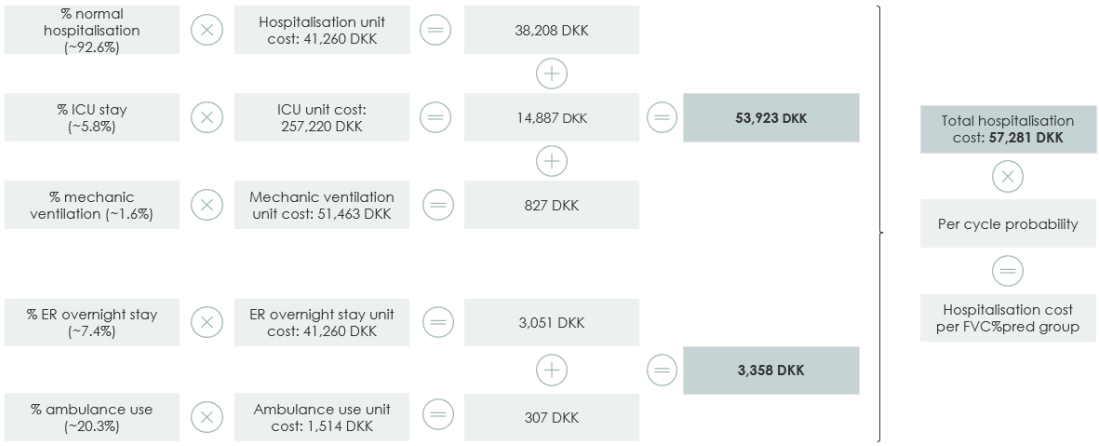

Figure 12: Illustration of how the cost of a hospitalisation was estimated. The 92.6% normal hospitalisation was estimated by subtracting the proportion of hospitalisations associated with ICU (5.8%) and mechanic ventilations (1.6%) from 100%. The approximation signs are used to show that the percentages had many decimals

Table 19 **Per cycle and annual probabilities of hospitalisation in each FVC%pred group**

FVC%pred group	Per cycle probability	Annual probability
>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]

The annual probability in the different groups was calculcated by multiplying the per cycle probability with the number of cycles in a year, which was 12.175. It should be noted, that the numbers in this table are rounded due to many decimals.

Calculation of the per cycle probability of hospitalisation in each FVC%pred group was based on the observed number of hospitalisations in each FVC%pred group and the cumulative patient months spend in the respective FVC%pred group, using the formula for calculating probabilities presented in Fleurence et al. 2007 (32). The annual probabilities were calculated by multiplying the per cycle probability with the number of cycles in a year, which was 12.175.

Besides the ER visits associated with hospitalisation mentioned above, PF-ILD patients can visit the ER without it being associated with a hospitalisation. Based on data from the INBUILD trial, 20.3% of ER visits were associated with ambulance use. The per cycle probability of incurring an

ER cost in each FVC%pred group is presented in Table 21. The information used in the estimation is presented in Table 20. Calculation of the per cycle probability of visiting the ER in each FVC%pred group was based on the observed number of ER visits in each FVC%pred group and the cumulative patient months spend in the respective FVC%pred group, using the formula for calculating probabilities presented in Fleurence et al. 2007 (32). The annual probabilities were calculated by multiplying the per cycle probability with the number of cycles in a year, which was 12.175.

Table 20

	Unit cost (DKK)	Source and assumption
ER visit	1,732	Unit cost based on DRG 2021 tariff "04MA98" which was the tariff generated when combining the diagnosis DJ89 interstitial lung disease and the procedure BWST2A – multidisciplinary acute arrival of non-traumatic patient
Ambulance use	1,514	The unit cost for ambulance use was based on a unit cost reported in a publication from "Akutteam Odense" (31)

Source: interactive DRG and "akutteam Odense"

Table 21 **Per cycle and annual probability of ER visit in the FVC%pred groups**

FVC%pred group	Per cycle probability	Annual probability
>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]

The annual probability in the different groups was calculcated by multiplying the per cycle probability with the number of cycles in a year, which was 12.175.

Estimation of costs of outpatient visits (monitoring)

Based on the post-hoc analysis of patient data from the INBUILD trial, PF-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 (33). The PF-ILD patients in the INBUILD trial also incurred costs associated with physiotherapy and occupational therapy, which is described under cross-sectional costs in Section 2.9.3. Table 22 presents the information used to estimate the cost of specialist and nurse visits (outpatient visits). The interviewed Danish clinical experts informed us that patients visit the outpatient clinic approximately three times per year, and a per cycle probability of an outpatient visit of 25% was applied regardless of FVC%pred group.

Moreover, after interviewing the Danish clinical experts on how acute exacerbations are managed in Danish clinical practice, we applied an outpatient visit to account for the cost associated with acute exacerbations. In the base case, it was assumed that a patient could experience a maximum of 1 acute exacerbation in a lifetime. A maximum number of 3 can be selected.

Table 22 **Outpatient visits in the model**

	Unit cost (DKK)	Assumption/source
Outpatient visit associated with a specialist and nurse contact	1,732	The DRG tariff 04MA98 was used to estimate the unit cost. This was the tariff generated when applying the diagnosis of interstitial lung disease with ambulatory procedures
Outpatient visit associated with management of exacerbations	1,732	In the base case, it was assumed that a patient could experience 1 acute exacerbation during the patient's lifetime. DRG tariff 04MA98 was used to estimate the unit cost because this was the tariff generated when applying the diagnosis of interstitial lung disease with ambulatory procedures

Source: Interactive DRG and the INBUILD trial

Estimation of costs associated with oxygen therapy

In the post-hoc analysis of the INBUILD trial, utilisation of oxygen therapy was observed. The Danish clinical experts confirmed that some PF-ILD patients receive oxygen therapy in a Danish clinical practice. The post-hoc analysis showed that the average number of hours patients received oxygen therapy per day and the average number of treatment days were [redacted] hours and [redacted], respectively. The unit cost used were the DRG-tariff "04MP04" with [redacted] contact days of 51,463 DKK. This tariff was chosen because this was the generated tariff when combining the diagnosis of interstitial lung disease and non-invasive therapy in interactive DRG. This was transformed to an hourly cost of 5.87 DKK, which was multiplied with the average number of hours and the average number of days patients receive oxygen therapy. Thus, a unit cost of 4,119 DKK was applied in the model. The per cycle probabilities of receiving oxygen therapy is presented in Table 23. Calculation of the per cycle probability of oxygen therapy in each FVC%pred group were based on the observed use of oxygen therapy in each FVC%pred group and

the cumulative patient months spend in the respective FVC%pred group, using the formula for calculating probabilities presented in Fleurence et al. 2007 (32).

Table 23 **Per cycle probability of oxygen therapy**

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]

Table 24 shows the per cycle hospitalisation costs. The costs include hospitalisations, ER visits, outpatient visits and oxygen use.

Table 24 **Hospitalisation cost per cycle in each FVC%pred group calculated as illustrated in figure 23. The costs include hospitalisations, ER stays, outpatient visits and oxygen use.**

	Total hospitalisation costs (DKK) per cycle
>110	1,667
100-110	1,667
90-100	1,772
80-90	1,358
70-80	1,756
60-70	2,673
50-60	3,003
<50	3,717

Note: Due to practicalities, the FVC%pred >110 group was assumed equal to the 100-110 group.

2.9.3 Cross-sectional costs

The cross-sectional costs included in the model were estimated based on individual patient level data from the INBUILD trial as well. The resource use consisted of visits to the GP, physiotherapy

visits and occupational therapy. The unit costs were derived from the DMC catalogue for unit costs and the current GP fees (34). The unit costs are presented in Table 25 and per cycle probabilities of a GP visit in each FVC%pred group are presented in Table 26.

Table 27 presents the annual probabilities for a physiotherapist visit and an occupational visit. Annual probabilities are presented here instead of per cycle probabilities due to the very small per cycle probabilities. Calculations of per cycle probabilities of GP visits, physiotherapy visits and occupational visits in each FVC%pred group were based on the observed number of visits in each FVC%pred group and the cumulative patient months spend in the respective FVC%pred group, using the formula for calculating probabilities presented in Fleurence et al. 2007 (32). The annual probabilities were calculated by multiplying the per cycle probability with the number of cycles in a year, which was 12.175.

Table 25 **Cross-sectional resource use and unit costs**

	Unit cost	Source
GP	146.25 DKK per consultation	DMC catalogue for unit costs and current GP fees (34,35)
Physiotherapy	512 DKK per hour	
Occupational therapy	508 DKK per hour	

Table 26 **Per cycle probability of incurring a GP visit in each FVC%pred group**

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

Table 27 **Annual probability of a physiotherapy visit and an occupational therapy visit in each FVC%pred group**

FVC%pred group	Annual probability of physiotherapist	Annual probability of occupational therapy
>110	[redacted]	[redacted]
100-110	[redacted]	[redacted]
90-100	[redacted]	[redacted]
90-80	[redacted]	[redacted]
70-80	[redacted]	[redacted]
60-70	[redacted]	[redacted]
50-60	[redacted]	[redacted]
<50	[redacted]	[redacted]

Table 28 **Cross-sectional costs per cycle in each FVC%pred group calculated as illustrated in figure 23. The costs include GP visits, physiotherapist visits and occupational visits**

FVC%pred group	Total cross-sectional costs (DKK) per cycle
>110	7.03
100-100	7.03
90-100	11.59
80-90	18.55
70-80	15.72
60-70	11.47
50-60	11.89
<50	11.35

Liver function test

According to the consulted Danish clinical experts, changes in the hepatic enzymes levels should be monitored because elevations of hepatic enzymes are a known side effect of nintedanib, as can be seen in Table 54 where the percentages of patients experiencing increased hepatic enzymes in the nintedanib arm are higher than in the placebo arm. Thus, liver function tests were included in the model for the nintedanib arm. The cost of a liver blood test was based on the cost of a blood sample at the GP and a unit cost of 50.11 DKK was applied (35). The model

assumes that all patients on nintedanib treatment would incur this cost every three months, based on the frequency of maintenance test recommended in the SmPC on nintedanib (22).

2.9.4 Adverse event costs

The AEs included in the model (see Table 12) were mild to moderate in severity and assumed to resolve themselves without treatment. However, it was assumed that patients who experienced an AE in a cycle would incur a GP visit. A unit cost of 146.25 DKK for a GP consultation was applied (34). Table 29 shows the cost per AE event in the two treatment arms, which was calculated with the probabilities from Table 12 and the unit cost of a GP visit.

Table 29 **The cost per AE event**

	Nintedanib	Placebo
Cost per AE event (DKK)	16.61	3.68

2.9.5 End of life costs

End of life costs were assumed to be incurred when PF-ILD patients reached the end of their life. The costs were applied in the last year of a patient's life and was estimated with the DRG tariff 2021 "04MA17" of 41,260 DKK, which was transformed to a per cycle cost of 3,387 DKK.

2.9.6 Patient and transportation costs

Patient and transportation costs were included in the model in accordance with DMC guidelines (29). A unit cost of 179 DKK per hour was used in the estimation of the cost of patient time and a unit cost of 3.52 DKK per km was used in the estimation of transportation costs. Based on DMC guidelines, we assumed an average driving distance of 14 km and an average duration of 30 minutes of patient time each way to the hospital, summarising to a total of 28 km and one hour patient time associated with a hospital visit, respectively (34). 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.

The post-hoc analysis of patient data from the INBUILD trial estimated an average duration of a hospitalisation to be [redacted], which was applied as the patient time spent on hospitalisation. The [redacted] were calculated based on [redacted] admission days and

[redacted]admissions. The patient time spent on an ER overnight stay and an ER visit was assumed to be 1 day and 5 hours, respectively. We did not include any transportation costs associated with hospitalisation and no patient time was associated with oxygen therapy because we assumed patients would receive oxygen therapy at home.

Outpatient and cross-sectional visits (GP, physiotherapist, and occupational therapy) were assumed to last 30 minutes per visit. The outpatient visit associated with acute exacerbations were assumed to take 60 minutes. All visits were associated with 60 minutes 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 30.

Table 30 **Patient and transportation time spent on the various resources described above**

	Patient time	Transportation time	Total patient time
Hospitalisation	[redacted]	-	[redacted]
ER overnight stay	1 day	-	1 day
ER visit	5 hours	60 minutes	6 hours
Lung transplant	30 days	-	30 days
Outpatient visit	30 minutes	60 minutes	1.5 hour
Outpatient visit due to exacerbation	60 minutes	60 minutes	2 hours
GP visit	30 minutes	60 minutes	1.5 hours
Physiotherapist visit	30 minutes	60 minutes	1.5 hours
Occupational therapy	30 minutes	60 minutes	1.5 hours
GP visit due to AE	30 minutes	60 minutes	1.5 hours

Source: Assumptions and post-hoc analysis of the INBUILD trial. Lung transplants are not included in base case.

Table 31 **The total patient costs and total transportation costs per cycle. The costs include all the elements mentioned in Table 30, except GP visits associated with AEs, outpatient visits associated with acute exacerbations and lung transplants. Patient costs associated with lung transplants are presented in section 2.10.**

FVC%pred group	Total patient cost (DKK) per cycle	Total transportation cost (DKK) per cycle
≥110	1,211	105
100-110	1,211	105
90-100	1,312	106
80-90	1,012	109
70-80	1,213	110
60-70	1,835	108
50-60	1,958	108
<50	2,403	107

Note: patient and transportation costs for GP visits associated with AEs, outpatient visits associated with acute exacerbations and lung transplants were not included in the costs in each FVC%pred group, because acute exacerbations, AEs and lung transplants were events in the model and not depended on a probability in each FVC%pred group

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 32, 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. It should be noted that the model takes approximately 10 minutes to run the one-way sensitivity analyses.

Inclusion of lung transplants

According to the DMC protocol on nintedanib, a minority of highly specified patients can undergo a lung transplant; therefore, the option to undergo a lung transplant was included in a sensitivity analysis. Lung transplants were not included in the base case because no data on the mortality, progression, or resource use of patients who have received a lung transplant exists and therefore, we decided not to include it in the base case. Lung transplantation was allowed if a patient was under the age of 65 and experienced a decrease in FVC%pred of ≥10% compared to baseline for the first time. Patients eligible for lung transplantation would incur a one-time cost and would thereafter not incur additional PF-ILD-related costs (e.g., drug costs and hospital costs). Only the end of life cost would still be incurred in the last year of the patient's life. The unit cost of a lung transplant was based on the DRG 2021 tariff "26MP07" of 817,016 DKK. Patient costs associated with lung transplantation were included in the model, but we were not able identify an average hospitalisation time associated with lung transplants; therefore, we assumed the

patient time associated with a lung transplantation to be 30 days, which equals a patient cost of 128,888 DKK. The model is flexible for the user to define other inputs.

Parametric models for extrapolating OS, TTFAE and TTD INBUILD data

The parametric model used to extrapolate OS in the base case was the Weibull model. In this sensitivity analysis, nintedanib and placebo were modelled with the log-logistic model instead. Figure 11 shows that the exponential, Gompertz, generalised gamma and log-normal models seemed to either overestimate or underestimate OS in the nintedanib arm. Therefore, these were not included in the sensitivity analysis.

For TTFAE and TTD, sensitivity analyses on the parametric model with the best-fit were also performed. Only curves that seemed clinically plausible on visual inspection were included. The TTFAE extrapolated curves are presented for nintedanib in [redacted] and for placebo in [redacted]. Both figures show that the log-normal and generalised gamma models seem unlikely when considering the mortality of PF-ILD patients. Therefore, only the Gompertz, Weibull and log-logistic models were included in the sensitivity analysis. The extrapolated curves for TTD are presented in [redacted] and [redacted]. For TTD, sensitivity analyses using the Weibull, log-logistic and log-normal models were included.

Nintedanib dose reduction

According to the SmPC on nintedanib, 100 mg twice daily can be administered to patients who do not tolerate the 150 mg twice daily dose (22). It is not well established which PF-ILD patients who do not tolerate the 150 mg twice daily dose; therefore, we conducted a sensitivity analysis assuming that 30% of patients would receive the 100 mg twice daily dose and 70% would receive the 150 mg twice daily dose. The 30% was based on dose reductions from the INBUILD trial, where dose reductions occurred in 33.1% of patients receiving nintedanib (15).

Inclusion of a stopping rule for nintedanib treatment

A stopping rule for treatment discontinuation can be applied in the model. When applied, patients will stop nintedanib treatment if they experience a 10-point decline in FVC%pred over six months. When patients discontinue nintedanib treatment, they are moved to BSC.

Probabilities of various events in the model

Sensitivity analyses on the probabilities of various events in the model were included to assess the impact of these probabilities on the cost per patient analysis. The probabilities were varied between the lowest and highest limit of their 95% confidence intervals (CI). An overview of the sensitivity analyses performed is presented in Table 32.

Table 32 **Overview of the sensitivity analyses conducted on assumptions and parameters in the cost per patient analysis.**

Parameter	Base case analysis	Sensitivity analysis
Time horizon	25 years	10 years
Lung transplant	Not included	Included
OS parametric model	Weibull	Log-logistic
TTFAE parametric model	exponential	Gompertz, Weibull, log-logistic
TTD parametric model	exponential	Weibull, Log-logistic, Log-normal
Progression modelling	Independent model	General model
Exacerbation probabilities	Mean	95% CI of all model parameter values included in the base case.
Progression probabilities	Mean	95% CI of all model parameter values included in the base case.
Discontinuation probabilities	Mean	95% CI of all model parameter values included in the base case.
Mortality probabilities	Mean	95% CI of all model parameter values included in the base case.
Adverse events probabilities	Mean	95% CI of all model parameter values included in the base case.
Dose reduction to 100 mg in 30% of patients	None	30% of patients reduce their dose to 200 mg per day, 70% receive 300 mg per day
Number of acute exacerbations	1	3
Inclusion of a stopping rule	Not included	Included

2.11 Overview of the base case settings in the model

Table 33 **Overview of the base case settings and assumptions in the model and alternative options**

Parameter	Base case setting	Alternative setting options
	Cost per patient analysis	
Applied model	Individual patient simulation model	None
Patient population	PF-ILD patients	None
Intervention	Nintedanib	None
Comparator	Best supportive care (Placebo)	None
Time horizon	25 years	Flexible from 1-25 years
Discount rate	3.5%	Flexible
Perspective	Limited societal	None
OS parametric model	Weibull	Gompertz, log-logistic, log-normal, exponential
TTFAE parametric model	exponential	Gompertz, log-logistic, log-normal, Weibull
TTD parametric model	exponential	Log-logistic, log-normal, Weibull
Progression model	Independent	General
Included costs	Drug costs Hospital costs Cross-sectional costs End of life costs AE costs Patient and transportation costs	Elements within the overall cost categories can be excluded.
Subsequent treatments	Not included	None
Inclusion of waste	No	None
Number of acute exacerbations per lifetime	1	Maximum number of 3
Inclusion of lung transplant	No	Can be included
Dose adjustments	No	Proportion of patients who receive 100 mg can be specified

3 Results: Cost per patient analysis

In the following, we present the result of the cost per patient analysis. The result of the cost per patient analysis can be found in the "Results cost per patient" 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 PF-ILD patients with nintedanib compared to placebo (BCS) of 618,991 DKK over a lifetime time horizon (25 years). An overview of the total costs in each cost category included in the analysis is presented in Table 34.

Table 34 **Results of the cost per patient analysis of nintedanib compared to placebo (BSC) over a lifetime (25 years), with discounted costs (DKK)**

	Nintedanib	Placebo (BCS)	Incremental costs
Drug costs	574,897	0	574,897
Hospital costs	136,837	92,109	44,728
Cross-sectional costs	1,194	433	762
AE costs	611	125	486
End of life costs	31,850	37,164	-5,314
Patient costs	8,097	4,664	3,433
Total costs	**753,486**	**134,495**	**618,991**

Note: treatment costs consisted of drug costs and liver panel test costs. Hospital costs consisted of hospitalisation costs and ER costs and the cost of acute exacerbations. Patient costs consisted of patient time and transportation costs.

3.2 Results of the sensitivity analyses

Results of the one-way sensitivity analyses are presented in Table 35. 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 35 shows that the parameter with the highest impact on the result of the cost per patient analysis is inclusion of lung transplants and the parametric model used to extrapolate TTD, which increases the cost per patient with more than 100,000 DKK. Other analysis with an impact on the result of the cost per patient analysis are using the 95% Cl of the mortality probabilities and using the lower limit of the 95% Cl the probability of progressing. Aside from these sensitivity analyses, the other sensitivity analyses reveal small changes in the result of the cost per patient when different parameters are changed.

Table 35 **Overview of the results of each sensitivity analysis**

Sensitivity analysis	Incremental cost (DKK)	
Base case	**618,991**	
Time horizon of 10 years	603,874	
Inclusion of lung transplant	267,916	
OS parametric model Log-logistic	593,495	
TTFAE parametric model:		
Gompertz	618,590	
Weibull	618,036	
Log-logistic	620,307	
TTD parametric model:		
Weibull	721,305	
Log-logistic	758,223	
Log-normal	783,356	
Progression model	658,207	
Dose reduction to 100 mg twice daily in 30% of patients	592,048	
Three acute exacerbations	618,992	
Inclusion of a stopping rule	618,991	
Sensitivity analyses with 95% CI	**Low limit**	**High limit**
Exacerbation probabilities	620,067	616,902
Progression probabilities	504,557	687,760
Discontinuation probabilities	682,236	557,115
Mortality probabilities	439,451	714,354
Adverse events probabilities	618,809	619,172

4 Methods: Budget impact analysis

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

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 (21). The cycle length in the cost per patient analysis was 30 days, which meant that the time horizon of the budget impact analysis would be approximately 4.8 years (1 cycle short). Therefore, to make the time horizon of the budget impact analysis 5 years, we added a cycle in year 2. Thus, year 1 includes: cycle 0-11, year 2: cycle 12-24, year 3: cycle 25-36, year 4: cycle 37-48 and year 5: cycle 49-60.

4.1 Patient numbers

According to the expert committee, 60 to 80 new patients with PF-ILD are potentially candidates for treatment with nintedanib each year and no separation of prevalence and incidence is made (21). Therefore, we calculated the budget impact of nintedanib assuming 70 new treatment eligible patients each year in the budget impact. The number of new patients treated with nintedanib and placebo (BSC) per year with a recommendation is presented in Table 36. Table 37 shows that all new patients will receive BSC 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 36 **Number of new patients treated with nintedanib and placebo (BSC) each year in the budget impact analysis if nintedanib is recommended**

	Year 1	Year 2	Year 3	Year 4	Year 5
Nintedanib	70	+70	+70	+70	+70
Placebo (BSC)	0	0	0	0	0

Note: The numbers in the table do not reflect that some patients die every year. It is unlikely that the PF-ILD patients entering the model in year 1 are alive throughout all five years in the budget impact analysis. However, the mortality of PF-ILD patients each year in the budget impact is included in the cost per patient in that given year; thus, mortality is accounted for in the budget impact, even though the patient numbers in the table do not explicitly reflect this.

Table 37 **Number of new patients treated with nintedanib and placebo (BSC) 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
Placebo (BSC)	70	+70	+70	+70	+70

Note: The numbers in the table do not reflect that some patients die every year. It is unlikely that the PF-ILD patients entering the model in year 1 are alive throughout all five years in the budget impact analysis. However, the mortality of PF-ILD patients each year in the budget impact is included in the cost per patient in that given year; thus, mortality is accounted for in the budget impact, even though the patient numbers in the table do not explicitly reflect this.

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%, 35 new patients were treated each year. In the sensitivity analysis with an increase of 50%, 105 new patients were treated 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. The result of the budget impact can be found in "Results budget impact" sheet in the Excel model.

The budget impact of recommending nintedanib as standard treatment of PF-ILD patients is 12,8 mil DKK the first year and 36,7 mil DKK in year 5. In Table 38, the budget impact in each year is presented.

Table 38 **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	14,9	26,9	35,1	41,2	45,7
Without recommendation	2,1	4,5	6,5	8,0	9,0
Budget impact	**12,8**	**22,4**	**28,6**	**33,2**	**36,7**

Note: The fluctuating budget impact in some years are due mortality.

5.1 Results of the sensitivity analysis on the budget impact analysis

If the number of new patients who are potentially candidates for treatment is reduced to 35 patients each year, the budget impact in year 5 changes from 36,7 mill DKK to 18,4 mill DKK. Results of the sensitivity analysis with a reduction in the number of new patients each year are presented in Table 39.

If the number of new patients who are potentially candidates for treatment is increased to 105 patients each year, the budget impact in year 5 changes from 36,7 mill DKK to 55,2 mill DKK. Results of the sensitivity analysis with an increase in the number of new patients each year are presented in Table 40.

Table 39 **Result of the sensitivity analysis with 35 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	7,4	13,4	17,5	20,6	22,9
Without recommendation	1,0	2,2	3,2	4,0	4,5
Budget impact	**6,4**	**11,2**	**14,3**	**16,6**	**18,4**

Table 40 **Result of the sensitivity analysis with 105 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	22,3	40,3	52,6	61,8	68,6
Without recommendation	3,1	6,7	9,7	12,0	13,4
Budget impact	**19,2**	**33,6**	**42,9**	**49,8**	**55,2**

6 Discussion

In the cost per patient analysis, an incremental cost of treating PF-ILD patients with nintedanib compared to placebo was estimated to be 618,991 DKK over a time horizon of 25 years. The higher cost of nintedanib compared to BSC is not surprising, especially since nintedanib extends PF-ILD patients' lives.

The cost per patient analysis was based on patient-level evidence from the INBUILD trial, which was an international, prospective, double-blind, placebo-controlled, randomised controlled trial evaluating the efficacy and safety of nintedanib for patients with PF-ILD. Therefore, a strength of the analysis is the availability and use of good clinical evidence in conjunction with economic evidence from the same source (post-hoc analysis of the patient-level INBUILD trial data). The INBUILD trial was the first of its kind to evaluate PF-ILD patients who are currently treated with off-label treatments in Danish clinical practice. This nintedanib trial may be one of the first steps to cover a clear unmet need in PF-ILD patients' limited treatment options.

A technical strength of this analysis is the use of an individual patient simulation model instead of a cohort model. An individual patient simulation model was used because it was more flexible and transparent than a cohort-based state transition model. The variability in the patient profile was relevant in the PF-ILD analysis since the causes of the disease are known and the patient profile or history of disease can impact disease progression. An individual patient simulation model more accurately reflected the heterogeneity and complexity of PF-ILD by allowing outcomes to be linked to prior events. The choice of this model also allowed for a more realistic calculation of FVC%pred patient values, based on a number of regression covariates that were informed by INBUILD data. The modelled patient population is assumed to be highly comparable with the Danish PF-ILD patient population. According to the DMC protocol on nintedanib, approximately 2/3 of PF-ILD patients have a UIP-like pattern which correlates well with what is stated in Table 14 and the average age of the patient population is also representative of the Danish population.

In the extrapolation of OS data, we applied external long-term IPF data as part of selecting the parametric curve with the best fit. IPF data was used due to lack of long-term PF-ILD data. In the Medicines Council guideline for using time-to-event data in the analysis, it is stated that external data can be used, if the patient populations are comparable. We applied a pooled dataset from the INPULSIS trials and INPULSIS-ON. In the following, we describe the comparability of the patient populations in the INPULSIS trials and the INBUILD trial.

INPULSIS comprised two studies and a total of 1066 patients were randomised. The studies had an overweight of male participants and the average age was approximately 67. A large percent in both studies were former smokers (70.2% and 70.6% in the nintedanib and placebo-arm, receptively, in INPULSIS-1 and 66.3% and 63.5% in the nintedanib-arm and the placebo-arm, respectively, in the INPULSIS-2). The mean time since diagnosis of IPF was approximately 1.7 years. FVC and DLCO values from INPULSIS-1 and INPULSIS-2 are given in the table below.

Patients from these studies, who completed the 52-week treatment period could be enrolled in the open-label extension trial of nintedanib (INPULSIS-ON). (36)

Table 41 **Patient characteristics from the INPULSIS trials**

	INPULSIS-1		INPULSIS-2	
	Nintedanib (N=309)	Placebo (N=204)	Nintedanib (N=329)	Placebo (N=219)
FVC				
Mean – mL	2757±735	2845±820	2673±776	2619±787
Median - mL	2700	2721	2615	2591
Percentage of predicted value	79.5±17.0	80.5±17.3	80.0±18.1	78.1±19.0
FEV_1:FVC(%)	81.5±5.4	80.8±6.1	81.8±6.3	82.4±5.7
DLCO				
Mmol/min/kPa	4.0±1.2	4.0±1.1	3.8±1.2	3.7±1.3
Percentage of predicted value	47.8±12.3	47.5±11.7	47.0±14.5	46.4±14.8

* Plus–minus values are means ±SD. FEV1 denotes forced expiratory volume in 1 second.

Source: (36)

In the INBUILD trial had a smaller sample size than INPULSIS as a total of 663 patients were treated. The gender distribution was more balanced in the INBUILD trial than in the INPULSIS trial, but the average age was almost the same (65.2 in the nintedanib-arm and 66.3 in the placebo arm). Patients were stated as former or current smoker in the INBUILD trial and 50.9% in the nintedanib-arm and 51.1% in the placebo-arm were either former or current smoker, which is a smaller percentage than in the INPULSIS trials. When comparing the FVC and DLCO values in the patient populations it can be seen that patients in the INPULSIS trials had a higher mean FVC in mL than the patients in the INBUILD trial. Also, their FVC%pred were higher in the INPULSIS trial than in the INBUILD trial. (15)

Table 42 **FVC and DLCO characteristics from INBUILD**

	INBUILD	
	Nintedanib (N=332)	Placebo (N=331)
FVC		
Mean – mL	2340±740	2321±728
Percentage of predicted value	68.7±16.0	69.3±15.2
Diffusing capacity for carbon monoxide		
Mmol/min/kPa	3.5±1.2	3.7±1.3
Percentage of predicted value	44.4±11.9	47.9±15.0

Source: (15)

The performed sensitivity analyses revealed that the result of the cost per patient analysis is sensitive to inclusion of lung transplants and changes in the parametric model used to extrapolate TTD, as this made the result increase by more than 100,000 DKK. Inclusion of lung transplants in the model being a parameter with impact on the result is not surprising, as this is an expensive cost element in the model. Inclusion of lung transplantation decreased the incremental cost from 618,991 DKK to 267,916 DK. Furthermore, applying the 95% Cl of the probabilities of mortality and progression also impacted the result.

If nintedanib is recommended by the DMC, it will be the first treatment alternative to be recommended for patients with PF-ILD. Our analysis shows that nintedanib can prolong PF-ILD patients' survival at an acceptable cost per patient of 618,991 DKK over a time horizon of 25 years and a limited budget impact in year 1-5.

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8 Appendix

Extrapolation of OS

Table 43 **Coefficients for OS parametric models in the placebo arm**

Model	Variable	Coefficient	Std. Dev	95% Conf. Interval	
Exponential	Rate	-8.405	2.951	-8.723	-8.087
Generalised Gamma	mu	7.241	3.603	6.852	7.629
	sigma	-1.098	35.116	-4.881	2.685
	q	1.462	52.729	-4.219	7.142
Gompertz	Shape	0.004	0.017	0.002	0.006
	Rate	-9.732	7.276	-10.515	-8.948
Log-logistic	Shape	0.791	2.716	0.498	1.083
	Scale	7.223	2.906	6.91	7.536
Log-normal	Meanlog	7.547	3.77	7.141	7.953
	sdlog	0.04	2.424	-0.221	0.302
Standard Weibull	Scale	0.754	2.729	0.46	1.048
	Shape	7.288	2.989	6.966	7.61

Source:

Table 44 **Coefficients of parametric OS models in the nintedanib arm**

Model	Variable	Coefficient	Std. Dev	95% Conf. Interval	
Exponential	**Rate**	-8.750	3.507	-9.127	-8.372
Generalised Gamma	**mu**	7.989	7.879	7.142	8.837
	sigma	-0.964	84.697	-10.075	8.146
	q	1.982	167.769	-16.065	20.029
Gompertz	**Shape**	0.002	0.020	0.000	0.004
	Rate	-9.320	7.418	-10.118	-8.522
Log-logistic	**Shape**	0.322	3.351	-0.039	0.682
	Scale	8.040	6.506	7.341	8.740
Log-normal	**Meanlog**	8.716	8.418	7.810	9.621
	sdlog	0.555	2.975	0.235	0.874
Standard Weibull	**Scale**	0.301	3.375	-0.062	0.664
	Shape	8.107	6.667	7.390	8.825

Source:

Table 45 **Variance-covariance matrix for OS – placebo arm**

Model	Variable	Rate	Shape	Scale	meanlog	sdlog	mu	sigma	q
Exponential	Rate	0.026	NA	NA	NA	NA	NA	NA	NA
Weibull	Shape	NA	0.022	-0.022	NA	NA	NA	NA	NA
	Scale	NA	-0.022	0.027	NA	NA	NA	NA	NA
Log-normal	meanlog	NA	NA	NA	0.043	0.025	NA	NA	NA
	sdlog	NA	NA	NA	0.025	0.018	NA	NA	NA
Log-logistic	Shape	NA	0.022	-0.021	NA	NA	NA	NA	NA
	Scale	NA	-0.021	0.026	NA	NA	NA	NA	NA
Gompertz	Shape	0	0	NA	NA	NA	NA	NA	NA
	Rate	0.16	0	NA	NA	NA	NA	NA	NA
Generalised gamma	mu	NA	NA	NA	NA	NA	0.039	0.259	-0.359
	sigma	NA	NA	NA	NA	NA	0.259	3.726	-5.577
	q	NA	NA	NA	NA	NA	-0.359	-5.577	8.4

Source:

Table 46 **Variance-covariance matrix for OS – nintedanib arm**

Model	Variable	Rate	Shape	Scale	meanlog	sdlog	mu	sigma	q
Exponential	Rate	0.037	NA	NA	NA	NA	NA	NA	NA
Weibull	Shape	NA	0.034	-0.062	NA	NA	NA	NA	NA
	Scale	NA	-0.062	0.134	NA	NA	NA	NA	NA
Log-normal	meanlog	NA	NA	NA	0.213	0.07	NA	NA	NA
	sdlog	NA	NA	NA	0.07	0.027	NA	NA	NA
Log-logistic	Shape	NA	0.034	-0.06	NA	NA	NA	NA	NA
	Scale	NA	-0.06	0.127	NA	NA	NA	NA	NA
Gompertz	Shape	0	0	NA	NA	NA	NA	NA	NA
	Rate	0.166	0	NA	NA	NA	NA	NA	NA
Generalised gamma	mu	NA	NA	NA	NA	NA	0.187	-1.162	2.419
	sigma	NA	NA	NA	NA	NA	-1.162	21.608	-42.767
	q	NA	NA	NA	NA	NA	2.419	-42.767	84.781

Source:

Extrapolation of TTFAE

Table 47 **Coefficients for TTFAE parametric models – placebo arm**

Model	Variable	Coefficient	Std. Dev	95% Conf. Interval	
Exponential	Rate	-8.541	3.216	-8.887	-8.194
Generalised Gamma	mu	9.136	13.915	7.637	10.635
	sigma	0.772	16.618	-1.019	2.562
	q	0.053	26.715	-2.825	2.931
Gompertz	Shape	0	0.019	-0.002	0.002
	Rate	-8.567	6.021	-9.215	-7.918
Log-logistic	Shape	0.002	3.075	-0.329	0.334
	Scale	8.484	7.729	7.651	9.317
Log-normal	Meanlog	9.155	9.541	8.128	10.183
	sdlog	0.804	2.75	0.507	1.1
Weibull	Scale	-0.021	3.11	-0.356	0.314
	Shape	8.59	7.972	7.731	9.449

Source:

Table 48 **Coefficients for TTFAE parametric models – nintedanib arm**

Model	Variable	Coefficient	Std. Dev	95% Conf. Interval	
Exponential	Rate	-8.891	3.799	-9.299	-8.482
Generalised Gamma	mu	5.597	29.47	2.426	8.767
	sigma	1.015	10.235	-0.086	2.116
	q	-9.108	138.533	-24.01	5.794
Gompertz	Shape	0	0.022	-0.002	0.003
	Rate	-8.965	7.219	-9.742	-8.189
Log-logistic	Shape	0.153	3.632	-0.237	0.544
	Scale	8.484	8.787	7.539	9.429
Log-normal	Meanlog	9.112	10.749	7.956	10.269
	sdlog	0.66	3.307	0.304	1.016
Weibull	Scale	0.134	3.664	-0.26	0.528
	Shape	8.562	9.022	7.591	9.532

Source:

Progression FVC%pred

Table 49 **General model - linear mixed effects estimates (FVC%pred – first 52 weeks)**

Term	Estimate	SE	P-value
(Intercept)	0.34	1.18	0.78
TRT01PNintedanib	0.39	0.31	0.2
fvc_base	0.99	0.01	0
AGE	0	0.02	0.97
acute_ild_exacerbation1	-5.7	1.05	0
TRT01PPlacebo:analysis_year	1.12	2.12	0.6
TRT01PNintedanib:analysis_year	4.23	2.09	0.04
AGE:analysis_year	-0.1	0.03	0

Source:

Covariance matrixes for fixed effects (FVC%pred first 52 weeks)

Table 50 **General model - fixed effects covariance matrix (FVC%pred – first 52 weeks)**

	Intercept	Treatment Nintedanib	FVC (BL)	AGE	Acute ILD exacerbation	Treatment Placebo: Analysis Year	Treatment Nintedanib: Analysis Year	AGE: analysis year
(Intercept)	1.40	-0.06	-0.01	-0.02	0.01	-0.57	-0.54	0.01
TRT01PNintedanib	-0.06	0.09	0.00	0.00	0.00	0.03	-0.01	0.00
fvc_base	-0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00
AGE	-0.02	0.00	0.00	0.00	0.00	0.01	0.01	0.00
acute_ild_exacerbation1	0.01	0.00	0.00	0.00	1.11	-0.01	-0.01	0.00
TRT01PPlacebo:analysis_year	-0.57	0.03	0.00	0.01	-0.01	4.51	4.24	-0.07
TRT01PNintedanib:analysis_year	-0.54	-0.01	0.00	0.01	-0.01	4.24	4.36	-0.06
AGE:analysis_year	0.01	0.00	0.00	0.00	0.00	-0.07	-0.06	0.00

Source:

Table 51 **Independent model placebo - fixed effects covariance matrix (FVC%pred – first 52 weeks)**

	(Intercept)	fvc_base	AGE	PGGR1_marginal	PGGR1_worsening	acute_ild_exacerbation1	AGE:analysis_year	PGGR1_marginal:analysis_year	PGGR1_worsening:analysis_year
(Intercept)	2.736	-0.011	-0.029	-0.029	-0.094	0.019	0.000	-0.002	0.002
fvc_base	-0.011	0.000	0.000	-0.002	-0.002	0.000	0.000	0.000	0.000
AGE	-0.029	0.000	0.000	0.001	0.002	0.000	0.000	0.001	0.001
PGGR1_marginal	-0.029	-0.002	0.001	0.258	0.101	0.000	0.001	-0.110	-0.036
PGGR1_worsening	-0.094	-0.002	0.002	0.101	0.354	-0.037	0.001	-0.038	-0.147
acute_ild_exacerbation1	0.019	0.000	0.000	0.000	-0.037	2.028	-0.001	0.054	0.100
AGE:analysis_year	0.000	0.000	0.000	0.001	0.001	-0.001	0.000	-0.004	-0.004
PGGR1_marginal:analysis_year	-0.002	0.000	0.001	-0.110	-0.038	0.054	-0.004	0.850	0.287
PGGR1_worsening:analysis_year	0.002	0.000	0.001	-0.036	-0.147	0.100	-0.004	0.287	1.130

Source:

Table 52 **Independent model nintedanib - Fixed effects covariance matrix (FVC%pred – first 52 weeks)**

	(Intercept)	fvc_base	AGE	acute_ild_exacerbation1	AGE:analysis_year
(Intercept)	2.477	-0.009	-0.028	0.022	0.000
fvc_base	-0.009	0.000	0.000	0.000	0.000
AGE	-0.028	0.000	0.000	0.000	0.000
acute_ild_exacerbation1	0.022	0.000	0.000	2.355	0.000
AGE:analysis_year	0.000	0.000	0.000	0.000	0.000

Source:

Coefficients for TTD parametric models in the nintedanib arm

Table 53 **Coefficients for TTD parametric models – nintedanib arm**

Model	Variable	Coefficient	Std. Dev	95% Conf. Interval	
Exponential	**Rate**	-7.336	1.831	-7.533	-7.139
Generalised Gamma	**mu**	7.740	6.068	7.087	8.393
	sigma	0.940	4.604	0.445	1.436
	q	0.047	10.538	-1.087	1.180
Gompertz	**Shape**	-0.003	0.011	-0.004	-0.001
	Rate	-6.735	2.979	-7.056	-6.415
Log-logistic	**Shape**	-0.321	1.686	-0.502	-0.140
	Scale	7.504	3.866	7.088	7.920
Log-normal	**Meanlog**	7.722	4.550	7.232	8.211
	sdlog	0.959	1.499	0.798	1.121
Weibull	**Scale**	-0.407	1.742	-0.594	-0.220
	Shape	7.887	4.018	7.455	8.320

Source:

Adverse events

Table 54 **Full list of adverse events from the clinical trial report of the INBUILD trial. The table presents the investigator defined drug-related AEs reported for more than 1.5% of patients in either arm**

MedDRA system organ class preferred term	Placebo		Nintedanib	
	N	%	N	%
Number of patients	331	100.0	332	100.0
Patients with any drug-related AE	126	38.1	262	78.9
Gastrointestinal disorders	82	24.8	228	68.7
Diarrhoea	59	17.8	196	59.0
Nausea	19	5.7	79	23.8
Vomiting	7	2.1	41	12.3
Abdominal pain	2	0.6	21	6.3
Abdominal pain upper	2	0.6	18	5.4
Abdominal distension	2	0.6	8	2.4
Dyspepsia	5	1.5	7	2.1
Investigations	18	5.4	77	23.2
Alanine aminotransferase increased	8	2.4	36	10.8
Aspartate aminotransferase increased	6	1.8	32	9.6
Weight decreased	4	1.2	31	9.3
Gamma-glutamyltransferase increased	3	0.9	14	4.2
Blood alkaline phosphatase increased	0	0	7	2.1
Metabolism and nutrition disorders	10	3,0	38	11.4
Decreased appetite	10	3.0	37	11.1
Hepatobiliary disorders	6	1.8	27	8.1
Hepatic function abnormal	3	0.9	16	4.8
General disorders and administration site conditions	11	3.3	25	7.5
Fatigue	3	0.9	11	3.3
Asthenia	7	2.1	9	2.7
Nervous system disorders	12	3.6	18	5.4
Headache	5	1.5	9	2.7
Respiratory, thoracic, and mediastinal disorders	11	3.3	7	2.1
Epistaxis	3	0.9	6	1.8
Vascular disorders	4	1.2	7	2.1
Hypertension	0	0	6	1.8

Source: Clinical trial report of the INBUILD trial.

Tables referred to in the resource use section

Table 55 **Number of resource use observations in each FVC%pred group**

FVC%pred group	Number of observations (months)
>110	117
100-110	236
90-100	519
80-90	1054
70-80	1735
60-70	2271
50-60	2110
<50	1252

Abbreviations: FVC%pred: forced vital capacity percent predicted, HCRU: healthcare resource use.

Table 56 **Resource use inputs from DBL 1 in the INBUILD trial**

FVC% pred	Hospitalisation	ER	GP visit	Specialist visit	Nurse visit	Physio visit	Other visits	Occupational therapy	Oxygen use	Outpatient stays
>110	5	4	5	3	1	0.5*	1	1	6	0
100-110	4	4	8	13	0.5*	0.5*	0.5*	0.5*	14	0
90-100	10	4	28	48	6	1	3	3	30	0
80-90	13	13	63	69	9	5	16	16	52	0
70-80	29	21	174	129	19	3	3	3	154	0
60-70	70	43	148	194	21	2	8	8	271	0
50-60	71	43	123	130	17	3	12	12	353	0
< 50	55	23	66	69	8	0.5*	9	9	265	0

*some values were changed from 0 to 0.5 to avoid sampling errors.
Source: INBUILD trial data

Medicinrådet

Medicinrådets protokol for vurdering vedrørende nintedanib til behandling af interstitiel lungesygdom med progredierende fibrose

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*)

CI: Konfidensinterval

DL_{CO}: Diffusionskapacitet

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

EPAR: *European Public Assessment Report*

EUnetHTA: *European Network for Health Technology Assessment*

FDA: *The Food and Drug Administration*

FGFR: Fibroblast vækstfaktorreceptor (*Fibroblast Growth Factor Receptor*)

FINOSE: Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger

FVC: Forceret vitalkapacitet (*Forced Vital Capacity*)

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

HRCT: Højopløsnings-CT-skanning

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)*

PP: *Per-protocol*

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

SAE:	Alvorlig uønsket hændelser (*Serious Adverse Event*)
SMD:	*Standardized Mean Difference*
SSc-ILS:	Systemisk sklerose-associeret interstitiel lungesygdom
UIP:	*Usual Interstitial Pneumonia*
VEGFR:	Vaskulær endotelial vækstfaktorreceptor (*Vascular Endothelial Growth Factor*)

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Boehringer Ingelheim, som ønsker, at Medicinrådet vurderer nintedanib til interstitiel lungesygdom (ILS) med progredierende fibrose (PF-ILS). Vi modtog den foreløbige ansøgning den 21. februar 2020.

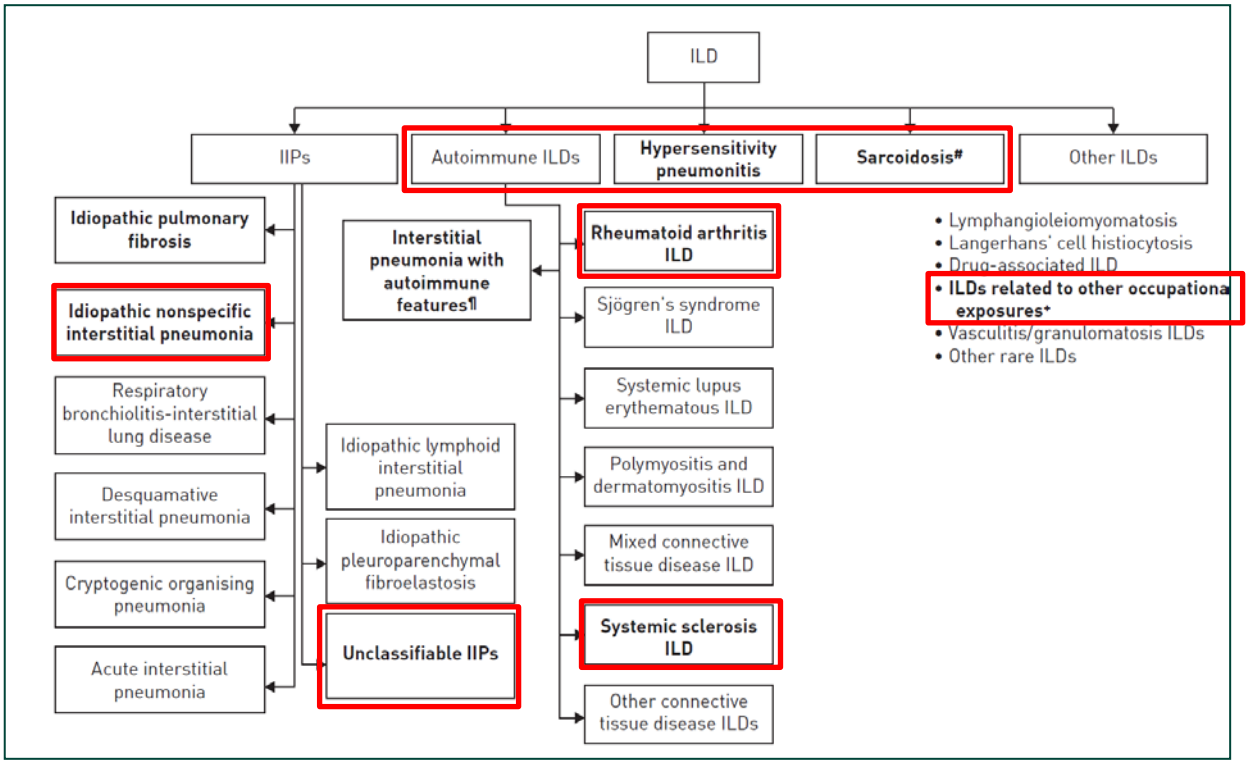
2.1 Interstitiel lungesygdom med progredierende fibrose

Interstitielle lungesygdomme (ILS) er en heterogen gruppe af lungesygdomme, hvor det mest almindelige symptom er åndenød (dyspnø). Årsagen til ILS er forskellig og kan både skyldes miljøpåvirkning, underliggende autoimmun sygdom eller ukendte årsager. ILS kan udvikles som følge af inflammation med efterfølgende fibrosedannelse (arvævsdannelse) eller alene ved fibrose [1–3]. Lungefibrose er en kronisk sygdom, som kan ramme alle dele af lungevævet. Lungefibrose opstår, når celler i bindevævet, som kaldes fibroblaster, aktiveres til at udskille øget mængde af ekstracellulært materiale, som medfører stivhed i lungevævet og nedsat alveolar funktion. Jo mere fibrose, der opstår i lungerne, jo mere bliver lungefunktionen påvirket [4].

Diagnosen af ILS er kompleks og bliver foretaget af et tværfagligt team af læger med ekspertise inden for lungemedicin, thorax-radiologi, reumatologi, kardiologi og patologi [5,6]. Udredning af ILS kræver en del undersøgelser, både for at påvise tilstedeværselen af ILS og for at klassificere, hvilken undertype ILS patienten har. Disse inkluderer blandt andet grundig anamneseoptag, lungefunktionsundersøgelse, røntgen af thorax, højopløsnings-CT-skanning (HRCT) 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 [1].

Der findes mange typer af ILS, se oversigt i figur 1, hvoraf en af de mest undersøgte er idiopatisk pulmonal fibrose (IPF). IPF er kendetegnet ved irreversibel udvikling af progredierende lungefibrose med et radiologisk-patologisk mønster kaldet *usual interstitial pneumonia* (UIP), som diagnosticeres ved enten HRCT-skanning eller histologisk på lungevævsbiopsi [7–9]. Sygdommen optræder kun hos voksne, oftest over 50 år, og med en overvægt af mænd og rygere/eksrygere. IPF er forbundet med nedsat lungefunktion, dyspnø med gradvis forværring, forværret livskvalitet og dårlig prognose, hvor den gennemsnitlige overlevelse er på 3-5 år efter diagnose. Nogle patienter med IPF kan være stabile i en årrække, mens andre oplever hurtig progression over få måneder [7–10].

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.

ILS med progredierende lungefibrose (PF-ILS)

Udover IPF kan andre undertyper af ILS også medføre progredierende lungefibrose, selvom de ikke kan kategoriseres som værende IPF, se figur 1. Disse bliver samlet kaldt for PF-ILS. PF-ILS er en heterogen gruppe af sygdomme med varierende grad af lungefibrose og inflammation, som medfører gradvis forværring af respiratoriske symptomer, nedsat lungefunktion og tiltagende fibrose på HRCT-skanning [9,11–13]. De patogenetiske mekanismer, det kliniske sygdomsbillede og patienternes prognose er på mange måder sammenlignelig mellem PF-ILS og IPF [5,13–15]. PF-ILS er dermed ligeledes forbundet med forværret livskvalitet og tidlig død trods behandling [9,11,12]. Omkring 2/3 dele af PF-ILS-patienterne har et UIP-mønster på HRCT-skanning eller histologi, mens øvrige patienter har andre fibrotiske mønstre på HRCT-skanning [16]. På grund af sygdommens progressive karakter oplever PF-ILS-patienter en væsentlig højere symptombyrde sammenlignet med øvrige ILS-patienter [11], som påvirker patienternes livskvalitet og daglige aktivitetsniveau [17–21]. Patienternes prognose er afhængig af omfanget af fibrosen, hvorvidt UIP-mønster er til stede, hvor hurtigt deres lungefunktion falder og frekvensen af akutte eksacerbationer, dvs. akutte kliniske forværringer af patientens respiratoriske symptomer, som kræver behandling med prednisolon og/eller antibiotika eller hospitalsindlæggelse.

Incidensen af ILS, herunder PF-ILS, er svær at vurdere. Der foreligger et nationalt register over ILS i Danmark, men det indeholder overvejende patienter med IPF. 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 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 stigning i antallet af CT-skanninger, som involverer thorax, som kan rejse mistanke om ILS. Fagudvalget skønner, at ca. 60-80 nye patienter med PF-ILS årligt potentielt kan være kandidater til behandling med nintedanib. Fagudvalget understreger, at dette er et konservativt bud. 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 lav-molekylær 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 af nintedanib til PDGFR og FGFR blokeres receptorernes intracellulære signalveje, som er med til at stimulere proliferation, migration og differentiering af lungefibroblaster, hvilket bremser videre udvikling af lungefibrosen [24].

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 ved IPF er livsforlængende og gives indtil forekomsten af uacceptable bivirkninger eller død.

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

> *Ofev er også indiceret til behandling af andre kroniske fibroserende interstitielle lungesygdomme (ILS) med en progressiv fænotype 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 PF-ILS har nintedanib samtidig fået følgende indikationsudvidelse i 2020 hos EMA til systemisk sklerose-associeret ILS (SSc-ILS):

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

2.3 Nuværende behandling

Dødeligheden af PF-ILS korrelerer i høj grad med reduktionen i lungefunktion (fald i forceret vitalkapicitet (FVC)) som følge af progression af lungefibrosen [9,11,12,14]. 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 PF-ILS, og som specifikt er rettet mod fibrosedannelsen. Da PF-ILS er en heterogen gruppe af forskellige sygdomme, rettes nuværende behandlingsmuligheder mod den underliggende sygdomsårsag. Der er generelt sparsom evidens for behandling af de enkelte sygdomme med kun få randomiserede kliniske studier (*randomized clinical trial* (RCT)). Evidensen er ofte baseret på retrospektive studier, case-series og klinisk erfaring [9]. Behandlingen kan derfor variere imellem de enkelte ILS-centre, men følger generelt accepterede behandlingsprincipper. Hvis der identificeres en udløsende årsag, forsøges den elimineret. De enkelte sygdomme har varierende grader af inflammation og fibrosedannelse. For at dæmpe den skadelige inflammatoriske proces anvendes oftest immunmodulerende lægemidler som førstelinjebehandling. Disse omfatter blandt andet glukokortikoid, azathioprin, methotrexat, mycophenolat mofetil og cyclophosphamid [9]. Derudover anvendes i visse situationer biologiske lægemidler, fx TNF-hæmmer, rituximab, abatacept eller interleukin-6-hæmmer [25–28]. Ingen af de nævnte lægemidler har PF-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 lungefunktionsmåling, evt. suppleret med gangtest og HRCT-skanning [9].

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 PF-ILS-patienter i dag ikke yderlige 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 PF-ILS-patienter [9,13], jf. afsnit 3. 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
En international ILS-ekspertgruppe har for nyligt defineret, at ILS-patienter, der opfylder nedenstående kriterier, kan defineres som havende progredierende lungefibrose og dermed være kandidater til antifibrotisk behandling med nintedanib [13]. Fagudvalget tilslutter sig denne definition og mener, at PF-ILS-patienter, som a) progredierer over 3-6 måneder til trods for førstelinjebehandling med immunmodulerende medicin, og som b) opfylder de følgende kriterier, er kandidater til antifibrotisk behandling med nintedanib:

- Relativt fald i FVC $\geq$ 10 % over 24 måneder på trods af behandling
- Relativt fald i FVC $\geq$ 5 - < 10 % samt $\geq$ 15 % fald i DLco over 24 måneder på trods af behandling
- Relativt fald i FVC $\geq$ 5 – < 10 % + forværret fibrose på HRCT over 24 måneder på trods af behandling
- Relativt fald i FVC $\geq$ 5 – < 10 % samt forværrede symptomer over 24 måneder på trods af behandling
- Forværrede symptomer samt forværret fibrose på HRCT over 24 måneder på trods af behandling.

3.1 Klinisk spørgsmål 1

Hvilken værdi har nintedanib sammenlignet med placebo for patienter med interstitiel lungesygdom med progredierende fibrose?

Population
Voksne patienter med PF-ILS, der progredierer ved førstelinjebehandling med immunmodulerende lægemidler[*]. Patienterne skal opfylde én eller flere af kriterierne oplistet ovenfor.

Intervention
Nintedanib, 150 mg to gange dagligt.

Komparator
Placebo

Effektmål
De valgte effektmål fremgår af tabel 1.

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

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.

Tabel 1. Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Dødelighed	Kritisk	Dødelighed	Median overlevelse	6 måneder
	Kritisk[1]	Livskvalitet, alvorlige symptomer og bivirkninger	Lungefunktion målt ved årlig FVC-faldhastighed	50 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
Akut eksacerbations-rate	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever mindst én akut eksacerbation pr. år	20 %-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

PF-ILS er en uhelbredelig, dødelig sygdom, hvor den gennemsnitlige overlevelse er på 3-5 år [9,11,12,14]. Behandlingsmålet er at bremse sygdomsprogressionen med henblik på stabilisering og dermed forlænget overlevelse. Derfor er dødelighed et kritisk effektmål ved vurderingen af nintedanibs værdi til patienter med PF-ILS.

Behandling med nintedanib er livsforlængende ved IPF og bremser hastigheden for udvikling af lungefibrosen. Hos PF-ILS-patienter kan lægemidlet forventes at have en tilsvarende effekt og kan dermed teoretisk påvirke dødeligheden. Fagudvalget er klar over, at de kliniske studier med nintedanib ikke er designet til at vise en effekt på dødelighed [16,29]. Fagudvalget vurderer trods disse forhold, at et væsentligt mål med behandling af PF-ILS er at nedsætte risikoen for tidlig død.

Fagudvalget ønsker effektmålet opgjort som median overlevelse og vurderer, at en forbedring på 6 måneder er klinisk relevant. Fagudvalget har ved fastsættelsen af den mindste klinisk relevante forskel taget udgangspunkt i PF-ILS-patienternes prognose [5].

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 surrogatmål 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 PF-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 til behandling af IPF, at fald i FVC er et klinisk relevant effektmål på grund af dens korrelation med dødelighed [30,31]. 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[†] [32]. 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 [33]. På grund af kliniske og patofysiologiske ligheder mellem IPF og PF-ILS [5,14,15], forventes fald i FVC ligeledes at korrelere med dødelighed hos PF-ILS-patienter.

Fagudvalget ønsker effektmålet opgjort som forskel i årlig FVC faldhastighed, målt som ml/år, og vurderer, at en forskel på 50 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 [34] og omkring 190 ml/år hos PF-ILS-patienter [16]. Således vurderer fagudvalget, at en forskel på 50 ml/år vil være af klinisk betydning, set i lyset af FVC-faldhastigheden hos PF-ILS-patienter.

[†] 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.

Livskvalitet
Livskvalitet er et patientrelevant effektmål, som påvirkes i væsentlig grad af sygdomsprogressionen ved PF-ILS [17–21], 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 stabilisere patienternes livskvalitet. Fagudvalget betragter derfor livskvalitet som et kritisk effektmål i vurderingen af nintedanibs værdi til patienter med PF-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 [35,36]. Et dansk studie har defineret, at en forværring på 2,7 point fra baseline er klinisk relevant hos IPF-patienter [37]. 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 PF-ILS, 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 [38].

Akut eksacerbationsrate
En akut eksacerbation er en akut klinisk forværring af patientens respiratoriske symptomer og livskvalitet og kræver ofte hospitalsindlæggelse. Svære tilfælde af akutte eksacerbationer er potentielt en livstruende tilstand [32]. På grund af alvorligheden af hændelsen betragter fagudvalget akut eksacerbationsrate som et kritisk effektmål.

Jf. den nyeste internationale retningslinje [39] defineres en akut eksacerbation ved ILS som en akut klinisk signifikant respiratorisk forværring, karakteriseret ved ny og udbredt alveoleskade, som opfylder alle følgende kriterier:

- Akut forværring eller udvikling af dyspnø (typisk < 1 måneds varighed)
- Evidens for fibrose på CT-skanning
- Forværring, som ikke er konsekvens af hjertesvigt eller ødem

Akutte eksacerbationer forekommer med en årlig incidens på omkring 5-10 % hos PF-ILS-patienter [40–43].

Fagudvalget ønsker effektmålet opgjort som andel patienter, der oplever mindst én akut eksacerbation pr. år, jf. ovenstående definition, og vurderer, at en forskel på 20 %-point er klinisk relevant. Fagudvalget har ved fastsættelsen af den mindste klinisk relevante forskel taget udgangspunkt i den rapporterede effekt på effektmålet ved IPF[‡] [33].

3.2.2 Vigtige effektmål

Bivirkninger
Fagudvalget vægter effektmålet bivirkninger som vigtigt i vurderingen af nintedanibs værdi til patienter med PF-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

[‡] 4,9 % af patienterne i nintedanib-armen oplevede mindst én akut eksacerbation sammenlignet med 7,6 % i placebo-armen.
[§] For yderligere detaljer se Medicinrådets kriteriepapir om anvendelse af upublicerede data

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, INBUILD-studiet, hvor nintedanib er sammenlignet direkte med placebo. Studiet er rapporteret i følgende publikationer:

- Flaherty KR et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med. 2019 Oct 31;381(18):1718-1727 [16].
- Flaherty KR et al. Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. BMJ Open Respiratory Research. 2017;4(1):e000212 [44].

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.

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 INBUILD-studiet
Jf. det kliniske spørgsmål ønsker fagudvalget data på PF-ILS-patienter, der progredierer på førstelinjebehandling med immunmodulerende lægemidler. Det er uklart, om dette er tilfældet for studiepopulationen i INBUILD-studiet. Ansøger bedes derfor redegøre for sammenligneligheden mellem studiepopulationen i INBUILD-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 PF-ILS eller SSc-ILS.

Medicinrådets sekretariat

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11. Versionslog

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