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The safety of nintedanib for the treatment of interstitial lung disease: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Introduction

Nintedanib can inhibit processes involved in the progression of fibrosis and can reduce the decline in forced vital capacity in patients with idiopathic pulmonary fibrosis (IPF) and fibrotic-interstitial lung disease (fibrotic-ILDs). Although the adverse events associated with nintedanib in IPF patients are well known, its safety in other fibrotic-ILD patients remained unclear.

Methods

We searched PubMed, EMBASE, Cochrane CENTRAL and Cochrane CDSR for randomized controlled studies which compared nintedanib with a placebo in ILD patients. We estimated pooled odds ratios (ORs) and 95% confidence intervals (CIs) for adverse events using the DerSimonian–Laird random-effects model.

Results

Six studies with a total of 2,583 patients were included in the meta-analysis. The pooled estimates showed that patients treated with nintedanib had a significantly higher likelihood of having any adverse events (OR = 2.39; 95% CI = 1.71-3.36) or adverse events leading to treatment discontinuation (OR = 1.73; 95% CI = 1.34-2.25). However, they had trend to lower likelihood of having fatal adverse events (OR = 0.69; 95% CI = 0.41-1.14) compared with the placebo group. Use of nintedanib was positively associated with diarrhea (OR = 5.96; 95% CI = 4.35-8.16), nausea (OR = 3.00; 95% CI = 1.93-4.66), vomiting (OR = 3.22;

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95% CI = 2.17–4.76) and weight loss (OR = 3.38; 95% CI = 1.1.76–6.47). Whereas, patients treated with nintedanib were less likely to have a cough (OR = 0.73; 95% CI = 0.56–0.96) and dyspnea (OR = 0.70; 95% CI = 0.53-0.94).

Conclusions

Compared to a placebo, nintedanib was associated with a higher risk of adverse events, especially for diarrhea, nausea, vomiting and weight loss, but it was also associated with a lower risk of cough and dyspnea in IPF and fibrotic-ILD patients.

Introduction

Interstitial lung disease (ILD) is a group of lung diseases affecting the interstitium, which can result in restrictive lung defects and impaired gas-exchange. Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias and most severe form of ILD, and is characterized by progressive fibrosis of the lung parenchyma occurring primarily in older adults due to an unknown cause. The prognosis for patients with IPF is quite poor with a median survival time of 2 to 3 years if left untreated; the disease has a variable clinical course [1, 2]. There are other forms of ILD which can present with progressive fibrosis, including connective tissue disease-related ILDs, ILD related to chronic sarcoidosis, chronic hypersensitivity pneumonitis, idiopathic non-specific interstitial pneumonia and unclassifiable ILD. Patients with these fibrotic-ILDs have early mortality and are believed to have similar underlying pathogenetic mechanisms to IPF [3].

Nintedanib is a tyrosine-kinase inhibitor that mainly targets platelet-derived growth factor receptor, vascular endothelial growth factor receptor, and fibroblast growth factor receptor [4]. It can inhibit processes involved in fibrosis progression [5]. Previous studies have suggested that nintedanib could reduce the decline in forced vital capacity (FVC), preserve quality of life, lower the incidence of acute exacerbations, and increase survival time in patients with IPF [6–8]. In previous network meta-analysis of randomized controlled trials (RCTs) comparing 11 treatments in IPF, nintedanib was 1 of 4 medications had benefit, including in pulmonary function decline, exacerbation and mortality [9–13]. More recent studies have shown that nintedanib can also reduce the decline in FVC in patients with systemic sclerosis (SSc)–associated ILD and progressive fibrosis ILD (PF-ILD) in addition to those with IPF [14, 15].

Although early initiation of anti-fibrotic treatment to preserve health lung tissue is recommended [16], the possible side effects of the drugs, the symptoms of the lung disease and comorbidities due to old age can make this decision more complicated. A real world retrospective observational study of 224 IPF cases treated with nintedanib revealed that 55.7% of patients had adverse events, 28.3% of patients received a reduced treatment dose, and 13.1% of patients had to discontinue nintedanib [17]. Adverse events are the main reason for early discontinuing in clinical practice.

Cumulative evidence has focused on the safety and tolerability of nintedanib in IPF patients by evaluating a wide range of data, including clinical trials, post-hoc analyses of clinical trials, post-marketing surveillance, and real-world or epidemiological data [18–20]. However, the safety profile of nintedanib for fibrotic-ILD patients remains unclear. In a recent network meta-analysis, nintedanib was one of three medications for SSc-associated ILD resulting higher withdrawing due to adverse events compared with placebo [21]. Therefore, we performed a comprehensive systematic review and meta-analysis of double-blinded, RCTs in

patients with IPF and other forms of fibrotic-ILDs to evaluate adverse events when they were treated with nintedanib compared with placebo.

Materials and methods

Search strategy

A literature search was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [22]. PubMed, Embase, Cochrane Central Trials databases and the Cochrane Database of Systematic Reviews (CDSR) were searched for prospective, double blinded, RCTs published from inception to 29th January 2020. The text and medical subject heading (MeSH) terms included: "nintedanib" [MeSH term], Ofev, Vargatef, BIBF 1120, BIBF1120, and BIBF-1120 [Text Word]. Articles were not limited to the English language. Reference lists were also searched for additional eligible articles.

Study selection and data extraction

Two investigators (Chen and Wang) independently screened and reviewed each study. Studies were included if they met the following criteria: (1) patients with ILD, (2) prospective, double blinded RCT, (3) nintedanib as the intervention, (4) placebo as the comparison, (5) a study outcome of adverse events. Populations with any malignancies were excluded.

The following information was extracted from the included studies: the name of the trial, year of publication, intervention groups, patient number, duration of trial, randomization procedures, study population, age, sex, and interval since diagnosis with IPF. Data extraction was performed by two independent reviewers. A third reviewer (Lin) was consulted to resolve any disagreements.

Quality assessment

The quality of each included study was assessed using a risk-of-bias assessment tool [23]. Two reviewers subjectively reviewed all included studies and rated then "low risk," "high risk," or "unclear" according to the following items: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and inclusion of intention-to-treat analyses. Any disagreement was resolved and decided by a third reviewer.

Outcome measures and statistical analysis

The primary outcome of this study was adverse events, including severe, serious and fatal adverse events. In addition, the most common adverse events were listed and included in the analyses. The odds ratio (OR) and 95% confidence interval (CI) were used as the measure of association between adverse events and the use of nintedanib.

A DerSimonian–Laird random-effects model was performed to calculate the pooled estimates of ORs [24]. A two-sided P value of <0.05 was considered to indicate a significant difference. Study heterogeneity was presented using a χ^2 -based Cochran's Q statistic and I². Cochran's Q was defined by summing the square of the amount that each study's estimate deviated from the overall estimate. For the Q statistic, P values <0.10 were considered statistically significant for heterogeneity. For the I² statistic, heterogeneity was assessed as follows: no heterogeneity (I² = 0–25%), moderate heterogeneity (I² = 25–50%), large heterogeneity (I² = 50–75%), and extreme heterogeneity (I² = 75–100%). A sensitivity analysis was conducted using a leave-one-out approach. All statistical analyses were performed using Review Manager version 5.3. Adverse events were defined according to the FDA and previous studies, including TOMORROW [6], INPULSIS [7], NCT01979952 [25], INBUILD [15] and SENSCIS [14]. Safety was assessed by means of clinical and laboratory evaluation at study visits and recording of adverse events. In the studies, the frequency and severity of adverse events were documented according to the Medical Dictionary for Regulatory Activities, version 16.1. An adverse event was defined as any untoward medical occurrence associated with the use of the drug in humans, whether or not it was considered drug related. Severe adverse events were defined as events that were incapacitating or that caused the inability to work or to perform usual activities. Serious adverse events were defined as an event that resulted in death, in hospitalization or the prolongation of hospitalization, or a persistent or clinically significant disability or incapacity; or was life-threatening, or a congenital anomaly or birth defect, or deemed to be serious for any other reason. Fatal adverse events were defined as death caused by treatment.

Results

Literature search and evaluation for study inclusion

A total of 2,312 articles were identified from a search of PubMed (n = 849), EMBASE (n = 1,005), Cochrane CENTRAL (n = 456), and Cochrane CDSR (n = 2). After removing duplicate records (n = 592) and ineligible articles based on a review of their title and abstract (n = 1,687) a total of 33 studies remained. A further 28 articles were removed after a full-text review process, so a total of 6 studies were included in the final study (Fig 1).

Study characteristics

Table 1 shows the characteristics of the 6 included trials from four different articles [6, 7, 14, 15] and one unpublished trial [25]. A total of 2,583 patients were included in the meta-analysis (1,399 in the nintedanib group and 1,184 in the placebo group). One trial (NCT01979952) [25] was completed in 2016 but has not been published. That study did not describe the randomization procedures in detail and the duration of the trial was only 6 months, which was shorter than the other included trials. Nintedanib was administered twice daily with a dosage of 150 mg in five trials [6, 7, 14, 15]. The TOMORROW study included four nintedanib groups with different dosages (50 mg once daily, 50 mg twice daily, 100 mg twice daily, and 150 mg twice daily) [6]. Stratified randomization was performed in two studies [14, 15]. The INBUILD study stratified patients according to UIP-like fibrotic patterns, while the SENSCIS study stratified patients based on the presence of anti-topoisomerase I antibody. Two studies [14, 15] recruited patients \geq 18 years of age while others had patients aged \geq 40 years. The SENSCIS study enrolled patients who were younger (54.6±11.8 years in the nintedanib group and 53.4 ±12.6 in the placebo group) and had a higher proportion of female patients compared with the other studies. The mean interval since diagnosis of IPF ranged from 1.0 to 1.7 years, as reported by 3 studies [6, 7] (Table 1). In total, >90% of patients had adverse events during the study period, especially in the nintedanib group. Five trials with a follow-up duration of 52 weeks were included. In the TOMORROW study, only patients treated with nintedanib 150 mg twice daily and patients in the placebo group were included for comparison. Details of the studies are described in Table 2.

Meta-analyses for the association between adverse events and the use of nintedanib

Fig 2 shows forest plots of the meta-analysis for the six included studies [6, 7, 14, 15, 25]. There was no heterogeneity across the six studies for any adverse events (Q = 2.08; P = 0.84; $I^2 = 0\%$),

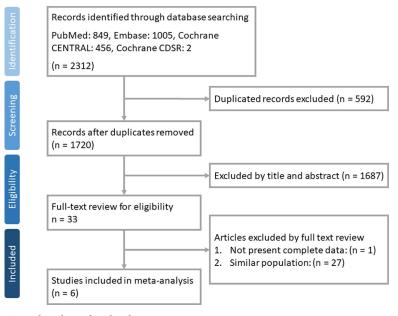


Fig 1. Flow chart of study selection.

serious adverse events (Q = 2.80; P = 0.73; $I^2 = 0\%$), or adverse events leading to treatment discontinuation (Q = 5.10; P = 0.28; $I^2 = 22\%$). However, there was moderate heterogeneity for fatal adverse events (Q = 5.83; P = 0.21; $I^2 = 31\%$) and high heterogeneity for severe adverse events (Q = 8.49; P = 0.08; $I^2 = 53\%$).

Pooling estimates showed that patients treated with nintedanib had a significantly higher likelihood of having any adverse events (OR = 2.39; 95% CI = 1.71–3.36; P < 0.001) and having adverse events leading to treatment discontinuation (OR = 1.73; 95% CI = 1.34–2.25; P < 0.001). Whereas, they had a trend to lower likelihood of having a fatal adverse event (OR = 0.69; 95% CI = 0.41–1.14; P = 0.14) compared with the placebo group.

Fig 3 and S1 Fig shows the pooled results for the most frequent adverse events. There was a large heterogeneity observed for diarrhea (Q = 13.53; P = 0.02; I² = 63%), nausea (Q = 16.82; P = 0.005; I² = 70%), weight loss (Q = 11.36; P = 0.02; I² = 65%), abdominal pain (Q = 8.02; P = 0.05; I² = 63%), and decreased appetite (Q = 8.27; P = 0.08; I² = 52%). Moderate heterogeneity existed among the 6 studies for vomiting (Q = 7.83; P = 0.17; I² = 36%), while no heterogeneity was observed for cough (Q = 6.52; P = 0.26; I² = 23%), nasopharyngitis (Q = 4.04; P = 0.54; I² = 0%), bronchitis (Q = 1.78; P = 0.78; I² = 0%), dyspnea (Q = 1.05; P = 0.90; I² = 0%), and upper respiratory tract infection (Q = 2.13; P = 0.71; I² = 0%).

Use of nintedanib was associated with the higher risk of diarrhea (66.3% vs 25.4%; OR = 5.96; 95% CI = 4.35–8.16; P < 0.001), nausea (27.1% vs 10.6%; OR = 3.00; 95% CI = 1.93–4.66; P < 0.001), vomiting (16.2% vs 6.0%; OR = 3.22; 95% CI = 2.17–4.76; P < 0.001), weight loss (11.4% vs 3.8%; OR = 3.38; 95% CI = 1.76–6.47; P < 0.001), and decreased appetite (12.7% vs 5.2%; OR = 2.53; 95% CI = 1.45–4.39; P = 0.001) than placebo. Although the risk of abdominal pain was higher in nintedanib than placebo, the difference did not reach statistical significance (10.5% vs 4.9%; OR = 2.19; 95% CI = 1.00–4.77; P = 0.05), Whereas, patients treated with nintedanib were less likely to have a cough (12.1% vs 15.6%; OR = 0.73; 95% CI = 0.56–0.96; P = 0.02), and dyspnea (8.9% vs 12.5%; OR = 0.70; 95% CI = 0.53–0.94; P = 0.02) (Fig 3 and S1 Fig).

Trial name	Year of publication	Intervention	Patient number	Duration of trial ^a	Randomization	Study population	Age (yr) ^b	Male (%)	Interval since diagnosis of IPF (yr) ^b
INBUILD [15]	2019	Nintedanib 150 mg bid	332	52 weeks	1:1 ratio with interactive- response technology and	At least 18 y/o with fibrosing interstitial lung	65.2 ±9.7	53.9	NR
		Placebo	331		stratified according to UIP-like fibrotic pattern or not. An enrichment design was performed to ensure two thirds of patients having UIP-like pattern.	disease and with a more progressive fibrotic phenotype. Having features of fibrosing lung disease affecting more than 10% of lung volume on HRCT. FVC \geq 45% of predicted value and DL _{CO} between 30% and 80% of predicted value.	66.3 ±9.8	53.5	NR
INPULSIS-1 [7]	2014	Nintedanib 150 mg bid	309	52 weeks	3:2 ratio by an interactive telephone and web-based	At least 40 y/o with diagnosis of IPF within 5	66.9 ±8.4	81.2	1.7±1.4
		Placebo	204		response system.	years and had an FVC \geq 50% of predicted value, and had DL _{CO} between 30% and 79%.	66.9 ±8.2	79.9	1.6±1.4
INPULSIS-2 [7]	2014	Nintedanib 150 mg bid	329	52 weeks	The same as above.	The same as above.	66.4 ±7.9	77.8	1.6±1.3
		Placebo	219				67.1 ±7.5	78.1	1.6±1.3
NCT01979952 [25]	2016 ^c	Nintedanib 150 mg bid	56	6 months (up to 18	NR	At least 40 y/o with IPF diagnosis confirmed by	NR	80.4	NR
		Placebo	57	months)		HRCT and had an FVC≧50% of predicted value, and had DL _{CO} between 30% and 79%.	NR	64.9	NR
SENSCIS [14]	2019	Nintedanib 150 mg bid	288	52 weeks	1:1 ratio with an interactive response system and stratified by	At least 18 y/o and had systemic sclerosis with the	54.6 ±11.8	23.3	NR
		Placebo	288		the presence of antitopoisonmerase I antibody.	first onset of non- Raynaud's symptom within 7 years, had an $FVC \ge 40\%$ of predicted value, and had DL_{CO} between 30% and 89% of predicted value. ILD was defined as fibrosis affecting at least 10% of lungs by HRCT.	53.4 ±12.6	26.4	NR
TOMORROW [6]	2011	Nintedanib 50 mg qd	86	52 weeks	Patients were randomized into four treatment groups and	At least 40 y/o with IPF and had a FVC≧50% of	65.3 ±9.4	75.6	1.4±1.3
		Nintedanib 50 mg bid	86	_	placebo group. A stepwise increasing-dose approach was used.	predicted value, had DL_{CO} between 30% and 79% of predicted value,	64.9 ±8.5	72.1	1.1±1.2
		Nintedanib 100 mg bid	86			and had a partial PaO_2 either when breathing	65.1 ±8.6	75.6	1.2±1.2
		Nintedanib 150 mg bid	85			ambient air≧55 mmHg or greater at altitudes up to	65.4 ±7.8	76.5	1.0±1.2
		Placebo	85			1500 m.	64.8 ±8.6	74.1	1.4±1.5

Table 1. Summary of baseline characteristics of included studies.

IPF, idiopathic pulmonary fibrosis; FVC, forced vital capacity; DL_{CO} , diffusing capacity of the lung for carbon monoxide; SpO_2 , oxygen saturation of peripheral blood; NR, not reported.

^aDefined by the duration from start of trial to the time of end points measurements.

^bPresented as mean±standard deviation.

https://doi.org/10.1371/journal.pone.0251636.t001

							No. of na	No. of natients (%)					
		INBL	ILD	INPUI	SIS-1	INPUL	SIS-2	SEN	SCIS	TOMOR	ROW ^b	To	tal
	Events	Nintedanib	placebo	Nintedanib	placebo		placebo	Nintedanib	placebo	Nintedanib	placebo	Nintedanib	placebo
		(N = 332)	(N = 331)	(N = 309)	(N = 204)	(N = 329)	(N = 219)	(N = 288)	(N = 288)	(N = 85)	(N = 85)	(N = 1343)	(N = 1127)
	Any adverse event	317 (95.5)	296 (89.4)	298 (96.4)	181 (88.7)	311 (94.5)	198 (90.4)	283 (98.3)	276 (95.8)	80 (94.1)	77 (90.6)	1289 (96.0)	1031 (91.5)
	Severe adverse event	60 (18.1)	73 (22.1)	81 (26.2)	37 (18.1)	93 (28.3)	62 (28.3)	52 (18.1)	36 (12.5)	19 (22.4)	20 (23.5)	305 (22.7)	228 (20.2)
	Serious adverse event	107 (32.2)	110 (33.2)	96 (31.1)	55 (27.0)	98 (29.8)	72 (32.9)	69 (24.0)	62 (21.5)	23 (27.1)	26 (30.6)	393 (29.3)	325 (28.8)
	Fatal adverse event	11 (3.3)	17 (5.1)	12 (3.9)	10 (4.9)	25 (7.6)	21 (9.6)	5 (1.7)	4 (1.4)	1 (1.2)	12 (14.1)	54 (4.0)	64 (5.7)
	Most frequent adverse event												
66 (38.9)31 (9.4) $76 (2.27)$ $12 (5.9)$ $86 (5.4)$ $16 (7.3)$ $21 (7.6)$ $80 (3.5)$ $80 (3.5)$ $80 (3.5)$ $80 (3.7)$ $21 (7.6)$ 16 (16.4) $41 (13.3)$ $40 (12.1)$ $40 (12.3)$ $40 (12.3)$ $41 (13.3)$	Diarrhea	222 (66.9)	79 (23.9)	190 (61.5)	38 (18.6)	208 (63.2)	40 (18.3)	218 (75.7)	91 (31.6)	47 (55.3)	13 (15.3)	885 (65.9)	261 (23.2)
initial conditioninitial conditioni	Nausea	96 (28.9)	31 (9.4)	70 (22.7)	12 (5.9)	86 (26.1)	16 (7.3)	91 (31.6)	39 (13.5)	20 (23.5)	8 (9.4)	363 (27.0)	106(9.4)
iii ii	Vomiting	61 (18.4)	17 (5.1)	40 (12.9)	4 (2.0)	34 (10.3)	7 (3.2)	71 (24.7)	30 (10.4)	11 (12.9)	4 (4.7)	217 (16.2)	62 (5.5)
	Nasopharyngitis	44 (13.3)	40 (12.1)	39 (12.6)	34 (16.7)	48 (14.6)	34 (15.5)	36 (12.5)	49 (17.0)	6 (7.1)	11 (12.9)	173 (12.9)	168 (14.9)
41 (12.3)11 (3.3)25 (8.1)13 (6.4)37 (11.2)2 (0.9)34 (11.8)12 (4.2)(0.0)137 (0.2)etite48 (4.4.5)17 (5.1)26 (8.4)14 (6.9)42 (12.8)10 (4.6)13 (15.3)0 (0.0)13 (15.3)0 (0.0)13 (15.3)tory tractinfection41 (12.3)47 (14.2)28 (9.1)28 (9.1)28 (13.3)24 (1.0)33 (11.5)55 (12.2)7 (8.2)13 (5.3)8 (7.3)ftPf (11)36 (10.8)41 (13.3)23 (10.0)18 (8.8)30 (9.1)24 (1.0)33 (11.5)55 (12.2)7 (8.2)13 (6.8)ain36 (10.8)44 (13.3)21 (10.0)21 (10.3)23 (10.0)40 (8.3)24 (1.0)24 (1.0)24 (1.0)24 (1.0)ain36 (10.8)39 (11.8)31 (10.0)21 (10.3)33 (10.0)40 (8.3)24 (1.0)33 (5.1)24 (6.3)ain34 (10.2)80 (1.8)31 (10.0)21 (10.3)33 (10.0)40 (8.3)24 (1.3)24 (6.3)24 (6.3)ain34 (10.2)80 (1.8)31 (10.0)21 (10.3)33 (11.5)21 (7.4)10 (1.9)33 (5.3)ain34 (10.2)80 (1.8)31 (10.0)21 (10.3)33 (11.5)21 (7.4)11 (1.2)24 (6.3)ain34 (10.2)80 (1.8)31 (1.5)21 (1.6)33 (1.5)21 (1.6)21 (1.6)23 (5.9)23 (5.9)ain35 (10.5)23 (6.9)12 (1.6)21 (1.6)33 (1.5)21 (1.6)21 (1.6)21 (1.6)	Cough	33 (9.9)	44 (13.3)	47 (15.2)	26 (12.7)	38 (11.6)	31 (14.2)	34 (11.8)	52 (18.1)	8 (9.4)	17 (20.0)	160 (11.9)	170 (15.1)
eite $48 (14.5)$ $17 (5.1)$ $26 (8.4)$ $14 (6.9)$ $42 (12.8)$ $10 (4.6)$ $10 (4.6)$ $10 (1.5)$ $10 (1.5)$ $10 (0.0)$ $129 (9.6)$ $11 (12.3)$ $47 (14.2)$ $36 (11.7)$ $28 (13.7)$ $31 (9.4)$ $17 (7.8)$ $32 (11.5)$ $32 (12.2)$ $7 (8.2)$ $11 (2.9)$ $11 (7.8)$ $10 vy tractinfection41 (12.3)47 (13.3)28 (1.1)18 (8.8)30 (9.1)28 (11.9)33 (11.5)35 (12.2)7 (8.2)11 (2.9)8 (7.3)36 (10.8)41 (13.3)21 (1.1)21 (10.3)31 (10.0)21 (10.3)31 (10.0)21 (10.3)31 (10.0)21 (10.3)31 (10.0)31 (10.0)31 (10.0)31 (10.0)10 P (1LD)16 (4.8)30 (11.8)31 (10.0)21 (10.3)31 (10.0)21 (10.3)31 (10.0)21 (10.3)31 (10.0)31 (10.0)31 (10.0)10 P (12.8)30 (11.8)31 (10.0)31 (10.0)21 (10.3)31 (10.0)31 (11.9)31 (11.9)31 (11.9)31 (11.9)31 (11.9)31 (11.9)10 P (11.8)31 (10.0)31 (10.0)31 (10.0)31 (10.0)31 (10.0)31 (10.0)31 (10.0)31 (10.0)10 P (11.8)31 (11.9)31 (11.9)31 (11.9)31 (11.9)31 (11.9)31 (11.9)31 (11.9)31 (11.9)31 (11.9)10 P (11.8)31 (11.9)31 (11.9)31 (11.9)31 (11.9)31 (11.9)31 (11.9$	Weight loss	41 (12.3)	11 (3.3)	25 (8.1)	13 (6.4)	37 (11.2)	2 (0.9)	34 (11.8)	12 (4.2)			137 (10.2)	38 (3.4)
41 (12.3) $47(14.2)$ $36(11.7)$ $28(13.7)$ $31(9.4)$ $17(7.8)$ $17(7.8)$ $11(16.8)$ $117(8.7)$ troy tract infection X X X $28(11.1)$ $28(11.2)$ $28(11.2)$ $38(12.5)$ $36(12.3)$ $113(2.9)$ $98(7.3)$ $67(10)$ $16(48)$ $39(10.8)$ $44(13.3)$ $22(7.1)$ $23(11.3)$ $27(8.2)$ $25(11.4)$ 11 112.9 $98(7.3)$ $61(12)$ $36(10.8)$ $39(10.3)$ $31(10.0)$ $21(10.3)$ $33(10.0)$ $40(18.3)$ $10(11.8)$ $3(1.5)$ 112.9 $14(12)$ $16(48)$ $12(10.2)$ $23(11.5)$ $23(11.5)$ $23(12.4)$ 112.9 112.9 $14(12)$ $12(10.2)$ $38(10.5)$ $22(11.4)$ $12(11.6)$ $3(1.5)$ $7(5.7)$ $11(12)$ $23(6.9)$ $12(10.0)$ $21(10.6)$ $21(1.6)$ $3(1.5)$ $7(3.2)$ $12(10.5)$ $23(6.9)$ $12(1.6)$ $12(1.6)$ $21(1.6)$ $3(1.5)$ $7(3.2)$ $12(10.5)$ $23(6.9)$ $12(10.6)$ $21(1.6)$ $21(1.6)$ $3(1.5)$ $7(3.2)$ $12(10.5)$ $23(6.9)$ $12(1.6)$ $21(1.6)$ $21(1.6)$ $21(1.6)$ $21(2.6)$ $12(10.5)$ $23(6.9)$ $12(1.6)$ $21(1.6)$ $21(1.6)$ $21(2.6)$ $21(2.6)$ $12(10.5)$ $23(1.6)$ $12(1.6)$ $21(1.6)$ $21(1.6)$ $21(1.6)$ $21(2.6)$ $12(10.6)$ $21(1.6)$ $21(1.6)$ $21(1.6)$ $21(1.6)$ $21(1.6)$ $21(1.6)$ $12(10.6)$	Decrease appetite	48 (14.5)		26 (8.4)	14 (6.9)	42 (12.8)	10 (4.6)			13 (15.3)	0 (0.0)	129 (9.6)	41 (3.6)
tory tractinfection $=$ <	Bronchitis	41 (12.3)	47 (14.2)	36 (11.7)	28 (13.7)	31 (9.4)	17 (7.8)			9 (10.6)	11 (12.9)	117 (8.7)	103 (9.1)
	Upper respiratory tract infection			28 (9.1)	18 (8.8)	30 (9.1)	24 (11.0)	33 (11.5)	35 (12.2)	7 (8.2)	13 (15.3)	98 (7.3)	90 (8.0)
If IF (ILD) $16 (4.8)$ $39 (11.8)$ $31 (10.0)$ $21 (10.3)$ $33 (10.0)$ $40 (18.3)$ $4(4.7)$ 11 $8(4.3)$ ain $34 (10.2)$ $8 (2.4)$ $10 (11.8)$ $3 (1.5)$ $21 (7.3)$ $10 (11.8)$ $3 (3.5)$ $77 (57)$ ain $41 (10.2)$ $8(2.4)$ $10 (1)$ $10 (1)$ $3 (1.5)$ $21 (7.3)$ $10 (11.8)$ $3 (1.5)$ $27 (5.7)$ $41 (10.2)$ $23 (10.5)$ $23 (6.9)$ $41 (10.2)$ $10 (1)$ $10 (1)$ $3 (1.5)$ $23 (3.9)$ $51 (10.5)$ $23 (6.9)$ $10 (1)$ $12 (3.6)$ $10 (1)$ $12 (3.6)$ $10 (1)$ $12 (3.6)$ $10 (1)$ $10 (11.8)$ $12 (3.6)$ $12 (3.6)$ $10 (1)$ $12 (3.6)$ $10 (1)$ $12 (3.6)$ $10 (1)$ $12 (3.6)$ $10 (1)$ $10 (11.8)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $10 (1)$ $12 (3.6)$ $10 (1)$ $12 (3.6)$ $10 (1)$ $10 (11.8)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $10 (11.8)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $10 (11.8)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $10 (11.8)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 (3.6)$ $12 ($	Dyspnea	36 (10.8)	44 (13.3)	22 (7.1)	23 (11.3)	27 (8.2)	25 (11.4)			6 (7.1)	11 (12.9)	91 (6.8)	103 (9.1)
ain $34(10.2)$ $8(2.4)$ \cdots \cdots \cdots $33(11.5)$ $21(7.3)$ $10(11.8)$ $3(3.5)$ $77(57)$ $10(11.8)$ $10(12.9)$ $10(11.8)$ $10(12.9)$ $10(11.8)$ $10(1.8)$ $17(5.7)$ $17(5.7)$ $10(11.8)$ $12(10.5)$ $23(69)$ $10(12)$ $10(12)$ $10(12)$ $10(3.4)$ $10(3.4)$ $10(11.8)$ $12(15.6)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(3.4)$ $10(11.8)$ $12(15.6)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(11.8)$ $12(15.6)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(11.8)$ $12(15.6)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(11.8)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(11.8)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(11.8)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(11.8)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(11.8)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(12)$ $10(11.8)$ $10(12)$ $10(12)$ $10(12)$ <td< td=""><td>Progression of IPF (ILD)</td><td>16 (4.8)</td><td>39 (11.8)</td><td>31 (10.0)</td><td>21 (10.3)</td><td>33 (10.0)</td><td>40 (18.3)</td><td></td><td></td><td>4 (4.7)</td><td>11 (12.9)</td><td>84 (6.3)</td><td>111 (9.8)</td></td<>	Progression of IPF (ILD)	16 (4.8)	39 (11.8)	31 (10.0)	21 (10.3)	33 (10.0)	40 (18.3)			4 (4.7)	11 (12.9)	84 (6.3)	111 (9.8)
(1,1,1) $(1,1,1)$ <td>Abdominal pain</td> <td>34 (10.2)</td> <td>8 (2.4)</td> <td></td> <td></td> <td></td> <td></td> <td>33 (11.5)</td> <td>21 (7.3)</td> <td>10 (11.8)</td> <td>3 (3.5)</td> <td>77 (5.7)</td> <td>32 (2.8)</td>	Abdominal pain	34 (10.2)	8 (2.4)					33 (11.5)	21 (7.3)	10 (11.8)	3 (3.5)	77 (5.7)	32 (2.8)
35 (10.5)23 (69)11 (12.9)5 (5.9)46 (3.4)otransferase increased43 (13.0)12 (3.6)40 (3.0)inotransferase increased38 (11.4)12 (3.6)40 (3.0)inotransferase increased38 (11.4)12 (3.6)40 (3.0)inotransferase increased38 (11.4)12 (3.6)	skin ulcer							53 (18.4)	50 (17.4)			53 (3.9)	50 (4.4)
otransferase increased 43 (13.0) 12 (3.6) ··· ··· ··· 43 (3.2) inotransferase increased 38 (11.4) 12 (3.6) ··· × 31 (10.8) 20 (6.9) 9 (10.6) 7 (8.2) 40 (3.0) inotransferase increased 38 (11.4) 12 (3.6) ··· × 31 (10.8) 20 (6.9) 9 (10.6) 7 (8.2) 40 (3.0) eading to 65 (19.6) 34 (10.3) 65 (21.0) 22 (10.8) 58 (17.6) 33 (15.1) 46 (16.0) 25 (8.7) 26 (3.6) 27 (3.9) eading to 65 (19.6) 34 (10.3) 65 (21.0) 21 (6.4) 26 (16.0) 26 (3.6) 27 (3.6) 27 (3.6) eading to 65 (19.6) 34 (10.3) 65 (11.6) 21 (6.9) 26 (3.6) 26 (3.6) 27 (3.6) 26 (3.6) 26 (3.6) 27 (3.6) 28 (3.8) eading to 26 (19.6) 31 (1.5) 26 (16.0) 26 (3.6) 26 (3.6) 27 (3.6) 27 (3.6) 27 (3.6) 28 (3.6) 28 (3.6) 28 (3.6) 28 (3.6) 28 (3.6	Headache	35 (10.5)	23 (6.9)							11 (12.9)	5 (5.9)	46 (3.4)	28 (2.5)
Inotransferase increased38 (11.4)12 (3.6) $()$ </td <td>Alanine aminotransferase increased</td> <td>43 (13.0)</td> <td>12 (3.6)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>43 (3.2)</td> <td>12 (1.1)</td>	Alanine aminotransferase increased	43 (13.0)	12 (3.6)									43 (3.2)	12 (1.1)
inotransferase increased38 (11.4)12 (3.6)12 (3.6)12 (3.6)38 (17.6)33 (15.1)46 (16.0)25 (8.7)26 (30.6)2238 (2.8)eading to65 (19.6)34 (10.3)65 (21.0)22 (10.8)58 (17.6)33 (15.1)46 (16.0)25 (8.7)26 (30.6)22259 (19.3)horacic & mediastonal11221 (6.4)2 (0.9)2 (0.9)14 (16.5)2 (2.4)61 (4.5)horacic & mediastonal112 (3.9)10 (4.9)8 (2.4)18 (8.2)14 (16.5)2 (2.4)61 (4.5)horacic & mediastonal110 (3.2)10 (4.9)8 (2.4)18 (8.2)14 (4.7)1024 (1.8)results110 (3.2)1 (0.5)8 (2.4)1 (0.5)8 (2.4)1 (0.5)10 (1.8)18 (1.3)der111 (0.5)2 (0.6)3 (1.4)1 (0.0)6 (7.1)7 (0.5)	Fatigue							31 (10.8)	20 (6.9)	9 (10.6)	7 (8.2)	40 (3.0)	27 (2.4)
adding to 65 (19.6) 34 (10.3) 65 (21.0) 22 (10.8) 58 (17.6) 33 (15.1) 46 (16.0) 25 (8.7) 26 (30.6) 22 59 (19.3) horace model model model 33 (15.1) 46 (16.0) 25 (8.7) 26 (30.6) 22 259 (19.3) horace model model 3 (1.5) 21 (6.4) 2 (0.9) model 14 (15.7) 27.4) 61 (4.5) horace model 12 (3.9) 10 (4.9) 8 (2.4) 18 (8.2) 14 (4.7) 10 24 (1.8) results model 10 (3.2) 1 (0.5) 8 (2.4) 1 (0.5) 2 (1.8) 10 24 (1.3) der model 1 (0.5) 8 (2.4) 1 (0.5) 3 (1.4) 1 (0.5) 1 (1.8) 1 (1.8) 1 (1.3)	Aspartate aminotransferase increased		12 (3.6)									38 (2.8)	12 (1.1)
acic & mediastonal $26 (8.4)$ $3 (1.5)$ $21 (6.4)$ $2 (0.9)$ $14 (16.5)$ $2 (2.4)$ $61 (4.5)$ acic & mediastonal $12 (3.9)$ $10 (4.9)$ $8 (2.4)$ $18 (8.2)$ $4 (4.7)$ 10 $24 (1.8)$ ults $10 (3.2)$ $10 (4.9)$ $8 (2.4)$ $18 (8.2)$ $4 (4.7)$ 10 $24 (1.8)$ ults $10 (3.2)$ $1 (0.5)$ $8 (2.4)$ $1 (0.5)$ $8 (2.4)$ $1 (0.5)$ $8 (2.4)$ $1 (0.5)$	Adverse events leading to discontinuation	65 (19.6)	34 (10.3)	65 (21.0)	22 (10.8)	58 (17.6)	33 (15.1)	46 (16.0)	25 (8.7)	26 (30.6)	22 (25.9)	259 (19.3)	136 (12.1)
acic & mediastonal $12 (3.9)$ $10 (4.9)$ $8 (2.4)$ $18 (8.2)$ $4 (4.7)$ 10 $24 (1.8)$ acic & mediastonal $10 (3.2)$ $1 (0.5)$ $8 (2.4)$ $1 (0.5)$	GI disorder			26 (8.4)	3 (1.5)	21 (6.4)	2 (0.9)			14 (16.5)	2 (2.4)	61 (4.5)	7 (0.6)
ults 10 (3.2) 1 (0.5) 8 (2.4) 1 (0.5) <th1 (0.5)<="" th=""> 1 (0.5) <th1< td=""><td>Respiratory, thoracic & mediastonal disorder</td><td></td><td></td><td>12 (3.9)</td><td>10 (4.9)</td><td>8 (2.4)</td><td>18 (8.2)</td><td></td><td></td><td>4 (4.7)</td><td>10 (11.8)</td><td>24 (1.8)</td><td>38 (3.4)</td></th1<></th1>	Respiratory, thoracic & mediastonal disorder			12 (3.9)	10 (4.9)	8 (2.4)	18 (8.2)			4 (4.7)	10 (11.8)	24 (1.8)	38 (3.4)
5 (1.6) 4 (2.0) 2 (0.6) 3 (1.4) 0 (0.0) 6 (7.1) 7 (0.5)	Investigation results			10 (3.2)	1 (0.5)	8 (2.4)	1 (0.5)					18 (1.3)	2 (0.2)
	Cardiac disorder			5 (1.6)	4 (2.0)	2 (0.6)	3 (1.4)			0 (0.0)	6 (7.1)	7 (0.5)	13 (1.2)

Table 2. Summary of adverse events of five published trials^a.

Table 2. (Continued)										
						No. of pa	No. of patients (%)			
	INBUILD	ILD	INPUI	I-SISINANI	INPULSIS-2	SIS-2	SENSCIS	CIS	TOMORROW ^b	tОW ^b
Events	Nintedanib	placebo	Nintedanib	placebo	Nintedanib	placebo	Nintedanib placebo Nintedanib placebo Nintedanib placebo Nintedanib placebo Nintedanib placebo	placebo	Nintedanib	placebo
	(N = 332)	(N = 331)	(N = 309)	(N = 204)	(N = 329)	(N = 219)	(N = 332) (N = 331) (N = 309) (N = 204) (N = 329) (N = 219) (N = 288) (N = 288) (N = 85) ((N = 288)	(N = 85)	(N = 85)
General disorder and condition involving site of study-drug administration			8 (2.6)	3 (1.5)	8 (2.6) 3 (1.5) 2 (0.6) 1 (0.5)	1 (0.5)				
Infections and infestations									0 (0.0) 6 (7.1)	6 (7.1)

"NCT01979952 is excluded due to different follow-up duration from other included trials.

^bOnly patients treated with nintedanib 150 mg twice daily and placebo were selected for comparison.

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(N = 1127)

(N = 1343)10 (0.7)

4(0.4)

6(0.5)

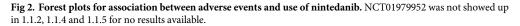
0 (0.0)

Nintedanib placebo

0 0

Total

	Ninteda		Placel			Odds Ratio	Odds Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
I.1.1 Any adverse ev	ents						
NBUILD	317	332	296	331	29.3%	2.50 [1.34, 4.67]	
NPULSIS-1	298	309	181	204	20.8%	3.44 [1.64, 7.23]	
NPULSIS-2	311	329	198	219	26.8%	1.83 [0.95, 3.53]	
NCT01979952	54	56	51	57	4.2%	3.18 [0.61, 16.46]	
SENSCIS	283	288	276	288	10.3%	2.46 [0.86, 7.08]	
TOMORROW	80	85	77	85	8.5%	1.66 [0.52, 5.30]	
Subtotal (95% CI)		1399		1184	100.0%	2.39 [1.71, 3.36]	•
Total events	1343		1079				
Heterogeneity: Tau ² =	0.00; Chi ²	= 2.08,	df = 5 (P	= 0.84); l² = 0%		
Test for overall effect:	Z = 5.05 (F	^o < 0.00	0001)				
1.1.2 Severe adverse							
NBUILD	60	332	73	331	23.5%	0.78 [0.53, 1.14]	
NPULSIS-1	81	309	37	204	21.0%	1.60 [1.04, 2.48]	
NPULSIS-2	93	329	62	219	23.6%	1.00 [0.68, 1.46]	
SENSCIS	52	288	36	288	20.0%	1.54 [0.97, 2.44]	
TOMORROW	19	85	20	85	11.9%	0.94 [0.46, 1.91]	
Subtotal (95% CI)		1343		1127	100.0%	1.13 [0.84, 1.51]	T
Total events	305		228				
Heterogeneity: Tau ² =				= 0.08); l² = 53%		
Test for overall effect:	Z = 0.79 (F	P = 0.43	3)				
1.1.3 Serious adverse							<u> </u>
NBUILD	107	332	110	331	28.4%	0.96 [0.69, 1.32]	
NPULSIS-1	96	309	55	204	19.4%	1.22 [0.83, 1.81]	
NPULSIS-2	98	329	72	219	22.1%	0.87 [0.60, 1.25]	
NCT01979952	11	56	14	57	3.7%	0.75 [0.31, 1.83]	
SENSCIS	69	288	62	288	19.6%	1.15 [0.78, 1.70]	
TOMORROW	23	85	26	85	6.8%	0.84 [0.43, 1.64]	
Subtotal (95% CI)		1399		1184	100.0%	1.00 [0.84, 1.19]	Y
Total events	404		339				
Heterogeneity: Tau ² =				= 0.73); l² = 0%		
Test for overall effect:	Z = 0.01 (i	P = 0.99	9)				
	1						
1.1.4 Adverse events	-						
NBUILD	65	332	34	331	24.7%	2.13 [1.36, 3.32]	
NPULSIS-1	65	309	22	204	19.6%	2.20 [1.31, 3.71]	
NPULSIS-2	58	329	33	219	23.1%	1.21 [0.76, 1.92]	Τ
SENSCIS	46	288	25	288	19.7%	2.00 [1.19, 3.35]	
TOMORROW	26	85	22	85	12.9%	1.26 [0.65, 2.47]	
Subtotal (95% CI)		1343		1127	100.0%	1.73 [1.34, 2.25]	
Total events	260	.	136				
Heterogeneity: Tau ² =				= 0.28); l² = 22%	l)	
Test for overall effect:	∠ = 4.17 (i	- < 0.00	JU1)				
1.1.5 Fatal adverse e	vonte						
		005	4-	001	05.00/	0.00 (0.00	_ _
NBUILD	11	332	17	331	25.9%	0.63 [0.29, 1.37]	
NPULSIS-1	12	309	10	204	22.8%	0.78 [0.33, 1.85]	
NPULSIS-2	25	329	21	219	33.8%	0.78 [0.42, 1.42]	
SENSCIS	5	288	4	288	12.0%	1.25 [0.33, 4.72]	
	1	85	12	85	5.5%	0.07 [0.01, 0.57]	
Subtotal (95% CI)	_	1343	_	1127	100.0%	0.69 [0.41, 1.14]	
Total events	54		64				
Heterogeneity: Tau ² =				= 0.21); I² = 31%	1	
Test for overall effect:	∠ = 1.46 (i	- = 0.14	+)				
							0.01 0.1 1 10 1

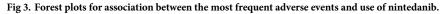


Sensitivity analysis

Studies were removed one at a time and it was determined that no individual trial had a significant impact on the overall pooled results for all adverse events outcomes. The magnitude and direction of association were consistent with the results when all studies were pooled together (Table 3).

For the most frequent adverse events, no individual study had a significant impact on the magnitude and direction of association for diarrhea, nausea, vomiting or weight loss. As for cough, the pooled results became insignificance when the INBUILD, INPULSIS-2, NCT01979952, SENSCIS or TOMORROW studies were removed one at a time. As for

	Ninteda		Place			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Ci
NBUILD	222	332	79	331	21.2%	6.44 [4.58, 9.05]	
NPULSIS-1	190	309	38	204	18.8%	6.97 [4.58, 10.62]	
NPULSIS-2	208	329	40	219	19.1%	7.69 [5.11, 11.59]	
CT01979952	43	56	40	57	9.3%	1.41 [0.61, 3.26]	
SENSCIS	218	288	91	288	20.4%	6.74 [4.67, 9.72]	
OMORROW	47	85	13	85	11.2%	6.85 [3.30, 14.20]	
Subtotal (95% CI)		1399		1184	100.0%	5.96 [4.35, 8.16]	•
otal events	928		301				
leterogeneity: Tau ² =		= 13.53		P = 0.0	(2): $ ^2 = 639$	4	
est for overall effect:				0.0	2),1 - 00		
2.1.2 Nausea							
NBUILD	96	332	31	331	19.9%	3.94 [2.54, 6.11]	
NPULSIS-1	70	309	12	204	16.2%	4.69 [2.47, 8.90]	
NPULSIS-2	86	329	16	219	17.6%	4.49 [2.55, 7.90]	
ICT01979952	16	56	20	57	13.7%	0.74 [0.33, 1.64]	
SENSCIS	91	288	39	288	20.2%	2.95 [1.94, 4.48]	
OMORROW	20	85	8	85	12.4%	2.96 [1.22, 7.17]	
Subtotal (95% CI)	20	1399		1184	100.0%	3.00 [1.93, 4.66]	•
otal events	379		126				
leterogeneity: Tau ² = est for overall effect: 2	0.20; Chi ²		2, df = 5 (P = 0.0	05); l² = 70)%	
1.3 Vomiting							_
NBUILD	61	332	17	331	24.3%	4.16 [2.37, 7.29]	
NPULSIS-1	40	309	4	204	10.9%	7.43 [2.62, 21.12]	
NPULSIS-2	34	329	7	219	15.2%	3.49 [1.52, 8.02]	
ICT01979952	10	56	9	57	11.9%	1.16 [0.43, 3.11]	
SENSCIS	71	288	30	288	28.8%	2.81 [1.77, 4.47]	
OMORROW	11	85	4	85	8.9%	3.01 [0.92, 9.86]	
Subtotal (95% CI)		1399		1184	100.0%	3.22 [2.17, 4.76]	•
otal events	227		71				
leterogeneity: Tau ² =		= 7 83		= 0 17); ² = 36%		
				•	/		
est for overall effect:	Z = 5.84 (P < 0.00	1001)				
2.1.4 Cough				0.94	64 0 %	0.70.00.45.4.401	_
2.1.4 Cough NBUILD	33	332	44	331	21.9%	0.72 [0.45, 1.16]	-
2.1.4 Cough NBUILD NPULSIS-1	33 47	332 309	44 26	204	19.8%	1.23 [0.73, 2.06]	
2.1.4 Cough NBUILD NPULSIS-1 NPULSIS-2	33 47 38	332 309 329	44 26 31	204 219	19.8% 20.2%	1.23 [0.73, 2.06] 0.79 [0.48, 1.32]	
2.1.4 Cough NBUILD NPULSIS-1 NPULSIS-2 ICT01979952	33 47 38 9	332 309 329 56	44 26 31 15	204 219 57	19.8% 20.2% 7.6%	1.23 [0.73, 2.06] 0.79 [0.48, 1.32] 0.54 [0.21, 1.35]	
2.1.4 Cough NBUILD NPULSIS-1 NPULSIS-2 NCT01979952 SENSCIS	33 47 38 9 34	332 309 329 56 288	44 26 31 15 52	204 219 57 288	19.8% 20.2% 7.6% 22.7%	1.23 [0.73, 2.06] 0.79 [0.48, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97]	
2.1.4 Cough NBUILD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS TOMORROW	33 47 38 9	332 309 329 56 288 85	44 26 31 15	204 219 57 288 85	19.8% 20.2% 7.6% 22.7% 7.9%	1.23 (0.73, 2.06) 0.79 (0.48, 1.32) 0.54 (0.21, 1.35) 0.61 (0.38, 0.97) 0.42 (0.17, 1.02)	
2.1.4 Cough NBUILD NPULSIS-1 NPULSIS-2 NCT01979952 SENSCIS	33 47 38 9 34	332 309 329 56 288	44 26 31 15 52 17	204 219 57 288	19.8% 20.2% 7.6% 22.7%	1.23 [0.73, 2.06] 0.79 [0.48, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97]	
2.1.4 Cough NBUILD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS TOMORROW	33 47 38 9 34	332 309 329 56 288 85	44 26 31 15 52	204 219 57 288 85	19.8% 20.2% 7.6% 22.7% 7.9%	1.23 (0.73, 2.06) 0.79 (0.48, 1.32) 0.54 (0.21, 1.35) 0.61 (0.38, 0.97) 0.42 (0.17, 1.02)	
1.1.4 Cough NBULD NPULSIS-1 NPULSIS-2 ICT01979952 EINSCIS 'OMORROW Subtotal (95% CI) 'otal events feterogenetity: Tau ² =	33 47 38 9 34 8 169 0.03; Chi ²	332 309 329 56 288 85 1399 = 6.52,	44 26 31 15 52 17 185 df = 5 (P	204 219 57 288 85 1184	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%	1.23 [0.73, 2.06] 0.79 [0.48, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96]	
1.1.4 Cough NBUILD NPULSIS-1 NPULSIS-2 ICT01979952 ENSCIS ENSCIS OMORROW Jubtotal (95% CI) Total events leterogeneity: Tau ² =	33 47 38 9 34 8 169 0.03; Chi ²	332 309 329 56 288 85 1399 = 6.52,	44 26 31 15 52 17 185 df = 5 (P	204 219 57 288 85 1184	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%	1.23 [0.73, 2.06] 0.79 [0.48, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96]	
1.4 Cough NBUILD NPULSIS-1 NPULSIS-2 ICT01979952 IENSCIS OMORROW Jubtotal (95% CI) total events teterogeneity: Tau ² = est for overall effect: : .1.5 Nasopharyngitti	33 47 38 9 34 8 169 0.03; Chi ² Z = 2.25 (1	332 309 329 56 288 85 1399 = 6.52, P = 0.02	44 26 31 15 52 17 185 df = 5 (P 2)	204 219 57 288 85 1184	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%	1.23 [0.73, 2.06] 0.79 [0.48, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96]	
.1.4 Cough NBUILD NPULSIS-1 CTO1979952 EINSCIS OMORROW Uibtotal (95% CI) tolai events leterogeneity: Tau ² = set for overall effect : .1.5 Nasopharyngitta UBUILD	33 47 38 9 34 8 169 0.03; Chi ² Z = 2.25 (I	332 309 329 56 288 85 1399 = 6.52, P = 0.02 332	44 26 31 15 52 17 185 df = 5 (P 2)	204 219 57 288 85 1184 = 0.26	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); I ² = 23% 24.5%	1.23 [0.73, 2.08] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76]	
1.1.4 Cough NBUILD NPULSIS-1 (CTO1979952 SENSCIS COMORROW Subtotal (95% CI) Total events feterogeneity: Tau ² = Test for overall effect: : 1.1.5 Nasopharyngitt NBUILD NPULSIS-1	33 47 38 9 34 8 169 0.03; Chi ² Z = 2.25 (l 8 44 39	332 309 329 56 288 85 1399 = 6.52, P = 0.02 332 309	44 26 31 15 52 17 185 df = 5 (P 2) 40 34	204 219 57 288 85 1184 = 0.26 331 204	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); I ² = 23% 24.5% 20.7%	1.23 [0.73, 2.08] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.19]	
.1.4 Cough NBUILD NPULSIS-1 VPULSIS-2 ICTO1979952 IENSCIS OMORROW Jubtotal (95% CI) otal events Ieterogeneity: Tau ² = est for overall effect: . .1.5 Nasopharyngitt NBUILD NPULSIS-1 NPULSIS-2	33 47 38 9 34 8 169 0.03; Chi ² Z = 2.25 (l 8 44 39 48	332 309 329 56 288 85 1399 = 6.52, P = 0.02 332 309 329	44 26 31 15 52 17 185 df = 5 (P 2) 40 34 34	204 219 57 288 85 1184 = 0.26 331 204 219	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); ² = 23% 24.5% 20.7% 22.6%	1.23 [0.73, 2.06] 0.79 [0.48, 1.32] 0.54 [0.21, 1.35] 0.41 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.19] 0.73 [0.58, 1.50]	
.1.4 Cough NBUILD NPULSIS-1 CTO1979952 EINSCIS OMORROW Jubtotal (95% CI) Total events Reterogeneity: Tau ² = est for overall effect: . .1.5 Nasopharyngitta NBUILD NPULSIS-1 NPULSIS-2 CTO1979952	33 47 38 9 34 8 169 0.03; Chi ² Z = 2.25 (1 8 44 39 48 5	332 309 329 56 288 85 1399 = 6.52, P = 0.02 332 309 329 56	44 26 31 15 52 17 185 df = 5 (P 2) 40 34 34 34 9	204 219 57 288 85 1184 = 0.26 331 204 219 57	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); ² = 23% 24.5% 20.7% 22.6% 3.8%	1.23 [0.73, 2.08] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.16] 0.52 [0.58, 1.50] 0.52 [0.16, 1.67]	
1.1.4 Cough NBUILD NPULSIS-1 ICTO1979952 IENSCIS OMORROW Jubtotal (95% CI) Total events leterogeneity: Tau ² = rest for overall effect: : .1.5 Nasopharyngitt NBUILD NPULSIS-1 NPULSIS-1 NPULSIS-2 ICT01979952 IENSCIS	33 47 38 9 34 8 169 0.03; Chi ² Z = 2.25 (1 8 44 39 48 5 36	332 309 329 56 288 85 1399 = 6.52, P = 0.02 332 309 329 56 288	44 26 31 15 52 17 185 df = 5 (P 2) 40 34 34	204 219 57 288 85 1184 = 0.26 331 204 219 57 288	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); ² = 23% 24.5% 20.7% 22.6% 3.8% 23.7%	1.23 [0.73, 2.06] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.19] 0.93 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11]	
1.1.4 Cough NBUILD NPULSIS-1 CTO1979952 EINSCIS OMORROW iubtotal (95% CI) otal events teterogeneity: Tau ² = iest for overall effect: : .1.5 Nasopharyngitik NBUILD NPULSIS-1 NPULSIS-2 ICTO1979952 EINSCIS OMORROW	33 47 38 9 34 8 169 0.03; Chi ² Z = 2.25 (1 8 44 39 48 5	332 309 329 56 288 85 1399 = 6.52, P = 0.02 332 309 329 56 288 85	44 26 31 15 52 17 185 df = 5 (P 2) 40 34 34 34 9	204 219 57 288 85 1184 = 0.26 331 204 219 57 288 85	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); l ² = 23% 24.5% 20.7% 22.6% 3.8% 23.7% 4.7%	1.23 [0.73, 2.08] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.17] 0.73 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11] 0.51 [0.18, 1.45]	
2.1.4 Cough NBUILD NPULSIS-1 NPULSIS-2 ICT01979952 SENSCIS TOMORROW Subtotal (95% CI) Total events	33 47 38 9 34 8 169 0.03; Chi ² Z = 2.25 (1 8 44 39 48 5 36	332 309 329 56 288 85 1399 = 6.52, P = 0.02 332 309 329 56 288	44 26 31 15 52 17 185 df = 5 (P 2) 40 34 34 9 9	204 219 57 288 85 1184 = 0.26 331 204 219 57 288	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); ² = 23% 24.5% 20.7% 22.6% 3.8% 23.7%	1.23 [0.73, 2.06] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.19] 0.93 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11]	
1.1.4 Cough NBUILD NPULSIS-1 CTO1979952 EINSCIS OMORROW iubtotal (95% CI) otal events teterogeneity: Tau ² = iest for overall effect: : .1.5 Nasopharyngitik NBUILD NPULSIS-1 NPULSIS-2 ICTO1979952 EINSCIS OMORROW	33 47 38 9 34 8 169 0.03; Chi ² Z = 2.25 (1 8 44 39 48 5 36	332 309 329 56 288 85 1399 = 6.52, P = 0.02 332 309 329 56 288 85	44 26 31 15 52 17 185 df = 5 (P 2) 40 34 34 9 9	204 219 57 288 85 1184 = 0.26 331 204 219 57 288 85	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); l ² = 23% 24.5% 20.7% 22.6% 3.8% 23.7% 4.7%	1.23 [0.73, 2.08] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.17] 0.73 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11] 0.51 [0.18, 1.45]	
1.4 Cough VBUILD VPULSIS-1 VPULSIS-2 CT01979952 ENSCIS OMORROW iubtotal (95% CI) otal events leterogeneity: Tau ² = est for overall effect: : .1.5 Nasopharyngitit VBUILD VPULSIS-1 VPULSIS-2 CT01979952 ENSCIS OMORROW iubtotal (95% CI) otal events leterogeneity: Tau ² =	33 47 38 9 34 8 169 0.03; Ch ² Z = 2.25 (l 8 44 39 48 5 36 6 6 6 6 6 6 178 0.00; Ch ²	332 309 329 56 288 85 1399 = 6.52, P = 0.02 332 309 329 56 288 85 1399 = 4.04,	44 26 31 15 52 17 185 df = 5 (P 2) 40 34 9 49 49 11 177 df = 5 (P	204 219 57 288 85 1184 = 0.26 331 204 219 57 288 85 1184	19.8% 20.2% 7.6% 22.7% 100.0%); l ² = 23% 24.5% 20.7% 22.6% 3.8% 23.7% 4.7% 100.0%	1.23 [0.73, 2.08] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.17] 0.73 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11] 0.51 [0.18, 1.45]	
1.4 Cough VBUILD VPULSIS-1 VPULSIS-2 (CTO1979952 EINSCIS COMORROW Jubtotal (95% CI) otal events leterogeneity: Tau ² = est for overall effect: : .1.5 Nasopharyngttl NBUILD VPULSIS-1 VPULSIS-2 (CTO1979952 EINSCIS CMORROW Jubtotal (95% CI) otal events leterogeneity: Tau ² = est for overall effect: :	33 47 38 9 34 8 169 0.03; Ch ² Z = 2.25 (l 8 44 39 48 5 36 6 6 6 6 6 6 178 0.00; Ch ²	332 309 329 56 288 85 1399 = 6.52, P = 0.02 332 309 329 56 288 85 1399 = 4.04,	44 26 31 15 52 17 185 df = 5 (P 2) 40 34 9 49 49 11 177 df = 5 (P	204 219 57 288 85 1184 = 0.26 331 204 219 57 288 85 1184	19.8% 20.2% 7.6% 22.7% 100.0%); l ² = 23% 24.5% 20.7% 22.6% 3.8% 23.7% 4.7% 100.0%	1.23 [0.73, 2.08] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.17] 0.73 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11] 0.51 [0.18, 1.45]	
1.1.4 Cough NBUILD NPULSIS-1 CTO1979952 SENSCIS COMORROW Subtotal (95% CI) Total events feterogeneity: Tau ² = est for overall effect: : 2.1.5 Nasopharyngitt NBUILD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS COMORROW	33 47 38 9 34 8 169 0.03; Ch ² Z = 2.25 (l 8 44 39 48 5 36 6 6 6 6 6 6 178 0.00; Ch ²	332 309 329 56 288 85 1399 = 6.52, P = 0.02 332 309 329 56 288 85 1399 = 4.04,	44 26 31 15 52 17 185 df = 5 (P 2) 40 34 9 49 49 11 177 df = 5 (P	204 219 57 288 85 1184 = 0.26 331 204 219 57 288 85 1184	19.8% 20.2% 7.6% 22.7% 100.0%); l ² = 23% 24.5% 20.7% 22.6% 3.8% 23.7% 4.7% 100.0%	1.23 [0.73, 2.08] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.17] 0.73 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11] 0.51 [0.18, 1.45]	
1.1.4 Cough NEULD NPULSIS-1 CTO1979952 SENSCIS COMORROW Subtotal (95% CI) Total events teterogeneity: Tau ² = rest for overall effect: : 2.1.5 Nasopharyngitik NBUILD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS COMORROW Subtotal (95% CI) Total events teterogeneity: Tau ² = rest for overall effect: : 2.1.6 Weight Loss	33 47 38 9 34 8 169 0.03; Ch ² Z = 2.25 (I 8 48 5 36 6 6 178 0.00; Ch ² Z = 1.73 (I	332 309 329 56 85 1399 = 6.52, P = 0.02 332 339 56 288 85 1399 = 4.04, P = 0.08	44 26 31 15 52 17 185 6f = 5 (P 2) 40 34 9 49 49 11 177 df = 5 (P 3)	204 219 57 288 85 1184 = 0.266 3311 204 219 57 288 85 1184 = 0.54	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); ² = 23% 24.5% 20.7% 22.6% 3.8% 23.7% 4.7% 100.0%); ² = 0%	1.23 [0.73, 2.08] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.18] 0.83 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11] 0.51 [0.18, 1.45] 0.82 [0.65, 1.03]	
1.4 Cough NBUILD NPULSIS-1 (CTO1979952 EINSCIS COMORROW Subtotal (95% CI) total events teterogeneity: Tau ² = est for overall effect: : .1.5 Nasopharyngitti NBUILD NPULSIS-1 NPULSIS-2 (CTO1979952 EINSCIS CMORROW Subtotal (95% CI) total events teterogeneity: Tau ² = est for overall effect: : .1.6 Weight Ioss NBUILD NPULSIS-1 NPULSIS-1	33 47 38 9 34 8 169 0.03; Ch ^p Z = 2.25 (I 5 48 5 36 6 6 6 6 6 8 0.00; Ch ^p Z = 1.73 (I 41 25	332 309 329 56 85 1399 = 6.52, P = 0.02 332 309 56 288 85 1399 = 4.04, P = 0.06 332 332 332 332 332 332 332 332 332 33	44 26 31 15 52 17 185 52 17 185 52 17 185 52 17 185 40 34 34 9 49 34 9 49 11 177 6f = 5 (P	204 219 57 288 85 1184 = 0.26 3311 204 219 57 288 85 1184 = 0.54 331	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); P = 23% 24.5% 20.7% 22.6% 3.8% 23.7% 4.7% 100.0%); P = 0% 24.0% 23.8%	1.23 [0.73, 2.08] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.19] 0.73 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11] 0.51 [0.48, 1.45] 0.82 [0.65, 1.03] 4.10 [2.07, 8.12] 1.29 [0.65, 2.59]	
1.1.4 Cough NBUILD NPULSIS-1 ICTO1979952 EINSCIS CITO1979952 EINSCIS OMORROW iubtotal (95% CI) iotal events leatrogeneity: Tau ² = iest for overall effect: : 1.5 Nasopharyngitk NBUILD NPULSIS-1 NBULD NPULSIS-1 NPULSIS-2 EINSCIS INBUILD NPULSIS-1 NPULSIS-2 EINSCIS NBUILD NPULSIS-1 NPULSIS-2 EINSCIS NBUILD NPULSIS-1 NPULSIS-2 EINSCIS NPULSIS-1 NPULSIS-2 EINSCIS EINSCIS EINSCIS NPULSIS-1 NPULSIS-2 EINSCIS	33 47 38 9 34 8 169 0.03; Ch ² Z = 2.25 (1 8 48 5 36 6 6 6 6 178 0.00; Ch ² Z = 1.73 (1 25 37	332 309 329 56 85 1399 = 6.52, 79 = 0.02 332 309 56 288 85 1399 = 4.04, P = 0.05 332 332 332 332 339 329 56 288 85 332 332 332 332 332 332 332 332 332 33	44 26 31 15 52 17 18 5 ff = 5 (P 34 40 34 49 49 49 11 11 17 7 ff = 5 (P 11 13 3 2	204 219 57 288 85 1184 204 219 57 288 85 1184 = 0.54 331 204 219	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); I ² = 23% 24.5% 22.6% 22.6% 22.6% 23.8% 100.0%); I ² = 0% 24.0% 23.8% 12.6%	1.23 [0.73, 2.08] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.19] 0.33 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11] 0.51 [0.18, 1.45] 0.82 [0.65, 1.03] 4.10 [2.07, 8.12] 1.29 [0.65, 2.59] 1.29 [0.65, 2.59]	
2.1.4 Cough NEULD NPULSIS-1 NPULSIS-2 ICT01979952 IENSCIS COMORROW Subtotal (95% CI) Total events Ieterogeneity: Tau ² = rest for overall effect: : 2.1.5 Nasopharyngitti NEULD NPULSIS-1 NPULSIS-2 ICT01979952 State overall effect: : 2.1.6 Weight Iosa NBULD NPULSIS-2 ICT01979952	33 47 38 9 34 8 169 0.03; Chi ^p Z = 2.25 (i 8 44 39 48 5 36 6 6 178 0.00; Ch ^p Z = 1.73 (i 41 25 37 13	332 309 329 56 288 85 1399 = 6.52, 79 = 0.02 332 332 332 309 = 4.04, P = 0.02 332 332 309 56 50 55 55 55 55 55 55 55 55 55 55 55 55	44 26 31 15 52 17 185 52 17 185 52 17 40 34 34 9 9 49 11 177 4f = 5 (P 4) 0 177 177 4f = 5 (P 17 17 17 17 17 18 5 17 18 5 17 17 18 5 17 17 18 5 17 17 18 5 17 17 18 5 17 17 18 18 18 18 18 18 18 18 18 18 18 18 18	204 219 57 288 85 1184 204 219 57 288 85 1184 219 57 288 85 1184 219 57 3311 204 219 57 57 57 57 57 57 57 57 57 57 57 57 57	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); P = 23% 24.5% 20.7% 22.6% 23.8% 4.7% 100.0%); P = 0% 24.0% 23.8% 12.6%	1.23 [0.73, 2.06] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.17] 0.93 [0.58, 1.50] 0.52 [0.18, 1.57] 0.52 [0.18, 1.54] 0.52 [0.65, 1.53] 4.10 [2.07, 8.12] 1.29 [0.65, 2.59] 13.75 [3.28, 67.66] 4.01 [1.22, 13.18]	
1.1.4 Cough NEULD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS OMORROW Bubtotal (95% CI) Total events feterogeneity: Tau ² = "est for overall effect: : 1.1.5 Nasopharyngtt/ NBULD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS OMORROW Bubtotal (95% CI) Total events feterogeneity: Tau ² = "est for overall effect: : 2.1.6 Weight Ioss NBUILD NPULSIS-1 NPULSIS-1 NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS	33 47 38 9 34 8 169 0.03; Ch ² Z = 2.25 (1 8 48 5 36 6 6 6 6 178 0.00; Ch ² Z = 1.73 (1 25 37	332 309 329 56 288 85 1399 = 6.52, P = 0.02 332 309 56 6288 85 1399 = 4.04, P = 0.05 332 309 3329 56 6288 85 289 288 289 289 289 289 289 289 289 289	44 26 31 15 52 17 18 5 ff = 5 (P 34 40 34 49 49 49 11 11 17 7 ff = 5 (P 11 13 3 2	204 219 57 288 85 1184 = 0.266 3311 204 219 57 288 85 1184 = 0.54 3311 204 219 57 288 85 288 85 288 85 288 288 283 288 288 288 288 288 288 288	19.8% 19.8% 20.2% 7.8% 22.7% 7.9% 100.0%); ² = 23% 24.5% 22.6% 22.6% 23.8% 23.7% 4.7% 4.7% 100.0%); ² = 0%	1.23 [0.73, 2.08] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.17] 0.73 [0.58, 1.50] 0.52 [0.18, 1.45] 0.52 [0.18, 1.45] 0.52 [0.18, 1.45] 0.82 [0.55, 1.03] 4.10 [2.07, 8.12] 1.29 [0.65, 2.59] 13.75 [3.28, 57.86] 4.01 [1.22, 13.18] 3.08 [1.56, 6.08]	
1.1.4 Cough NEULD NPULSIS-1 NPULSIS-2 (CTC1979952 SENSCIS OMORROW Subtotal (95% CI) Total events leterogeneity: Tau ² = est for overall effect : 1.1.5 Nasopharyngitk NBUILD NPULSIS-1 NPULSIS-2 ICTC1979952 SENSCIS OMORROW Subtotal (95% CI) Total events leterogeneity: Tau ² = est for overall effect : 1.1.6 Weight loss NBUILD NPULSIS-1 NPULSIS-1 NPULSIS-2 ICTC1979952 SENSCIS Subtotal (95% CI)	33 47 38 9 34 8 169 7 2 = 2.25 (1 8 44 39 48 5 36 6 6 6 6 77 7 2 = 1.73 (1 25 377 13 34	332 309 329 56 288 85 1399 = 6.52, 79 = 0.02 332 332 332 309 = 4.04, P = 0.02 332 332 309 56 50 55 55 55 55 55 55 55 55 55 55 55 55	44 26 31 15 52 17 48 5 47 5 2 17 40 34 34 9 49 11 177 cf = 5 (P 17 5 40 34 17 17 7 49 11 17 7 49 117 17 18 5 18 5 18 5 18 5 18 5 18 5 18	204 219 57 288 85 1184 204 219 57 288 85 1184 219 57 288 85 1184 219 57 3311 204 219 57 57 57 57 57 57 57 57 57 57 57 57 57	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); P = 23% 24.5% 20.7% 22.6% 23.8% 4.7% 100.0%); P = 0% 24.0% 23.8% 12.6%	1.23 [0.73, 2.06] 0.79 [0.44, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.17, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.17] 0.93 [0.58, 1.50] 0.52 [0.18, 1.57] 0.52 [0.18, 1.54] 0.52 [0.65, 1.53] 4.10 [2.07, 8.12] 1.29 [0.65, 2.59] 13.75 [3.28, 67.66] 4.01 [1.22, 13.18]	
2.1.4 Cough NEULD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS OMORROW Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: : 2.1.5 Nasopharyngitis NBULD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS OMORROW Bubtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: : 2.1.6 Weight Ioss NBUILD NPULSIS-1 NEULSIS-2 ICTO1979952 SENSCIS Bubtotal (95% CI) Total events	33 47 38 9 34 8 169 0.03; Chi ² Z = 2.25 (i 8 44 39 9 48 5 36 6 178 0.00; Chi ² Z = 1.73 (i 41 25 37 13 34	332 309 329 56 288 288 339 = 6.52, P = 0.02 332 339 56 288 339 9 = 4.04, P = 0.05 332 332 9 = 6.52, 1399 56 288 332 9 = 5 56 288 332 9 = 5 56 288 332 9 = 5 56 288 329 56 288 329 56 288 329 329 56 56 288 329 329 329 329 329 329 329 329 329 329	44 26 31 52 52 47 = 5 (P 40 34 34 9 9 9 9 11 177 77 49 9 9 9 9 9 11 177 77 185 5 2 185 19 19 19 19 19 19 19 19 19 19 19 19 19	204 219 57 288 85 1184 219 57 288 85 1184 219 57 288 85 1184 219 57 288 1099	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); P = 23% 24.5% 20.7% 22.6% 23.7% 4.7% 100.0%); P = 0% 24.0% 23.8% 12.6% 24.1% 100.0%	1.23 [0.73, 2.06] 0.79 [0.48, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.71, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.19] 0.73 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11] 0.51 [0.18, 1.45] 0.82 [0.65, 1.03] 4.10 [2.07, 8.12] 1.29 [0.65, 2.59] 13.76 [3.28, 57.66] 3.38 [1.56, 6.08] 3.38 [1.56, 6.08]	
1.1.4 Cough NEULD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS OMORROW Bubtotal (95% CI) Total events feterogeneity: Tau ² = est for overall effect: : 1.1.5 Nasopharyngtt/ NBULD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS OMORROW Bubtotal (95% CI) Total events feterogeneity: Tau ² = est for overall effect: : 1.1.6 Weight Ioss NBUILD NPULSIS-1 NPULSIS-1 NPULSIS-1 NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS	33 47 38 9 34 8 169 0.03; Chi ^p Z = 2.25 (l 8 48 5 36 6 6 6 8 0.00; Chi ^p Z = 1.73 (l 41 25 37 37 13 34 4 150 0.03; Chi ^p	332 309 329 56 288 85 1399 = 6.52, 7 9 = 0.02 332 309 56 85 1399 = 4.04, P = 0.02 332 309 329 56 83 288 85 1399 = 4.04, P = 1.05 288 312 9 329 56 83 288 85 1399 9 56 83 288 85 1399 84 56 85 1399 85 85 85 85 85 85 85 85 85 85 85 85 85	44 26 31 15 52 17 185 52 17 185 6 df = 5 (P 40 34 9 49 49 49 34 9 49 11 177 7 (df = 5 (P 5) 11 13 2 2 4 2 42 42 5 5 5 5 17 17 18 5 5 18 5 5 17 18 5 18 5	204 219 57 288 85 1184 219 57 288 85 1184 219 57 288 85 1184 219 57 288 1099	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); P = 23% 24.5% 20.7% 22.6% 23.7% 4.7% 100.0%); P = 0% 24.0% 23.8% 12.6% 24.1% 100.0%	1.23 [0.73, 2.06] 0.79 [0.48, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.71, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.19] 0.73 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11] 0.51 [0.18, 1.45] 0.82 [0.65, 1.03] 4.10 [2.07, 8.12] 1.29 [0.65, 2.59] 13.76 [3.28, 57.66] 3.38 [1.56, 6.08] 3.38 [1.56, 6.08]	
2.1.4 Cough NEULD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS OMORROW Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: : 2.1.5 Nasopharyngitis NBULD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS OMORROW Bubtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: : 2.1.6 Weight Ioss NBUILD NPULSIS-1 NEULSIS-2 ICTO1979952 SENSCIS Bubtotal (95% CI) Total events	33 47 38 9 34 8 169 0.03; Chi ^p Z = 2.25 (l 8 48 5 36 6 6 6 8 0.00; Chi ^p Z = 1.73 (l 41 25 37 37 13 34 4 150 0.03; Chi ^p	332 309 329 56 288 85 1399 = 6.52, 7 9 = 0.02 332 309 56 85 1399 = 4.04, P = 0.02 332 309 329 56 83 288 85 1399 = 4.04, P = 1.05 288 312 9 329 56 83 288 85 1399 9 56 83 288 85 1399 84 56 85 1399 85 85 85 85 85 85 85 85 85 85 85 85 85	44 26 31 15 52 17 185 52 17 185 6 df = 5 (P 40 34 9 49 49 49 34 9 49 11 177 7 (df = 5 (P 5) 11 13 2 2 4 2 42 42 5 5 5 5 17 17 18 5 5 18 5 5 17 18 5 18 5	204 219 57 288 85 1184 219 57 288 85 1184 219 57 288 85 1184 219 57 288 1099	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); P = 23% 24.5% 20.7% 22.6% 23.7% 4.7% 100.0%); P = 0% 24.0% 23.8% 12.6% 24.1% 100.0%	1.23 [0.73, 2.06] 0.79 [0.48, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.71, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.19] 0.73 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11] 0.51 [0.18, 1.45] 0.82 [0.65, 1.03] 4.10 [2.07, 8.12] 1.29 [0.65, 2.59] 13.76 [3.28, 57.66] 3.38 [1.56, 6.08] 3.38 [1.56, 6.08]	
1.1.4 Cough NEULD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS OMORROW Bubtotal (95% CI) Total events feterogeneity: Tau ² = est for overall effect: : 1.1.5 Nasopharyngtt/ NBULD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS OMORROW Bubtotal (95% CI) Total events feterogeneity: Tau ² = est for overall effect: : 1.1.6 Weight Ioss NBUILD NPULSIS-1 NPULSIS-1 NPULSIS-1 NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS	33 47 38 9 34 8 169 0.03; Chi ^p Z = 2.25 (l 8 48 5 36 6 6 6 8 0.00; Chi ^p Z = 1.73 (l 41 25 37 37 13 34 4 150 0.03; Chi ^p	332 309 329 56 288 85 1399 = 6.52, 7 9 = 0.02 332 309 56 85 1399 = 4.04, P = 0.02 332 309 329 56 83 288 85 1399 = 4.04, P = 1.05 288 312 9 329 56 83 288 85 1399 9 56 83 288 85 1399 84 56 85 1399 85 85 85 85 85 85 85 85 85 85 85 85 85	44 26 31 15 52 17 185 52 17 185 6 df = 5 (P 40 34 9 49 49 49 34 9 49 11 177 7 (df = 5 (P 5) 11 13 2 2 4 2 42 42 5 5 5 5 17 17 18 5 5 18 5 5 17 18 5 18 5	204 219 57 288 85 1184 219 57 288 85 1184 219 57 288 85 1184 219 57 288 1099	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); P = 23% 24.5% 20.7% 22.6% 23.7% 4.7% 100.0%); P = 0% 24.0% 23.8% 12.6% 24.1% 100.0%	1.23 [0.73, 2.06] 0.79 [0.48, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.71, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.19] 0.73 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11] 0.51 [0.18, 1.45] 0.82 [0.65, 1.03] 4.10 [2.07, 8.12] 1.29 [0.65, 2.59] 13.76 [3.28, 57.66] 3.38 [1.56, 6.08] 3.38 [1.56, 6.08]	
1.1.4 Cough NEULD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS OMORROW Bubtotal (95% CI) Total events feterogeneity: Tau ² = est for overall effect: : 1.1.5 Nasopharyngtt/ NBULD NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS OMORROW Bubtotal (95% CI) Total events feterogeneity: Tau ² = est for overall effect: : 1.1.6 Weight Ioss NBUILD NPULSIS-1 NPULSIS-1 NPULSIS-1 NPULSIS-1 NPULSIS-2 ICTO1979952 SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS SENSCIS	33 47 38 9 34 8 169 0.03; Chi ^p Z = 2.25 (l 8 48 5 36 6 6 6 8 0.00; Chi ^p Z = 1.73 (l 41 25 37 37 13 34 4 150 0.03; Chi ^p	332 309 329 56 288 85 1399 = 6.52, 7 9 = 0.02 332 309 56 85 1399 = 4.04, P = 0.02 332 309 329 56 83 288 85 1399 = 4.04, P = 1.05 288 312 9 329 56 83 288 85 1399 9 56 83 288 85 1399 84 56 85 1399 85 85 85 85 85 85 85 85 85 85 85 85 85	44 26 31 15 52 17 185 52 17 185 6 df = 5 (P 40 34 9 49 49 49 34 9 49 11 177 7 (df = 5 (P 5) 11 13 2 2 4 2 42 42 5 5 5 5 17 17 18 5 5 18 5 5 17 18 5 18 5	204 219 57 288 85 1184 219 57 288 85 1184 219 57 288 85 1184 219 57 288 1099	19.8% 20.2% 7.6% 22.7% 7.9% 100.0%); P = 23% 24.5% 20.7% 22.6% 23.7% 4.7% 100.0%); P = 0% 24.0% 23.8% 12.6% 24.1% 100.0%	1.23 [0.73, 2.06] 0.79 [0.48, 1.32] 0.54 [0.21, 1.35] 0.61 [0.38, 0.97] 0.42 [0.71, 1.02] 0.73 [0.56, 0.96] 1.11 [0.70, 1.76] 0.72 [0.44, 1.19] 0.73 [0.58, 1.50] 0.52 [0.16, 1.67] 0.70 [0.44, 1.11] 0.51 [0.18, 1.45] 0.82 [0.65, 1.03] 4.10 [2.07, 8.12] 1.29 [0.65, 2.59] 13.76 [3.28, 57.66] 3.38 [1.56, 6.08] 3.38 [1.56, 6.08]	



nasopharyngitis, the pooled results changed from insignificant to significant if the INBUILD study was removed (S1 Table).

Quality assessment

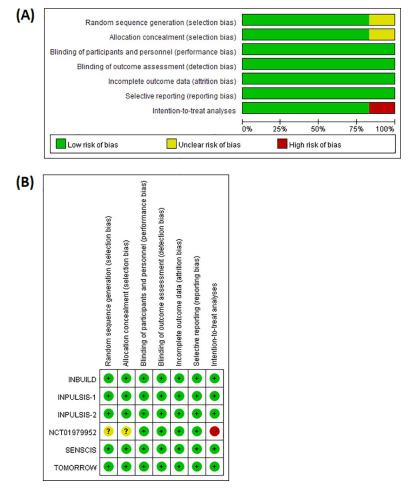
Fig 4 summarizes the overall quality of the included studies and the risk of bias for individual trials included in the meta-analysis. All studies were double-blind and had a low risk of attrition and reporting bias (Fig 4A). One unpublished trial had unclear randomization procedures and did not analyze the data in the intention-to-treat approach (Fig 4B) [25].

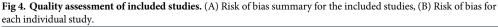
		Statistics wit	th study removed	
Study name	OR	Lower limit	Upper limit	P-value
Any adverse events				
INBUILD	2.35	1.57	3.52	< 0.001
INPULSIS-1	2.18	1.49	3.19	< 0.001
INPULSIS-2	2.64	1.78	3.92	< 0.001
NCT01979952	2.37	1.67	3.34	< 0.001
SENSCIS	2.39	1.67	3.41	< 0.001
TOMORROW	2.48	1.74	3.53	< 0.001
Severe adverse events				
INBUILD	1.26	0.96	1.66	0.093
INPULSIS-1	1.02	0.76	1.38	0.885
INPULSIS-2	1.17	0.79	1.73	0.436
SENSCIS	1.04	0.75	1.44	0.809
TOMORROW	1.16	0.82	1.63	0.402
Serious adverse events				
INBUILD	1.02	0.83	1.25	0.873
INPULSIS-1	0.95	0.79	1.15	0.615
INPULSIS-2	1.04	0.86	1.27	0.693
NCT01979952	1.01	0.85	1.20	0.911
SENSCIS	0.97	0.80	1.17	0.721
TOMORROW	1.01	0.85	1.21	0.901
Adverse events leading t	o treatment discont	inuation		
INBUILD	1.62	1.19	2.21	0.002
INPULSIS-1	1.63	1.21	2.21	0.001
INPULSIS-2	1.95	1.50	2.53	< 0.001
SENSCIS	1.67	1.21	2.31	0.002
TOMORROW	1.82	1.37	2.42	< 0.001
Fatal adverse events				
INBUILD	0.68	0.33	1.37	0.279
INPULSIS-1	0.64	0.32	1.26	0.194
INPULSIS-2	0.62	0.29	1.31	0.211
SENSCIS	0.63	0.36	1.10	0.101
TOMORROW	0.77	0.52	1.15	0.197

Discussion

The pooled analysis of safety data from the 6 clinical trials for patients with IPF and fibrotic-ILDs, showed that adverse events were more frequent in patients treated with nintedanib compared with the placebo. There was a higher likelihood of having adverse events leading to treatment discontinuation, but a lower likelihood of having fatal adverse events.

The most common adverse event associated with nintedanib use compared with the placebo was diarrhea. The underlying cause of diarrhea development remains unclear, but it may be due to direct irritation of the gastrointestinal (GI) tract due to high concentrations of the drug [26]. For most patients with an adverse event of diarrhea, first onset occurred within the first 3 months after the administration of nintedanib [27]. In a subgroup analysis of the INPULSIS trial [28], Japanese patients suffered from diarrhea more frequently compared with the overall population (75.0% vs. 62.4%). A retrospective study showed that low body mass





index (BMI; <21.6) was a risk factor for diarrhea [29]. If diarrhea develops, adequate hydration and anti-diarrheal medication (*e.g.* loperamide) are suggested [30]. Treatment interruption and dose reduction may only be necessary if diarrhea persists despite treatment. Most patients with diarrhea were able to control it with treatment, and only 4.5% (0.6% in the placebo) needed permanent discontinuation of nintedanib in the pooled data from the TOMOR-ROW and INPULSIS trials [8].

The risk of diarrhea was consistently higher in the nintedanib group compared with the placebo group. However, in the INBUILD and SENSCIS studies, the prevalence of diarrhea remained higher than in the TOMORROW and INPULSIS trials in both the nintedanib (71.0% vs. 61.5%) and placebo groups (27.5% vs. 17.9%). In addition, the proportion of patients with nausea and vomiting in the INBUILD and SENSCIS trials were also higher than in the other trials. This may be because the INBUILD and SENSCIS trials included patients with autoimmune-related ILD. All patients in the SENSCIS trial had SSc, and 25.6% of patients in the INBUILD trial had an autoimmune disease (rheumatoid arthritis 13.4%, SSc 5.9%, mixed connective tissue disease (MCTD) 2.9%, other 3.5%). Patients with an autoimmune disease had more systemic involvement and a higher prevalence of diarrhea (50% in SSc patients and 8% in MCTD patients) compared with IPF before the administration of nintedanib [31, <u>32</u>]. Approximately 90% of patients with SSc had some degree of GI involvement [<u>33</u>], and the use of nintedanib may have to be more carefully considered/monitored in these patients.

Nausea, vomiting, weight loss, and decreased appetite were other adverse events that occurred significantly more frequently in the nintedanib group compared with the placebo group. A poor performance status (ECOG PS 2–4), and a low BMI were risk factors for nausea [29]. Most of these adverse events were of a mild to moderate intensity and less frequently led to the discontinuation of nintedanib compared with diarrhea [6]. Elevation of hepatic enzymes also occurred more frequently in patients treated with nintedanib compared with the placebo group. One study pooling results from the TOMORROW, INPULSIS and NCT01979952 trials reported a higher rate of liver enzyme elevation in the nintedanib group compared with the placebo group among IPF patients [19]. Similar results were also found in the INBUILD trial. Patients with a progressive fibrotic phenotype of ILD were more likely to have elevated ALT and AST after treatment with nintedanib (13.0% vs. 3.6% for ALT and 11.4% vs. 3.6% for AST). Elevation of hepatic enzymes may be an early presentation of hepatotoxicity and asymptomatic, periodic monitoring prior to and during treatment with nintedanib should be conducted. Elevated hepatic enzymes is almost always reversible with dose reduction or treatment interruption [30].

Although the placebo is a dummy medication without pharmacological effects, >90% of patients in the placebo group suffered from some kind of adverse event across all 6 included trials. One possible explanation for this is the nocebo effect, a phenomenon where negative effects are attributed to the placebo [34, 35]. On the other hand, clinical characteristics of disease per se may also explain the higher proportion of adverse events in the placebo groups. For example, a certain degree of GI involvement occurs in autoimmune-related ILD [33]. Furthermore, in our pooled results, respiratory-related adverse events were more frequent in the placebo group, such as a cough, bronchitis, dyspnea, nasopharyngitis, and upper respiratory tract infection. These may be related to the high prevalence of respiratory symptoms in IPF patients, such as dyspnea (54-98%) or cough (59-100%) [36]. A study analyzing the serious adverse events in the placebo arms of 6 randomized clinical trials for interferon- γ 1b or pirfenidone, found that respiratory-related conditions, infections and infestations were the most frequently reported serious adverse events in IPF patients [37]. These results imply that respiratoryrelated adverse events are more likely to be related to the progression of IPF or PF-ILD itself than to the medication, and may evaluate as trial outcome parameters rather than adverse events. Discontinuation of nintedanib due to such adverse events may not be helpful.

The exacerbation rate of ILD was lower in nintedanib group compared with in placebo group, although presented in different definition across these studies as following (not mentioned in SENSCIS): 7.8% vs 9.8% (INBUILD, acute exacerbation of ILD or death at 52 weak); 6.1% vs 5.4%, 3.6% vs 9.6% (INPULSIS-1&2, proportion of patients with at least one investigator reported acute exacerbation); 1.8% vs 1.8% (NCT01979952, percentage of subjects experienced first acute IPF exacerbations between 0 to 6 months); 2.4 vs 15.7 (TOMORROW, per 100 patient-years). The hospitalization rate was only described in NCT01979952 (0.0% vs 7.0%, percentage of subjects hospitalized due to respiratory problems between 0 to 6 months) and TOMORROW (27.1% vs 25.9%, adverse events requiring hospitalization) studies. In other studies, only the serious adverse events, which including adverse events that resulted in hospitalization, were reported (Table 2).

A strength of the current analysis was the fact that it is the first meta-analysis to include studies of fibrotic-ILD patients as well as IPF patients. It provides a more comprehensive view of the safety profile of nintedanib in ILD patients. We only included high quality RCTs and compared with a placebo to avoid possible confounding factors. A limitation of this analysis is the fact that the included trials excluded patients with severely impaired pulmonary function,

certain comorbidities, or current medication. This may lead to the results having a different prevalence of adverse events after treatment with nintedanib compared with patients in the real world.

Conclusions

Compared to a placebo, nintedanib is associated with a higher risk of adverse events, especially diarrhea, nausea and weight loss, but it was also associated with a lower risk of cough and dyspnea in IPF and fibrotic-ILD patients. Nintedanib had similar risk of adverse events in fibrotic-ILD compared with in IPF patients, but higher prevalence of diarrhea, nausea or vomiting in fibrotic-ILD patients suggested careful management of these adverse events if use nintedanib in fibrotic-ILD patients.

Supporting information

S1 Checklist. PRISMA 2009 checklist. (DOC)

S1 Fig. Forest plots for association between the other adverse events and use of nintedanib. (TIFF)

S1 Table. Leave-one-out sensitivity analyses for most frequent adverse events. (DOCX)

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