EU Risk Management Plan for Ofev (nintedanib)

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RMP version to be assessed as part of this application:	
RMP version number:	12.3
Data lock point for this RMP:	31 May 2023
Date of final sign off:	10 Sep 2024
Rationale for submitting an updated RMP:	New proposed indication for children and adolescents from 6 to 17 years old for the treatment of clinically significant fibrosing interstitial lung diseases
Summary of significant changes in this RMP:	<u>New indication</u> - Update of Module SI to include the epidemiology of the proposed indication and information on incidence rates of co-morbidities of the underlying disease - Update of the clinical trial exposure tables in Modules SIII to include data from the paediatric trial (1199-0337) - Update of the exclusion criteria in Module SIV with the paediatric trial (1199-0337) - Update of the risk characterisation section in Module SVII to include risk analyses from the paediatric trial (1199-0337) and to add 1 paediatric important identified risk and 2 paediatric important potential risks - Update of information in Part III, V, VI, and Appendices 2 and 3 regarding additional pharmacovigilance activity (trial 1199-0378) for the new proposed indication in line with the latest protocol - Update of Part V to include the new safety concerns for the proposed paediatric indication and the related risk minimisation measures including clinical measures; added clinical measures related to DILI and hepatic failure for completeness

	- Update of Part VI with the new proposed indication and updated information from Part III and Part V - Update of Appendix 4 to include 2 new questionnaires on 'Effect on bone development and growth in paediatric population' and 'Effect on tooth development disorders in paediatric population', and update of remaining questionnaires Other Update of post-marketing exposure in Module SV and of post-marketing information in SVII
Other RMP versions under evaluation:	Not applicable
RMP version number:	
Submitted on:	
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Date of approval (opinion date):	28 Jul 2023
QPPV name:	Sven Kohler
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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PART I PRODUCT OVERVIEW

PI.Table 1 Product Overview

Active substance (INN or common name)	Nintedanib (nintedanib)
Pharmacotherapeutic group (ATC code)	Tyrosine kinase inhibitor (L01EX09)
Marketing Authorisation Holder	Boehringer Ingelheim International GmbH
Medicinal product to which this RMP refers	1
Invented name in the EEA	Ofev
Marketing authorisation procedure	Centralised
Brief description of the product	*Chemical class* Oxoindole derivative *Summary of mode of action* Ofev is a small molecule inhibitor of tyrosine kinases targeting platelet derived growth factor receptor α and β, fibroblast growth factor receptor 1-3, and vascular endothelial growth factor receptor. Ofev binds competitively to the adenosine triphosphate binding pocket of these receptors and blocks the intracellular signalling which is crucial for the proliferation, migration, and transformation of fibroblasts representing essential mechanisms of the IPF pathology. *Important information about its composition* Not applicable
Hyperlink to the Product Information	Product information
Indication in the EEA	*Current* Ofev is indicated in adults for the treatment of: • Idiopathic pulmonary fibrosis (IPF) • Other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype • Systemic sclerosis associated interstitial lung disease (SSc-ILD)

PI.Table 1 (cont'd) Product Overview

Indication in the EEA (cont'd)	*Proposed* Ofev is indicated in children and adolescents from 6 to 17 years old for the treatment of clinically significant fibrosing interstitial lung diseases (ILDs)
Dosages in the EEA	*Current* Adults: 150 mg b.i.d., with dose reduction to 100 mg b.i.d. as required. Doses to be administered approximately 12 hours apart. *Proposed* Paediatric: Dosing regimen (based on patient's weight): • 50 mg b.i.d. for patients with a weight of 13.5 kg to <23.0 kg • 75 mg b.i.d. for patients with a weight of 23.0 kg to <33.5 kg • 100 mg b.i.d. for patients with a weight of 33.5 kg to <57.5 kg • 150 mg b.i.d. for patients with a weight of ≥57.5 kg with the option of dose reductions to the next lower dose (down to 25 mg b.i.d.) to manage AEs
Pharmaceutical form and strengths	*Current* Soft capsules, 100 mg and 150 mg *Proposed* Soft capsules, 25 mg
Is/will the product be subject to additional monitoring in the EU?	No

ABBREVIATIONS

AE	Adverse event
ATC	Anatomical Therapeutic Chemical
b.i.d.	*bis in die*, twice daily
EEA	European Economic Area
EU	European Union

ILD	Interstitial lung disease
INN	International Non-proprietary Name
IPF	Idiopathic pulmonary fibrosis
RMP	Risk Management Plan

PART II SAFETY SPECIFICATION

MODULE SI EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATIONS

This module includes epidemiological information related to the following indications of use for Ofev:

- Treatment of idiopathic pulmonary fibrosis (approved)
- Treatment of systemic sclerosis-associated interstitial lung disease (approved)
- Treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (approved)
- Treatment of children and adolescents from 6 to 17 years old with fibrosing interstitial lung disease (proposed)

SI.1 IDIOPATHIC PULMONARY FIBROSIS (IPF)

The following section aims to provide an overview of the epidemiology of IPF including patient characteristics, treatment patterns, and co-morbidities of interest. Nevertheless, the following potential limitations of the included studies have to be considered:

- Differences in the definition of clinical cases and the criteria used to diagnose IPF
- Differences in the case definition and criteria used to identify the co-morbidities of interest, or in some cases the lack of a disease definition
- Given that IPF is a rare disease, the majority of the included observational studies assessed relatively small samples of IPF patients
- Across the studies, IPF patients were in different stages of the disease. Newly diagnosed patients are likely to differ from patients at advanced stages, such as that awaiting lung transplantation. Hence, there may be differences in the prevalence of various co-morbidities among different stages of IPF severity
- Only studies published in English language were included
- The majority of the included studies were conducted based on existing data, which may be affected by information bias
- Differences in health care systems, population characteristics, and other factors such as local treatment guidelines may limit the generalisability of findings across countries

SI.1.1 Incidence

In Europe, the estimated overall IPF incidence ranged from 0.22 per 100 000 PY in Belgium from 1992 to 1996, to 9.3 per 100 000 PY in Italy between 2000 and 2010 [R03-2088, R03-2090, R10-2818, R11-4826, R11-5060, R11-5070, R16-1739, R16-1749, R16-1968]. Incidence increased with age [R03-2088, R10-2818, R11-4826, R16-1739, R16-1749] and dropped again for the population aged 85 years and older [R10-2818, R11-4826, R16-1739]. As shown in SI.Table 1, the incidence is higher in men compared to women; this is especially true for the older population aged 55 years and older (SI.Table 3).
A summary of the studies reporting the IPF incidence in Europe from 1981 to 2010 is presented in the table below.

SI.Table 1 Incidence of IPF in Europe from 1981 to 2010

Country	Study period	Sample size, n	IPF case ascertainment	IPF incidence (95% CI)		
				Male	Female	Total
				Per 100 000 PY		
Belgium [R03-2090]	Jan 1992-Jul 1996	59	Biopsy proven UIP	NR	NR	0.22 (NR)
Denmark [R16-1968]	Apr 2003-Mar 2009	121	IPF patients part of an ILD registry, diagnosis according to ATS/ERS/JRS/ALAT 2011 consensus	NR	NR	1.3 (NR)
Greece [R11-5060]	Jan-Dec 2004	52	ATS/ERS consensus (2002)	NR	NR	0.93 (NR)
Italy [R16-1749]	2005-2009	1752[a]	ICD-9, ≥18 years	NR	NR	7.5 (7.3, 7.7) 9.3 (9.2, 9.4)[b]
Italy [R16-1739]	2005-2010	2951	Generic case definition[c]	6.18 (5.88, 6.45)	4.37 (4.13, 4.61)	5.25 (5.06, 5.44)
		2093	Broad case criteria[d]	4.63 (4.37, 4.89)	2.88 (2.69, 3.08)	3.74 (3.58, 3.90)
		1309	Narrow case criteria[e]	2.85 (2.65, 3.05)	1.84 (1.68, 2.00)	2.33 (2.20, 2.46
UK [R11-4826]	2000-2008	2074	Read codes[f]	9.46 (8.96, 9.98)	5.46 (5.07, 5.86)	7.44 (7.12, 7.77)
UK [R10-2818]	1991-2003	920	Read codes[g]	5.69 (5.24, 6.18)	3.44 (3.10, 3.82)	4.6 (4.3, 4.9)
				Per 100 000 persons		
Czech Republic [R03-2088]	1981-1990	379	NR	NR	NR	0.94 (NR)
Norway [R11-5070]	1984-1998	158[h]	ICD-8/ICD-9	4 (3.1, 4.9)	4.6 (3.7, 5.6)	4.3 (NR)

[a] Hospitalised cases: both as ordinary admission and as day hospital admission.
[b] Adjusted IR after chart review.
[c] Generic case definition: Subjects with at least 1 hospital admission or outpatient visit with IPF diagnosis (ICD-9-CM code 516.3).
[d] Broad case definition: Inclusion of patients of the generic case definition, who had no hospital admission or outpatient visit with ILDs diagnosis on or after date of last IPF diagnosis.
[e] Narrow case definition: Inclusion of patients of the broad case definition, who had at least 1 surgical lung biopsy, transbronchial lung biopsy or CT of the thorax performed during an hospitalisation or outpatient visit, on or before date of last IPF diagnosis.
[f] The term "IPF clinical syndrome" was used to describe the individuals considered in the analyses. People were included in the cohort if they had ≥recorded IPF-CS diagnosis, their first diagnosis was recorded at least 12 months after their start date and they were aged ≥40 years at their first diagnosis. Exclusion of individuals with a co-existing diagnosis of connective tissue disease and with a co-existing diagnosis of extrinsic allergic alveolitis, sarcoidosis, pneumoconiosis and asbestosis.
[g] Patients required at least 1 recorded IPF diagnosis and that their first IPF diagnosis was recorded at least 12 months after their start date, age ≥40 years at first diagnosis.
[h] Hospitalised cases.

In the US, the estimated overall IPF incidence ranged from 14.0 to 93.7 per 100 000 PY (see table below). However, the highest incidence rate was reported in a study using a very broad claims based algorithm in an elderly population of 65 years and above [R14-2284]. The study of Esposito et al. (2015) showed a PPV of 54.0% for their broad case algorithm, which is similar to the primary definition in the study of Raghu et al. (2014), which underlines that the estimates of Raghu et al. (2014) are very likely subject to overestimation. Furthermore, 2 studies showed an increasing trend of incidence with age (SI.Table 3).

The table below depicts the IPF incidence in the US by gender.

SI.Table 2 Incidence of IPF in the US, by gender

Study period	Sample size, n	Study population	IPF case ascertainment	IPF incidence (95% CI)		
				Male	Female	Total
				Per 100 000 PY		
Jan 1997-Dec 2005 [R10-2800]	24[a]	Community-based historical cohort based on medical records	Narrow case criteria	13.38[b] (6.51, 20.24)	6.08[b] (2.08, 10.08)	8.8[c] (5.28, 12.38)
	47[a]		Broad case criteria	24.02[b] (14.84, 33.20)	13.43[b] (7.50, 19.37)	17.43[c] (12.42, 22.44)
Oct 1988-Sep 1990 [R03-2075]	63 (36 male)	Population-based ILD registry	ICD-9	10.7 (NR)	7.4 (NR)	NR
Jan 2006-Sep 2012 [R16-1737]	4598	Health care claims database	Broad case criteria[d]	20.2[e] (18.9, 21.7)	10.4[f] (9.6, 11.4)	14.6[e, f] (13.8, 15.4)
2001-2011 [R14-2284]	12 066	Claims database	All[g]	104.8 (102.0, 107.7)[h]	86.1 (84.0, 88.3)[h]	93.7 (91.9, 95·4)[h] 78.7-93.2[i]
	5197		Narrow case criteria[g]	NR	NR	15.9-31.1[i]
	3195		Broad case criteria[g]	NR	NR	31.1-43.0[i]
Jan 1996-Dec 2000 [R10-2858]	387	IPF cases identified from a large health care claims database	Narrow case criteria[j]	NR	NR	6.8 (NR)
	1211		Broad case criteria[j]	NR	NR	16.3 (NR)

[a] Residents aged 50 years or older.
[b] Age adjusted.
[c] Age- and gender-adjusted.
[d] Broad case definition: Patients 50-100 years of age with at least 6 months of enrolment, ≥1 diagnosis with IPF (ICD-9-CM code 516.3) made by a physician and no alternative diagnoses recorded after the date of the last recorded diagnosis of IPF and within 6 months of the first physician assigned diagnosis of IPF.
[e] Estimates are age and gender-adjusted and corrected for the PPV.
[f] Estimate is standardised to the US population, the non-standardised estimate was 12.8 per 100 000 PY.
[g] Primary cohort: age ≥65 years, excluding patients who received Medicare benefits because of disability or end-stage renal disease, ≥1 medical claims with a diagnosis code for IPF (ICD-9-CM 516.3) between 01 Jan 2000 and 31 Dec 2011, ≥1 year of continuous coverage of Medicare Part A and Part B without and an ICD-9-CM diagnosis code for IPF (ICD-9-CM 516.3) before the index quarter. Broad case definition: additional exclusion of patients with a claim with the code 515 on or after the quarter of the last claim with the ICD-9-CM diagnosis code 516.3. Narrow case definition: inclusion of patients of the broad case definition, who had a claim for a surgical lung biopsy, transbronchial lung biopsy, or CT scan of the thorax before the last 516.3 claim.
[h] Unadjusted incidence estimates.
[i] Incidence estimates varied dependent on the year (reported as range).
[j] Broad case definition: age ≥18 years, ≥1 medical claims with a diagnosis code for IPF (ICD-9-CM 516.3), no medical claims with a diagnosis code for any other ILDs on or after date of last medical claim with a diagnosis code for IPF. Narrow case definition: meet broad case definition, ≥1 medical claims with a procedure code for surgical lung biopsy, transbronchial lung biopsy, or CT of the thorax, on or before date of last medical claim with a diagnosis code for IPF.

In general, IPF incidence increased with age in both EU and US data, while it decreased for the population aged 85 years and older based on 2 UK studies and 1 Italian study where these older aged group patients were included. The table below shows the IPF incidence in Europe and the US, stratified by gender and age.

SI.Table 3 IPF incidence in Europe and the US, stratified by gender and age

Region/ country	Study period	Sample size, n	Age group [years]	IPF incidence (95% CI)		
				Male	Female	Total
Europe				**Per 100 000 PY**		
Italy [R16-1749]	2005-2009	1752	18-34	0.3	0.4	0.4 (0.3-0.4)
			35-44	1.0	1.1	NR
			45-54	2.8	2.4	NR
			55-64	9.9	5.8	NR
			65-74	24.1	17.1	28.1 (27.1, 29.2)
			≥75	38.5	21.8	NR
				Generic case definition[a]		
Italy [R16-1739]	2005-2010	2951	<55	0.98 (0.85-1.13)	0.86 (0.73-1.00)	0.92 (0.82-1.01)
			55-59	5.68 (4.64-6.88)	5.05 (4.09-6.17)	5.36 (4.62-6.10)
			60-64	10.98 (9.45-12.69)	6.19 (5.09-7.46)	8.51 (7.54-9.49)
			65-69	15.81 (13.90-17.91)	8.74 (7.41-10.24)	12.08 (10.90-13.27)
			70-74	21.67 (19.20-24.36)	13.81 (12.04-15.76)	17.40 (15.88-18.93)
			75-79	33.80 (30.18-37.72)	16.37 (14.30-18.64)	23.69 (21.70-25.68)
			80-84	40.98 (35.90-46.58)	16.83 (14.47-19.46)	25.59 (23.13-28.06)
			85+	34.53 (28.41-41.59)	13.26 (11.04-15.78)	18.91 (16.50-21.31)
				Broad case definition[a]		
		2093	<55	0.70 (0.59-0.82)	0.53 (0.43-0.65)	0.62 (0.54-0.69)
			55-59	4.15 (3.27-5.20)	2.95 (2.23-3.83)	3.54 (2.93-4.14)
			60-64	7.80 (6.52-9.26)	3.99 (3.12-5.04)	5.84 (5.03-6.65)
			65-69	11.65 (10.02-13.47)	6.05 (4.96-7.32)	8.70 (7.70-9.70)
			70-74	16.33 (14.20-18.68)	8.47 (7.10-10.03)	12.06 (10.79-13.34)

SI.Table 3 (cont'd) IPF incidence in Europe and the US, stratified by gender and age

Region/ country	Study period	Sample size, n	Age group [years]	IPF incidence (95% CI)		
				Male	Female	Total
			75-79	25.61 (22.48-29.06)	10.21 (8.59-12.04)	16.68 (15.01-18.36)
			80-84	31.87 (27.41-36.86)	12.30 (10.29-14.57)	19.40 (17.26-21.55)
			85+	28.00 (22.52-34.42)	10.21 (8.28-12.45)	14.93 (12.79-17.07)
				Narrow case definition[a]		
		1309	<55	0.42 (0.34-0.52)	0.36 (0.28-0.46)	0.39 (0.33-0.46)
			55-59	2.57 (1.89-3.41)	1.90 (1.33-2.62)	2.22 (1.75-2.70)
			60-64	5.46 (4.40-6.71)	2.87 (2.14-3.77)	4.13 (3.45-4.80)
			65-69	7.49 (6.20-8.98)	3.88 (3.02-4.92)	5.59 (4.78-6.39)
			70-74	9.83 (8.19-11.69)	5.59 (4.49-6.87)	7.53 (6.52-8.53)
			75-79	16.05 (13.59-18.82)	6.30 (5.05-7.77)	10.40 (9.08-11.72)
			80-84	18.74 (15.36-22.64)	7.30 (5.78-9.10)	11.45 (9.81-13.10)
			85+	14.62 (10.74-19.44)	6.00 (4.54-7.77)	8.29 (6.69-9.88)
					Per 100 000 persons	
Norway [R11-5070]	1984–1998	158[b]	16–34	0.8 (NR)	0.4 (NR)	0.6 (NR)
			35–54	1.6 (NR)	1.4 (NR)	1.6 (NR)
			55–74	6.1 (NR)	8.6 (NR)	7.5 (NR)
			≥75	30.6 (NR)	19.3 (NR)	23.3 (NR)
					Per 100 000 PY	
UK [R11-4826]	2000–2008	2074[c]	≤54	NR	NR	0.86 (0.75, 1.00)
			55–59	NR	NR	10.48 (9.06, 12.13)
			60–64	NR	NR	20.76 (18.34, 23.50)
			65–69	NR	NR	36.45 (32.99, 40.27)
			70–74	NR	NR	47.57 (43.26, 52.32)
			75–79	NR	NR	47.38 (42.76, 52.49)

SI.Table 3 (cont'd) IPF incidence in Europe and the US, stratified by gender and age

Region/ country	Study period	Sample size, n	Age group [years]	IPF incidence (95% CI)		
				Male	Female	Total
			80–84	NR	NR	60.05 (52.47, 68.73)
			≥85	NR	NR	34.82 (27.55, 44.01)
						Per 100 000 PY
UK [R10-2818]	1991–2003	920	<55	NR	NR	0.54 (0.43, 0.67)
			55–64.9	NR	NR	7.3 (6.27, 8.50)
			65–74.9	NR	NR	17.06 (15.20, 19.14)
			75–84.9	NR	NR	25.37 (22.67, 28.40)
			≥85	NR	NR	22.37 (18.04, 27.74)
North America						Per 100 000 PY
US [R03-2075]	Oct 1988 – Sep 1990	63	35–44	4.0 (NR)	NR	NR
			45–54	2.2 (NR)	4.0 (NR)	NR
			55–64	14.2 (NR)	10.0 (NR)	NR
			65–74	48.6 (NR)	21.1 (NR)	NR
			≥75	101.9 (NR)	57.0 (NR)	NR
US [R14-2284]	Jan 2001-Dec 2011	12 066	66-69	NR	NR	63.3 (61.1, 65.6)[d]
			70-74	NR	NR	95.2 (91.7, 98.9)[d]
			75-79	NR	NR	118.7 (114.2, 123.3)[d]
			≥80			129.8 (125.3, 134.5)[d]
US [R16-1737]	Jan 2006-Sep 2012	4598	50-59	NR	NR	5.2 (4.6, 5.9)[e]
			60-69	NR	NR	18.8 (17.1, 20.6)[e]
			70-79	NR	NR	45.9 (42.3, 49.8)[e]
			≥80	NR	NR	77.3 (71.1, 83.8)[e]

[a] Generic case definition: subjects with at least 1 hospital admission or outpatient visit with IPF diagnosis (ICD-9-CM code 516.3). Broad case definition: inclusion of patients of the generic case definition, which had no hospital admission or outpatient visit with ILDs diagnosis on or after date of last IPF diagnosis. Narrow case definition: Inclusion of patients of the broad case definition, who had at least 1 surgical lung biopsy, transbronchial lung biopsy or CT of the thorax performed during an hospitalisation or outpatient visit, on or before date of last IPF diagnosis.
[b] Hospitalised cases.
[c] The term "IPF clinical syndrome" was used to describe the individuals considered in the analyses.
[d] Unadjusted incidence estimates for the primary cohort.
[e] Estimates are age and gender-adjusted and corrected for the PPV.

For the 4 studies where IPF incidence by year was evaluated, incident IPF cases seemed to increase over time in the UK, while in the US the trend was less clear (see table below). The incidence of IPF decreased between 1997 and 2005 in 1 US study [R10-2800]. Another study assessed the timely trend of incidence in the US from 2001 to 2011, in a population aged 65 years and older. The incidence remained relatively stable for the primary definition.

However, an overall increasing trend was evident for the broad and narrow case definition rising from 38.4 to 41.9 per 100 000 PY and from 15.9 to 31.1 per 100 000 PY from 2001 to 2011, respectively [R14-2284].

SI.Table 4 Time trend of incidence of IPF in Europe and the US

Region/country	Period	Sample size, n	IPF incidence per 100 000 PY (95% CI)		
			Male	Female	Total
Europe					
UK	2000	160	NR	NR	5.77 (4.95, 6.74)
[R11-4826]	2001	179	NR	NR	6.12 (5.28, 7.08)
	2002	203	NR	NR	6.69 (5.83, 7.68)
	2003	221	NR	NR	7.14 (6.26, 8.15)
	2004	253	NR	NR	8.08 (7.14, 9.14)
	2005	260	NR	NR	8.14 (7.21, 9.19)
	2006	243	NR	NR	7.54 (6.65, 8.55)
	2007	294	NR	NR	9.05 (8.07, 10.15)
	2008	261	NR	NR	8.04 (7.12, 9.08)
UK	1991–1995	920	NR	NR	2.73 (2.35, 3.17)
[R10-2818]	1996–1999		NR	NR	3.83 (3.38, 4.32)
	2000–2003		NR	NR	6.78 (6.21, 7.41)
North America			**Narrow case criteria[b]**		
US	1997–1999	24[a]	21.31[c] (5.31, 37.30)	9.03[c] (0.17, 17.89)	13.68[d] (5.57, 21.80)
[R10-2800]	2000–2002		10.04[c] (0.00, 20.08)	5.68[c] (0.00, 12.18)	7.52[d] (1.92, 13.11)
	2003–2005		9.90[c] (0.11, 19.70)	3.88[c] (0.00, 9.27)	5.96[d] (1.15, 10.76)
			Broad case criteria[b]		
	1997–1999	47[a]	33.50[c] (13.45, 53.56)	19.57[c] (6.72, 32.43)	24.65[d] (13.81, 35.49)
	2000–2002		26.26[c] (9.72, 42.80)	12.22[c] (2.37, 22.07)	17.79[d] (9.03, 26.55)
	2003–2005		14.41[c] (2.75, 26.07)	9.15[c] (1.05, 17.26)	11.04[d] (4.47, 17.61)

SI.Table 4 (cont'd) Time trend of incidence of IPF in Europe and the US

Region/country	Period	Sample size, n	IPF incidence per 100 000 PY (95% CI)		
			Male	Female	Total
			Primary cohort[e]		
US [R14-2284]	2001	1186			92.4
	2002	1230			93.2
	2003	1197			89.0
	2004	1097			80.7
	2005	1070			78.7
	2006	1049	NR	NR	80.2
	2007	1009			78.8
	2008	1014			80.6
	2009	1027			82.9
	2010	1044			83.7
	2011	1143			90.6
			Broad case definition[e]		
	2001	494			38.4
	2002	567			43.0
	2003	485			36.0
	2004	442			32.2
	2005	461			33.7
	2006	410	NR	NR	31.1
	2007	406			31.4
	2008	443			35.2
	2009	474			38.3
	2010	485			38.9
	2011	530			41.9

SI.Table 4 (cont'd) Time trend of incidence of IPF in Europe and the US

Region/country	Period	Sample size, n	IPF incidence per 100 000 PY (95% CI)		
			Male	Female	Total
			Narrow case definition[e]		
	2001	204			15.9
	2002	256			19.4
	2003	259			19.2
	2004	255			18.5
	2005	277			20.2
	2006	279	NR	NR	21.2
	2007	269			20.7
	2008	307			24.3
	2009	347			28.0
	2010	349			28.0
	2011	393			31.1

[a] Residents aged 50 years or older.
[b] Narrow case definition: evidence of UIP on surgical lung biopsy specimens or definite UIP pattern on HRCT images. Broad case definition: evidence of UIP on surgical lung biopsy specimens or a definite or possible UIP pattern on HRCT images (representing the entire patient study cohort).
[c] Age adjusted.
[d] Age- and gender-adjusted.
[e] Primary cohort: age ≥ 65 years, excluding patients who received Medicare benefits because of disability or end-stage renal disease, ≥1 medical claims with a diagnosis code for IPF (ICD-9-CM 516.3) between 01 Jan 2000 and 31 Dec 2011, ≥1 year of continuous coverage of Medicare Part A and Part B without and an ICD-9-CM diagnosis code for IPF (ICD-9-CM 516.3) before the index quarter. Broad case definition: additional exclusion of patients with a claim with the code 515 on or after the quarter of the last claim with the ICD-9-CM diagnosis code 516.3. Narrow case definition: inclusion of patients of the broad case definition, which had a claim for a surgical lung biopsy, transbronchial lung biopsy, or CT scan of the thorax before the last 516.3 claim.

The generally wide variation in the reported incidence and prevalence estimates may most likely be due to previous lack of uniform definition used in identifying cases of IPF and by differences in study designs and populations. Furthermore, “there are no large-scale studies of the prevalence of IPF on which to base formal estimates”, as claimed by the international guidelines on IPF [P11-07084].

SI.1.2 Prevalence

Overall, in European countries the IPF prevalence ranged from 1.25 per 100 000 persons in Belgium during 1992 to 1996 [R03-2090] to 35.51 per 100 000 persons in Italy from 2005 to 2010 [R16-1739] (see table below).

SI.Table 5 Prevalence of IPF in Europe from 1981 to 2010

Country	Study period	Sample size, n	IPF case ascertainment	IPF prevalence per 100 000 persons (95% CI)		
				Male	Female	Total
Belgium [R03-2090]	Jan 1992–Jul 1996	72	Biopsy proven UIP	NR	NR	1.25 (NR)
Czech Republic [R03-2088]	1981–1990	488	NR	NR	NR	6.5–12.1 (NR)
Greece [R11-5060]	Jan–Dec 2004	189	ATS/ERS consensus (2002)	NR	NR	3.38 (NR)
Italy [R16-1749]	Jan 2005-Dec 2009	1212	ICD-9	26.32[a]	25.01[a]	25.6 (25.1, 26.2) 31.6 (30.9, 32.2)[b]
Italy [R16-1739]	2005-2010	5441	GCD[c]	35.19 (34.51, 35.87)	35.84 (35.13, 36.55)	35.51 (35.02, 36.00)
		3573	BCD[d]	23.64 (23.08, 24.20)	21.07 (20.52, 21.62)	22.39 (21.99, 22.78)
		2097	NCD[e]	13.23 (12.82, 13.65)	11.84 (11.43, 12.25)	12.55 (12.26, 12.84)
Finland [R03-2091]	1997–1998	833–943	ICD-10	NR	NR	16–18 (NR)
Norway [R11-5070]	1984–1998	61[f]	ICD-8/ICD-9	16.8	30.7	23.4 (14.9, 33)
UK [R03-2089]	ca. 1989–1990	46	IPF patients seen by respiratory physicians or tested in the pulmonary function laboratories in Nottingham	NR	NR	6 (NR)

[a] Calculated by the author.
[b] Adjusted prevalence estimate after chart review.
[c] Generic case definition: subjects with at least 1 hospital admission or outpatient visit with IPF diagnosis (ICD-9-CM code 516.3).
[d] Broad case definition: inclusion of patients of the generic case definition, who had no hospital admission or outpatient visit with ILDs diagnosis on or after date of last IPF diagnosis.
[e] Narrow case definition: inclusion of patients of the broad case definition, who had at least 1 surgical lung biopsy, transbronchial lung biopsy or CT of the thorax performed during an hospitalisation or outpatient visit, on or before date of last IPF diagnosis.
[f] Hospitalised cases by 31 Dec 1998.

An increasing trend in prevalence was observed from 1981 to 1990 in the Czech Republic from 6.5 to 12.1 per 100 000, respectively [R03-2088]. In Italy the prevalence also increased from 2005 to 2010 for the broad and narrow case definition, while there was stabilisation from 2008 onwards for the generic case definition [R16-1739].

The following table shows the IPF prevalence stratified by gender and age. Increasing prevalence estimates with age were observed for men and women, respectively.

SI.Table 6 IPF prevalence, stratified by gender and age

Country/ study period	Sample size, n	Age group (years)	IPF prevalence per 100 000 persons (95% CI)		
			Male	Female	Total
Norway 1984-1998 [R11-5070]	61a	16–34	10.3 (NR)	6.4 (NR)	8.4 (NR)
		35–54	16.1 (NR)	19.3 (NR)	17.6 (NR)
		55–74	24.8 (NR)	52.1 (NR)	39.2 (NR)
		≥75	35.2 (NR)	96.7 (NR)	74.9 (NR)
Italy 2005-2009 [R16-1749]	1212b	18-34	1.2	2.3	NR
		35-44	5.6	5.4	NR
		45-54	10.6	11.2	NR
		55-64	39.2	26.4	NR
		65-74	75.8	70.7	NR
		≥75	89.3	63.8	NR
Italy 2005-2010 [R16-1739]	5441 (GCD)c	<55	10.29 (9.84, 10.75)	9.28 (8.86, 9.71)	9.77 (9.46, 10.08)
		55-59	46.65 (43.63, 49.83)	43.98 (40.99, 47.12)	45.34 (43.18, 47.51)
		60-64	63.57 (59.91, 67.38)	57.13 (53.56, 60.88)	60.45 (57.85, 63.05)
		65-69	84.07 (79.83, 88.48)	85.60 (81.07, 90.31)	84.79 (81.66, 87.93)
		70-74	100.67 (95.80, 105.72)	113.12 (107.40, 119.07)	106.36 (102.60, 110.13)
		75-79	118.03 (112.37, 123.91)	154.52 (146.68, 162.67)	133.37 (128.66, 138.08)
		80-84	108.53 (102.41, 114.92)	205.43 (193.84, 217.53)	143.71 (137.89, 149.53)
		85+	53.87 (49.31, 58.75)	224.63 (208.54, 241.63)	99.20 (93.66, 104.74)
	3573 (BCD)[d]	<55	4.96 (4.65, 5.28)	6.42 (6.07, 6.79)	5.67 (5.44, 5.91)
		55-59	23.27 (21.11, 25.59)	30.75 (28.31, 33.35)	27.09 (25.42, 28.76)
		60-64	28.87 (26.34, 31.57)	41.68 (38.74, 44.80)	35.47 (33.48, 37.46)
		65-69	51.28 (47.79, 54.96)	56.32 (52.85, 59.94)	53.94 (51.44, 56.44)
		70-74	69.17 (64.71, 73.86)	68.53 (64.53, 72.72)	68.83 (65.80, 71.85)
		75-79	91.82 (85.80, 98.15)	79.07 (74.45, 83.91)	84.43 (80.69, 88.17)
		80-84	131.18 (121.95, 140.92)	77.75 (72.58, 83.18)	97.14 (92.36, 101.92)
		85+	158.36 (144.90, 172.73)	41.77 (37.76, 46.09)	72.72 (67.98, 77.46)

SI.Table 6 (cont'd) IPF prevalence, stratified by gender and age

Country/ study period	Sample size, n	Age group (years)	IPF prevalence per 100 000 persons (95% CI)		
			Male	Female	Total
	2097	<55	3.51 (3.25, 3.76)	2.93 (2.70, 3.18)	3.22 (3.04, 3.39)
	(NCD)[e]	55-59	19.38 (17.45, 21.46)	14.48 (12.79, 16.33)	16.98 (15.66, 18.30)
		60-64	25.26 (22.97, 27.71)	16.26 (14.39, 18.32)	20.90 (19.37, 22.43)
		65-69	33.47 (30.81, 36.29)	30.80 (28.10, 33.67)	32.21 (30.27, 34.14)
		70-74	37.97 (35.00, 41.12)	41.24 (37.81, 44.90)	39.47 (37.17, 41.76)
		75-79	42.43 (39.07, 46.01)	51.86 (47.36, 56.67)	46.40 (43.62, 49.17)
		80-84	41.88 (38.11, 45.92)	67.78 (61.19, 74.88)	51.28 (47.81, 54.75)
		85+	19.68 (16.96, 22.71)	68.13 (59.41, 77.78)	32.54 (29.37, 35.71)

[a] Hospitalised cases by 31 Dec 1998.
[b] Patients ≥18 years, admitted as primary or secondary idiopathic fibrosing alveolitis (516.3) to the hospital.
[c] Generic case definition: subjects with at least 1 hospital admission or outpatient visit with IPF diagnosis (ICD-9-CM code 516.3).
[d] Broad case definition: inclusion of patients of the primary cohort, who had no hospital admission or outpatient visit with ILDs diagnosis on or after date of last IPF diagnosis.
[e] Narrow case definition: inclusion of patients of the broad case definition, who had at least 1 surgical lung biopsy, transbronchial lung biopsy, or CT of the thorax performed during an hospitalisation or outpatient visit, on or before date of last IPF diagnosis.

In the studies conducted in US, the prevalence of IPF varied depending on the population studied and the case definition used (see table below).

SI.Table 7 Prevalence of IPF in the US

Study period	Sample size, n	Age [years]	Case ascertainment	IPF prevalence per 100 000 persons (95% CI)			Reference
				Male	Female	Total	
Jan 1997-Dec 2005	10[a]	>50	Narrow case[b] criteria	NR	NR	27.9[c] (10.4, 45.4)	[R10-2800]
	22[a]		Broad case criteria[b]	NR	NR	63[c] (36.4, 89.6)	
Jan 1996-Dec 2000	387	≥18	Narrow case criteria[d]	NR	NR	14.0 (NR)	[R10-2858]
	1211		Broad case criteria[d]	NR	NR	42.7 (NR)	
Oct 1988-Sep 1990	58 (34 male)	≥18	ICD-9	20.2 (NR)	13.2 (NR)	NR	[R03-2075]
Jan 2006-Sep 2012	4598	50-100	Broad base criteria[e]	78.3[f] (74.2, 82.5)	41.5[f] (38.7, 44.5)	58.7[f] (56.3, 61.2)	[R16-1737]
2009-2011	1136-1292[f]	NR	ICD-9[g]	20.7-29.1[h]	18.9-28.7[h]	19.8-28.8[h]	[R16-1743]

[a] IPF cases alive on 31 Dec 2005.
[b] Narrow case definition: evidence of UIP on surgical lung biopsy specimens or definite UIP pattern on HRCT images. Broad case definition: evidence of UIP on surgical lung biopsy specimens or a definite or possible UIP pattern on HRCT images (representing the entire patient study cohort).
[c] Age- and gender-adjusted.
[d] Broad case definition: age ≥18 years, ≥1 medical claims with a diagnosis code for IPF (ICD-9-CM 516.3), no medical claims with a diagnosis code for any other ILDs on or after date of last medical claim with a diagnosis code for IPF. Narrow case definition: meet broad case definition, ≥1 medical claims with a procedure code for surgical lung biopsy, transbronchial lung biopsy, or CT of the thorax, on or before date of last medical claim with a diagnosis code for IPF.
[e] Broad case algorithm: age 50-100 years and ≥6 months of enrolment, ≥1 diagnosis with IPF (ICD-9-CM code 516.3) made by a physician and no alternative diagnoses recorded after the date of the last recorded diagnosis of IPF and within 6 months of the first physician assigned diagnosis of IPF.
[f] Age standardised and corrected for the PPV.
[g] Patients were required to have ≥1 inpatient claim or 2 outpatient claims with IPF (516.3) anytime in the calendar year, to be continuously enrolled with the health plan in the same calendar year and have no other type of ILD after their last IPF claim in that calendar year.
[h] Ranges, as only annual results were reported for the years 2009 to 2011.

In general, IPF prevalence increases with age, and males have a higher prevalence than females (see table below).

SI.Table 8 IPF prevalence in the US, stratified by gender and age

Study period	Sample size, n	Age group [years]	IPF prevalence per 100 000 persons			Reference
			Male	Female	Total	
			Narrow case criteria[a]			
Jan 1996–Dec 2000	387	18–34	0.8	0.9	0.8	[R10-2858]
		35–44	2.2	5.9	NR	
		45–54	10.8	11.3	NR	
		55–64	18.7	23.3	NR	
		65–74	50.0	29.3	NR	
		≥75	87.9	48.4	64.7	
			Broad case criteria[a]			
	1211	18–34	3.8	4.2	4.0	
		35–44	4.9	12.7	NR	
		45–54	23.3	22.6	NR	
		55–64	62.8	50.9	NR	
		65–74	148.5	106.7	NR	
		≥75	276.9	192.1	227.2	
Oct 1988–Sep 1990	58	35–44	2.7	NR	NR	[R03-2075]
		45–54	8.7	8.1	NR	
		55–64	28.4	5.0	NR	
		65–74	104.6	72.3	NR	
		≥75	174.7	73.2	NR	
Jan 2006-Sep 2012	4598[b]	50-59	NR	NR	12.3 (10.9, 14.0)[c]	[R16-1737]
		60-69	NR	NR	42.7 (38.9, 46.9)[c]	
		70-79	NR	NR	135.9 (125.3, 147.4)[cc]	
		80+	NR	NR	234.5(216.1, 254.4)	

SI.Table 8 (cont'd) IPF prevalence in the US, stratified by gender and age

Study period	Sample size, n	Age group [years]	IPF prevalence per 100 000 persons			Reference
			Male	Female	Total	
2009-2011	1136-1292[d, e]	≤11			<5[f]	[R16-1743]
		12-24			<5[f]	
		25-44			2-5[f]	
		45-64	NR	NR	15-25[f]	
		65-74			63-100[f]	
		75-79			122-160[f]	
		≥80			165.9-185.5	

[a] Broad case definition: age ≥18 years, ≥1 medical claims with a diagnosis code for IPF (ICD-9-CM 516.3), no medical claims with a diagnosis code for any other ILDs on or after date of last medical claim with a diagnosis code for IPF. Narrow case definition: meet broad case definition, ≥1 medical claims with a procedure code for surgical lung biopsy, transbronchial lung biopsy, or CT of the thorax, on or before date of last medical claim with a diagnosis code for IPF.
[b] Broad case definition: patients 50-100 years of age with at least 6 months of enrolment, ≥1 diagnosis with IPF (ICD-9-CM code 516.3) made by a physician and no alternative diagnoses recorded after the date of the last recorded diagnosis of IPF and within 6 months of the first physician assigned diagnosis of IPF.
[c] Age standardised and corrected for the PPV.
[d] Ranges, as only annual results were reported for the years 2009 to 2011.
[e] Patients were required to have ≥1 inpatient claim or 2 outpatient claims with IPF (516.3) anytime in the calendar year, to be continuously enrolled with the health plan in the same calendar year and have no other type of ILD after their last IPF claim in that calendar year.
[f] Prevalence estimates were extracted from graphs, no exact values were reported.

SI.1.3 Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

SI.1.3.1 Demographics

Several studies have evaluated demographics including age, gender, smoking history, and co-morbidities for IPF patient populations. Regarding the age-distribution of IPF patients, several publications reported the mean age at diagnosis, others at time of presentation, and some referred to the mean age of the study cohort at the time of analysis. Nevertheless, in concordance with the guidelines for the diagnosis and management of IPF patients, the retrieved observational studies showed that primarily older adults are affected typically in their sixties and seventies [P11-07084]. In addition, most studies describing the demographic profile of IPF patients reported that men were more frequently affected.

A case-control study in the UK (1991–2003), based on longitudinal primary care database THIN sought to determine the association of diabetes mellitus and GERD with IPF [R12-2784]. The patient characteristics of the incident IPF cases considered in the analysis are described in the table below.

SI.Table 9 Characteristics of an incident IPF cohort identified in a UK primary care database

Characteristics	IPF cases [n = 920]	%
Mean age [years], (SD)	71.4 (11)	NR
Age group [years]		
<55	79	9
55–64.9	166	18
65–74.9	290	32
75–84.9	302	33
≥85	83	9
Gender		
Females	352	38
Males	568	62
Smoking habit		
Non-smoker	355	39
Current smoker	240	26
Ex-smoker	192	21
Status not available	133	14
Socio-economic status (Townsend quintile)		
1 (least deprived)	174	19
2	169	18
3	189	21
4	158	17
5 (most deprived)	130	14
0 (unavailable)	100	11

Data source: [R12-2784]

A community-based historical cohort study of IPF in the US aimed to describe the trends in the incidence, prevalence, and clinical course of IPF in the community [R10-2800]. Baseline characteristics of the incident IPF cases from a community-based historical cohort study of IPF in the US are provided in the table below, stratified by calendar year of IPF diagnosis.

SI.Table 10 Baseline characteristics of a US community-based historical cohort study of IPF, stratified by calendar year of IPF diagnosis

	Calendar year of IPF diagnosis			
	Overall, 1997–2005	**1997–1999**	**2000–2002**	**2003–2005**
N	47	20	16	11
Age [years]				
Mean ±SD	73.5 ±7.8	74.6 ±8.9	72 ±7.2	74.2 ±7.0
Age groups (%)				
50–59	2 (4)	1 (5)	1 (6)	0
60–69	15 (32)	6 (30)	5 (31)	4 (36)
70–79	20 (42)	8 (40)	8 (50)	4 (36)
≥ 80	10 (22)	5 (25)	2 (12)	3 (27)
Men (%)	28 (59)	11 (55)	11 (69)	6 (54)
Body mass index [kg/m^2] ±SD	27.1 ±4.9	26.1 ±3.8	29.2 ±6	26.2 ±2
Smoking, pack years (%)				
<20	5 (11)	1 (5)	3 (19)	1 (9)
20–40	14 (29)	5 (25)	6 (37)	3 (27)
>40	9 (19)	3 (15)	3 (19)	3 (27)
Never	19 (40)	11 (55)	4 (27)	4 (36)
New York Heart Association Class (%)				
1–2	40 (85)	16 (80)	14 (87)	10 (90)
3–4	7 (15)	4 (20)	2 (12)	1 (9)
Co-morbidities (%)				
Pulmonary hypertension[a]	25 (53)	11 (55)	9 (56)	5 (45)
COPD	13 (28)	5 (25)	5 (31)	3 (27)
Obstructive sleep apnoea	8 (17)	2 (10)	4 (25)	2 (18)
GERD	26 (55)	9 (45)	12 (75)	5 (45)

SI.Table 10 (cont'd) Baseline characteristics of a US community-based historical cohort study of IPF, stratified by calendar year of IPF diagnosis

	Calendar year of IPF diagnosis			
	Overall, 1997–2005	**1997–1999**	**2000–2002**	**2003–2005**
Coronary artery disease	21 (45)	7 (35)	8 (50)	6 (54)
Diabetes mellitus	8 (17)	3 (15)	4 (25)	1 (9)
Hypertension	31 (66)	9 (45)	15 (94)	7 (63)
Lung cancer	4 (8)	3 (15)	1 (7)	0
Hypothyroidism	14 (29)	7 (35)	4 (25)	3 (27)
Congestive heart failure	5 (11)	3 (15)	0	2 (18)
Atrial fibrillation	9 (19)	2 (10)	4 (25)	3 (27)
Depression	5 (11)	2 (10)	2 (12)	1 (9)
Dementia	2 (4)	1 (5)	1 (6)	0

[a] Right ventricular systolic pressure ≥40 mm Hg and peak tricuspid regurgitation ≥2.9 m/s on transthoracic echocardiographic examination.
Data source: [R10-2800]

Von Plessen et al. (2003) studied the incidence and prevalence of physician-diagnosed and hospitalised IPF in Bergen, a well-defined adult population in Norway, between 1984 and 1998. According to the authors, a higher IPF incidence was observed among females relative to males: 4.0 (95% CI 3.1, 4.9) versus 4.6 per 100 000 persons (95% CI 3.7, 5.6) for males and females, respectively. However, while the incidence in females of child-bearing age (<35 years) was only 0.4 per 100 000 persons, it was 19.3 for those ≥75 years of age [R11-5070]. Also, data from the UK confirm that IPF incidences are very low below the age of 55 [R11-4826, R10-2818]. Coultas et al. evaluated small numbers of patients in New Mexico (1988–1993) and did not find female IPF patients below the age of 45 [R03-2075].

In the US, Raghu et al. (2006) estimated and extrapolated incidences for IPF based on claims data from 1996–2000 using broad and narrow IPF definitions. They concluded that using the broad case definition, the annual incidence of IPF was estimated to range from 1.2 per 100 000 persons aged 18 to 34 years to 76.4 per 100 000 among those aged 75 years or older; based on the narrow definition, estimated incidence ranged from 0.4 (age 18–34 years) to 27.1 (age 75 years) per 100 000. Incidence was generally higher among men than women, which confirms the very low incidence in women in child-bearing age [R10-2858]. 2 US insurance claims data based studies confirmed the trend of rising incidence with age, as described in SI.Table 3 [R14-2284, R16-1737].

In terms of race or ethnicity, few studies reported on this demographic characteristic; the majority of those with data on race/ethnicity are from the US. SI.Table 12 summarises the race/ethnicity distribution within the IPF population as described in the literature.

SI.Table 11 IPF race/ethnicity distribution in the UK and the US

Country	Study period	Sample size, n	Study population	Race/ethnicity distribution, %	
Germany					
[P15-03426]	Nov 2012-Oct 2014	502	IPF patients managed at 19 pulmonary centres	White	99.6
UK					
[R03-2080]	Dec 1990–Nov 1992	588	IPF patients diagnosed by respiratory physicians	White	98
[R14-4268]	1997-2012	592	IPF patients evaluated at a tertiary referral centre	White	75
US					
[R12-3678]	Jan 2000–Nov 2009	521	Patients with IPF evaluated at an ILD centre	White	78
				Black	14
				Hispanic	5
				Asian	3
				Native American	1
[R11-5065]	1995–2003	2635	IPF cases listed for lung transplantation at 94 transplant centres	White	82
				Black	11
				Hispanic	7
[R11-5078]	1988–1992	209	IPF patients from an ILD registry	Non-Hispanic White	61
				Hispanic	23
				Other	12
				Black	1
				Native American	2
[R11-5053]	1982–1996	156	IPF cases prospectively enrolled into a specialised centre	White	88
				Other	12
[R14-2284]	Jan 2001-Dec 2011	12 066	Primary cohort[a]	White	91
				Black	4
				Hispanic	2
				Other	3
		5197	Narrow case criteria[a]	White	90
				Black	5
				Hispanic	2
				Other	3
		3195	Broad case criteria[a]	White	90
				Black	5
				Hispanic	2
				Other	3

SI.Table 11 (cont'd) IPF race/ethnicity distribution in the UK and the US

Country	Study period	Sample size, n	Study population	Race/ethnicity distribution, %	
[R16-1962]	Jan 2000-Dec 2011	7855	Incident IPF cases of a claims database with 1 year pre- and post-index period	White	4.1
				Black	91.5
				Hispanic	1.9
				Other	2.4
[R16-1966]	2004-2012	196	IPF patients of 1 ILD clinic, identified through ICD-9 codes in the charts and re-evaluated according to 2011 guideline criteria	White	80.1
				Black	8.2
				Hispanic	9.2
				Asian	2.5
[R16-1963]	Jan 2011-Jun 2013	490	Incident IPF cases reported by pulmonologist in the US	White	75.3
				Black/African American	14.1
				Hispanic/Latino/ Spanish origin	9.0
				Asian	1.8
				Other	0.4

[a] Primary cohort: age ≥65 years, excluding patients who received Medicare benefits because of disability or end-stage renal disease, ≥1 medical claim with the diagnosis code for IPF (ICD-9-CM 516.3), no medical claims with a diagnosis code for any other ILDs (exception: ICD-9-CM diagnosis code 515) on or after the calendar quarter of the last claim with the diagnosis code IPF. Broad case definition: additional exclusion of patients with a claim with the code 515 on or after the quarter of the last claim with the ICD-9-CM diagnosis code 516.3. Narrow case definition: inclusion of patients of the broad case definition, who had a claim for a surgical lung biopsy, transbronchial lung biopsy, or CT scan of the thorax before the last 516.3 claim.

SI.1.3.2 Risk factors

The official clinical guidelines on the diagnosis and management of IPF [P11-07084] have strengthened several potential risk factors:

- Cigarette smoking
- GERD
- Environmental exposures
- Microbial agents
- Genetic factors

For more information on some co-morbid conditions identified, please refer to Section SI.1.6 (important co-morbidities).

SI.1.4 The main existing treatment options

SI.1.4.1 International guidelines

The latest update of the ATS, ERS, JRS, and ALAT 2011 international guidelines published in 2015 revised the treatment recommendations for IPF. According to the guideline,

nintedanib and pirfenidone were the only treatments given a conditional recommendation for the treatment of IPF [P15-07539].

Results from the 2013 Advancing IPF Research survey showed that oxygen therapy, pirfenidone, and NAC monotherapy were the treatments most commonly used for IPF [R14-3542].

The 2 replicate 52 weeks Phase III INPULSIS trials included 1066 patients, which were randomly assigned in a 3:2 ratio to receive nintedanib versus placebo. The studies showed that nintedanib reduces disease progression by significantly reducing the annual rate of decline in FVC compared to placebo and a benefit with regard to patient-reported outcomes and time to first acute exacerbation was observed in the INPULSIS-2 trial for the nintedanib group [P14-07514]. A pooled analysis of data from the TOMORROW and INPULSIS trials showed a trend toward a reduction in all-cause and respiratory mortality in patients treated with nintedanib. HRs for time to all-cause and on-treatment mortality were 0.70 (95% CI 0.46, 1.08; p = 0.0954) and 0.57 (95% CI 0.34, 0.97; p = 0.0274), respectively, in favour of nintedanib. The HR for time to first acute exacerbation was 0.53 (95% CI 0.34, 0.83; p = 0.0047). Adjusted mean change from baseline in SGRQ score at week 52 was 2.92 with nintedanib and 4.97 with placebo (difference: -2.05 [95% CI -3.59, -0.50]; p = 0.0095) [P16-04370].

The phase III ASCEND trial showed that pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with mild or moderate idiopathic pulmonary fibrosis [R14-2103].

NAC monotherapy, anticoagulation therapy, and triple combination therapy with prednisone, azathioprine and NAC had been most widely used in the past on an empirical basis with limited evidence. However, recently 2 clinical trials conducted by the US National Institute of Health showed unfavourable results for triple combination therapy (prednisone, azathioprine and NAC) and anticoagulation with warfarin compared to placebo, respectively. In the PANTHER trial (Prednisone, Azathioprine and N-acetylcysteine: A Study that Evaluates Response in Idiopathic Pulmonary Fibrosis), triple therapy was stopped prematurely in October 2011 due to a higher rate of mortality and hospitalisations compared with placebo, based on an interim analysis by the Data and Safety Monitoring Board [P12-06085]. A current publication revealed that NAC monotherapy did not confer benefit in patients with IPF [P14-07665].

Also the ACE-IPF (AntiCoagulant Effectiveness in Idiopathic Pulmonary Fibrosis) trial evaluating warfarin versus placebo in patients with IPF was stopped prematurely in April 2011 due to a higher mortality and low likelihood of benefit with warfarin [R12-3430]. These results further limit potential empirical treatment options for these patients.

Based on extrapolation from data from 2 large randomised COPD studies showing a survival benefit in patients with resting hypoxaemia who receive long-term oxygen therapy [R08-4073, R08-4108], patients with IPF should also receive supportive long-term oxygen supplementation in case of resting hypoxaemia [P11-07084]. However, appropriate data on benefit in patients with IPF is lacking.

Non-pharmacological treatment options recommended in the official joint ATS/ERS/JRS/ALAT statement include pulmonary rehabilitation and lung transplantation [P11-07084]. However, the committee did not give a recommendation regarding single versus bilateral lung transplantation in the latest update of the international guideline [P15-07539]. Adjusted analyses suggest no benefit with regard to long-term survival for bilateral lung transplantation [R14-4011]. Studies with a limited number of IPF patients suggest a short-term benefit on exercise capacity and health related quality of life by pulmonary rehabilitation [R12-3470, R12-3471, R12-3472], although the long-term effects remain to be determined.

Lung transplant is the only intervention that has been shown to positively impact survival in patients with IPF. Median survival after lung transplant in IPF patients is approximately 4.5 years. The 1-, 3- and 5-year survival ranged from 75%-81%, 59%-64% and 47%-53%, respectively [R14-4011].The number of patients who have had lung transplants due to IPF has increased steadily over the last years, particularly in the US, where IPF has become the most common indication for transplantation since the introduction of the Lung Allocation Score [R12-3676, R12-3680, R12-3474, R14-4011]. However, broader application of this approach is limited given the scarce availability of donor organs. In addition, co-morbidities and advanced age preclude many patients from referral to lung transplant given a mean age of IPF patients at presentation of 66 years [R10-2843].

SI.1.4.2 Drug utilisation patterns

In the retrieved studies, corticosteroids and immunosuppressive agents were most commonly used on an empirical basis. The use of other agents varied between countries and treatment centres. A large proportion of IPF patients are receiving no treatment.

The table below shows the IPF treatment patterns in Europe as reported in the retrieved studies.

SI.Table 12 IPF treatment patterns in Europe

Country /region	Study period	Sample size, n	Study population	Treatment	%
Worldwide (mainly Europe) – AIR survey [R14-3542]	Oct 2013–Nov 2013	145	Respiratory experts answering survey on prescribing preferences	(% of physicians who prescribed each treatment)	
				Oxygen	96
				Pirfenidone	81
				NAC monotherapy	76
				Pirfenidone + NAC	58
				Corticosteroids	34
				Corticosteroids + NAC	16
				Corticosteroids + immunosuppressant + NAC	11
				AZA + immunosuppressant	8
				Corticosteroids + immunosuppressant	7
				Anticoagulant	5
				Cyclosporine A	1
Denmark [R16-1968]	Apr 2003-Mar 2009	121	Incident IPF patients of an ILD registry	Prednisolone	75
				High-dose methylprednisolone courses	53
				Prednisolone and high-dose methylprednisolone	43
				Azathioprine	62
				NAC[a]	57
				NAC, prednisolone and azathioprine	48
				Cyclophosphamide	7
				Oxygen therapy	55
Germany [R16-1740]	Jan 2004-Apr 2012	272	IPF patients diagnosed in a tertiary referral centre	Best supportive care	19.1
				Immunosuppressive drugs	49.3
				Antioxidants (NAC)	20.6
				Anti-fibrotic drugs	11.0

SI.Table 12 (cont'd) IPF treatment patterns in Europe

Country /region	Study period	Sample size, n	Study population	Treatment	%
Germany [P15-03426]	Nov 2012-Oct 2014	502	Consecutive IPF patients enrolled in a multicentre disease registry (expert centres)	Oral steroids	26.1[c]
				Prednisone	23.7
				Other steroids	2.4
				Azathioprine	2.6
				Cyclophosphamide	0.2
				NAC	33.7[d]
				Mycophenolate mofetil	0.2
				Pirfenidone	44.2[e]
				Anticoagulants	20.5
				VKA	6.0
				Heparin	1.2
				Oral anticoagulants other than VKA	11.3
				Investigational/study drug	0
				Other drug	4.6
				Long term oxygen tp	33.1
				No drugs	17.9
France [R14-2526]	Dec 2011-Feb 2012	2714	Survey of 509 pulmonologist	No treatment	27
				Oral corticosteroids alone	27
				Oral corticosteroids with NAC or immunosuppressive therapy	22
Greece [P12-04188]	Nov 2005–Dec 2006	139	Patients with a confirmed IPF diagnosis admitted to 8 pulmonary departments	Prednisone[f]	67
				Oxygen therapy	41
				None	33
				Prednisone monotherapy	14
				Steroids with interferon-γ	14
				Steroids with cyclophosphamide	12
				Steroids and AZA	11
				Steroids, AZA, and NAC	9
				Steroids and colchicine	7
UK [R12-4884]	Dec 1990–Nov 1996	588	Patients with a clinical presentation of IPF	Prednisolone alone	55
				None	24
				Prednisolone with other drugs[g]	12
				Other drug alone	2

SI.Table 12 (cont'd) IPF treatment patterns in Europe

Country /region	Study period	Sample size, n	Study population	Treatment	%
[R03-2078]	1992–1994	244	Cases attending 4 teaching hospitals and 5 district general hospitals in the Trent Region of England	*Prevalent cases (N = 168)*	
				Corticosteroids	65
				Cyclophosphamide	12
				AZA	13
				Incident cases (N = 76)	
				Corticosteroids	47
				Cyclophosphamide	7
				AZA	3

[a] NAC was only used as part of combination therapy, none of the patients used NAC alone.
[b] These are the results for the entire cohort. The study also reports drug utilisation for prevalent and incident patients separately, which is not displayed in this table.
[c] As monotherapy in 6.8%.
[d] As monotherapy in 12.0%, as triple therapy with azathioprine and steroids in 1.4%.
[e] As monotherapy in 26.7%, in combination with NAC in 10.4% and in combination with prednisone in 6.2%.
[f] Monotherapy or combined.
[g] Mainly AZA and cyclophosphamide.

Studies reporting IPF treatment patterns in the US are summarised in the table below.

SI.Table 13 IPF treatment patterns in the US

Study period	Sample size, n	Study population	Treatment	%	Reference
Jan 2000-Dec 2013	7298	Primary cohort[a]	Any corticosteroids	34.3	[P20-01023]
			NAC	0.9	
			Azathioprine	1.4	
			Cyclophosphamide	0.8	
			Oxygen therapy	16.2	
	3930	Sub-cohort[a]	Any corticosteroids	40.2	
			NAC	1.1	
			Azathioprine	1.4	
			Cyclophosphamide	1.1	
			Oxygen therapy	18.7	
2004-2012	196	IPF patients evaluated at 1 ILD clinic	Corticosteroid mono	12.8[b]	[R16-1966]
			Azathioprine mono	3.1[b]	
			PAN triple therapy	2.6[b]	
Jan 2000-Dec 2011	7855	Incident IPF cases identified using 1 US claims databases	Oxygen therapy	16.3[c]-32.4[d]	[R16-1962]

SI.Table 13 (cont'd) IPF treatment patterns in the US

Study period	Sample size, n	Study population	Treatment	%	Reference
Jan 2001–Sep 2008	9286	Prevalent and incident IPF cases identified using 2 US claims databases	Corticosteroid[e]	36	[R13-0297]
			Oxygen therapy[e]	27	
			AZA or cyclophosphamide[e]	6	
			Pulmonary rehabilitation therapy[e]	1	
Feb 2007–Jun 2010	129	IPF patients evaluated at a tertiary care centre	Prednisone[f]	34	[R12-4152]
			NAC[f]	32	
			AZA[f]	8	
			Pirfenidone[f]	2	
			Cyclophosphamide[f]	1	
			Interferon-γ[f]	1	
Apr 2001–Jul 2008	204	IPF patients identified from 2 longitudinal cohorts of patients with ILD seen at 2 centres	Long-term oxygen	31	[R12-1583]
			Prednisone	20	
			AZA	4	
			Warfarin	4	
			NAC	3	
Jan 2003–Jan 2008	76	Consecutive IPF patients evaluated at a single centre	None	61	[R12-2789]
			Prednisone	20	
			NAC	9	
			Cyclophosphamide	5	
			AZA	4	
			Mycophenolate mofetil	1	
Jan 1994–Dec 1996	197	IPF patients evaluated at the Mayo Clinic Rochester	None	45	[P11-14606]
			Colchicine only	42	
			Prednisone only	9	
			Prednisone and colchicine	3	
			Oxygen use[g]	6	
			Other	1	
1995–2003	2635	Patients with IPF listed for lung transplantation at 94 transplant centres	Corticosteroids	62	[R11-5065]

SI.Table 13 (cont'd) IPF treatment patterns in the US

Study period	Sample size, n	Study population	Treatment	%	Reference
18-month period	65	Consecutive patients who were newly referred at an ILD clinic	Prednisone and AZA[h]	48	[P11-14603]
			Prednisone alone	19	
			None	17	
			Prednisone and pirfenidone	7	
			Other	6	
			Prednisone and cyclophosphamide	3	
Jan 1994–Dec 1996	478	IPF patients seen at a single hospital	Oxygen use prior to index visit[i]	16	[P04-09274]
			Colchicine	35	
			None	32	
			Prednisone/colchicine	14	
			Prednisone	11	
			Other	8	
NR	17	Consecutive patients newly diagnosed with IPF evaluated in an interstitial lung disease clinic	Prednisone	47	[R12-4883]
			Inhaled beta-agonists	12	
			Pirfenidone[j]	12	
NR	74	IPF patients identified as part of an ongoing research effort to prospectively study patients with ILD	None	58	[R03-2083]
			Corticosteroids	27	
			Cyclophosphamide and corticosteroids	14	

[a] Primary cohort: ≥40 years with at least 1 claim for IPF (516.3 before August 2011 and 516.31 from August 2011) and without a claim for IPF in the 12 month baseline period. Patients with a claim for another form of ILD during the 12 month baseline period were excluded. Sub-cohort: primary cohort definition and additional requirement of a procedure code related to testing for IPF during the 12 months baseline period.
[b] Prior to index visit.
[c] During the post-index period.
[d] Calculated, as results were only presented stratified by presence of hypothyroidism.
[e] During 6-months pre-index period (date of the second qualifying code for IPF).
[f] Original reported numbers stratified by quartile of delay access to sub-specialty care.
[g] Prior to index visit.
[h] 5 patients were additionally treated with cyclosporine.
[i] Index visit corresponds to the participants' first visit in the study window (1994–1996).
[j] Phase II drug.

SI.1.5 Natural history of the indicated condition in the population, including mortality and morbidity

IPF is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathological and/or radiological pattern of usual interstitial pneumonia [P11-07084]. While IPF is the most common of the 7 idiopathic interstitial pneumonias, it is a rare [R12-5527] and fatal disease, with a median survival time of 2 to 3 years following diagnosis [P11-07084]. The natural history of IPF is variable and unpredictable [R11-2587]. Disease progression is manifested by increasing respiratory symptoms, worsening pulmonary function test results, progressive fibrosis on HRCT, acute respiratory decline, or death.

SI.1.5.1 Mortality and morbidity

IPF has been shown to have a significant mortality rate in numerous studies.

Hutchinson et al. (2014) collated death certifications data from multiple countries to assess the global trends in mortality from idiopathic pulmonary fibrosis. The cause of death data was obtained from national statistics agencies. Mortality rates were reported separately for IPF as the main cause of death or also listed as secondary cause of death. Crude and age-adjusted mortality rates were calculated for the codes J84 (other interstitial pulmonary diseases), J84.1 (other interstitial pulmonary disease with fibrosis) and J84.1 combined with J84.9 (interstitial pulmonary disease, unspecified). Rate ratios were determined by gender, age, and year and an overall estimate of change in mortality over time across countries was calculated by using the random effects model. The age standardised mortality rates are shown for all definitions in the table below.

Males were at higher risk of mortality than women over time in all countries; mortality rate ratios ranged from 1.59 (95% CI 1.57, 1.60) in the US to 2.68 (95% CI 2.63, 2.74) in Japan. The overall estimate across all countries for males versus females was 2.06 (95% CI 1.77, 2.40; $p<0.001$) (only reported for J84). Across all definitions mortality increased with age, while the rate ratios were higher for J84.1. The meta-analysis of mortality rate ratios over time showed an annual 3% increase for J84 (RR 1.03; 95% CI 1.02, 1.04; $p<0.001$), 2% increase for J84.1 (RR 1.02; 95% CI 1.01, 1.03; $p<0.001$) and 3% increase for the combination of J84.1 and J84.9 (RR 1.03; 95% CI 1.01, 1.04). The analysis of multiple cause of death data led to higher age-standardised mortality rates, which was highest in England and Wales with 12.98 per 100 000 in 2010 compared to Australia and the US with 9.85 and 9.37 per 100 000, respectively (for the code J84.1). This was similar for the combination of codes, the rates being slightly higher. Mortality rate ratios overs time were similar for England and Wales, but was less for Australia and no increase over time could be observed for the US anymore. Subnational data of the US showed the age standardised mortality rate was lowest in NY with 6.42 and highest in Texas with 10.69 per 100 000 (J84.1). For this analysis no increase in mortality was observed over the time (RR 1.00; 95% CI 0.99, 1.01; $p = 0.687$) [R14-4266].

SI.Table 14 Yearly age-standardised mortality rates

Country	Age-standardised mortality rates per 100 000 population over time												
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
	J84 used as underlying cause of death												
England Wales		6.39	6.19	6.42	6.82	6.72	6.97	7.57	7.93	7.85	8.47	9.41	9.84
Australia	5.11	5.63	5.89	5.33	5.41	4.78	5.72	5.69	6.46	6.11	6.87	6.49	
Canada	5.93	6.30	6.05	5.81	7.31	7.74	7.11	7.21	7.14	7.36	7.57	7.52	
Japan										9.42	9.93	10.26	
	J84 used as underlying cause of death												
Northern Ireland										8.22	9.80	13.36	
New Zealand							4.79	5.74	5.52	5.35	5.55		
Scotland		6.43	7.47	7.84	7.67	8.82	8.82	9.26	9.55	9.72	9.70	11.34	10.71
Spain	3.73	4.07	4.37	4.47	4.51		4.63	5.23	4.87	4.97	5.33	5.38	
Sweden	2.84	3.10	3.59	3.72	4.01	4.07	4.04	3.90	4.13	4.14	4.60	4.37	4.68
USA	7.01	7.22	6.57	6.86	7.95	7.50	7.63	7.62	7.76	7.71	7.80		
	J84.1 used as underlying cause of death												
England Wales		6.09	5.84	6.03	6.33	6.15	6.23	6.75	6.96	6.71	7.19	8.13	8.28
Australia	4.23	4.80	5.04	4.60	4.65	4.13	4.74	4.84	5.44	4.97	5.59	5.08	
Canada	5.09	5.40	5.36	5.09	6.47	6.82	6.29	6.25	6.16	6.33	6.33	6.38	
Spain	3.51	3.80	4.11	4.17	4.21		4.22	4.78	4.40	4.40	4.63	4.64	
USA	5.62	5.78	5.40	5.70	6.62	6.21	6.18	6.21	6.24	6.14	6.16		
	J84.1 + J84.9 used as underlying cause of death												
England Wales		6.33	6.15	6.35	6.76	6.66	6.89	7.47	7.83	7.74	8.37	9.33	9.76
Australia	5.08	5.57	5.78	5.28	5.31	4.74	5.64	5.65	6.35	5.93	6.79	6.38	
Canada	5.88	6.23	6.00	5.74	7.26	7.69	7.03	7.13	7.06	7.29	7.48	7.45	
Spain	3.69	4.04	4.31	4.43	4.45		4.60	5.20	4.82	4.86	5.24	5.25	
USA	6.93	7.13	6.46	6.77	7.86	7.43	7.47	7.55	7.69	7.63	7.72		

Data source: [R14-4266]

Thomeer et al. (2001) reported that according to the registry of causes of mortality in Belgium obtained from the National Institute of Statistics, between 1986 and 1992, the mortality rate from IPF was 0.04 per 100 000 PY [R03-2090].

Navaratnam et al. (2011) estimated mortality rates of IPF in England and Wales between 1968 and 2008 using routine death certificate data and a computerised longitudinal general

practice database like the THIN database. The authors reported that the number of recorded deaths attributed to IPF from 1968 to 2008 increased from 479 to 3019. The overall mortality rate standardised to the 2008 UK population over this period of time was 2.54 per 100 000 PY (95% CI 2.52, 2.56). After controlling for the effects of gender and age, the overall year on year increase in mortality was about 5% (rate ratio 1.05; 95% CI 1.04, 1.05) [R11-4826].

The standardised mortality rates for England and Wales over this period are shown in the table below.

SI.Table 15 Deaths attributed to IPF in England and Wales from 1968 to 2008

Period	Standardised[a] mortality rates of IPF per 100 000 PY (95% CI)
ICD-8	
1968–1972	0.92 (0.87, 0.96)
1973–1978	1.07 (1.04, 1.11)
1979–1983	1.42 (1.37, 1.46)
ICD-9	
1984–1988	2.16 (2.11, 2.22)
1989–1994	2.65 (2.60, 2.71)
1995–2000	3.55 (3.48, 3.61)
ICD-10	
2001–2004	4.40 (4.32, 4.49)
2005–2008	5.10 (5.00, 5.19)

[a] To the total population from England and Wales during 2008.
Data source: [R11-4826]

An examination of mortality ascribed to IPF in England and Wales between 1979 and 1988 based on existing data showed that the number of deaths reported due to this disease increased from 336 in 1979 to 702 in 1988. During this period of time, 5135 deaths were coded as being due to IPF, of which 3093 (60%) were in men, with an odds of death of 2.24 (95% CI 2.11, 2.38) compared to women [R11-5059].

In the UK, Gribbin et al. (2006) analysed data from the THIN database between 1991 and 2003. During the mean follow-up period after diagnosis (2.7 years), 48% of the 920 patients with IPF died. Moreover, the crude mortality rate for people with IPF was 180 per 1000 PY (95% CI 164, 198) and, after adjusting for gender and age, there was a marked increase in mortality in people with IPF compared with the general population (HR 4.49; 95% CI 3.97, 5.09) [R10-2818].

Dalleywater et al. (2015) conducted a population-based study using the THIN database. During the study period of 2000 to 2011, 3211 newly diagnosed IPF patients aged 40 years or older could be included into the study. The follow-up was only done for patients without a diagnosis of ischaemic heart disease or stroke prior to their IPF diagnosis. The reported

mortality rate among this IPF population was 193.7 per 1000 PY (95% CI 184.2, 203.8) [R14-3479].

Another study conducted in the UK based on a survey, medical records, and the mortality database assessed if people with IPF were more likely to have a pro-thrombotic state than general population controls, and if this altered subsequent survival. The median follow-up time was 1.14 years and 26.5% of the IPF patients died during this time. The reported overall mortality rate was 215.0 per 1000 PY (95% CI 165.5, 279.4). This was higher in men compared to women with a crude mortality rate of 222.4 per 1000 PY (95% CI 164.9, 299.9) and 193.6 (95% CI 112.5, 333.8), respectively. Furthermore the crude mortality rate was highest in the subgroup of patients aged 85 years and above (330.1; 95% CI 157.3, 692.5), with an adjusted HR of 1.54 (95% CI 0.54, 4.43) compared to patients below the age of 65 years [R16-2228].

The table below describes mortality among IPF patients in Europeans as reported in the retrieved studies.

SI.Table 16 Mortality among IPF patients in Europe, as reported in the retrieved studies

Country	Study period	Sample size, n	Study population	Follow-up	Mortality, %
Denmark [R16-1968]	Apr 2003-Mar 2009	121	Incident IPF patients of an ILD database of 1 hospital	Mean: 23.6 months (SD 19.2)	50.4
Finland [R16-2218]	2012	111	IPF patients enrolled in the Finish IPF registry	NR	12.6
France [R11-4795]	Jan 1986–Jul 2008	32	Patients with asymmetrical IPF[a] evaluated at 2 different centres	Mean: 37 months (3 years) (SD 30)	47
[R12-5570]	May 1977–May 1987	27	Consecutive newly diagnosed patients	As of June 1989	59
UK [R12-5559]	Dec 1990–Nov 1996	588	Members of the BTS study	As of 31 Dec 2001	83
[R10-2818]	1991–2003	920	Cases from the THIN database	2.7 years[b] (mean)	48
[R16-2228]	Jan 2010-Feb 2012	211	Incident IPF patients at 5 teaching hospitals and 8 general hospitals in the Greater Trent region	1.14 years (median)	26.5

[a] Defined as by an asymmetry ratio (most affected - least affected fibrosis score) / (most affected + least affected fibrosis score) >0.2.
[b] After diagnosis.

IPF mortality has also been evaluated in US populations. Collard et al. (2012) assessed the burden of illness associated with IPF using 2 US insurance claims databases. Between 01 Jan 2001 and 30 Sep 2008, 9286 IPF patients were identified. The reported inpatient mortality for IPF cases was 52.6 deaths per 1000 PY, significantly higher than in matched controls (14.8 per 1000 PY; rate ratio 3.64; 95% CI 3.12, 4.26) [R13-0297].

Another study based on US claims data assessed all-cause mortality in newly diagnosed IPF patients from 2000 to 2013. The reported mortality rate was 97.1 per 1000 PY (95% CI 91.7, 102.7) in all IPF patients and 106.4 per 1000 PY (95% CI 98.5, 114.8) in a more restrictive sub-cohort [P20-01023].

The primary cause of death among IPF patients is the progression of the disease itself and respiratory failure [P11-07084]. The table below shows the most frequent causes of death reported in IPF patients.

SI.Table 17 Cause of death in IPF patients as reported in the retrieved studies

Region/country	Study period	Study population	IPF deceased patients, n (%)	Cause of death	%
Europe					
Finland [R16-2218]	2012	IPF patients diagnosed acc. to 2011 criteria	14 out of 111 (12.6)	IPF	50
				Pneumonia	36
				Intestinal strangulation	0.9
				Rupture of abdominal aortic aneurysm	0.9
Germany [R16-1740]	Jan 2004-Apr 2012	IPF patients diagnosed in a tertiary referral centre	171 out of 272 (62.9%)	IPF	53.2
				Cardiovascular	4.7
				Lung cancer	7.6
				Other reasons	4.7
				Unknown	29.8
France [R12-5570]	May 1977–May 1987	Consecutive newly diagnosed patients	16 out of 27 (59)	Respiratory insufficiency	94
				Lung cancer	6
UK [R12-4884]	Dec 1990–Nov 1992	Patients with a clinical presentation of IPF	398 out of 588 (68)	IPF as the main or contributory cause of death	73

SI.Table 17 (cont'd) Cause of death in IPF patients as reported in the retrieved studies

Region/country	Study period	Study population	IPF deceased patients, n (%)	Cause of death	%
North America					
US [R13-4821]	Jan 1996–Dec 2004	Patients with IPF who underwent a post-mortem evaluation	42	*Immediate cause of death*	
				Respiratory	64
				Acute exacerbation of IPF	29
				Gradual progression of IPF	12
				Pneumonia	15
				Aspiration	2
				Drug-induced lung disease	2
				Cardiovascular	21
				Arrhythmia	7
				Myocardial infarction	7
				Cor pulmonale	3
				Stroke	3
				Other	14
				Multiorgan failure	5
				Trauma	5
				Acute renal failure	3
				Anoxic encephalopathy	3
			42	*Contributing causes of death*	
				Respiratory conditions	74
				IPF	60
				Emphysema	12
				Pneumonia	10
				Pulmonary embolism	2
				Bronchiectasis	2
				Radiation fibrosis	2
				Cardiovascular	57
				Cor pulmonale	40
				Ischaemic heart disease	31
				Cerebrovascular disease	7
				Other	57
				Chronic renal disease	21

SI.Table 17 (cont'd) Cause of death in IPF patients as reported in the retrieved studies

Region/country	Study period	Study population	IPF deceased patients, n (%)	Cause of death	%
US [R13-4821]	Jan 1996–Dec 2004	Patients with IPF who underwent a post-mortem evaluation	42	*Contributing causes of death*	
				Chronic liver disease	10
				Cancer	10
				Dementia	7
				Surgical complications	7
				Sepsis	5
				Hypoxic encephalopathy	5
				Gastroduodenal ulcer	5
				Acute pancreatitis	2
				Radiation therapy	2

SI.1.6 Important co-morbidities

Important co-morbidities of patients with IPF include:

- Cardiovascular diseases
  - Arterial hypertension
  - Coronary artery disease
  - Myocardial infarction
  - Congestive heart failure
  - Pulmonary hypertension
- Cerebrovascular diseases
- Respiratory diseases
- Gastrointestinal diseases
- Metabolic co-morbidities
  - Diabetes mellitus
  - Hypothyroidism
  - Hyperlipidaemia
- Kidney diseases
- Lung cancer
- Depression
- Pulmonary infections

SI.1.6.1 Supplemental information: Incidence rates of co-morbidities of the underlying diseases

As requested by the PRAC (EMEA/H/C/003821/II/0046), incidence rates of co-morbidities associated with the underlying disease are presented in the following.

SI.1.6.1.1 Literature

Incidence rates of co-morbidities associated with IPF are presented in the table below.

SI.Table 18 Incidence rates of co-morbidities associated with IPF

IPF co-morbidity	Study	Description (population, age, data source)	Incidence measures
Cardiovascular diseases	Mortimer 2020 [P20-01023]	Patients with ≥1 claim with an IPF diagnosis were identified from a United States healthcare insurer's database (2000–2013). Patients with other known causes of ILD or aged <40 years were excluded. A total of 7298 IPF cases were identified. Subgroups were compared based on the 2011 change in ICD-9 definition of IPF and occurrence of IPF testing.	*Pulmonary hypertension* IPF Cohort – IR per 1000 PY: 22.5 (20.0–25.4) IPF Subcohort* – IR per 1000 PY: 26.4 (22.4–30.9) *Pulmonary arterial hypertension* IPF Cohort – IR per 1000 PY: 2.1 (1.4–3.0) IPF Subcohort* – IR per 1000 PY: 2.7 (1.6–4.4) *Arterial hypertension* IPF Cohort – IR per 1000 PY: 228.9 (214.6–243.8) IPF Subcohort* – IR per 1000 PY: 224.3 (204.3–245.7) *Acute myocardial infarction* IPF Cohort – IR per 1000 PY: 13.8 (11.8–16.0) IPF Subcohort* – IR per 1000 PY: 13.0 (10.3–16.2) *Congestive heart failure* IPF Cohort – IR per 1000 PY: 70.9 (65.7–76.3) IPF Subcohort* – IR per 1000 PY: 68.9 (61.7–76.6) *Acute coronary syndrome* IPF Cohort – IR per 1000 PY: 17.7 (15.4–20.2) IPF Subcohort* – IR per 1000 PY: 18.3 (15.0–22.0) *Ischaemic heart disease* IPF Cohort – IR per 1000 PY: 91.3 (84.9–97.9) IPF Subcohort* – IR per 1000 PY: 92.2 (83.2–101.9)

SI.Table 18 (cont'd) Incidence rates of co-morbidities associated with IPF

IPF co-morbidity	Study	Description (population, age, data source)	Incidence measures
Cardiovascular diseases (cont'd)			*Cardiac arrhythmia* IPF Cohort – IR per 1000 PY: 99.8 (93.5–106.4) IPF Subcohort* – IR per 1000 PY: 107.6 (98.2–117.5) *Angina pectoris* IPF Cohort – IR per 1000 PY: 25.0 (22.2–28.0) IPF Subcohort* – IR per 1000 PY: 24.7 (20.8–29.1) *Venous thrombosis* IPF Cohort – IR per 1000 PY: 37.6 (34.1–41.3) IPF Subcohort* – IR per 1000 PY: 41.0 (35.9–46.6) *Pulmonary embolism* IPF Cohort – IR per 1000 PY: 17.7 (15.5–20.3) IPF Subcohort* – IR per 1000 PY: 20.9 (17.4–24.9)
	Clarson 2020 [R21-0678]	A population-based cohort study used electronic patient records from the Clinical Practice Research Datalink and linked Hospital Episode Statistics to identify 68 572 patients (11 688 ILD exposed and 56 884 unexposed controls) with 349 067 PY of follow-up. ILD-exposed patients (pulmonary sarcoidosis or idiopathic pulmonary fibrosis) were matched (by age, sex, registered general practice and available follow-up time) to patients without ILD or ischaemic heart disease/myocardial infarction.	*Myocardial infarction* Incidence rate per 10 000 PY: 72.57 (62.95-83.65) *Ischaemic heart disease* Incidence rate per 10 000 PY: 102.61 (91.06-115.64)

SI.Table 18 (cont'd) Incidence rates of co-morbidities associated with IPF

IPF co-morbidity	Study	Description (population, age, data source)	Incidence measures
Cardiovascular diseases (cont'd)	Yan 2015 [R22-1539]	Hospitalised patients (Beijing Institute of Respiratory Medicine Interstitial Lung Disease Group, Beijing Chao-Yang Hospital, Capital Medical University, China) with IPF, who were evaluated for sPAP by Doppler echocardiography from January 2004 to December 2011, were enrolled in the study. Patients were defined as PH by an estimated sPAP >50 mmHg and graded as PH likely, PH possible and PH unlikely, based on the 2009 European Society of Cardiology/European Respiratory Society PH Guidelines. In total, 119 IPF patients were enrolled in the study.	*Pulmonary hypertension* Incidence (PH Likely): 23.5% Incidence (PH Likely or Possible): 40.3%
	Dalleywater 2014 [R14-3479, R15-4491]	Data from THIN, a UK longitudinal database of EMR. Incident cases of IPF-CS were identified using Read codes. Cases were included if they were first diagnosed after 01 Jan 2000, and ≥12 months after registration and excluded people under 40 years at diagnosis, as well as those with certain co-existing disorders. 3211 incident cases of IPF-CS and 12 307 matched controls were identified.	*Pulmonary embolus* Incidence rate per 1000 PY: 9.3 (7.4-11.7) Rate ratio (adjusted for matching variables, smoking, and warfarin prescription): 6.42 (4.30-9.57) *Deep vein thrombosis* Incidence rate per 1000 PY: 4.3 (3.0-6.0) Rate ratio (adjusted for matching variables, smoking, and warfarin prescription): 2.11 (1.37-3.27)

SI.Table 18 (cont'd) Incidence rates of co-morbidities associated with IPF

IPF co-morbidity	Study	Description (population, age, data source)	Incidence measures
Cardiovascular diseases (cont'd)	Collard 2012 [R13-0297]	2 cohorts (patients with IPF and matched controls) were retrospectively identified from US claims databases between 01 Jan 2001 and 30 Sep 2008. A total of 9286 IPF cases were identified. Cases with IPF were defined by age of 55 years or older and either 2 or more claims with a code for idiopathic fibrosing alveolitis, or one claim with ICD 516.3 and a subsequent claim with a code for post-inflammatory pulmonary fibrosis.	*Heart failure* Incidence per 1000 PY: 67.5 RR: 1.90 (1.70–2.13) *Coronary artery disease (exclusive of MI)* Incidence per 1000 PY: 49.1 RR: 1.42 (1.24–1.61) *Atrial fibrillation* Incidence per 1000 PY: 37.2 RR: 1.53 (1.33–1.76) *Myocardial infarction* Incidence per 1000 PY: 21.7 RR: 1.66 (1.38–1.99) *Deep vein thrombosis* Incidence per 1000 PY: 4.6 RR: 1.60 (1.09–2.37) *Pulmonary embolism* Incidence per 1000 PY: 10.7 RR: 2.24 (1.69–2.98) *Pulmonary hypertension* Incidence per 1000 PY: 6.8 RR: 4.49 (2.84–7.10)

SI.Table 18 (cont'd) Incidence rates of co-morbidities associated with IPF

IPF co-morbidity	Study	Description (population, age, data source)	Incidence measures
Cardiovascular diseases (cont'd)	Nathan 2008 [R22-1538]	A retrospective review of all patients with IPF at Inova Fairfax Hospital who underwent lung transplantation from 2000 to 2005 and in whom serial right heart catheterisations were available. The final cohort consisted of 44 patients with serial right heart catheterisation data.	*Pulmonary hypertension* Incidence: 77.8%
	Agarwal 2004 [R12-2792]	27 patients with IPF attending the Chest Clinic (India) over a period of one-and-a-half-years underwent echocardiography for evidence of pulmonary hypertension, which was defined as pulmonary artery systolic pressure ≥40 mmHg by Doppler echocardiography, or pulmonary acceleration time ≤100 milliseconds or two-dimensional echocardiographic findings of right ventricular hypertrophy or overload.	*Pulmonary hypertension* Incidence: 36%
Cerebrovascular diseases	Mortimer 2020 [P20-01023]	See above	*Stroke* IPF Cohort – IR per 1000 PY: 19.2 (16.8–21.9) IPF Subcohort* – IR per 1000 PY: 17.2 (14.1–20.9)
	Collard 2012 [R13-0297]	See above	*Cerebrovascular disease* Incidence per 1000 PY: 33.7 RR: 1.21 (1.05–1.39)
Respiratory diseases	Mortimer 2020 [P20-01023]	See above	*Acute respiratory worsening of unknown cause* IPF Cohort – IR per 1000 PY: 12.6 (10.7–14.7) IPF Subcohort* – IR per 1000 PY: 14.0 (11.1–17.3) *COPD* IPF Cohort – IR per 1000 PY: 157.9 (148.5–167.7) IPF Subcohort* – IR per 1000 PY: 185.1 (170.0–201.1) *Obstructive sleep apnoea* IPF Cohort – IR per 1000 PY: 31.7 (28.5–35.1) IPF Subcohort* – IR per 1000 PY: 37.5 (32.7–42.9)

SI.Table 18 (cont'd) Incidence rates of co-morbidities associated with IPF

IPF co-morbidity	Study	Description (population, age, data source)	Incidence measures
Respiratory diseases (cont'd)	Collard 2012 [R13-0297]	See above	*Emphysema* Incidence per 1000 PY: *11.0* *RR: 3.06 (2.24–4.19)* *Asthma* Incidence per 1000 PY: 6.9 RR: 1.65 (1.19–2.28) *Sleep apnoea* Incidence per 1000 PY: 1.2 RR: 1.03 (0.53–2.03)
Gastrointestinal diseases	Mortimer 2020 [P20-01023]	See above	*GI perforation* IPF Cohort – IR per 1000 PY: 3.5 (2.5–4.7) IPF Subcohort* – IR per 1000 PY: 3.2 (2.0–5.0) *GERD* IPF Cohort – IR per 1000 PY: 123.9 (116.4–131.7) IPF Subcohort* – IR per 1000 PY: 136.3 (125.1–148.3)
	Collard 2012 [R13-0297]	See above	*GERD* Incidence per 1000 PY: 7.5 RR: 1.63 (1.19–2.22)
Metabolic co-morbidities	Mortimer 2020 [P20-01023]	See above	*Type 2 diabetes mellitus* IPF Cohort – IR per 1000 PY: 60.2 (55.3–65.5) IPF Subcohort* – IR per 1000 PY: 64.5 (57.3–72.4)
	Collard 2012 [R13-0297]	See above	*Diabetes* Incidence per 1000 PY: 18.0 RR: 1.77 (1.41–2.22)

SI.Table 18 (cont'd) Incidence rates of co-morbidities associated with IPF

IPF co-morbidity	Study	Description (population, age, data source)	Incidence measures
Kidney diseases	Mortimer 2020 [P20-01023]	See above	*Chronic renal failure/insufficiency* IPF Cohort – IR per 1000 PY: 67.4 (62.5–72.5) IPF Subcohort* – IR per 1000 PY: 68.5 (61.6–75.9)
Lung cancer	Chen 2021 [R22-1545]	Nine studies fulfilled the selection criteria and were included in a systematic review and meta-analysis. In total, the selected population was 933 patients, of which 559 were patients with IPF but without emphysema.	*Lung cancer* Summary incidence: 8.1%
	Mortimer 2020 [P20-01023]	See above	*Lung cancer* IPF Cohort – IR per 1000 PY: 17.6 (15.3–20.2) IPF Subcohort* – IR per 1000 PY: 24.2 (20.2–28.7)
	Brown 2019 [R22-1537]	25 cohort studies were included in a systematic review and meta-analysis. A total of 13 578 IPF patients were included across the studies.	*Lung cancer* Summary incidence rate: 2.07 per 100 PY (1.46–2.67) Adjusted IRR: 6.42 (3.21–9.62)
	Kato 2018 [R22-1542]	Retrospective review of 910 patients with IPF were treated at Saitama Cardiovascular and Respiratory Center, Japan from January 1995 to July 2011. All patients fulfilled the criteria for IPF of the ATS and ERS or the official ATS/ERS/Japanese Respiratory Society/Latin American Thoracic Society statement on IPF.	*Lung cancer* Incidence rate per 1000 PY: 25.2 (19.7–31.7)
	Hyldgaard 2014 [R14-0776]	A study cohort included all patients diagnosed with IPF at Aarhus University Hospital, Denmark between April 2003 and April 2009. A total of 121 patients were included.	*Lung cancer* Incidence rate per 100 PY: 3.55 (1.44–7.18)
	Kwak 2014 [R22-1541]	Retrospective review of medical records of 48 IPF patients who were diagnosed using chest CT scans at Seoul National University Hospital from Jan 2000 to Dec 2011.	*Lung cancer* Incidence rate per 1000 PY: 23.1 (7.6–53.2) Adjusted HR: 4.15 (1.03-16.78)
	Collard 2012 [R13-0297]	See above	*Lung cancer or bronchogenic carcinoma* Incidence per 1000 PY: 11.8 RR: 2.13 (1.63–2.78)

SI.Table 18 (cont'd) Incidence rates of co-morbidities associated with IPF

IPF co-morbidity	Study	Description (population, age, data source)	Incidence measures
Lung cancer (cont'd)	Lee 2011 [R22-1540]	Medical record review of newly diagnosed adult (≥20 years) IPF patients of from South Korean tertiary hospitals consisting of 1685 patients who had been diagnosed between 2003 and 2007.	*Lung cancer* Incidence rate per 100 PY: 1.03
	Ozawa 2009 [R12-2782]	The study was a retrospective cohort analysis of 103 IPF patients attending Japanese institutions between 1986 and 2005 who did not have lung cancer at the diagnosis of IPF. The entry criteria were: (i) patients whose diagnosis of IPF was based on clinical or histological criteria as defined by the international consensus statement of the ATS/ERS; and (ii) patients did not have lung cancer at the initial diagnosis of IPF.	*Lung cancer* Incidence: 20.4% Cumulative incidence: 3.3%, 15.4% and 54.7% at 1, 5 and 10 years
	Le Jeune 2007 [R11-5075]	1064 incident cases of IPF were identified from a longitudinal computerised health care dataset (THIN, UK). Patients were included in the IPF cohort if they had at least 1 recorded IPF diagnosis and their first IPF diagnosis was recorded at least 12 months after their start date at initial diagnosis. Those with connective tissue diseases and under the age of 40 were excluded from the dataset to increase the diagnostic specificity.	*All malignancies* Incidence rate: 373 per 10 000 PY Rate ratio (adjusted for age and gender): 1.51 (1.20-1.90) Rate ratio (adjusted for age, gender, and smoking): 1.51 (1.20-1.90) *Lung cancer* Incidence rate: 112 per 10 000 PY Rate ratio (adjusted for age and gender): 4.99 (3.03-8.22) Rate ratio (adjusted for age, gender, and smoking): 4.96 (3.00-8.18)
	Hubbard 2000 [R12-0052]	A population-based cohort study involving 890 subjects with cryptogenic fibrosing alveolitis and 5884 control subjects drawn from the United Kingdom General Practice Research Database.	*Lung cancer* IRR (adjusted for age, gender, smoking): 8.25 (4.70-11.48)
Depression	Collard 2012 [R13-0297]	See above	*Depression* Incidence per 1000 PY: 6.3 RR: 1.90 (1.34–2.71)

SI.Table 18 (cont'd) Incidence rates of co-morbidities associated with IPF

IPF co-morbidity	Study	Description (population, age, data source)	Incidence measures
Pulmonary infections	Mortimer 2020 [P20-01023]	See above	*Pneumonia* IPF Cohort – IR per 1000 PY: 40.4 (36.8–44.2) IPF Subcohort* – IR per 1000 PY: 47.2 (41.6–53.3) *Sepsis* IPF Cohort – IR per 1000 PY: 31.1 (28.0–34.4) IPF Subcohort* – IR per 1000 PY: 34.4 (29.9–39.5) *Bronchitis* IPF Cohort – IR per 1000 PY: 187.8 (177.3–198.7) IPF Subcohort* – IR per 1000 PY: 202.6 (186.7–219.5) *Upper respiratory tract infection* IPF Cohort – IR per 1000 PY: 70.9 (65.8–76.4) IPF Subcohort* – IR per 1000 PY: 70.4 (63.1–78.3)
	Collard 2012 [R13-0297]	See above	*Pulmonary infection* Incidence per 1000 PY: 95.8 RR: 2.21 (1.99–2.45) *Chronic bronchitis* Incidence per 1000 PY: 31.5 RR: 2.51 (2.10–2.99)

*Restricted to the IPF cohort with ≥1 procedure related to testing for IPF during the 12-month baseline period.

SI.2 SYSTEMIC SCLEROSIS (SSc)

SI.2.1 Incidence

A global systematic review revealed that the incidence estimates for SSc varied widely and ranged between 0.06 (from the US, published in 1971) and 12.2 (from Australia, published in 1999) per 100 000 person-years [R16-0123].

In Europe and North America, the incidence rates of SSc in the general population are similar [R16-1343, R18-1404]. Results from both regions demonstrated similar trends towards an increase in the reported incidence of this condition over time [R16-1343, R18-1404].

Europe
Several studies assessed the incidence rates of SSc in European countries/regions [R16-1340, R16-1342, R16-1343, R16-1352, R18-4025, R18-4026, R18-4036]. The annual incidence estimates in these studies range between 0.6-1.1 per 100 000 persons [R18-4026] and 2.3 per 100 000 persons [R16-1343].

North America
Studies conducted in North America yielded prevalence estimates slightly higher than European countries/regions. Estimates of the incidence of SSc appear to vary according to the data sources considered, with higher estimates obtained using health care databases compared to medical chart review. For example, over the period 1989-1991, a cross-sectional study conducted in the US reported an annual incidence of SSc of 1.9 (95% CI 1.2, 3.0) per 100 000 [R16-0120]. Similar results were reported in a historical population-based cohort study in Olmsted County, Minnesota, over the period 1980-2010 [R18-1404], in which the overall adjusted incidence rate of SSc was 2.4 per 100 000 PY (95% CI 1.8, 3.0) using the broader case definition (1980 ACR criteria and/or LeRoy and Medsger criteria) and 1.4 cases per 100 000 PY (95% CI 0.9 ,1.8) using the narrower case definition (1980 ACR criteria only). A US study based on claims data reported incidence rates of SSc using electronic health care databases [R16-0122]. Between 2003 and 2008, the overall age- and sex-adjusted annual incidence rate of SSc was estimated at 5.6 cases per 100 000.

SI.2.2 Prevalence

A systematic literature review and pragmatic web-based searches were conducted using Medline and Embase electronic bibliographical databases for the prevalence of SSc. In addition, a review of potentially relevant websites such as those of learned societies, rare diseases associations, patient organisations or health agencies was also conducted. For this step, searches were conducted using both English and, to the extent possible, local languages for the countries of interest. Estimates were converted to denominators of 100 000 persons.

Orphanet includes SSc is listed as a “rare disease”, with the prevalence estimated at about 1/6500 adults (15.4/100 000 adults) [R19-0200].

Europe

In Europe, several studies evaluated the prevalence rate of SSc in the general population (see SI.Table 19). Estimates varied 4-fold across studies, ranging from 9.9 per 100 000 in Norway for the year 2009 [R16-1346, R18-4026] to 34.8 per 100 000 in Sardinia, Italy in 2012 [R18-4035].

Variation in the observed prevalence estimates of SSc may be due to actual geographic differences, differences in case definitions or methodological differences between studies. In 3 studies that used more than 1 case definition, the use of 1980 ACR criteria alone yielded lower prevalence estimates compared to broader criteria [R16-1342, R16-1343, R18-4026]. For example, estimates of SSc prevalence reported for Sweden in 2010 were 23.5 per 100 000 and 30.5 per 100 000, using respectively, the 1980 ACR diagnostic criteria and the 2013 ACR/EULAR criteria, respectively, with the broader criteria identifying 30% more cases compared to the 1980 ACR criteria [R16-1342].

North America

The reported prevalence of SSc in North America was slightly higher compared to Europe, ranging from 13.5 per 100 000 individuals in the US in 2003 to 44.3 per 100 000 individuals in Quebec, Canada in 2003 (see SI.Table 19).

Only 1 study used the entire population as the denominator for prevalence. Its prevalence estimate was 44.3 (95% CI 41.1, 47.6) per 100 000 population [R18-0713], which was higher compared to the range of estimates that used only adults (27.6 to 39.9 per 100 000 adults) R16-0118, R18-1404, R19-0010].

SI.Table 19 Estimates of prevalence of SSc (Europe and North America)

Study/ Source	Country/ Region	Study type	Data collection period	Diagnostic approach	Reference population size/ N cases with SSc	Estimated prevalence per 100 000
Europe						
Andreasson *et al*. 2013 [R16-1343]	Southern Sweden	Patients captured in the Skåne Healthcare Register via ICD-10 diagnosis codes	31 Dec 2010	1980 ACR criteria and 2013 ACR-EULAR criteria	990 464 inhabitants above 18 years of age/ 233 (with ACR) and 302 (with ACR-EULAR)	**30.5** (with ACR-EULAR criteria) – 23.5 (with ACR criteria)
Arias-Muñez *et al*. 2008 [R16-1343]	Northwestern Spain	Patient records from 1 hospital (referral centre)	31 Dec 2006	1980 ACR criteria and/or 2001 LeRoy and Medsger criteria	Population aged 15 years or older not specified (78 incident cases on the period 1988-2006)	**27.7** (aged-adjusted) – 14.9 (when applying only the 1980 ACR criteria)
Eaton *et al*. 2010 [R16-1857]	Denmark	Patients captured in the National Hospital Register (capturing all admissions to Danish hospitals since 1977)	31 Oct 2006	ICD-8/-10 diagnosis codes	5 506 574 inhabitants/ Not specified	**23.0** with ICD-10 codes only – **25.0** using both ICD-8 and ICD-10 codes
El Adssi *et al*. 2013 [R16-1344]	Northeastern France	Multiple sources, capture-recapture analysis	30 Jun 2006	1980 ACR criteria and/or 2001 LeRoy and Medsger criteria	1 831 328 adults older than 18 years of age/193 and 233 (with the capture-recapture method)	**13.2** (after capture-recapture) – 10.5 (crude)
Hoffmann-Vold *et al*. 2012 [R16-1346]	South-East Norway	Multiple sources	31 Dec 2009	1980 ACR criteria and/or 2001 LeRoy and Medsger criteria	2 707 012 inhabitants/ 269	**9.9** – 7.2 (when applying only the 1980 ACR criteria)
Piga et al. 2016 [R18-4035]	Italy (Sardinia)	Population-based identified in regional healthcare hospital discharge database (all ages) or through tertiary referral rheumatology clinic	2012	Specialty clinic attendees between 2001 and 2012	Approximately 1.6 million residents (all ages)/not stated[a] for prevalence year (2012)	**34.8** Females: 55.5 Males: 13.1 Female: male ratio, 4.3

SI.Table 19 (cont'd) Estimates of prevalence of SSc (Europe and North America)

Study/ Source	Country/ Region	Study type	Data collection period	Diagnostic approach	Reference population size/ N cases with SSc	Estimated prevalence per 100 000
Radic *et al*. 2010 [R16-1350]	Southern Croatia	1 public hospital	2008	1980 ACR criteria	313 365 inhabitants aged over 18 years/49	**15.6**
Vonk *et al*. 2009 [R16-1352]	The Netherlands	Data from the POEMAS (Pulmonary Hypertension Screening, a Multidisciplinary Approach in Scleroderma) registry with questionnaires sent to all registered rheumatologists and clinical immunologists	01 Jan 2007	1980 ACR criteria and/or 2001 LeRoy and Medsger criteria	12 793 440 adults aged 18 years or older/1148	**8.9**
North America						
Bernatsky (2009) [R18-0713]	Québec Canada	Administrative hospitalisation and physician billing records for the province.	December 2003	ICD-9 codes	All residents of Quebec (approximately 7.5 million individuals)	**44.3 (41.1, 47.6)** Females: 74.4 (69.3, 79.7) Males: 13.3 (10.2–14.8) Female: male ratio, 5.6
Bauer (2013) [R18-1404]	Minnesota, US	Rochester Epidemiology Project	December 2010	1980 ACR criteria and/ or 1988 LeRoy and Medsger criteria	Number of county residents aged 18 and older on the prevalence date / 43	**39.9 (27.9, 52.0)**
Furst (2012)[b] [R16-0122]	US		2003 2008	ICD-9 codes		**13.5 (12.4, 14.5)** **18.4 (17.3, 19.5)**
Helmick (2008) [R19-0010]	Michigan, US	Multiple sources used: hospital discharge data, outpatient data from 2 academic centres, private-practice rheumatologists, and the local chapter of a scleroderma support group	December 2005	ACR 1980 or 2 of 5 CREST features	Extrapolated to US adult population / 706	**27.6 (24.5, 31.0)** Female: male ratio, 4.6

SI.Table 19 (cont'd) Estimates of prevalence of SSc (Europe and North America)

Study/ Source	Country/ Region	Study type	Data collection period	Diagnostic approach	Reference population size/ N cases with SSc	Estimated prevalence per 100 000
Robinson (2008) [R16-0118]	US	US insured population IMS Health and MarketScan databases	Not stated	ICD-9 codes - at least 1 inpatient stay or at least 2 ambulatory encounters	5 492 052 adults who were continuously enrolled from 01 Jan 2001 through 31 Dec 2002 for medical benefits either plan / 1360	**30.0 (ND)**

[a] Authors stated that the patients not alive in 2012 were not included in the prevalence estimate
[b] Incomplete data, publication was not accessed; available information is from the abstract only

SI.2.3 Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

SI.2.3.1 Demographics

Age
Although SSc can develop at any point between infancy and old age, the incidence increases with age [R16-0121]. The estimated incidence of SSc significantly increased in individuals aged ≥45 years in Spain [R16-1343]. Similar findings were retrieved in a cohort study conducted in Greece over the period 1981-2002, where the mean annual incidence rates were higher in the age groups ≥65 years than in other age groups for men (0.7 per 100 000), and in the age group 45-64 years than in other age groups for women (3.9 per 100 000) [R16-1340].

Results from studies conducted, over the period 1999-2009, in the UK and in Norway reported a mean age of SSc patients at diagnosis of 51.6 (±13.7) years [R16-1351] and 47 years [R18-4026], respectively. Similarly, in North America, a population-based cohort study conducted in the US reported a median age at diagnosis of 49.1 years (IQR: 39.8-67.6) [R18-1404]. A Canadian study reported statistically different mean ages at diagnosis for women and men: 41.3±2.8 years and 49.7±1.2 years, respectively [R18-4005].

Gender
Regarding the gender distribution, the literature suggests that SSc predominantly affects women with a reported sex ratio (women/men) ranging from 4:1 in Spain [R16-1343] to 9:1 in Greece [R16-1340]. Several studies reported an unbalanced female to male ratio for this condition [R18-0713, R18-1404, R18-4035, R19-0010].

In the long-term cohort study conducted in Spain, over the period 1988-2006, the annual incidence rates reported were 0.7 (95% CI 0.3, 1.2) and 1.8 (95% CI 1.2, 2.5) per 100 000 in men and women, respectively. In the recent UK study that used the GPRD data, women had a nearly 5-fold higher incidence rate of SSc than men (incidence rate ratio 4.7 [95% CI 4.1, 5.4]) [R18-4036]. Incidence rates were 3.5 times higher for women than men in a US study as well. As noted above, estimated incidence rates for women and men were 2.1 (95% CI 1.4, 2.9) and 0.6 (95% CI 0.2, 1.0), respectively [R18-1404].

Gender-specific prevalence estimates of 13.3 (95% CI 11.1, 16.1) per 100 000 men and 74.4 (95% CI 69.3, 79.7) per 100 000 women were reported in Quebec in 2003 [R18-0713].

Ethnicity
In Europe, 1 study reported that prevalence rates of SSc might vary according to the ethnic background of the population, with higher estimates found in non-Caucasians individuals [R16-1347]. In North America, an older study suggested that the prevalence of SSc was higher among Black individuals (31.5 per 100 000, 95% CI 28.2, 35.2) compared to White individuals (22.5 per 100 000, 95% CI 19.7, 25.6), with an adjusted prevalence rate ratio of 1.2 (95% CI 1.0, 1.3) [R16-0120].

SI.2.3.2 Risk factors

Environmental and Occupational Exposures
Occupational chemical exposure may increase risk of SSc. A French case-control study compared the occupational exposures of 80 consecutively enrolled cases of SSc and 160 age-, gender-, and

smoking history-matched controls who were contemporaneously hospitalised for other indications [R18-4013]. Compared to controls, patients with SSc had statistically significant increased risk of exposure to ketones (OR [95% CI] 8.8 [1.8, 42.4]), crystalline silica (OR [95% CI] 5.5 [1.7, 18.4]), epoxy resins (OR [95% CI] 4.2 [1.0, 17.4]), welding fumes (OR [95% CI] 3.7 [1.1, 13.2]), white spirit (OR [95% CI] 3.5 [1.5, 8.1]), toluene (OR [95% CI] 3.4 [1.1, 10.9]), aromatic solvents (OR [95% CI] 2.7 [1.1, 6.8]), chlorinated solvents (OR [95% CI] 2.6 [1.2, 5.7]) and trichloroethylene (OR [95% CI] 2.4 [1.0, 5.2]). 2 case-control studies conducted in the provinces of Trento and Verona, Italy, identified increased risks of SSc among those exposed to occupational organic solvents [R18-4008, R18-4009]. Similar results were found in a cross-sectional study conducted in Hungary, over the period 1995-2000, where 16 out of the 63 female SSc patients had been exposed to solvents. These results were significantly higher compared to matched controls ($p<0.05$) [R18-4007].

Over the period 1997-2010, a cohort study conducted among male construction workers in Sweden reported that men exposed to silica dust were at increased risk of developing systemic lupus erythematosus, SSc and dermatomyositis (adjusted relative risk [RR] [95% CI] 1.8 [1.2, 2.7]) [R18-4017]. In addition, authors also reported cigarette smoking was a risk factor for these conditions with an adjusted ever smoker/never smoker (RR [95% CI] 1.7 [1.2, 2.6]).

Regarding the role of other occupational factors in SSc, a hospital-based case-control study including 226 participants (55 SSc cases and 171 controls matched on gender and age group) was conducted in Verona, Italy, over the period 1997-1999 [R18-4008]. In this study, textile and tailoring workers and teachers were at increased risk of developing SSc, with age- and gender-adjusted ORs of 2.0 (95% CI 1.0, 4.3) and 3.2 (95% CI 1.2, 8.8), respectively.

Genetic factors
As in other autoimmune diseases, the current paradigm for the pathogenesis of SSc considers that genetic susceptibility, together with several external factors, may trigger a series of events, mainly implying autoimmunity and microvascular dysfunction, which eventually lead to fibrosis and the clinical manifestations of SSc. The genetic contribution derives from numerous genetic variants, which predispose individuals to the disease [R18-3934].

Gender
As summarised in section SI.2.3.1, SSc is much more frequent in females than in males. Female gender is considered as a risk factor for SSc. However, studies found that male patients carry a worse prognosis, with higher disease-related mortality and shorter survival [R15-2532, R19-0015].

Antibodies
Additionally, approximately 90% of patients with SSc have antinuclear antibodies characteristic of the disease, including anticentromere, antitopoisomerase-I (Scl-70), anti–RNA polymerase, or U3-RNP antibodies [R15-6198].

SI.2.4 The main existing treatment options

SI.2.4.1 International guidelines

To date, no pharmacological treatment is approved for disease-modification in SSc. Below we mainly describe symptomatic treatments. Currently, treatment of SSc involves managing a chronic multisystem autoimmune disease that consists of a widespread obliterative vasculopathy

of small arteries associated with varying degrees of tissue fibrosis. The goal of therapy is to improve the quality of life by minimising specific organ involvement and subsequent life-threatening diseases. Evidence based guidelines for the treatment of patients with SSc from the EULAR and EULAR Scleroderma Trials and Research (EUSTAR) group were originally published in 2009 [P15-00879] and were updated in 2017 [R17-3833]. The guidelines included new treatment options, but did not cover biologics in great detail because data regarding their use in SSc were insufficient to warrant firm recommendations. Recommended therapies are presented by system below.

Raynaud's phenomenon
Cold avoidance and stress management are the cornerstone of management of Raynaud's phenomenon. The guidelines also recommend vasodilator therapy (extended release dihydropyridine-type calcium channel blockers as first-line therapy) for every patient. A prostacyclin analogue (e.g. iloprost) is recommended for severe Raynaud's. Additionally, phosphodiesterase-5 inhibitors, HMG-CoA reductase inhibitors (e.g. atorvastatin) and fluoxetine are recommended treatment options for this symptom.

Recurrent digital ulcers
A prostacyclin analogue (e.g. iloprost) or phosphodiesterase-5 inhibitor is recommended for active ulcers. Treatment with an endothelin receptor antagonist (i.e. bosentan) or an HMG-CoA reductase inhibitor (e.g. atorvastatin) should be considered in patients with multiple digital ulcers in spite of other therapy.

Pulmonary symptoms
For PAH, oral therapy (bosentan, ambrisentan, sildenafil, taldalafil) is recommended for moderate to severe PAH with clinical status of WHO class II-III. For severe cases or for those failing oral therapy, continuous infusion of a prostacyclin analogue (epoprostenol, treprostinil or iloprost) via a centrally placed intravenous line or subcutaneous route should be used. Aerosolised prostaglandins (iloprost, treprostinil) are now available for severe PAH. For ILD, cyclophosphamide with or without oral corticosteroid is strongly recommended, although no drugs have been approved for the treatment of SSc-ILD (ILD, see Section SI.3.4 for more details).

Scleroderma skin disease
For patients with mild skin disease limited to the face and fingers, there is no indication to use systemic therapy, and disease management should be limited to an observation period of 3 to 6 months. Treatment options for active skin disease include methotrexate, antithymocyte globulin, imatinib or rituximab. Haematopoietic stem cell transplant is recommended only for carefully selected patients with progressive SSc who are at risk of developing organ failure.

Scleroderma renal crisis
Angiotensin-converting enzyme inhibitors are strongly recommended to prevent scleroderma renal crisis; dialysis may be required in some patients.

Gastrointestinal manifestations
Proton pump inhibitors (strictures, reflux ulcers), prokinetic drugs (dysmotility) and antibiotics (bacterial overgrowth) are all recommended treatments for patients with gastrointestinal manifestations of SSc.

SI.2.4.2 Drug utilisation patterns

Results from a post-marketing study that aimed to characterise the profile of patients with SSc treated with bosentan in clinical practice in France, demonstrated that treatment modalities and target dosing of bosentan were prescribed as recommended in prescribing guidelines [R18-4006]. In this study, concomitant treatments included oral prednisone (25.3%), mycophenolate (9.0%), methotrexate (6.7%), and cyclophosphamide (3.4%). In a cohort study from Italy, over the period 2005-2009, all of the 130 patients with SSc (100%) were treated with iloprost (intravenous prostacyclin). In addition, patients received calcium channel blockers (nifedipine), D-penicillamine, and aspirin [R18-4004].

The host of medications to address manifestations in several body systems is evident in the table below. It describes the medication use of the 326 participants of a recent multinational prospective observational study of immunosuppressant regimens for early diffuse cutaneous systemic sclerosis (with less than 3 years of skin thickening) [R18-2822]. The diffuse cutaneous subtype is less common and is associated with lower 5- and 10-year mortality. Concomitant medications at enrolment in this study are reviewed in the table below.

SI.Table 20 Baseline medication use in early diffuse cutaneous systemic sclerosis

Therapeutic class	Medication or medication class	Percentage at baseline (%)
Immunosuppressants	Methotrexate	19.9
	Mycophenolate	36.2
	Cyclophosphamide	26.4
Endothelin receptor antagonist		3.7
Musculoskeletal	Non-steroidal anti-inflammatory drugs	12.9
	Hydroxychloroquine	7.7
	Other	0.9
Renal	Angiotensin converting enzyme inhibitors	15.9
	Angiotensin II receptor blockers	8.3
Gastrointestinal	Proton pump inhibitors	96.4
	Histamine-2 blockers	4.5
	Antacids	5.4
	Antibiotics for overgrowth syndrome	1.8
	Prokinetic drugs	4.5
Antiplatelet medications		18.2
Prostanoids		17.2

Data source: [R18-2822]

SI.2.5 Natural history of the indicated condition in the population, including mortality and morbidity

SI.2.5.1 Mortality and morbidity

Systemic sclerosis has a highly variable course, and a relatively high mortality rate among the rheumatic diseases. Survival improved significantly over the last decades; the 10-year cumulative survival rate was around 54% in the 1970s, and mortality was higher before the use of angiotensin converting enzyme inhibitors to reduce scleroderma renal crisis in the 1980s [R14-4918].

In a recent meta-analysis, the cumulative survival from diagnosis of SSc was 84% at 5 years, and 71% at 10 years [R16-0117]. 5- and 10-year survival estimates were similar across several studies: 83% and 70%, respectively in Greece [R16-1340]; 84% (95% CI 73%, 91%) and 65% (95% CI 49%, 77%), respectively in Spain [R16-1343]; 84% and 73%, respectively in Hungary [R17-2748], and 90% and 82%, respectively in Canada [R18-4005].

Higher 5- and 10-year survival was observed among patients with the lcSSc subtype compared to the dcSSc subtype [R16-1340, R18-4005]. In these studies, estimates of 5-year survival for the lcSSc subtype were 91% to 95%, and were 67% to 81% for the dcSSc subtype. Similarly, estimates of 10-year survival for the lcSSc subtype were 82% to 92% and were 49% to 65% for the dcSSc subtype in these 2 studies.

In comparison to the general population, the age- and sex-adjusted SMR was estimated at 2.0 (95% CI 1.2, 2.8), with higher survival rates reported in patients with lcSSc compared to those with dcSSc [R16-1340]. Similar SMR findings were obtained in other cohort studies [R16-1351, R17-2748, R18-4005, R18-4026]. Furthermore, a cohort study of SSc patients conducted in the UK over the period 1999-2010 reported that the SMR was higher in men (1.5, 95% CI 0.7, 3.0) than in women (1.3, 95% CI 1.0, 1.7) [R16-1351].

Increases in survival rates may also be explained by methodological differences across studies and this trend is difficult to evaluate based on results from the studies summarised above. In a US study based on data collected in consecutive SSc patients included in the Pittsburgh Scleroderma Databank that was conducted over a period of 20 years (1972-1991), survival improved over time [R14-4929]. The 10-year survival improved steadily for each time interval, ranging from 54% in the period 1972-1976 to 66% in the period 1987-1991 ($p<0.001$).

Between 1980 and 2010, results from a historical, population-based, cohort study conducted in the US that included 64 patients with incident SSc showed that median survival time after diagnosis was 22.9 years [R18-1404]. In France, over the period 1997-2005, a cohort study of 121 patients with SSc, reported a mean survival of 13 years in men (95% CI 10, 16) and 23 years in women (95% CI 10, 36) [R18-4011].

Common causes of mortality
3 broad categories of cause of mortality among patients with SSc were evident in the literature: pulmonary disease (i.e. primary arterial hypertension, respiratory failure, lung cancer, interstitial lung disease, fibrosis, aspiration), cardiac disease (i.e. myocardial infarction, heart failure) and renal failure. As stated above, trends in mortality and the causes of mortality are attributable to the use of angiotensin converting enzyme inhibitors to prevent scleroderma renal crisis since the

1980s. These changes were evident in the results of a study conducted in the US between 1972 and 1996 that used data collected from consecutive patients with SSc from the Pittsburgh Scleroderma Databank [R14-4929]. The frequency of scleroderma-related deaths due to renal crisis significantly decreased over the 30-year time period, ranging from 42% in 1972 to 6% in 1996 ($p<0.001$), whereas during the same timeframe, the proportion of scleroderma-related deaths from pulmonary fibrosis increased from 6% to 33% ($p<0.001$).

Today, ILD and PAH are the most frequent causes of death in patients with SSc [R14-4918]. In several European studies, cardiorespiratory manifestations were the leading causes of death in patients with SSc, representing about 65% of all deaths [R16-0564, R16-1343, R17-2748, R18-4011]. In a recent meta-analysis, more than half of the SSc-related deaths were attributed to lung involvement (57.0%, including 18 studies with mid-cohort years after 1990) [R16-0117].

In a study based on the EULAR EUSTAR database [R16-0564], between 2004 and 2008, 284 deaths occurred in patients with SSc, of which 55% were attributed directly to SSc and 41% to non-SSc causes. Among the SSc-related deaths, 35% were attributed to pulmonary fibrosis and 26% to PAH and 26% to cardiac causes (mainly heart failure and arrhythmias).

A similar pattern was observed in a cohort study from Canada that included 185 patients with SSc over the period 1994-2004 [R18-4005]. Of 33 deceased patients for whom the cause of death could be ascertained, the primary causes of death included ILD and PAH (n=10 and 5, respectively, 45%), cardiac complications (n=9, 27%) and renal complications (n=9, 27%).

Prognostic factors
Using a multivariate Cox proportional hazards model applied to a cohort of 366 SSc patients in Hungary, renal involvement, diffuse scleroderma, coexistence of a malignant disease, and increased ESR were independent prognostic factors for poor survival in patients with SSc [R17-2748].

A European multicentre cohort study that included 1049 patients with SSc identified the following baseline factors as predictors of poor 5-year survival: older age, male gender, presence of urine protein, ESR ≥25 mm/h, and reduced DLCO (< 70%) [R18-4012].

Significant predictors of reduced survival in patients with SSc in a database study from the UK were: RNA polymerase III antibody (HR 11.5, 95% CI 1.1, 119.6), male gender (HR 5.0, 95% CI 2.0, 12.5), the presence of ILD (HR 3.8, 95% CI 1.7, 8.5) and older age at diagnosis (HR 1.1, 95% CI 1.0, 1.1) [R16-1351]. Moreover, in a longitudinal 3-year cohort study conducted in France, among 546 SSc patients diagnosed over the period 2002-2003, the following factors were associated with increased mortality: PAH, age at first symptom, duration of SSc, and Rodnan skin score [R18-4028]. These findings were further supported by a study conducted among 5860 patients with SSc (284 deaths) enrolled in the EUSTAR database over the period 2004-2008. Independent risk factors for mortality in SSc were: proteinuria (HR 3.3), presence of PAH based on echocardiography (HR 2.0), pulmonary restriction (presence of FVC < 80% of normal) (HR 1.6), dyspnoea above NYHA class II (HR 1.6), patient age at onset of Raynaud's Phenomenon (HR 1.3 per 10 years), DLCO (HR 1.2 per 10% decrease) and the modified Rodnan skin score (HR 1.2 per 10 score points increase) [R16-0564].

In North America, among 185 SSc patients followed prospectively in a single centre in Canada between 1994 and 2004, the following factors were significantly associated with death: the

presence of cardiac disease (OR 9.5, 95% CI 4.4, 20.6), the presence of ILD (OR 3.4, 95% CI 1.5, 8.1), the presence of hypertension (OR 2.6, 95% CI 1.3, 5.3) and dcSSc subtype (OR 2.3, 95% CI 1.2, 4.7) [R18-4008]. In a historical, population-based, cohort study conducted in Olmsted County, Minnesota in the US of 64 incident cases of SSc, an increased risk of death was associated with the presence of ILD, PAH, and chronic kidney disease [R18-1404].

SI.2.6 Important co-morbidities

Important co-morbidities include [R18-4040]:

- Malignancy
- Primary biliary cirrhosis
- SSc overlap syndromes (SSc with other autoimmune disorders such as myositis or rheumatoid arthritis or Sjögren's syndrome or systemic lupus erythematosus)
- Atherosclerosis (myocardial infarction and stroke)
- Depression
- Osteoporosis (complication of chronic glucocorticoid use)

SI.2.6.1 Supplemental information: Incidence rates of co-morbidities of the underlying diseases

As requested by the PRAC (EMEA/H/C/003821/II/0046), incidence rates of co-morbidities associated with the underlying disease are presented in the following.

SI.2.6.1.1 Literature

Incidence rates of co-morbidities associated with SSc are presented in the table below.

SI.Table 21 Incidence rates of co-morbidities associated with SSc

SSc co-morbidity	Study	Description (population, age, data source)	Incidence measures
Malignancy	Morrisroe 2020 [R22-1543]	Consecutive patients with SSc who prospectively enrolled in the ASCS, a multicentre study of risk and prognostic factors for clinically important outcomes in SSc, were included. The cohort consisted of 1727 patients with SSc contributing to 7081 PY of follow-up. The study included all adult patients (age >18 years) with SSc recruited between January 2008 (ASCS cohort inception) and December 2015 (the most recent date for which cancer registry and health service utilisation data are available). All patients fulfilled the American College of Rheumatology/ European League Against Rheumatism classification criteria for SSc.	*Overall cancer* SIR (overall): 2.15 (1.84 - 2.49) SIR (early*): 2.53 (1.82 - 3.44) SIR (late**): 1.54 (1.22 - 1.91) *Breast cancer* SIR (overall): 1.51 (0.98 - 2.21) SIR (early*): 3.07 (1.47 - 5.64) SIR (late**): 1.38 (0.79 - 2.25) *Lung cancer* SIR (overall): 2.12 (1.21 - 3.44) SIR (early*): 2.05 (0.42 - 6.00) SIR (late**): 2.51 (1.34 - 4.29) *Melanoma skin cancer* SIR (overall): 1.30 (0.59 - 2.46) SIR (early*): 3.40 (1.10 - 7.93) SIR (late**): 0.87 (0.24 - 2.22) *Colon cancer* SIR (overall): 1.26 (0.58 - 2.40) SIR (early*): 2.94 (0.80 - 7.53) SIR (late**): 1.03 (0.33 - 2.39) *Cervical cancer* SIR (overall): 4.68 (0.97 - 13.68) SIR (early*): 6.89 (0.17 - 38.39) SIR (late**): 4.94 (0.60 - 17.84)

SI.Table 21 (cont'd) Incidence rates of co-morbidities associated with SSc

SSc co-morbidity	Study	Description (population, age, data source)	Incidence measures
Malignancy (cont'd)			*Ovarian cancer* SIR (overall): 1.86 (0.38 - 5.44) SIR (early*): 6.46 (0.78 - 23.35) SIR (late**): 0.92 (0.02 -5.14) *Uterine cancer* SIR (overall): 1.53 (0.50 - 3.58) SIR (early*): 1.63 (0.04 - 9.08) SIR (late**): 1.82 (0.50 - 4.66) *Prostate cancer* SIR (overall): 1.34 (0.49 -2.92) SIR (early*): 1.56 (0.19 - 5.62) SIR (late**): 1.36 (0.37 - 3.48) *Haematological cancers* SIR (overall): 1.36 (0.55 - 2.81) SIR (early*): 0.97 (0.02 - 5.42) SIR (late**): 0.97 (0.02 - 5.42) *Non-Hodgkin's Lymphoma* SIR (overall): 1.98 (0.73 - 4.30) SIR (early*): 1.66 (0.04 - 9.25) SIR (late**): 2.43 (0.79 - 5.68) *Leukaemia* SIR (overall): 0.52 (0.01 - 2.91)

SI.Table 21 (cont'd) Incidence rates of co-morbidities associated with SSc

SSc co-morbidity	Study	Description (population, age, data source)	Incidence measures
Malignancy (cont'd)	Hashimoto 2012 [R22-1544]	A cohort of 405 Japanese patients with SSc who visited Kitasato University hospital between 1973 and 2008 was analysed retrospectively until the end of 2009.	*Overall malignancies* SIR: 1.24 (0.77-1.71) *Lung cancer* SIR: 5.73 (2.18-9.29) *Breast cancer* SIR: 1.02 (0.02-2.02) *Gastric cancer* SIR: 0.84 (-0.11-1.79) *Lymphoma* SIR: 4.36 (-1.68-10.39)
	Kang 2009 [R22-1545]	The study subjects consisted of 112 patients who were treated at Kangnam St Mary's Hospital, Korea between 1990 and 2007. Medical records were reviewed retrospectively.	*All cancers* SIR: 4.2 (2.3–6.1) *Lung* SIR: 18.6 (13.8–23.4) *Stomach* SIR: 3.0 (1.9–4.1) *Oesophagus* SIR: 35.0 (33.6–36.4) *Liver* SIR: 4.9 (3.0–6.9)

SI.Table 21 (cont'd) Incidence rates of co-morbidities associated with SSc

SSc co-morbidity	Study	Description (population, age, data source)	Incidence measures
Malignancy (cont'd)			*Pancreas* SIR: 23.5 (14.3–32.7) *Squamous cell carcinoma, unknown primary origin* SIR: 25.3 (24.3–26.3)
	Chatterjee 2005 [R22-1546]	Scleroderma patients in the Detroit metropolitan area was assessed by linking patient identification codes of the Michigan Scleroderma Registry to the Metropolitan Detroit Cancer Surveillance System database. Patients were screened between the years 1973 and 2002, with additional follow-up to 2004. Of 934 patients in the Scleroderma Registry, 538 were included in the study based on tri-county residency.	*All invasive* SIR: 0.91 (0.66–1.22) *Lung* SIR: 1.23 (0.59–2.25) *Liver* SIR: 7.35 (1.52–21.49) *Non-Hodgkin's Lymphoma* SIR: 1.18 (0.14–4.28)
	Rosenthal 1995 [R22-1547]	Patients in Sweden with a discharge diagnosis of systemic sclerosis or localised scleroderma were obtained from the computerized database of hospital discharge diagnoses for the years 1965-1983. 917 patients with systemic sclerosis and 102 with localised scleroderma were identified.	*All cancers* SIR: 1.5 (1.2-1.9) *Lung cancer* SIR: 4.9 (2.8-8.1) *Non-melanoma skin cancers* SIR: 4.2 (1.4-9.8) *Primary liver cancer* SIR: 3.3 (1.1-7.6) *Hematopoietic cancers* SIR: 2.3 (0.9-4.8)

SI.Table 21 (cont'd) Incidence rates of co-morbidities associated with SSc

SSc co-morbidity	Study	Description (population, age, data source)	Incidence measures
Malignancy (cont'd)	Abu-Shakra 1992 [R22-1548]	A retrospective chart review of 248 patients who attended the Scleroderma Clinic at the Wellesley Hospital between 1978 and 1992 and who were followed up prospectively was conducted.	*All cancers* Age-standardised incidence rate per 1000 PY: 7.9
Primary biliary cholangitis (primary biliary cirrhosis)	See SI.Table 22		
SSc overlap syndromes	Tseng 2016 [R22-1550]	The study enrolled patients with SSc from Taiwan's Registry of Catastrophic Illness Database and referent subjects from the National Health Insurance Research Database. The study enrolled 1171 patients with SSc and 3409 control subjects matched by sex, age, month and year of initial diagnosis of systemic sclerosis.	*Multiple sclerosis* Incidence rate per 1000 PY: 9.35 (6.86–11.85)
	Tseng 2015 [R22-1561]	The study enrolled patients with SSc from Taiwan's Registry of Catastrophic Illness Database and referent subjects from the National Health Insurance Research Database. The study enrolled 2217 patients with SSc and 6485 control subjects matched by sex, age, month and year of initial diagnosis of systemic sclerosis.	*Sjogren's syndrome* Incidence rate per 1000 PY: 27.06 Relative risk: 7.69 (6.45-9.17) Relative risk (adjusted for age): 7.75 (5.79–10.42)
	Tseng 2015 [R22-1549]	The study enrolled patients with SSc from Taiwan's Registry of Catastrophic Illness Database and referent subjects from the National Health Insurance Research Database. The study enrolled 2829 patients with SSc and 8257 control subjects matched by sex, age, month and year of initial diagnosis of systemic sclerosis.	*Crohn's disease* Incidence rate per 1000 PY: 0.56 Incidence ratio: 0.12 (0.07-0.22) Incidence ratio (adjusted for age): 0.12 (0.06-0.22)

SI.Table 21 (cont'd) Incidence rates of co-morbidities associated with SSc

SSc co-morbidity	Study	Description (population, age, data source)	Incidence measures
Atherosclerosis (myocardial infarction and stroke)	Michel 2020 [R22-1551]	Using UK electronic primary care data (THIN 2000–2012), 1314 patients with SSc and a matched SSc-free comparison cohort of 19 992 were followed until December 2013.	*Haemorrhagic stroke* IR per 1000 PY: 0.5 HR (adjusted): 1.51 (0.54-4.21)
	Butt 2019 [R22-1552]	In the Danish administrative registries between 1995 and 2015, all patients aged ≥18 years with a first diagnosis of SSc were matched by age and sex with controls (1:5) from the general population. The final study population included 2778 SSc patients.	*Hypertension* IR per 100 PY: 15.21 (14.42–16.06) *Atrial fibrillation* IR per 100 PY: 0.92 (0.81–1.04) *Heart failure* IR per 100 PY: 0.92 (0.81–1.05) *Myocardial infarction* IR per 100 PY: 0.39 (0.32–0.48) *Ischaemic stroke* IR per 100 PY: 0.43 (0.36–0.52) *Aortic aneurism* IR per 100 PY: 0.08 (0.05–0.12) *Aortic stenosis* IR per 100 PY: 0.29 (0.23–0.36) *Aortic regurgitation* IR per 100 PY: 0.16 (0.12–0.22)

SI.Table 21 (cont'd) Incidence rates of co-morbidities associated with SSc

SSc co-morbidity	Study	Description (population, age, data source)	Incidence measures
Atherosclerosis (myocardial infarction and stroke) (cont'd)			*Mitral stenosis* IR per 100 PY: 0.02 (0.01–0.05) *Mitral regurgitation* IR per 100 PY: 0.18 (0.14–0.24) *Conduction block (left bundle- branch or atrioventricular block)* IR per 100 PY: 0.11 (0.08–0.16) *Pacemaker or implantable cardioverter-defibrillator* IR per 100 PY: 0.18 (0.13–0.23) *Pericarditis* IR per 100 PY: 0.11 (0.08–0.16) *Peripheral vascular disease* IR per 100 PY: 0.75 (0.65–0.87) *Pulmonary hypertension* IR per 100 PY: 0.58 (0.49–0.68) *Venous thromboembolism* IR per 100 PY: 0.37 (0.30–0.46)
	Baek 2016 [R22-1555]	In a retrospective study conducted at referral centres in South Korea, 20 772 consecutive ARD patients, including 303 SSc patients were analysed from 2005 to 2015.	*Atrial fibrillation* HR (crude): 3.00 (1.54–5.85) HR (adjusted by age and sex): 1.09 (1.08–1.10) HR (adjusted by age, sex, hypertension, diabetes mellitus, CHF, obesity, obstructive sleep apnoea, and high hsCRP): 1.76 (0.90–3.45)

SI.Table 21 (cont'd) Incidence rates of co-morbidities associated with SSc

SSc co-morbidity	Study	Description (population, age, data source)	Incidence measures
Atherosclerosis (myocardial infarction and stroke) (cont'd)	Chiang 2013 [P13-02141]	From the Registry of Catastrophic Illness in Taiwan, data for 1280 patients with a diagnosis of SSc from 1997 to 2006 was obtained and matched with control patients from the Longitudinal Health Insurance 2000. 1238 SSc patients and 12 380 controls were identified. Patients with an initial SSc diagnosis before the age of 18 and diagnosis of cerebrovascular disease before and at SSc diagnosis were excluded from the study.	*Ischaemic stroke* Incidence per 1000 PY: 16.5
	Chu 2013 [R18-3784]	The study cohort included 1344 patients with SSc and 13 440 (1:10) age-, sex-, and co-morbidity-matched controls during the period between 1997 and 2006, from the National Health Insurance Research Database. Patients with MI before the diagnosis of systemic sclerosis and patients younger than 18 years were excluded.	*Acute myocardial infarction* Incidence rate per 100 000 PY: 535
	Man 2013 [R18-3843]	A cohort study using a UK primary care database containing records from 1986 to 2011 was conducted among 865 individuals with SSc.	*Myocardial infarction* IR: 4.4 per 1000 PY HR (adjusted): 1.80 (1.07 – 3.05) *Stroke* IR: 4.8 per 1000 PY HR (adjusted): 2.61 (1.54 – 4.44) *Peripheral vascular disease* IR: 7.6 per 1000 PY HR (adjusted): 4.35 (2.74 – 6.93)

SI.Table 21 (cont'd) Incidence rates of co-morbidities associated with SSc

SSc co-morbidity	Study	Description (population, age, data source)	Incidence measures
Depression	Baubet 2011 [R22-1553]	Between May 2002 and May 2004, 100 SSc patients fulfilling the American Rheumatism Association and/or Leroy & Medsger criteria were recruited: 51 were from a SSc patient association meeting, and 49 were hospitalised in an internal medicine department and recruited consecutively. Mood and anxiety disorders were assessed by use of a structured clinical interview (MINI) performed by a psychiatrist and a self-reporting questionnaire (HADS).	*Symptoms of depression* Summary of incidence: 36% to 65%
Osteoporosis	Lai 2014 [R22-1554]	A cohort study was conducted using the Taiwan National Health Insurance database. 1712 patients with SSc and respective age- and gender-matched controls without SSc were enrolled. Patients who (1) experienced an OF before enrolment, (2) were aged less than 18 years, or (3) had pathological fractures (ICD-9-CM: 733.14 and 733.15) or malignancies were excluded.	*Overall fracture* IR per 1000 PY: 9.50 IRR: 1.69 (1.30 to 2.18) *Vertebral fracture* IR per 1000 PY: 6.99 IRR: 1.78 (1.30 to 2.39) *Hip fracture* IR per 1000 PY: 2.18 IRR: 1.89 (1.05 to 3.22) *Radius fracture* IR per 1000 PY: 0.90 IRR: 1.23 (0.47 to 2.72)

*Early cancer defined as cancer incidence within 5 years of onset of SSc (Raynaud phenomenon or other)
**Late cancer defined as cancer incidence after 5 years since onset of SSc (Raynaud phenomenon or other)

SI.2.6.1.2 OPTUM CDM

The SSc patients were identified from a large US healthcare insurance data base (OPTUM CDM) in a selection period from 01 Jan 2017 to 30 Sep 2021.

To calculate the incidence rate of a co-morbidity among SSc patients, the patients will be required to meet the following criteria in the denominator.

- Had at least 2 claims with SSc diagnosis on different dates within one year as confirmed SSc diagnosis in the selection period. The second SSc diagnosis date was the index date.
- Had at least 1-year continuous enrolment with the health plan (30 days gap allowed) prior to the index date to assess if they were truly incident patients. The 1-year period prior to index date was defined as baseline period.
- Did not have any diagnosis of the co-morbidity during the baseline period.
- Had at least 30 days continuous enrolment with the health plan (follow up) after index date. The follow up period was censored at discontinued enrolment after index date, death, or end of selection period, whichever was earlier.

The incidence rate of the co-morbidity among SSc patients was calculated by dividing the number of patients with a new diagnosis of the co-morbidity by the sum of all observed person-to-event-time for all subjects in the denominator,

$$Incidence\ rate = \frac{Number\ of\ newly\ diagnosed\ comorbidity}{Sum\ of\ person-year\ at\ risk}$$

Patients with a new diagnosis of co-morbidity after index date contribute their PY at risk from index date to the first diagnosis of the co-morbidity after index date, while the other patients in the denominator contribute their PY at risk from index date to the end of follow up date.

The table below shows the number of SSc patients at risk of the co-morbidity, number of patients with newly diagnosed co-morbidity, sum of PY at risk of the co-morbidity, incidence rate of the co-morbidity and its' 95% CI.

SI.Table 22 Number of SSc patients at risk of the co-morbidity, number of patients with newly diagnosed co-morbidity, sum of PY at risk of the co-morbidity, incidence rate of the co-morbidity and 95% CI

SSC	**Adult population (≥18 years)**					**Paediatric population (<18 years)**				
Co-morbidity	**Denominator N**	**New events**	**PY**	**Incidence rate (per 100 000 PY)**	**95% CI of incidence rate**	**Denominator N**	**New events**	**PY**	**Incidence rate (per 100 000 PY)**	**95% CI of incidence rate**
Primary biliary cholangitis	8177	96	17 859	336	261.3, 432.5	49	0	96	0	0.0, 3847.0

*OPTUM (study period: 2017-01-01 to 2021-09-30)

SI.3 SYSTEMIC SCLEROSIS ASSOCIATED-INTERSTITIAL LUNG DISEASE (SSc-ILD)

The following section aims to provide an overview of the epidemiology of SSc-ILD including patient characteristics, treatment patterns, and co-morbidities of interest. The overview includes studies if they included at least 25 patients with SSc-ILD (with the exception of prevalence estimates, which were derived from cohorts of patients with SSc; see below).

Nevertheless, the following potential limitations of the included studies have to be considered:

- Differences in the definition of clinical cases and the criteria used to diagnose SSc-ILD
- Differences in the case definitions, the criteria used and data sources used to identify the co-morbidities of interest, or in some cases the lack of a disease definition
- Given that SSc-ILD is a rare disease, the majority of the included observational studies assessed relatively small samples of SSc-ILD patients
- Only studies published in English language were included
- Differences in health care systems, population characteristics, and other factors such as local treatment guidelines may limit the generalisability of findings across countries

SI.3.1 Incidence

No studies of the incidence of SSc-ILD were identified.

SI.3.2 Prevalence

No studies reporting the prevalence data specific to SSc-ILD were identified. The prevalence estimates included herein were derived from cohorts of patients with SSc (see Section SI.2.2). In order to estimate the prevalence of SSc-ILD, studies of SSc-ILD, with population bases of patients with SSc, were identified. Estimates of the proportion of patients with SSc who had SSc-ILD ranged from 30% to 60% (see SI.Table 23); the median estimate was 36.4%.

Several Europe and North American studies evaluated the prevalence of SSc in the general population (see Section SI.2.2). In Europe, estimates varied from 9.9 per 100 000 in Norway for the year 2009 [R16-1346, R18-4026] to 34.8 per 100 000 in Sardinia, Italy in 2012 [R18-4035]. The reported prevalence of SSc in North America was slightly higher compared to Europe, ranging from 13.5 per 100 000 individuals in the US in 2003 to 44.3 per 100 000 individuals in Quebec, Canada in 2003.
Available data suggest that SSc-ILD affects about 35.0% of patients with SSc [R16-1345; R16-1351; R16-1352; R16-1858]. The proportions published in the literature, however, vary between 19% and 52% depending notably on the disease definition (see SI.Table 23).

Summary of prevalence estimation:

- No studies of SSc-ILD prevalence were identified
- According to the literature search performed, the maximum prevalence of SSc is estimated to be below 35 per 100 000 persons in the EU, of whom approximately 35% have SSc-ILD, which suggests that the prevalence of SSc-ILD in Europe is approximately 12 per 100 000 persons
- The maximum prevalence of SSc in literature from North America is estimated to be below 45 per 100 000 persons, of whom approximately 35% have SSc-ILD, which suggests that the prevalence of SSc-ILD in the US and Canada is approximately 16 per 100 000 persons

SI.Table 23 Estimates of proportion of patients with systemic sclerosis with interstitial lung disease

Study/ Source	Country	Study type	Data collection period	Diagnostic approach	SSc population size	Proportion of patients with ILD
Europe						
Groseanu et al. 2013 [R16-1345]	Romania	Single hospital	2010 to 2012	Not specified	44	36.4%
Foti et al. 2014 [R16-1858]	Italy	Single hospital	2006 to 2013	Not specified	44 (all treated with iloprost)	32.6%
Mulla et al. 2015 [R16-1348]	UK	University Hospitals of Leicester NHS trust (one of the largest NHS hospital trusts in the UK)	Not specified	Annual pulmonary function tests	70, of which 10 (14%) were South Asian, 58 (83%) Caucasian and 2 (3%) Black	60.0% in South Asian *vs* 29.8% in Caucasian (p=0.64)
Panapoulos et al. 2013 [R16-1349]	Greece	Single university hospital	1995 to 2011	HRCT	231 (200 women and 31 men)	Comparable prevalence of ILD between genders during the first 3-year interval (Women: 40.7% *vs* men: 45.5%; p=0.676), the second 3-year interval (51.6% *vs* 56.2%, respectively; p=0.732), and the third 3-year interval (60.7% *vs* 75.0%, respectively; p=0.435)
Strickland et al. 2013 [R16-1351]	UK	Patients registered on the Royal National Hospital for Rheumatic Diseases Connective Tissue Disease database	1999 to 2010	HRCT or lung biopsy	223 (151 living patients and 53 dead patients)	32.3% (27.2% in living patients *vs* 48.0% in dead patients)
Vonk et al. 2009 [R16-1352]	The Netherlands	Data from the POEMAS (Pulmonary Hypertension Screening, a Multidisciplinary Approach in Scleroderma) registry	2005 to 2007	Pulmonary function tests or HRCT	654	19% case defined as FVC% <70% 47% case defined by HRCT
North America						
Bauer (2013) [R18-1404]	US	Olmsted County Minnesota, US	1980 to 2010	HRCT	64	30%
Steele (2012) [R17-0318]	Canada	Canadian Scleroderma Research Group registry	2004 to 2010	HRCT	1168	52.3%

SI.3.3 Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

SI.3.3.1 Demographics

Several cohorts of patients with SSc-ILD were identified. Baseline demographic factors including age, gender, smoking history, and co-morbidities for SSc-ILD patient populations were reported and are included in SI.Table 24. When there were multiple publications by the same research group [R17-0136, R17-0316, R18-3760, R18-4010], the publication with the most comprehensive information or most recent data was selected.

Because there were no SSc-ILD-specific incidence and prevalence data available, stratification by demographic variables such as age, gender and race was also unavailable. Studies of SSc did not provide demographic breakdowns of the subgroups of patients with SSc-ILD. Risk factors for developing SSc-ILD (see Section SI.3.3.2) include African-American ethnicity and diffuse cutaneous subtype.

The identified publications presented follow-up data from the 1990s through 2014. Patients in the identified observational studies were primarily older adults, with the mean age (whether defined at diagnosis or at baseline) of each cohort in the late forties to mid-fifties. Additionally, patients in these cohorts were predominantly female (61% to 97% overall and 81% to 90% in the European cohorts).

Generally, studies from the US were more likely to provide data on race/ethnicity. 1 of the 2 US studies provided a distribution of race/ethnicity, which are summarised in the table below, the other reported no race- or ethnicity-specific data.

SI.Table 24 Baseline characteristics of populations of patients with SSc-ILD

Reference Country	Study years	Study design/ population	N	Case definition[a]	Age, years Mean (SD)	Gender, % female	Smoking history	SSc-ILD subtype[b]	Biomarkers	FVC%, Mean (SD)
European cohorts										
De Santis (2012)/Italy / [R17-0107]	2003 to 2005	Single centre retrospective series/ rheumatology clinic	73	SSc: ACR ILD: HRCT	55.6 (12.8)[c]	85	14%	Diff use: 34%	Topoisomerase I Ab+: 55% Anticentromere Ab+:19%	92.7 (22.2)
Goh (2008)/UK/ [R15-6265]	1990 to 1999	Single centre with prospective clinical protocol/hospital	215	SSc: ACR ILD: HRCT	49.1 (13)[c]	81	Prior smoker: 43%	NR	NR	78.7 (21.4)
Volpinari (2011)/Italy [R18-4039]	NR	Retrospective cohort study/Italy	79	SSc: ACR ILD: HRCT Other: no current smokers, no + BAL culture	55 (13)[d]	90	Current smoker: 0%	Diff use: 30%	Topoisomerase I Ab+: 38% Anticentromere Ab+:28%	NR
Non-European cohorts										
Gleason (2017)/US/ [R17-1626]	1999 to 2012	Retrospective series from 2 centres/ pulmonology clinic	70	SSc: ACR ILD: HRCT Other: no aortic aneurysms or lung transplantation	55[c]	61	NR	NR	NR	60.2
Lopes (2011)/ Brazil/[R18-4022]	2002 to 2005	Prospective cohort study / NR	35	SSc: Clinical diagnosis ILD: HRCT Other: no smokers	47.6, Range: 28, 65[e]	97	Ever? 0%	NR	NR	81.3 (18.2)

SI.Table 24 (cont'd) Baseline characteristics of populations of patients with SSc-ILD

Reference Country	Study years	Study design/ population	N	Case definition[a]	Age, years Mean (SD)	Gender, % female	Smoking history	SSc-ILD subtype [b]	Biomarkers	FVC%, Mean (SD)
Moore (2013)/ Australia/ [R18-4019]	NR	Multicentre cohort study/NR	172	SSc: ACR or Leroy Medsger ILD: HRCT	55.5 (13.0)[d]	80	Ever? 41%	Diffuse: 38% Limited: 57% Overlap: 5%	Topoisomerase I Ab+: 33% Anticentromere Ab+: 13%	84.1 (17.4)
Morisset (2017)/US/ [R18-2984]	NR	2 centres retrospective series /rheumatology clinics	225	SSc: Rheumatologist confirmed ILD: HRCT or lung biopsy	55.5 (12.3)[e]	72	Ever? 42%	Diffuse: 82%	Topoisomerase I Ab+: 41% Anticentromere Ab+: 20%	71.0 (19.7)
Okamoto (2016)/Japan/ [R18-3757]	1990 to 2010	Retrospective cohort study/NR	35	SSc: ACR ILD: HRCT Other: no infection, heart failure or hypersensitivity pneumonia	60.0 Range: 53.0, 69.0 [e, f]	89	Smoker? 17%	Diffuse: 89%	NR	92.0 Range: 78.7, 102.2
Patiwetwiton (2012)/ Thailand/[R18-4029]	2005 to 2010	Retrospective single centre series/ hospital	71	SSc: ACR ILD: HRCT	54.8 (11.8)[e]	69	NR	NR	NR	NR
Ryerson (2015)/Canada/ [R17-0316]	1997 to 2013	Prospective cohort		SSc: ACR ILD: Radiologic or pathologic findings consistent with non-specific interstitial pneumonia or usual interstitial pneumonia	54.5 (13.2)[e]	84	Current or prior? 42%	NR	Topoisomerase I Ab+: 34% Anticentromere Ab+: 22%	81 (20)

SI.Table 24 (cont'd) Baseline characteristics of populations of patients with SSc-ILD

Reference Country	Study years	Study design/ population	N	Case definition[a]	Age, years Mean (SD)	Gender, % female	Smoking history	SSc-ILD subtype[b]	Biomarkers	FVC %, Mean (SD)
Swigris (2009)/ US/[R18-4031]	1983 to 2005	Single centre retrospective series/ ILD clinic	83	SSc: ACR ILD: HRCT or CXR or biopsy Other: no overlap syndrome, no PAH	49.5 (11.5)[d]	80	Ever? 49%	NR	NR	NR
Winstone (2018)/Canada/ [R18-3760]	1998 to 2014	Single centre retrospective series/ ILD clinic	145	SSc: ACR ILD: HRCT	54.4 (13.1) [d]	84	Ever? 43%	NR	Topoisomerase I Ab+: 37% Anticentromere Ab+: 8%	77.0 (20.5)

[a] Most reports did not specify the timing of the diagnostic criteria
[b] Skin involvement, diffuse or limited
[c] Timing of age estimate not reported
[d] Age at baseline
[e] Age at diagnosis
[f] Median (Interquartile range)

SI.Table 25 The distribution of race and ethnicity from 2 cohorts of patients with SSc-ILD in the US

Race or Ethnicity	Overall N=225	San Francisco, CA N=135	Rochester, MN N=90
White, n (%)	170 (76)	87 (64)	83 (90)
Asian, n (%)	21 (9)	18 (13)	3 (3)
Black/African-American, n (%)	14 (6)	10 (7)	4 (4)
Hispanic/Latino, n (%)	12 (5)	12 (9)	.
Native American, n (%)	2 (2)	2 (3)	.
Pacific Islander, n (%)	4 (2)	4 (3)	.

Data source: [R18-2984]

SI.3.3.2 Risk factors

Risk factors for SSc-ILD
Risk factors for development of ILD in SSc-patients include African–American ethnicity, skin score, serum creatinine and creatine phosphokinase levels, hypothyroidism, and cardiac involvement [P15-00686]. Anti-topoisomerase and anti-endothelial cell antibodies predict the presence of lung involvement, while anti-centromere and anti-RNA polymerase III antibodies are less associated with lung disease. Patients with dcSSc have a higher incidence of interstitial disease [P15-00686].

Among 305 consecutive patients with SSc who were enrolled in the Norwegian Systemic Connective Tissue Disease and Vasculitis Registry (a study based at a hospital in Oslo, Norway) and who had at least 2 HRCT scans, 108 had no lung fibrosis at baseline. Of these, 0 patients developed pulmonary fibrosis at follow-up (mean duration 3.1 years). Compared with ‘no pulmonary fibrosis at baseline’, ‘extensive pulmonary fibrosis (more than 20%) at the baseline’ assessment was associated with males, dcSSc subtype, pulmonary hypertension, antibodies to topoisomerase I and not having anti-centromere antibodies [R17-0145].

In contrast to the gender demographics described for SSc, where women have higher incidence and prevalence of SSc, men are more likely to have the more aggressive dcSSc subtype. Men with SSc were nearly twice as likely as women with SSc to develop ILD among 1506 patients with SSc who were enrolled in the Spanish SSc registry (OR (95% CI); for men vs women for the development of ILD [not otherwise defined] 1.83 [1.32, 2.53]) [R19-0015].

Risks for SSc-ILD progression
A recent meta-analysis identified 20 primary studies published between 2000 and 2013 that evaluated predictors of ILD progression among patients with SSc [R17-0354]. In the included studies, disease progression was defined primarily as a change in FVC or FVC% (e.g. time to FVC% decline, rate of FVC% decline, change from baseline of FVC%). SI.Table 26 includes

factors that were associated with a measure of disease progression from the meta-analysis-sourced studies from 2007 forward (also excluding 2 studies sourced from an SSc-ILD treatment trial), as well as more recently published studies of SSc-ILD progression. Most factors that were predictors of progression did not remain statistically significant when controlled for other parameters (particularly disease severity at baseline).

Imaging parameters
Of the 20 studies identified for above-mentioned meta-analysis, scan fibrosis severity (HRCT) was 1 of 2 significant predictors of progression identified in more than 1 study (the other was shorter duration of disease at baseline) [R17-0354]. In 1 of the recently published studies, progression was associated with honeycombing on HRCT, worsening pulmonary function (at least 10% relative decline FVC parameters and at least 15% relative decline in DLCO parameters) over the 5-year of follow-up period [R18-4022].

Progression of SSc-ILD was also studied in the Norwegian study described under risk factors for SSc-ILD (that was not included in the meta-analysis) [R17-0145]. Patients with SSc-ILD evident on their baseline HRCT were assessed for further ILD on the follow up HRCT. At baseline, patients were categorised based on the extent of fibrosis on HRCT (0%, 1 to 20%, greater than 20%). Over the 3.1 year mean duration of follow-up, only 6 patients had an annual fibrosis progression rate greater than 10%; they included 2 of 40 (5%) patients who had at least 20% fibrosis at baseline, 4 of 157 (2.5%) patients who had 1 to 20% fibrosis at baseline and 0 of 108 (0%) of patients who had 0% fibrosis at baseline [R17-0145].

BAL parameters
In a single centre study from Italy, progression due to bronchoalveolar lavage parameters were considered as predictors of progression among 73 patients with SSc-ILD [R17-0107]. The outcome ‘progression’ was defined as worsening (greater than 1-point change) of the alveolar score or the honeycombing score on HRCT, both of which were scored 0 to 5 by 2 readers, or worsening of FVC or the DLCO (relative declines of greater than 10% and 15%, respectively) after 1-year of follow-up. Worsening honeycombing score and worsening FVC were associated with isolation of fungi in BAL fluid. Worsening DLCO was associated with the presence of CD4/CD8 ratio less than 1, the presence of eosinophils, and increasing CD19 percentage count [R17-0107].

In contrast, in a time to progression model that controlled for baseline disease parameters, no BAL parameters (cellular profile) were predictive of disease progression (defined as at least a 10% change from baseline in FVC% predicted or at least a 15% change in DLCO% predicted, with the change recorded on at least 2 visits) from in a study of 134 patients with SSc-ILD from a hospital in London, UK [R17-0136].

Measures of epithelial injury
With a hypothesis that epithelial injury is linked to the presence and progression of ILD, investigators in the UK retrospectively evaluated aspects of the clearance of inhaled DTPA, a marker of epithelial permeability (and thus, injury). Total DTPA clearance and the presence of abnormally rapid clearance of DTPA predicted a shorter time to an at least 10% decline in FVC, when controlled for baseline disease severity in 168 patients with SSc-ILD in the UK

[R18-4010]. Several other parameters were individually associated with statistically significant declines in FVC, but were no longer significant after controlling for baseline severity.

Other
The Norwegian study that was not included in the meta-analysis identified the following characteristics, present at baseline, that were associated with a decline of at least 10% FVC: pulmonary hypertension (OR [95% CI] 2.0 [1.03, 3.89]), dcSSc (vs lcSSc) (OR [95% CI] 1.9 [1.16, 3.38]) and the presence of anti-centromere an antibodies (OR [95% CI] 0.5 [0.26, 0.76]); pulmonary hypertension and the presence of anti-centromere antibodies remained significant predictors of FVC decline in the multivariate model [R17-0145].

KL-6 is a glycoprotein that is strongly expressed by both alveolar and bronchiolar epithelial cells. It is expressed following cellular injury and/or regeneration and declines with cyclophosphamide treatment. Serum KL-6 is elevated in several subtypes of ILD and is significantly higher in SSc patients with pulmonary fibrosis than in SSc alone. KL-6 predicted alveolitis in the Scleroderma Lung Study (trial, threshold 500 U/ml), “active progressive ILD” that required intervention (threshold 1000 U/ml) and death during follow-up (threshold 1000 U/ml) [R18-4021]. A single institution study from Japan followed 50 patients who had early stage SSc-ILD and no prior ILD treatment; patients were followed for an average of 14.5 (SD 5.4) years [R17-0298]. Baseline serum KL-6 was predictive of end stage pulmonary disease. Baseline serum KL-6 levels of at least 1273 U/ml had the best discriminating capacity to identify patients who would go on to develop end stage pulmonary disease ($p<0.0001$). Serial measures are not yet standard of care [R17-3833].

SI.Table 26 Predictors of progression among patients with SSc-ILD (univariate analyses)

Predictor Variable	Reference	N	Outcome	Measure of association	p-value
Radiological parameters					
Honeycombing	Lopes (2011)/[R18-4022]	35	FVC decline	Honeycombing present: FVC decline 0.45 +/- 0.05 L Honeycombing absent: FVC decline 0.16 +/- 0.02 L	0.0001
Honeycombing	Lopes (2011)/[R18-4022]	35	FVC% decline	Honeycombing present: FVC decline 14.77 +/- 2.12 L Honeycombing absent: FVC decline 3.94 +/- 0.91 L	0.0001
Bronchoscopic parameters					
Presence of alveolitis (BAL)	De Santis (2012)/ [R17-0107]	73	Worsening honeycombing score	Alveolitis present: 51.4% Alveolitis absent: 22.2%	0.01
Positive culture (BAL)	De Santis (2012)/ [R17-0107]	73	FVC decline	Positive culture: FEC decline 30.0% Negative culture: FVC decline 7.5%	0.02
Presence of fungus (BAL)	De Santis (2012)/ [R17-0107]	73	Worsening honeycombing score	OR (95% CI): 12.0 (1.4, 106.3)	<0.05
Presence of fungus (BAL)	De Santis (2012)/ [R17-0107]	73	Worsening FVC	OR (95% CI): 44.0 (3.6, 530.5)	<0.05
SSc-related parameters					
Oesophageal diameter	Winstone (2018)/ [R18-3760]	145	Worsening fibrosis score (HRCT) over 1 year	1 cm increase = 1.8% increase in score	0.02
Presence of hiatal hernia	Winstone (2018)/ [R18-3760]	145	Worsening fibrosis score (HRCT) over 1 year	Hiatal hernia present: Score 3.94% higher	0.02
Presence of pulmonary hypertension	Hoffmann Vold (2015)/ [R17-0145]	305[a]	FVC decline >10% at follow-up	OR (95% CI): 2.0 (1.03, 3.89)	0.040

SI.Table 26 (cont'd) Predictors of progression among patients with SSc-ILD (univariate analyses)

Predictor variable	Reference	N	Outcome	Measure of association	p-value
Diffuse cutaneous SSc	Hoffmann Vold (2015)/ [R17-0145]	305[a]	FVC decline >10% at follow-up	OR (95% CI): 1.9 (1.16, 3.38)	0.013
Presence of anticentromere antibodies	Hoffmann Vold (2015)/ [R17-0145]	305[a]	FVC decline >10% at follow-up	OR (95% CI): 0.5 (0.26, 0.76)	0.003
Other parameters					
DTPA[a] rapid total clearance	Goh (2011)/ [R18-4010]	168	Time to FVC decline	HR (95% CI): 1.02 (1.01, 1.03)	0.001
DTPA[a] abnormal clearance	Goh (2011)/ [R18-4010]	168	Time to FVC decline	HR (95% CI): 2.1 (1.25, 3.53)	0.005
DTPA[a] rapid fast clearance	Goh (2011)/ [R18-4010]	168	Time to FVC decline	HR (95% CI): 1.15 (1.04, 1.28)	<0.01
DTPA[a] % fast component	Goh (2011)/ [R18-4010]	168	Time to FVC decline	HR (95% CI): 1.02 (1.00, 1.04)	0.02
DTPA[a] rapid total clearance in mild disease	Goh (2011)/ [R18-4010]	168	Time to FVC decline	HR (95% CI): 1.01 (1.00, 1.03)	0.02
DTPA[a] rapid total clearance in extensive disease	Goh (2011)/ [R18-4010]	168	Time to FVC decline	HR (95% CI): 1.03 (1.00, 1.06)	<0.05
DTPA[a] abnormally rapid clearance in mild disease	Goh (2011)/ [R18-4010]	168	Time to FVC decline	HR (95% CI): 1.01 (1.01, 3.19)	<0.05
DTPA[a] speed of total clearance	Goh (2011)/ [R18-4010]	168	Rate of FVC decline	Correlation: r=0.17	0.03

[a] Regression used all patients with SSc (n=305), not patients with SSc-ILD (n=197)

SI.3.4 The main existing treatment options

SI.3.4.1 International guidelines

The latest update of the EULAR treatment guidelines for SSc were published in 2017 [R17-3833]. Treatment of SSc in general is reviewed in Section SI.2.4.1; the guidelines below address only SSc-ILD specific treatment, and are a subset of the guidelines for the treatment of SSc.

Patients with SSc-ILD are considered candidates for pharmacotherapy if they have at least 20% fibrosis on HRCT, or have between 10% and 30% fibrosis on HRCT and an FVC of less than 70%, or decreased pulmonary functional assessment for at least 12 months follow-up (regardless of extent of lung involvement). In these patients, cyclophosphamide was recommended, especially for patients with SSc with progressive ILD [R17-3833]. This recommendation was based on data from 2 randomised, placebo-controlled trials. Over 12 months, compared with placebo, patients who received cyclophosphamide experienced less decrease in lung volumes (FVC, total lung capacity), improved dyspnoea score (transitional dyspnoea index) and quality of life (Health Assessment Questionnaire disability index and the vitality and health-transition domains of the SF-36), although no significant effect on DLCO was demonstrated. In the second trial, 45 patients with SSc-ILD were randomised to a 6-month regimen of monthly cyclophosphamide infusion followed by azathioprine for 6 months. Patients randomised to cyclophosphamide experienced a mean adjusted difference in FVC of 4.2%, which was not statistically significant. Like the Scleroderma Lung Study, DLCO did not improve with cyclophosphamide treatment. The beneficial effect of cyclophosphamide in the 2 trials was mainly due to inhibition of progression of SSc-ILD. Though the trials were small, they were considered of high-quality by the guideline reviewers. Although other immunosuppressant therapy (mycophenolate, azathioprine, methotrexate) is used to treat various manifestations of SSc (skin, primarily), cyclophosphamide is the only recommended pharmacological therapy for SSc-ILD based on Scleroderma Lung Study results.

Additionally, haematopoietic stem cell transplantation for selected patients with rapidly progressive SSc (not necessarily SSc-ILD) who are in danger of organ failure is recommended and may be considered for patients who are unresponsive to pharmacotherapy.

The British Society for Rheumatology and British Health Professionals in Rheumatology guidelines for the treatment of systemic sclerosis were updated in 2016. Recommendations for patients with progressing SSc-ILD include cyclophosphamide (intravenously) and, if an alternative is needed, mycophenolate [R18-2801].

SI.3.4.2 Drug utilisation patterns

Observational data from the EUSTAR cohort (2004 to 2014) described immunosuppressant therapy among 3778 patients with SSc-ILD. A large proportion (29%) of patients with SSc-ILD had never received immunosuppressant therapy, including 34% of patients with the dcSSc subtype. Immunosuppressant therapies patients were most commonly treated with

(ever used) included glucocorticoids (58%), cyclophosphamide (19.1%), azathioprine (15.0%), methotrexate (14.7%), and mycophenolate (13.1%). Patients commonly received monotherapy (34.0%) or combination therapy with 2 immunosuppressants (32.4%), and only 4.5% of patients ever used a regimen that contained more than 2 immunosuppressants [R18-0427].

The treatments described in the table below suggest that, in several cohorts, fewer than half of patients with SSc-ILD were treated. The exception was a cohort from Japan in which 77% of patients received drug treatment, which had a large proportion of patients who received corticosteroid monotherapy [R18-3757]. The available data appear to primarily address SSc-ILD-related treatment and available data are insufficient to properly assess or summarise. It is not clear from available data whether there is undertreatment of patients or with SSc-ILD or whether providers were highly selective about treatment, as the guidelines suggest is prudent.

SI.Table 27 Pharmacotherapy among patients with SSc-ILD

Country/region	Study period	Sample size, n	Study population	Treatment	%
Italy/De Santis (2012)/ [R17-0107]	2003 to 2005	73	Single centre retrospective series patients with SSc-ILD	In the 3 years prior to BAL Cyclophosphamide + Azathioprine Azathioprine Corticosteroids	 12.3 19.2 0
UK/Goh (2017)/[R17-1625]	1990 to 1999	141	Single centre with prospective clinical protocol, patients with SSc-ILD who had no overlapping connective tissue disorder, were not current smokers and underwent BAL (of the n=212 patients in the overall study)	Active treatment at time of BAL	46
US/Morisset (2017)/ [R18-2984]	NR	225	Retrospective review from 2 centres with ILD specialty clinics, patients had rheumatologist confirmed SSc and ILD based on HRCT or lung biopsy	At baseline visit[a] Immunosuppressive therapy Prednisone Cyclophosphamide Mycophenolate Vasodilators	 47 37 9 28 9
Australia/Moore (2103)/ [R18-4019]	NR	162	Multicentre cohort study (Australia), patients with SSc-ILD	Over the course of follow-up[b] Prednisolone Cyclophosphamide IV Cyclophosphamide PO Azathioprine Mycophenolate Methotrexate Endothelin receptor antagonist	 37 9 6 16 13 12 9

SI.Table 27 (cont'd) Pharmacotherapy among patients with SSc-ILD

Country/region	Study period	Sample size, n	Study population	Treatment	%
Japan/Ando (2013)/ [R18-4003]	1996 to 2009	71	Single centre retrospective series, patients with SSc-ILD	Any SSc-ILD Treatment at Baseline	29.5
				Cyclophosphamide	8.5
				Prednisolone	19.7
				Tacrolimus	1.4
Japan/Okamoto (2016)/ [R18-3757]	1990 to 2010	35	Single centre retrospective review, patients with SSc-ILD and no infection, heart failure or hypersensitivity pneumonia	Treatment during the follow up period[c]	
				Corticosteroid alone	46
				Corticosteroid with cyclosporine	23
				Cyclophosphamide	9
				Azathioprine	3
				Mizoribine	3
				No treatment	23
Thailand/Patiwetwitoon (2012)/[R18-4029]	2005 to 2010	71	Single centre retrospective review, patients with SSc and clinically suspected ILD or pulmonary fibrosis warranting HRCT	Current medications at baseline	
				Cyclophosphamide	21
				Azathioprine	7
				Prednisolone	38
				Proton pump inhibitor	55
				Promotility drug	31

[a] Denominator 196 for immunosuppressants and 225 for vasodilators

[b] Follow-up for the cohort lasted mean (SD) of 3.5 (2.9) years

[c] Authors explicitly delineated that 8 patients received no treatment, the total number of treatment regimens does not add up (sums to 37 patients, not 35, thus the percentages sum to 107%)

SI.3.5 Natural history of the indicated condition in the population, including mortality and morbidity

Up to 90% of patients with SSc will have interstitial abnormalities on HRCT and 40–75% will experience ILD-related declines in pulmonary function [P15-00686]. It is associated with significant morbidity and, since treatment with angiotensin converting enzyme inhibitors substantially reduced mortality from scleroderma renal crisis, SSc-ILD is one of the major causes of mortality in patients with SSc [P15-00686, R18-2984, R18-4016]. The course of SSc-ILD is heterogeneous, with some patients experiencing rapidly progressive disease and others experiencing a more chronic stable course [R18-2984]. The progression of SSc-ILD is manifested by increasing respiratory symptoms, worsening pulmonary function test results, progressive fibrosis on HRCT, acute respiratory decline, or death.

SI.3.5.1 Mortality and morbidity

A 2014 systematic review identified 14 studies that evaluated predictors of mortality that were published between 2000 and 2013 [R17-0354]. The applicable studies from that review (e.g. published after 2007 and including only observational cohorts of patients with SSc-ILD), as well as newer publications, are included in SI.Table 28. In this table, the variables listed were all predictors of mortality in univariate analyses, yet few were independent predictors of mortality in multivariate models. These included baseline DLCO, baseline fibrosis severity scores, and the presence of pulmonary hypertension. Age, lower oxygen saturation, and higher neutrophil counts from bronchoalveolar lavage were independently associated with increased mortality in at least 1 study.

Several of the SSc-ILD cohorts identified for this review reported 3-year survival approximately 85% to 90% [R17-0107, R18-2984, R18-4019]. Median survival, reported in 2 North American cohorts, was 9.5 years [R18-4031] and 11.2 years [R18-3760] (see SI.Table 29). Causes of death in patients with SSc-ILD, when reported in these cohorts, were predominantly respiratory or related to progressive disease.

3 reports of SSc-ILD-related mortality were published by the same research group in the UK [R15-6265, R17-0316, R18-4010]. The research cohort included 330 SSc-ILD patients from the Royal Brompton Hospital (London) enrolled between 1990 and 1999. The primary report [R15-6265] used data from 305 patients to test a risk prediction tool categorising limited and extensive SSc-ILD as a predictor of disease of disease progression. 10-year survival was 59%. Most of the predictors of mortality in SI.Table 28 come from this report. Mortality was associated with baseline DLCO (HR [95% CI]: 0.95 [0.94, 0.97]), the extent of disease on HRCT (for extent >20% HR [95% CI]: 2.48 [1.57, 3.92]); see SI.Table 28 for other thresholds), the extent of the reticular pattern on HRCT (HR [95% CI]: 1.05 [1.03, 1.07), and the presence of pulmonary hypertension HR [95% CI]: 1.15 [1.06, 5.25]) [R15-6265]. Another report used a smaller subset of non-smoking patients with SSc-ILD (n=212) to test whether BAL parameters predicted mortality [R17-0136]. Overall mortality was associated with neutrophilia on BAL (neutrophils >4%, a marker for alveolitis) (HR [95%CI]: 2.23 [1.20, 4.14]) on univariate analysis, but not in multivariate models that controlled for disease severity. Early mortality (within 2 years of presentation) was associated with neutrophilia on

BAL (HR [95% CI]: 8.40 [1.91, 36.95]) independent of disease severity. The authors concluded that BAL findings provided limited prognostic information in SSc-ILD [R17-0136]. Last, to test whether markers of epithelial injury predicted SSc-ILD progression or mortality, investigators evaluated aspects of the clearance of DTPA, a marker of epithelial permeability (and thus, injury) in 168 members of the cohort. Mortality was associated with increasingly rapid total clearance (HR [95% CI]: 1.02 [1.00, 1.03]), but the association was no longer significant when adjusted for other relevant factors, including baseline severity of disease [R18-4010].

In a study that used data from the 595 patients in the Spanish Scleroderma Study Group with SSc-ILD, mortality was associated with gender (OR [95% CI] for women compared to men: 0.5 [0.31, 0.80]), poor pulmonary function at baseline (OR [95% CI] for FVC% <70%: 1.49 [1.01, 2.19]) and the presence of numerous indicators of cardiac involvement (see SI.Table 28). Additionally, older age at diagnosis and with lower DLCO% at baseline were also predictive of mortality [R18-2499].

3-year survival among 73 patients with SSc-ILD from a clinic in Italy was 87.7%, and 6 of 9 deaths were respiratory in nature (see SI.Table 29). Mortality in this cohort was related to having dcSSc subtype (HR [95% CI]: 10.7 [2.1, 56.0]), which was the only factor that was an independent risk factor for mortality after adjustment for other covariates. Other univariate predictors of mortality included baseline alveolar and honeycombing scores, the occurrence of bilateral honeycombing, and BAL neutrophil percentage count (estimates not provided) [R17-0107].

Mortality data from 70 patients with SSc-ILD from 2 ILD clinics in the US suggested a 4-year survival of 59% (29 deaths). Death or lung transplant was predicted by a ratio of pulmonary artery to aortic artery size of greater than 1.1 (HR [95% C]: 3.30 [1.77, 6.35]), and higher values for DLCO%, FVC% and BMI were protective: DLCO% (HR [95% CI]: 0.93 [0.89, 0.96]), FVC% (HR [95% CI]: 0.98 [0.96, 1.0]), and BMI, HR (95% CI): 0.89 (0.83, 0.93). As a tertiary referral centre, many patients were seen for lung transplant evaluation; patients with advanced disease may have contributed to selection bias in the study [R17-1626].

Data from patients with SSc-ILD from 2 large ILD clinics in the US were used in another study that evaluated a risk prediction model as a predictor of mortality. The model (SADL model) including variables for smoking history, age, and DLCO%, was developed in a derivation cohort of 137 patients from the University of California, San Francisco clinic and was predictive of mortality in the validation cohort of 72 patients from the Mayo Clinic. In the University of California, San Francisco clinic, 1-, 2-, and 3-year survival (95% CI) was 95.5% (88.6, 98.3), 93.0% (85.0, 96.8) and 85.8% (75.6, 91.9). In the Mayo clinic, 70% of deaths were attributed to respiratory causes [R18-2984].

83 patients who received care at an ILD clinic in Denver, CO underwent cardiopulmonary exercise testing to assess whether measures of oxygenation were prognostic for SSc-ILD mortality. Median survival in this cohort was 9.5 years (interquartile range: 4, 16) and

20-year survival was 53% (39 deaths). Measures of oxygen saturation were predictive of mortality over the median 10.3 years of follow up (see SI.Table 28) [R18-4031].

Researchers in Canada evaluated the association of oesophageal measures (obtained using HRCT) with mortality over 4 years among 145 patients with SSc-ILD who received care at a hospital in Vancouver. In this cohort, the crude 4-year mortality rate was 26.9% and the median survival was 11.2 years. Larger oesophageal diameter predicted mortality HR [95% CI]: 1.36 [1.15, 1.61]) and remained an independent predictor after multivariate control for baseline demographic and severity variables. The presence of hiatal hernia was also a univariate predictor of mortality that did not remain significant after adjustment [R18-3760].

In a study from Japan that included 35 patients with SSc-ILD, 12 deaths occurred (crude mortality rate 34%) during follow up (median 7.9 years). Factors that were associated with overall mortality included: age (threshold 58 years, RR [95% CI]: 10.6 [2.0, 194.9]), HRCT pattern consistent with usual interstitial pneumonia (RR [95% CI]: 13.0 [2.4, 240.3]), ground glass attenuations with traction bronchiectasis (cut-off at least 17.5, RR [95% CI]: 7.6 [1.5, 35.8]), and a history of a complicated acute exacerbation (defined as all of the following: unexplained worsening or development of dyspnoea within 30 days, new bilateral ground glass attenuation or consolidation superimposed on a background reticular or honeycomb pattern, no evidence of pulmonary infection and no other identifiable causes, RR [95% CI]: 6.1 [1.6, 20.6]). Treatment with immunosuppressants (including cyclosporine A/ cyclophosphamide/azathioprine/mizoribine) was associated with longer survival (RR [95% CI]: 0.2 [0.03, 0.9]) [R18-3757].

In a multicentre study that used patient data from the 172 patients with SSc-ILD in the Australia Scleroderma Cohort Study, patients were followed for a mean of 3.5 years (SD, 2.9), during which 19 deaths occurred (crude mortality rate 11%) [R18-4019].

SI.Table 28 Predictors of mortality among patients with SSc-ILD

Predictor variable	Reference/ country	N	Mortality outcome	Measure of association	p-value
Patient specific parameters					
Gender, males vs females	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 1.98 (1.20, 3.26)	<0.01
Gender, females vs males	Sánchez-Cano (2018)/Spain/ [R18-2499]	595	Mortality	OR (95% CI): 0.5 (0.31, 0.80)	0.005
Age 58 years or older vs younger	Okamoto (2016)/ Japan/[R18-3757]	35	Mortality	RR (95% CI): 10.6 (2.0, 194.9)	0.0053
Age, continuous	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 1.03 (1.01, 1.05)	0.001
BMI, continuous	Gleason (2017)/ US/[R17-1626]	70	Mortality/transplant	HR (95% CI): 0.888 (0.829, 0.925)	0.001
ILD-specific parameters					
Physiologic variables					
FVC, continuous	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 0.99 (0.97, 1.05)	<0.01
Threshold FVC% <60	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 1.92 (1.14, 3.23)	0.01
Threshold FVC% <65	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 1.78 (1.11, 2.85)	0.02
Threshold FVC% <70	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 2.11 (1.34, 3.32)	0.001

SI.Table 28 (cont'd) Predictors of mortality among patients with SSc-ILD

Predictor variable	Reference/ country	N	Mortality outcome	Measure of association	p-value
Threshold FVC% <75	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 1.93 (1.22, 3.05)	0.005
Threshold FVC% <80	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 1.62 (1.00, 2.60)	0.05
FVC%, continuous	Gleason (2017)/ UK/[R17-1626]	70	Mortality/transplant	HR (95% CI): 0.978 (0.958, 0.998)	0.028
FVC% <70	Sánchez-Cano (2018)/Spain/ [R18-2499]	595	Mortality	OR (95% CI): 1.49 (1.01, 2.19)	0.047
DLCO, continuous	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 0.95 (0.94, 0.97)	<0.0005
DLCO%, continuous	Gleason (2017)/ US	70	Mortality/transplant	HR (95% CI): 0.925 (0.890, 0.961)	<0.001
FEV1, continuous	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 0.98 (0.97, 0.99)	<0.01
Maximum exercise peripheral oxygen saturation, <89% vs at least 89%	Swigris (2009)/ US/[R18-4031]	83	Mortality	HR (95% CI): 2.4 (1.2, 4.9)	0.02
Maximum exercise peripheral oxygen saturation, fall of at least 4 points from baseline	Swigris (2009)/ US/[R18-4031]	83	Mortality	HR (95% CI): 2.4 (1.1, 5.0)	0.02
Difference between exercise peripheral and arterial oxygen saturations, continuous	Swigris (2009)/ US/[R18-4031]	83	Mortality	HR (95% CI): 1.08 (1.03, 1.14)	0.02

SI.Table 28 (cont'd) Predictors of mortality among patients with SSc-ILD

Predictor variable	Reference/ country	N	Mortality outcome	Measure of association	p-value
Radiological variables					
Threshold extent of disease >15%	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 2.05 (1.30, 3.23)	0.002
Threshold extent of disease >20%	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 2.48 (1.57, 3.92)	<0.0005
Threshold extent of disease >25%	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 2.31 (1.43, 3.72)	0.001
Threshold extent of disease >30%	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 2.86 (1.72, 4.76)	<0.0005
Threshold extent of disease >35%	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 2.80 (1.53, 5.15)	0.001
Threshold extent of disease >40%	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 2.79 (1.38, 5.64)	0.004
Extent of reticular pattern, continuous	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 1.05 (1.03, 1.07)	<0.0005
Proportion of ground glass, continuous	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 0.99 (0.98, 0.99)	0.001
Coarseness of reticulation	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 1.15 (1.06, 5.25)	0.001
Ratio of pulmonary artery to aortic artery at least 1.1, vs not	Gleason (2017)/ US/[R17-1626]	70	Mortality/transplant	HR (95% CI): 3.30 (1.772, 6.349)	<0.001
Usual interstitial pneumonia pattern vs not	Okamoto (2016)/ Japan/[R18-3757]	35	Mortality	RR (95% CI): 13.0 (2.4, 240.3)	0.0016

SI.Table 28 (cont'd) Predictors of mortality among patients with SSc-ILD

Predictor variable	Reference/ country	N	Mortality outcome	Measure of association	p-value
Ground glass attenuation with traction bronchiectasis (cut-off at least 17.5)	Okamoto (2016)/ Japan/[R18-3757]	35	Mortality	RR (95% CI): 7.6 (1.5, 35.8)	0.0022
Larger oesophageal diameter, per 1 cm increase	Winstone (2018)/ Canada/[R18-3760]	135	Mortality	HR (95% CI): 1.36 (1.15, 1.61)	<0.001
Hiatal hernia, presence	Winstone (2018)/ Canada/[R18-3760]	135	Mortality	NR	0.01
Alveolar score at baseline, continuous	De Santis (2012)/ Italy/[R17-0107]	73	3-year mortality	NR	0.035
Honeycombing score at baseline, increase in category	De Santis (2012)/ Italy/[R17-0107]	73	3-year mortality	NR	0.014
Occurrence of bilateral honeycombing, presence	De Santis (2012)/ Italy/[R17-0107]	73	3-year mortality	NR	0.045
Bronchoscopic variables					
% neutrophils, continuous	De Santis (2012)/ Italy/[R17-0107]	73	Mortality	NR	0.007
Neutrophils >4%[a], presence	Goh (2007) / UK / [R17-0136]	212	Mortality	HR (95% CI): 2.23 (1.20, 4.14)	0.01
Neutrophils >4%[a], presence	Goh (2007)/UK/ [R17-0136]	141	Early Mortality	HR (95% CI): 8.40 (1.91, 36.95)	0.005
Other variables					
DTPA[b] increasing time to rapid total clearance	Goh (2011)/UK	168	Mortality	HR (95% CI): 1.02 (1.00, 1.03)	0.05

SI.Table 28 (cont'd) Predictors of mortality among patients with SSc-ILD

Predictor variable	Reference/ country	N	Mortality outcome	Measure of association	p-value
Treatment with Immunosuppressant, yes vs no	Okamoto (2016)/ Japan/[R18-3757]	35	Mortality	RR (95% CI): 0.2 (0.03, 0.9)	0.042
Adverse event to treatment, presence	Okamoto (2016)/ Japan/[R18-3757]	35	Mortality	RR (95% CI): 6.1 (1.6, 20.6)	0.0013
Anti-nuclear antibody positive	Sánchez-Cano (2018)/Spain/ [R18-2499]	595	Mortality	OR (95% CI): 0.39 (0.21, 0.71)	0.003
SSc-related variables					
Diffuse vs limited cutaneous SSc	De Santis (2012)/ Italy/[R17-0107]	73	Mortality	HR (95% CI): 10.7 (2.1, 56.0)	0.001
Pulmonary (artery) hypertension, presence	Goh (2008)/UK/ [R15-6265]	215	Mortality	HR (95% CI): 1.15 (1.06, 5.25)	0.001
Pulmonary (artery) Hypertension, presence	De Santis (2012)/ Italy/[R17-0107]	73	Mortality	NR	0.048
Pulmonary artery hypertension, presence	De Santis (2012)/ Italy/[R17-0107]	73	3-year mortality	NR	0.048
Heart involvement, presence	Sánchez-Cano (2018)/Spain/ [R18-2499]	595	Mortality	OR (95% CI): 3.17 (2.16, 4.65)	<0.001
Left ventricular injection fraction less than 50%	Sánchez-Cano (2018)/Spain/ [R18-2499]	595	Mortality	OR (95% CI): 2.44 (1.19, 4.99)	0.023

SI.Table 28 (cont'd) Predictors of mortality among patients with SSc-ILD

Predictor variable	Reference/ country	N	Mortality outcome	Measure of association	p-value
Pericardial effusion, presence	Sánchez-Cano (2018)/Spain/ [R18-2499]	595	Mortality	OR (95% CI): 3.51 (2.00, 6.17)	<0.001
Ischaemic cardiomyopathy, presence	Sánchez-Cano (2018)/Spain/ [R18-2499]	595	Mortality	OR (95% CI): 1.85 (1.06, 3.24)	0.035
Conduction alteration, presence	Sánchez-Cano (2018)/Spain/ [R18-2499]	595	Mortality	OR (95% CI): 3.40 (2.05, 5.65)	<0.001
Diastolic dysfunction, presence	Sánchez-Cano (2018)/Spain/ [R18-2499]	595	Mortality	OR (95% CI): 0.54 (0.33, 0.89)	0.016
Pulmonary hypertension[c], presence	Sánchez-Cano (2018)/Spain/ [R18-2499]	595	Mortality		<0.05

[a] Neutrophils >4% was considered a marker of alveolitis in this study
[b] DTPA, a marker of epithelial injury
[c] Measured variously: presence via echocardiogram, threshold pulmonary artery pressure >40 mmHg via echocardiogram, continuous measure of pulmonary artery pressure via echocardiogram, presence via right-sided heart catheterisation, continuous measure of pulmonary artery pressure via right-sided heart catheterisation

SI.Table 29 Survival / mortality estimates and causes of death in patients with SSc-ILD

Reference	Study years	N	Survival/mortality estimates	Cause of death
European cohorts				
De Santis (2012)/ Italy/[R17-0107]	2003 to 2005	73	Crude mortality rate: 12.3% over 3 years	Lung carcinoma (n=3) Respiratory failure (n=1) Right heart failure due to PAH (n=1) Haemorrhagic alveolitis (n=1) Renal failure (n=1) Breast cancer (n=1) Gut haemorrhage (n=1)
Goh (2008)/UK/ [R15-6265]	1990 to 1999	215	10-year survival: 59%	NR
Non-European cohorts				
Gleason (2017)/US/ [R17-1626]	1999 to 2012	70	4-year survival: 59%	NR
Moore (2013)/ Australia/[R18-4019]	NR	172	Crude mortality rate: 11.0% over 3.5 (SD 2.9) years	NR
Morisset (2017)/US/ [R18-2984]	NR	135/90[a]	1-year survival (95% CI): 95.5% (88.6, 98.3)/NR 2-year survival (95% CI): 93.0% (85.0, 96.8)/NR 3-year survival (95% CI): 85.8% (75.6, 91.9)/NR	NR/70% of deaths were attributed to respiratory causes
Okamoto (2016)/ Japan/[R18-3757]	1990 to 2010	35	Crude mortality rate: 34% over median 7.9 years	Infection (n=4) Acute exacerbation of ILD (n=4) Subacute or chronic deterioration of ILD (n=2) Heart disease (n=2)
Swigris (2009)/US/ [R18-4031]	1983 to 2005	83	Median survival: 9.5 years (IQR 4, 16) 20-year survival: 53%	NR
Winstone (2018)/ Canada/[R18-3760]	1998 to 2014	145	Median survival: 11.2 years Crude mortality rate: 26.9% over median 4.0 years	NR

[a] Derivation cohort (University of California, San Francisco, California)/validation cohort (Mayo Clinic, Rochester Minnesota)

SI.3.6 Important co-morbidities

In addition to the disease manifestations and comorbidities that occur with SSc (see Section SI.2.6), important co-morbid disorders in patients with SSc-ILD include the following [P15-00686]:

- Combined ILD - pulmonary hypertension
- Gastro-oesophageal reflux and aspiration
- Infection
- Malignancy
- Respiratory muscle weakness
- COPD/emphysema
- Asthma
- Pulmonary nodules
- Cardiac involvement/heart failure
- Kidney disease/avoid nephrotoxic medications

SI.3.6.1 Supplemental information: Incidence rates of co-morbidities of the underlying diseases

As requested by the PRAC (EMEA/H/C/003821/II/0046), incidence rates of co-morbidities associated with the underlying disease are presented in the following.

SI.3.6.1.1 OPTUM CDM

The SSc-ILD patients were identified from a large US healthcare insurance data base (OPTUM CDM) in a selection period from 01 Jan 2017 to 30 Sep 2021.

To calculate the incidence rate of a co-morbidity among SSc-ILD patients, the patients will be required to meet the following criteria in the denominator.

- Had at least 2 claims with SSc diagnosis on different dates within one year as confirmed SSc diagnosis in the selection period. Had at least 2 claims with ILD diagnosis on different dates within one year as confirmed ILD diagnosis in the selection period. The latest date of the second SSc diagnosis date and the second ILD diagnosis date was the index date.
- Had at least 1-year continuous enrolment with the health plan (30 days gap allowed) prior to the index date to assess if they were truly incident patients. The 1-year period prior to index date was defined as baseline period.
- Did not have any diagnosis of the co-morbidity during the baseline period.
- Had at least 30 days continuous enrolment (follow up) after index date. The follow up period was censored at discontinued enrolment after index date, death, or end of selection period, whichever was earlier.

The incidence rate of the co-morbidity among SSc-ILD patients was calculated by dividing the number of patients with a new diagnosis of the co-morbidity by the sum of all observed person-to-event-time for all subjects in the denominator,

$$Incidence\ rate = \frac{Number\ of\ newly\ diagnosed\ comorbidity}{Sum\ of\ person - year\ at\ risk}$$

Patients with a new diagnosis of co-morbidity after index date contribute their PY at risk from index date to the first diagnosis of the co-morbidity after index date, while the other patients in the denominator contribute their PY at risk from index date to the end of follow up date.

The table below shows the number of SSc-ILD patients at risk of the co-morbidity, number of patients with newly diagnosed co-morbidity, sum of PY at risk of the co-morbidity, incidence rate of the co-morbidity and its' 95% CI.

SI.Table 30 Number of SSc-ILD patients at risk of the co-morbidity, number of patients with newly diagnosed co-morbidity, sum of PY at risk of the co-morbidity, incidence rate of the co-morbidity and 95% CI

SSC-ILD	**Adult population (≥18 years)**					**Paediatric population (<18 years)**				
Co-morbidity	**Denominator N**	**New events**	**PY**	**Incidence rate (per 100 000 PY)**	**95% CI of incidence rate**	**Denominator N**	**New events**	**PY**	**Incidence rate (per 100 000 PY)**	**95% CI of incidence rate**
Combined ILD - pulmonary hypertension	7435	1249	13 421	9307	8804.8, 9837.3	48	2	88	2268	701.3, 8190.0
Gastro-oesophageal reflux	4719	1853	6477	28610	27336.8, 29942.7	39	6	62	9631	4520.4, 20976.1
Infection	4719	972	8091	12013	11281.5, 12792.5	39	4	64	6299	2555.1, 16118.3
Malignancy	7367	849	13 766	6168	5766.7, 6596.8	48	1	91	1100	266.4, 6128.7
Respiratory muscle weakness	7846	1057	14 750	7166	6747.0, 7611.3	42	4	74	5413	2197.4, 13861.8
COPD/emphysema	7028	907	13 165	6890	6455.8, 7352.9	48	2	90	2220	686.3, 8014.6
Asthma	7542	573	14 457	3964	3652.2, 4301.7	43	8	71	11220	5772.4, 22110.2
Pulmonary nodules	8068	652	13 171	4950	4585.0, 5345.4	48	1	88	1134	266.3, 6126.1
Cardiac involvement/heart failure	6077	1748	9945	17577	16772.7, 18421.1	46	2	86	2336	723.0, 8443.1
Kidney disease	7201	1298	13 355	9719	9205.1, 10262.9	46	0	85	0	0.0, 4325.4

*OPTUM (study period: 2017-01-01 to 2021-09-30)

SI.4 PROGRESSIVE FIBROSING INTERSTITIAL LUNG DISEASE (PF-ILD)

The term ILD encompasses a large group of over 200 pulmonary disorders including IIPs and autoimmune or environmental ILDs. Although there is no universally accepted single classification of ILDs, they can generally be categorised based on:

- Aetiology: idiopathic or ILDs with known association/cause
- Clinical course: acute, subacute or chronic ILDs
- Main pathological features: inflammatory or fibrotic/fibrosing ILDs

Fibrosing ILDs can be subdivided into 3 groups based on their longitudinal disease behaviour [P18-05024]:

- Intrinsically non-progressive, e.g. drug-induced lung disease after removal of the drug or some cases of HP after removal of a trigger
- Progressive but stabilised by immunomodulation, e.g. some cases of CTD-ILDs [R14-5407, R14-4449, R18-0122, R18-1815]
- Progressive despite treatment considered appropriate in individual ILDs (chronic fibrosing ILDs with a progressive phenotype, in the following referred to as progressive fibrosing ILD, PF-ILD)

IPF is, by definition, a progressive fibrosing ILD [R18-2794, P18-04471]. Based on expert consensus, other main chronic fibrosing ILDs that may show a progressive phenotype include:

- iNSIP
- Unclassifiable IIP
- Autoimmune ILD that includes CTD-ILD (mainly RA-ILD and SSc-ILD)
- CHP
- Environmental/occupational fibrosing lung diseases

The following section aims to provide an overview of the epidemiology of non-IPF PF-ILD including patient characteristics, treatment patterns, and co-morbidities of interest. Nevertheless, the following potential limitations of the included studies have to be considered:

- Differences in the definition of clinical cases and the criteria used to diagnose ILD
- Differences in the ILDs included in each study, and how these ILDs were grouped for classification
- The majority of the included observational studies assessed relatively small samples and/or samples from very specific sub-populations
- No specific data on PF-ILD were identified and there were very limited data on fibrosing ILDs. Most studies report data in ILD not specifying which proportion qualifies as fibrosing ILD and/or PF-ILD. As such, when data on PF-ILD were not found, and data on fibrosing ILD were not found either, data on ILD overall were reported (with no regard to fibrosing or progressive nature of the ILD)
- Only studies published in English or German language were included

- Differences in healthcare systems, population characteristics, and other factors such as local treatment guidelines may limit the generalisability of findings of individual study findings across countries

SI.4.1 Incidence

No published studies were identified estimating the incidence of PF-ILD.

SI.4.2 Prevalence

There are limited data on the prevalence of PF-ILD [R18-1800]. Consequently, the prevalence of PF-ILD was estimated as follows:

1. A systematic literature review was conducted using most recent and relevant data in the US and Europe to establish the overall prevalence of ILD, as well as the prevalence of the main chronic fibrosing ILDs that may show a progressive phenotype (reported per 10 000 persons). The following inclusion criteria were defined for this systematic literature review:
   - Study design: Non-interventional studies
   - Species: Humans
   - Population: General population or ILD population
   - Outcome: Prevalence of ILD and/or main chronic fibrosing ILDs that may show a progressive phenotype or proportions of individual ILDs in the prevalent ILD population
   - Availability: Full text publications in English and German
   - Location: Studies conducted in the US and/or in Europe
   - Timeframe: Studies published between 01 Jan 1990 and September 2017

The literature review was conducted using the OVIDSP platform in MEDLINE and Embase. MESH terms and subject headings were combined with free search terms in every group of search terms. To have an exhaustive approach, the reference lists of the selected studies were examined manually to identify further potential studies of interest. In addition, a search for ‘prevalence’ and ‘interstitial lung disease’ in the online archives of the ‘American Journal of Respiratory and Critical Care Medicine’, ‘New England Journal of Medicine’ and ‘European Respiratory Journal’ for the years 2016 and 2017 was conducted to assure that no relevant publications were missed due to delay in indexing. Case reports, case series, editorials, letters and opinions were excluded from the final list of publications.

2. The proportion of the main most common chronic fibrosing ILDs that may show a progressive phenotype within the ILD population as a whole was extracted from the literature (expressed in percentage)
3. Condition-specific estimates for the proportion of patients with a progressive fibrosing phenotype were obtained through literature review. When literature was not available, a quantitative survey of 486 physicians who treat patients with ILDs (243 pulmonologists, 203 rheumatologists and 40 internists in the US, France, Germany, Italy, Spain, UK and Japan) was used to establish a benchmark for the proportion of patients within each main ILD estimated to develop a progressive fibrosing phenotype [R19-2487]

4. Overall ILD prevalence estimates; disease-specific prevalence and/or the proportion of patients with the main chronic fibrosing ILDs that may show a progressive phenotype; and estimates of the percentage who develop a progressive fibrosing phenotype were multiplied to calculate disease-specific PF-ILD prevalence estimates per 10 000 people. This process was performed based on data from studies that presented overall ILD prevalence and the prevalence and/or proportions of specific ILDs to obtain a range of likely estimates, based on data in the published literature
5. These disease-specific prevalence estimates of PF-ILD were summed to estimate overall prevalence of PF-ILD at the population level

SI.4.2.1 Overall prevalence of ILD

The ILD prevalence as a whole, reported in the 5 studies identified in the systematic literature review, ranged from 0.63 to 7.6 per 10 000 persons [R17-2810, R17-2902, R11-5060, R03-2090, R03-2075]. Only 2 studies reported data on the prevalence of fibrosing ILD specifically. 1 study in France estimated fibrotic IIP prevalence (including IPF, idiopathic NSIP, and cases with the ICD-10 code for pulmonary fibrosis) at 1.26 per 10 000 people; another older study, conducted in the US, estimated the prevalence of pulmonary fibrosis in ILD patients at 2.9 per 10 000 for men and 2.7 for women [R17-2810, R03-2075]. A summary of the studies used to obtain ILD and fibrosing ILD prevalence estimates, including the case definitions, population specifications, and ascertainment methods, is included below for the major studies that were used to estimate the prevalence of PF-ILD, shown in SI.Table 32.

Across all reported studies of ILD, the prevalence was low, and either in line with, or close to, the prevalence cut-off for an orphan indication, even without estimating the proportion of patients with a progressive fibrosing phenotype.

Proportions of the main chronic fibrosing ILDs , among ILD population overall, that may show a progressive phenotype
In addition to the overall ILD prevalence estimates, the literature was examined for the proportions of patients diagnosed with each main chronic fibrosing ILD that may show a progressive phenotype. These proportions were used in the calculation of weighted estimates for PF-ILD based on total population ILD prevalence since the proportion of patients who develop a progressive phenotype varies across different ILDs.

There were studies that provided data on both the prevalence and distribution of individual ILDs, as shown in SI.Table 32. The most common ILDs noted in these prevalence studies were IPF, HP, CTD-ILD, sarcoidosis (though most studies only evaluated patients with sarcoidosis and not specifically sarcoidosis stage IV, which corresponds to pulmonary fibrosis), and ILD associated with environmental or occupational exposures, though the exact ordering of these diagnoses, the diagnostic criteria used to obtain them, and the terms used to refer to them, varied between studies [R03-2075, R03-2090, R11-5060, R12-2817, R12-5564, R12-5582, R17-2810].

SI.4.2.1.1 IIP (iNSIP, unclassifiable IIP)

3 observational studies evaluated the prevalence of IIP in the European population. The reported prevalence estimates per 10 000 were 1.19 in France, 1.2 in Belgium, and 0.51 in Greece [R17-2810, R11-5060, R12-5564]. This variability likely reflects the different diagnostic criteria used, since studies used a variety of different guidelines (based on when they were conducted) and some criteria are more likely to characterise ILD as other types, rather than as idiopathic. The underlying populations in these studies also differed; in particular, the study in Belgium was in an area where industrial labour was a major occupation, increasing the likelihood that observed ILDs would be associated with occupational exposure.

The prevalence of iNSIP was evaluated in 2 European studies. 1 study in France based diagnoses on presence of diffuse infiltration of the lung parenchyma based on CT or HRCT, symptom duration, and confirmation by 3 clinicians based on 2011 guidelines; the estimated prevalence was 0.13 per 10 000 [R17-2810]. A second study in Greece based diagnoses on ATS/ERS 2002 criteria and provided data on the number and proportion of patients with ILDs who had various underlying conditions; these along with population estimates were used to estimate a prevalence of 0.05 per 10 000 [R11-5060].

The prevalence of unclassifiable IIP was reported by 3 European studies [R03-2090, R11-5060, R17-2810]. The prevalence ranged from 0.04 per 10 000 persons in France to 0.15 per 10 000 persons in Greece [R11-5060, R17-2810]. These studies had very different study periods so that the lower estimate in the most recent French study could also be due to the introduction of new diagnostic guidelines and tools.

SI.4.2.1.2 HP (or chronic HP)

1 study reported a prevalence of HP of 0.00 in the US [R03-2075] and 4 studies evaluated the prevalence of HP in Europe, using a variety of guidelines (depending on when and where the study was conducted), with prevalence estimates ranging from 0.05 to 0.8 per 10 000 [R17-2810, R03-2090, R11-5060, R12-5564]. The lowest prevalence in Europe was reported in a Greek study by Karakatsani and colleagues, in which expert pulmonologists of the participating sites were responsible for identifying ILDs based on actual histological and radiological reports from pathology/BAL specimens and HRCT [R11-5060]. The highest prevalence was reported in a study from Belgium which was based on standardised guidelines and conducted in a region with a high proportion of industrial labour [R12-5564].

SI.4.2.1.3 Autoimmune or CTD-ILDs

CTDs (also referred to as collagen vascular diseases) like SSc, RA, and PM/DM are frequently associated with ILD [R17-3004, R17-3005]. CTD-ILDs comprise between 19% to 34% of ILD cases, with an estimated prevalence of 0.05 to 1.02 per 10 000 [R03-2075, R03-2090, R11-5060, R17-2810, R17-3118].

SSc-ILD, like IPF, was the subject of a previous orphan designation application in the US and EU [ra00799357, ra00829480]. While prevalence was not explicitly reported in any

studies in the US or Europe, this condition appears to affect about 35.0% of patients with SSc [R16-1345, R16-1351, R16-1352, R16-1858] and SSc-ILD accounted for 4.6% of all patients with ILD, for an estimated prevalence of 0.08 per 10 000 [R11-5060].

Data on the prevalence of RA-ILD in the US and Europe are sparse; in most publications, RA-ILD is included in aggregate with other CTD-ILDs, or as a proportion of patients with RA. Coultas et al. 1994 reported a prevalence of 0.40 per 10 000 in the US [R03-2075]. This is in line with results of a Greek registry study which based diagnoses on physician diagnosis and guidelines based on ATS/ERS/WASOG 1999 criteria; data from this study allowed estimation of a prevalence of 0.08 per 10 000 [R11-5060].

Only 1 study in the US reported prevalence estimates for MCTD, PM/DM associated ILD, SjS, and SLE-ILD which were 0.06, 0.06, 0.00, and 0.17 per 10 000, respectively [R03-2075]. In Europe, a registry conducted in Greece in 2004, reported the prevalence of MCTD-ILD, SLE-ILD, SjS or PM/DM related ILD; the estimated prevalences were 0.004, 0.009, 0.009, and 0.013 people per 10 000, respectively [R11-5060]. These diagnoses were based on 2002 ATS/ERS international consensus diagnostic algorithm for IIP [R09-5338].

SI.4.2.1.4 Sarcoidosis

Sarcoidosis is among the most common ILDs reported in the literature, occurring in 11.6% to 45.8% of the overall ILD population, and with a prevalence ranging from 0.86 to 7.1 per 10 000 in the US and from 0.19 to 7.0 per 10 000 people in Europe [R03-2075, R03-2090, R11-5060, R12-5564, R17-2810, R12-5581, R12-5582, R17-2930, R17-2974, R17-2973, R17-2972]. It is important to note, however, that while sarcoidosis was commonly reported in the literature, these estimates include all stages of sarcoidosis, and are not limited to the stage IV patients that might develop the progressive phenotype. The highest sarcoidosis prevalence estimate was reported in a study from Sweden in 2013, which identified cases via the National Patient Register. Based on patients with a claim for the condition in the year 2013, the prevalence ranged from 4.7 to 7.0 per 10 000 persons for the strictest to broadest definitions, respectively. In the Greek registry, sarcoidosis was found to be the most frequent disease among the prevalent ILD cases (34.1%) [R11-5060]. A German registry is the only one that reports the different stages of sarcoidosis separately, including sarcoidosis without information on the type (8.4%), type I (37.3%), type II (47.0%), and type III (7.2%); type IV (pulmonary fibrosis) was not reported in this publication [R12-5581]. The lower proportion of sarcoidosis reported in a US registry (7.8% of ILD cases) is likely due in part to the characteristics of the registry's region, where ILDs associated with environmental and occupational exposures are likely to be more common [R03-2075].

SI.4.2.1.5 Other exposure ILDs (occupational and environmental, e.g. asbestosis, silicosis)

A wide variety of conditions are included as ILDs related to occupational or environmental exposure, including entities such as asbestosis, silicosis and, coal worker's pneumonitis. No studies were identified that estimated the prevalence of these ILDs based on the general population individually in the US and Europe. 2 studies from the US, reporting CWP, only explored prevalence among coal miners [R17-2819, R17-2817]. In Europe, 2 studies reported

data allowing calculation of aggregate prevalence of these ILDs, which occurred in 0.36 and 0.35 cases per 10 000 in Greece and Belgium, respectively [R11-5060, R03-2090].

In addition, there were several ILD studies that did not report population prevalence of ILD but assessed the proportion of prevalent ILD cases with various underlying diagnoses. The results were similar to those from the prevalence studies, with sarcoidosis (without differentiation of stage) and IPF generally the most commonly reported ILDs [R12-2817, R12-5582]. In a German ILD registry performed between (1995 to 1999) that involved 1142 patients, sarcoidosis (44.7%) was the most commonly reported condition, followed by IPF (27.0%), extrinsic allergic alveolitis (12.7%), bronchiolitis obliterans organizing pneumonia (8.1%), and others (7.4%) [R12-5582]. An Italian registry (RIPID) reported that out of 3152 ILD cases, 33.7% were sarcoidosis, 27.4% were IPF, 11.6% IIP, and a lower number of other ILDs [R12-2817]. 2 US studies based on the ILD registry of a single tertiary hospital (University of Chicago) also assessed the distribution of pre-specified ILDs [R17-3016, R17-3118]. Vij and colleagues reported that within the ILD cohort (n=200) 32% had autoimmune-featured ILD, 29% had IPF and 19% had CTD-ILD [R17-3118]. The more recent study reported a proportion of 11.5% for chronic fibrotic HP between January 2006 and February 2015 [R17-3016].

SI.4.2.1.6 Estimation of PF-ILD prevalence

The table below shows the proportions of patients expected to develop a progressive fibrosing phenotype across different ILDs. These are based on estimates from the literature and/or a survey of clinicians treating patients with ILD [R19-2487]. With the exception of IPF, which is by definition a progressive fibrosing ILD (and, therefore, 100% of patients are expected to have a progressive fibrosing phenotype), 13% to 40% of patients with other ILDs were estimated to develop a progressive fibrosing phenotype.

SI.Table 31 Estimated percentage of patients with a progressive fibrosing phenotype across different ILDs

Category	ILD subtype	Estimated % of ILD with progressive fibrosing phenotype	Source[1]
IIPs	iNSIP	32%	[R19-2487]
Exposure-related	HP	21%	[R19-2487]
Autoimmune ILDs[2]	RA-ILD	40%	[R16-5198]
	SSc-ILD	21%	[R17-0145]
	PM/DM-ILD	16%	[R17-2996]
	Sjögren's-ILD	24%	[R19-2487]
	SLE-ILD	24%	[R19-2487]
	MCTD-ILD	24%	[R19-2487]
Other systemic	Sarcoidosis	13%	[R17-2997]
Other ILDs		18%	[R19-2487]

[1] Clinician survey that included 243 pulmonologists, 203 rheumatologists, and 40 internal medicine specialists from Europe, US, and Japan [R19-2487].

[2] The estimated % of ILD with progressive fibrosing phenotype are from 2 publications which explains why the total above does not sum up to 100%.

The values in the table above were applied to the prevalence estimates for the corresponding ILDs to derive disease-specific prevalences of PF-ILD. These were summed to estimate the overall prevalence of PF-ILD at the population level. Where values for the proportion expected to develop a progressive fibrosing phenotype were not available, the value for other diseases within the same category was used.

These analyses were repeated for each study that presented overall ILD prevalence along with the proportion of patients with each specific ILD, to obtain a range of likely estimates based on data in the published literature, as shown in the table below.

SI.Table 32 Estimated prevalence of PF-ILD per 10 000 population, based on ILD prevalence studies

Study	ILD diagnosis	Proportion within overall ILD population	ILD prevalence estimate per 10 000[1]	Main analysis		Sensitivity analysis	
				Proportion with progressive fibrosing phenotype	PF-ILD prevalence estimate per 10 000	Proportion with progressive fibrosing phenotype	PF-ILD prevalence estimate per 10 000
US [R03-2075]	IPF	22.5%	1.67	100%	1.70	100%	1.70
	HP	0.0%	0.00	21%	0.00	42%	0.00
	RA-ILD	5.4%	0.40	40%	0.16	80%	0.32
	SSc-ILD	3.5%	0.26	21%	0.05	42%	0.11
	PM/DM-ILD	0.8%	0.06	16%	0.01	32%	0.02
	Sjögren's - ILD	0.0%	0.00	24%	0.00	48%	0.00
	SLE-ILD	2.3%	0.17	24%	0.04	48%	0.08
	MCTD-ILD	0.8%	0.06	24%	0.01	48%	0.03
	Sarcoidosis	11.6%	0.86	13%	0.11	26%	0.22
	Other ILDs	53.1%	3.95	18%	0.71	36%	1.42
	Total		**7.43**		**2.80**		**3.90**
Greece [R11-5060]	IPF	19.5%	0.34	100%	0.34	100%	0.34
	iNSIP	2.8%	0.05	32%	0.02	64%	0.03
	HP	2.6%	0.05	21%	0.01	42%	0.02
	RA-ILD	4.4%	0.08	40%	0.03	80%	0.06
	SSc-ILD	4.6%	0.08	21%	0.02	42%	0.03
	PM/DM-ILD	0.7%	0.01	16%	0.00	32%	0.00
	Sjögren's - ILD	0.5%	0.01	24%	0.00	48%	0.00
	SLE-ILD	0.7%	0.01	24%	0.00	48%	0.00
	MCTD-ILD	0.2%	0.004	24%	0.00	48%	0.00
	Sarcoidosis	34.1%	0.59	13%	0.08	26%	0.15
	Other ILDs	29.9%	0.51	18%	0.09	36%	0.18
	Total		**1.73**		**0.59**		**0.84**

SI.Table 32 (cont'd) Estimated prevalence of PF-ILD per 10 000 population, based on ILD prevalence studies

Study	ILD diagnosis	Proportion within overall ILD population	ILD prevalence estimate per 10 000[1]	Main analysis		Sensitivity analysis	
				Proportion with progressive fibrosing phenotype	PF-ILD prevalence estimate per 10 000	Proportion with progressive fibrosing phenotype	PF-ILD prevalence estimate per 10 000
Belgium [R03-2090]	IPF	20%	0.13	100%	0.13	100%	0.13
	HP	13%	0.08	21%	0.02	42%	0.03
	CTD-ILD	7%	0.05	24%	0.01	48%	0.02
	Sarcoidosis	31%	0.19	13%	0.02	26%	0.05
	Other ILDs	29%	0.18	18%	0.03	36%	0.07
	Total		**0.63**		**0.22**		**0.30**
France [R17-2810]	IPF	11.5%	0.88	100%	0.88	100%	0.88
	iNSIP	1.7%	0.13	32%	0.04	64%	0.08
	HP	2.4%	0.18	21%	0.04	42%	0.08
	CTD-ILD	13.4%	1.02	24%	0.24	48%	0.49
	Sarcoidosis	45.8%	3.48	13%	0.45	26%	0.90
	Other ILDs	25.2%	1.91	18%	0.34	36%	0.69
	Total		**7.60**		**2.00**		**3.12**

[1] Prevalences of individual ILDs are either obtained directly from the publication [R11-5060, R03-2090] or calculated based on applying the proportion of cases of that specific ILD in the overall ILD prevalence estimate reported in the publication [R03-2075, R17-2810].

In summary: The prevalence estimates for PF-ILD in Europe range from 0.22 per 10 000 in Belgium to 2.00 per 10 000 in France based on the main analysis; in the US the prevalence is estimated at 2.80 per 10 000.

SI.4.3 Demographics of patients with PF-ILD – age, gender, racial and/or ethnic origin and risk factors for the disease

SI.4.3.1 Demographics

Published literature on demographics of patients with PF-ILD is very limited. Data presented in this chapter derive from small studies pertaining to the main ILDs that may show a progressive fibrosing phenotype, which include CTD-ILDs, HP, sarcoidosis, IIP (including iNSIP and unclassifiable IIPs), and ILDs associated with environmental or occupational exposure. For the CTD-ILDs, data are presented for the most common: RA-ILD, PM/DM-ILD, SjS-ILD, MCTD-ILD, and SLE-ILD. Data on SSc-ILD has not been included in this section as it is presented separately. Most of the studies identified consisted of small sample sizes and recruited patients in specialised or referral healthcare institutions and therefore may

not be representative of the populations with PF-ILD. Additionally, differences in the study methods including the case definition of ILD and the selection criteria for the study population may have contributed to the variability in the study results.

Data on age and gender are presented in addition from 1 large unpublished US claims database study completed in 2019 that analysed data on 49 377 patients with incident PF-ILD from 2011 to 2015.

SI.4.3.2 Age

In a large US claims database study completed in 2019 that analysed data on 49 377 patients with incident PF-ILD from 2011 to 2015, the mean age of the population was 68 years (SD 14.1) (unpublished data). A summary of the published data in individual ILDs that may show a progressive fibrosing phenotype is presented in the next sub-chapters. The average age of the study populations ranged from 35 years to 72.5 years.

SI.4.3.2.1 Autoimmune or CTD-ILDs

Data on the age distribution of patients with CTD-ILD are provided in the table below. A total of 16 studies were identified that reported on the age of patients with CTD-ILD (6 studies from Europe, 4 from the US, and 6 studies from Asia and other regions). Some studies reported the age at the time of diagnosis of ILD, while other studies reported on the age of the study participants at the time of entry into the study. The mean age (SD) of patients with CTD-ILD in studies conducted in Europe ranged from 40.5 (18.5) years to 68 years. The mean (SD) age of patients recruited in studies in the US ranged from 51 (13) years to 61 (13) years, and for studies conducted in Asia and other regions the mean (SD) age ranged from 49.0 (11.9) years to 66.3 (11.0) years. None of the studies specifically reported the age distribution of patients with fibrosing or progressive fibrosing CTD-ILD.

SI.Table 33 Age distribution in studies of patients with CTD-ILD (overall population)

Citation	Country	Study period	Number of study participants	Age [years]: mean (SD) or median (IQR)
[R03-2090]	Belgium	1992 - 1996	22	63.0 (12.6)
[R11-4826]	UK	2000 - 2009	324	68[1]
[R13-2611]	Denmark	2003 - 2009	54	58.4 (11.9)
[R14-4379]	Turkey	2007 - 2009	201	40.5 (18.5)
[R17-2810]	France	2012	138	59.4 (1.2)
[R16-0805]	France	Not indicated	29	51.6 (14.4)
[R15-3262]	US	1985 - 2011	56	59.3 (11.3)
[R16-0554]	US	1995 - 2010	89	59.3 (11.5)
[R19-0997]	US	1998 - 2002	46	51 (13)
[R19-0946]	US	2013 - 2016	12	61 (13)
[R19-1000][2]	China	1999 - 2013	288	59.7 (13.2) to 61.4 (12.1)
[R19-0993]	Japan	2006 - 2008	29	66.3 (11.0)
[R19-0941]	Saudi Arabia	2008 - 2013	67	56.8 (14.1)
R19-0988]	China	2009 - 2012	63	57.24 (1.55)
[R19-0989]	India	2012 - 2015	151	50.8 (13.8)
[R19-0948]	India	2015 - 2017	102	49.0 (11.9)

[1] The study only reported the mean without SD.

[2] The age presented separately for patients with CTD-ILD and pulmonary signs or symptoms as the initial manifestation and for patients with UCTD-ILD and extra-pulmonary signs and symptoms as the initial manifestation.

Data on the age distribution of patients with RA-ILD are provided in the table below. A total of 21 studies reported on the age of patients with RA-ILD (6 from Europe, 7 from the US; note that there were 2 studies that recruited patients from the same institution but at different study periods with different sample sizes [R16-0820, R16-0556], and 8 from Asia). The mean (SD) or median age (IQR) of patients with RA-ILD in studies conducted in Europe ranged from 61 (IQR 56-70) years to 68.5 years. The mean or median age of patients recruited in studies the US ranged from 58 (10) years to 67.3 (10) years, and for studies conducted in Asia the mean or median age ranged from 57.6 (13.2) years to 72.5 (IQR 64.0-76.3) years. 1 study, conducted in the US, included 48 patients with RA-ILD and reported that the mean age of the 23 patients with fibrotic RA-ILD was 61(11.1) years [R16-0820]. This was similar to the age of the 25 patients with non-fibrotic RA-ILD: 59 (11.1) years.

SI.Table 34 Age distribution in studies of patients with RA-ILD

Citation	Country	Study period	Number of study participants	Age [years]: mean (SD) or median (IQR)
[R14-4451]	UK	1986 - 1998	52	65 (58-71)
[R17-4283]	UK	1987 - 2012	230	64 (42-83)
[R18-0423]	Finland	2000 - 2015	59	66 (11.1)
[R17-1636]	UK	2004 - 2005	56	64 (59-72)
[R17-1163]	Denmark	2004 - 2016	679	68.5[1]
[R19-0947]	UK	Not indicated	29	61 (56-70)
[R16-0820][2]	US	1977 - 1999	48 (23 with fibrotic ILD and 25 with non-fibrotic ILD)	Fibrotic ILD (61 [11.1]) and non-fibrotic ILD (59 [11.1])
[R15-3262]	US	1985 - 2011	13	62.9 (10.8)
[R16-0556][2]	US	1995 - 2013	137	64.7 (10.6)
[R17-1635]	US	1995 - 2014	158	67.3 (60.6-73.5)
[R19-0997]	US	1998 - 2002	14	58 (10)
[R16-5198]	US	1998-2014	167	67.3 (10)
[R15-3264]	US	2001 - 2008	82	65 (10) to 69 (6)
[R18-1265]	Korea	1991 - 2008	84	62.6 (10.0)
[R19-0959]	Korea	1991 - 2011	77	59.0 (13.3)
[R11-4796]	Japan	1996 - 2009	84	65.2 (98)
[R16-2148]	Japan	2004 - 2006	18	62.43 (12.62)
[R19-0983]	China	2006-2011	83	59.60 (9.66)
[R17-0790]	China	2008 -2013	237	57.6 (13.2)
[R17-4280]	Japan	2009 - 2011	26	72.5 (64.0-76.3)
[R17-2768]	South Korea	2009 - 2017	64	63.2 (9.2)

[1] The study only reported the mean without SD.

[2] The 2 studies included patients who were recruited from the same institution but with different study periods and therefore may have an overlap in the study population.

Data on the age distribution of patients with PM/DM-ILD are provided in the table below. A total of 15 studies were identified that reported on the age of patients with PM/DM-ILD (3 studies from Europe, 4 from the US, and 8 studies from Asia; note that there were 2 studies that recruited patients from the same institution but at different study periods with different sample sizes [R19-0950, R19-0951]). The mean or median age of patients with PM/DM-ILD in studies conducted in Europe ranged from 48 (15) years to 53 years. The mean or median age of patients recruited in studies in the US ranged from 46 (11.0) years to 52.6 (14.1) years, and for studies conducted in Asia the mean or median age ranged from 46.7 (13.11) years to 57 (IQR 29 80) years. 1 study from China recruited 40 patients with PM/DM-ILD of whom

11 had rapidly progressing PM/DM-ILD. The criteria for defining rapid progression of ILD were not provided. The mean age of the rapidly progressing group was higher than that of patients without rapidly progressing disease (53.6 [9.7] years versus 48.8 [13.1] years) [R19-0951]. Another study conducted in Japan that recruited 34 patients with PM/DM-ILD reported a median age of 56.5 (IQR 38-68) years in patients who deteriorated during follow-up compared with a median age of 55 (IQR 41-76) years in patients who were stable during follow-up [R19-0951]. Deterioration was defined as the occurrence of 2 or more of the following during the follow-up period: 1) symptomatic exacerbation (e.g. dyspnoea upon exertion); 2) an increase in opacity on a chest high-resolution computed tomography (HRCT) scan; and 3) a >10% decrease in percentage of predicted forced vital capacity (%FVC) or >10 mmHg decrease in arterial oxygen tension (PaO2). Patients who did not fulfil these criteria were considered stable.

SI.Table 35 Age distribution in studies of patients with PM/DM-ILD

Citation	Country	Study period	Number of study participants	Age [years]: mean (SD) or median (IQR)
[R19-0987]	France	1994 - 2012	48	49.5 (range 18-76)
[R17-2996]	France	1995 - 2010	107	53[1]
[R19-0944]	UK	1999 - 2009	40	48 (15)
[R19-0994]	US	1985 - 2013	35	48.2 (16.9) - 44.8 (17.6)
[R17-3039]	US	1985-2014	43	46 (11.0)
[R16-0817]	US	1990 - 1998	70	52.6 (14.1)
[R19-0957]	US	1995-2010	103	49.5 (range 20.1-76.5)
[R19-0950][2]	Japan	1990 - 2012	114	56 (46, 65)
[R19-0951][2]	Japan	1990 - 2013	34	Stable patients (55 [41,76]), patients who deteriorated (56.5 [38-68])
[R19-0954]	Japan	1995 - 2013	48	ARS group (55 [37-76]) and non-ARS (55 [32-75])
[R19-0985]	Japan	2007 - 2011	16 without myositis, 20 with myositis	With myositis 51.7 (11.6), without myositis 56.7 (7.4)
[R18-0014]	China/Japan	2007 - 2016	43 (anti-MDA5 positive), 56 (anti-aaRS positive), 83 (without anti-MDA5 or anti-aaRS antibodies)	anti-MDA5 positive (49.5 [10.8]), anti-ARS positive (50.6 [9.6]), without anti-MDA5 or anti-aaRS antibodies (52.2 [14.4])
[R19-0943]	China	2010 - 2011	26	46.7 (13.11)
[R18-1437]	Japan	2011 - 2015	497	57 (29-80)
[R19-0951]	China	Not indicated	11 patients (rapidly progressing ILD), 29 patients (without)	Rapidly progressing ILD 53.6 (9.7), without 48.8 (13.1)

[1] The study only reported the mean without the standard deviation

[2] The 2 studies included patients who were recruited from the same institution but with different study periods and therefore may have an overlap in the study population.

Data on the age distribution of patients with SjS-ILD are provided in the following table. A total of 6 studies were identified that reported on the age of patients with SjS-ILD (2 studies from Europe, on1e from the US, and 3 studies from Asia). The mean or median age of patients in studies conducted in Europe ranged from 63 (range 42-81) years to 66.9 (9.5) years. The median age of patients recruited in studies in the US was 62 (range 34-78) years, and for studies conducted in Asia the mean or median age ranged from 61.3 (9.9) years to 66

(IQR 62-71) years. None of the studies specifically reported the age distribution of patients with fibrosing or progressive fibrosing SjS-ILD.

SI.Table 36 Age distribution in studies of patients with SjS-ILD

Citation	Country	Study period	Number of study participants	Age [years]:mean (SD) or median (IQR)
[R17-0461]	France	1996 - 2012	21	63 (range 42-81)
[R19-0992]	Italy	2013 - 2016	13	66.9 (9.5)
[P06-12207]	US	1992 - 2004	18	62 (range 34-78)
[R18-0583]	Japan	1998 -2008	33	66 (62-71)
[R19-0952]	China	2003 - 2012	165	61.25 (9.93)
[R19-0982]	China	2012- 2014	158	61.6 (11.3)

Data on the age distribution of patients with MCTD-ILD, and undifferentiated or unclassifiable CTD-associated ILD (UCTD-ILD) are provided in the table below. A total of 3 studies (2 from Europe and 1 from the US) that reported on the age distribution of patients with MCTD-ILD were identified. The mean age of patients with MCTD-ILD was 35 (16) years in 1 study [R18-0628] and 44.9 (95% CI 40.0-53.9) years for the other study [R19-0953] from Europe. The mean age of patients from the US study was 52 (17) years [R19-0997]. A total of 14 studies were identified that reported on the age distribution of patients with UCTD-ILD (5 from Europe, 3 from the US and 6 from Asia and other regions). The mean age of patients with UCTD-ILD ranged from 53.0 (14.6) years to 64.3 (13.6) years in studies from Europe. The mean or median age for patients recruited in the US studies ranged from 50 (IQR 31-68) years to 67.8 (12.9), and 56.4 (14.7) years to 63.6 (1.5) years in studies from Asia and other regions. None of the studies specifically reported the age distribution of patients with fibrosing or progressive fibrosing MCTD-ILD or UCTD-ILD.

SI.Table 37 Age distribution in studies of patients with MCTD-ILD or undifferentiated/unclassifiable CTD-associated ILD (UCTD-ILD)

Citation	Country	Study period	Number of study participants	Age [years]: mean (SD) or median (IQR)
MCTD-ILD				
[R19-0953]	Norway	2005 – 2008	126	44.9 (95% CI 40.0-53.9)
[R18-0628]	Norway	2005 – 2008	118	35 (16)
[R19-0997]	US	1998 – 2002	6[1]	52 (17)
Undifferentiated/unclassifiable CTD-ILD				
[P16-01479]	Denmark	2003- 2009	62	59.3 (14.5)
[R17-3007]	Denmark	2003 – 2009	105	64.3 (13.6)
[R17-2802]	Romania	2005 – 2015	27	53.0 (14.6).
[R19-0949]	Italy	2009 – 2015	52	55 (13)
[R16-0805]	France	Not indicated	32	56.5 (12.8)
[R15-3262]	US	1985 – 2011	19	59.5 (12.0)
[R16-0804]	US	2000 – 2011	132	67.8 (12.9)
[R19-0998]	US	2004 – 2006	28	50 (31-68)
[R19-0984]	Japan	1990 – 2009	22	57 (24-77)
[R19-1000][2]	China	1999 – 2013	756	61.6 (12.5) to 63.5 (10.7)
[R19-0999]	South Korea	2005 – 2012	105	59.0 (10.4)
[R19-0941]	Saudi Arabia	2008 – 2013	22	56.4 (14.7)
[R19-0988]	China	2009 – 2012	65	63.58 (1.53)
[R19-0996]	Japan	2009 – 2011	24	62.4 (9.2)

[1] Smaller and pre-2007 study included since it was the only US study identified for MCTD-ILD.

[2] The age presented separately for patients with UCTD-ILD and pulmonary signs or symptoms as the initial manifestation and for patients with UCTD-ILD and extra-pulmonary signs and symptoms as the initial manifestation.

No published studies were identified that reported on the age distribution of patients with SLE-ILD.

SI.4.3.2.2 IIP (iNSIP, unclassifiable IIP)

Data on the age distribution of patients with IIP (including iNSIP and unclassifiable IIP) are provided in the following table. A total of 13 studies were identified that reported on the age of patients with IIPs (5 studies from Europe, 2 from America [US and Canada], and 6 studies from Asia). The mean age of patients with IIP in studies conducted in Europe ranged from 52.1 (11.9) years to 63 (12) years. The mean or median age of patients recruited in studies conducted in America ranged from 54.6 (10.3) years to 67 (IQR 63-74) years, and for studies conducted in Asia and other regions the mean age ranged from 52.8 (10.4) years to 67.5 (IQR 59.0-76.0) years. 1 study from Korea recruited 72 patients with fibrotic IIPs and reported a

mean age of 54.3 (10.1) years in this patient population [R18-0595]. However, there were no published data identified that reported on the age distribution of progressive fibrosing IIP.

SI.Table 38 Age distribution in studies of patients with IIP

Citation	Country	Study period	Number of study participants	Age [years]: mean (SD) or median (IQR)
[P16-01479]	Denmark	2003 - 2009	30	53.8 (16.0)
[R17-2802]	Romania	2005 - 2015	14	57.4 (12.2)
[R14-4379]	Turkey	2007 - 2009	21	52.1 (11.9)
[R19-0949]	Italy	2009 - 2015	35	63 (12)
[R16-0805]	France	Not indicated	51	55.8 (11.5)
[R17-3227]	Canada	2006 - 2013	13	67 (63-74)
[R18-0486]	US	2008 - 2014	56	54.6 (10.3)
[R19-0984]	Japan	1990 - 2009	25	58 (38-83)
[R18-0595]	Korea	1991 - 2006	72 (fibrotic), and 11 (cellular)	Cellular: 54.4 (10.1) Fibrotic: 54.3 (10.1)
[R18-0614]	South Korea	1991 - 2008		53.8 (10.3)
[R19-1001]	Japan	1999 - 2015	98	67.5 (59.0-76.0)
[R19-0989]	India	2012 - 2015	92	55.6 (13.1)
[R19-0948]	India	2015 - 2017	74	52.8 (10.4)

SI.4.3.2.3 HP (or chronic HP)

Data on the age distribution of patients with HP are provided in the table below. A total of 19 studies were identified that reported on the age of patients with HP (6 studies from Europe, 9 from the US, and 4 studies from Asia). The mean age of patients with HP or chronic HP in studies conducted in Europe ranged from 48.6 (14.6) years to 58.5 years. The mean or median age of patients recruited in studies the US ranged from 44 (23) years to 67 (7) years, and for studies conducted in Asia the mean or median age ranged from 47.6 (13.9) years to 64 (IQR 57.0-70.5) years. 2 studies from the US reported the age of patients with fibrotic HP. 1 study recruited 72 patients with HP including 46 patients with fibrotic HP reported a mean age of 61 (13) years in these patients [R16-0557]. The patients with fibrotic HP were older than the patients with non-fibrotic HP (mean age 52 [13] years). The other study recruited 69 patients with HP, of whom 26 had fibrotic HP. The mean age in patients with fibrotic HP was 60 (12) years. There were no published data on the age distribution in patients with progressive fibrosing HP.

SI.Table 39 Age distribution in studies of patients with HP

Citation	Country	Study period	Number of study participants	Age [years]: mean (SD) or median (IQR)
[R03-2090]	Belgium	1992 - 1996	47	49.4 (14.6)
[R18-0489]	UK	2000 - 2006	92	55.1 (12.6)
[P16-01479]	Denmark	2003 - 2009	32	48.6 (14.6)
[R14-4379]	Turkey	2007 - 2009	82	51.8 (17.1)
[R17-1653]	UK	2007 - 2011	129	58.5
[R16-0805]	France	Not indicated	15	52.7 (10.3)
[R16-0557]	US	1982 - 2000	46 patients with fibrotic HP and 26 with non-fibrotic HP	Fibrotic hypersensitivity pneumonia (61 [13]) and non-fibrotic hypersensitivity pneumonia: (52 [13])
[R16-0553]	US	1997 - 2002	69	Overall: 54 (14); fibrotic patients (n=26) 60 (12)
[R17-1995]	US	2000 - 2010	177	60.76 (11.3)
[R19-0982]	US	2003 - 2013	119	60 (31-87)
[R17-4298]	US	2003 - 2014	4093	52.4 (20.1)
[R19-0945]	US	2006 - 2015	132	62.1 (11.5)
[R17-3016]	US	2006 - 2015	120	63 (10)
[R19-0946]	US	2013 - 2016	16	56 (13)
[R19-0947]	US	Not indicated	49	44 (23) - 67 (7)[1]
[R17-1654]	Japan	1994 - 2007	16	58.3[2]
[R16-2149]	Japan	2000 - 2009	222	64.0 (57.0-70.5)
[R19-0989]	India	2012 - 2015	513	56.4 (13)
[R19-0948]	India	2015 - 2017	86	47.6 (13.9)

[1] The age of the study population was presented for 3 patient populations based on pathologic patterns and include UIP-like, NSIP-like, and only periobronchiolar fibrosis.

[2] The study only reported the mean without SD.

SI.4.3.2.4 Sarcoidosis

Data on the age distribution of patients with sarcoidosis-related ILD are provided in the table below. A total of 5 studies (3 from Europe and 2 from the Asia) were identified that reported on the age of patients with sarcoidosis. The mean or median age of patients with sarcoidosis-related ILD in studies conducted in Europe ranged from 43.7 (13.8) years to 44.7 (12.5) years. The mean age of patients recruited in the 2 studies from Asia was 44.8 (11.8) years and 46.9 (11.6) years. There were no published data on the age distribution in patients with fibrosing and progressive fibrosing sarcoidosis-related ILD.

SI.Table 40 Age distribution in studies of patients with sarcoidosis-related ILD

Citation	Country	Study period	Number of study participants	Age [years]: mean (SD) or median (IQR)
[R03-2090]	Belgium	1992 -1996	112	43.7 (13.8)
[R14-4379]	Turkey	2007- 2009	771	44.7 (12.5)
[R17-2810]	France	2012	361	43.7 (15.0-89.0)
[R19-0989]	India	2012-2015	85	46.9 (11.6)
[R19-0948]	India	2015- 2017	339	44.8 (11.8)

SI.4.3.2.5 Other exposure ILDs (occupational and environmental, e.g. asbestosis, silicosis)

Data on the age distribution of patients with exposure-related ILD are provided in the table below. A total of 5 studies (1 from Europe, 1 from US, and 3 from Asia) were identified that reported on the age of patients with exposure-related ILD. The mean age of patients with exposure-related in the study conducted in Europe was 56.9 (13.5) years. The median age of patients recruited in the study from US was 35.8 (range 16.1 to 83.1) years. The mean or median age for 2 studies conducted in Asia was 42.3 (14) years and 58 (IQR 49-71) years. The third study only reported age categories, and 76.3% of the study participants were 40 years or older [R19-0991].

SI.Table 41 Age distribution in studies of patients with exposure-related ILD

Citation	Country	Study period	Number of study participants	Age [years]: mean (SD) or median (IQR) or age categories
[R14-4379]	Turkey	2007 - 2009	241	56.9 (13.5)
[R17-2819]	US	1970 - 2009	485	35.8 (range 16.1-83.1)
[R16-0834]	Japan	1999 - 2006	14	58 (49-71)
[R19-0991]	China	2006 - 2009	308	3.9% (less than <30 years), 19.8%1 (30 to 39 years), 33.44% (40 to 49 years), 37.01% (50 to 59 years) and 5.84% (greater than >60 years)
[R19-0989]	India	2012 - 2015	330	42.3 (14)

SI.4.3.3 Gender

A large US claims database study completed in 2019, which analysed data on 49 377 patients with incident PF-ILD from 2011 to 2015, reported 52.5% females (unpublished data).

A summary of the published data in individual ILDs that may show a progressive fibrosing phenotype is presented in the next sub-chapters. There were no population-based studies and therefore these studies do not confirm any real differences by gender in the incidence or prevalence of fibrosing ILDs, for example if CTD-ILD is higher in women. Most of the studies identified recruited more women than men. There were wide ranges in the proportions of women and men recruited in the studies that may reflect differences in health care access, and variation in the risk of the underlying disease by gender.

SI.4.3.3.1 Autoimmune or CTD-ILDs

Data on the gender distribution of patients with CTD-ILD are provided in the following table. There were no published data on the gender distribution in patients with fibrosing or progressive fibrosing CTD-ILD. A total of 22 studies were identified that reported on the gender of patients with CTD-ILD (7 studies from Europe, 4 from the US, and 11 studies from Asia and other regions). All studies conducted in Europe except one recruited more women than men. The percentage of women in the studies ranged from 20% to 73.1%. In the US, 1 study recruited more men, and the remaining 3 studies recruited more women. The percentage of women in the studies ranged from 44.7% to 65. In Asia and other regions, 9 studies recruited more women, whilst 2 studies recruited more men than women. The percentage of women in the studies ranged from 38.5% to 76%.

SI.Table 42 Gender distribution of published cohorts of patients with CTD-ILD

Citation	Country	Study years	Study N	Females, (%)
[R03-2090]	Belgium	1992 – 1996	362	20
[P16-01479]	Denmark	2003 – 2009	54	59.3
[R14-4379]	Turkey	2007 – 2009	201	73.1
[R17-2810]	France	2012	145	67.6
[R16-0805]	France	Not indicated	29	65.5
[R19-0944]	UK	1999 – 2009	40	70
[R13-2611]	UK	2000-2009	324	56.5
[R15-3262]	US	1985 – 2011	56	44.7
[R16-0817]	US	1990 – 1998	70	52.9
[R16-0554]	US	1995-2010	89	58
[R19-0997]	US	1998 – 2002	46	65
[R19-0950]	Japan	1990 – 2012	114	65.8
[R19-0951]	Japan	1990 – 2013	34	61.8
[R19-1000]	China	1999 – 2013	1044	45
[R19-0993]	Japan	2006 – 2008	29	69
[R18-0014]	China/Japan	2007-2016	182	70.0
[R19-0940]	Saudi Arabia	2008- 2010	57	70.2
[R19-0941]	Saudi Arabia	2008 – 2013	45	76
[R19-0988]	China	2009 – 2012	128	52.3
[R19-0943]	China	2010 – 2011	26	38.5
[R19-0989]	India	2012-2015	151	74.5
[R19-0948]	India	2015 – 2017	102	74.5

[1] The 2 studies included patients who were recruited from the same institution but with different study periods and therefore may have an overlap in the study population.

Data on the gender distribution of patients with RA-ILD are provided in the table below. A total of 20 studies were identified that reported on the gender of patients with RA-ILD (6 studies from Europe, 5 from the US, and 9 studies from Asia). All studies conducted in Europe except one [R18-0423] recruited more women than men. The percentage of women in these studies ranged from 41.5% to 70%. In the US, only 1 study had more men, 2 studies had an equal number of men and women, and 2 studies had more women; the percentage of women in these studies ranged from 49% to 56.3%. In Asia, 1 study recruited more men, another study recruited an equal number of men and women, and the remaining 7 studies recruited more women than men, with the percentage of women ranging from 48.6% to 87.5%.

SI.Table 43 Gender distribution in cohorts of patients with RA-ILD

Citation	Country	Study years	Study N	Females, (%)
[R14-4451]	UK	1986 - 1998	52	57.7
[R17-4283]	UK	1987 - 2012	230	52
[R18-0423]	Finland	2000 - 2015	59	41.5
[R17-1636]	UK	2004 - 2005	56	64
[R17-1163]	Denmark	2004 - 2016	679	54.8
[R19-0947]	UK	Not indicated	29	70
[R16-0820]	US	1977 - 1999	48	56.3
[R16-0556]	US	1995 - 2013	137	50
[R17-1635]	US	1995 - 2014	158	50
[R16-5198]	US	1998-2014	167	49
[R15-3264]	US	2001 - 2008	82	52.5
[R18-1265]	Korea	1991 - 2008	84	48.6
[R19-0959]	Korea	1991 - 2011	77	75.3
[R11-4796]	Japan	1996 - 2009	84	71.4
[R16-2148]	Japan	2004 - 2006	18	61.5
[R19-0995]	Korea	2004 - 2011	24	87.5
[R19-0983]	China	2006 - 2011	83	65.1
[R17-0790]	China	2008 -2013	237	63.7
[R17-4280]	Japan	2009 - 2011	24	50
[R17-2768]	South Korea	2009 - 2017	64	70.3

Data on the gender distribution of patients with PM/DM-ILD are provided in the following table. A total of 9 studies were identified that reported on the gender of patients with PM/DM-ILD (2 studies from Europe, 3 from the US, and 4 studies from Asia). All studies conducted in Europe recruited more women than men. The percentage of women in these studies was 59.8% and 64.6%. Similarly, in the US, all studies recruited more women than men with the percentage of women ranging from 62% to 70%. In Asia as well, all studies recruited more women than men with the percentage ranging from 55% to 82.6%.

SI.Table 44 Gender distribution in cohorts of patients with PM/DM-ILD

Citation	Country	Study years	Study N	Females, (%)
[R19-0987]	France	1994 - 2012	48	64.6
[R17-2996]	France	1995 - 2010	107	59.8
[R19-0994]	US	1985 - 2013	61	62
[R17-3039]	US	1985 - 2014	43	65
[R19-0957]	US	1995 - 2010	103	70
[R19-0954]	Japan	1995 - 2013	48	82.6
[R19-0985]	Japan	2007 - 2011	43	60.4
[R18-1437]	Japan	2011 - 2015	497	66
[R19-0951]	China	Not indicated	40	55

Data on the gender distribution of patients with SjS-ILD are provided in the table below. A total of 6 studies were identified that reported on the gender distribution of patients with SjS-ILD (2 studies from Europe, 1 from the US, and 3 studies from Asia). All studies recruited more women than men. The percentage of women in the 2 studies from Europe was 85.7% and 92.3%. In the US study, the percentage of women was 83%. In the studies from Asia, the percentage of women recruited ranged from 69.7% to 91.5%.

SI.Table 45 Gender distribution of cohorts of patients with SjS-ILD

Citation	Country	Study years	Study N	Females, (%)
[R17-0461]	France	1996 – 2012	21	85.7
[R19-0992]	Italy	2013 – 2016	13	92.3
[P06-12207]	US	1992 – 2004	18	83
[R18-0583]	Japan	1998 – 2008	33	69.7
[R19-0952]	China	2003 – 2012	165	91.5
[R19-0982]	China	2012 – 2014	158	85

Data on the gender distribution of patients with MCTD-ILD or UCTD-ILD are provided in the table below. There were 2 studies from Europe that reported on the gender distribution of patients with MCTD-ILD, both recruited more women than men (75% and 76%). There were 8 studies identified that reported on the gender distribution of patients with UCTD-ILD (2 from Europe, 1 from the US, and 5 from Asia). Both studies from Europe, and the study from the US recruited more women than men with the percentage ranging from 65.6% to 86%. Only 1 study in Asia recruited more men, whilst the other 4 studies recruited more women than men ranging from 42% to 72.4%.

SI.Table 46 Gender distribution of cohorts of patients with MCTD-ILD or UCTD-ILD

Citation	Country	Study years	Study N	Females, (%)
MCTD-related ILD				
[R19-0953]	Norway	2005 - 2008	126	75
[R18-0628]	Norway	2005 - 2008	118	76
Undifferentiated/unclassifiable CTD associated ILD				
[R19-0949]	Italy	2009 - 2015	52	86
[R16-0805]	France	Not indicated	32	65.6
[R19-0998]	US	2004 - 2006	28	68
[R19-0984]	Japan	1990 - 2009	22	63.6
[R19-1000]	China	1999 - 2013	756	60
[R19-0999]	South Korea	2005 - 2012	105	72.4
[R19-0941]	Saudi Arabia	2008 - 2013	22	64
[R19-0996]	Japan	2009 - 2011	24	42

No data were identified that reported on the gender distribution of patients with SLE-ILD.

SI.4.3.3.2 IIP (iNSIP, unclassifiable IIP)

Data on the gender distribution of patients with IIP are provided in the table below. There was a total of 18 studies that reported on the gender distribution of patients with IIP (9 from Europe, 2 from the US, and 7 from Asia). 4 of the studies in Europe recruited more men than women and the remaining 5 studies recruited more women than men (percentage of women ranged from 36.7% to 80%). In the US, 1 study recruited more men and the other more women. The percentage of women recruited in these studies were 47% and 71.4%, respectively. For studies conducted in Asia, 2 studies recruited more men whilst 5 studies recruited more women (range 38.5% to 72.1%).

SI.Table 47 Gender distribution of cohorts of patients with IIP

Citation	Country	Study years	Study N	Females, (%)
[R03-2090]	Belgium	1992 - 1996	33	49
[P16-01479]	Denmark	2003 - 2009	62	53.2
[P16-01479]	Denmark	2003 - 2009	30	53.3
[R17-3007]	Denmark	2003 - 2009	105	47
[R17-2802]	Romania	2005 - 2015	14	36.7
[R17-2802]	Romania	2005 - 2015	27	66.3
[R14-3479]	Turkey	2007 - 2009	21	66.7
[R19-0949]	Italy	2009 - 2015	35	69
[R16-0805]	France	Not indicated	51	37.3
[R16-0804]	US	2000 - 2011	132	47
[R18-0486]	US	2008 - 2014	56	71.4
[R19-0984]	Japan	1990 - 2009	25	44
[R18-0595]	Korea	1991 - 2006	83	67.5
[R18-0614]	South Korea	1991 - 2008	68	72.1
[R19-1001]	Japan	1999 - 2015	98	58.2
[R19-0993]	Japan	2006 - 2008	104	38.5
[R19-0989]	India	2012 - 2015	92	53.3
[R19-0948]	India	2015 - 2017	74	67.6

SI.4.3.3.3 HP (or chronic HP)

Data on the gender distribution of patients with HP are provided in the following table. There was a total of 17 studies that reported on the gender distribution of patients with HP (5 from Europe, 8 from the US, and 4 from Asia). 2 of the studies in Europe recruited more men and the other 3 recruited more women than men. The percentage of women recruited ranged from 35% to 60.6%. 3 studies in the US recruited more men, 1 study had an equal number of men and women, the remaining 4 studies recruited more women. The percentage of women recruited ranged from 43.9% to 69%. In Asia, only 1 of the 4 studies recruited more women. The percentage of women recruited ranged from 22% to 59.5%.

SI.Table 48 Gender distribution of cohorts of patients with HP

Citation	Country	Study years	Study N	Females, (%)
[R03-2090]	Belgium	1992 - 1996	47	35
[R18-0489]	UK	2000 - 2006	92	56.5
[P16-01479]	Denmark	2003 - 2009	32	37.5
[R19-0945]	UK	2006 - 2015	132	60.6
[R17-1653]	UK	2007 - 2011	129	59.9
[R16-0557]	US	1982 - 2000	82	43.9
[R16-0553]	US	1997 - 2002	69	64
[R17-1995]	US	2000 - 2010	177	69
[R19-0982]	US	2003-2013	119	37
[R17-4298]	US	2003 - 2014	4,093	57.6
[R17-3016]	US	2006-2015	120	58
[R19-0946]	US	2013 - 2016	28	50
[R16-0497]	US	Not indicated	49	44.9
[R17-1654]	Japan	1994 - 2007	16	22
[R16-2149]	Japan	2000 - 2009	222	45.9
[R19-0989]	India	2012-2015	513	59.5
[R19-0948]	India	2015 - 2017	86	48.8

SI.4.3.3.4 Sarcoidosis

Data on the gender distribution of patients with sarcoidosis associated-ILD are provided in the following table. There was a total of 5 studies (3 in Europe and 2 in Asia) that reported on the gender distribution of patients with sarcoidosis associated-ILD. 2 of the 3 studies in Europe recruited more women (range 48% to 69.9%), and the studies in Asia recruited more women than men (51% and 52.9%).

SI.Table 49 Gender distribution of cohorts of patients with sarcoidosis-associated ILD

Citation	Country	Study years	Study N	Females, (%)
[R03-2090]	Belgium	1992 - 1996	362	48
[R14-4379]	Turkey	2007 - 2009	771	69.9
[R17-2810]	France	2012	361	54.9
[R19-0989]	India	2012-2015	85	52.9
[R19-0948]	India	2015 - 2017	339	51

SI.4.3.3.5 Other exposure ILDs (occupational and environmental, e.g. asbestosis, silicosis)

Data on the gender distribution of patients with exposure-related ILD are provided in the table below. There was a total of 4 studies (1 in Europe, 1 in US and 2 in Asia) that reported on the gender distribution of patients with exposure-related ILD. All studies recruited more men than women. The percentage of women recruited ranged from 2.5% to 33.5%.

SI.Table 50 Gender distribution of cohorts of patients with exposure-related ILD

Citation	Country	Study years	Study N	Females, (%)
[R14-4379]	Turkey	2007 - 2009	241	5.4
[R17-2819]	US	1970-2009	11 753	2.5
[R19-0991]	China	2006 - 2009	308	33.5
[R19-0989]	India	2012 - 2015	33	6.1

SI.4.3.4 Ethnicity

Published literature on the incidence or prevalence of fibrosing ILD or PF-ILD by ethnicity was not identified.

There were 9 studies (5 from Europe and 4 from the US) that categorised patients racially or ethnically (see table below). In these studies, the majority of the study participants were from Caucasian/Non-Hispanic White populations. Only 1 of the studies identified evaluated the variation in the prevalence of ILD by ethnicity. This study was conducted in the UK and involved 40 patients with PM/DM-ILD [R19-0944]. Patients of Black ethnicity were found to have increased odds of developing ILD (OR of 3.42 (95% CI 1.35, 8.65) compared to all non-Black patients. Patients of White ethnicity had lower odds of developing ILD compared to all other ethnicities (OR 0.55, 95% CI 0.34, 0.94). These data are very limited; the effect of ethnicity/race on the incidence or prevalence of ILD remains unknown.

SI.Table 51 Race/ethnicity[1] distribution of patients with ILD

Citation	Country	Study years	Study N	Race/ethnicity, N (%)
CTD associated ILD				
[R17-2810]	France	2012	145	Europeans 46 (35.1), North Africans 35 (26.7), Afro Caribbean 37 (28.2), others 13 (9.9)
[R19-0997]	US	1998 - 2002	46	White (70), African-American (24), unknown (4), Asian/Hispanic (2)
MCTD associated ILD				
[R19-0953]	Norway	2005 - 2008	126	Caucasians (100)
PM/DM associated ILD				
[R19-0944]	UK	1999 - 2009	40	ILD was present in 15/25 (60) of Black ethnicity, 4/9 (44) of Asian ethnicity, 20/68 (29) of White ethnicity. Patients with Black ethnicity were significantly more likely to have ILD than all non-Black patients
Undifferentiated/unclassifiable CTD ILD				
[R19-0998]	US	2004 - 2006	28	White 19 (68), Black 1 (4), Hispanic 4 (14), Asian 3 (11), other 1 (4)
HP				
[R19-0945]	UK	2006 - 2015	132	Non-Hispanic Whites (84.8), Hispanic (7.6), African-Americans (5.3), Asians (2.2)
[R17-3016]	US	2006-2015	120	HP without AF: Caucasian (85.3), Hispanic (8.8), African-American (4.9), Asian (1.0) HPAF: Caucasian (72.2), Hispanic (5.6), African-American (11.1), Asian (11.1) All ILD: Caucasian (83.3)
Idiopathic ILD				
[R18-0486]	US	2008 - 2014	56	Non-Hispanic 53 (94.6), Hispanic (5.6), race white 50 (89.3), Afro-American 4 (7.1), Asian 1 (1.8), American Native or Alaskan Native 1 (1.8)
Sarcoidosis associated ILD				
[R17-2810]	France	2012	361	Europeans 95 (30.3), North Africans 87 (27.7), Afro-Caribbeans 106 (33.8), Others 26 (8.3)

[1] Race/ethnicity categories are based on what was reported in the articles.

SI.4.4 Risk factors for PF-ILD

Data on the risk factors for PF-ILD are provided in SI.Table 52. Most of the published data that was identified on the risk factors for PF-ILD were for CTD-ILDs. There were no data on risk factors identified for IIPs, HP, sarcoidosis-related ILD and exposure-related ILD. There were no population-based studies identified. Most of the studies consisted of small sample sizes and recruited patients from specialised or referral health care institutions and therefore may not be representative. Additionally, the studies did not indicate whether the study participants were incident or prevalent cases. Furthermore, differences in the study methods including the case definition of ILD and progression of disease, and the selection criteria for the study populations limit the ability to compare results across the studies.

SI.4.4.1 Autoimmune or CTD-ILDs

Several studies reported the risk factors for disease progression in patients with CTD-ILDs.

2 risk factors were identified for progression of RA-ILD including a low baseline TLCO at diagnosis [R19-0947, R17-1636, R16-5198] and the presence of a UIP pattern [R17-1636, R16-5198, R18-1265].

In patients with PM/DM-ILD factors that were associated with disease progression included older age [R17-2996], lower median values of FVC [R17-2996, R19-0951] and DLCO [R17-2996] at initial ILD diagnosis, elevated CRP >50 µg/L levels [R19-0951], high levels of serum ferritin >2000 µg/L [R19-0951], decreased counts of lymphocytes <500/µL [R19-0951], the presence of a UIP pattern [R17-2996], presence of anti-MDA5 antibodies [R19-0943, R18-0014, R19-0994, R19-0951], and positive tests for anti-PL-7 [R19-0951].

In patients with SjS-ILD, factors associated with disease progression were older age and oesophageal involvement [R17-0461].

In patients with MCTD-ILD, male gender, elevated anti-RNP antibody titre (per 50 U/L increase), and presence of anti-ro-52 antibodies were associated with disease progression [R18-0628].

No studies were identified that reported the risk factors for disease progression in patients with SLE-ILD.

SI.4.4.2 IIP (iNSIP, unclassifiable IIP)

The risk factors for disease progression in patients with IIP were lower baseline DLCO and a higher fibrosis score on HRCT [R16-0804].

SI.4.4.3 HP (or chronic HP)

No studies were identified that reported the risk factors for disease progression in patients with HP.

SI.4.4.4 Sarcoidosis

No studies were identified that reported the risk factors for disease progression or fibrosis in patients with sarcoidosis associated ILD.

SI.4.4.5 Other exposure ILDs (occupational and environmental, e.g. asbestosis, silicosis)

No studies were identified that reported the risk factors for disease progression or fibrosis in patients with exposure-related ILDs.

SI.Table 52 Risk factors for ILD disease progression

Citation	Country	Study years	Study N	Risk factors for ILD or ILD progression
RA-ILD				
[R17-1636]	UK	2004 – 2005	56	Disease progression was defined by any of the following: a decrease of pre-rituximab treatment FVC>10% or DLCO>15% predicted, worsening of ILD score or death from progressive ILD. The risk factors for progression were the presence of a UIP radiologic pattern (64% versus 29%), a previous history of lung progression (79% versus 20%), and lower pre-rituximab therapy DLCO (median 42 [IQR 41, 49] versus 59 [IQR 54-64]).
[R19-0947]	UK	Not indicated	29	Disease progression was defined as a decline of >15% from the baseline value of TLCO. The risk factor for disease progression was TLCO values. Patients with a lower baseline TLCO had an increased risk for progression (OR 0.85, 95% CI 0.74-0.98).
[R16-5198]	US	1998 – 2014	167	Disease progression was defined as DLCO<40% predicted or too ill to perform, or FVC<50% predicted Risk factors for progression included: Patients with a UIP radiologic pattern were more likely to progress than those with NSIP (HR 3.29; 95% CI 1.28-8.41). Lower percent predicted DLCO and FVC at ILD diagnosis increased the risk for progression to a DLCO<40% (HR 3.74 per 10 unit decrease, 95% CI 1.96-7.14; HR 1.25 per 10 unit decrease, 95% CI 0.97-1.64 respectively), and an FVC<50% (HR 1.67 per 10 unit decrease, 95% CI 1.16-2.44; HR 2.38 per 10 unit decrease; 95% CI 1.37-4.17, respectively)

SI.Table 52 (cont'd) Risk factors for ILD disease progression

Citation	Country	Study years	Study N	Risk factors for ILD or ILD progression
RA-ILD (cont'd)				
[R18-1265]	Korea	1991 - 2008	84	Disease progression was defined as more than 10% change in FVC and/or more than 15% change in DLCO. The risk factors for progression were the presence of a UIP pattern on HRCT and a low TLCO (OR 0.963, 95% CI 0.925-1.003)
PM/DM-ILD				
[R17-2996]	France	1995 - 2010	107	ILD deterioration was defined as when any of the features of pulmonary condition i.e. ≥10% decrease in FVC and/or ≥ 15% decrease in DLCO worsened despite institution of therapy. Patients who had ILD deterioration were of older age (median age 62 years versus 52 years, had lower median values of FVC (66 versus 71), VC (70 versus 75), and DLCO (36 versus 54) at initial ILD diagnosis, and a UIP pattern was more frequent in the group of patients (66.7 versus 32.2) with ILD deterioration
[R19-0994]	US	1985 - 2013	35	Rapidly progressive ILD was defined as acute and progressive worsening of dyspnoea secondary to ILD requiring hospitalisation, supplementary oxygen, or respiratory failure requiring intubation within 3 months of diagnosis of ILD. Presence of anti-MDA5 Ab+ was associated with ILD and strongly associated with rapidly progressive ILD (50% versus 25.5%).
[R19-0951]	Japan	1990 - 2013	34	ILD deterioration was defined as the occurrence of two or more of the following during the follow-up period: (1) symptomatic exacerbation (e.g. dyspnoea upon exertion); (2) an increase in opacity on a chest HRCT scan; and (3) a >10% decrease in %FVC or 410 mmHg decrease in arterial oxygen tension (PaO2) Positive tests for anti-PL-7 antibody (62.5% versus 7.7%) and decreased %FVC (49% versus 66.2%) were both independent predictors of ILD long-term deterioration.

SI.Table 52 (cont'd) Risk factors for ILD disease progression

Citation	Country	Study years	Study N	Risk factors for ILD or ILD progression
PM/DM-ILD (cont'd)				
[R18-0014]	China/ Japan	2007 - 2016	182	Rapidly progressing ILD was defined as a condition of worsening radiologic interstitial change with symptoms of progressive dyspnoea and hypoxemia that occurred within 3 months of onset of respiratory issues. A higher percentage of patients with rapidly progressive ILD were observed in the MDA5 group (55.8%) compared to ARS group (25%) and MSN group (16.9%).
[R19-0943]	China	2010 - 2011	26	Rapidly progressing ILD was defined as a condition of worsening radiologic interstitial change with progressive dyspnoea and hypoxemia within 1 month of onset of respiratory symptoms. Presence of anti-MDA5 antibodies was associated with an increased risk for rapidly progressing ILD (38.5% versus 4.8%).
[R19-0951]	China	Not indicated	40	ILD progressive disease was defined as a progressive deterioration of ILD within 3 months The risk factors for rapidly progressive ILD were the presence of anti-MDA5 Ab+, elevated CRP >50 µg/L (73% versus 14%), high levels of serum ferritin >2000 µg/L (64% versus 10%), and decreased counts of lymphocytes <500/µL (55% versus 17%).
SjS-ILD				
[R17-0461]	France	1996 - 2012	21	ILD deterioration was defined as worsening of any of the features of pulmonary conditions despite institution of therapy according to an international consensus statement of the American thoracic society on idiopathic ILD: decreases of ≥10% in FVC and/or ≥15% in DLCO Factors associated with an increased risk for ILD deterioration were older age and oesophageal involvement.
MCTD-ILD				
[R18-0628]	Norway	2005 - 2008	118	ILD progression was defined as a disease extension as a percentage of total lung volume. Predictors of progression were male gender (HR 4.0, 95% CI 1.4-11.5), elevated anti-RNP titre (per 50 U/l increase) (HR 1.5, 95% CI 1.1-2.0), the presence of anti-ro-52 antibodies (HR 3.5, 95% CI 1.2-10.2) and absence of arthritis (HR 0.22, 95% CI 0.08-0.61)

SI.Table 52 (cont'd) Risk factors for ILD disease progression

Citation	Country	Study years	Study N	Risk factors for ILD or ILD progression
Idiopathic ILD				
[R16-0804]	US	2000 - 2011	132	ILD disease progression was defined as any of the following within 12 months of initial visits: 10% decline in FVC, 15% decline in DLCO, lung transplantation or death. Predictors of ILD disease progression were low baseline DLCO (HR 0.66, 95% CI 0.48-0.91), and high HRCT fibrosis score (HR 2.16, 95% CI 1.32-3.56)
HP				
No studies were identified				
Sarcoidosis-ILD				
No studies were identified				
Other exposure-ILD				
No studies were identified				

SI.4.5 The main existing treatment options

No drugs are approved for treatment of fibrosing ILD other than IPF. There are also no treatment guidelines issued by professional associations for PF-ILD other than IPF [P15-07539] and SSc-ILD [R17-3833, P15-00879], and there are no well-established treatment algorithms. Management of the different types of ILDs is challenging given the lack of robust data regarding the therapies used, the heterogeneity of diseases within this group, and the scarcity of well-defined outcome measures. Optimal guidelines have not been established due to the lack of large population studies and proven therapeutic strategies. The decision on whether treatment is indicated, and if needed, the choice of treatment regimen, will depend on a combination of factors, including: disease severity, rate of disease progression and the potential reversibility with immunomodulation, as well as key factors such as age, extrapulmonary comorbidities and patient preference. Given the wide variation in manifestations of ILD, no management strategy is appropriate for every possible clinical scenario.

A large US claims database study completed in 2019 that analysed data on 49 377 patients with incident PF-ILD from 2011 to 2015 reported a number of relevant medications administered: the most common prescription medication was corticosteroids while other commonly prescribed medications included methotrexate, nitrofurantoin and amiodarone; a significant proportion of the patients were not prescribed medications related to fibrosing ILD or PF- ILD [R19-2487].

The remainder of the data in this section are presented on the treatment options specific to the respective ILDs.

SI.4.5.1 Autoimmune or CTD-ILDs

There are no treatment guidelines for CTD-ILD or progressive forms of CTD-ILD. The heterogeneity of patients with CTD-ILDs makes treatment challenging in this patient population. Corticosteroids are often used as the first line treatment. There is no consensus on the optimal timing and duration of treatment for CTD-ILD, clinically significant (severe, extensive, or progressive) CTD-ILD is commonly treated with immunomodulatory agents [P19-02278].

SI.4.5.2 IIP (iNSIP, unclassifiable IIP)

There are no treatment guidelines for IIP or progression of disease. Initial treatment is often with high-dose corticosteroids, with review of steroid-responsiveness at 4 to 6 weeks. The steroids are usually tapered to the lowest possible maintenance dose, while monitoring clinical and functional parameters. If the response to high-dose corticosteroid therapy is suboptimal, addition of other immunosuppressive drugs may be necessary. Other immunosuppressive drugs may also be needed such as steroid-sparing drugs when corticosteroids cannot be reduced to acceptable doses. The drugs commonly used in maintenance therapy include azathioprine, mycophenolate mofetil, and oral or intravenous cyclophosphamide. They are usually used in combination with low-dose prednisone [P17-06892]).

SI.4.5.3 HP (or chronic HP)

There are no treatment guidelines for HP/chronic HP or progression of disease. Treatment involves antigen avoidance, consideration of treatment with steroids and/or cytotoxic drugs directed at suppression of ongoing inflammatory/immune response, and management of comorbidities [R17-4287].

SI.4.5.4 Sarcoidosis

There are no treatment guidelines for sarcoidosis associated ILD or progression of disease. Decision to treat is based on patient symptoms. Oral glucocorticoids such as prednisone or prednisolone are usually given as the first line of treatment. If the disease progresses or the patients cannot tolerate treatment, antimetabolites such as methotrexate, azathioprine, leflunomide, and mycophenolate, are often used as alternatives to steroids. For patients who cannot be treated with low-dose glucocorticoids and an antimetabolite, anti-TNF monoclonal antibodies are also used for treatment [R19-0942].

SI.4.5.5 Other exposure ILDs (occupational and environmental, e.g. asbestosis, silicosis)

There are no treatment guidelines for exposure-related ILD or progression of disease. Management of patients includes management of underlying disease, comorbidities and prevention of further loss of lung function and major complications [R19-0990].

SI.4.5.6 Drug utilisation patterns

Data on treatment patterns in patients with ILD are provided in SI.Table 53. There were no studies identified that evaluated treatment in patients with fibrosing ILD or PF-ILD. Most of the identified studies reported on treatment of the overall ILD population. Because most the study participants were recruited from specialised or tertiary health institutions, and the small sample sizes, the results are not generalisable to the larger population of patients with ILD or PF-ILD.

SI.4.5.6.1 Autoimmune or CTD-ILDs

Overall, 25 studies reported on treatment in patients with CTD-ILDs including 2 for the overall CTD-ILD population, 7 studies RA-ILD, 10 studies PM/DM-ILD, 4 studies SjS-ILD, 2 studies UCTD-ILD). In all studies, most patients were treated with corticosteroids and/or immunosuppressants.

SI.4.5.6.2 IIP (iNSIP, unclassifiable IIP)

5 studies were identified that reported on treatment of patients with IIP. In all studies, most patients were treated with corticosteroids or immunosuppressants.

SI.4.5.6.3 HP (or chronic HP)

2 studies were identified that reported on treatment of patients with HP. In both studies, most patients were treated with corticosteroids or immunosuppressants.

SI.4.5.6.4 Sarcoidosis

No studies were identified that reported on treatment in patients with sarcoidosis associated-ILD.

SI.4.5.6.5 Other exposure ILDs (occupational and environmental, e.g. asbestosis, silicosis)

No studies were identified that reported on treatment in patients with exposure-related ILDs.

SI.Table 53 Treatment patterns in patients with ILD

Citation	Region	Country	Study years	Study N	Treatment patterns Treatment (number of patients)
CTD-ILD					
[R19-0997]	Americas	US	1998 - 2002	46	Prednisone (38), intravenous corticosteroids (11), cyclophosphamide (15), methotrexate (15), azathioprine (19)
[R19-0941]	Other	Saudi Arabia	2008 - 2013	67	Corticosteroids (46), immunomodulators (31)
RA-ILD					
[R18-0423]	Europe	Finland	2000 - 2015	59	Prednisone (10), azathioprine (8), methotrexate (15), hydroxychloroquine (16), sulfasalazine (16), leflunomide (2), rituximab (1), podophyllotoxin (7), sodium aurothiomalate (7)
[R17-1636]	Europe	UK	2004 - 2005	56	Disease-modifying antirheumatic drugs included: methotrexate (28), azathioprine (5), leflunomide (2), mycophenolate mofetil (1)
[R17-1163]	Europe	Denmark	2004 - 2016	679	Corticosteroids (294), methotrexate oral (133), salazopyrin (96), azathioprine (41), hydroxychloroquine (46)
[R15-3264]	Americas	US	2001 - 2008	82	Prednisone (58), methotrexate (46) and anti-tumour necrosis factor agent (18)
[R18-1265]	Asia	Korea	1991 - 2008	84	Corticosteroid (9), azathioprine (14), cyclophosphamide (4), cyclosporine (2)
[R19-0959]	Asia	Korea	1991 - 2011	77	Methotrexate (30), leflunomide (22), hydroxychloroquine (46), sulfasalazine (48), tacrolimus (2), Tumour necrosis factor inhibitor (4), rituximab (2)
[R11-4796]	Asia	Japan	1996 - 2009	84	No treatment (44), prednisolone (9); of the 16 patients with non-specific interstitial pneumonia: prednisolone (3), prednisolone plus cyclosporine (1)

SI.Table 53 (cont'd) Treatment patterns in patients with ILD

Citation	Region	Country	Study years	Study N	Treatment patterns Treatment (number of patients)
PM/DM-ILD					
[R19-0987]	Europe	France	1994 - 2012	48	Steroid therapy (45), immunosuppressive therapy (41), mycophenolate mofetil (23, with 7 as first line immunosuppressive therapy), azathioprine (21, with 13 as first line), cyclophosphamide (16, with 9 as first line), methotrexate (10, with 5 as first line), rituximab (9, always after failure of 2 lines of treatment), intravenous immunoglobulins (8, with 2 as first line therapy). Mean number of treatment lines of immunosuppressive therapy was 1.9 (47 patients were treated in total)
[R19-0944]	Europe	UK	1999 - 2009	40	Systemic corticosteroids plus up to 5 other agents including azathioprine, methotrexate, mycophenolate mofetil, leflunomide and cyclosporine A (numbers not provided.)
[R16-0817]	Americas	US	1990 - 1998	70	Corticosteroid usually in the form of prednisone occasionally hydrocortisone, as initial treatment (67), azathioprine (25), methotrexate (14), cyclophosphamide (7), cyclosporine (3), intravenous immunoglobulins (2), colchicine (15), hydroxychloroquine (10), sulfa drugs (6)
[R19-0957]	Americas	US	1995-2010	103	Immunosuppressive therapy with prednisone in addition to a variety of immunomodulating drugs (e.g. cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, rituximab; All patients except 1). A median of 3 (IQR 2-3) drugs were used in each patient over a median duration of 60 (IQR 23-96) months.
[R19-0950]	Asia	Japan	1990 - 2012	114	Corticosteroids alone (23), immunosuppressive agents, corticosteroids plus immunosuppressive agents (88) such as cyclosporine (75), cyclophosphamide (22), azathioprine (13), intravenous immunoglobulins (11)

SI.Table 53 (cont'd) Treatment patterns in patients with ILD

Citation	Region	Country	Study years	Study N	Treatment patterns Treatment (number of patients)
[R19-0951][1]	Asia	Japan	1990 - 2013	34	Patients with stable disease (n=26): corticosteroids alone (7), corticosteroids plus immunosuppressive agents (19) which included cyclosporine (16), tacrolimus (4), cyclophosphamide (1), azathioprine 1, intravenous immunoglobulins (2) Patients who experienced deterioration (n=8): corticosteroids alone (1), corticosteroids + immunosuppressive agents (7) which included cyclosporine (7), tacrolimus (1), cyclophosphamide (2), azathioprine (1), intravenous immunoglobulins (2), and home oxygen therapy (2)
[R19-0954]	Asia	Japan	1995 - 2013	48	ARS group n=23: prednisolone alone (10), prednisolone + cyclosporine (11), prednisolone + cyclophosphamide (1) non-ARS group n=25: prednisolone alone (6), prednisolone + cyclosporine (14), prednisolone +cyclophosphamide (1), prednisolone + tacrolimus (2)
[R19-0985]	Asia	Japan	2007 - 2011	43	Corticosteroid (33), immunosuppressive agents (27), long-term oxygen therapy (4)
[R18-0014]	Asia	China/Japan	2007-2016	182	Corticosteroid pulse therapy (11), 1 or more immunosuppressants including cyclophosphamide, mycophenolate mofetil, azathioprine, tacrolimus, cyclosporine A, methotrexate and leflunomide (65)
[R18-1437]	Asia	Japan	2011 - 2015	497	Corticosteroid alone (30), corticosteroids and cyclosporine (5), corticosteroid and cyclosporine A/Tacrolimus (110), corticosteroids and cyclophosphamide and cyclosporine A/Tacrolimus (145)
Sjögren's-ILD					
[R19-0992]	Europe	Italy	2013 - 2016	13	Immunosuppressive therapy (10), mycophenolate mofetil (5), cyclophosphamide (4), azathioprine (1)
[P06-12207]	Americas	US	1992 - 2004	18	Corticosteroids (15), hydroxychloroquine (5), azathioprine (2), cyclophosphamide (2)
[R18-0583]	Asia	Japan	1998 and 2008	33	One or more anti-inflammatory agents (corticosteroids, cyclosporine, azathioprine cyclophosphamide) (27), corticosteroid therapy (1)
[R19-0982]	Asia	China	2012 - 2014	158	Prednisolone or immunosuppressants or combination of the two (133)

SI.Table 53 (cont'd) Treatment patterns in patients with ILD

Citation	Region	Country	Study years	Study N	Treatment patterns Treatment (number of patients)
Undifferentiated/unclassifiable CTD-ILD					
[R19-0948]	Asia	Japan	1990 - 2009	22	corticosteroids alone (6), corticosteroids plus immunosuppressive agents (9), cyclosporine (6), cyclophosphamide (2), azathioprine (1).
[R19-0996]	Asia	Japan	2009 – 2011	24	Pirfenidone (5), cyclosporine plus prednisolone (11), tacrolimus plus prednisolone (2), pirfenidone plus cyclosporine plus prednisolone (3), no therapy (3)
HP					
[R17-4298]	Americas	US	2003 - 2014	4093	Glucocorticoids (2,521), azathioprine (209), cyclophosphamide (31), mycophenolate mofetil (119), oxygen supplement (1,341)
[R16-2149]	Asia	Japan	2000 - 2009	222	Steroids (134), immunosuppressants in combination therapy with steroids (42)
IIP					
[R16-0805]	Europe	France	Not indicated	127	No treatment (14), corticosteroids (99), and/or at least one immunosuppressive agent (azathioprine (52), cyclophosphamide (33), mycophenolate mofetil (24), methotrexate (4), rituximab (3), cyclosporine (1), leflunomide (1), plasmapheresis (1))
[R18-0486]	Americas	US	2008 - 2014	56	Corticosteroids (n=45) in combination with a corticosteroid-sparing agent most commonly mycophenolate mofetil (n=42) (All but one patient was treated with immunosuppressive medications.)
[R18-0595]	Asia	Korea	1991 - 2006	72	Corticosteroid alone (68), corticosteroid plus cytotoxic agent, colchicine (1)
[R19-0999]	Asia	South Korea	2005 - 2012	105	Steroid only (30), steroid plus immunosuppressant (24)
[R18-1574]	Asia	China	2010 - 2016	IPAF (177) non-IPAF (996)	Corticosteroids: IPAF 128, non-IPF 654; immunosuppressant IPAF 44, non-IPF 59; combined IPAF 40, non-IPF 52
Sarcoidosis associated ILD					
No studies that reported treatment in patients with sarcoidosis related ILD were identified					
Exposure-related ILDs					
No studies that reported treatment in patients with exposure-related-ILD were identified					

[1] The 2 studies included patients who were recruited from the same institution but with different study periods and therefore may have an overlap in the study population.

SI.4.6 Natural history of the indicated condition in the population, including mortality and morbidity

SI.4.6.1 Survival rates

Data on survival rates in patients with ILD are provided in SI.Table 54. There were no studies that reported on the survival rates in patients with fibrosing ILD or in patients with non-IPF PF ILD. Data are therefore been presented on the survival rates among patients with each of the ILDs. There were no population-based studies identified, patients were recruited from specialised or referral health care institutions, and the sample sizes were small. Therefore, the results are not generalisable. Additionally, there was wide variation in the follow-up period for the patients. Furthermore, the studies did not report the stage of disease when the patients were evaluated.

SI.4.6.1.1 Autoimmune or CTD-ILDs

There were 5 studies that reported the survival in patients with CTD-ILD. The median survival ranged from 5.6 years to 7.1 years. The 5-year survival ranged from 43.4% to 98.8%.

There were 13 studies that reported on survival in patients with RA-ILD. The median survival ranged from 3 years to 10.5 years. The 5-year survival ranged from 38.8% to 84%.

There were 7 studies that reported on survival in patients with PM/DM-ILD. The median survival ranged from 10 months to 16.2 years. The 5-year survival ranged from 54% to 100%, and the 10-year survival from 59% to 69.1%.

There were 2 studies that reported on survival in patients with SjS-ILD. The 5-year survival was 87.3% and 88.5%.

There was 1 study that reported on survival in patients with MCTD-ILD based on the extent of lung parenchyma involvement on HRCT at entry into the study. The extent of involvement was evaluated independently for each lung zone and each zone was assigned a percentage of the lung parenchyma that showed evidence of ILD. The total extent of disease in each patient was added in the four lung zones and expressed as a percentage of TLV. The 5-year survival ranged from 82% in patients with ≥5% disease extent to 94% in patients with <5 disease extent. The 10-year survival ranged from 70% in patients with ≥5% disease extent to 87% in patients with <5 disease extent.

There were 5 studies that reported the survival in patients with UCTD-ILD. The median survival was reported in one study and was 3.8 years. The 5-year survival ranged from 57% to 97.9%.

SI.4.6.1.2 HP (or chronic HP)

There were 5 studies that reported on the survival in patients with HP. The median survival ranged from 4.9 years to 6.9 years. The 5-year survival was reported by 2 studies and was 41.9% and 93%.

SI.4.6.1.3 IIP (iNSIP, unclassifiable IIP)

There were 8 studies that reported on the survival in patients with IIP. The median survival ranged from 5.6 years to 13.5 years. The 5-year survival ranged from 48.2% to 77.1%.

SI.4.6.1.4 Sarcoidosis

There were no data identified on survival in patients with sarcoidosis ILD.

SI.4.6.1.5 Other exposure ILDs (occupational and environmental, e.g. asbestosis, silicosis)

There were no data identified on survival in patients with exposure ILD.

SI.Table 54 Reported survival in patients with ILD (including patients without progressive disease)

Citation	Country	Study years	Study N	Survival rate
CTD-ILD				
[R13-2611]	UK	2000-2009	324	Median survival: 5.6 years
[R15-3262]	US	1985 - 2011	56	Median survival: 7.1 (4.6-11.3) years
R16-0554]	US	1995 - 2010	89	Median survival: 6.6 (0.08-18.9) years[1]
[R19-0997]	US	1998 - 2002	46	5-year survival: 43.4% (95% CI 21.1-63.9)
[R19-1000]	China	1999 - 2013	288	5-year survival: 97.6% to 98.8%
RA-ILD				
[R14-4451]	UK	1986 - 1998	52	Median survival: 3 years 5-year survival: 38.8% (95% CI 23.3-54.1)
[R13-2611]	UK	2000 - 2009	213	Median survival: 6.6 years
[R18-0423]	Finland	2000 - 2015	59	Median survival: 7.7 years in the UIP group, and 11.4 years in the non-UIP group
[R17-1636]	UK	2004 - 2005	56	3-year survival: 87% 5-year survival: 84% 7-year survival: 84%
[R17-1163]	Denmark	2004 - 2016	679	Median survival: 6.6 years (95% CI 5.6-8.6)

SI.Table 54 (cont'd) Reported survival in patients with ILD (including patients without progressive disease)

Citation	Country	Study years	Study N	Survival rate
RA-ILD (cont'd)				
[R14-4455]	US	1955 - 1994	23	Median survival: 2.6 years
[R16-0820]	US	1977 - 1999	48	Median survival: 3.7 years[1]
[R15-3262]	US	1985 - 2011	13	Median survival: 5.5 years
[R16-0556]	US	1995 - 2013	137	Median survival: 10.35 years (95% CI 8.24-13.85 years)
[R17-1635]	US	1995 - 2014	158	Median survival: 8.27 years (UIP), 6.14 years (possible UIP)
[R15-3264]	US	2001 - 2008	82	Median survival: 5.0 years
[R18-1265]	Korea	1991 - 2008	84	Median survival: 4.7 years
[R11-4796]	Japan	1996 - 2009	84	Median survival: 8.1 years 5-year survival 60.1% 10-year survival 46.0%
PM/DM-ILD				
[R16-0817]	US	1990 - 1998	70	1-year survival: 85.8% 5-year survival: 60.4%
[R17-3039]	US	1985-2014	43	Median survival 16.2 years 5-year survival: 80% 10-year survival: 59%
[R19-0957]	US	1995-2010	103	5-year survival: 86%
[R19-0950]	Japan	1990 - 2012	114	5-year survival: 82% for PM-ILD, 71% for DM-ILD - 59% for CADM-ILD
[R19-0954]	Japan	1995 - 2013	48	5-year survival: 100% 10-year survival: 69.1%
[R19-0958]	China	1998 - 2005	145	Median survival: 0.9 years[1] (CADM-ILD), 7.5 years[1] (PM-ILD) 5-year survival: 54% (CADM-ILD) - 72.4% (PM-ILD)
[R18-0014]	China/ Japan	2007-2016	43	5-year survival: 50.2% for MDA5 group, 97.7% for ARS group - 91.4% for MSN group
SjS ILD				
[R18-0583]	Japan	1998 - 2008	33	5-year survival: 87.3%
[R19-0952]	China	2003 - 2012	165	5-year survival: 88.5%

SI.Table 54 (cont'd) Reported survival in patients with ILD (including patients without progressive disease)

Citation	Country	Study years	Study N	Survival rate
MCTD ILD				
[R18-0628][2]	Norway	2005 - 2008	118	5-year survival: 94% (<5% disease extent), 82% (≥5% disease extent) 10-year survival: 87% (<5% disease extent), 70% (≥5% disease extent) as
UCTD ILD				
[R17-3007]	Denmark	2003 - 2009	105	1-year survival: 87% 5-year survival: 57%
[R15-3262]	US	1985 - 2011	19	Median survival: 3.8 years
[R19-0984]	Japan	1990 - 2009	47	5-year survival: 58% (non-UCTD NSIP), 100% (UCTD-NSIP)
[R19-1000]	China	1999 - 2013	756	5-year survival: 97.9%
[R19-0999]	South Korea	2005 - 2012	105	1-year survival: 97.7% 5-year survival: 6.6%
HP				
[P16-01479]	Denmark	2003 - 2009	32	5-year survival: 93%
[R16-0805]	France	Not indicated	14	2-year survival: 73.3% 5-year survival: 41.9% 10-year survival: 27.9%
[R17-3016]	US	2006-2015	120	Mean survival: 1.4 years[1] for patients with HPAF, and 2.5 years[1] (1.8) for HP patients without AF
[R16-0497]	US	Not indicated	49	Median survival: 4.9 years
[R16-2149]	Japan	2000 - 2009	222	Median survival: 6.9 years
IIP				
[P16-01479]	Denmark	2003 - 2009	54	5-year survival: 48.2%
[P16-01479]	Denmark	2003 - 2009	30	5-year survival: 73.6%
[R17-2802]	Romania	2005 - 2015	27	Median survival: 7.0 years (95% CI 5.7-8.2 years)
[R16-0805]	France	Not indicated	51	2-year survival: 94.1% 5-year survival: 77.1% 10-year survival: 72.5%
[R18-0595]	Korea	1991 - 2006	83	1-year survival: 91% 2- year survival: 85% 5-year survival: 74%

SI.Table 54 (cont'd) Reported survival in patients with ILD (including patients without progressive disease)

Citation	Country	Study years	Study N	Survival rate
IIP (cont'd)				
[R18-0614]	South Korea	1991 - 2008	68	Median survival: 13.5 years (11.8 -15.2)
[R19-1001]	Japan	1999 - 2015	98	Median survival: 12.5 years 5-year survival: 71.1%
[R18-1574]	China	2010 - 2016	177	Median survival: 5.7 years
Sarcoidosis ILD				
No data identified				
Exposure ILD				
No data identified				

[1] Units converted to years by reviewer.

[2] The extent of involvement was evaluated independently for each lung zone and each zone was assigned a percentage of the lung parenchyma that showed evidence of ILD. The total extent of disease in each patient was added in the 4 lung zones and expressed as a percentage of TLV.

Mortality data in patients with ILD are provided in SI.Table 55. Only 1 study reported mortality in patients with a progressive phenotype. In a retrospective medical chart review study in France of 107 patients with PM/DM-ILD during the period from 1995 to 2010, the mortality rate was 47.1% among those who experienced ILD deterioration compared to 3.3% among those who did not [R17-2996]. Since only 1 study was identified with data on progressive disease, mortality among patients with each of the ILDs is presented.

Most of the reported deaths were due to disease progression/respiratory-related causes. There were no population-based studies identified, patients were recruited from specialised or referral health care institutions, and the sample sizes were small. Therefore, the results are not generalisable to the populations of patients with fibrosing ILD or PF-ILD. Additionally, there was wide variation in the follow-up period for the patients. Furthermore, the studies did not report the stage of disease when the patients were evaluated. It is expected that the mortality in patients with PF-ILD will be higher than the reported study due to progressive course of the disease.

SI.4.6.1.6 Autoimmune or CTD-ILDs

There were 5 studies that reported on the number of deaths in patients with CTD-ILD. In 1 study the crude mortality rate was 123.6 per 1000 PY (95% CI 102.8-148.7). The percentage of study participants who died during follow-up in studies of patients with CTD-ILD ranged from 20.6% to 57%.

There were 11 studies that reported on the number of deaths in patients with RA-ILD. The crude mortality rate was reported in 1 study as 132.9 per 1000 PY (95% CI 106.0-166.6).

Age-adjusted mortality rates were 2.9 per million population in women and 1.8 per million population in men. The percentage of study participants who died during follow-up in studies of patients with RA-ILD ranged from 9.4% to 75%. The most common causes of death were disease progression, cardiovascular disease, or infection.

There were 11 studies that reported on the number of deaths in patients with PM/DM-ILD. 1 study reported the mortality in patients with ILD progression. The mortality in patients with deterioration was 47.1% compared to 3.3% in patients without ILD deterioration. The percentage of study participants who died during follow-up in studies of patients with PM/DM-ILD ranged from 6.4% to 62.8%. The most common cause of death was disease progression.

There were 3 studies that reported on the number of deaths in patients with SjS-ILD. The percentage of study participants who died during follow-up ranged from 21.2% to 38.9%. The most common cause of death was disease progression.

There was 1 study that reported on the number of deaths in patients with MCTD-ILD. The percentage of study participants who died during follow-up was 7.9%. The causes of death were not reported.

SI.4.6.1.7 HP (or chronic HP)

There were 3 studies that reported on the number of deaths in patients with HP. The percentage of study participants who died during follow-up ranged from 17.4% to 54.3%. The most common cause of death was disease progression.

SI.4.6.1.8 IIP (iNSIP, unclassifiable IIP)

There were 5 studies that reported on the number of deaths in patients with SjS-ILD. The percentage of study participants who died during follow-up ranged from 10.6% to 38%. The most common causes of death were disease progression and malignancy.

SI.4.6.1.9 Sarcoidosis

There were no data identified on mortality in patients with sarcoidosis ILD.

SI.4.6.1.10 Other exposure ILDs (occupational and environmental, e.g. asbestosis, silicosis)

There was 1 study that reported on the number of deaths in patients with exposure-related ILD. The percentage of study participants who died during follow-up was 71.4%. The causes of death were disease progression, malignancies, infection, and cardiovascular disease.

SI.Table 55 Mortality and causes of death in patients with ILD (including patients without progressive disease)

Citation	Country	Study years	Number of study participants	Mortality rate, number of deaths, and causes of death
CTD-ILD				
[R13-2611]	UK	2000 - 2009	324	Mortality rate: 123.6 per 1000 PY (95% CI 102.8-148.7)
[R16-0554]	US	1995 - 2010	89	Number of deaths: 50 (57%)
[R19-0993]	Japan	2006 - 2008	29	Number of deaths: 6 (20.7%) Causes of death: Disease progression (3), pneumonia (2), alveolar haemorrhage (1)
[R19-0940]	Saudi Arabia	2008 -2010	28	Number of deaths: 8 (28.6%) Causes of death: Acute exacerbation (4), secondary to respiratory failure (3), and cerebrovascular accident (1)
[R19-0941]	Saudi Arabia	2008 - 2013	45	Number of deaths: 12 (26.7%)
RA-ILD				
[R14-4451]	UK	1986 -1998	52	Number of deaths: 39 (75%) Causes of death: Bronchopneumonia (4), ischemic heart disease (3), heart failure (2), pulmonary embolus (2), cerebrovascular disease (2), miscellaneous (5), chronic obstructive pulmonary disease (5)
[R13-2611]	UK	2000 - 2009	213	Mortality rate: 132.9 (106.0-166.6) per 1000 PY
[R18-0423]	Finland	2000 - 2015	59	Number of deaths: 33 (55.90%) Causes of death: RA-ILD (13), coronary artery disease (7), rheumatoid arthritis in 5 patients. Other causes were Alzheimer's disease, universal atherosclerotic disease with acute ischemia in legs, acute pancreatitis, intestinal tuberculosis, chronic obstructive pulmonary disease, massive bleeding due to pelvic fracture, lung cancer and suspected viral infection in the central nervous system

SI.Table 55 (cont'd) Mortality and causes of death in patients with ILD (including patients without progressive disease)

Citation	Country	Study years	Number of study participants	Mortality rate, number of deaths, and causes of death
RA-ILD (cont'd)				
[R17-1163]	Denmark	2004 - 2016	679	1-year mortality rate: 19.3% (95% CI 11.4% to 16.7%); 5-year mortality 39.0% (95% CI 34.4% to 43.5%); 10-year mortality rate: 60.1% (52.9% to 66.5%)
[R19-0947]	UK	Not indicated	29	Number of deaths: 4 (13.8%)
[R14-4453]	US	1988 - 2004	10 725	Age-adjusted mortality rates: 2.9 per million population in women and 1.8 per million population in men.
[R18-1265]	Korea	1991 - 2008	84	Number of deaths: 46 (54.8%) Causes of death: Disease progression (7), infection (9), malignancy 2, cardiovascular disease (3), and unknown (7)
[R19-0959]	Korea	1991 - 2011	77	Number of deaths: 28 (36.4%) Causes of death: identified in 13 patients, pneumonia (6), ILD (3), lung cancer (2), acute myocardial infarction (1), temporal bone cancer (1)
[R11-4796]	Japan	1996 - 2009	84	Number of deaths: 70 (49.3%) Causes of death: Respiratory lesions (58)
[R19-0995]	Korea	2004 - 2011	24	Number of deaths: 6 (25%) Causes of death: Alveolar haemorrhage (2), acute exacerbation of ILD (2), septic shock (1), pneumonia (1)
[R17-2768]	South Korea	2009 - 2017	64	Number of deaths: 6 (9.4%)
PM/DM-ILD				
[R19-0987]	France	1994 -2012	48	Number of deaths: 3 (6.4%)
[R17-2996]	France	1995 - 2010	107	Mortality rate in patients with ILD deterioration: 47.1% compared to 3.3% in those without deterioration

SI.Table 55 (cont'd) Mortality and causes of death in patients with ILD (including patients without progressive disease)

Citation	Country	Study years	Number of study participants	Mortality rate, number of deaths, and causes of death
PM-ILD (cont'd)				
[R17-3039]	US	1985 - 2014	43	Number of deaths: 16 (37%) Causes of death: Respiratory failure from pulmonary fibrosis (8), infection (3), lung cancer (1), pulmonary artery hypertension (1) and unknown cause (3).
[R16-0817]	US	1990 - 1998	70	Number of deaths: 17 (24.3%) Causes of death: Progressive ILD (6), superimposed pneumonia (4), lung cancer (1)
[R18-0014]	China/Japan	2007 - 2016	43	Number of deaths: 27 (62.8%) Causes of death: Tumour (4), respiratory failure (24)
[R19-0950]	Japan	1990 - 2012	114	Number of deaths: 30 (27.2%)
[R19-0951]	Japan	1990 - 2013	34	Number of deaths: 4 (11.8%) Causes of death: Heart failure (1), sudden death (1), respiratory failure due to deterioration of ILD (1), myocarditis (1)
[R19-0954]	Japan	1995 - 2013	48	Number of deaths: 8 (16.7%) Causes of death: Respiratory failure (6), oropharyngeal cancer (1) and rupture of abdominal aortic aneurism (1)
[R19-0985]	Japan	2007 - 2011	43	Number of deaths: 6 (14.0%) Causes of death: Acute exacerbation (4), pneumonia (2)
[R18-1437]	Japan	2011 - 2015	497	Number of deaths: 93 (18.7%) Causes of death: Respiratory insufficiency due to ILD (76), infection (5), malignancy (5)
[R19-0951]	China	Not indicated	40	Number of deaths: 10 (25%)

SI.Table 55 (cont'd) Mortality and causes of death in patients with ILD (including patients without progressive disease)

Citation	Country	Study years	Number of study participants	Mortality rate, number of deaths, and causes of death
SjS ILD				
[P06-12207]	US	1992 - 2004	18	Number of deaths: 7 (38.9%) Causes of death: Acute exacerbation of ILD (2), no identifiable cause (2), non-small cell lung cancer (1), non-Hodgkin's lymphoma (1) septic shock (1)
[R18-0583]	Japan	1998 - 2008	33	Number of deaths 10 (30.3%) Causes of death: chronic respiratory failure (5), acute exacerbation (3), bacterial pneumonia (1) and sepsis with unknown aetiology (1).
[R19-0952]	China	2003 - 2012	165	Number of deaths: 34 (21.2%) Causes of death: Respiratory failure (27), progression of malignant disease (5), gastrointestinal bleeding (1), viral meningoencephalitis (1), cerebral haemorrhage (1)
MCTD-ILD				
[R19-0953]	Norway	2005 - 2008	126	Number of deaths: 10 (7.9%)
HP				
[R17-1653]	UK	2007 - 2011	129	Number of deaths: 50 (38.8%)
[R16-0557]	US	1982 - 2000	46	Number of deaths: 25 (54.3%) Causes of death: Respiratory related deaths (16)
[R16-0553]	US	1997 - 2002	69	Number of deaths: 12 (17.4%)
IIP				
[R16-0804]	US	2000 - 2011	132	1-, 2- and 5- year mortality rates: 10.6%, 23.8%, and 31.1%, respectively
[R17-3227]	Canada	2006 - 2013	52	Number of deaths: 4 (38%)
[R18-0595]	Korea	1991 - 2006	83	Number of deaths: 26 (31.3%) Causes of death: Fibrotic: Respiratory disease related (16), secondary to treatment (1), gastric cancer (2)

SI.Table 55 (cont'd) Mortality and causes of death in patients with ILD (including patients without progressive disease)

Citation	Country	Study years	Number of study participants	Mortality rate, number of deaths, and causes of death
IIP (cont'd)				
[R19-1001]	Japan	1999 - 2015	98	Number of deaths: 27 (27.6%) Causes of death: Respiratory failure (15), lung cancer (3), other malignant disease (3), severe infection (2), acute myocardial infarction (1), gastrointestinal perforation (1), unknown (2)
[R18-1574]	China	2010 - 2016	177	Number of deaths 35 (19.8%)
Sarcoidosis-ILD				
No studies were identified				
Exposure-Related ILD (Silica)				
[R16-0834]	Japan	1999 - 2006	14	Number of deaths: 10 (71.4%) Causes of death: malignancy (3), pneumonia (2), cardiac failure (2), respiratory failure due to pneumoconiosis and coexisting interstitial pneumonia (3)

[1] The 2 studies included patients who were recruited from the same institution but with different study periods and therefore may have an overlap in the study population.

SI.4.6.2 Prognostic factors

Data on prognostic factors in patients with ILD are provided in SI.Table 56. No data were identified on the risk factors for mortality in patients with PF-ILD. Data are therefore presented on the risk factors for mortality for the ILDs.

SI.4.6.2.1 Autoimmune or CTD-ILDs

There were 2 studies that reported on the risk factors for mortality in patients with CTD-ILD. Risk factors included older age at diagnosis or onset of disease, the presence of a UIP pattern, a high honey-combing score or emphysema score on HCRT, and presence of cardiovascular disease.

8 studies reported on the risk factors for mortality in patients with RA-ILD. The risk factors included old age at diagnosis or disease onset, male gender, a presence of a UIP pattern, a low FVC or DLCO at diagnosis, and presence of fibrosis.

5 studies reported on the risk factors for mortality in patients with PM/DM-ILD. The risk factors included presence of deterioration, acute exacerbation, or disease progression, male gender, low DLCO at diagnosis, presence of anti-MDA5 antibodies, increased levels of CRP and low levels of SpO2.

1 study reported the risk factors for mortality in patients with SjS-ILD. The risk factors included the extent of reticular abnormality on HRCT, a high PaCO2, and the severity of fibroblastic foci.

SI.4.6.2.2 HP (or chronic HP)

There were 5 studies that reported on the risk factors for mortality in patients with HP. The risk factors included severity of traction bronchiectasis, increasing global interstitial disease extent, macrocystic and microcystic honeycombing, presence of fibroblastic foci and fibrosis, and increase pulmonary artery/aorta ratio. The presence of ground-glass opacity was associated with lower mortality risk.

SI.4.6.2.3 IIP (iNSIP, unclassifiable IIP)

There were 4 studies that reported on the risk factors for mortality in patients with IIP. The risk factors included older age at diagnosis, low DLCO at diagnosis, a high fibrosis score, or honeycombing or reticulation on HRCT, and presence of non-specific interstitial pneumonia.

SI.4.6.2.4 Sarcoidosis

There were no data identified on risk factors for mortality in patients with sarcoidosis-ILD.

SI.4.6.2.5 Other exposure ILDs (occupational and environmental, e.g. asbestosis, silicosis)

There were no data identified on risk factors for mortality in patients with exposure-related-ILD.

SI.Table 56 Factors associated mortality in patients with ILD

Citation	Country	Study years	Number of study participants	Risk factors for mortality
CTD-ILD				
[R19-0940]	Saudi Arabia	2008 - 2010	28	Univariate analyses: Higher ground-glass opacity (HR 2.51, 95% CI 0.93-6.76), a higher honey combing score (HR 12.04, 95% CI 1.14-126.83), and a higher emphysema score (HR 3.66, 95% CI 1.23-11.96) were associated with an increased risk for mortality
[R19-0941]	Saudi Arabia	2008 - 2013	45	Multivariate analysis: increasing age (HR 1.09, 95% CI 1.03-1.15), presence of ischemic heart disease (HR 5.76, 95% CI 1.72-19.20), and the diagnosis of UCTD-UIP (HR 3.05, 95% CI 0.96-9.63) were predictors of mortality
RA-ILD				
[R14-4451]	UK	1986 - 1998	52	Older age was a significant predictor of death (HR 1.04, 95% CI 1.00-1.09)
[R18-0423]	Finland	2000 - 2015	59	The number of deceased patients was significantly higher in the UIP group (23/35 i.e. 65.7%) versus 9/24 (37.5%) of the non-UIP group.
[R16-0820]	US	1977 - 1999	48	Multivariate analysis: age (HR 1.04, 95% CI 1.01-1.07) and presence of fibrosis (HR 2.1, 95% CI 1.1-4.3) were predictors of mortality
[R18-1265]	Korea	1991 - 2008	84	Multivariate analysis: increasing age (HR 1.16, 95% CI 1.04-1.28), FVC% predicted (0.96, 95% CI 0.93-0.99), and change in FVC (0.94, 95% CI 0.88-1.00) or DLCO (HR 0.95, 95% CI 0.92-0.99) were significant independent predictors for mortality
[R19-0959]	Korea	1991 - 2011	77	Multivariate analyses: older age at time of ILD diagnosis (OR 1.08, 95% CI 1.02-1.15), patients with UIP pattern on HRCT had poorer survival than those without UIP (Log rank test $p<0.05$)
[R16-0556]	US	1995 - 2013	137	A lower baseline % predicted forced vital capacity (HR 1.46, 95% CI 1.23-1.73) and a 10% decline in FVC% predicted (HR 2.57, 95% CI 1.79-3.70) from baseline to any time during the follow-up was associated with an increased risk of death
[R17-1635]	US	1995 - 2014	158	The group with definite or possible UIP had worse survival than those with NSIP ($p=0.03$)

SI.Table 56 (cont'd) Factors associated mortality in patients with ILD

Citation	Country	Study years	Number of study participants	Risk factors for mortality
RA-ILD (cont'd)				
[R15-3264]	US	2001 - 2008	82	Multivariate analysis: found that UIP pattern on HCRT (HR 2.34), female sex (0.30) and increased baseline DLCO (0.96) were associated with survival time
PM/DM-ILD				
[R17-2996]	France	1995 - 2010	107	The mortality rate in patients with ILD deterioration was 47.1% compared to 3.3% in those without deterioration
[R19-0957]	US	1995 - 2010	103	Male gender (HR 2.60; 95% CI 1.05-6.09), and DLCO at initial presentation (HR 0.94; 95% 0.90-0.98) were significant predictors of mortality
[R19-0950]	Japan	1990 - 2012	114	The risk factors for mortality were acute/subacute form (HR 4.23, 95% CI 1.69-12.09), age (HR 1.06, 95% CI 1.02-1.10), %FVC (HR 0.96, 95% CI 0.93-0.99) and a diagnosis of CADM (versus PM) (HR 4.18, 95% CI 1.32-18.53)
[R19-0985]	Japan	2007 - 2011	43	Univariate analysis: Chronic progression (HR 5.34, 95% CI 1.15-37.4) and acute exacerbations (HR 28.4, 95% CI 4.65-547.5) increased the risk of mortality
[R18-1437]	Japan	2011 - 2015	497	Multivariate analyses: older age at onset (HR 3.8, 95% CI 2.2-6.7), presence of anti-MDA5 antibody (HR 6.5, 95% CI 2.3-17.9), CRP (HR 2.6, 95% CI 1.5-4.7) and SpO2 (HR 2.1, 95% CI 1.2-3.5) were independent risk factors for mortality
SjS-ILD				
[R18-0583]	Japan	1998 - 2008	33	PaC02 (per 1 Torr increase) (HR 1.68, 95% CI 1.24-2.28), extent of reticular abnormality on HRCT (per 1 grade increment HR 4.17, 95% CI 1.18-14.73), and severity of fibroblastic foci (per 1 grade increment HR 9.26, 95% CI 1.74-49.35) were found to be independent and statistically significant prognostic factors
HP				
[R18-0489]	UK	2000 - 2006	92	Increasing severity of traction bronchiectasis (HR 1.10, 95% CI 1.04-1.16), increasing global interstitial disease extent (HR 1.02, 95% CI 1.00-1.03), microcystic honeycombing (HR 1.09, 95% CI 1.01-1.17) and macrocystic honeycombing (HR 1.06, 95% CI 1.01-1.10) were independent predictors of mortality

SI.Table 56 (cont'd) Factors associated mortality in patients with ILD

Citation	Country	Study years	Number of study participants	Risk factors for mortality
HP (cont'd)				
[R16-0553]	US	1997 - 2002	69	Mortality was highest in patients with >40% lung involvement (5/6 patients died 83%), followed by those with 10-40% involvement (3/6 died 50%), followed by those with <10% involvement (3/14 patients died 2%), and 1/43 in those with no lung involvement
[R19-0982]	US	2003-2013	119	Multivariate analysis: presence of fibroblastic foci (HR 3.69, 95% CI 1.63-8.36) and fibrosis (HR 4.45, 95% CI 1.59-12.40) were predictors of mortality
[R17-3016]	US	2006-2015	120	Caucasians had a reduced survival time compared with non-Caucasians (p=0.036)
[R19-0945]	US	2006 - 2015	132	Multivariate analysis: Presence of ground-glass opacity was associated with improved survival (HR 0.31, 95% CI 0.12-0.79), while traction bronchiectasis (HR 8.34, 95% CI 1.98-35.21) and increased pulmonary artery/aorta ratio (HR 2.49, 95% CI 1.27-4.89) were associated with worse survival
IIP				
[R17-2802]	Romania	2005 - 2015	27	Higher age at diagnosis (HR 1.04 per 1-year increase), and lower DLCO (HR 0.97) had a significant impact on the risk of mortality
[R16-0804]	US	2000 - 2011	132	Multivariate analysis: Baseline DLCO% predicted (HR 0.59, 95% 0.43-0.80) and HRCT fibrosis score (HR 1.60, 95% CI 1.08-2.37) were independent predictors of mortality
[R18-0614]	South Korea	1991 - 2008	68	Multivariate analysis: honeycombing (HR 1.58, 95 % CI 1.25-2.00) and reticulation (HR 1.08, 95% CI 1.04-1.13) were independent prognostic factors of survival
[R19-1001]	Japan	1999 - 2015	98	Patients with NSIP patterns had significantly worse survival than those with NSIP+Organising Pneumonia or Organising Pneumonia patterns (HR 4.48, 95% CI 1.28-15.77) and age (HR 1.07, 95% CI 1.02-1.11).
Sarcoidosis-ILD				
No studies identified				
Exposure-related ILD				
No studies identified				

SI.4.7 Important co-morbidities

Published literature on co-morbidities in patients with fibrosing ILD or PF- ILD was not identified. However, 1 unpublished study using a large US claims database was completed in 2019 and analysed data on 49 377 patients with incident PF-ILD from 2011 to 2015. This study reported higher prevalence of the following co-morbidities: arterial hypertension, cardiac arrhythmias, GERD, T2DM, acute and chronic renal failure/insufficiency, COPD, and pneumonia (unpublished data).

Aside from the above unpublished study, data are presented on the co-morbidities (some of which may or may not be consequences of ILD) that occur in patients with ILDs and include [R19-2749]:

- Vascular manifestations
  - Pulmonary artery hypertension
  - Coronary artery disease
  - Ischaemic heart disease
  - Increased risk of venous thromboembolism
- Pulmonary manifestations
  - Emphysema
  - Pulmonary hypertension
  - Lung cancer
- Gastrointestinal
  - Reflux
- Sleep disorders
  - Sleep apnoea
- Psychiatric
  - Depression

SI.4.7.1 Supplemental information: Incidence rates of co-morbidities of the underlying diseases

As requested by the PRAC (EMEA/H/C/003821/II/0046), incidence rates of co-morbidities associated with the underlying disease are presented in the following.

SI.4.7.1.1 OPTUM CDM

The PF-ILD patients were identified from a large US healthcare insurance data base (OPTUM CDM) in a selection period from 01 Jan 2017 to 30 Sep 2021.

To calculate the incidence rate of a co-morbidity among PF-ILD patients, the patients will be required to meet the following criteria in the denominator.

- Had at least 2 claims with fibrotic ILD diagnosis on different dates within one year as confirmed fibrotic ILD diagnosis in the selection period. The earliest date of the proxy criterion of progressive fibrosing phenotype after the second fibrotic ILD date was defined as the index date.
- The proxy criterion of progressive fibrosing phenotype was

≥2 pulmonary function tests within 90 days; ≥2 HRCT within 360 days; ≥ 3 Chest CT within 360 days; ≥2 oxygen titration tests within 90 days; ≥1 claim for oxygen therapy; ≥1 respiratory hospitalisation (not including emergency room visits); ≥1 claim for palliative care; ≥1 lung transplant; ≥1 new claim for immunosuppressive; ≥1 claim for corticosteroid with a dose of >20mg [R21-2387]

- Had at least 1-year continuous enrolment with the health plan (30 days gap allowed) prior to the index date to assess if they were truly incident patients. The 1-year period prior to index date was defined as baseline period.
- Did not have any diagnosis of the - during the baseline period.
- Had at least 30 days continuous enrolment (follow up) after index date. The follow up period was censored at discontinued enrolment after index date, death, or end of selection period, whichever was earlier.

The incidence rate of the co-morbidity PF-ILD patients was calculated by dividing the number of patients with a new diagnosis of the co-morbidity by the sum of all observed person-to-event-time for all subjects in the denominator,

$$Incidence\ rate = \frac{Number\ of\ newly\ diagnosed\ comorbidity}{Sum\ of\ person-year\ at\ risk}$$

Patients with a new diagnosis of co-morbidity after index date contribute their PY at risk from index date to the first diagnosis of the co-morbidity after index date, while the other patients in the denominator contribute their PY at risk from index date to the end of follow up date.

The table below shows the number of PF-ILD patients at risk of the co-morbidity, number of patients with newly diagnosed co-morbidity, sum of PY at risk of the co-morbidity, incidence rate of the co-morbidity and its' 95% CI.

SI.Table 57 Number of PF-ILD patients at risk of the co-morbidity, number of patients with newly diagnosed co-morbidity, sum of PY at risk of the co-morbidity, incidence rate of the co-morbidity and 95% CI

PF-ILD	**Adult population (≥18 years)**					**Paediatric population (<18 years)**				
Co-morbidity	**Denominator N**	**New events**	**PY**	**Incidence rate (per 100 000 PY)**	**95% CI of incidence rate**	**Denominator N**	**New events**	**PY**	**Incidence rate (per 100 000 PY)**	**95% CI of incidence rate**
Pulmonary artery hypertension	64 963	10 629	86 060	12351	12118.1, 12587.7	73	6	101	5964	2797.4, 12980.9
Coronary artery disease	42 973	9818	54 780	17923	17571.7, 18280.8	89	0	138	0	0, 2677.3
Ischaemic heart disease	42 133	10 851	53 380	20328	19948.9, 20713.8	89	0	138	0	0, 2677.3
Venous thromboembolism	69 901	6392	98 078	6517	6359.5, 6679.0	79	0	122	0	0, 3034.5
Emphysema (pulmonary)	57 994	8313	76 791	10825	10595.3, 11060.7	93	1	145	691	167.4, 3851.9
Lung cancer	72 607	2230	106 526	2093	2008.3, 2182.1	93	0	145	0	0, 2547.7
Gastrointestinal reflux	42 933	11 941	49 091	24324	23891.9, 24764.5	51	12	63	19 008	
Sleep apnoea	56 955	5956	73 943	8055	7852.9, 8262.1	66	15	87	17 315	
Depression	52 070	9800	66 867	14656	14368.6, 14948.9	83	14	112	12 554	

*OPTUM (study period: 2017-01-01 to 2021-09-30)

SI.5 CHILDREN INTERSTITIAL LUNG DISEASE (chILD)

The following section aims to provide an overview of the available epidemiology of paediatric ILD referred to as chILD including patient characteristics, treatment patterns, and co-morbidities of interest. It should be noted that there is little data in the literature on the epidemiology of chILD. No population-based studies were identified regarding incidence or prevalence of fibrosis within chILD, however 2 observational case studies in the UK and France provide some information. Therefore, the potential limitations noted below for the included studies in this section need to be considered:

- Differences in the ILDs in each study, definition of clinical cases, and criteria used to diagnose chILD.
- Most of the included observational studies assessed relatively small samples and/or samples from very specific populations.
- 2 observational case series were identified in the UK and France, suggesting that the proportion paediatric patients with fibrosis among those with chILD may range between 2% to 7% [R17-2822, R18-0138]. No population-based observational studies on PF-ILD or fibrosing ILDs in children were identified. Most of the studies identified report data for incidence or prevalence of chILD overall and do not specify which proportion qualifies as fibrosing ILD. As such, when data on fibrosing ILD in children were not found, data on chILD overall were reported (with no regard to fibrosing or progressive nature of the ILD).
- Differences in healthcare systems, population characteristics, and other factors such as local treatment practices may limit the generalisability of findings from individual studies across countries.

Childhood interstitial lung disease or chILD is a spectrum of heterogeneous diffuse lung diseases affecting infants, children and teenagers including more than 200 rare disorders [R18-1145, P20-06867]. Despite the name, chILD can involve more than the interstitium, with involvement of the airways, airspaces, vasculature and lymphatics and is therefore also referred to as diffuse lung disease [R22-2235].

Diagnosis and classification of chILD is complex due to the wide diversity of disorders and the low frequency at which they occur [R22-2234]. For example, 65 different disorders of chILD were observed among a national patient cohort in Spain and for 24 of the chILD entities observed, only 1 patient was diagnosed in that category [R22-2234]. While chILD disorders may share common radiologic patterns or interstitial indicators, the aetiologies of chILD and consequently their clinical presentation, management and prognosis are highly variable, from newborns to teenagers, from milder symptoms to fatal diseases and from supportive care to lung transplantation [R22-2236].

Some ILDs (e.g. RA-ILD) occur in both children and adults, while others are primarily or exclusively seen in children (e.g. surfactant protein disorders [R16-4788] or only seen in adults (e.g. IPF). The pattern and diversity of paediatric ILD poorly fit the classification used for adults and thus classifications specific to paediatric ILD conditions have been proposed

over time [R22-2236]. However, ILD in the paediatric population remains a challenging and multidisciplinary diagnosis, with no standardised approach to its diagnosis and management [R21-4100].

Further, pulmonary fibrosis is a rare condition in children that is not well characterised in specific forms of chILD. The pathogenesis of fibrosing ILD involves tissue damage that results in the release of fibrogenic growth factors, fibroblast proliferation and transformation to myofibroblasts, excess deposition of extracellular matrix and aberrant remodelling of the lung architecture [P18-00369, R20-0428, R12-3678]. This injurious process can occur in both children and adults [R19-2536, R21-3866]. It is not clear whether the mechanisms of fibrosis in adults are the same as the mechanisms of fibrosis in children with ongoing alveolarisation [P18-00369, R20-0428, R12-3678, R19-2536]. It has been postulated that in chILD, in the context of the growth and development of the lung, processes are in place to help counteract the fibrotic process [P18-00369]. Observations regarding the pathophysiology of fibrosis from clinical trials and case reports suggest that expression of pulmonary fibrosis may differ with age and likely covers distinct entities with disorders of onset in infancy/early childhood having separate presentation than diseases with late childhood or adult onset. In younger children, pulmonary fibrosis seems to present with more inflammatory cell recruitment and less fibroblast recruitment and ECM deposition [P20-06867].

SI.5.1 Incidence

There is scarce data in the literature on the epidemiology of chILD and only case reports were available specifically for fibrosis within chILD. The incidence and prevalence of chILD are not well established, and it is uncertain whether estimates may be similar or different across different populations. Studies mostly from Europe and Australia show the prevalence of paediatric ILD is substantially less than that observed in adults [R11-5060, R12-0229, R12-0358, R12-0974, R14-4379, R17-2810, R17-2902, R17-2907, R03-2090, R03-2075, P16-01479], and has been reported to range from 1.5 to 3.8 per million [R12-2794, R16-4790, R17-2776]. In the few published studies reporting incidence of chILD, the rates range widely from 1.32 to 162 per million PY for children R16-1141, R12-0229, R18-1147]. Published prevalence and incidence estimates for chILD are summarised in SI.Table 58.

However, a recent multi-centre prospective study conducted in Spain during 2018 to 2019 found higher prevalence of chILD in children ages 0 to 18 years (46.5 per million) than reported in previous studies that ranged from 1.5 to 3.8 per million [R22-2234, R12-2794, R16-4790, R17-2776]. While the prevalence of chILD in this study was much higher than previous estimates, the incidence of new chILD cases in Spain was 8.18 cases per million PY falling at the lower range of estimates reported in Germany and Denmark [R22-2234].

It is possible that the reported estimates from earlier studies may underestimate the frequency of chILD due to differences in diagnostic criteria and disease definitions included across these studies. Further, there could be better identification and reporting of chILD in more recent studies due to increased access to genetic testing and identification of new chILD entities [R22-2234]. A strength of the recent study in Spain is that the chILD patient cohort closely resembles a national screening effort where study recruitment represented nearly 92% of the paediatric population in Spain of less than 18 years [R22-2234, R22-2236].

No population-based studies regarding incidence or prevalence of fibrosis within chILD were identified. Limited data regarding evidence of pulmonary fibrosis among patients with chILD was noted from 2 observational case studies in the UK and France. These case-series studies suggest the presence of fibrosis may range between 2% to 7% of paediatric ILD patients [R18-0138, P20-06867]. In the UK, a study including lung biopsies of 211 patients with various forms of chILD found the presence of pulmonary fibrosis in only 2% of 93 patients under 2 years of age and in 7% of the patients ages 2 to 18 years [R18-0138]. A review of lung biopsy or autopsy within a sample of 119 patients with chILD at a referral centre for rare lung disease in France determined a small number (3%) of patients were considered to meet criteria for pulmonary fibrosis (i.e. fibroblast recruitment with ECM deposition) [P20-06867].

SI.Table 58 Reported prevalence and incidence of chILD

Citation	Country	Study years	Age Range	Study N	Estimate
Prevalence					
[R22-2234]	Spain	2018 – 2019	0-18 years	381	46.53 per million
			< 2 years	231	220.29 per million
			2-18 years	150	22.77 per million
[R16-4790]	Australia	2009 – 2014	0-18 years	21	3.8 per million
[R17-2776]	Australasia	2003 – 2013	0-18 years	115	1.5 per million
[R12-2794]	UK and Ireland	1998 – 2008	0-16 years	46	3.6 per million
Incidence					
[R22-2234]	Spain	2018 – 2019	0-18 years	381	8.18 per million/year
[R16-1141]	Germany	2009	0-16 years	56	1.3 per million/year
[R12-0229]	Denmark	2001 – 2005	0-14 years	815	163.3 per million/year
		1995 – 2000	0-14 years	609	107.6 per million/year

SI.5.2 Prevalence

See Section SI.5.1

SI.5.3 Demographics of the population in the proposed indication – age, gender, and risk factors for the disease

SI.5.3.1 Age and gender

Current categorisation of disorders that comprise chILD are based on 2 age groups separated as disorders occurring in infants and young children less than age 2 and disorders among

older children from 2 to 18 years [R22-2236]. chILD specific to children younger than 2 years of age include diffuse developmental disorders, growth abnormalities, specific conditions of undefined aetiology (i.e. NEHI and PIG) and surfactant protein disorders and related disorders [P22-04780] whereas in older children and teenagers chILD present a spectrum of diseases more similar to adults and includes systemic disorders [R22-2234]. The entities comprising chILD more prevalent in infancy account for an estimated 68% of diffuse lung diseases in children younger than 2 years of age but make up only 5% of diffuse lung diseases in children 2 to 18 years of age [R22-2235]. Age-specific prevalence reported in a nationally based population study in Spain observed that most chILD patients were less than age 2 at diagnosis with a corresponding prevalence of 220.9 cases per million, whereas the prevalence in older children ages 2 to 18 years in this study was much lower at 22.77 cases per million [R22-2234].

There is some information available regarding the gender distribution of chILD as described in specific cohorts of chILD patients. Reported gender frequency of chILD varied across these studies and sample sizes. A higher frequency of chILD was observed among males ranging from 51% to 63% in studies from China, US, Europe, and Australia (see SI.Table 59) [R20-2484, R16-4794, R17-3712, R17-2776, R12-2794]. However, a somewhat higher female to male ratio of chILD patients was reported in cohorts in France and Germany [R16-1141, R17-2822].

SI.Table 59 Gender distribution of cohorts of patients with chILD

Citation	Country	Study years	Study N	Males, (%)
[R17-2822]	France	2008 – 2011	205	0.9 (M:F ratio)
[R16-1141]	Germany	2005 - 2006	56	0.9 (M:F ratio)
[R20-2484]	China	2013 – 2018	84	63.2
[R16-4794]	US	1994 – 2011	93	51.0
[R17-3712]	Europe	2014 – 2016	575	53.0
[R17-2776]	Australia	2003 – 2013	115	57.0
[R12-2794]	UK and Ireland	1995 – 1998	46	63.0

SI.5.3.2 Risk factors

Childhood ILD can be related to a number of risk factors such as genetics, infections, environmental exposures, exposure to medications, and existing medical conditions. Specifically, mutations in genes that influence lung development or changes in genes that affect surfactant production are related to development of chILD. Surfactant dysfunction disorders can be attributed to mutations in multiple genes, including genes for SFTPB, SFTPC, and ABCA3 [R21-4100]. Although surfactant dysfunction disorders typically present early in the neonatal periods, SFTPC and ABCA3 mutations can have variable clinical presentations, and may remain asymptomatic until later in childhood [R21-4100].

The main viruses implicated in chILD include adenovirus, members of human herpes virus family (Epstein-Barr virus and cytomegalovirus), and respiratory synctial virus. Viruses such as Influenza A, hepatitis C, or even HIV in immunocompetent children can also be involved in development and progression of paediatric ILD [R16-4789]. LIP is a rare disorder strongly associated with infection. In children, LIP is particularly common, but not exclusive to children with HIV), estimated to occur in approximately 30% to 40% of cases [R21-4100].

Repeated and long-term exposure to environmental factors such as bacteria, fungi, chemicals, tobacco smoke, and air pollution can be related to development of chILD. Specifically, HP in children is often associated with exposure to antigens in the home environment and with certain hobbies, such as bird fancier's diseases, humidifier lung diseases, and chemical lung diseases induced by various vaporised paints and plastics [R16-4789]. Chronic aspiration is also commonly seen in children with recurrent lower respiratory tract infections and is predicted to be present in 26% to 49% of children with chILD [R21-4100].

Certain medications and drugs used in inflammatory disease or paediatric cancers can cause ILD. They include anti-inflammatory agents (e.g. aspirin, etanercept), immunosuppressive and chemotherapeutic agents (e.g. azathioprine, methotrexate, cyclophosphamide), antibiotics, and cardiovascular agents. Exposure to therapeutic radiation in the management of paediatric cancer may also results in ILD [R16-4789]. For teenagers, illicit drugs can also play a role in development of chILD [R16-4789].

Connective tissue disorders of childhood are frequently associated with pulmonary disease. Primary disorders in childhood include rheumatoid arthritis, systemic sclerosis, and systemic lupus erythematosus as well as Sjögren syndrome, dermatomyositis and polymyositis, ankylosing spondylitis, and mixed connective tissue disease [R16-4789]. Pulmonary disease has been reported in up to 90% of paediatric patients with juvenile systemic sclerosis (scleroderma) [R21-4100].

Other medical conditions associated with chILD include IPH, particularly among patients with Down syndrome [R21-4100]. Children with IPH have a more rapid and severe prognosis and mortality rates are estimated up to 50% [R21-4100].

Several forms of ILD have been reported to occur with inflammatory bowel diseases (Crohn's disease) and celiac disease as well as primary biliary cirrhosis and chronic hepatitis [R16-4789]. Pulmonary vasculitis occurring in syndromes that preferentially affect small vessels (arterioles, venules, and capillaries) are associated with chILD. These syndromes include the ANCA-associated vasculitis (Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangitis); anti-GBM disease; Henoch-Schönlein purpura and cryoglobulinemia vasculitis [R16-4789].

Causal mechanisms of fibrosis are likely to include a genetic component but may also include microbial triggers, inhalational injury, and autoimmune dysregulation [R19-2536].

SI.5.4 The main existing treatment options

Treatment of patients with chILD is mainly focused on supportive care (e.g. oxygen therapy, nutritional support, ventilator support, prevention of infections, and avoidance of exposure to irritants). Empirical pharmacological therapies used to treat chILD are based on anti-inflammatory and immunomodulatory drugs such as corticosteroids, hydroxychloroquine, and azithromycin [R16-4820, R16-4799, R16-4819, P16-11832, R16-4789]. Lung transplantation is a therapeutic option for children with severe progressive disease (e.g. surfactant B deficiency, ABCA3 mutations) or terminal chronic respiratory failure and is associated with a survival rate of 51% and 45% over 5 and 7 years, respectively [P22-04780]. There are no approved therapies for the treatment of lung fibrosis in children. To date, none of the anti-fibrotic therapies currently approved (nintedanib and pirfenidone) for lung fibrosis in adults has been approved for children.

SI.5.5 Natural history of the indicated condition in the population, including mortality and morbidity

There is limited evidence on the natural history of ILDs in children and even less on those associated with chronic fibrosis. The severity of chILD presentation is highly variable, ranging from mild nonspecific symptoms, which may lead to a late diagnosis, to a very severe clinical picture. Usually, the earlier the onset of the disease, the more severe are the presenting symptoms [P22-04780]. In most cases, children with chILD have non-specific respiratory signs and symptoms, such as dyspnoea, polypnoea, dry cough, wheezing, recurrent respiratory infections, and exercise intolerance. Older children can show tachypnoea, hypoxia, digital clubbing, and/or cyanosis during exercise or at rest [P22-04780].

The available data suggests overall that the clinical course is associated with better outcome compared to adult ILDs with survival among the paediatric population at 2, 4, and 5 years after symptom onset reported to be 83%, 72% and 64%, respectively [R09-5337]. Paediatric ILD has been associated with high morbidity and mortality, and studies suggest outcomes may be particularly poor for infants and young children. In the younger age groups an overall mortality rate of 30% has been observed, although this depends on the specific disease and the presence or absence of associated pulmonary hypertension [R16-4793, R22-2235].

SI.5.6 Important co-morbidities

Published population-based observational studies on co-morbidities in paediatric patients with ILD or fibrosing ILD were not identified. A systemic review of available literature on the occurrence of pulmonary hypertension in chILD indicates the frequency among the paediatric population varies widely with reported estimates between 1% and 64% [R22-2246]. Similar to observations in the adult population, pulmonary hypertension in chILD appears related to substantially increased risk of mortality. 3 studies found that among patients with chILD, those with pulmonary hypertension had a significantly higher risk (up to 7-fold) of death compared with those without pulmonary hypertension [R22-2246].

Information from observational case series have reported the presence of some co-morbidities in specific forms of chILD such as PIG and NEHI. A retrospective case series study of a

small sample of US children with PIG (n=10) reported congenital heart defects and pulmonary hypertension as the most common co-morbidities [R22-2247]. In a US sample of 199 paediatric patients with NEHI, observed co-morbidities included gastrointestinal reflux (51%), aspiration (35%), and immune system abnormalities (17%) [R21-3361].

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ABBREVIATIONS

%FVC	Percentage of predicted forced vital capacity
Ab	Antibody
Ab+	Antibody positivity
ABCA3	Adenosine triphosphate-binding cassette transporter protein A3
ACR	American College of Rheumatology
AF	Autoimmune features
AIR	Study acronym; Advancing IPF Research survey
ALAT	Latin American Thoracic Association
ANCA	Anti-neutrophil cytoplasmic antibody
Anti-aaRS/anti-ARS	Anti-aminoacly-transfer RNA synthetase antibodies
Anti-MDA5	Anti-melanoma differentiation-associated gene 5
Anti-PL-7	Anti-threonyl-tRNA synthetase
ARD	Autoimmune rheumatic disease
ARS	Antiaminoacyl-tRNA synthetase
ASCEND	Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis
ASCS	Australian Scleroderma Cohort Study
ATS	American Thoracic Society
AZA	Azathioprine
BAL	Bronchoalveolar lavage
BCD	Broad case defintion
BMI	Body Mass Index
BTS	British Thoracic Society
CA	California
CADM	Clinically amyopathic dermatomyositis
CDM	Clinformatics Data Mart
CHF	Congestive heart failure
chILD	Children interstitial lung disease
CHP	Chronic fibrosing hypersensitivity pneumonitis
CI	Confidence interval
CM	Clinical modification

CO	Colorada
COPD	Chronic obstructive pulmonary disease
CREST	Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasias
CRP	C-reactive protein
CS	Clinical syndrome
CT	Computed tomography
CTD	Connective tissue disease
CTD-ILD	Connective tissue disease-associated ILDs
CWP	Coal worker's pneumoconiosis
CXR	Chest x-ray
dcSSc	Diffuse cutaneous systemic sclerosis
DLCO	Diffusion capacity for carbon monoxide
DM	Dermatomyositis
DTPA	Diethylene tiamine pentacetate
ECM	Extracellular matrix
EMR	Electronic medical record
ERS	European Respiratory Society
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
EUSTAR	EULAR Scleroderma Trials and Research
F	Female
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
FVC%	Forced vital capacity, percentage of predicted for age and gender
GBM	Glomerular basement membrane
GCD	Generic case definition
GERD	Gastro-oesophageal reflux disease
GI	Gastrointestinal
GPRD	General Practice Research Datalink
HADS	Hospital Anxiety and Depression Scale
HIV	Human immunodeficiency virus

HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HP	Hypersensitivity pneumonitis
HPAF	Hypersensitivity pneumonitis with autoimmune features
HR	Hazard ratio
HRCT	High-resolution computed tomography
hsCRP	High-sensitivity C-reactive protein
ICD	International Classification of Diseases
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
iNSIP	Idiopathic non-specific interstitial pneumonia
IPAF	Idiopathic pneumonia with autoimmune features
IPF	Idiopathic pulmonary fibrosis
IPH	Idiopathic pulmonary hemosiderosis
IQR	Interquartile range
IR	Incidence rate
IRR	Incidence rate ratio
JRS	Japanese Respiratory Society
KL-6	Krebs Von Den Lungen 6
lcSSc	Localised cutaneous systemic sclerosis
LIP	Lymphocytic interstitial pneumonia
M	Male
MCTD	Mixed connective tissue disease
MESH	Medical Subject Headings
MI	Myocardial infarction
MINI	Mini International Neuropsychiatric Interview
MN	Minnesota
MSN	Without anti-MDA5 or anti-ARS antibody
NAC	N-acetylcysteine
NCD	Narrow case definition
ND	Not different
NEHI	Neuroendocrine cell hyperplasia of infancy
NHS	National Health Service

NR	Not reported
NSIP	Non-specific idiopathic pneumonia
NY	New York
NYHA	New York Heart Association
OF	Osteoporotic fracture
OPTUM	US healthcare insurance data base
OR	Odds ratio
PaCO2	Partial pressure of carbon dioxide
PAH	Pulmonary arterial hypertension
PaO2	Partial pressure of oxygen
PF	Progressive fibrosing
PF-ILD	Progressive fibrosing interstitial lung disease
PH	Pulmonary hypertension
PIG	Pulmonary interstitial glycogenosis
PM	Polymyositis
PO	Per os; oral
PPF	Progressive pulmonary fibrosis
PPV	Positive predicted value
PRAC	Pharmacovigilance Risk Assessment Committee
PY	Person-years
RA	Rheumatoid arthritis
RA-ILD	Rheumatoid arthritis-associated ILD
RIPID	Registro Italiano delle pneumopatie infiltrative diffuse
RNA	Ribonucleic acid
RNP	Ribonucleoprotein
RR	Risk ratio
SD	Standard deviation
SFTPB	Surfactant protein B
SFTPC	Ssurfactant protein C
SGRQ	St George’s Respiratory Questionnaire
SIR	Standardised incidence ratio
SjS	Sjögren’s syndrome

SLE	Systemic lupus erythematosus
SMR	Standardised mortality ratio
sPAP	Systolic pulmonary artery pressure
SpO2	Peripheral capillary oxygen saturation
SSc	Systemic sclerosis
SSc-ILD	Systemic sclerosis-associated ILD
THIN	The Health Improvement Network
TLCO	Total diffusion capacity for carbon monoxide
TLV	Total lung volume
TNF	Tumour necrosis factor
UCTD	Undifferentiated/unclassifiable connective tissue disease
UIP	Usual interstitial pneumonia
UK	United Kingdom
US(A)	United States (of America)
VC	Vital capacity
WASOG	World Association of Sarcoidosis and Other Granulomatous Diseases
WHO	World Health Organization

MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE

Potential adverse reactions of Ofev that may be expected in humans, based on non-clinical safety data, include gastrointestinal side effects, increases of liver transaminases, and mild, clinically not relevant, haematological alterations. Non-clinical safety data also indicate that the adverse effects of Ofev are generally reversible.

The pharmacological, pharmacokinetic, and toxicological characteristics of Ofev were investigated in a programme of non-clinical studies. The selectivity and potency of Ofev was tested in a series of *in vitro* assays. Pharmacology studies were performed to investigate potential neurological, haematological, gastrointestinal, renal, pulmonary, and cardiovascular effects of Ofev.

The pharmacokinetic evaluation included plasma/blood concentration time-profiles of the parent substance BIBF 1120 and the metabolites BIBF 1202 and BIBF 1202 glucuronide. Whole body autoradiography in albino and pigmented rats, quantitative tissue distribution after repeated dose, plasma protein binding of BIBF 1120, BIBF 1202, and BIBF 1202 glucuronide were also carried out. ADME studies assessed excretion balance and biliary excretion, and investigations on metabolism used plasma, urine, faeces and bile samples, microsomes and hepatocytes.

The toxicity of Ofev was investigated in an extensive programme of non-clinical studies including single-dose toxicity studies in rodents, local tolerance studies in rabbits, repeat-dose toxicity studies in mice (up to 3 months), rats (up to 6 months), dogs (up to 2 weeks), Cynomolgus monkeys (up to 13 weeks), and Rhesus monkeys (up to 52 weeks). In addition, the complete package of reproductive toxicology studies was conducted in rats and rabbits. The genotoxic potential of Ofev was assessed in bacterial (Ames-Test) and mammalian systems. 2-year carcinogenicity studies were conducted in mice and rats.

SII.1.1 Toxicity

SII.1.1.1 Single and repeat-dose toxicity

In oral single-dose toxicity studies in mice and rats, the ALDs were above 2000 mg/kg [U04-1066, U02-1491]. Therefore, the acute toxicity of Ofev after oral administration may be considered to be low. At the maximum dose of 40 mg/kg, no evidence of acute toxicity was observed in mice and rats after intravenous administration [U09-1057-01, U09-1058-01].

Subacute, subchronic, and chronic toxicity of Ofev were assessed in oral and intravenous repeat-dose toxicity studies in CD-1 mice (up to 13 weeks), Wistar (Han) rat strains (up to 26 weeks), Beagle dogs (up to 2 weeks), Cynomolgus monkeys (up to 13 weeks), and Rhesus monkeys (up to 52 weeks). Intravenous repeat-dose toxicity studies were carried out in

Wistar (Han) rats and Rhesus monkeys (each up to 2 weeks). In all studies, toxicokinetic analyses showed substantial systemic exposure to Ofev and, when measured, to its main metabolites BIBF 1202 and BIBF 1202 glucuronide. The changes observed during repeat-dose studies of oral Ofev were either directly (e.g. thickened epiphyseal growth plates) or indirectly related (e.g. changes of red blood cell parameters) to the pharmacological activity of Ofev.

Adverse effects observed in Cynomolgus and Rhesus monkeys were diarrhoea, vomiting, increased salivation, and reduced body weight. Yellow discolouration of the skin was observed at the high dosage of 80 mg/kg (given up to 10 days) in the escalating dose study in Cynomolgus monkeys [n00230654-02]. In the 4-week toxicity study in Cynomolgus monkeys, no discolouration was observed at 60 mg/kg, and in the 13-week study no discolouration was noted at 30 mg/kg. No other observation of yellow discoloration of the skin or alterations of skin colour such as hypopigmentation or leucoplakia has been reported in mice, rats, rabbits and Rhesus monkeys. In none of the non-clinical single or repeat-dose toxicity studies with proven significant systemic exposure in mice (up to 2 years), rats (up to 2 years), rabbits (Segment II, 13 days), dogs (up to 2 weeks), mini-pigs (up to 7 days), Cynomolgus (up to 13 weeks), and Rhesus monkeys (up to 52 weeks), there was any consistent evidence of drug-related discoloration of the skin.

Severe gastrointestinal effects were observed in dogs and mini-pigs, leading to high mortality. Observed effects included liquid faeces, vomiting, salivation, and paralysis/abnormal motor activity. The intestinal mucosa showed erosions, villous atrophy, and basophilia of crypt epithelium with nuclear crowding and mitoses, i.e. evidence for primary damage to the epithelial cells of the intestine. The high mortality in Beagle dogs was apparently due to a dose-limiting sensitivity for gastrointestinal adverse effects such as diarrhoea and vomiting, to which Beagle dogs were substantially more sensitive than other species.

Haematological changes across the studies were generally minimal to mild changes in red blood cell parameters (red blood cell count, haematocrit, haemoglobin, MCH, MCV, and reticulocytes). Changes in white blood cell, lymphocyte, and platelet count were also observed. Blood chemistry investigations revealed mild increases in ALT, AST, ALKP, total bilirubin, gamma-glutamyltransferase, and aldolase. However, increases in enzyme activities were not very prominent, were also occasionally observed in control animals, and were often interpreted as incidental, not as unequivocally drug-related.

Histopathological changes related to treatment with Ofev included dentopathy of the incisors, thickening of the growth plate (due to increased number of layers of hypertrophic chondrocytes) and increased swelling of chondrocytes in the basal layers of the articular cartilage in femur and tibia. The principal pathological changes observed included the presence of growth plate thickening in the femur/tibia and sternum, cortex and trabecular bone thinning in the sternum, and adrenal zona fasciculata atrophy in both sexes. There was no increase in the severity of the zona fasciculata atrophy with dose. All treatment-related changes showed complete or partial reversibility within the timescale of the toxicity studies; all changes were recoverable in principle. Growth plate changes recovered quickly.

Cellular depletion was observed in the thymus, spleen, and bone marrow. In the kidneys, tubular dilatation and PAS-positive hyaline intracytoplasmic granules in podocytes and glomerular endothelium were observed. An increased number of mature corpora lutea, often reduced in size, and of luteinised follicles was observed in the ovaries. Atrophy was apparent in the exocrine pancreas, submandibular glands, parotis, and serous glands of the tongue, with epithelial atrophy in the oesophagus, tongue, and skin, and villous atrophy of the small intestine. Hemosiderosis (e.g. of Kupffer cells and hepatocytes) and extramedullary haemopoiesis were observed in the spleen and in the liver. In the spleen, lymphoid depletion as well as mineralisation of the capsule and trabecules were seen; erosions in the gastrointestinal tract, inflammatory processes adjacent to the extra-hepatic bile ducts, as well as peliosis/angiectasis and diffuse cortical hyperplasia of the adrenals were also observed.

Several repeat-dose toxicity studies were conducted with Ofev in combination with other compounds. Combination partners were the ERBb family inhibitor (EGFR/HER 2, 3, and 4 inhibitor) afatinib [U06-1624, U06-1606, U06-1196, U06-1605], the serine/threonine- PLK1 inhibitor volasertib [U11-1368-01, U09-1962-01] and an Aurora B-inhibitor, BI 811283 [U11-2658-01, U12-1780-01]. The combination of Ofev with other agents did not reveal any additional, toxicologically meaningful information with respect to the toxicological profile of Ofev not already known from non-clinical studies with this compound alone.

SII.1.1.2 Reproductive and developmental toxicity

A complete programme of reproductive toxicology studies was conducted with nintedanib in rats and rabbits [U10-1128-01, U13-2650, U07-1710, U07-1814, U13-1923-01, U13-1937-01, U13-2641].

A study of male fertility and early embryonic development to implantation in rats did not reveal effects on the male reproductive tract and male fertility [U10-1128-01]. In rats, female fertility was not impaired at a systemic exposure below that at the MRHD of 150 mg b.i.d. [U13-2650].

In rats [U07-1710, U07-1814, U13-1923-01], slight effects on the development of the axial skeleton and on the development of the great arteries were noted at an exposure below the MRHD of 150 mg b.i.d. At a slightly higher exposure, but still below that at the MRHD, embryo-foetal lethality and teratogenic effects were observed.

In rabbits, embryo-foetal lethality and teratogenic effects were observed at an exposure approximately 7 times higher than at the MHRD and slight teratogenic effects on the axial skeleton, the aortic arches, the heart and the urogenital system were noted at an exposure approximately 5 times higher than at the MHRD of 150 mg b.i.d. [U13-1420-01, U13-1937-01].

In a pre- and post-natal development study in rats, effects on pre- and post-natal development were seen at an exposure below the AUC at the MRHD. The no observed adverse effect level for pre- and post-natal development of the offspring was 5 mg/kg [U13-2641].

In summary, based on the mechanism of action, teratogenic class effects have to be anticipated for VEGFR inhibitors in general. In rats and rabbits, nintedanib was shown to induce teratogenic effects, most prominently on blood vessels and skeleton. Those in rats were observed at an exposure below the human exposure at MRHD, those in rabbits at a 5 fold higher exposure.

The induction of similar effects in humans cannot be excluded.

SII.1.1.3 Genotoxicity

The genotoxic potential of Ofev was assessed in bacterial and mammalian systems (Ames [U02-1481], mouse lymphoma [U02-1512] and rat bone marrow micronucleus assay [U02-1650]). Test concentrations were selected up to bacterio-/cytotoxic or precipitating concentration levels in in vitro assays and up to maximum tolerated/limit doses under in vivo conditions. The results of the in vitro and in vivo mutagenicity studies showed that Ofev is free from any genotoxic potential up to toxic/limit concentration/dose levels. For the drug substance and drug product, no impurities are individually specified.

SII.1.1.4 Phototoxicity

In accordance with the OECD Guideline 432, a phototoxicity assay was conducted with Balb/c 3T3 cells [U05-2272]. A phototoxic threshold concentration of approximately 0.5 mcg/mL was estimated. At this concentration, the photo effect at any concentration was around the phototoxicity limit of 0.15. A photo irritation factor of 18.4 and a mean photo effect of 0.554 and 0.560 do not rule out potential phototoxicity of BIBF 1120.

SII.1.1.5 Immunotoxicity

Immunological investigations (phenotyping of lymphoid subpopulations in blood, spleen, and thymus, as well as determination of spleen natural killer cell activity) were performed in the 4-week toxicity study in rats [U04-1812], in the 13-week toxicity study in Cynomolgus monkeys [U05-2245], and in the 52-week toxicity studies in Rhesus monkeys [U07-1875]. No consistent adverse effects on the immune system of rats, Cynomolgus and Rhesus monkeys were observed.

SII.1.2 Safety pharmacology

Safety pharmacology investigations were conducted for Ofev, both in vitro and in vivo. In telemetered conscious male rats [U02-1398], a dose-dependent increase in systemic blood pressure was observed, whereas in anaesthetised pigs [U02-1674], a dose-dependent decrease in systolic and diastolic blood pressure was noted. Studies of renal and hepatic function in rats [U02-1260, U04-1416] showed up to 1.6-fold increase in ALT and a comparable increase in serum triglycerides and increases in urine volume, urine sodium, beta-NAG and Ca++ output. Studies on gastric emptying and secretion, gastrointestinal motility and transit [U02-1248, U02-1258, U02-1259] indicated a potential for Ofev to cause inhibition of both gastric and intestinal functions in a dose-dependent manner. No meaningful effects were observed with respect to central nervous system and respiratory functions [U02-1587, U02-1589].

In safety pharmacology (Good Laboratory Practice Core Battery) studies, there was no evidence for adverse cardiovascular, respiratory, or neurological effects of Ofev. Despite high passive permeability of Ofev through biomembranes into various cell lines, oral bioavailability was limited in rats by an incomplete absorption followed by first pass metabolism mainly by ester cleavage. Therefore, oral bioavailability was incomplete with 12% in rats and 19% in monkeys. Ofev was extensively distributed into all tissues except the central nervous system, in all investigated species (volume >8 L/kg).

SII.1.2.1 Cardiotoxicity

It has been surmised that the presence of a fluorine-based side chain may be related to class III electrophysiological off-target effects on cardiomyocytes resulting in a higher incidence of QT interval prolongation [P14-02206]. Neither BIBF 1120 nor BIBF 1202 contain a fluorine pharmacophore.

Experiments on hERG-mediated potassium current were performed using HEK293 cells stably expressing the hERG-mediated potassium current [U02-1288]. In addition, APs were measured in isolated guinea pig papillary muscles. Cumulative concentrations of BIBF 1120 BS were 0.1, 0.3, 1.0, 3.0, and 10.0 pM (n = 5). Measurements were taken at a stimulation frequency of 0.33 Hz (20 cycles per minute) and included APD to 10%, 30%, and 90% repolarisation (APD1O, APD30, and APD90, respectively), resting membrane potential, maximal velocity of phase 0 upstroke, AP overshoot, AP amplitude, and the force of contraction. The half maximal IC50 for BIBF 1120 BS on the hERG-mediated current was 4.0 mcM. In the guinea pig papillary muscle, no changes were caused by BIBF 1120 BS on the AP configuration in concentrations up to 10 mcM. Although similar studies were not conducted with BIBF 1202, by virtue of its being the carboxylic acid metabolite of BIBF 1120, this can be expected to lead to a lower potency on the hERG channel based on structure-activity considerations of the hERG channel, and effects on the action potential would also not be anticipated. The data of these studies suggest a low pro-arrhythmic potential for BIBF 1120 BS.

SII.1.3 Other toxicity-related information or data

SII.1.3.1 Drug transport

In vitro transporter profiling was performed for BIBF 1120, BIBF 1202, and BIBF 1202 glucuronide [U05-3076, U12-2279-01]. BIBF 1120 was shown to be a P-gp substrate and clinical drug-drug interaction studies were initiated. BIBF 1202 was a substrate of OATP-1B1 and OATP-2B1; BIBF 1202 glucuronide a substrate of multidrug resistance protein 2 and BCRP.

Only a weak inhibitory potential on organic anion transporter 1, BCRP, and P-gp was concluded for BIBF 1120; BIBF 1202 was an inhibitor of various transporters. In all cases, IC50 values were substantially higher than the therapeutic maximum plasma concentration at steady state and interactions on transporter substrates therefore considered unlikely. Also, the likelihood of relevant drug-drug interactions by BIBF 1120 mediated inhibition of P-gp or BCRP in the intestine is considered to be low.

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ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
ALD	Approximate lethal dose
ALKP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Action potential
APD	Action potential duration
AST	Aspartate aminotransferase
AUC	Area under the curve
beta-NAG	N-acetyl-beta-glucosaminidase
BCRP	Breast cancer resistance protein
b.i.d.	bis in die; twice daily
CA^{++}	Calcium
CD-1	Cluster of differentiation 1
EGFR	Endothelial growth factor receptor
HEK	Human embryonic kidney
HER	Human epidermal growth factor receptor
hERG	Human ether-a-go-go
IC_{50}	Half maximal inhibitory concentration
MCH	Mean corpuscular haemoglobin
mcM	MicroMol
MCV	Mean corpuscular volume
MHRD	Maximum recommended human dose
OECD	Organisation for Economic Co-operation and Development
PAS	Periodic acid-Schiff stain
P-gp	P-glycoprotein
pM	PicoMol
PLK	Serine/threonine-protein kinase
VEGFR	Vascular endothelial growth factor receptor

MODULE SIII CLINICAL TRIAL EXPOSURE

An overview of the analyses sets used for the exposure calculations is given in the following table.

SIII.Table 1 Overview of safety analysis sets

Analysis set	Indication	Description	Trials included
SG-8	All indications	Pooled indications IPF + SSc-ILD + PF-ILD + fibrosing ILD in paediatric patients	1199-0032, 1199-0034, 1199-0214, 1199-0247[1], 1199-0337[2]
SG-1.1	IPF	Phase III, randomised, double-blind, placebo-controlled trials, 52-weeks duration	1199-0032, 1199-0034
SG-5.1	SSc-ILD	Phase III, randomised, double-blind, placebo-controlled trials, with at least 52-weeks duration	1199-0214[1]
SG-6.1	PF-ILD	Phase III, randomised, double-blind, placebo-controlled trial, 52-weeks duration, in patients with PF-ILD	1199-0247[1]
1199-0337	Fibrosing ILD in paediatric patients	Phase III, randomised, double-blind, placebo-controlled trial with 24 weeks duration, followed by open label treatment with nintedanib of variable duration, in children and adolescents (6 to 17 year-old) with clinically significant fibrosing ILD	1199-0337[2]
1199-0337 and 1199-0378 (pooled)	Fibrosing ILD in paediatric patients	Pooled analysis including: • 1199-0337 (see above) • 1199-0378: ongoing trial Phase III, prospective open-label extension trial, at least 3 years duration, in children and adolescents (6 to 17 years old) with clinically significant fibrosing ILD	1199-0337, 1199-0378

[1] Trials 1199-0214 and 1199-0247: exposure analysis over 52 weeks.

[2] Trial 1199-0337: exposure analysis for the 24 weeks double-blind period.

[3] Snapshot date for trial 1199-0378 for pooled analysis: 31 May 2023. This trial included 30 roll-over patients from trial 1199-0337 and 9 new patients.

Note: the following abbreviations are used in this section:

- IPF: treatment of idiopathic pulmonary fibrosis
- PF-ILD: treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (in the following referred to as progressive fibrosing interstitial lung disease)
- SSc-ILD: treatment of systemic sclerosis associated interstitial lung disease
- Fibrosing ILD in paediatric patients: treatment of fibrosing ILDs in children and adolescents from 6 to 17 years old

New indication: fibrosing ILD in paediatric patients

1199-0337 and 1199-0337 + 1199 0378 (pooled) – Cut-off date for snapshot analysis: 31 May 2023

An extension trial (1199-0378) is currently ongoing. This is a phase III, prospective open-label extension trial of at least 3 years duration in children and adolescents (6 to 17 years old) with clinically significant fibrosing ILD. Patients from 1199-0337 can participate to this trial if eligible, and new patients can enter the trial directly. At data snapshot, this trial included 30 roll-over patients from trial 1199-0337 and 9 new patients.

A data snapshot was performed on 31 May 2023 to enable a pooled analysis of data from the combined nintedanib exposure period of trials 1199-0337 and 1199-0378. The objective of the pooled analyses was to provide a complete account of selected safety and efficacy data over the entire treatment duration with nintedanib. The combined nintedanib exposure period for the pooled analysis comprises the time from first nintedanib intake of a given patient in either trial 1199-0337 or trial 1199-0378 until the last nintedanib intake or the snapshot date.

The mean (SD) duration of exposure nintedanib in trials 1199-0337 and 1199-0378 combined was 70.0 (41.5) weeks (compared with 42.1 [22.2] weeks of nintedanib exposure in trial 1199-0337 alone). In the 2 trials combined, median (range) exposure was 78.4 weeks, with a large range from 0.3 to 138.4 weeks for individual patients. The majority of patients (52.1%) received nintedanib for longer than 76 weeks (see table below).

SIII.Table 2 Nintedanib exposure during the nintedanib-exposure period of trial 1199-0337 alone or of trials 1199-0337 and 1199-0378 (pooled) – TS[1]

	Trial 1199-0337 (nintedanib-exposure period)	Trials 1199-0337 and 1199-0378 (pooled nintedanib-exposure period)
	Total	Total
Number of patients (N, %)	37 (100.0)	48 (100.0)
Duration of exposure [weeks]		
Mean (SD)	42.1 (22.2)	70.0 (41.5)
Median	41.1	78.4
Minimum, maximum	2.1, 85.1	0.3, 138.4
Duration of exposure in categories [weeks] (N, %)		
≤6	1 (2.7)	3 (6.3)
>6 to ≤24	8 (21.6)	7 (14.6)
>24 to ≤52	13 (35.1)	6 (12.5)
>52 to ≤76	13 (35.1)	7 (14.6)
>76	2 (5.4)	25 (52.1)
Total exposure[2] [patient-years]	29.8	64.4

[1] Only patients who received at least 1 dose of nintedanib in trial 1199-0337 and/or trial 1199-0378 up to the snapshot date were included in this analysis set.

[2] The total exposure [patient-years] is defined as the sum of duration of exposure of all patients [days]/365.25.

Data source: CO [c42238250-01], Table 18

Exposure break-downs (pooled and by indication - DLP: 15 Jun 2022)

All indications (IPF + SSc-ILD + PF-ILD + fibrosing ILD in paediatric patients)

The clinical trial exposure in SG-8 is presented for both treatment groups in the tables below. 1055 patients received placebo (970.8 PY) and 1284 patients received nintedanib (1097.9 PY).

Indication IPF

The clinical trial exposure in SG-1.1 is presented for both treatment groups in the tables below. A total of 1061 patients with IPF have been treated in these 2 trials, with 638 patients receiving nintedanib. In this group of patients, the total duration of treatment with nintedanib amounted to 548 PY.

Indication SSc-ILD

The clinical trial exposure in SG-5.1 is presented for both treatment groups in the tables below. 288 patients received placebo (273.0 PY) and 288 patients received nintedanib (253.0 PY).

Indication PF-ILD

The clinical trial exposure in SG-6.1 (exposure analysis over 52 weeks) is presented for both treatment groups in the tables below. 331 patients received placebo (310.6 PY) and 332 patients received nintedanib (285.8 PY).

Fibrosing ILD in paediatric patients

Trial 1199-0337

13 patients received placebo (5.6 PY) and 26 patients received nintedanib (11.1 PY) during the double-blind period of trial 1199-0337 (see tables below). Over the whole trial, 26 patients received nintedanib (23.1 PY) (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Table 2.2.1).

SIII.Table 3 Duration of exposure - TS

Duration of exposure	Placebo		Nintedanib[1]	
	Number of patients, N (%)	Patient-time [years]	Number of patients, N (%)	Patient-time [years]
All indications (SG-8)				
≥1 day	1055 (100.0)	970.8	1284 (100.0)	1097.9
≥1 month	1039 (98.5)	970.1	1236 (96.3)	1095.7
≥3 months	1008 (95.5)	964.4	1161 (90.4)	1082.5
≥6 months	955 (90.5)	943.0	1072 (83.5)	1047.6
≥9 months	913 (86.5)	916.9	1006 (78.3)	1006.0
≥12 months	570 (54.0)	581.1	570 (44.4)	580.5
Indication IPF (SG-1.1)				
1 day	423 (100.0)	383	638 (100.0)	548
1 month	413 (97.6)	382	621 (97.3)	547
3 months	401 (94.8)	380	580 (90.9)	540
6 months	384 (90.8)	373	547 (85.7)	528
9 months	364 (86.1)	361	508 (79.6)	503
12 months	103 (24.3)	105	152 (23.8)	154
Indication SSc-ILD (SG-5.1)[2]				
≥1 day	288 (100.0)	273.0	288 (100.0)	253.0
≥1 month	284 (98.6)	272.7	276 (95.8)	252.3
≥3 months	278 (96.5)	271.5	263 (91.3)	250.0
≥6 months	269 (93.4)	268.1	247 (85.8)	244.1
≥9 months	261 (90.6)	263.0	235 (81.6)	236.4
≥12 months	192 (66.7)	195.8	170 (59.0)	173.4

SIII.Table 3 (cont'd) Duration of exposure - TS

Duration of exposure	Placebo		Nintedanib[1]	
	Number of patients, N (%)	Patient-time [years]	Number of patients, N (%)	Patient-time [years]
Indication PF-ILD (SG-6.1)[2]				
≥1 day	331 (100.0)	310.6	332 (100.0)	285.8
≥1 month	329 (99.4)	310.5	313 (94.3)	285.0
≥3 months	318 (96.1)	308.6	294 (88.6)	281.8
≥6 months	303 (91.5)	302.7	277 (83.4)	274.9
≥9 months	289 (87.3)	293.9	263 (79.2)	266.4
≥12 months	276 (83.4)	281.7	248 (74.7)	253.2
Indication fibrosing ILD in paediatric patients (1199-0337)[3]				
≥1 day	13 (100.0)	5.6	26 (100.0)	11.1
≥1 month	13 (100.0)	5.6	26 (100.0)	11.1
≥3 months	12 (92.3)	5.4	24 (92.3)	10.7
≥6 months	0 (0.0)	--	1 (3.8)	0.5

[1] IPF, SSc-ILD, and PF-ILD indications: 150 mg b.i.d; paediatric indication: 25 mg b.i.d., 50 mg b.i.d, 75 mg b.i.d., 100 mg b.i.d., 150 mg b.i.d.

[2] Exposure analysis over 52 weeks.

[3] Exposure analysis for the 24 weeks double-blind period.

1 month is defined as 30.5 days.

Data source:
All indications: data on file, SG-8_pooled exposure IPF+SSc+PF-ILD+paed ILD, Table 45.1.1.1
Indication IPF: data on file, analyses for RMP analyses v3.0, Table 2.1.1
Indication SSc-ILD: data on file, RMP v7.0 analyses for SSc-ILD , Table 2.2.1
Indication PF-ILD: data on file, RMP v9.0 analyses for PF-ILD , Table 2.1.2.1.1
Indication fibrosing ILD in paediatric patients: data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Table 2.1.1

SIII.Table 4 Age group and gender – TS

Gender/ Age group [years]	Placebo		Nintedanib[1]	
	Number of patients	Patient-time [years]	Number of patients	Patient-time [years]
All indications (SG-8)				
Male				
6 to < 12	2	0.64	4	1.64
12 to <18	3	1.40	6	2.48
18 to <65	230	213.85	327	297.46
≥65	357	324.54	426	364.52
Female				
6 to < 12	2	0.92	4	1.63
12 to <18	6	2.66	12	5.36
18 to <65	265	252.88	294	258.26
≥65	190	173.92	211	166.52
Indication IPF (SG-1.1)				
Male				
<65	115	105	207	189
≥65 to <75	171	152	211	188
≥75	48	43	89	69
Female				
<65	30	29	51	44
≥65 to <75	45	42	52	40
≥75	14	12	28	19
Indication SSc-ILD (SG-5.1)[2]				
Male				
<40	8	8.1	6	4.9
40 to <65	49	47.6	49	45.9
≥65	19	18.2	12	10.6
Female				
<40	33	30.0	30	26.7
40 to <65	139	131.3	139	120.1
≥65	40	37.7	52	44.7
Indication PF-ILD (SG-6.1)[2]				
Male				
<65	58	54.1	65	58.1
≥65	119	111.5	114	97.3
Female				
<65	63	62.9	74	67.4
≥65	91	82.0	79	63.0

SIII.Table 4 (cont'd) Age group and gender – TS

Gender/ Age group [years]	Placebo		Nintedanib[1]	
	Number of patients	Patient-time [years]	Number of patients	Patient-time [years]
Indication fibrosing ILD in paediatric patients (1199-0337)[3]				
Male				
≥6 to <12	2	0.6	4	1.6
≥12 to <18	3	1.4	6	2.5
Female				
≥6 to <12	2	0.9	4	1.6
≥12 to <18	6	2.7	12	5.4

[1] IPF, SSc-ILD, and PF-ILD indications: 150 mg b.i.d; paediatric indication: 25 mg b.i.d., 50 mg b.i.d, 75 mg b.i.d., 100 mg b.i.d., 150 mg b.i.d.

[2] Exposure analysis over 52 weeks.

[3] Exposure analysis for the 24 weeks double-blind period.

Data source:
All indications: data on file, SG-8_pooled exposure IPF+SSc+PF-ILD+paed ILD, Table 45.1.1.3
Indication IPF: data on file, analyses for RMP analyses v3.0, Table 2.1.3
Indication SSc-ILD: data on file, RMP v7.0 analyses for SSc-ILD , Table 2.2.3
Indication PF-ILD: data on file, RMP v9.0 analyses for PF-ILD , Table 2.1.2.1.3
Indication fibrosing ILD in paediatric patients: data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Table 2.1.3

SIII.Table 5 Dose – TS

Dose	Placebo		Nintedanib[1]	
	Number of patients	Patient-time [years]	Number of patients	Patient-time [years]
All indications (SG-8)				
25 mg b.i.d.	-	-	2	0.05
50 mg b.i.d.	3	0.95	6	1.85
75 mg b.i.d.	4	1.03	2	0.90
100 mg b.i.d.	51	17.54	426	169.33
150 mg b.i.d.	1046	944.97	1260	901.31
Indication IPF (SG-1.1)				
100 mg b.i.d.	16	4	178	65
150 mg b.i.d.	423	375	638	472
Indication PF-ILD (SG-6.1)[2]				
100 mg b.i.d.	18	7.4	112	46.3
150 mg b.i.d.	331	301.6	332	232.6
Indication fibrosing ILD in paediatric patients (1199-0337)[3]				
25 mg b.i.d.	-	-	2	0.05
50 mg b.i.d.	3	0.95	6	1.85
75 mg b.i.d.	4	1.03	2	0.90
100 mg b.i.d.	4	1.78	18	7.42
150 mg b.i.d.	4	1.85	2	0.73

[1] IPF, SSC-ILD, and PF-ILD indications: 150 mg b.i.d; paediatric indication: 25 mg b.i.d., 50 mg b.i.d, 75 mg b.i.d., 100 mg b.i.d., 150 mg b.i.d.

[2] Exposure analysis over 52 weeks.

[3] Exposure analysis for the 24 weeks double-blind period.

Note: exposure by dose is not applicable for indication SSc-ILD (SG-5.1).

Data source:
All indications: data on file, SG-8_pooled exposure IPF+SSc+PF-ILD+paed ILD, Table 45.1.1.2
Indication IPF: data on file, analyses for RMP analyses v3.0, Table 2.1.2
Indication PF-ILD: data on file, RMP v9.0 analyses for PF-ILD, Table 2.1.2.1.2
Indication fibrosing ILD in paediatric patients: data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Table 2.1.2

SIII.Table 6 Ethnic origin - TS

Race	Placebo		Nintedanib[1]	
	Number of patients	Patient-time [years]	Number of patients	Patient-time [years]
All indications (SG-8)				
White	692	638.53	822	706.22
Asian	293	268.94	346	291.70
Black	21	19.08	30	22.40
Other	49	44.25	86	77.54
Indication IPF (SG-1.1)				
White	248	225	360	313
Black	0	NA	2	2
Asian	128	116	194	158
Missing	47	42	82	74
Indication SSc-ILD (SG-5.1)[2]				
White	186	176.6	201	178.3
Asian	81	77.8	62	54.1
Black	16	14.5	20	15.6
Other	5	4.1	5	5.1
Indication PF-ILD (SG-6.1)[2]				
White	246	232.9	242	206.5
Asian	80	73.1	84	74.8
Black	5	4.6	5	3.5
Other	0	NA	1	1.0
Indication fibrosing ILD in paediatric patients (1199-0337)[3]				
White	12	5.25	19	8.18
Asian	1	0.37	3	1.40
Black	-	-	3	1.37
Other	-	-	1	0.16

[1] IPF, SSc-ILD, and PF-ILD indications: 150 mg b.i.d; paediatric indication: 25 mg b.i.d., 50 mg b.i.d, 75 mg b.i.d., 100 mg b.i.d., 150 mg b.i.d.

[2] Exposure analysis over 52 weeks.

[3] Exposure analysis for the 24 weeks double-blind period.

Data source:
All indications: data on file, SG-8_pooled exposure IPF+SSc+PF-ILD+paed ILD, Table 45.1.1.4
Indication IPF: data on file, analyses for RMP analyses v3.0, Table 2.1.4
Indication SSc-ILD: data on file, RMP v7.0 analyses for SSc-ILD , Table 2.2.4
Indication PF-ILD: data on file, RMP v9.0 analyses for PF-ILD , Table 2.1.2.1.4
Indication fibrosing ILD in paediatric patients: data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Table 2.1.4

SIII.1 REFERENCES

SIII.1.1 Published references

Not applicable.

SIII.1.2 Unpublished references

c42238250-01 Nintedanib (BIBF 1120). Clinical Overview. Treatment of fibrosing interstitial lung diseases (ILDs) in paediatric patients (including pooled data).

ABBREVIATIONS

b.i.d.	Bis in die (twice a day)
CO	Clinical Overview
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
NA	Not applicable
PF-ILD	Progressive fibrosing interstitial lung disease
PY	Patient year
RMP	Risk management plan
SG	Safety grouping
SSc-ILD	Systemic sclerosis and interstitial lung disease
TS	Treated set

MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL TRIALS WITHIN THE DEVELOPMENT PROGRAMME

Pregnancy and breastfeeding	
Reason for exclusion	The efficacy and safety of Ofev has not been established in these populations. Regarding pregnancy, Ofev is strictly contraindicated. Regarding breastfeeding, there is no information on the excretion of Ofev and its metabolites in human breast milk. Data from non-clinical studies showed that only small amounts (<0.5% of the administered dose of the mother substance and its metabolites) were secreted into the milk of lactating rats. As a risk to newborns/infants cannot be excluded, breastfeeding women should not be treated with Ofev.
Is it considered to be included as missing information?	No
Rationale	Ofev is contraindicated in pregnant women. Further routine risk minimisation measures are in place and include recommendations on contraception, pregnancy testing before and during treatment, and treatment discontinuation during pregnancy and breast-feeding.
Patients with known hypersensitivity to Ofev or any of the excipients	
Reason for exclusion	Patients with known hypersensitivity reactions to the active substance or to any of the excipients are excluded from clinical trials for safety reasons, to safeguard the wellbeing of susceptible patients.
Is it considered to be included as missing information?	No
Rationale	Ofev is contraindicated in these patients to prevent hypersensitivity reactions.
Patients who are allergic to soya or peanut	
Reason for exclusion	Patients with known allergies to soya or peanut are excluded from clinical trials for safety reasons, as Ofev capsules contain soya lecithin.
Is it considered to be included as missing information?	No
Rationale	Ofev is contraindicated in these patients as Ofev capsules contain soya lecithin.

AST and/or ALT and/or bilirubin >1.5x ULN	
Reason for exclusion	To protect the safety of patients.
Is it considered to be included as missing information?	No
Rationale	Ofev is predominantly eliminated by metabolism and biliary/faecal excretion (>90%). Patients with increased liver enzymes should be monitored; monitoring and dose adjustments should be applied according to EU-SmPC sections 4.2 and 4.4. Hepatic impairment is adequately addressed in the warnings and precautions section of the EU-SmPC. The safety and efficacy of Ofev have not been studied in patients with hepatic impairment classified as Child Pugh B and C. Ofev is therefore not recommended for patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A). Patients with mild hepatic impairment (Child Pugh A) should be treated with a reduced dose of Ofev (100 mg b.i.d.).
Recent history of acute myocardial infarction or acute coronary syndrome	
Reason for exclusion	Patients may have been in a clinical condition unsuitable for trial participation.
Is it considered to be included as missing information?	No
Rationale	The treatment of patients with higher cardiovascular risk factors, including known coronary disease, is adequately addressed in the warnings and precautions section and the undesirable effects section of the EU-SmPC. Arterial thromboembolism is taken up as an important potential risk of treatment with Ofev. Myocardial infarction is taken up as an important identified risk of treatment with Ofev. Caution should be taken when treating patients at higher cardiovascular risk, including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischaemia.

Recent history of or predisposition to bleeding events. Full-dose anticoagulation and high-dose platelet therapy was excluded throughout the trials	
Reason for exclusion	VEGFR inhibition might potentially be associated with an increased risk of bleeding [R12-3827].
Is it considered to be included as missing information?	No
Rationale	Across the wider clinical trial programme, there was no consistent higher rate of bleeding events in patients receiving Ofev than in patients receiving placebo. The majority of bleeding events across the clinical trial programme were non-serious. Bleeding is adequately addressed in the warnings and precautions section of the EU-SmPC. Bleeding is considered an adverse reaction for Ofev and taken up as an important identified risk for treatment with Ofev.
Administration of other therapies less than 2 weeks prior to treatment with Ofev	
Reason for exclusion	To maintain the integrity of the trials.
Is it considered to be included as missing information?	No
Rationale	Co-administration with Ofev should be carefully considered. These interactions are adequately addressed in the EU-SmPC.

Recent history of or predisposition to thrombosis	
Reason for exclusion	Patients may have been in a clinical condition unsuitable for trial participation.
Is it considered to be included as missing information?	No
Rationale	In the phase III trials with Ofev (all indications), the number of patients who experienced venous thromboembolism was small and comparable between the treatment arms. These findings were consistent across the Ofev clinical trial programme. More IPF patients in the Ofev arm than in the placebo arm experienced arterial thromboembolism (2.5% vs 0.7%, corresponding to an incidence rate of 0.73 vs 2.70 per 100 PY). The difference between the treatment groups was mainly driven by the PTs 'Myocardial infarction' (0.5% of all patients in the placebo arm and 1.1% of all patients in the Ofev arm) and 'Acute myocardial infarction' (no patients in the placebo arm and 0.5% of all patients in the Ofev arm). In SSc patients arterial thromboembolic events were balanced between Ofev and placebo (0.7% vs. 0.7%). In PF-ILD patients, ATE events were balanced between treatment groups (0.9% in each treatment group). Thrombosis (including myocardial infarction) is adequately addressed in the warnings and precautions section and in the undesirable effects section of the EU-SmPC. Due to the small number of patients who experienced thromboembolism, it is not possible to draw valid conclusions on any possible association with Ofev. Venous and arterial thromboembolism excluding myocardial infarction are taken up as important potential risks for treatment with Ofev. Myocardial infarction is taken up as important identified risk for Ofev.
Life expectancy for disease other than IPF <2.5 years	
Reason for exclusion	To maintain the integrity of the trials.
Is it considered to be included as missing information?	No
Rationale	Patients with an expected short life expectancy were excluded primarily to ensure the integrity of data. Further information may be obtained through post-marketing surveillance.

Aged <40 years (only applicable for the IPF development programme)	
Reason for exclusion	To ensure that trial patients had been accurately diagnosed with IPF. Age <40 years was not an exclusion criteria in trials with patients with SSc-ILD or PF-ILD.
Is it considered to be included as missing information?	No
Rationale	IPF may occur in patients <40 years. These patients are likely to benefit from Ofev treatment in the same way as older patients do.
Diagnosis of IPF not within the last 5 years	
Reason for exclusion	To maintain the integrity of the trials and ensure accurate diagnosis of IPF.
Is it considered to be included as missing information?	No
Rationale	This exclusion criterion was included to ensure all participating patients had been accurately diagnosed with IPF, in order to maintain the integrity of the trial data. This is not a consideration in the post-marketing setting.
Drug or alcohol abuse	
Reason for exclusion	To maintain the integrity of the trials.
Is it considered to be included as missing information?	No
Rationale	There is no evidence to suggest that the efficacy or safety of Ofev is affected by concurrent abuse of recreational drugs or alcohol.
Treatment of SSc patients with pulmonary hypertension	
Reason for exclusion	Patients may have been in a clinical condition unsuitable for trial participation.
Is it considered to be included as missing information?	Yes
Rationale	The safety and efficacy of Ofev have not been studied in patients with significant pulmonary hypertension (cardiac index <2 L/min/m^2, or concomitant use of parenteral epoprostenol/treprostinil, or significant right heart failure). In the phase III trial with Ofev in SSc-ILD, the number of patients with mild to moderate pulmonary hypertension was small and definitive conclusions regarding efficacy and safety could not be made. Patients may have been in a clinical condition unsuitable for trial participation.

Paediatric patients with any diagnosed growth disorder	
Reason for exclusion	In the paediatric trial 1199-0337 the impact on bone development and growth was monitored through regular bone imaging and height measurements. Patients with growth disorder were excluded to allow for the accurate evaluation of the safety concern.
Is it considered to be included as missing information?	No
Rationale	Bone development and growth in paediatric population is an important potential risk for Ofev. There is no evidence suggesting that patients with diagnosed growth disorders might have an increased risk for the potential risk. All paediatric patients are going to be regularly monitored for impact on growth and epiphyseal growth plate alterations.
Paediatric patients <13.5 kg of weight	
Reason for exclusion	In order to match the efficacious systemic exposure reached in adult IPF patients, the nintedanib doses in paediatric patients were predicted based on body weight dependent allometric scaling. The exposure predictions that correlate to 50 mg b.i.d. Ofev dosing (with the opportunity to do a dose reduction to 25 mg b.i.d. Ofev) cover the bioequivalence criteria of up to 125% for patients with a weight of 13.5 kg. For patients below this weight the predicted plasma exposure would be higher than 125% in comparison to the adult exposure.
Is it considered to be included as missing information?	No
Rationale	Treatment with Ofev in patients with a weight below 13.5 kg is not recommended.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

SIV.Table 1 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure			
Pregnant women	Not included in the clinical development programme. 2 cases (both nintedanib; 1 case from clinical trials, 1 case from post-marketing).			
Breastfeeding women	Not included in the clinical development programme. No cases have been received on drug exposure via breastfeeding so far.			
Patients with relevant co-morbidities				
• Patients with hepatic impairment	Not included in the clinical development programme.			
• Patients with renal impairment (SG-7)[1]	Placebo (Number/person-time)		Nintedanib 150 mg b.i.d. (Number/person-time)	
o Control	500	475.1	626	565.5
o Mild	414	379.1	495	414.5
o Moderate	124	109.2	132	101.7
o Severe	2	1.5	2	2.0
• Patients with cardiovascular impairment	Not specifically addressed in the clinical development programme.			
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme.			
Population with relevant different ethnic origin	See SIII.Table 5 for information on ethnic origin.			
Subpopulations carrying relevant genetic polymorphisms	Not specifically addressed in the clinical development programme.			
Other				
• Smoking status (SG-6)[2]	Placebo (Number/person-time)		Nintedanib 150 mg b.i.d. (Number/person-time)	
o Never smoked	284	262.3	337	290.1
o Ex-/current smoker	470	430.8	633	543.6

[1] Renal impairment categories: control is defined as CrCl ≥90 mL/min, mild as CrCl 60-89 mL/min, moderate as CrCl 30-59 mL/min, severe as CrCl 15-29 mL/min. CrCl was calculated using the Cockcroft-Gault formula. Note: analyses by degree of renal impairment were not performed for the paediatric population.

[2] Trial 1199-0247: exposure analysis over 52 weeks.

Data source: BI GSP,
All indications (SG-7): data on file, SG-7_pooled exposure IPF+SSc+PF-ILD, Table 10.1.1.5
Indications IPF+PF-ILD (SG-6): data on file, RMP v9.0 analyses for PF-ILD, Table 2.1.1.7

SIV.4 REFERENCES

SIV.4.1 Published references

R12-3827 Verheul HMW, Pinedo HM. Possible molecular mechanisms involved in the toxicity of angiogenesis inhibition. Nat Rev Cancer 2007;7:475–485.

SIV.4.2 Unpublished references

Not applicable.

ABBREVIATIONS

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATE	Arterial thromboembolism
b.i.d.	*Bis in die* (twice a day)
BI	Boehringer Ingelheim
CrCl	Creatinine clearance
EU	European Union
GSP	Global Safety Platform
IPF	Idiopathic pulmonary fibrosis
PF-ILD	Progressive fibrosing interstitial lung disease
PT	Preferred term
PY	Patient year
RMP	Risk Management Plan
SG	Safety grouping
SmPC	Summary of Product Characteristics
SSc	Systemic sclerosis
SSc-ILD	Systemic sclerosis and interstitial lung disease
ULN	Upper limit of normal
VEGFR	Vascular endothelial growth factor receptor

MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

SV.1.1 Method used to calculate exposure

Ex-factory (commercial) sales numbers for Ofev as the basis for the estimation of the post-authorisation (non-clinical trial) exposure are only available for complete months, beginning in October 2014.

The method used to estimate patient exposure to the marketed drug is based on the number of Ofev capsules sold (ex-factory sales). It was assumed that all capsules were used by the patients and that each patient was treated with 2 capsules per day. The total days of medication was calculated by dividing the number of capsules sold (ex-factory sales) by the number of capsules taken per day. The total number of days of medication was then divided by 365.25 to calculate the total patient exposure in PY.

Exposure data is presented by region/country and dose. Exposure data by gender, age, race/ethnicity, and/or indication are not available for Ofev. As there is only 1 formulation for Ofev, a presentation by this variable is not applicable.

SV.1.2 Exposure

The overall cumulative patient exposure to Ofev is 242 108 PY for the period October 2014 to March 2022.

SV.Table 1 Cumulative patient exposure from marketing experience by region/country and dose for Ofev (October 2014 to March 2022)

	Cumulative exposure [PY][1]				
	EU/EEA	**Japan**	**Other**	**US/Canada**	**Total**
Capsule, 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Capsule, 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] All numbers are rounded to the nearest integer.
Data source: Ofev PBRER (reporting interval 16 Oct 2021 to 15 Apr 2022), Table 4 [s00106744-01]

SV.Table 2 Cumulative patient exposure from marketing experience EU/EEA country and dose for Ofev (October 2014 to March 2022)

	Cumulative exposure [PY]	
EU/EEA country	**Capsule 100 mg**	**Capsule 150 mg**
Germany	[redacted]	[redacted]
Denmark	[redacted]	[redacted]
Finland	[redacted]	[redacted]
Norway	[redacted]	[redacted]
Sweden	[redacted]	[redacted]
Ireland	[redacted]	[redacted]
Netherlands	[redacted]	[redacted]
Belgium	[redacted]	[redacted]
France	[redacted]	[redacted]
Italy	[redacted]	[redacted]
Croatia	[redacted]	[redacted]
Slovenia	[redacted]	[redacted]
Austria	[redacted]	[redacted]
Spain	[redacted]	[redacted]
Portugal	[redacted]	[redacted]
Bulgaria	[redacted]	[redacted]
Poland	[redacted]	[redacted]
Romania	[redacted]	[redacted]
Hungary	[redacted]	[redacted]
Czech Republic	[redacted]	[redacted]
Slovak Republic	[redacted]	[redacted]
Greece	[redacted]	[redacted]
Cyprus	[redacted]	[redacted]
Estonia	[redacted]	[redacted]
Latvia	[redacted]	[redacted]
Lithuania	[redacted]	[redacted]
Total	[redacted]	[redacted]

Data source: data on file, EA-005 Ofev exposure (2022 03) PBRER

SV.2 REFERENCES

SV.2.1 Published references

Not applicable.

SV.2.2 Unpublished references

s00106744-01 Periodic Benefit-Risk Evaluation Report Ofev (reporting interval 16 Oct 2021 to 15 Apr 2022. 08 Jun 2022

ABBREVIATIONS

EEA	European Economic Area
EU	European Union
PBRER	Periodic Benefit-Risk Evaluation Report
PY	Patient year
US	United States

MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Ofev is available as prescription medicine only. Pharmacological properties, non-clinical, and clinical data do not indicate an impact on the central nervous system suggestive for stimulant, depressant, hallucinogenic, or mood-elevating effects; or other effects that might lead to dependency. Abuse for illegal purpose is not expected with Ofev. No dependence studies have been conducted in humans or animals.

SVI.2 REFERENCES

Not applicable.

ABBREVIATIONS

EU	European Union

MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Since this is not an initial RMP submission, only an overview of the safety concerns identified at the time of first authorisation is provided below.

SVII.Table 1 Summary of safety concerns at the time of first marketing authorisation

Important identified risks	Diarrhoea
	Liver enzyme and bilirubin elevations
Important potential risks	Venous thromboembolism
	Arterial thromboembolism
	Bleeding
	Perforation
	Hepatic failure
	Treatment of pregnant women and teratogenicity
	Cardiac failure
	QT prolongation
Missing information	Treatment of patients with hepatic impairment (Child Pugh B/C)
	Treatment of Black patients
	Treatment of patients with healing wounds
	Treatment of patients with severe renal impairment or end-stage renal disease
	Treatment of patients receiving full-dose therapeutic anticoagulation
	Interaction of Ofev with hormonal contraceptives
	Concomitant treatment with pirfenidone
	Treatment of breastfeeding women

Data source: Ofev EU-RMP v1.2, date 30 Dec 2014 [s00020175-04].

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Based on data from the paediatric clinical trial 1199-0337, 2 new important potential risks have been added to the Ofev EU-RMP:

- Effect on bone development and growth in paediatric population
- Effect on tooth development disorders in paediatric population

These risks are characterised in Section SVII.3.1.9 and Section SVII.3.1.10.

As agreed with EMA during the procedure EMEA/H/C//003821/X/0057/G, 1 new important identified risk was added to the Ofev EU-RMP:

- Weight decreased in paediatric population

This risk is characterised in Section SVII.3.1.4.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following abbreviations are used in this section:

- IPF: treatment of idiopathic pulmonary fibrosis
- PF-ILD: treatment of other chronic fibrosing ILDs with a progressive phenotype (in the following referred to as progressive fibrosing interstitial lung disease)
- SSc-ILD: treatment of systemic sclerosis associated interstitial lung disease
- Fibrosing ILD in paediatric patients: treatment of fibrosing ILDs in children and adolescents from 6 to 17 years old

An overview of the analyses sets used for the evaluation of risks in clinical trials is given in the following table.

SVII.Table 2 Overview of safety analysis sets

Analysis set	Indication	Description	Trials included
SG-1.1	IPF	Phase III, randomised, double-blind, placebo-controlled trials, 52-weeks duration	1199-0032, 1199-0034
SG-5.1	SSc-ILD	Phase III, randomised, double-blind, placebo-controlled trials, with at least 52-weeks duration	1199-0214
SG-6.1	PF-ILD	Phase III, randomised, double-blind, placebo-controlled trial, 52-weeks duration, in patients with PF-ILD	1199-0247
1199-0337	Fibrosing ILD in paediatric patients	Phase III, randomised, double-blind, placebo-controlled trial with 24 weeks duration, followed by open-label treatment with nintedanib of variable duration, in children and adolescents (6 to 17 year-old) with clinically significant fibrosing ILD[1]	1199-0337
1199-0337 and 1199-0378 (pooled)	Fibrosing ILD in paediatric patients	Pooled analysis including: • 1199-0337 (see above) • 1199-0378: ongoing trial[2] Phase III, prospective open-label trial, at least 3 years duration, in children and adolescents (6 to 17 years old) with clinically significant fibrosing ILD	1199-0337, 1199-0378

[1] After the 24 weeks double-blind period, patients received open-label nintedanib during the whole trial; the treatment groups for the whole trial are designated as placebo/nintedanib and nintedanib/nintedanib.

[2] Snapshot date for trial 1199-0378 for pooled analysis: 31 May 2023. This trial included 30 roll-over patients from trial 1199-0337 and 9 new patients.

SVII.3.1 Presentation of important identified risks and important potential risks

SVII.3.1.1 Important identified risk: Drug-induced liver injury (DILI)

SVII.3.1.1.1 Potential mechanisms

Although the mechanism has not been elucidated, metabolic pathways in the liver may be implicated. Nintedanib is mainly metabolised by esterases. The by far most frequent metabolites in the human ADME trial were BIBF 1202, resulting from ester cleavage of nintedanib, and BIBF 1202-glucuronide, formed by subsequent glucuronidation. The glucuronidation of BIBF 1202 occurs mainly through UGT1A1 (liver and intestine), UGT1A7, UGT1A8, and UGT1A10 (intestine). The major route of elimination of total drug related [14C]-radioactivity after oral administration of [14C]-BIBF 1120 was via faecal/biliary excretion (93.4% of dose) [c01585838-06].

SVII.3.1.1.2 Evidence source and strength of evidence

In clinical trials, liver enzyme and bilirubin elevation AEs occurred more frequently in patients treated with Ofev than in those treated with placebo. Whereas liver enzyme elevations are among the most common reported adverse events in the post-marketing setting, reports of DILI are uncommon.

SVII.3.1.1.3 Characterisation of the risk

Clinical trial data
For the purpose of the RMP, DILI was analysed using the PT 'Drug-induced liver injury'. For detailed information on broader analyses of liver enzyme and bilirubin elevations based on the AESI 'liver-related investigation', please refer to EU-RMP v10.0 [s00020175-26], Section SVII.3.1.2.3.

Indication IPF
Randomised, double-blind, placebo-controlled trials (analysis set SG-1.1)
The frequency of patients with 'Liver related investigation' was higher in the nintedanib than in placebo group: 2.8% placebo, 14.9% nintedanib. The incidence rate ratio and risk ratio for nintedanib vs. placebo showed substantial differences between the treatment groups.

Overall, the number of patients with serious events in the AESI 'Liver-related investigation' was low (0% placebo; 0.5% nintedanib; all of them requiring or prolonging hospitalisation). There were no fatal events. The reported events of 'Liver related investigation' were mainly of mild to moderate severity.
Among these patients, there were 2 cases of DILI in the nintedanib group, while no DILI cases occurred in the placebo group (incidence rate difference of nintedanib vs placebo group [95% CI]: 0.34 [-0.13, 0.80]; risk difference of nintedanib vs placebo group [95% CI]: 0.31 [-0.12, 0.75]). Both cases were considered non-serious. The intensity of DILI was categorised as moderate in 1 case and as severe in the other one. In both patients, DILI led to permanent discontinuation of treatment; the events resolved in 1 patient, whereas the outcome in the other patient was unknown (EU-RMP v10.0 [s00020175-26], Section SVII.3.1.2.3).

Indication SSc-ILD
Randomised, double-blind, placebo-controlled trial (analysis set SG-5.1)
The frequency of patients with 'Liver related investigation' was higher in the nintedanib than in placebo group: 3.1% placebo vs. 13.9% nintedanib. The incidence rate ratio and risk ratio for nintedanib vs. placebo showed substantial differences between the treatment groups.

There were no serious events. The reported events of 'Liver related investigation' were mainly of mild to moderate severity.

Out of these patients, there was 1 patient (0.3%) with DILI in each treatment group. Both events were serious (due to 'other' reason) and both patients had recovered from the event. The intensity of DILI was categorised as severe in the placebo group and as mild in the nintedanib group (EU-RMP v10.0 [s00020175-26], Section SVII.3.1.2.3).

Indication PF-ILD
Randomised, double-blind, placebo-controlled trial (analysis set SG-6.1)
The frequency of patients with 'Liver related investigation' adverse events was higher in the nintedanib than in the placebo group: 6.3% placebo vs. 24.1% nintedanib. The incidence rate ratio and risk ratio for nintedanib vs. placebo showed substantial differences between the treatment groups.

The number of patients with serious events was low with 2 patients in the placebo group and 4 patients in the nintedanib group (requiring/prolonging hospitalisation or serious due to 'other' reasons). The reported events of 'Liver related investigation' were mainly of mild to moderate severity.

There were 6 patients (1.8%) with DILI in the nintedanib group; none in the placebo group. All events were serious and all patients had recovered from the event. The intensity of DILI was categorised as moderate or severe. 1 patient in each treatment group had liver enzyme elevations concurrent with an elevation in bilirubin that met Hy's law criteria (nintedanib: based on local laboratory and not included in the database, placebo: based on central laboratory. Their hepatic enzyme and bilirubin concentrations fully recovered to within normal ranges (EU-RMP v10.0 [s00020175-26], Section SVII.3.1.2.3).

Indication fibrosing ILD in paediatric patients
Randomised, double-blind, placebo-controlled trial (1199-0337)
AEs reported during the double-blind period
1 patient (3.8%) with 'Liver related investigation' AEs was reported in the nintedanib group; there were no patients reported in the placebo group. The reported PT was 'Liver function test increased'; the event was of mild intensity and non-serious. The rate/100 PY was 9.07 (95% CI 1.28, 64.39). The incidence rate difference was 9.07 (95% CI -8.71, 26.85). The median time to first onset was 71 days and the median duration 77 days (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Tables 3.1.1.3, 3.1.1.4, 3.1.1.6).

1 patient (3.8%) with the PT 'Liver injury' was reported in the nintedanib group. The event was of mild intensity and non-serious. The rate/100 PY was 8.88 (95% CI 1.25, 63.07). The incidence rate difference was 8.88 (95% CI -8.53, 26.30). The median time to onset was 85 days and the median duration 65 days (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Tables 3.1.1.2, 3.1.1.4, 3.1.1.6).

No patients with DILI were reported in either treatment group (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722).

AEs reported over the whole trial
3 patients (11.5%) with 'Liver related investigation' AEs were reported in the nintedanib/nintedanib group; the were no patients reported in the placebo/nintedanib group. The reported PTs were 'Hepatic enzyme increased' (n=2) and 'Liver function test increased' (n=1). All events were non-serious; 2 events were of mild intensity and 1 event of moderate intensity. The rate/100 PY was 12.65 (95% CI 4.08, 39.22). The incidence rate difference was 12.65 (95% CI -1.66, 26.96). The median time to onset was 248.0 days and the median

duration was 77.0 days (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Tables 3.2.1.3, 3.2.1.4, 3.2.1.6).

2 patients (7.7%) with the PT 'Liver injury' were reported in the nintedanib/nintedanib group. One of the events was non-serious and of mild intensity, the other event was serious and of moderate intensity. The rate/100 PY was 8.42 (95% CI 2.11, 33.66). The incidence rate difference was 8.42 (95% CI -3.25, 20.08). The median time to onset was 236.0 days and the median duration 47.0 days (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Tables 3.2.1.2, 3.2.1.4, 3.2.1.6).

1 adolescent [redacted] patient (7.7%) in the placebo/nintedanib group was reported with 'DILI' over the whole trial. The event was serious ('other medically important serious event') and of mild intensity. The AE was reported based an increase level of ALT of >5x ULN, with bilirubin within the normal range. As per SMC review, the event was not confirmed as a DILI and restart of treatment was recommended. The rate/100 PY was 7.94 (95% CI 1.12, 56.36). The incidence rate difference was -7.94 (95% CI -23.50, 7.62). The median time to onset was 229 days and the median duration 54 days (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Tables 3.2.1.2, 3.2.1.4, 3.2.1.6, and Listing 3.2.1.9).

Over the whole trial, 4 of the 6 patients reported with hepatobiliary AEs had possibly clinically significant liver enzymes elevations (i.e. ≥3x ULN). In all these cases the liver enzymes elevations normalised upon treatment interruption, dose reduction, or treatment discontinuation (at follow-up in trial 1199-0337 or in the extension trial 1199-0378). None of the cases met the Hy's law criteria.

Trials 1199-0337 and 1199-0378 (pooled)
5 patients (10.4%) were reported with 'Liver related investigation' AEs in the pooled analysis. The reported PTs were 'Hepatic enzyme increased' (n=3), 'Aspartate aminotransferase increased' (n=1), 'Blood alkaline phosphatase increased' (n=1), 'Transaminases increased' (n=1), and 'Liver function test increased' (n=1). All events were non-serious; 4 events were of mild intensity and 3 events of moderate intensity. The incidence rate of 'liver related investigation' AEs was 8.47 per 100 PY (Data Source: data on file, submission-outputs-pediatrics_v2.0, Table 3.2.11).

In the pooled analysis, 2 patients were reported with PT 'Liver injury' (incidence rate 3.30 per 100 PY) and 1 patient was reported with DILI (incidence rate 1.65 per 100 PY) (Data Source: data on file, submission-outputs-pediatrics_v2.0, Table 3.2.11). All 3 patients were reported with the hepatic events in the trial 1199-0337. Up to the snapshot date, there was no new event of Liver injury/DILI in the trial 1199-0378 [c42238250-01].

In trial 1199-0378, 3 additional patients were reported with a hepatic AE. 1 patient was reported with a SAE of hepatitis, which manifested by increased liver enzymes (no values reported). The AE was considered severe, but not assessed as drug-related (as per investigator, the most likely cause of the elevated liver enzymes was viral hepatic inflammation). Following treatment interruption of approximately 1 month, the AE had resolved, and the patient restarted nintedanib treatment on a reduced dose. For 1 patient, AEs

of increased hepatic enzymes and increased transaminases were reported. Both AEs were of moderate intensity and resolved while treatment with nintedanib was interrupted. The third patient was reported with mild increased aspartate aminotransferase, which was ongoing at the time of snapshot. No patients fulfilled the Hy's law criteria.

Post-marketing data
A cumulative search in the BI GSP (up to 15 Apr 2022) was performed for serious events of DILI and serious enzymes of liver enzymes increases and DILI, using the following searches (MedDRA version 24.1):

- MedDRA PT 'Drug-induced liver injury'; DILI cases are reported as always serious events
- Combination of the SMQs 'Liver related investigations, signs and symptoms (broad)', 'Drug related hepatic disorders-comprehensive search (narrow)', 'Cholestasis and jaundice of hepatic origin (narrow)', and 'Hepatitis non-infectious (narrow)', and considered as serious on event level
  (Ofev PBRER, reporting interval 16 Oct 2021 to 15 Apr 2022 [s00106744-01], Section 16.4.2.2).

Serious liver enzymes elevations including DILI
1305 cases were identified with the above search criteria, the majority being report from study (other studies 75.6%, individual patient use 1.9%). Most patients were male: 56.2% vs. 38.8% female. Most cases were reported in patients being between 65 to 74 years (39.5%) and between 75 to 84 years old (30.0%).

There were 39 fatal cases (3.0%). Other outcomes were reported as follows: 35.2% recovered/resolved, 34.6% missing/not applicable/not reported/unknown, 27.4% not recovered/not resolved/ongoing, 3.1% recovering/resolving, and 0.5% recovered/resolved with sequelae.
DILI
73 cases were identified with the above search criteria, the majority being report from study (other studies 72.6%, individual patient use 4.1%). Most patients were male: 57.5% vs. 39.7% female. Most cases were reported in patients being between 65 to 74 years (43.8%) and between 75 to 84 years old (26.0%).

There were 3 fatal cases (4.1%). Other outcomes were reported as follows: 54.8% recovered/resolved, 21.9% missing/not applicable/not reported/unknown, 13.7% not recovered/not resolved/ongoing, and 6.8% recovering/resolving.

Conclusion
The available safety information does not suggest any change to the current characterisation of this safety concern. The EU-RMP and the EU-SmPC correctly reflect the current benefit-risk profile and this safety concern; no updates are warranted at present.

SVII.3.1.1.4 Risk factors and risk groups

A study based on the DILIN in the US assessed the characteristics of DILI patients aged 65 years and above. In this cohort (n = 149), 60% of the patients were female and 85% were White. The highest proportion of patients (58%) took at least 6 medications. Among the DILI patients, antimicrobial agents were the most common class of causative drugs with 57.7% [P15-06939].

Indication IPF
DILI was reported in 2 patients (0.3%) in the nintedanib group and was not reported in the placebo group (EU-RMP v10.0 [s00020175-26], Section SVII.3.1.2.3).

It is important to note that a broader analysis of 'Liver related investigation' suggested that the subgroup of Asian patients and the subgroup of female patients treated with Ofev may be at higher risk of 'Liver related investigation' than White patients and male patients, respectively.

Based on PK population analysis, patients with low body weight (<65 kg), Asian and female patients have a higher risk of elevations of liver enzymes. Nintedanib exposure increased linearly with patient age, which may also result in a higher risk of developing liver enzyme elevations.

For details on the subgroup analyses, please refer to EU-RMP v10.0 [s00020175-26], Section SVII.3.1.2.3.

Indication SSc-ILD
DILI was reported in 1 patient (0.3%) in each treatment group (nintedanib and placebo) (EU-RMP v10.0 [s00020175-26], Section SVII.3.1.2.3).

It is important to note that a broader analysis of 'Liver related investigation' indicated a higher frequency in female than male patients and in Asian than in White/Black patients. There was an increase in frequency with increasing age. No clinically meaningful difference in frequency of 'Liver related investigation' between nintedanib and placebo was observed in the remaining subgroups.

For details on the subgroup analyses, please refer to EU-RMP v10.0 [s00020175-26], Section SVII.3.1.2.3.

Indication PF-ILD
DILI was reported in 6 (1.8%) patients in the nintedanib group and was not reported in the placebo group (EU-RMP v10.0 [s00020175-26], Section SVII.3.1.2.3).

There were no observational data on risk factors for liver related investigation in patients with PF-ILD.

It is important to note that, in line with the known safety profile of nintedanib, a broader subgroup analysis of AEs related to elevated liver enzymes showed that female gender, Asian

patients, and patients with low body weight have a higher risk for liver enzyme elevations with nintedanib treatment. No clinically meaningful differences were observed in the remaining subgroups.

For details on the subgroup analyses, please refer to EU-RMP v10.0 [s00020175-26], Section SVII.3.1.2.3.

Indication fibrosing ILD in paediatric patients
The DILIN was established in 2003 to recruit patients with suspected DILI and create a repository of biological samples for analysis. Of the 300 patients enrolled, children represented only a small percentage (<10%). In this prospective observational study, idiosyncratic DILI in children was most commonly caused by antimicrobial or central nervous system agents and usually presented with a hepatocellular injury pattern [P09-00288, R22-2184].

There are no observational data on risk factors for liver related investigations/DILI in paediatric patients with fibrosing ILD.

In trial 1199-0337, all hepatobiliary disorders were reported in female patients. 5 of 6 the patients with reported AE under hepatobiliary disorders were in the age subgroup 12 to <18 years. However, due to relatively low number of patients in the evaluated subgroups, no firm conclusions could be drawn based on subgroup analyses.

SVII.3.1.1.5 Preventability

Hepatic transaminase and bilirubin levels should be investigated before the initiation of treatment with Ofev, and periodically thereafter (e.g. at each patient visit) or as clinically indicated. Close monitoring is recommended in patients with risk factors (Asian, females, low body weight, and advanced age).

If transaminase (AST or ALT) elevations >3x ULN are measured, dose reduction or interruption of the therapy with Ofev is recommended and the patient should be monitored closely. Once transaminases have returned to baseline values, treatment with Ofev may be resumed at the full dose (e.g. 150 mg twice daily in adult patients) or reintroduced at a reduced dose (e.g. 100 mg twice daily in adult patients), which subsequently may be increased to the full dose. If any liver test elevations are associated with clinical signs or symptoms of liver injury, e.g. jaundice, treatment with Ofev should be permanently discontinued. Alternative causes of the liver enzyme elevations should be investigated. Similar management of liver enzyme elevations and hyperbilirubinaemia is recommended in the paediatric population.

SVII.3.1.1.6 Impact on the risk-benefit balance of the product

Administration of Ofev is associated with elevations of liver enzymes and bilirubin, including DILI. Most hepatic events are mild or moderate in intensity. Severe hepatic events are rare. In the phase III clinical trials with Ofev (SG-1.1, SG-5.1, and SG.6.1), elevations of liver enzymes or bilirubin were generally manageable with dose interruption, and/or dose

reduction [U13-2384-01, c22686034-01]. Increases in liver enzymes and bilirubin are generally reversible upon dose reduction or interruption. In the paediatric population, the hepatic events were in line with the data in adult patients with regard to severity, outcome, and management of liver enzymes elevations. Close monitoring and appropriate actions are recommended to prevent serious/severe events.

SVII.3.1.1.7 Public health impact

There is no public health impact of liver enzyme and bilirubin elevations resulting in DILI in patients treated with Ofev.

SVII.3.1.2 Important identified risk: Bleeding

SVII.3.1.2.1 Potential mechanisms

VEGFR inhibition might be associated with an increased risk of bleeding.

SVII.3.1.2.2 Evidence source and strength of evidence

In the clinical trials in adult patients, the frequency of patients who experienced bleeding AEs was slightly higher or similar in the nintedanib group than in the placebo group. Bleeding events were mostly not serious in clinical trials. In the post-marketing period, non-serious and serious bleeding events have been reported (including patients with or without anticoagulant therapy or other drugs that could cause bleeding).

SVII.3.1.2.3 Characterisation of the risk

Clinical trial data
Indication IPF
The analysis of bleeding was based on the AESI 'Bleeding'. For details of the PTs included in this AESI, refer to the RMP analyses v3.0, Listing 3.10.1 (data on file).

Randomised, double-blind, placebo-controlled trials (analysis set SG-1.1)
The frequency of patients with bleeding was 7.8% in the placebo group and 10.3% in the nintedanib group. The incidence rate ratio and risk ratio for nintedanib vs. placebo showed no substantial differences between the treatment groups (table below).

Overall, the number of patients with serious events was <2% in both treatment groups, most of them requiring or prolonging hospitalisation. There was 1 fatal event in the nintedanib group. The reported events of bleeding were mainly of mild to moderate intensity in both treatment groups. The majority of the patients had recovered from the bleeding. The median time to first onset of bleeding was shorter in the nintedanib group; the median duration of bleeding was longer in the nintedanib group. Further details are given in the table below.

SVII.Table 3 Overview on bleeding - SG-1.1 - TS

	Placebo	**Nintedanib 150 b.i.d.**
Number of patients treated, N (%)	423 (100.00)	638 (100.00)
Total overall time at risk (PY)	396	559
Patients with bleeding, N (%)	33 (7.80)	66 (10.34)
95% CI	5.61, 10.75	8.21, 12.95
Rate/100 PY	8.34	11.82
Incidence rate ratio (95% CI)[1]	1.42 (0.93, 2.15)	
Incidence rate difference (95% CI)[1]	3.47 (−0.56, 7.50)	
Risk ratio (95% CI)[1]	1.33 (0.89, 1.98)	
Risk difference (95% CI)[1]	2.54 (−0.94, 6.03)	
Seriousness[2], N (%)		
Fatal	0 (0.00)	1 (0.16)
Immediately life-threatening	1 (0.24)	2 (0.31)
Requires or prolongs patient hospitalisation	6 (1.42)	7 (1.10)
Outcome[3], N (%)		
Recovered	29 (6.86)	55 (8.62)
Not yet recovered	2 (0.47)	7 (1.10)
Intensity, N (%)		
Mild	22 (5.20)	44 (6.90)
Moderate	5 (1.18)	15 (2.35)
Severe	6 (1.42)	7 (1.10)
Time to first onset, median (days)	142.0	71.5
Duration, median (days)	5.0	14.5

[1] Ratio nintedanib 150 b.i.d. vs. placebo

[2] Patients can be counted in more than 1 seriousness category.

[3] Each of the outcomes could be individually assigned to an event, i.e. not recovered would not be a subset of fatal.

Data source: data on file, analyses for RMP analyses v3.0, Tables 3.1.2; 3.1.3; 3.1.4; 3.1.5

Indication SSc-ILD

Randomised, double-blind, placebo-controlled trial (analysis set SG-5.1)

The frequency of patients with bleeding was 8.3% in the placebo group and 11.1% in the nintedanib group. The incidence rate ratio and risk ratio for nintedanib vs. placebo showed no substantial differences between the treatment groups (see table below).

Overall, the number of patients with serious events was low (≤1.4%) in both treatment groups, most of them requiring or prolonging hospitalisation. There were no fatal events. The reported events of bleeding were mainly of mild to moderate intensity in both treatment groups. The majority of the patients had recovered from the event. The median time to first

onset of bleeding and the median duration of bleeding was longer in the nintedanib than in the placebo group. Further details are given in the table below.

SVII.Table 4 Overview on bleeding - SG-5.1 - TS

	Placebo	**Nintedanib 150 b.i.d.**
Number of patients treated, N (%)	288 (100.0)	288 (100.0)
Total overall time at risk (PY)	266.83	243.45
Patients with bleeding, N (%)	24 (8.3)	32 (11.1)
95% CI	5.7, 12.1	8.0, 15.3
Rate/100 PY	8.99	13.14
Incidence rate ratio (95% CI)[1]	1.46 (0.86, 2.48)	
Incidence rate difference (95% CI)[1]	4.15 (-1.65, 9.95)	
Risk ratio (95% CI)[1]	1.33 (0.81, 2.21)	
Risk difference (95% CI)[1]	2.78 (-2.06, 7.61)	
Seriousness[2], N (%)	2 (0.7)	4 (1.4)
Requires or prolongs patient hospitalisation	2 (0.7)	4 (1.4)
Other	0 (0.0)	1 (0.3)
Outcome[3], N (%)		
Recovered	23 (8.0)	28 (9.7)
Not yet recovered	1 (0.3)	4 (1.4)
Intensity, N (%)		
Mild	22 (7.6)	21 (7.3)
Moderate	1 (0.3)	9 (3.1)
Severe	1 (0.3)	2 (0.7)
Time to first onset, median (days)	80.5	93.0
Duration, median (days)	15.0	23.0

[1] Ratio nintedanib 150 b.i.d. vs. placebo

[2] Patients can be counted in more than 1 seriousness category.

[3] Each of the outcomes could be individually assigned to an event, i.e. not recovered would not be a subset of fatal.

Data source: data on file, RMP v7.0 analyses for SSc-ILD, Tables 3.1.2, 3.1.4, 3.1.5, 3.1.6, System: Blood, Safety topic: Bleeding (SMQ − narrow)

Indication PF-ILD

The analysis of bleeding was based on the narrow SMQ ‘Haemorrhage terms (excluding laboratory terms)’.

Randomised, double-blind, placebo-controlled trial (analysis set SG-6.1)

The frequency of patients with bleeding was 12.7% in the placebo group and 11.1% in the nintedanib group. The incidence rate ratio and risk ratio for nintedanib vs. placebo showed no substantial differences between the treatment groups (see table below).

Overall, the number of patients with serious events was low (≤1.5%) in both treatment groups, most of them requiring or prolonging hospitalisation. There was 1 fatal event in the placebo group. The reported events of bleeding were mainly of mild to moderate intensity in both treatment groups. The majority of the patients had recovered from the event. The median time to first onset of bleeding was shorter in the nintedanib group and the median duration of bleeding was longer in the nintedanib than in the placebo group. Further details are given in the table below.

SVII.Table 5 Overview on bleeding - SG-6.1 – TS

	Placebo	**Nintedanib 150 b.i.d.**
Number of patients treated, N (%)	331 (100.0)	332 (100.0)
Total overall time at risk (PY)	294.36	271.59
Patients with bleeding, N (%)	42 (12.7)	37 (11.1)
95% CI	9.5, 16.7	8.2, 15.0
Rate/100 PY	14.27	13.62
Incidence rate ratio (95% CI)[1]	0.95 (0.61, 1.49)	
Incidence rate difference (95% CI)[1]	−0.65 (−6.80, 5.51)	
Risk ratio (95% CI)[1]	0.88 (0.58, 1.33)	
Risk difference (95% CI)[1]	−1.54 (−6.48, 3.39)	
Seriousness[2], N (%)	5 (1.5)	3 (0.9)
Fatal (all causes)	1 (0.3)	0 (0.0)
Immediately life-threatening	1 (0.3)	0 (0.0)
Requires or prolongs patient hospitalisation	3 (0.9)	2 (0.6)
Other	0 (0.0)	1 (0.3)
Outcome[3], N (%)		
Recovered	25 (7.6)	29 (8.7)
Not yet recovered	13 (3.9)	8 (2.4)
Fatal	1 (0.3)	0 (0.0)
Unknown	3 (0.9)	0 (0.0)
Intensity, N (%)		
Mild	31 (9.4)	30 (9.0)
Moderate	9 (2.7)	7 (2.1)
Severe	2 (0.6)	0 (0.0)
Time to first onset, median (days)	146.0	133.0
Duration, median (days)	7.0	11.0

Note: data over the 52 weeks period were analysed.

[1] Ratio or difference nintedanib 150 b.i.d. vs. placebo

[2] Patients can be counted in more than 1 seriousness category.

[3] Patients are counted only once; in case of multiple episodes, only the worst outcome is counted.

* Significantly different from 1

Significantly different from 0

Data source: data on file, RMP v9.0 analyses for PF-ILD, Tables 3.1.1.1.1.2, 3.1.1.1.1.4, 3.1.1.1.1.5; System: Blood, Safety topic: Bleeding

Data source: CTR 1199-0247 [c26471552-01]: Appendix 16.1.13.1, Table 8.1.5.1.2

Indication fibrosing ILD in paediatric patients

Randomised, double-blind, placebo-controlled trial (1199-0337)

AEs reported during the double-blind period

There were 2 patients with events of bleeding in the placebo group (reported PTs 'Rectal haemorrhage' [n=1] and 'Epistaxis' [n=2]) and 1 patient in the nintedanib group (reported PT 'Lower gastrointestinal haemorrhage' [n=1]) (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Table 3.1.1.4). The reported events of bleeding were non-serious and of mild intensity in both treatment groups. Further details are given in the table below.

SVII.Table 6 Overview on bleeding – Trial 1199-0337 (double-blind period) – TS

	Placebo	**Nintedanib**
Number of patients treated, N (%)	13 (100.00)	26 (100.00)
Total overall time at risk (PY)	4.93	11.35
Patients with bleeding, N (%)	2 (15.4)	1 (3.8)
95% CI	4.3, 42.2	0.7, 18.9
Rate/100 PY	40.54 (10.14, 162.09)	8.81 (1.24, 62.57)
Incidence rate ratio (95% CI)[1]	0.22 (0.02, 2.40)	
Incidence rate difference (95% CI)[1]	-31.72 (-90.50, 27.05)	
Risk ratio (95% CI)[1]	0.25 (0.02, 2.51)	
Risk difference (95% CI)[1]	-11.54 (-32.50, 9.42)	
Seriousness[2], N (%)	0 (0.0)	0 (0.0)
Outcome[3], N (%)		
Recovered	2 (15.4)	1 (3.8)
Intensity, N (%)		
Mild	2 (15.4)	1 (3.8)
Time to first onset, median (days)	26.0	166.0
Duration, median (days)	2.0	1.0

[1] Ratio nintedanib vs. placebo

[2] Patients can be counted in more than 1 seriousness category.

[3] Each of the outcomes could be individually assigned to an event, i.e. not recovered would not be a subset of fatal.

MedDRA version used for reporting: 24.1

Data source: data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Tables 3.1.1.2, 3.1.1.4, 3.1.1.5, 3.1.1.6

AEs reported over the whole trial

4 patients (30.8%) with bleeding events were reported in the placebo/nintedanib group and 2 patients (7.7%) in the nintedanib/nintedanib group. In the placebo/nintedanib group, the reported PTs were 'Rectal haemorrhage' (n=1) and 'Epistaxis' (n=4); in the nintedanib/nintedanib group the reported PTs were 'Lower gastrointestinal haemorrhage' (n=1) and 'Heavy menstrual bleeding' (n=1). All events were non-serious, and mainly of mild intensity. In the placebo/nintedanib group, the rate/100 PY was 42.57 (95% CI 15.98, 113.42) and 8.57 (95% CI 2.14, 34.27) in the nintedanib/nintedanib group. The incidence rate

ratio was 0.20 (95% CI 0.04, 1.10) and the incidence rate difference -34.00 (95% CI -77.37, 9.38). In the placebo/nintedanib group, the median time to onset was 160.5 days and the median duration 2 days. In the nintedanib/nintedanib group, the median time to onset was 172 days and the median duration 5.5 days (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Tables 3.2.1.2, 3.2.1.4, 3.2.1.6).

Trials 1199-0337 and 1199-0378 (pooled)
A total of 7 (14.6%) patients were reported with the AEs in the bleeding safety topic during the nintedanib-exposure period of trials 1199-0337 and 1199-0378 pooled. The incidence rate of bleeding (12.7 per 100 PY) during the nintedanib-exposure period is lower than the incidence rate of bleeding observed with placebo during the double-blind period of the trial 1199-0337 (incidence rate 40.54 per 100 PY).

SVII.Table 7 AEs and SAEs by safety topic during the nintedanib-exposure period of trial 1199-0337 alone or of trials 1199-0337 and 1199-0378 (pooled) – TS[1]

Organ system ***Safety topic***	**Patients with**	**Trial 1199-0337 (nintedanib-exposure period)**		**Trials 1199-0337/0378 (pooled nintedanib-exposure period)**	
		N (%)	**Rate/ 100 PY**	**N (%)**	**Rate/ 100 PY**
Number of patients		**37 (100.0)**		**48 (100.0)**	
Blood AEs					
Bleeding[2]	any AE	4 (10.8)	13.6	7 (14.6)	12.7
	SAE	0	0	0	0

[1] Only patients who received at least 1 dose of nintedanib in trial 1199-0337 and/or trial 1199-0378 up to the snapshot date were included in this analysis set

[2] Grouping of MedDRA PTs

Data source: CO [c42238250-01], based on Table 26

3 patients experienced AEs of bleeding in the ongoing trial 1199-0378. New AEs reported were ‘Epistaxis’, ‘Haemoptysis’ and ‘Haematuria’. All AEs were non-serious and resolved while treatment with nintedanib was maintained [c35674886-03].

Post-marketing data
A cumulative search in the BI GSP (up to 15 Apr 2022) was performed using the narrow SMQ ‘Haemorrhage terms (excluding laboratory terms)’ (MedDRA version 24.1) (Ofev PBRER, reporting interval 16 Oct 2021 to 15 Apr 2022 [s00106744-01], Section 16.4.2.3).

7003 cases were identified with the above search criteria, the majority being report from study (other studies 88.6%, individual patient use 0.8%).

Most patients were male: 61.1% vs. 36.9% female. Most cases were reported in patients being between 65 to 74 years (32.9%) and between 75 to 84 years old (36.4%).

The majority of cases were non-serious (81.1%). The outcome was reported as follows: missing/not applicable/not reported/unknown (45.3%), not recovered/not resolved/ongoing (33.0%), recovered/resolved (27.7%), recovering/resolving (2.8%), fatal (2.0%), and recovered/resolved with sequelae (0.9%).

140 cases reported 151 events with a fatal outcome. The 151 events can be grouped by source/origin of bleeding into central nervous, gastrointestinal, general, respiratory, skin, urogenital, and vascular body systems.

In the fatal cases, the haemorrhagic events are confounded by concomitant underlying disease and complex medical conditions associated with chronic, life-threatening IPF.

The most commonly reported MedDRA PTs (≥1.3% of the cases) involve the gastrointestinal and respiratory system, representing lower gastrointestinal bleeding (haematochezia and rectal haemorrhage) in the gastrointestinal tract, and epistaxis and haemoptysis in the respiratory system. The most frequently reported events are in line with preceding clinical trial experience.

Conclusion
The EU-RMP and the EU-SmPC correctly reflect the current benefit-risk profile and this safety concern; no updates are warranted at present.

SVII.3.1.2.4 Risk factors and risk groups

Indication IPF
Patients at known risk for bleeding including patients with inherited predisposition to bleeding or patients receiving a full dose of anticoagulant treatment were not included in the INPULSIS trials.

Subgroup analyses showed similar results between treatment groups. No clinically meaningful difference in frequency of bleeding was observed with regard to gender, race, age, renal impairment, or smoker status (table below).

SVII.Table 8 Frequency of bleeding AEs by subgroup - SG-1.1 – TS

Characteristic	Placebo			Nintedanib 150 b.i.d.		
	Patients with AE, n (%)	Time at risk for bleeding [PY]	IR [100 PY]	Patients with AE, n (%)	Time at risk for bleeding [PY]	IR [100 PY]
Patients with any bleeding AE, n (%)	33 (7.80)	396	8.34	66 (10.34)	559	11.82
Male	25 (7.5)	311.20	8.03	48 (9.5)	455.89	10.53
Female	8 (9.0)	84.35	9.48	18 (13.7)	102.70	17.53
White	23 (9.3)	229.86	10.01	43 (11.9)	315.09	13.65
Asian	4 (3.1)	124.12	3.22	14 (7.2)	165.44	8.46
Age <65 years	13 (9.0)	136.41	9.53	27 (10.5)	237.05	11.39
Age ≥65 to <75 years	16 (7.4)	201.59	7.94	26 (9.9)	232.04	11.20
Age ≥75 years	4 (6.5)	57.55	6.95	13 (11.1)	89.50	14.53
No renal impairment at baseline	19 (10.7)	168.07	11.30	28 (9.2)	285.75	9.80
Mild renal impairment at baseline	8 (4.2)	182.23	4.39	32 (12.5)	212.53	15.06
Moderate renal impairment at baseline	6 (11.5)	45.04	13.32	6 (8.1)	58.17	10.32
Never smoked	10 (8.2)	115.74	8.64	13 (7.5)	151.79	8.56
Ex-/current smoker	23 (7.6)	279.81	8.22	53 (11.4)	406.80	13.03

Frequencies may not sum to totals as not all levels of categories are displayed.

Data source: data on file, RMP analyses v3.0; Tables 3.1.2; 3.1.5; 3.1.8; 3.1.9; 3.1.10; 3.1.11; 3.1.12

Indication SSc-ILD

Because systemic sclerosis may lead to diffuse vasculopathy, both telangiectasias and gastric antral vascular ectasia are more common than in the general population (gastric antral vascular ectasia occurs in 5.7 to 22.3% of patients with SSc and telangiectasias are the T in CREST syndrome). Both predispose patients with SSc to higher risks of bleeding than the general population [R16-0051, R18-4024]. However, no observational studies that reported the incidence or prevalence of bleeding in patients with SSc were identified.

Subgroup analyses showed comparable results between treatment groups. No clinically meaningful difference in frequency of bleeding was observed with regard to gender, race, age, renal impairment, or body weight (data on file, RMP v7.0 analyses for SSc-ILD, Tables 3.1.9 to 3.1.13, System: Blood, Safety topic: Bleeding [SMQ – narrow]).

Indication PF-ILD

There were no observational data on risk factors for bleeding in patients with PF-ILD.

No clinically meaningful difference in frequency of bleeding was observed in the analysed subgroups (data on file, RMP v9.0 analyses for PF-ILD, Tables 3.1.1.1.1.8 to 3.1.1.1.1.10, CTR 1199-0247 [c26471552-01], Section 15.3, Tables 15.3.1.1.5.1.1: 8, 15.3.1.1.5.2.1: 8, 15.3.1.1.5.3.1: 8, and CTR 1199-0247 [c26471552-01], Appendix 16.1.13.1, Table 10.4.1.3.1.8 - System: Blood, Safety topic: Bleeding).

Indication fibrosing ILD in paediatric patients
There are no observational data on risk factors for bleeding in paediatric patients with fibrosing ILD.

Subgroup analyses showed comparable results between treatment groups. No clinically meaningful difference in frequency of bleeding was observed with regard to age, gender, use of immunosuppressant or use of corticosteroid at baseline. However, due to low number of bleeding events and relatively low number of patients in the evaluated subgroups, no firm conclusions could be drawn with regard to the frequency of bleeding in the analysed subgroups.

SVII.3.1.2.5 Preventability

Preventability of bleeding in the context of Ofev use is not known. Patients with inherited predisposition to bleeding or patients receiving full dose anticoagulant treatment should only be treated with Ofev if the anticipated benefit outweighs the potential risk.

SVII.3.1.2.6 Impact on the risk-benefit balance of the product

Bleeding can lead to hospitalisation, and can be fatal or life-threatening. Severe bleedings may need to be treated with a surgical intervention and/or may require blood transfusions.

SVII.3.1.2.7 Public health impact

There is no public health impact of bleeding in patients treated with Ofev.

SVII.3.1.3 Important identified risk: Myocardial infarction

SVII.3.1.3.1 Potential mechanisms

ATE has been associated with VEGF inhibitors in combination treatment with chemotherapy for patients with cancer [R12-3827].

SVII.3.1.3.2 Evidence source and strength of evidence

In clinical trials with IPF patients, while AEs reflecting ischaemic heart disease were balanced between the nintedanib and placebo groups, a higher percentage of patients experienced MI in the nintedanib group (1.7%) compared to the placebo group (0.5%). In clinical trials with SSc patients, no MI was reported in the nintedanib group. In the clinical trial with PF-ILD patients, 3 patients with MI were reported in each treatment group.

SVII.3.1.3.3 Characterisation of the risk

Clinical trial data
Indication IPF
The analysis of MI was based on the AESI 'Myocardial infarction', which consisted in the narrow SMQ 'Myocardial infarction'. For details of the PTs included in this AESI, refer to the RMP analyses v3.0, Listing 3.10.1 (data on file).

Randomised, double-blind, placebo-controlled trials (analysis set SG-1.1)
The frequency of patients with MI was low, but higher in the nintedanib group: 0.5% placebo, 1.7% nintedanib. The incidence rate ratio and risk ratio for nintedanib vs. placebo showed differences between the treatment groups (table below).
Overall, the number of patients with serious events was low (≤0.2% in the placebo and ≤0.3% in the nintedanib group, most of them requiring or prolonging hospitalisation). There was 1 fatal event in the placebo and 2 fatal events in the nintedanib group. The reported events of MI were of moderate or severe intensity in the placebo group and mainly of severe intensity in the nintedanib group. The majority of patients had recovered from the MI. Further details are given in the table below.

SVII.Table 9 Overview on MI - SG-1.1 – TS

	Placebo	**Nintedanib 150 b.i.d.**
Number of patients treated, N (%)	423 (100.00)	638 (100.00)
Total overall time at risk (PY)	413	593
Patients with MI, N (%)	2 (0.47)	11 (1.72)
95% CI	0.12, 1.94	1.03, 3.35
Rate/100 PY	0.48	1.85
Incidence rate ratio (95% CI)[1]	3.83 (0.85, 17.27)	
Incidence rate difference (95% CI)[1]	1.37 (0.09, 2.66)	
Risk ratio (95% CI)[1]	3.65 (0.81,16.36)	
Risk difference (95% CI)[1]	1.25 (0.05, 2.45)	
Seriousness[2], N (%)		
Fatal	1 (0.24)	2 (0.31)
Immediately life−threatening	0 (0.00)	2 (0.31)
Requires or prolongs patient hospitalisation	1 (0.24)	8 (1.25)
Other	0 (0.00)	1 (0.16)
Outcome[3], N (%)		
Recovered	1 (0.24)	7 (1.10)
Not yet recovered	0 (0.00)	1 (0.16)
Sequelae	0 (0.00)	1 (0.16)
Intensity, N (%)		
Moderate	1 (0.24)	1 (0.16)
Severe	1 (0.24)	10 (1.57)
Time to first onset, median (days)	290.5	110.0
Duration, median (days)	2.5	9.0

[1] Ratio nintedanib 150 b.i.d. vs. placebo

[2] Patients can be counted in more than 1 seriousness category.

[3] Each of the outcomes could be individually assigned to an event, i.e. not recovered would not be a subset of fatal.

Data source: data on file, analyses for RMP analyses v3.0, Tables 3.1.2; 3.1.3; 3.1.4; 3.1.5

Indication SSc-ILD

Randomised, double-blind, placebo-controlled trial (analysis set SG-5.1)

There were 2 patients (0.7%) with MI in the placebo group only, with 1 patient having a fatal outcome of the event. 1 patient had recovered from the event. With regard to intensity, 1 of the event was categorised as moderate, the other as severe (data on file, RMP v7.0 analyses for SSc-ILD, Tables 3.1.2, 3.1.4, 3.1.5, 3.1.6, System: Cardiovascular, Safety topic: Myocardial infarction (SMQ − narrow)).

Indication PF-ILD

The analysis of MI was based on the narrow SMQ 'Myocardial infarction'.

Randomised, double-blind, placebo-controlled trial (analysis set SG-6.1)

3 patients in each treatment group were reported with MI. All events were serious, mainly requiring or prolonging hospitalisation. The intensity of the events was categorised as either moderate or severe; all patients had recovered from the event. The time to first onset and the median duration were shorter in the placebo group. Further details are given in the table below.

SVII.Table 10 Overview on MI - SG-6.1 – TS

	Placebo	**Nintedanib 150 b.i.d.**
Number of patients treated, N (%)	331 (100.0)	332 (100.0)
Total overall time at risk (PY)	314.15	291.34
Patients with MI, N (%)	3 (0.9)	3 (0.9)
95% CI	0.3, 2.6	0.3, 2.6
Rate/100 PY	0.95	1.03
Incidence rate ratio (95% CI)[1]	1.08 (0.22, 5.34)	
Incidence rate difference (95% CI)[1]	0.07 (−1.51, 1.66)	
Risk ratio (95% CI)[1]	1.00 (0.20, 4.90)	
Risk difference (95% CI)[1]	0.00 (−1.44, 1.44)	
Seriousness[2], N (%)	3 (0.9)	3 (0.9)
Immediately life−threatening	1 (0.3)	0 (0.0)
Requires or prolongs patient hospitalisation	3 (0.9)	3 (0.9)
Outcome[3], N (%)		
Recovered	3 (0.9)	3 (0.9)
Intensity, N (%)		
Moderate	2 (0.6)	1 (0.3)
Severe	1 (0.3)	2 (0.6)
Time to first onset, median (days)	199.0	251.0
Duration, median (days)	2.0	5.0

Note: data over the 52 weeks period were analysed.

[1] Ratio or difference nintedanib 150 b.i.d. vs. placebo

[2] Patients can be counted in more than 1 seriousness category.

[3] Patients are counted only once; in case of multiple episodes, only the worst outcome is counted.

* Significantly different from 1

Significantly different from 0

Data source: data on file, RMP v9.0 analyses for PF-ILD, Tables 3.1.1.1.1.2, 3.1.1.1.1.4, 3.1.1.1.1.5; System: Cardiovascular, Safety topic: Myocardial infarction

Data source: CTR 1199-0247 [c26471552-01]: Appendix 16.1.13.1, Table 8.1.5.1.2

Indication fibrosing ILD in paediatric patients

Randomised, double-blind, placebo-controlled trial (1199-0337)

No cases of MI were reported either in the double-blind period or in the whole trial in any of the treatment groups (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722).

Trials 1199-0337 and 1199-0378 (pooled)

Up to the snapshot date, there was no event of myocardial infarction in the paediatric trials 1199-0337 and 1199-0378 [c42238250-01].

Post-marketing data

A cumulative search in the BI GSP (up to 15 Apr 2022) was performed using the narrow SMQ 'Myocardial infarction' (MedDRA version 24.1) (Ofev PBRER, reporting interval 16 Oct 2021 to 15 Apr 2022 [s00106744-01], Section 16.4.2.4).

957 cases were identified with the above search criteria, the majority being reports from study (other studies 77.6%, individual patient use 2.5%).

Most patients were male: 72.6% vs. 24.6% female. Most cases were reported in patients being between 65 to 74 years (35.3%) and between 75 to 84 years old (36.2%).

All but 8 cases were serious. The outcome was reported as follows: missing/not applicable/not reported/unknown (37.4%), recovered/resolved (27.2%), fatal (24.3%), not recovered/not resolved/ongoing (10.6%), recovering/resolving (3.4%), and recovered/resolved with sequelae (2.1%)

Overall, 233 events with fatal outcome were reported that concerned 48 females and 175 males (10 events with no information). Age ranged from 36 to 92 years with the majority of patients (70.0%) aged 65 to 84 years. The age range includes an outlier of a 36 year-old male who had significant risk factors on being a smoker (15 pack years) and overweight (BMI of 33).

Risk factors for the fatal MI event (42.9% of cases), included mainly hypertension, history of arteriosclerosis or coronary artery disease, smoking, diabetes or dyslipidaemia/ hyperlipidaemia/hypercholesterolaemia or concomitant medications that may indicate presence of cardiovascular risk factors (21.5%), e.g. ASA or statins were reported in 47.6% of cases. In 38.2.% of the cases, the documentation was too poor to perform a proper medical and causal assessment. No striking case, no cluster or pattern was identified upon review of the myocardial events with a fatal outcome.

The most commonly reported MedDRA PTs included myocardial infarction (77.5%), acute myocardial infarction (12.9%), and coronary artery occlusion (6.8%).

Conclusion
The available safety information does not suggest any change to the current characterisation of this safety concern. The EU-SmPC and the EU-RMP correctly reflect the current benefit-risk profile and this safety concern; no updates are warranted at present.

SVII.3.1.3.4 Risk factors and risk groups

Indication IPF
Patients with a recent history of myocardial infarction or stroke were excluded from the INPULSIS trials. Based on the low number of patients affected in clinical trials, no clinically meaningful difference in frequency of MI was observed with regard to gender, race, age, renal impairment, or smoker status. For information on this data, refer to the RMP analyses v3.0, Tables 3.1.8 through 3.1.12 (data on file).

Independently of treatment, there is an increased risk within the IPF population for cardiovascular events including coronary artery disease, MI, and stroke based on epidemiological data [R13-0297, R11-5057, R14-3479, c25243997-01].

Indication SSc-ILD
As a disease with underlying vasculopathy, patients with SSc are at increased risk of coronary artery disease [R18-3842]. Thus, MI is one of the known disease manifestations SSc. Using data from the Health Improvement Network general practice populations in the UK, the incidence rate of MI (excluding unstable angina and angina) among patients with SSc was 4.4 per 1000 PY; the HR for developing MI was 1.80 (95% CI 1.07, 3.05) after control for demographic and cardiovascular factors and use of non-steroidal or glucocorticoid medications compared to the control population (up to 10 controls without SSc in the database for each patient with SSc) [R18-3843]. In another population-based study from Taiwan, patients with SSc experienced MIs at 2.5 times the rate of the general population (after adjustment for age, gender and other predictors of coronary artery disease). The incidence rate of MI among patients with SSc in this population was 5.4 per 1000 PY [R18-3784].

There are very limited observational data available on the risk of MI in SSc-ILD patients. A single centre retrospective study from Israel was identified that reported the long-term (4 to 7 years) treatment outcomes of 26 patients with SSc-ILD who were treated with cyclophosphamide. In this study, 1 patient (3.8%) died of an MI 1 year after completion of treatment [R18-4018].

Due to the low numbers of patients affected in SG-5.1, no clinically meaningful differences in the subgroup analyses can be observed with regard to gender, race, age, renal impairment, or body weight (data on file, RMP v7.0 analyses for SSc-ILD, Tables 3.1.9 to 3.1.13, System: Cardiovascular, Safety topic: Myocardial infarction (SMQ − narrow).

Indication PF-ILD
There were no observational data on risk factors for myocardial infarction in patients with PF-ILD.

Based on the low numbers of patients affected in SG-6.1, no clinically meaningful differences were observed in the subgroup analyses (data on file, RMP v9.0 analyses for PF-ILD, Tables 3.1.1.1.1.8 to 3.1.1.1.1.10, CTR 1199-0247 [c26471552-01], Section 15.3, Tables 15.3.1.1.5.1.1: 8, 15.3.1.1.5.2.1: 8, 15.3.1.1.5.3.1: 8, and CTR 1199-0247 [c26471552-01], Appendix 16.1.13.1, Table 10.4.1.3.1.8 - System: Cardiovascular, Safety topic: Myocardial infarction).

Indication fibrosing ILD in paediatric patients
There are very limited observational data available on the risk of arterial thromboembolism in the paediatric population. These data are presented in Section SVII.3.1.6.4 ("Arterial thromboembolism excluding myocardial infarction").

There are no observational data on risk factors for myocardial infarction in paediatric patients with fibrosing ILD.

No cardiovascular events were reported in the paediatric trial, and no analysis of the risk factors could be performed.

SVII.3.1.3.5 Preventability

Preventability of MI in the context of Ofev use is not known. Addressing underlying predisposing conditions with adequate treatment of hypertension and/or hyperlipidaemia is important for general health. Caution should be used when treating patients at higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischaemia.

SVII.3.1.3.6 Impact on the risk-benefit balance of the product

MI is a serious and life-threatening condition that requires medical intervention.

SVII.3.1.3.7 Public health impact

There is no public health impact of MI in patients treated with Ofev.

SVII.3.1.4 Weight decreased in paediatric population

SVII.3.1.4.1 Potential mechanism

The mechanism of weight loss during nintedanib therapy is unknown. It is hypothesised that weight decreased may be related to reduction of food intake due to nausea or malabsorption due to diarrhoea [P23-02598].

SVII.3.1.4.2 Evidence source and strength of evidence

'Weight decreased' is a known ADR for nintedanib based on the clinical trials conducted in the adult population with IPF, SSc-ILD, and PF-ILD. In the paediatric clinical trials 'weight decreased' was a pre-defined safety topic. In the pooled analysis of the trials 1199-0337 and 1199-0378, the frequency and incidence of an AE of 'weight decreased' in children was

similar as in adults (11.1% and incidence rate 9.27 per 100 PY in the paediatric population vs. 11.1% and incidence rate 13.05 per 100 PY in the adult population) ([c44205813] Table 3.2.11; [s00101642] Table 1.3.4.3.1.1).

SVII.3.1.4.3 Characterisation of the risk

Clinical trial data
Weight decrease was assessed based on reporting of a group of MedDRA PTs (detailed in 1199-0337 [c35674886-03], Appendix 16.2.7, Listing 4.1), as well as body weight and BMI measurements.

Indication fibrosing ILD in paediatric patients
Randomised, double-blind, placebo-controlled trial (1199-0337)
AEs reported during the double-blind period
No patients with weight decrease were reported during the double-blind period (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Table 3.1.1.2).

AEs reported over the whole trial
No patients with weight decrease were reported in the placebo/nintedanib group. Weight decrease was reported in 2 patients (7.7%) in the nintedanib/nintedanib group (reported PTs 'Weight decreased'). Both events were non-serious and of mild or moderate intensity. The median time to onset was 268 days. The rate/100 PY was 8.47 (95% CI 2.12, 33, 87) (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Tables 3.2.1.2, 3.2.1.4, 3.2.1.6).

Change in BMI-for-age z-score (BAZ) from baseline to Week 24 and Week 52
The mean (SD) baseline BAZ was -0.54 (1.54) in the nintedanib group and -0.75 (2.40) in the placebo group ([c35674886-03], Appendix 16.1.13.1, Table 13.1.3.9). The mean BAZ values at baseline, Week 24, and Week 52 in both randomised treatment groups suggest slightly lower BMI in the trial population compared with the reference healthy population.

The adjusted mean changes from baseline at Week 24 were -0.30 (95% CI -0.48, -0.13) in the nintedanib group and 0.08 (95% CI -0.16, 0.32) in the placebo group. At Week 52, the adjusted mean changes from baseline were -0.29 (95% CI -0.61, 0.03) in the nintedanib/nintedanib group and -0.02 (95% CI-0.45, 0.42) in the placebo/nintedanib group ([c35674886-03] Appendix 16.1.13.1, Table 13.1.3.10). These findings indicate no relevant effect of nintedanib on BMI in the investigated time frame.

Trials 1199-0337 and 1199-0378 (pooled)
In the pooled analysis, 6 patients (11.1%) were reported with AE of 'weight decreased' (incidence rate 9.27 per 100 PY) (data on file, submission-outputs-pediatrics_v2.0, Table 3.2.11). All events were non-serious; 2 events were of mild intensity, 3 events of moderate intensity, and 1 event of severe intensity (data on file, submission-outputs-pediatrics_v2.0, Listing 4.5.2.1). 1 AE led to treatment discontinuation; this AE was of severe intensity and occurred in a patient reported with anorexia nervosa as baseline condition and who was diagnosed with a new episode of anorexia nervosa in the trial 1199-0337 [c43286125-01].

Change in BMI-for-age z-score
The mean (SD) BAZ was -0.524 (1.751) at baseline. The adjusted mean (SE) of the absolute change from baseline was -0.336 (0.168) at Week 52 (n=33) and -0.334 (0.231) at Week 88 (n=22). This observed change in BAZ during the extended nintedanib exposure was similar to the change observed during nintedanib treatment in trial 1199-0337 alone and is not considered clinically meaningful [c43286125-01].

SVII.3.1.4.4 Risk factors and risk groups

Weight loss is a common co-morbidity in children with interstitial lung disease. In fact, 'failure to thrive' is one of the diagnosis criteria of childhood interstitial lung disease (chILD) [R17-3035].

The chILD-EU Register was established in 2012 with prospective enrolment of patients from Europe and non-European countries. As of December 2020, 772 patients with a confirmed diagnosis of childhood ILD (chILD) were enrolled in the registry. Of those, 5.8% (n=45) were confirmed as having fibrosis. In the registry, among children with ILD, failure to thrive and weight loss were more frequently reported in patients with confirmed fibrosis (73.3%) vs. patients with no confirmed fibrosis (45.1%) [ra01268993].

In the trials 1199-0337 and 1199-0378, all AEs of 'weight decreased' were reported in the age subgroup 12 to <18 years. However, due to relatively low number of patients in the evaluated subgroups, no firm conclusions could be drawn based on subgroup analyses.

SVII.3.1.4.5 Preventability

'Weight decreased' is a known ADR for nintedanib and it is managed by dose reduction, temporary interruption, or treatment discontinuation (if the decreased dose is not tolerated). Measurement of weight in paediatric patients is required for the initiation of treatment with nintedanib and subsequent dose adjustments. Furthermore, monitoring of weight and nutritional support are part of the standard of care of paediatric children with chronic pulmonary fibrosis [R17-3035, R16-4788, R24-1368].

SVII.3.1.4.6 Impact on the risk-benefit balance of the product

Hypothetically, there is a potential impact of weight decreased in growing children, and this would be expected in the period from birth to a few years of age, when critical developmental processes occur. Furthermore, the majority of organ development, including the nervous system, is finalised up to 5 years of age [R23-1584]. As the paediatric indication is restricted to children aged above 6 years, a significant impact of weight decreased on overall development is considered unlikely. Furthermore, the routine minimisation measures including nintedanib dose adjustments, and weight monitoring and nutritional support as per standard of care, are considered sufficient to minimise this risk.

SVII.3.1.4.7 Public health impact

There is no wider public health impact of "Weight decreased" in paediatric patients treated with Ofev.

SVII.3.1.5 Important potential risk: Venous thromboembolism

SVII.3.1.5.1 Potential mechanisms

VTE has been associated with VEGF inhibitors in combination treatment with chemotherapy for patients with cancer [R12-3827].

SVII.3.1.5.2 Evidence source and strength of evidence

In the clinical trials in adult patients, the frequency of patients with VTE was similar between both treatment groups. There was no evidence from the clinical trial programme with Ofev to suggest that VTE is an important identified risk in patients with IPF/SSc/PF-ILD. Nevertheless, the risk of VTE resulting from the mode of action of Ofev cannot be entirely ruled out, and so VTE is considered an important potential risk.

SVII.3.1.5.3 Characterisation of the risk

Clinical trial data
Indication IPF
The analysis of VTE was based on the AESIs 'Venous thromboembolism'. For details of the PTs included in this AESI, refer to the RMP analyses v3.0, Listing 3.10.1 (data on file).

Randomised, double-blind, placebo-controlled trials (analysis set SG-1.1)
The frequency of patients with VTE was similar between the treatment groups: 1.2% placebo, 1.1% nintedanib. The incidence rate ratio and risk ratio for nintedanib vs. placebo showed no substantial differences between the treatment groups (table below).

Overall, the number of patients with serious events was low (<1% in both treatment groups, most of them requiring or prolonging hospitalisation). There was 1 fatal event. The reported events of VTE were mainly of severe intensity in both treatment groups. The majority of the patients had recovered from the VTE. The median time to first onset of VTE was similar between the treatment groups; the median duration of VTE was shorter for patients in the nintedanib than in the placebo group. Further details are given in the table below.

SVII.Table 11 Overview on VTE - SG-1.1 – TS

	Placebo	**Nintedanib 150 b.i.d.**
Number of patients treated, N (%)	423 (100.0)	638 (100.0)
Total overall time at risk (PY)	413	593
Patients with VTE, N (%)	5 (1.2)	7 (1.1)
95% CI	0.51, 2.74	0.53, 2.25
Rate/100 PY	1.21	1.18
Incidence rate ratio (95% CI)[1]	0.97 (0.31, 3.07)	
Incidence rate difference (95% CI)[1]	-0.03 (-1.41, 1.34)	
Risk ratio (95% CI)[1]	0.93 (0.30, 2.91)	
Risk difference (95% CI)[1]	-0.08 (-1.39, 1.23)	
Seriousness[2], N (%)		
Fatal	0 (0.00)	1 (0.16)
Immediately life-threatening	0 (0.00)	1 (0.16)
Requires or prolongs patient hospitalisation	3 (0.71)	4 (0.63)
Other	3 (0.71)	2 (0.31)
Outcome[3], N (%)		
Recovered	2 (0.47)	3 (0.47)
Not yet recovered	1 (0.24)	2 (0.31)
Intensity, N (%)		
Mild	1 (0.24)	1 (0.16)
Moderate	1 (0.24)	2 (0.31)
Severe	3 (0.71)	4 (0.63)
Time to first onset, median (days)	143.0	159.0
Duration, median (days)	38.0	16.0

[1] Ratio nintedanib 150 b.i.d. vs. placebo

[2] Patients can be counted in more than 1 seriousness category.

[3] Each of the outcomes could be individually assigned to an event, i.e. not recovered would not be a subset of fatal.

Data source: data on file, analyses for RMP analyses v3.0, Tables 3.1.2; 3.1.3; 3.1.4; 3.1.5

Indication SSc-ILD

Randomised, double-blind, placebo-controlled trial (analysis set SG-5.1)

The frequency of patients with VTE was low and comparable between the treatment groups: 3 patients (1.0%) placebo vs. 4 patients (1.4%) nintedanib. All of the patients in the placebo group and 2 of the 4 patients in the nintedanib group had serious events; there were no fatal events. The reported events of VTE were mainly of moderate intensity. No cases of pulmonary embolism were reported in the nintedanib group (data on file, RMP v7.0 analyses for SSc-ILD, Tables 3.1.2, 3.1.4, 3.1.5, 3.1.6, System: Cardiovascular, Safety topic: Venous thromboembolism (SMQ – narrow)).

Indication PF-ILD
The analysis of VTE was based on the narrow SMQ 'Embolic and thrombotic events, venous'.

Randomised, double-blind, placebo-controlled trial (analysis set SG-6.1)
The frequency of patients with VTE was low and comparable between the treatment groups: 5 patients (1.5%) in the placebo vs. 3 patients (0.9%) in the nintedanib group. Nearly all of the events were serious, none of them being fatal. The reported events of VTE were mainly of moderate or severe intensity and most patients had recovered from it. The time to first onset was longer in the nintedanib group and the median duration was shorter in the nintedanib than in the placebo group. Further details are given in the table below.

SVII.Table 12 Overview on VTE - SG-6.1 – TS

	Placebo	Nintedanib 150 b.i.d.
Number of patients treated, N (%)	331 (100.0)	332 (100.0)
Total overall time at risk (PY)	314.82	292.26
Patients with VTE, N (%)	5 (1.5)	3 (0.9)
95% CI	0.6, 3.5	0.3, 2.6
Rate/100 PY	1.59	1.03
Incidence rate ratio (95% CI)[1]	0.65 (0.15, 2.70)	
Incidence rate difference (95% CI)[1]	−0.56 (−2.37, 1.25)	
Risk ratio (95% CI)[1]	0.60 (0.14, 2.48)	
Risk difference (95% CI)[1]	−0.61 (−2.27, 1.06)	
Seriousness[2], N (%)	4 (1.2)	3 (0.9)
Persistent or significant disability / incapacity	1 (0.3)	0 (0.0)
Requires or prolongs patient hospitalisation	2 (0.6)	1 (0.3)
Other	1 (0.3)	2 (0.6)
Outcome[3], N (%)		
Recovered	4 (1.2)	1 (0.3)
Not yet recovered	0 (0.0)	1 (0.3)
Unknown	1 (0.3)	1 (0.3)
Intensity, N (%)		
Mild	1 (0.3)	1 (0.3)
Moderate	1 (0.3)	2 (0.6)
Severe	3 (0.9)	0 (0.0)
Time to first onset, median (days)	141.0	164.0
Duration, median (days)	12.5	9.0

Note: data over the 52 weeks period were analysed.

[1] Ratio or difference nintedanib 150 b.i.d. vs. placebo

[2] Patients can be counted in more than 1 seriousness category.

[3] Patients are counted only once; in case of multiple episodes, only the worst outcome is counted.

* Significantly different from 1

Significantly different from 0

Data source: data on file, RMP v9.0 analyses for PF-ILD, Tables 3.1.1.1.1.2, 3.1.1.1.1.4, 3.1.1.1.1.5; System: Cardiovascular, Safety topic: Venous thromboembolism

Data source: CTR 1199-0247 [c26471552-01]: Appendix 16.1.13.1, Table 8.1.5.1.2

Indication fibrosing ILD in paediatric patients
Randomised, double-blind, placebo-controlled trial (1199-0337)
No cases of VTE were reported either in the double-blind period or in the whole trial in any of the treatment groups (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722).

Trials 1199-0337 and 1199-0378 (pooled)
Up to the snapshot date, there was no event of VTE in the paediatric trials 1199-0337 and 1199-0378 [c42238250-01].

Post-marketing data
A cumulative search in the BI GSP (up to 15 Apr 2022) was performed using the narrow SMQ 'Embolic and thrombotic events, venous' (MedDRA version 24.1) (Ofev PBRER, reporting interval 16 Oct 2021 to 15 Apr 2022 [s00106744-01], Section 16.4.3.1).

595 cases were identified with the above search criteria, the majority being report from study (other studies 76.6%, individual patient use 2.4%).

Most patients were male: 66.9% vs. 29.6% female. Frequency of the event increased with age (14.3% of events reported in patients being between 18 and 64, between 65 to 74 years: 33.6%, between 75 to 84 years: 33.9%, 85 years or older: 12.9%).

The majority of cases was serious (96.8%). The outcome was reported as follows: missing/not applicable/not reported/unknown (43.2%), recovered/resolved (22.0%), not recovered/not resolved/ongoing (19.5%), fatal (11.9%), recovering/resolving (5.9%), and recovered/resolved with sequelae (0.8%).

The most commonly reported MedDRA PTs were PE (59.3%), pulmonary thrombosis (24.4%), and DVT (15.0%).

Conclusion
The available safety information does not suggest any change to the current characterisation of this safety concern. The EU-SmPC and the EU-RMP correctly reflect the current benefit-risk profile and this safety concern; no updates are warranted at present.

SVII.3.1.5.4 Risk factors and risk groups

Indication IPF
Due to the small numbers of patients who experienced VTE in randomised, placebo-controlled clinical trials, the subgroup assessment is not considered meaningful. For information on this data, refer to the RMP analyses v3.0, Tables 3.1.8 through 3.1.12 (data on file).

Independently of treatment, a number of major risk factors for VTE/PE have been identified: old age (>65 years), long-haul travel, thrombophilia, obesity, cigarette smoking,

hypertension, metabolic syndrome, immobilisation, cancer, and acute medical illness, among others [P12-04560].

Studies reported higher incidence rates of VTE/PE for IPF patients compared to controls [R15-4491, R13-0297]. This is probably explained by the fact that IPF patients have advanced age and frequently 1 or more additional risk factors for thromboembolism [R16-2228]. Also, acute medical illness, such as pneumonia, has also been described as a risk factor for PE [R16-5365].

Indication SSc-ILD
Patients with SSc appear to have an increased risk of VTE, possibly due to the presence of inflammatory cytokines that occur with SSc and other autoimmune disorders. In a systematic review of the risk of VTE among patients with SSc that included 5 observational studies, the pooled risk ratio of VTE was 2.51 (95% CI 1.79, 3.54) comparing patients with SSc to non-SSc participants [R18-4032]. In another study that used provincial healthcare data from British Columbia to study the risk of VTE among patients with incident SSc, the estimated incidence rates of VTE were 6.6 per 1000 PY among 1245 patients with SSc, and 1.4 per 100 000 PY among 12 670 age-, gender-, and time of entry-matched general population controls. Rates of VTE where highest in the year after SSc diagnosis, decreasing from 12.0 per 1000 PY in the first year after diagnosis to 5.2 per 1000 PY in the 5 years after diagnosis [R18-4038]. The risk of VTE in another Canadian cohort study of patients with SSc from three hospitals in Toronto was 3.4%; at least 1 VTE event occurred in 40 of 1181 patients with SSc (DVT n = 20 and PE n = 26) [R18-4027].
No observational studies of the treatment of SSc-ILD reported the incidence or prevalence of VTE among patients with SSc-ILD.

Due to the low numbers of patients affected in SG-5.1, no clinically meaningful differences in the subgroup analyses can be observed with regard to gender, race, age, renal impairment, or body weight (data on file, RMP v7.0 analyses for SSc-ILD, Tables 3.1.9 to 3.1.13, System: Cardiovascular, Safety topic: Venous thromboembolism (SMQ − narrow).

Indication PF-ILD
In a study of 57 patients with either CTD-ILD (n = 30) or IIP (n = 27) who were admitted in 2011 to the ILD Centre at Guangzhou Institute of Respiratory Diseases, Guangzhou, China (the report is not clear about the nature of admissions), 15 (26.3%) had a VTE at admission or during the three months following admission (12 cases of pulmonary embolism and three of deep vein thrombosis) [R19-2729]. The study results were reported for the overall study population only, and not stratified by type of ILD. Patients with VTE were older than those without VTE (mean ages 67.7 years and 59.1 years, respectively, p = 0.01), had greater pack-year smoking history (mean pack-years 19.7 and 6.4, respectively, p = 0.04) and were more likely to have dyspnoea, lower extremity oedema and palpitations ($p<0.05$). Additionally, D-dimer >500 mg/L was present in 86.7% of patients with VTE and 42.9% of patients without VTE. Multivariate analysis suggested that older age, greater smoking history and the presence of palpitations were associated with the presence of VTE in this ILD population.

Based on the low numbers of patients affected in SG-6.1, no clinically meaningful differences were observed in the analysed subgroups (data on file, RMP v9.0 analyses for PF-ILD, Tables 3.1.1.1.1.8 to 3.1.1.1.1.10, CTR 1199-0247 [c26471552-01], Section 15.3, Table 15.3.1.1.5.1.1: 8, 15.3.1.1.5.3.1: 8, and CTR 1199-0247 [c26471552-01], Appendix 16.1.13.1, Table 10.4.1.3.1.8 - System: Cardiovascular, Safety topic: Venous thromboembolism).

Indication fibrosing ILD in paediatric patients
In a study evaluating the incidence of venous thromboembolism in infants and children discharged from non-federal short-stay hospitals in the US from 1979 through 2001, the rate of PE was 0.9/100 000 children/year and the rate of DVT was 4.9/100 000 children/year. The rates of diagnosis were higher in infants 0 to 1 year of age and in teenagers 15 to 17 years of age than in children 2 to 14 years of age [R11-4524].

The incidence rate of paediatric venous non-cerebral thromboembolism was assessed in a nationwide population-based study in Denmark. The study included all patients aged 0 to 18 years diagnosed with first-ever non-cerebral VTE in Denmark between 1994 and 2006 (n=331). The incidence rate of VTE was 2.09 per 100 000 PY, and was higher in infants (age<1 year; 3.82 per 100 000 PY) and adolescents (age 15 to 18 years: 8.46 per 100 000 PY [P11-14206].

99 patients were registered in prospective 2-year registry of VTE in children aged ≤18 years in the Netherlands. Of those, 47 children (47%) were neonates. The annual incidence of VTE was 0.14/10 000 children. The annual incidence of VTE per age category was 14.5 per 10 000 children from 0 to 28 days, 0.1 per 10 000 children from 5 to 9 years, 0.18 per 10 000 children from 10 to 14 years, and 0.05 per 10 000 children from 15 to 18 years. Of the children aged between 1 month and 18 years of age (n=52), 81% had at least 2 risk factors for VTE. Most frequently identified risk factors were infection (46%), central venous catheter (37%) and heart disease (19%) [R06-2301].

There are no observational data on risk factors for VTE in paediatric patients with fibrosing ILD.

No thromboembolic event was reported in the paediatric trial 1199-0337 and no analysis of the risk factors could be performed.

SVII.3.1.5.5 Preventability

Preventability of VTE in the context of Ofev use is not known.

SVII.3.1.5.6 Impact on the risk-benefit balance of the product

VTE may lead to hospitalisation, and can in cases of fulminant PE be life-threatening, have a fatal outcome, or can lead to sequelae such as post thrombotic syndrome. Patients who have experienced VTE are at an increased risk of experiencing further thromboembolic events [R12-5534].

SVII.3.1.5.7 Public health impact

There is no public health impact of VTE in patients treated with Ofev.

SVII.3.1.6 Important potential risk: Arterial thromboembolism excluding myocardial infarction

SVII.3.1.6.1 Potential mechanisms

ATE has been associated with VEGF inhibitors in combination treatment with chemotherapy for patients with cancer [R12-3827].

SVII.3.1.6.2 Evidence source and strength of evidence

There was no evidence from the clinical trial programme with Ofev to suggest that ATE excluding myocardial infarction is an important identified risk in adult patients with IPF/SSc/PF-ILD or in paediatric patients with fibrosing ILD. Nevertheless, the risk of ATE resulting from the drug class (TKIs with VGEF inhibition) cannot be entirely ruled out, and so ATE excluding MI is considered an important potential risk.

SVII.3.1.6.3 Characterisation of the risk

Note that the used searches to analyse ATE include MI related PTs. MI is presented as a separate risk in Section SVII.3.1.3.

Clinical trial data
Indication IPF
The analysis of ATE was based on the AESI 'Arterial thromboembolism'. For details of the PTs included in this AESI, refer to the RMP analyses v3.0, Listing 3.10.1 (data on file).

Randomised, double-blind, placebo-controlled trials (analysis set SG-1.1)
The frequency of patients with ATE was low, but higher in the nintedanib group: 0.7% placebo, 2.5% nintedanib. The incidence rate ratio and risk ratio for nintedanib vs. placebo showed differences between the treatment groups (table below).

Overall, the number of patients with serious events was low (<1% in the placebo and <2% in the nintedanib group, most of them requiring or prolonging hospitalisation). There was 1 fatal event in the placebo and 2 fatal events in the nintedanib group. The reported events of ATE were mainly of severe intensity in both treatment groups. The majority of patients had recovered from the ATE. The median time to first onset of ATE was shorter in the nintedanib group; the median duration of ATE was similar between the treatment groups. Further details are given in the table below.

SVII.Table 13 Overview on ATE - SG-1.1 – TS

	Placebo	**Nintedanib 150 b.i.d.**
Number of patients treated, N (%)	423 (100.00)	638 (100.00)
Total overall time at risk (PY)	413	592
Patients with ATE, N (%)	3 (0.71)	16 (2.51)
95% CI	0.24, 2.06	1.55, 4.03
Rate/100 PY	0.73	2.70
Incidence rate ratio (95% CI)[1]	3.72 (1.08, 12.76)	
Incidence rate difference (95% CI)[1]	1.98 (0.42, 3.54)	
Risk ratio (95% CI)[1]	3.54 (1.04, 12.07)	
Risk difference (95% CI)[1]	1.80 (0.35, 3.25)	
Seriousness[2], N (%)		
Fatal	1 (0.24)	2 (0.31)
Immediately life-threatening	0 (0.00)	2 (0.31)
Requires or prolongs patient hospitalisation	1 (0.24)	10 (1.57)
Other	1 (0.24)	1 (0.16)
Outcome[3], N (%)		
Recovered	1 (0.24)	10 (1.57)
Not yet recovered	0 (0.00)	3 (0.47)
Sequelae	1 (0.24)	1 (0.16)
Intensity, N (%)		
Mild	0 (0.00)	1 (0.16)
Moderate	1 (0.24)	2 (0.31)
Severe	2 (0.47)	13 (2.04)
Time to first onset, median (days)	296.0	104.5
Duration, median (days)	4.0	8.5

[1] Ratio nintedanib 150 b.i.d. vs. placebo

[2] Patients can be counted in more than 1 seriousness category.

[3] Each of the outcomes could be individually assigned to an event, i.e. not recovered would not be a subset of fatal.

Data source: data on file, analyses for RMP analyses v3.0, Tables 3.1.2; 3.1.3; 3.1.4; 3.1.5

Indication SSc-ILD

Randomised, double-blind, placebo-controlled trial (analysis set SG-5.1)

There were 2 patients (0.7%) with ATE in each treatment group. Among them, 1 patient in the placebo and both patients in the nintedanib group had serious and fatal events; in addition, the 2 patients treated with nintedanib required/prolonged hospitalisation (data on file, RMP v7.0 analyses for SSc-ILD, Tables 3.1.2, 3.1.4, 3.1.5, 3.1.6, System: Cardiovascular, Safety topic: Arterial thromboembolism (SMQ – narrow)).

Indication PF-ILD

The analysis of ATE was based on the narrow SMQ 'Embolic and thrombotic events, arterial'.

Randomised, double-blind, placebo-controlled trial (analysis set SG-6.1)

There were 3 patients (0.9%) with ATE in each treatment group. All events were serious (requiring/prolonging hospitalisation) and of moderate or severe intensity. All patients had recovered from the event. The time to first onset and the median duration were longer in the nintedanib than in the placebo group. Further details are given in the table below.

SVII.Table 14 Overview on ATE - SG-6.1 – TS

	Placebo	**Nintedanib 150 b.i.d.**
Number of patients treated, N (%)	331 (100.0)	332 (100.0)
Total overall time at risk (PY)	313.39	291.34
Patients with ATE, N (%)	3 (0.9)	3 (0.9)
95% CI	0.3, 2.6	0.3, 2.6
Rate/100 PY	0.96	1.03
Incidence rate ratio (95% CI)[1]	1.08 (0.22, 5.33)	
Incidence rate difference (95% CI)[1]	0.07 (−1.52, 1.66)	
Risk ratio (95% CI)[1]	1.00 (0.20, 4.90)	
Risk difference (95% CI)[1]	0.00 (−1.44, 1.44)	
Seriousness[2], N (%)	3 (0.9)	3 (0.9)
Requires or prolongs patient hospitalisation	3 (0.9)	3 (0.9)
Outcome[3], N (%)		
Recovered	3 (0.9)	3 (0.9)
Intensity, N (%)		
Moderate	2 (0.6)	1 (0.3)
Severe	1 (0.3)	2 (0.6)
Time to first onset, median (days)	92.0	251.0
Duration, median (days)	4.0	5.0

Note: data over the 52 weeks period were analysed.

[1] Ratio or difference nintedanib 150 b.i.d. vs. placebo

[2] Patients can be counted in more than 1 seriousness category.

[3] Patients are counted only once; in case of multiple episodes, only the worst outcome is counted.

* Significantly different from 1

Significantly different from 0

Data source: data on file, RMP v9.0 analyses for PF-ILD, tables 3.1.1.1.1.2, 3.1.1.1.1.4, 3.1.1.1.1.5; System: Cardiovascular, Safety topic: Arterial thromboembolism

Data source: CTR 1199-0247 [c26471552-01]: Appendix 16.1.13.1, Table 8.1.5.1.2

Indication fibrosing ILD in paediatric patients

Randomised, double-blind, placebo-controlled trial (1199-0337)

No cases of ATE were reported either in the double-blind period or in the whole trial in any of the treatment groups (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722).

Trials 1199-0337 and 1199-0378 (pooled)

Up to the snapshot date, there was no event of ATE in the paediatric trials 1199-0337 and 1199-0378 [c42238250-01].

Post-marketing data

A cumulative search in the BI GSP (up to 15 Apr 2022) was performed using the narrow SMQ 'Embolic and thrombotic events, arterial' excluding terms from broad SMQ 'Ischaemic heart disease' (MedDRA version 24.1) (Ofev PBRER, reporting interval 16 Oct 2021 to 15 Apr 2022 [s00106744-01], Section 16.4.3.2).

470 cases were identified with the above search criteria, the majority being report from study (other studies 81.3%, individual patient use 0.2%).

Most patients were male: 64.9% vs. 32.6% female. Most cases were reported in patients being between 65 to 74 years (31.9%) and between 75 to 84 years old (40.2%).

The majority of cases was serious (91.7%). The outcome was reported as follows: missing/not applicable/not reported/unknown (47.0%), recovered/resolved (28.3%), not recovered/not resolved/ongoing (18.7%), recovering/resolving (5.3%), recovered/resolved with sequelae (3.0%), and fatal (1.9%).

Overall, 9 events reported in 9 cases had a fatal outcome. Of the 9 events reported overall, 5 concerned females and 4 males with an age range from 53 to 80 years (in 4 cases, no age was provided). Risk factors for the event, mainly hypertension, followed by diabetes, smoking and atrial fibrillation or concomitant medications that may indicate presence of cardiovascular risk factors, e.g. ASA or statins were reported in the majority (7 cases) of the cases. In 1 case, the patient died due to stroke complicated by pneumonia; the remaining case was poorly documented so that a proper medical and causal assessment was not possible. No striking case, no cluster or pattern was identified upon review of the fatal cases.

The most commonly reported MedDRA PTs were transient ischaemic attack (48.5%), arterial occlusive disease (13.6%), and ischaemic stroke (8.1%).

Conclusion

The available safety information does not suggest any change to the current characterisation of this safety concern. The EU-SmPC and the EU-RMP correctly reflect the current benefit-risk profile and this safety concern; no updates are warranted at present.

SVII.3.1.6.4 Risk factors and risk groups

Indication IPF
Based on the low number of patients affected, no clinically meaningful difference in frequency of ATE was observed with regard to gender, race, age, renal impairment, or smoker status. For information on this data, refer to the RMP analyses v3.0, Tables 3.1.8 through 3.1.12 (data on file).

Indication SSc-ILD
Due to the low numbers of patients affected in SG-5.1, no clinically meaningful differences in the subgroup analyses can be observed with regard to gender, race, age, renal impairment, or body weight (data on file, RMP v7.0 analyses for SSc-ILD, Tables 3.1.9 to 3.1.13, System: Cardiovascular, Safety topic: Arterial thromboembolism [SMQ – narrow]).

Independently of treatment, there is an increased risk within the SSc population for cardiovascular events, including coronary artery disease, myocardial infarction, and stroke based on epidemiological data. Due to underlying vasculopathy, patients with SSc are at increased risk of coronary artery disease. Thus, MI is one of the known disease manifestations SSc. Studies have reported an increased risk of ischaemic stroke among patients with SSc, probably due to the premature atherosclerosis related to chronic inflammation.

There were no observational studies that have reported the incidence, prevalence, or risk factors for ATE in patients with SSc or SSc-ILD.

Risk factors for MI are described in Section SVII.3.1.3.4

A few studies reported an increased risk of ischemic stroke among patients with SSc, probably due to the premature atherosclerosis related to chronic inflammation. In a systematic review and meta-analysis, the authors found a statistically significant elevated ischemic stroke risk in patients with SSc compared to participants without SSc with a pooled risk ratio of 1.68 (95% CI, 1.26, 2.24) [R18-4033].

2 studies reported the incidence of ischemic stroke among SSc patients. Chiang et al. analysed the Taiwan NHI Research Database from 1997 to 2006. They reported that the incidence rate of ischemic stroke among SSc patients was 16.5/1000 PY, compared to 11.5/1000 PY among subjects without SSc [P13-02141]. Another study reported that in the UK THIN data from 1986 to 2011, the incidence rate of ischemic stroke among SSc patients was 4.8/1000 PY, compared to 2.5/1000 PY among subjects without SSc [R18-3843].

1 study examined the prevalence of ischemic stroke among patients with SSc. Nordin et al. reported that 9 out of 111 SSc patients (8%) had previous ischemic cerebrovascular disease [R18-3863].

Indication PF-ILD
Risk factors for MI are described in Section SVII.3.1.3.4.
There were no observational data on risk factors for ATE in patients with PF-ILD.

Due to the low numbers of patients affected in SG-6.1, no meaningful subgroup analyses could be performed (data on file, RMP v9.0 analyses for PF-ILD, Tables 3.1.1.1.1.8 to 3.1.1.1.1.10, CTR 1199-0247 [c26471552-01], Section 15.3, Tables 15.3.1.1.5.1.1: 8, 15.3.1.1.5.2.1: 8, 15.3.1.1.5.3.1: 8, and CTR 1199-0247 [c26471552-01], Appendix 16.1.13.1, Table 10.4.1.3.1.8 - System: Cardiovascular, Safety topic: Arterial thromboembolism).

Indication fibrosing ILD in paediatric patients
In a nationwide population-based study in Denmark, the incidence rate of paediatric arterial non-cerebral thromboembolism was 0.29 per 100 000 PY. The study included all patients aged 0 to 18 years diagnosed with first-ever non-cerebral ATE in Denmark between 1994 and 2006 (n=46). The highest incidence of ATE was observed in infants (age<1 year; 2.32 per 100 000 PY). Most frequently reported risk factors for ATE were surgery (32.6%), infection (28.9%), and cardiac disease (28.3%) [P11-14206].

In a population-based cohort of Swedish children (n=409 727), the incidence of childhood stroke was 1.8 per 100 000 children and year. Risk factors of importance were oral contraceptives, smoking, and anaemia [R22-2185].

There are no observational data on risk factors for ATE in paediatric patients with fibrosing ILD.

No thromboembolic event was reported in the paediatric trial 1199-0337 and no analysis of the risk factors could be performed.

SVII.3.1.6.5 Preventability

Preventability of ATE in the context of Ofev use is not known.

SVII.3.1.6.6 Impact on the risk-benefit balance of the product

ATE may result in serious conditions such as MI or stroke.

SVII.3.1.6.7 Public health impact

There is no public health impact of ATE in patients treated with Ofev.

SVII.3.1.7 Important potential risk: Perforation

SVII.3.1.7.1 Potential mechanisms

GI perforations have been associated with VEGF inhibition in combination treatment with chemotherapy for patients with cancer [R12-3827]. VEGF inhibition on capillary beds of intestinal villi may directly contribute to perforation by inducing the regression of normal blood vessels. The occurrence of GI perforations with VEGF inhibitors has been linked to the presence of bowel pathologies [R18-0892].

SVII.3.1.7.2 Evidence source and strength of evidence

In the IPF and in the PF-ILD clinical trials, the frequency of patients with GI perforation was very low. In the SSc trial, no GI perforations were observed in patients treated with Ofev. GI perforations are known to occur in cancer patients treated with TKIs, and as such were defined as important potential risk.

SVII.3.1.7.3 Characterisation of the risk

Clinical trial data
Indication IPF
Perforation was analysed using the AESI 'GI perforation'. Some PTs included are not necessarily indicative of perforation (e.g. abscess). For details of the PTs included in this AESI, refer to the RMP analyses v3.0, Listing 3.10.1 (data on file).

The frequency of patients with perforation was very low in both treatment groups: 0% placebo, 0.3% nintedanib (involving 2 patients). One patient presented a perforated duodenal ulcer and the second one had an abdominal abscess after operated appendicitis (not a true perforation). For both patients treated with nintedanib, the perforation events were serious (requiring or prolonging hospitalisation) and of severe intensity. Both patients recovered from the perforation events (data on file, RMP analyses v3.0, Tables 3.1.2 through 3.1.5).

Indication SSc-ILD
Randomised, double-blind, placebo-controlled trial (analysis set SG-5.1)
Only 1 patient (0.3%) in the placebo group experienced gastrointestinal perforation (MedDRA PT 'Anal abscess'). The event was non-serious, of moderate intensity, and the patient recovered (data on file, RMP v7.0 analyses for SSc-ILD, Tables 3.1.2, 3.1.4, 3.1.5, 3.1.6, System: Gastrointestinal, Safety topic: Gastrointestinal perforation (SMQ − narrow)).

Indication PF-ILD
Perforation was analysed using the narrow SMQ 'Gastrointestinal perforation'.

Randomised, double-blind, placebo-controlled trial (analysis set SG-6.1)
1 patient (0.3%) in each treatment group experienced a PT from the narrow SMQ 'Gastrointestinal perforation' (each with the MedDRA PT 'Anal abscess'). Both events were non-serious, of moderate intensity, and the patients had recovered from it (data on file, RMP v9.0 analyses for PF-ILD, Tables 3.1.1.1.1.2 and 3.1.1.1.1.5, System: Gastrointestinal, Safety topic: Gastrointestinal perforation. Note: data over the 52 weeks period were analysed).

Indication fibrosing ILD in paediatric patients
Randomised, double-blind, placebo-controlled trial (1199-0337)
No cases of gastrointestinal perforation were reported either in the double-blind period or in the whole trial in any of the treatment groups (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722).

Trials 1199-0337 and 1199-0378 (pooled)
Up to the snapshot date, there was no event of perforation in the paediatric trials 1199-0337 and 1199-0378 [c42238250-01].

Post-marketing data
A cumulative search in the BI GSP (up to 15 Apr 2022) was performed using the narrow SMQ 'Gastrointestinal perforation' (MedDRA version 24.1) (Ofev PBRER, reporting interval 16 Oct 2021 to 15 Apr 2022 [s00106744-01], Section 16.4.3.3).

278 cases were identified with the above search criteria, the majority being report from study (other studies 72.3%, individual patient use 2.5%).

Most patients were male: 64.0% vs. 32.0% female. Most cases were reported in patients being between 65 to 74 years (33.5%) and between 75 to 84 years old (36.3%).

All but 11 cases were serious. The outcome was reported as follows: missing/not applicable/not reported/unknown (41.7%), recovered/resolved (27.7%), not recovered/not resolved/ongoing (19.8%), fatal (9.4%), recovering/resolving (3.6%), and recovered/resolved with sequelae (2.2%).

The most commonly reported MedDRA PTs were intestinal perforation (19.4%), gastric perforation (14.0%), large intestine perforation (11.2%), and gastrointestinal perforation (10.8%).

Conclusion
The available safety information does not suggest any change to the current characterisation of this safety concern. The EU-RMP and the EU-SmPC correctly reflect the current benefit-risk profile and this safety concern; no updates are warranted at present.

SVII.3.1.7.4 Risk factors and risk groups

Indication IPF
Due to the small numbers of patients who experienced perforation in randomised, placebo-controlled clinical trials, the subgroup assessment is not considered meaningful. For information on this data, refer to the RMP analyses v3.0, Tables 3.1.8 through 3.1.12 (data on file).

Independently of treatment, a number of risk factors for GI perforation such as preceding abdominal surgery and use of corticosteroids or NSAIDs have been identified.

Indication SSc-ILD
As only 1 patient in the placebo group experienced gastrointestinal perforation, no subgroup analyses can be done with regard to gender, race, age, renal impairment, or body weight (data on file, RMP v7.0 analyses for SSc-ILD, Tables 3.1.9 to 3.1.13, System: Cardiovascular, Safety topic: Myocardial infarction (SMQ − narrow).

There were no observational studies that reported on the incidence, prevalence or risk factors for GI perforation in patients with SSc or SSc-ILD.

Indication PF-ILD
There were no observational data on risk factors for perforation in patients with PF-ILD. Due to the low numbers of patients, no meaningful subgroup analyses could be performed (data on file, RMP v9.0 analyses for PF-ILD, Tables 3.1.1.1.1.8 to 3.1.1.1.1.10, CTR 1199-0247 [c26471552-01], Section 15.3, Tables 15.3.1.1.5.1.1: 8, 15.3.1.1.5.2.1: 8, 15.3.1.1.5.3.1: 8, and CTR 1199-0247 [c26471552-01], Appendix 16.1.13.1, Table 10.4.1.3.1.8 - Gastrointestinal, Safety topic: Gastrointestinal perforation).

Indication fibrosing ILD in paediatric patients
There are no observational studies that reported on the incidence, prevalence, or risk factors for GI perforation in paediatric patients or paediatric patients with fibrosing pulmonary fibrosis.

There was no event of GI perforation in the paediatric trial 1199-0337 and no subgroup analysis could be performed.

SVII.3.1.7.5 Preventability

Preventability of GI perforation in the context of Ofev use is not known. Caution should be exercised when treating patients with previous abdominal surgery, previous history of peptic ulceration, diverticular disease, or receiving concomitant corticosteroids or NSAIDs. Ofev treatment should only be initiated at least 4 weeks after abdominal surgery. Therapy with Ofev should be permanently discontinued in patients who develop GI perforation.

SVII.3.1.7.6 Impact on the risk-benefit balance of the product

Perforation usually requires surgery, and may have a fatal outcome.

SVII.3.1.7.7 Public health impact

There is no public health impact of perforation in patients treated Ofev.

SVII.3.1.8 Important potential risk: Hepatic failure

SVII.3.1.8.1 Potential mechanisms

Nintedanib is known to be associated with hepatotoxicity. Hepatotoxicity due to idiosyncratic drug reactions can lead to hepatic failure.

SVII.3.1.8.2 Evidence source and strength of evidence

In the clinical trials, hepatic failure was not reported. Liver enzyme and bilirubin elevations including DILI are identified risks of Ofev. Therefore, the potential for further sequelae of liver abnormality is warranted for monitoring ‘Hepatic failure’ as a potential risk.

SVII.3.1.8.3 Characterisation of the risk

Clinical trial data
Indication IPF
Cases of hepatic failure were analysed using the AESI 'Hepatic failure' (narrow). For details of the PTs included in this AESI, refer to the RMP analyses, v3.0, Listing 3.10.1 (data on file).

Randomised, double-blind, placebo-controlled trials (analysis set SG-1.1)
The frequency of patients with hepatic failure was low and similar between the treatment groups: 0.2% placebo, 1.6% nintedanib. The incidence rate ratio and risk ratio for nintedanib vs. placebo showed no substantial differences between the treatment groups (table below).

Overall, the number of patients with serious events was low (<1% in both treatment groups). There were no fatal events. The reported events of hepatic failure were of mild intensity in the placebo group, and of mild, moderate, and severe intensity in the nintedanib group. Half of the patients had recovered while the other half 'had not yet recovered' from the hepatic failure at the time of database lock. The median time to first onset and the median duration of hepatic failure are shown in the table below.

SVII.Table 15 Overview on hepatic failure - SG-1.1 - TS

	Placebo	**Nintedanib 150 b.i.d.**
Number of patients treated, N (%)	423 (100.00)	638 (100.00)
Total overall time at risk (PY)	413	591
Patients with hepatic failure, N (%)	1 (0.24)	10 (1.57)
95% CI	0.04, 1.33	0.85, 2.86
Rate/100 PY	0.24	1.69
Incidence rate ratio (95% CI)[1]	7.00 (0.90, 54.65)	
Incidence rate difference (95% CI)[1]	1.45 (0.30, 2.60)	
Risk ratio (95% CI)[1]	6.64 (0.85,51.75)	
Risk difference (95% CI)[1]	1.33 (0.26, 2.40)	
Seriousness[2], N (%)		
Requires or prolongs patient hospitalisation	0 (0.00)	1 (0.16)
Other	0 (0.00)	2 (0.31)
Outcome[3], N (%)		
Recovered	0 (0.00)	5 (0.78)
Not yet recovered	0 (0.00)	4 (0.63)
Intensity, N (%)		
Mild	1 (0.24)	3 (0.47)
Moderate	0 (0.00)	4 (0.63)
Severe	0 (0.00)	3 (0.47)
Time to first onset, median (days)	1.0	23.5
Duration, median (days)	317.0	69.5

[1] Ratio nintedanib 150 b.i.d. vs. placebo

[2] Patients can be counted in more than 1 seriousness category.

[3] Each of the outcomes could be individually assigned to an event, i.e. not recovered would not be a subset of fatal.

Data source: data on file, analyses for RMP analyses v3.0, Tables 3.1.2; 3.1.3; 3.1.4; 3.1.5

Indication SSc-ILD

Randomised, double-blind, placebo-controlled trial (analysis set SG-5.1)

The frequency of patients with hepatic failure was higher in the nintedanib than in the placebo group: 1.0% placebo vs. 3.8% nintedanib. The incidence rate ratio and risk ratio for nintedanib vs. placebo showed substantial differences between the treatment groups. The reported events included unspecific PTs suggestive of DILI (liver disorder, DILI, liver injury, hepatocellular injury, hepatic steatosis) but the PT ‘Liver failure’ itself was not reported.

Overall, the number of patients with serious events was low (0.3% placebo vs. 1.0% nintedanib). There were no fatal events. The reported events were mainly of mild intensity. Evaluation of the cases retrieved by the SMQ ‘Hepatic failure’ revealed that all cases in the nintedanib group represented increases in liver enzymes with or without symptoms, which

were reversible upon dose reduction or drug discontinuation. None of the cases matched the clinical definition of hepatic failure. The majority of patients in the nintedanib group and 1 of the 3 patients in the placebo group had recovered from the event. The median time to first onset and the median duration of hepatic failure was longer in the placebo group. Further details are given in the table below.

SVII.Table 16 Overview on hepatic failure - SG-5.1 - TS

	Placebo	**Nintedanib 150 b.i.d.**
Number of patients treated, N (%)	288 (100.0)	288 (100.0)
Total overall time at risk (PY)	280.58	256.62
Patients with hepatic failure, N (%)	3 (1.0)	11 (3.8)
95% CI	0.4, 3.0	2.1, 6.7
Rate/100 PY	1.07	4.29
Incidence rate ratio (95% CI)[1]	4.01 (1.12, 14.37)*	
Incidence rate difference (95% CI)[1]	3.22 (0.41, 6.02)#	
Risk ratio (95% CI)[1]	3.67 (1.03, 13.01)*	
Risk difference (95% CI)[1]	2.78 (0.27, 5.28)#	
Seriousness[2], N (%)	1 (0.3)	3 (1.0)
Other	1 (0.3)	3 (1.0)
Outcome[3], N (%)		
Recovered	1 (0.3)	10 (3.5)
Not yet recovered	2 (0.7)	1 (0.3)
Intensity, N (%)		
Mild	2 (0.7)	8 (2.8)
Moderate	0 (0.0)	0 (0.0)
Severe	1 (0.3)	3 (1.0)
Time to first onset, median (days)	127.0	18.0
Duration, median (days)	29.0	22.0

[1] Ratio nintedanib 150 b.i.d. vs. placebo

[2] Patients can be counted in more than 1 seriousness category.

[3] Each of the outcomes could be individually assigned to an event, i.e. not recovered would not be a subset of fatal.

* Significantly different from 1

Significantly different from 0

Data source: data on file, RMP v7.0 analyses for SSc-ILD, Tables 3.1.2, 3.1.4, 3.1.5, 3.1.6, System: Hepatobiliary, Safety topic: Hepatic failure (SMQ − narrow).

Indication PF-ILD

The analysis of hepatic failure was based on the narrow SMQ ‘Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions’. The presentation of DILI is included in Section SVII.3.1.1.3 above.

Randomised, double-blind, placebo-controlled trial (analysis set SG-6.1)
The frequency of patients with hepatic failure was higher in the nintedanib group than in the placebo group: 1.2% placebo vs. 5.1% nintedanib. The incidence rate ratio and risk ratio for nintedanib vs. placebo showed substantial differences between the treatment groups. The reported events included unspecific PTs suggestive of DILI (liver disorder, DILI, liver injury, hepatocellular injury, hepatic steatosis) but the PT 'Liver failure' itself was not reported (data on file, RMP v9.0 analyses for PF-ILD, Tables 3.1.1.1.1.5; System: Hepatobiliary, Safety topic: Hepatic failure).

The number of patients with serious events was low (0.6% placebo vs. 3.0% nintedanib). There were no fatal events. The reported events were mainly of mild or moderate intensity. The majority of the cases reflect liver enzyme elevations with or without additional symptoms, which were reversible upon dose reduction or drug discontinuation. All but 3 cases (1 liver cirrhosis in a patient with chronic hepatitis, 1 hepatic steatosis, and 1 non-alcoholic fatty liver) recovered. Most patients had recovered from the event. The median time to first onset and the median duration of hepatic failure was longer in the placebo than in the nintedanib group, especially in terms of a hepatic decompensation. Further details are given in the table below. Cases of DILI are presented in Section SVII.3.1.1.3.

SVII.Table 17 Overview on hepatic failure - SG-6.1 - TS

	Placebo	Nintedanib 150 b.i.d.
Number of patients treated, N (%)	331 (100.0)	332 (100.0)
Total overall time at risk (PY)	313.16	287.28
Patients with hepatic failure, N (%)	4 (1.2)	17 (5.1)
95% CI	0.5, 3.1	3.2, 8.0
Rate/100 PY	1.28	5.92
Incidence rate ratio (95% CI)[1]	4.63 (1.56, 13.77)*	
Incidence rate difference (95% CI)[1]	4.64 (1.56, 7.72)#	
Risk ratio (95% CI)[1]	4.24 (1.44, 12.46)*	
Risk difference (95% CI)[1]	3.91 (1.26, 6.56)#	
Seriousness[2], N (%)	2 (0.6)	10 (3.0)
Immediately life-threatening	0 (0.0)	1 (0.3)
Requires or prolongs patient hospitalisation	1 (0.3)	4 (1.2)
Other	1 (0.3)	5 (1.5)
Outcome[3], N (%)		
Recovered	3 (0.9)	13 (3.9)
Not yet recovered	1 (0.3)	4 (1.2)
Intensity, N (%)		
Mild	3 (0.9)	7 (2.1)
Moderate	1 (0.3)	7 (2.1)
Severe	0 (0.0)	3 (0.9)
Time to first onset, median (days)	204.5	28.0
Duration, median (days)	27.0	13.0

Note: data over the 52 weeks period were analysed.

[1] Ratio or difference nintedanib 150 b.i.d. vs. placebo

[2] Patients can be counted in more than 1 seriousness category.

[3] Patients are counted only once; in case of multiple episodes, only the worst outcome is counted.

* Significantly different from 1

Significantly different from 0

Data source: data on file, RMP v9.0 analyses for PF-ILD, Tables 3.1.1.1.1.2, 3.1.1.1.1.4, 3.1.1.1.1.5; System: Hepatobiliary, Safety topic: Hepatic failure

Data source: CTR 1199-0247 [c26471552-01]: Appendix 16.1.13.1, Table 8.1.5.1.2

Indication fibrosing ILD in paediatric patients

Randomised, double-blind, placebo-controlled trial (1199-0337)

AEs reported during the double-blind period

1 patient (3.8%) in the nintedanib group was reported with an event in the narrow SMQ 'Hepatic failure' (reported PT 'Liver injury'). This patient is described above in Section SVII.3.1.1.3 ("DILI").

AEs reported over the whole trial

2 patients (7.7%) in the nintedanib/nintedanib group were reported with an event in the narrow SMQ 'Hepatic failure' (reported PT 'Liver injury') (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Table 3.2.1.5). 1 patient (7.7%) in the placebo/nintedanib group was reported with an event in the narrow SMQ 'Hepatic failure' (reported PT 'Drug-induced liver injury'), see Section SVII.3.1.1.3 above ("DILI") for details. All events were reported during the nintedanib exposure. The PT 'Liver failure' itself was not reported in the trial. None of the cases match the clinical definition of hepatic failure. All cases were consistent with the hepatobiliary disorders reported in the adult population with IPF, SSc-ILD, and PF-ILD.

Trials 1199-0337 and 1199-0378 (pooled)

Up to the snapshot date, 3 patients (5.1%) were reported with an event in the narrow SMQ 'Hepatic failure'. The reported PTs were 'Liver injury' (n=2, incidence rate 3.30 per 100 PY) and 'DILI' (n=1, incidence rate 1.65 per 100 PY) (Data Source: data on file, submission-outputs-pediatrics_v2.0, Table 3.2.11). All events were reported in the trial 1199-0337. Up to the snapshot date, no new AE of 'hepatic failure' was reported in the ongoing trial 1199-0378 [c42238250-01]. The incidence rate of AEs of 'Hepatic failure' decreased with prolonged exposure (9.8 per 100 PY during the nintedanib exposure of trial 1199-0337 vs 5.1 per 100 PY during the pooled nintedanib exposure period) (data on file, [c42238250-01], Table 26).

Post-marketing data

A cumulative search in the BI GSP (up to 15 Apr 2022) was performed using the narrow SMQ 'Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions' (MedDRA version 24.1) (Ofev PBRER, reporting interval 16 Oct 2021 to 15 Apr 2022 [s00106744-01], Section 16.4.3.4). The presentation of DILI is included in Section SVII.3.1.1.3 above.

1741 cases were identified with the above search criteria, the majority being reports from study (other studies 82.7%, individual patient use 1.0%).

Most patients were male: 54.3% vs. 39.7% female. Most cases were reported in patients being between 65 to 74 years (36.2%) and between 75 to 84 years old (30.2%).

The majority of cases was non-serious (75.9%). The outcome was reported as follows: missing/not applicable/not reported/unknown (39.8%), recovered/resolved (39.5%), not recovered/not resolved/ongoing (19.1%), recovering/resolving (2.2%), fatal (1.4%), and recovered/resolved with sequelae (0.2%).

The most commonly reported MedDRA PTs were liver disorder (66.0%), liver injury (7.7%), hepatic steatosis (5.5%), and hepatotoxicity (5.5%).

Conclusion
The available safety information does not suggest a change to the current characterisation of this safety concern. The EU-RMP and the EU-SmPC correctly reflect the current knowledge and no amendments are warranted at present.

SVII.3.1.8.4 Risk factors and risk groups

Indication IPF
Based on the low number of patients affected, no clinically meaningful difference in frequency of hepatic failure was observed with regard to gender, race, age, renal impairment, or smoker status. For information on this data, refer to the RMP analyses v3.0, Tables 3.1.8 through 3.1.12 (data on file).

Indication SSc-ILD
Due to the low numbers of patients affected in SG-5.1, no clinically meaningful differences in the subgroup analyses can be observed with regard to gender, race, age, renal impairment, or body weight (data on file, RMP v7.0 analyses for SSc-ILD, Tables 3.1.9 to 3.1.13, System: Hepatobiliary, Safety topic: Hepatic failure (SMQ − narrow).

In an analysis from Japan of 607 patients with clinically diagnosed collagen diseases that included 47 patients with SSc, 21 patients (44.7%) had some liver dysfunction. This study reported zero cases of severe liver failure in patients with SSc [R19-0011].
There have been individual case reports of autoimmune hepatitis and systemic sclerosis with question raised as to a possible rare overlap syndrome [R19-0294]. The liver can be a target of an autoimmune reaction and overlap syndrome of autoimmune hepatitis with primary biliary cirrhosis and primary sclerosing cholangitis have been observed.

Indication PF-ILD
There were no observational data on risk factors for hepatic failure in patients with PF-ILD.

Asians (Asian 11.9% vs. White 2.9%) and patients with a bodyweight of ≤65 kg (9.9% ≤65 kg vs. 3.3% >65 kg) showed a higher frequency of patients affected with events of hepatic failure; however, the low patient numbers need to be taken into consideration. No clinically meaningful differences were observed in the remaining subgroup analyses (data on file, RMP v9.0 analyses for PF-ILD, Tables 3.1.1.1.1.8 to 3.1.1.1.1.10, CTR 1199-0247 [c26471552-01], Section 15.3 Tables 15.3.1.1.5.1.1: 8, 15.3.1.1.5.2.1: 8, 15.3.1.1.5.3.1: 8, and CTR 1199-0247 [c26471552-01], Appendix 16.1.13.1, Table 10.4.1.3.1.8).

Indication fibrosing ILD in paediatric patients
There are no observational data on risk factors for hepatic failure in paediatric patients with fibrosing ILD.

In trial 1199-0337, the events reported under SMQ ‘Hepatic failure’ were in line with the data in adult patients with IPF, PF-ILD, and SSc-ILD. 1 event was reported in the subgroup age

6 to <12 years and 2 events were reported in female patients. Due to the low number of patients in the evaluated subgroups, no firm conclusions could be drawn based on subgroup analyses.

SVII.3.1.8.5 Preventability

Hepatic failure may be the sequelae of unmonitored liver function. Hepatic transaminase and bilirubin levels should be investigated before the initiation of treatment with Ofev, and periodically thereafter (e.g. at each patient visit) or as clinically indicated. Close monitoring is recommended in patients with risk factors (Asian, females, low body weight, and advanced age).

If transaminase (AST or ALT) elevations >3x ULN are measured, dose reduction or interruption of the therapy with Ofev is recommended and the patient should be monitored closely. Once transaminases have returned to baseline values, treatment with Ofev may be resumed at the full dose (e.g. 150 mg twice daily in adult patients) or reintroduced at a reduced dose (e.g. 100 mg twice daily in adult patients) which subsequently may be increased to the full dose. If any liver test elevations are associated with clinical signs or symptoms of liver injury, e.g. jaundice, treatment with Ofev should be permanently discontinued. Alternative causes of the liver enzyme elevations should be investigated.

SVII.3.1.8.6 Impact on the risk-benefit balance of the product

Administration of Ofev was associated with elevations of liver enzymes and/or bilirubin. These increases were reversible in the majority of the cases.

Hepatic failure is thought to be a potential consequence or complication of liver enzyme elevation and is considered a severe and life-threatening condition.

The safety of Ofev has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment.

SVII.3.1.8.7 Public health impact

There is no wider public health impact of hepatic failure in patients treated with Ofev.

SVII.3.1.9 Important potential risk: Effect on bone development and growth in paediatric population

SVII.3.1.9.1 Potential mechanisms

VEGF and FGF signalling in humans plays a role in endochondral and intramembranous bone development, in growth plate functioning and in the regulation of chondrocyte and osteoblast differentiation and proliferation [R12-0383, R12-0384, R12-0546, R12-0453]. Based on the mode of action of nintedanib and preclinical findings, ‘Effect on bone development and growth in paediatric population’ was identified as an important potential risk specific for nintedanib treatment of growing children.

SVII.3.1.9.2 Evidence source and strength of evidence

In non-clinical studies on nintedanib, alterations of epiphyseal growth plates of large bones (femur and tibia) were observed. Changes were reported during bone growth and were reversible after discontinuation. These events were mostly related to the mechanism of action of nintedanib (see Section SVII.3.1.9.1) These findings may be particularly relevant for growing children with regard to development and skeleton growth. The current clinical evidence on this important potential risk is based on the trial 1199-0337 and the ongoing trial 1199-0378. In the paediatric trials, bone imaging was regularly to identify any pathological treatment-emergent findings and/or AEs in bones. Also, the dynamics of patient growth was closely monitored.

Analysis of the possible impact of nintedanib on patient growth included measurements of standing height, sitting height, and leg length. Based on height measurements, children and adolescents in this trial demonstrated normal linear growth while receiving nintedanib. Pathological findings on bone imaging and AEs related to growth plate disorders were balanced between the treatment groups over the placebo-controlled period. There was no evidence of documented (by bone imaging) premature closure of epiphyses over the whole trial. If an investigator reported a pathological finding, which was identified by central reading based on a baseline imaging/examination that occurred after start of treatment (up to Day 15), this baseline condition was assigned to baseline AEs. As these baseline AEs were reported on-treatment, they are also contained in the on-treatment AE listings and tables.

SVII.3.1.9.3 Characterisation of the risk

Clinical trial data
Growth plate disorders and impact on growth were assessed based on reporting of defined MedDRA searches (detailed in CTR 1199-0337 [c35674886-03], Appendix 16.2.7, Listing 4.1) and bone imaging results.

Indication fibrosing ILD in paediatric patients
Randomised, double-blind, placebo-controlled trial (1199-0337)
Growth plate disorders
AEs reported during the double-blind period
Growth plate disorders were reported in 2 patients (15.4%) in the placebo group (reported PT ‘X-ray limb abnormal’) and 1 patient (3.8%) in the nintedanib group (reported PT ‘Epiphyses premature fusion’). All events were non-serious and of mild intensity. The patient in the nintedanib group was reported with premature fusion of epiphyses based on local bone imaging interpretation that suggested a potential premature fusion of the epiphyses. However, the pathological finding was not confirmed by the central review and per SMC assessment. The status of epiphyseal closure in this patient was open at Week 12 and during the following visits at Weeks 24 to 76 (data on file, [c35674886-03], Appendix 16.1.13.1, Listing 16.7.1.1]. In the placebo group, the rate/100 PY was 39.44 (95% CI 9.86,157.71) and 8.93 (95% CI 1.26, 63.43) in the nintedanib group. The incidence rate ratio was 0.23 (95% CI 0.02, 2.50) and the incidence rate difference -30.51 (95% CI -87.91, 26.89). In the placebo group, the time to onset was 2 days and 70 days in the nintedanib group (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Tables 3.1.1.2, 3.1.1.4, 3.1.1.5, 3.1.1.6).

AEs reported over the whole trial
No additional AEs were reported in the safety topic of growth plate disorders in the whole trial (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Table 3.2.1.4).

Impact on growth
No AEs related to impact on growth were reported either in the double-blind or in the whole trial (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722).

CTR 1199-0337 [c35674886-03]
Bone examination/imaging
The frequency of pathological findings on bone imaging was similar across the treatment groups at both Weeks 24 and 52 (secondary endpoint). Up to Week 24, 2 (7.7%) patients in the nintedanib group and 1 (7.7%) patient in the placebo group were reported with at least 1 on-treatment pathological finding on the epiphyseal growth plate on imaging. Up to Week 52, 1 additional patient in each treatment group was reported with pathological findings on bone imaging (nintedanib/nintedanib 11.5%, placebo/nintedanib 15.4%). Both patients were female adolescents who were reported with potentially pathological progressive narrowing of lucent growth plate margin. In both cases, the SMC concluded that the findings were most likely physiologic given the patient's age. There was no documented premature closure of epiphyseal plates in the trial.

Change in HAZ from baseline to Week 24 and Week 52
The adjusted mean changes from baseline in HAZ at Week 24 were -0.05 (95% CI -0.11, 0.01) in the nintedanib group and -0.03 (95% CI -0.12, 0.05) in the placebo group. At Week 52, the adjusted mean changes from baseline were -0.05 (95% CI -0.18, 0.07) in the nintedanib/nintedanib group and -0.02 (95% CI -0.19, 0.15) in the placebo/nintedanib group Changes are considered not clinically relevant and support the observation of normal linear growth in both treatment groups.

Trials 1199-0337 and 1199-0378 (pooled)
Growth plate disorders [c35674886-03]

During the pooled nintedanib exposure period, only 1 AEs of 'growth plate disorder' was reported. This concerned the AE of the patient in the nintedanib group of trial 1199-0337, who was reported with premature fusion of epiphyses (details provided in the sub-section 'AEs reported during the double-blind period' of the trial 1199-0337). No new cases of 'growth plate disorders' were reported in trial 1199-0378 up to the snapshot date.

Impact on growth [c35674886-03]

Bone examination/imaging

During the pooled nintedanib exposure period, 3 patients (6.3%) were reported with at least 1 pathological finding on bone imaging up to Week 24, of which 2 patients were reported with pathological findings in the trial 1199-0337 and 1 patient in the trial 1199-0378.

Up to Week 52 of nintedanib treatment in trials 1199-0337 and 1199-0378, 2 additional patients (10.4% in total) were reported with at least 1 on-treatment pathological finding on the epiphyseal growth plate on imaging. None of the potential pathological findings on bone imaging were assessed as related to nintedanib by the SMC.

No additional patients were reported with pathological findings up to the time of the snapshot, which covered a nintedanib exposure period up to 138.4 weeks. Over both trials, up to the snapshot date, there was no documented premature closure of epiphysis during the nintedanib-exposure period.

Change in HAZ from baseline to Week 24 and Week 52

The adjusted mean change from baseline in HAZ at Week 24 of nintedanib treatment was -0.05 (95% CI -0.09, 0), at Week 52 of nintedanib treatment was -0.06 (95% CI -0.14, 0.02), and at Week 76 of nintedanib treatment was -0.04 (95% CI -0.15, 0.04). In the pooled analysis of trials 1199-0337 and 1199-0378, overall, patients demonstrated normal linear growth while receiving nintedanib. The growth velocity in patients treated with nintedanib was stable throughout the observation period by the snapshot date for the pooled analysis.

Conclusion
The clinical data show no evidence to confirm impact of nintedanib treatment on bone development and growth in children and adolescents. Based on the preclinical findings and mechanism of action ‘Effect on bone development and growth in the paediatric population’ is an important potential risk for nintedanib. Based on the longer-term data collected in the ongoing trial 1199-0378, there is no evidence to confirm the potential effect on bone development and growth in the paediatric population treated with nintedanib. Additional safety data to further characterise this safety concern are being collected from the ongoing trial 1199-0378 (see Part III.2.1). The EU-RMP and the EU-SmPC were updated to reflect the current knowledge on this safety concern.

SVII.3.1.9.4 Risk factors and risk groups

Indication fibrosing ILD in paediatric patients
There are no observational studies on risk factors for an effect on bone development and growth in paediatric patients with fibrosing ILD.

Acknowledged risk factors in the medical literature for growth impairment in children with fibrosing ILD include the underlying chronic disease [R22-2189, R22-2187, R22-2188] and treatment with corticosteroids R22-2186, P03-02261].

Patients in the trial 1199-0337 demonstrated normal linear growth and there was no premature closure of the epiphyseal plate documented by bone imaging. Therefore, the assessment of the risk factors and subgroup analyses for this safety topic could not be performed.

SVII.3.1.9.5 Preventability

As a precautionary measure, growth must be regularly monitored and evaluation of epiphyseal growth plate alteration via annual bone imaging is recommended in patients with open epiphyses. Treatment interruption should be considered in patients who develop signs of growth impairment or epiphyseal growth plates alterations.

SVII.3.1.9.6 Impact on the risk-benefit balance of the product

Growth plates alterations may lead to premature closure of the epiphyseal plates, with subsequent impact on growth. However, based on pre-clinical findings, potential effects on the epiphyseal growth plates are expected to be reversible upon drug discontinuation. Regular monitoring of growth and epiphyseal growth plate is recommended, to allow for early detection of growth plates alterations.

SVII.3.1.9.7 Public health impact

There is no wider public health impact of "Effect on bone development and growth disorders" in paediatric patients treated with Ofev.

SVII.3.1.10 Important potential risk: Effect on tooth development disorders in paediatric population

SVII.3.1.10.1 Potential mechanisms

VEGF signalling plays a role in tooth formation in animal species and in humans. In addition, Src deficiency may result in an impaired function of osteoclasts and less prominently of osteoblasts [R12-0557, R12-0496, R12-0497, R12-0403, R12-2339, R12-2340, R12-2341, R12-2344, R12-2345, R12-2348, R12-2349]. Based on the mode of action of nintedanib and on preclinical findings, 'Effect on tooth development disorders in paediatric population' was identified as an important potential risk specific for nintedanib treatment of growing children.

SVII.3.1.10.2 Evidence source and strength of evidence

In non-clinical studies on nintedanib, tooth changes with altered tooth structure and function were observed. Changes were reported during the growth phase of the teeth. These events were mostly judged related to the mechanism of action of nintedanib (see Section SVII.3.1.10.1). These findings may be particularly relevant for growing children with regard to development and tooth growth. The current clinical evidence on this important potential risk is based on the trial 1199-0337 and the ongoing trial 1199-0378. In the paediatric trials, dental examination and dental imaging were regularly performed. The frequencies of pathological findings on dental examination were balanced across the treatment groups. Dental imaging readings were assessed by central reviewers who were blinded to the patients' demographics and clinical data. None of the pathological findings reported based on dental imaging were subsequently confirmed as drug related events. If an investigator reported a pathological finding, which was identified by central reading based on a baseline imaging/examination that occurred after start of treatment (up to Day 15), this baseline

condition was assigned to baseline AEs. As these baseline AEs were reported on-treatment, they are also contained in the on-treatment AE listings and tables.

SVII.3.1.10.3 Characterisation of the risk

Clinical trial data
Tooth development disorders were assessed based on reporting of defined MedDRA searches (detailed in CTR 1199-0337 [c35674886-03], Appendix 16.2.7, Listing 4.1), as well as dental examination and imaging results.

Indication fibrosing ILD in paediatric patients
Randomised, double-blind, placebo-controlled trial (1199-0337)
AEs reported during the double-blind period
Tooth development disorders were reported in 4 patients (30.8%) in the placebo group and 3 patients (11.5%) in the nintedanib group. In the placebo group, the reported PTs were 'Supernumerary teeth' (n=1), 'Tooth development disorder' (n=1), and 'Tooth impacted' (n=2). In the nintedanib group, the reported PTs were 'Tooth development disorder' (n=1) and 'Tooth impacted' (n=2). All events were non-serious and of mild intensity. The rate/100 PY was 96.44 (95% CI 36.19,256.94) in the placebo group and 30.00 (95% CI 9.67, 93.00) in the nintedanib group. The incidence rate ratio was 0.31 (95% CI 0.07, 1.39) and the incidence rate difference -66.44 (95% CI -166.9, 33.98). In the placebo group, the median time to onset was 1 day and the median duration 365 days. In the nintedanib group, the median time to onset was 1 day and the median duration 254 days. All 7 patients were reported with AEs of 'Tooth development disorder' at baseline examination. 1 patient in the nintedanib group was subsequently reported with additional AEs in the safety topic 'Effect on tooth developmental disorders', outside of the baseline window (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Tables 3.1.1.2, 3.1.1.4, 3.1.1.6).

AEs reported over the whole trial
Tooth development disorders were reported in 4 patients (30.8%) in the placebo/nintedanib group and 7 patients (26.9%) in the nintedanib/nintedanib group. In the placebo/nintedanib group, the reported PTs were 'Supernumerary teeth' (n=1), 'Tooth development disorder' (n=1), and 'Tooth impacted' (n=2). In the nintedanib/nintedanib group, the reported PTs were 'Tooth development disorder' (n=7) and 'Tooth impacted' (n=2). All but one event were non-serious. No clear pattern regarding intensity was discernible. The rate/100 PY was 42.46 (95% CI 15.94, 113.13) in the placebo/nintedanib group and 37.78 (95% CI 18.01, 79.24) in the nintedanib/nintedanib group. The incidence rate ratio was 0.89 (95% CI 0.26, 3.04) and the incidence rate difference -4.68 (95% CI -54.83, 45.46). In the placebo group, the median time to onset was 1 day and the median duration 365 days. In the nintedanib group, the median time to onset was 165 day and the median duration 22 days. 7 patients (4 patients in the placebo/nintedanib group and 3 patients in the nintedanib/nintedanib group) were reported with AEs of 'Tooth development disorder' at baseline examination. Patients in the nintedanib/nintedanib group were reported with new AE of 'Tooth development disorder' during the open-label phase of the trial (data on file, 8-05-outputs-x1199p16-1199-337-rmp-dbl2-final-20220722, Tables 3.2.1.2, 3.2.1.4, 3.2.1.6).

CTR 1199-0337 [c35674886-03]

Dental examination/imaging

The proportion of patients with pathological findings on dental examination was slightly higher in the nintedanib group (19.2%) than in the placebo group (7.7%) up to Week 24, and remained balanced between the treatment groups (nintedanib/nintedanib 26.9%, placebo/nintedanib 23.1%) up to Week 52.

Pathological findings on dental imaging reported up to Weeks 24 and 52 (secondary endpoint) in the nintedanib or the placebo groups included stunted growth of the dental root, impacted permanent teeth, additional findings (such as cysts, abscesses, solid lesions, bone abnormalities), and other findings. Up to Week 24, 6 (23.1%) patients in the nintedanib group and no patients in the placebo group were reported with stunted growth of the dental root upon blinded and isolated central imaging review. For 5 out of 6 patients reported with stunted growth of dental root, no indication of stunted growth of dental root was reported by the central review based on follow-up dental imaging at Week 52. Cases were not substantiated by the trial SMC after further in-depth evaluation in the individual clinical context with provision of additional information on patient clinical data and availability of dental images to the SMC. No additional patients were reported with stunted growth of the dental root up to Week 52.

Trials 1199-0337 and 1199-0378 (pooled)

In the pooled analysis of the nintedanib-exposure period in trials 1199-0337 and 1199-0378, a total of 8 patients (16.7%) were reported with AEs of 'tooth developmental disorders'.

SVII.Table 18 AEs and SAEs by safety topic during the nintedanib-exposure period of trial 1199-0337 alone or of trials 1199-0337 and 1199-0378 (pooled) – TS[1]

Organ system *Safety topic*	**Patients with**	**Trial 1199-0337 (nintedanib-exposure period)**		**Trials 1199-0337/0378 (pooled nintedanib-exposure period)**	
		N (%)	**Rate/ 100 PY**	**N (%)**	**Rate/ 100 PY**
Number of patients		**37 (100.0)**		**48 (100.0)**	
Tooth developmental disorder[2,4]	any AE	7 (18.9)	27.4	8 (16.7)	16.2
	SAE	1 (2.7)	3.3	1 (2.1)	1.7

Note: An AE could be displayed in more than 1 safety topic.

[1] Only patients who received at least 1 dose of nintedanib in trial 1199-0337 and/or trial 1199-0378 up to the snapshot date were included in this analysis set.

[2] Grouping of MedDRA PTs

[4] Includes 3 patients (trial 1199-0337) with AEs related to baseline dental examination/imaging (performed up to Day 15 but after the start of treatment).

Data source: CO [c42238250-01], based on Table 26

The additional AE reported in the pooled analysis in the table above (compared to trial 1199-0337 alone) concerns a patient in trial 1199-0378, who was reported with an AE of

tooth development disorder. The AE was ‘tooth hypoplasia’ (reported as enamel hypoplasia). The AE was of mild intensity and was ongoing at the time of the snapshot [c35674886-03].

Dental examination/imaging [c35674886-03]
A total of 20 patients (41.7%) were reported with at least 1 pathological finding on dental examination or imaging during the first 24 weeks of nintedanib exposure. With prolonged exposure, the number of patients with reported pathological findings had increased slightly to 23 patients (47.9%) at Week 52 and to 25 patients (52.1%) at Week 100. None of the reported pathological findings on dental examination were assessed as related to trial medication, as confirmed by the SMC.

5 of the 6 patients reported with stunted growth of dental root in the trial 1199-0337 rolled over to the extension trial (1199-0378). No indication of stunted growth of dental root was reported by the central review based on follow-up dental imaging at Week 52 (all 5 patients) and Week 100 (imaging results available for 3 patients).

No additional patients were reported with stunted growth of the dental root up to snapshot date (a maximum of 148 weeks of nintedanib-exposure period in trials 1199-0337 and 1199-0378).

Conclusion
The clinical data show no evidence to confirm impact of nintedanib treatment on tooth development in humans. Based on the preclinical findings and mechanism of action ‘Effect on tooth development disorders in paediatric population’ is an important potential risk for nintedanib. Additional safety data to further characterise this safety concern are being collected from the ongoing trial 1199-0378. The EU-RMP and the EU-SmPC were updated to reflect the current knowledge on this safety concern.

SVII.3.1.10.4 Risk factors and risk groups

Indication fibrosing ILD in paediatric patients
There are no observational data on risk factors for an effect on tooth development disorders in paediatric patients with fibrosing ILD.

Patients at greater risk for the event of ‘Stunted growth of dental root’ include children aged 0 to 6 years and patients with underlying disorders which impact root development (such as dental trauma, Down syndrome, or Turner syndrome).

SVII.3.1.10.5 Preventability

Oral dental examination must be performed regularly, at least every 6 months, to monitor for any changes of the teeth until development of dentition is completed.

SVII.3.1.10.6 Impact on the risk-benefit balance of the product

Stunted growth of the dental root may lead to tooth loss. However, patients at greater risk would include children aged 0 to 6 years, for which use of nintedanib is not recommended. In

addition, an impacted tooth might be at a greater risk for mobility if strong forces were used during orthodontic treatment or if the patient developed periodontal disease. As these conditions are preventable, tooth loss would be extremely rare. Regular dental examination is recommended, to allow for early detection of tooth development disorders.

SVII.3.1.10.7 Public health impact

There is no wider public health impact of "Effect on tooth development disorders" in patients treated with Ofev.

SVII.3.2 Presentation of the missing information

SVII.3.2.1 Treatment of SSc-ILD patients with pulmonary hypertension

SVII.3.2.1.1 Evidence source

Treatment of SSc-ILD patients with pulmonary hypertension was added as a missing information topic to the EU-RMP in 2020 within the procedure for the extension of indication for Ofev in the treatment of SSc-ILD.

Pulmonary arterial hypertension is present in 7.5% to 12% of SSc patients, but evidence that pulmonary circulation has been compromised is more common. The main pathologic lesion in SSc-ILD patients with pulmonary hypertension is the obstructive proliferative vasculopathy of the small- and medium-sized pulmonary arterial circulation [R16-0051]. Defective angiogenic pathways have been identified in SSc patients and this is presumed to be one of the factors contributing to the pathogenesis of pulmonary hypertension in the SSc population [R16-0051, P15-00686]. The current scientific evidence shows both opposing and complementary actions of VEGF in pulmonary arterial hypertension [R19-2519].

Consequently, from a theoretical perspective, the known anti-angiogenic action of Ofev may either improve or worsen pulmonary hypertension, and there is no clear evidence in humans to establish which is more likely to occur in this patient population. Patients with significant pulmonary hypertension (significant right heart failure, cardiac index ≤2 L/min/m2, and parenteral therapy with epoprostenol/treprostinil) were excluded from the SENSCIS trial (1199-0214 [c22686034-01]). There were few patients (n=52) with mild/moderate pulmonary hypertension with limited data available in SENSCIS. Therefore, the treatment of SSc-ILD patients with pulmonary hypertension is taken up as missing information.

SVII.3.2.1.2 Anticipated risk/consequence of the missing information

In the SENSCIS study, Doppler echocardiography was at least to be performed in patients with a prior history of pulmonary hypertension at the time of screening. The proportion of patients with changes from baseline was low and similar in the 2 treatment groups (nintedanib 8 patients, placebo 7 patients). Changes primarily involved reports of worsening of estimated pulmonary arterial pressure (corresponding to pulmonary hypertension) and/or increased diameter of the right heart ventricle or atrium [c26224518-01].

Furthermore, a review of a subgroup of patients with mild or moderate pulmonary hypertension reported at baseline (nintedanib 23 patients, placebo 29 patients) showed no difference in reported AEs of pulmonary hypertension compared to placebo (nintedanib 4.3% vs. placebo 3.4%) [c26224518-01, c22686034-01].

During the post-marketing period (up to 15 Apr 2022), 99 cases of patients identified as having comorbidity of SSc-ILD and pulmonary hypertension were reported. Most of the cases (75.8%) were from report from study - other studies and related (82.8%). 79.8% of the cases were female, 18.2% male. 45.5% of the cases were serious, with 15 fatal cases. The reported AEs were in line with the known safety profile of nintedanib with diarrhoea (63.6%) being most frequently reported. The PT ‘Pulmonary hypertension’ was reported as an AE in 3 cases, indicating a worsening of the condition during course of treatment. Cardiac failure was co-reported in each of these cases. The PT ‘Pulmonary arterial hypertension’ was not reported as an AE in SSc-ILD patients (Ofev PBRER, reporting interval 16 Oct 2021 to 15 Apr 2022 [s00106744-01], Section 16.4.4.4).

Due to the limited clinical trial and post-marketing data, and the contradictory evidence from the scientific literature, the impact in SSc-ILD patients with pulmonary hypertension is considered unknown. The feasibility of further evaluating this population will be taken up in the PAES (trial 1199-0421). The topic will continue to be followed as a missing information topic in the EU-RMP. Monitoring and presentation of available data in the PBRER will be continued.

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ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
ATE	Arterial thromboembolism
b.i.d.	Bis in die; twice daily
BAZ	BMI-for-age z-score
BI	Boehringer Ingelheim
BMI	Body mass index
chILD	Childhood interstitial lung disease
CI	Confidence interval
CO	Clinical Overview
CREST syndrome	Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly and Telangiectasia
CTD	Connective tissue disease
CTR	Clinical Trial Report
DBL1	Database lock 1
DILI	Drug-induced liver injury
DILIN	Drug Induced Liver Injury Network
DVT	Deep vein thrombosis
EU	European Union
GI	Gastrointestinal
GSP	Global Safety Platform
HAZ	Height-for-age z-score
HR	Hazard ratio
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
IR	Incidence rate
MedDRA	Medical Dictionary for Regulatory Activities

MI	Myocardial infarction
NHI	National Health Insurance; Taiwanese research database
NSAID	Non-steroidal anti-inflammatory drug
PAES	Post-authorisation efficacy study
PBRER	Periodic Benefit-Risk Evaluation Report
PE	Pulmonary embolism
PF-ILD	Progressive fibrosing interstitial lung disease
PK	Pharmacokinetic
PT	Preferred term
PY	Patient years
QT interval	Measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
RMP	Risk Management Plan
SD	Standard deviation
SE	Standard error
SENSCIS	Safety and Efficacy of Nintedanib in Systemic SClerosIS (study acronym)
SG	Safety Grouping
SMC	Safety monitoring committee
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
SSc	Systemic sclerosis
SSc-ILD	Systemic sclerosis associated interstitial lung disease
THIN	The Health Improvement Network; UK database
TKI	Tyrosine kinase inhibitor
TS	Treated set
UGT	Uridine glucuronyl transferase
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
vs.	Versus
VTE	Venous thromboembolism

MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

SVIII.Table 1 Summary of safety concerns

Important identified risks	DILI
	Bleeding
	Myocardial infarction
	Weight decreased in paediatric population
Important potential risks	Venous thromboembolism
	Arterial thromboembolism excluding myocardial infarction
	Perforation
	Hepatic failure
	Effect on bone development and growth in paediatric population
	Effect on tooth development disorders in paediatric population
Missing information	Treatment of SSc-ILD patients with pulmonary hypertension

SVIII.1 REFERENCES

Not applicable.

ABBREVIATIONS

DILI	Drug-induced liver injury
SSc-ILD	Systemic sclerosis associated interstitial lung disease

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

PART III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
Specific adverse reaction follow-up questionnaires for:

Important identified risks

- DILI (restricted to serious events of liver enzyme increases, DILI, and hepatic failure)
- Myocardial infarction (note: one follow-up questionnaire for all arterial thromboembolism events)
- Bleeding (defined as serious according to GVP, assessed as serious by reporter, listed in IME list or initial case without enough information for assessment of seriousness)

Important potential risks

- Arterial thromboembolism excluding myocardial infarction (note: one follow-up questionnaire for all arterial thromboembolism events)
- Perforation
- Hepatic failure
- Effect on bone development and growth in paediatric population
- Effect on tooth development disorders in paediatric population

PART III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Part III.2.1 Trial 1199-0378 summary

Study short name and title
1199-0378 (InPedILD™-ON) - An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 3 years, in children and adolescents with clinically significant fibrosing Interstitial Lung Disease

Rationale and study objectives
To collect additional safety data of nintedanib in children and adolescents with clinically significant fibrosing ILD for at least 3 years. As agreed with EMA/CHMP, trial 1199-0378 will be extended by an additional year of treatment.

The main objective of the trial is to assess the safety and tolerability of long-term treatment with nintedanib in paediatric patients with clinically significant fibrosing ILD, as follows:

- Primary endpoint: incidence of treatment emergent adverse events over the whole trial
- Further safety endpoints: incidence of treatment-emergent pathological findings of epiphyseal growth plate on imaging over 24 weeks, over 52 weeks and over the whole

trial; incidence of treatment-emergent pathological findings on dental examination or imaging over 24 weeks, over 52 weeks and over the whole trial; DILI/hepatic failure in paediatric population; weight-for-age z-score (ΔWAZ) from baseline at week 24, week 52, week 76, week 104, and over the whole trial; BMI-for-age z-score (ΔBAZ) from baseline at week 24, week 52, week 76, week 104, and over the whole trial.

Study population
Paediatric patients (children and adolescents ≥6 and ≤17 years) with fibrosing ILD

Milestones
Final report, 12 Jan 2026

PART III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

PIII.Table 1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Trial 1199-0378 1199-0378 - (InPedILD™-ON) - An open-label trial of the long-term safety and tolerability of nintedanib per os, on top of standard of care, over at least 3 years, in children and adolescents with clinically significant fibrosing Interstitial Lung Disease Ongoing	To assess the safety and tolerability of long-term treatment with nintedanib in paediatric patients with clinically significant fibrosing ILD	Effect on bone development and growth in paediatric population Effect on tooth development disorders in paediatric population DILI/hepatic failure (in paediatric population) Weight decreased in paediatric population	Final report	12 Jan 2026

PART III.4 REFERENCES

Not applicable.

PART III.5 ABBREVIATIONS

BMI	Body mass index
DILI	Drug-induced liver injury
GVP	Good Pharmacovigilance Practice

ILD	Interstitial lung disease
IME	Important medical event; list from the EudraVigilance Expert Working Group

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

This part is not applicable as there are no planned or ongoing post-authorisation efficacy studies imposed for Ofev.

PART V RISK MINIMISATION MEASURES

RISK MINIMISATION PLAN

PART V.1 ROUTINE RISK MINIMISATION MEASURES

PV.Table 1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
DILI	*Routine risk communication* EU-SmPC sections 4.2, 4.4, and 4.8; PL sections 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk* Recommendation to investigate hepatic transaminase and bilirubin levels before treatment initiation and to monitor liver enzymes at regular intervals during treatment. Recommendation for dose reduction or treatment interruption as appropriate, and for permanent discontinuation if liver test elevations are associated with clinical signs or symptoms of liver injury. Recommendation to closely monitor patients with risk factors for elevation of liver enzymes. *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.
Bleeding	*Routine risk communication* EU-SmPC sections 4.4 and 4.8; PL sections 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.

PV.Table 1 (cont'd) Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks (cont'd)	
Myocardial infarction	*Routine risk communication* EU-SmPC sections 4.4 and 4.8; PL sections 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.
Weight decreased in paediatric population	*Routine risk communication* EU-SmPC sections 4.2, 4.8; PL section 3 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.
Important potential risks	
Venous thromboembolism	*Routine risk communication* EU-SmPC section 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.

PV.Table 1 (cont'd) Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important potential risks (cont'd)	
Arterial thromboembolism excluding myocardial infarction	*Routine risk communication* EU-SmPC section 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.
Perforation	*Routine risk communication* EU-SmPC section 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.
Hepatic failure	*Routine risk communication* EU-SmPC sections 4.2, 4.4, and 4.8; PL sections 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk* Recommendation to investigate hepatic transaminase and bilirubin levels before treatment initiation and to monitor liver enzymes at regular intervals during treatment. Recommendation for dose reduction or treatment interruption as appropriate, and for permanent discontinuation if liver test elevations are associated with clinical signs or symptoms of liver injury. Recommendation to closely monitor patients with risk factors for elevation of liver enzymes. *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.

PV.Table 1 (cont'd) Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important potential risks (cont'd)	
Effect on bone development and growth in paediatric population	*Routine risk communication* EU-SmPC section 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* Recommendation of regular monitoring of growth and evaluation of epiphyseal growth plate alteration via annual bone imaging in patients with open epiphyses. Recommendation for treatment interruption in patients who develop signs of growth impairment or epiphyseal growth plates alterations. *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indication.
Effect on tooth development disorders in paediatric population	*Routine risk communication* EU-SmPC section 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* Recommendation of regular oral dental examination (at least every 6 months) until development of dentition is completed. *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indication.
Missing information	
Treatment of SSc-ILD patients with pulmonary hypertension	*Routine risk communication* EU-SmPC section 4.4; PL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Medicinal product subject to restricted medical prescription. Treatment to be initiated by physicians experienced in the diagnosis and treatment of the respective indications.

PART V.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

PART V.3 SUMMARY OF RISK MINIMISATION MEASURES

PV.Table 2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
DILI	*Routine risk minimisation measures* EU-SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Recommendation to conduct liver tests before treatment initiation and regular monitoring during treatment. Recommendation for dose reduction or treatment interruption as appropriate, or for permanent discontinuation in case of clinical signs or symptoms of liver injury Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form *Additional pharmacovigilance activities* Trial 1199-0378 (final report, 12 Jan 2026), in paediatric population
Bleeding	*Routine risk minimisation measures* EU-SmPC sections 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form (for bleeding events defined as serious according to GVP, assessed as serious by reporter, listed in IME list or initial case without enough information for assessment of seriousness)

PV.Table 2 (cont'd) Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks (cont'd)		
Myocardial infarction	*Routine risk minimisation measures* EU-SmPC sections 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form (note: one follow-up questionnaire for all arterial thromboembolism events)
Weight decreased in paediatric population	*Routine risk minimisation measures* EU-SmPC section 4.2 and 4.8 PL section 3 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* None *Additional pharmacovigilance activities* Trial 1199-0378 (final report, 12 Jan 2026)
Important potential risks		
Venous thromboembolism	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications *Additional risk minimisation measures* None	None
Arterial thromboembolism excluding myocardial infarction	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form (note: one follow-up questionnaire for all arterial thromboembolism events)

PV.Table 2 (cont'd) Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks		
Perforation	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form
Hepatic failure	*Routine risk minimisation measures* EU-SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Recommendation to conduct liver tests before treatment initiation and regular monitoring during treatment. Recommendation for dose reduction or treatment interruption as appropriate, or for permanent discontinuation in case of clinical signs or symptoms of liver injury Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form *Additional pharmacovigilance activities* Trial 1199-0378 (final report, 12 Jan 2026), in paediatric population

PV.Table 2 (cont'd) Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Important potential risks (cont'd)		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Effect on bone development and growth in paediatric population	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Recommendation of regular monitoring of growth and annual bone imaging in patients with open epiphyses. Recommendation for treatment interruption in patients who develop signs of growth impairment or epiphyseal growth plates alterations Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indication *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form *Additional pharmacovigilance activities* Trial 1199-0378 (final report, 12 Jan 2026)
Effect on tooth development disorders in paediatric population	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Recommendation of regular oral dental examination (at least every 6 months) during development of dentition Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indication *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form *Additional pharmacovigilance activities* Trial 1199-0378 (final report, 12 Jan 2026

PV.Table 2 (cont'd) Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
Treatment of SSc-ILD patients with pulmonary hypertension	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications *Additional risk minimisation measures* None	None

PART V.4 REFERENCES

Not applicable.

ABBREVIATIONS

AE	Adverse event
DILI	Drug-induced liver injury
EU	European Union
GVP	Good Pharmacovigilance Practice
IME	Important medical event; list from the EudraVigilance Expert Working Group
PL	Package Leaflet
SmPC	Summary of Product Characteristic
SSc-ILD	Systemic sclerosis associated interstitial lung disease

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR OFEV (NINTEDANIB)

This is a summary of the risk management plan (RMP) for Ofev. The RMP details important risks of Ofev, how these risks can be minimised, and how more information will be obtained about Ofev's risks and uncertainties (missing information).

Ofev's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ofev should be used.

This summary of the RMP for Ofev should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ofev's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Ofev is authorised in adults for treatment of idiopathic pulmonary fibrosis, for treatment of systemic sclerosis associated interstitial lung disease, and for treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype, and for treatment of clinically significant fibrosing ILDs in children and adolescents from 6 to 17 years old (see SmPC for the full indications). It contains nintedanib as the active substance and it is given by oral administration.

Further information about the evaluation of Ofev's benefits can be found in Ofev's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Ofev, together with measures to minimise such risks and the proposed studies for learning more about Ofev's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Ofev is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Ofev are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely used. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ofev. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	DILI
	Bleeding
	Myocardial infarction
	Weight decreased in paediatric population
Important potential risks	Venous thromboembolism
	Arterial thromboembolism excluding myocardial infarction
	Perforation
	Hepatic failure
	Effect on bone development and growth in paediatric population
	Effect on tooth development disorders in paediatric population
Missing information	Treatment of SSc-ILD patients with pulmonary hypertension

II.B Summary of important risks

Important identified risks

DILI	
Evidence for linking the risk to the medicine	In clinical trials, liver enzyme and bilirubin elevation AEs occurred more frequently in patients treated with Ofev than in those treated with placebo. Furthermore, liver enzyme elevations are among the most common reported adverse events in the post-marketing setting whereas reports of DILI are uncommon.
Risk factors and risk groups	Network (DILIN) in the US assessed the characteristics of DILI patients aged 65 years and above. In this cohort (n=149), 60% of the patients were female and 85% were White. The highest proportion of patients (58%) took at least 6 medications. Among the DILI patients, antimicrobial agents were the most common class of causative drugs with 57.7%. Indication IPF: A broader analysis of 'liver related investigation' suggested that the subgroup of Asian patients and the subgroup of female patients treated with Ofev may be at higher risk of 'liver related investigation' than White patients and male patients, respectively. Based on PK population analysis, patients with low body weight (<65 kg), Asian and female patients have a higher risk of elevations of liver enzymes. Nintedanib exposure increased linearly with patient age, which may also result in a higher risk of developing liver enzyme elevations. Indication SSc-ILD: A broader analysis of 'liver related investigation' indicated a higher frequency of 'liver related investigation' in female than male patients and in Asian than in White/Black patients. There was an increase in frequency with increasing age. No clinically meaningful difference in frequency of 'liver related investigation' between nintedanib and placebo was observed in the remaining subgroups. Indication PF-ILD: A broader analysis of 'liver related investigation' suggested that Asian, female, and patients with a low body weight (≤65 kg) may be at higher risk of 'liver related investigation'. No clinically meaningful differences were observed in the remaining subgroups. Indication fibrosing ILD in paediatric patients: The events reported under hepatobiliary disorders were in line with the data in adult patients and consistent across the evaluated safety subgroups (age (6 to <12 years and 12 to <18 years in total) and gender). Due to the relatively low number of patients, no firm conclusions could be drawn based on subgroup analyses.

Risk minimisation measures	Routine risk minimisation measures EU-SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Recommendation to conduct liver tests before treatment initiation and regular monitoring during treatment. Recommendation for dose reduction or treatment interruption as appropriate, or for permanent discontinuation in case of clinical signs or symptoms of liver injury Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Trial 1199-0378 (in paediatric population) See Section II.C of this summary for an overview of the post-authorisation development plan
Bleeding	
Evidence for linking the risk to the medicine	In the clinical trials, the frequency of patients who experienced bleeding AEs was slightly higher or similar in the Ofev treatment group than in the placebo group. Bleeding events were mostly not serious in clinical trials. In the post-marketing period, non-serious and serious bleeding events have been reported (including patients with or without anticoagulant therapy or other drugs that could cause bleeding).
Risk factors and risk groups	Patients at known risk for bleeding including patients with inherited predisposition to bleeding or patients receiving a full dose of anticoagulant treatment were not included in the studies. Subgroup analyses showed similar results between treatment groups. No clinically meaningful difference in frequency of bleeding was observed in the analysed subgroups. SSc may affect the blood vessels in the stomach, which predisposes patients with SSc to a higher risk of gastrointestinal bleeding than the general population. No clinically meaningful difference in frequency of bleeding was observed in the analysed subgroups in paediatric patients with fibrosing ILD. Due to low number of bleeding events and the relatively low number of paediatric patients in the evaluated subgroups, no firm conclusions could be drawn based on subgroup analyses.

Risk minimisation measures	Routine risk minimisation measures: EU-SmPC sections 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications Additional risk minimisation measures: None
Myocardial infarction	
Evidence for linking the risk to the medicine	In the IPF (INPULSIS) studies, while AEs reflecting ischaemic heart disease were balanced between the nintedanib and placebo groups, a higher percentage of patients experienced myocardial infarction in the nintedanib group (1.7%) compared to the placebo group (0.5%). In the SSc-ILD (SENSCIS) studies, no MI was reported in the Ofev group. In the PF-ILD study, the frequency of MI was the same between the nintedanib and the placebo group (0.9% each).
Risk factors and risk groups	Patients with a recent history of myocardial infarction or stroke were excluded from the trials. Based on the low number of patients affected in clinical trials, no clinically meaningful difference in frequency of myocardial infarction was observed in the analysed subgroups. Independently of treatment, there is an increased risk within the IPF/SSc/PF-ILD population for cardiovascular events including coronary artery disease, myocardial infarction, and stroke based on epidemiological data. SSc may affect the blood vessels that supply the heart resulting in myocardial infarction. As a consequence, SSc patients have a higher risk of myocardial infarction than the general population. No cardiovascular events were reported in the paediatric study (InPedILD), and no analysis of the risk factors could be performed.
Risk minimisation measures	Routine risk minimisation measures: EU-SmPC sections 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications Additional risk minimisation measures: None

Weight decreased in paediatric population	
Evidence for linking the risk to the medicine	'Weight decreased' is a known ADR for nintedanib based on the clinical trials conducted in the adult population with IPF, SSc-ILD, and PF-ILD. In the paediatric clinical trials 'weight decreased' was a pre-defined safety topic. In the pooled analysis of the trials 1199-0337 and 1199-0378, the frequency and incidence of an AE of 'weight decreased' in children was similar as in adults (11.1% and incidence rate 9.27 per 100 PY in the paediatric population vs. 11.1% and incidence rate 13.05 per 100 PY in the adult population).
Risk factors and risk groups	In the trials 1199-0337 and 1199-0378, all AEs of 'weight decreased' were reported in the age subgroup 12 to <18 years. However, due to relatively low number of patients in the evaluated subgroups, no firm conclusions could be drawn based on subgroup analyses.
Risk minimisation measures	Routine risk minimisation measures: EU-SmPC section 4.2. and 4.8 PL section 3 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Trial 1199-0378 (in paediatric population) See Section II.C of this summary for an overview of the post-authorisation development plan

Important potential risks

Venous thromboembolism	
Evidence for linking the risk to the medicine	In the clinical trials, the frequency of patients with VTE was similar between both treatment groups. There was no evidence from the clinical trial programme with Ofev to suggest that venous thromboembolism is an important identified risk in patients with IPF/SSc/PF-ILD. Nevertheless, the risk of venous thromboembolism resulting from the mode of action of Ofev cannot be entirely ruled out, and so venous thromboembolism is considered an important potential risk.
Risk factors and risk groups	Due to the small numbers of patients who experienced venous thromboembolism in randomised, placebo-controlled clinical trials, the subgroup assessment is not considered meaningful. Independently of treatment, a number of major risk

	factors for venous thromboembolism/pulmonary embolism have been identified: old age (>65 years), long-haul travel, thrombophilia, obesity, cigarette smoking, hypertension, metabolic syndrome, immobilisation, cancer, and acute medical illness, among others. Studies reported higher incidence rates of venous thromboembolism/pulmonary embolism for IPF, SSc-ILD, and PF-ILD patients compared to controls. This is probably explained by the fact that IPF, SSc-ILD, and PF-ILD patients have advanced age and frequently 1 or more additional risk factors for thromboembolism. Also, acute medical illness, such as pneumonia, has also been described as a risk factor for pulmonary embolism. Autoimmune diseases such as SSc have been associated with an increased risk of VTE. No thromboembolic event was reported in the paediatric study (InPedILD) and no analysis of the risk factors could be performed.
Risk minimisation measures	Routine risk minimisation measures: EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications Additional risk minimisation measures: None
Arterial thromboembolism excluding myocardial infarction	
Evidence for linking the risk to the medicine	There was no evidence from the clinical trial programme with Ofev to suggest that ATE excluding myocardial infarction is an important identified risk in patients with IPF/SSc/PF-ILD. Nevertheless, the risk of ATE resulting from the drug class (TKIs with VGEF inhibition) cannot entirely be ruled out, and so ATE excluding MI is considered an important potential risk.
Risk factors and risk groups	Indication IPF: Based on the low number of patients affected, no clinically meaningful difference in frequency of arterial thromboembolism was observed in the analysed subgroups. There is an increased risk within the IPF population for cardiovascular disease, including coronary artery disease, myocardial infarction, and stroke based on epidemiological data. Indication SSc-ILD: SSc may affect the blood vessels that supply the heart resulting in myocardial infarction. As a consequence, SSc patients have a higher risk of

	coronary artery disease and myocardial infarction than the general population. Studies have reported an increased risk of ischaemic stroke among patients with SSc explained by the deleterious effects of this disease in the blood vessels. Indication PF-ILD: Subgroup analyses showed similar results between treatment groups. No clinically meaningful difference in frequency of arterial thromboembolism was observed in the analysed subgroups. Indication fibrosing ILD in paediatric patients: No thromboembolic event was reported in the paediatric study (InPedILD) and no analysis of the risk factors could be performed.
Risk minimisation measures	Routine risk minimisation measures: EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD Additional risk minimisation measures: None
Perforation	
Evidence for linking the risk to the medicine	In the IPF (INPULSIS) studies and in the PF-ILD study (INBUILD), the frequency of patients with GI perforation was very low. In SSc (SCENSIS) studies, no gastrointestinal perforations were observed in patients treated with Ofev.
Risk factors and risk groups	Due to the small numbers of patients who experienced perforation in randomised, placebo-controlled clinical trials, the subgroup assessment is not considered meaningful. Independently of treatment, a number of risk factors for gastrointestinal perforation such as preceding abdominal surgery and use of corticosteroids or non-steroid anti-inflammatory drugs have been identified. There was no event of GI perforation in the paediatric study (InPedILD) and no subgroup analysis could be performed.

Risk minimisation measures	Routine risk minimisation measures EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications Additional risk minimisation measures None
Hepatic failure	
Evidence for linking the risk to the medicine	In the clinical trials, hepatic failure did not occur. DILI is an identified risk of Ofev. Therefore, the potential for further sequelae of liver abnormality is warranted for monitoring 'hepatic failure' as a potential risk
Risk factors and risk groups	Indication IPF: Based on the low number of patients affected, no clinically meaningful difference in frequency of hepatic failure was observed in the analysed subgroups. Indication SSc-ILD: Overlap of SSc and autoimmune hepatitis has been observed in the SSc population. Indication IPF-ILD: Subgroup analyses suggest, that Asian and patients with a low body weight (≤65 kg) may be at higher risk of hepatic failure events. No clinically meaningful differences were observed in the remaining subgroups. Indication fibrosing ILD in paediatric patients: In the paediatric population, the hepatic events were in line with the data in adult patients. 1 event was reported in the subgroup age 6 to <12 years and 2 events were reported in female patients. Due to the low number of paediatric patients, no firm conclusions could be drawn based on subgroup analyses.
Risk minimisation measures	Routine risk minimisation measures EU-SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Recommendation to conduct liver tests before treatment initiation and regular monitoring during treatment. Recommendation for dose reduction or treatment interruption as appropriate, or for permanent discontinuation in case of clinical signs or symptoms of liver injury Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications Additional risk minimisation measures None

Additional pharmacovigilance activities	Additional pharmacovigilance activities Trial 1199-0378 (in paediatric population) See Section II.C of this summary for an overview of the post-authorisation development plan
Effect on bone development and growth in paediatric population	
Evidence for linking the risk to the medicine	In non-clinical studies on nintedanib, changes in bone development and growth plates were observed. In the InPedILD study, the frequency of paediatric patients with pathological findings bone imaging was similar across treatment groups.
Risk factors and risk groups	Risk factors for growth impairment in children with fibrosing ILD include the underlying chronic disease and treatment with corticosteroids. Due to the small number of paediatric patients, subgroup analyses were not performed.
Risk minimisation measures	Routine risk minimisation measures EU-SmPC section 4.4 PL section 2 Recommendation of regular monitoring of growth and annual bone imaging in patients with open epiphyses. Recommendation for treatment interruption in patients who develop signs of growth impairment or epiphyseal growth plates alterations Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indication Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Trial 1199-0378 See Section II.C of this summary for an overview of the post-authorisation development plan
Effect on tooth development disorders in paediatric population	
Evidence for linking the risk to the medicine	In non-clinical studies on nintedanib, changes in tooth structure and function were observed. In the InPedILD study, the frequency of paediatric patients with pathological findings on dental examination was similar across treatment groups.
Risk factors and risk groups	Patients at greater risk for the event of ‘Stunted growth of dental root’ include children aged 0 to 6 years and patients with underlying disorders which impact root development (such as dental trauma, Down syndrome, or Turner syndrome).

Risk minimisation measures	Routine risk minimisation measures EU-SmPC section 4.4 PL section 2 Recommendation of regular oral dental examination (at least every 6 months) during development of dentition Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indication Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Trial 1199-0378 See Section II.C of this summary for an overview of the post-authorisation development plan

Missing information

Treatment of SSc-ILD patients with pulmonary hypertension	
Risk minimisation measures	Routine risk minimisation measures: EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of the respective indications Additional risk minimisation measures: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Ofev.

II.C.2 Other studies in post-authorisation development plan

Trial 1199-0378
Purpose of the study: To collect additional safety data of nintedanib in children and adolescents with clinically significant fibrosing ILD for at least 3 years.

The main objective of the trial is to assess the safety and tolerability of long-term treatment with nintedanib in paediatric patients with clinically significant fibrosing ILD, as follows:

- Primary endpoint: incidence of treatment emergent adverse events over the whole trial

- Further safety endpoints: incidence of treatment-emergent pathological findings of epiphyseal growth plate on imaging over 24 weeks, over 52 weeks and over the whole trial; incidence of treatment-emergent pathological findings on dental examination or imaging over 24 weeks, over 52 weeks and over the whole trial; DILI/hepatic failure in paediatric population; weight-for-age z-score (ΔWAZ) from baseline at week 24, week 52, week 76, week 104, and over the whole trial; BMI-for-age z-score (ΔBAZ) from baseline at week 24, week 52, week 76, week 104, and over the whole trial.

ABBREVIATIONS

AE	Adverse event
ATE	Arterial thromboembolism
BMI	Body mass index
DILI	Drug-induced liver injury
DILIN	Drug-Induced Liver Injury Network
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
MI	Myocardial infarction
PF-ILD	Progressive fibrosing interstitial lung disease
PK	Pharmacokinetic
PL	Package Leaflet
PSUR	Periodic Safety Update Report

RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SSc	Systemic sclerosis
SSc-ILD	Systemic sclerosis associated interstitial lung disease
TKI	Tyrosine kinase inhibitor
VEGF	Vascular endothelial growth factor
VTE	Venous thromboembolism

PART VII APPENDICES

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APPENDIX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

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Questionnaire: Tooth development disorder form (Ofev)

Question ID	Questionnaire Name	Question
Tooth development disorder	Tooth development disorder form (Ofev)	Please provide patient's dental medical history (including dental caries, impacted teeth).
Tooth development disorder	Tooth development disorder form (Ofev)	Does the patient wear dental braces?
Tooth development disorder	Tooth development disorder form (Ofev)	Did the patient undergo orthodontic treatment in the past or recently? If yes, please specify (including the date).
Tooth development disorder	Tooth development disorder form (Ofev)	Did the patient have any dental trauma? If yes, please specify (including the date).
Tooth development disorder	Tooth development disorder form (Ofev)	Does the patient have a good oral hygiene?
Tooth development disorder	Tooth development disorder form (Ofev)	Did the patient receive treatment with antineoplastic drugs in the past or recently? If yes, please specify (including dosage, date when started and date when last administered).
Tooth development disorder	Tooth development disorder form (Ofev)	Did the patient undergo oral dental examination? If yes, please provide description of the findings (including the date when dental examination(s) was (were) performed).
Tooth development disorder	Tooth development disorder form (Ofev)	Did the patient undergo dental imaging(s)? If yes, please provide description of the findings (including the date when dental imaging was performed).

Tooth development disorder	Tooth development disorder form (Ofev)	Please provide the FDI (Fédération Dentaire Internationale) tooth/teeth number(s) for the affected teeth.
Tooth development disorder	Tooth development disorder form (Ofev)	Was treatment with Ofev interrupted/discontinued following the event? If yes, please provide the date when treatment with Ofev was interrupted/discontinued.
Tooth development disorder	Tooth development disorder form (Ofev)	Did the patient receive treatment for the event? If yes, please specify.

Questionnaire: Hepatic Event Form - Question Library Version 21.0

Question ID	Questionnaire Name	Question
Q:HO01	Hepatic Event Form (Ofev)	When did the first signs or symptoms of the reported hepatic event occur? [Before start of treatment with OFEV®, please specify days/weeks; After start of treatment with OFEV®, please specify days/weeks; Unknown] //
Q:HO02	Hepatic Event Form (Ofev)	Did the patient had a Past and Current History of: [Yes, if applicable; Specify diagnosis or signs and symptoms; Date] - Jaundice (personal or family history) - Hereditary metabolic diseases (e.g. M. Wilson, haemochromatosis) - Metabolic-induced liver disease (NASH) - Alcohol-induced liver disease //
Q:HO03	Hepatic Event Form (Ofev)	Did the patient had a Past and Current History of: [Yes, if applicable; Specify diagnosis or signs and symptoms; Date] - History of drug allergy/hypersensitivity reaction - Infectious diseases (e.g. HIV, EBV, CMV, Cocksackie, malaria) - Blood transfusions //
Q:HO04	Hepatic Event Form (Ofev)	Did the patient experienced in the Past and Current History: [Yes, if applicable; Specify diagnosis or signs and symptoms; Date] - Recent administration of drugs with known hepatic toxicity - Environmental exposure to liver toxins (CCl4, death cap, vinyl chloride) - Substance abuse/Intoxications - Autoimmune disorders (e.g. PBC, PSC) - Treatment of hepatitis B/C //

Questionnaire: Hepatic Event Form - Question Library Version 21.0

Q:HO05	Hepatic Event Form (Ofev)	Had the patient any malignancy or other manifestation (Past and Current History): [Yes, if applicable; Specify diagnosis or signs and symptoms; Date] - Extrahepatic manifestations (e.g. gallstones, infestations, pancreatitis) - Hepatic malignancy - Extrahepatic malignancy //
Q:HO06	Hepatic Event Form (Ofev)	Laboratory Parameter (include: exact value or ↑↓↔; Unit; Date; Baseline (Prior to event, Maximum or minimum, after event subsided] - AST - ALT - γ-GT - AP - CHE - Bili total - Bili direct - Bili indirect - Albumin - PT (INR) - ASM - AMA - ANA - AFP - CEA - Thrombocytes //
Q:HO07	Hepatic Event Form (Ofev)	Hepatitis-Serology (exact viral load or pos/neg) [Hepatitis A Parameter; Value; Unit] - Anti-IgM; +/-; ___ - Anti-IgG; +/-; ___ - HAV-RNA; ___ ; Copies/ml //

Questionnaire: Hepatic Event Form - Question Library Version 21.0

Q:HO08	Hepatic Event Form (Ofev)	Hepatitis-Serology (exact viral load or pos/neg) [Hepatitis B Parameter; Value; Unit] - HBsAg; +/-; ___ - Anti-HBs; +/-; ___ - HbeAg; +/-; ___ - Anti-Hbe; +/-; ___ - Anti-HBc; +/-; ___ - Anti-HBc-IgM; +/-; ___ - HBV-DNA; ___ ; Copies/ml //
Q:HO09	Hepatic Event Form (Ofev)	Hepatitis-Serology (exact viral load or pos/neg) [Hepatitis C Parameter; Value; Unit] - Anti-HCV; +/-; ___ - HCV-RNA; ___; Copies/ml //
Q:HO10	Hepatic Event Form (Ofev)	Evidence for viral relapse under current regimen? //
Q:HO11	Hepatic Event Form (Ofev)	Evidence for viral co-infections? - HBV/HDV [YES ; NO; UNKNOWN] - HBV/HIV [YES ; NO; UNKNOWN] - HCV/HIV [YES ; NO; UNKNOWN] - Others, please specify. //

Questionnaire: Hepatic Event Form - Question Library Version 21.0

Q:HO12	Hepatic Event Form (Ofev)	Liver biopsy results available? Please attach, and provide the findings: //
Q:HO13	Hepatic Event Form (Ofev)	Was any imaging performed (CT, MRI, ultrasound, etc.)? If yes please provide the findings: //
Q:HO14	Hepatic Event Form (Ofev)	Please enter all drugs where a dechallenge or rechallenge was performed: Tradename/Generic, for which a discontinuation was deemed necessary [Discontiuned due to AE- Y/N/NR; Dechallenge- Pos/neg/NR; Rechallenge- Pos/neg/NR; Results] //

Questionnaire: Perforation Event Form - Question Library Version 21.0

Question ID	Questionnaire Name	Question
Q:PO01	Perforation Event Form (Ofev)	What was the location/ nature of the perforation? - Gastric ulcer - Duodenal ulcer - Small-intestine diverticulum - Colon diverticulum / diverticulitis - Gastrointestinal tumour perforation - Peritonitis as sequel of chronic inflammatory bowel disease - Peritonitis as sequel of acute appendicitis - Procedural complication (e g endoscopy) - Other, please specify: //
Q:PO02	Perforation Event Form (Ofev)	When did the first signs or symptoms of the reported perforation occur? [Before start of treatment with OFEV®, please specify: days/weeks/months; After start of treatment with OFEV ®, please specify: days/weeks/months; Unknown] //
Q:PO03	Perforation Event Form (Ofev)	Did the patient have any past medical history of gastrointestinal perforation? If "Yes" please specify: //
Q:PO04	Perforation Event Form (Ofev)	Did the patient have any prior abdominal surgery (including endoscopic surgery)? //
Q:PO05	Perforation Event Form (Ofev)	If patient had prior abdominal surgery please give details: [Kind of surgery; Date of surgery; Indication for surgery; Outcome/Complications] //
Q:PO06	Perforation Event Form (Ofev)	Please provide recent diagnostic tests (e.g. imaging, endoscopy, histology, microbiology) relevant in the context for the reported perforation event. [Date; Reason for diagnostic test; Result] //
Q:PO07	Perforation Event Form (Ofev)	Past or concomitant disorders relevant for the reported gastrointestinal perforation event [Yes; No; Location/final diagnosis; Date/time of onset; Treatment (kind of treatment, ongoing or completed)] - Diverticular disease - Crohn's disease - Ulcerative colitis - Peptic ulcer disease - Other past or concomitant disorder relevant to the reported event //
Q:PO08	Perforation Event Form (Ofev)	Concomitant medications [Yes; No; Indication; Start date; Stop date / ongoing] - Corticosteroid - NSAID //

Questionnaire: Perforation Event Form - Question Library Version 21.0

Q:PO09	Perforation Event Form (Ofev)	Was there an alternative explanation, other than OFEV ®, for the perforation? If ”Yes” please specify: //
Q:PO10	Perforation Event Form (Ofev)	Which of the following treatments were administered for the perforation? - Surgical treatment, please specify: - Drug treatment, please specify: - Other treatment, please specify: - No treatment - Unknown //

Questionnaire: Bleeding Event Form - Question Library Version 21.0

Question ID	Questionnaire Name	Question
Q:BO01	Bleeding Event Form (valid only for Ofev)	What was the gastrointestinal/respiratory location of the bleeding? Haemoptysis: coughing up blood Epistaxis: nose bleed Gastrointestinal haemorrhage Haematemesis: red blood or coffee grounds material Melena: black, tarry, foul-smelling stool Haematochezia: bright red or maroon blood from rectum Occult GI bleeding: blood in stool in the absence of overt bleeding //
Q:BO02	Bleeding Event Form (valid only for Ofev)	Did the patient had the following locations of bleeding? Intracranial haemorrhage (including haemorrhagic stroke) Skinbleeding (including haematoma and contusion) Blood in urine Genital haemorrhage Wound haemorrhage /procedural site haemorrhage Other site (please specify) //
Q:BO03	Bleeding Event Form (valid only for Ofev)	When did the first signs or symptoms of the reported bleeding event occur? [Before start of treatment with OFEV®, please specify: days/weeks/months; After start of treatment with OFEV ®, please specify: days/weeks/months; Unknown] //
Q:BO04	Bleeding Event Form (valid only for Ofev)	Did the patient have any past medical history of bleeding? [Yes, No, Unknown] If ”Yes” please specify: //
Q:BO05	Bleeding Event Form (valid only for Ofev)	Was the patient on anticoagulation or anti-platelet or thrombolytic therapy? If ”Yes” please specify (including dose): //
Q:BO06	Bleeding Event Form (valid only for Ofev)	Was there an alternative explanation, other than OFEV®, for the bleeding event? If ”Yes” please specify: //
Q:BO07	Bleeding Event Form (valid only for Ofev)	Did the patient suffer from liver diseases that might have influenced the bleeding event? If ”Yes” please specify: //
Q:BO08	Bleeding Event Form (valid only for Ofev)	Did the patient suffer from an injury (e.g. fall, trauma, accident) that might have influenced the bleeding event? If ”Yes” please specify: //

Questionnaire: Bleeding Event Form - Question Library Version 21.0

Q:BO09	Bleeding Event Form (valid only for Ofev)	Which of the following treatments were provided for the bleeding event? - No treatment - Surgical procedure, please specify: - Blood transfusion [units] - Other drugs, please specify: - Unknown //

Questionnaire: Bone development and growth form (Ofev)

Question ID	Questionnaire Name	Question
Bone development and growth	Bone development and growth form (Ofev)	Was the patient diagnosed with any growth disorder such as growth hormone deficiency or any genetic disorder that is associated with short stature (e.g. Turner Syndrome)? If yes, please specify.
Bone development and growth	Bone development and growth form (Ofev)	What was patient's height before nintedanib administration? If available, please provide historical height measurements and the corresponding patient's age.
Bone development and growth	Bone development and growth form (Ofev)	What is the current patient's age and height?
Bone development and growth	Bone development and growth form (Ofev)	What is the patient's Tanner stage?
Bone development and growth	Bone development and growth form (Ofev)	For female patients: Did the patient have menarche? If yes, at which age?
Bone development and growth	Bone development and growth form (Ofev)	Did the patient undergo bone imaging(s)? If yes, please provide the date(s) and description of the findings.

Bone development and growth	Bone development and growth form (Ofev)	What is the status of epiphyseal closure (i.e., open/ partially closed physis/ closed physis)?
Bone development and growth	Bone development and growth form (Ofev)	Did patient receive treatment with medications that are known to have impact on growth (e.g. corticosteroids)? If yes, please specify (including dose and treatment duration).
Bone development and growth	Bone development and growth form (Ofev)	Did patient experience other medical conditions that might explain the growth impairment (e.g., chronic diarrhea, infections)? If yes, please specify.
Bone development and growth	Bone development and growth form (Ofev)	Was treatment with Ofev interrupted/discontinued following the event? If yes, please provide the date when treatment with Ofev was interrupted/discontinued.
Bone development and growth	Bone development and growth form (Ofev)	What was the clinical evolution following Ofev interruption (e.g. findings on follow-up bone imaging, height measurements)? If applicable, please provide the date(s) when follow-up was performed.

Questionnaire: ATE Form - Question Library Version 21.0

Question ID	Questionnaire Name	Question
Q:ATE01	Arterial Thromboembolic (ATE) Event form	When did the first signs or symptoms of the reported event occur? Before start of treatment with OFEV®, please specify: days/weeks/months. After start of treatment with OFEV®, please specify: days/weeks/months. //
Q:ATE02	Arterial Thromboembolic (ATE) Event form	What was the location / nature of the event? - Ischaemic stroke - Pulmonary embolism - Myocardial infarction - Acute extremity ischaemia - Other event; please specify. //
Q:ATE03	Arterial Thromboembolic (ATE) Event form	Did the patient have a past or recent medical history of an ATE event? //
Q:ATE04	Arterial Thromboembolic (ATE) Event form	Did the patient have any past or recent medical history of an underlying vascular disorder or are current vascular risk factors known? //
Q:ATE05	Arterial Thromboembolic (ATE) Event form	Is there a known history or a known risk factor of - Venous thrombosis - Coagulopathy - Atrial fibrillation - Arterial hypertension - Diabetes mellitus - Hypercholesterolaemia - Smoking - Coronary artery disease - Peripheral arterial occlusive disease - Coronary stent placement - PTCA - ACBG - Other, please specify. //

Questionnaire: ATE Form - Question Library Version 21.0

Q:ATE06	Arterial Thromboembolic (ATE) Event form	Are relevant laboratory parameters available? //
Q:ATE07	Arterial Thromboembolic (ATE) Event form	If relevant laboratory parameters are available, please specify. [Unit; Baseline (Prior to event); Date of Baseline; Maximum or minimum; Date of maximum or minimum] - AST - ALT - LDH - CK - CKMB - Troponin - Hb - Platelet count - INR - aPTT //
Q:ATE08	Arterial Thromboembolic (ATE) Event form	Are relevant ECG findings available? If yes, please specify. //
Q:ATE09	Arterial Thromboembolic (ATE) Event form	Was any relevant imaging (CT, MRI) performed? If yes, please specify findings. //
Q:ATE10	Arterial Thromboembolic (ATE) Event form	Which of the following treatments were provided for the ATE event? Please specify. [No treatment; surgical procedure; percutaneous intervention; thrombolytic drug treatment; other drug treatment] //

Questionnaire: ATE Form - Question Library Version 21.0

Q:ATE11	Arterial Thromboembolic (ATE) Event form	Was there an alternative explanation, other than OFEV®, for the current ATE event? If yes, please specify. //

APPENDIX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

There are no proposed additional risk minimisation activities for Ofev.