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Original article

Exploratory phase 2 study of the novel oral multi-kinase inhibitor TAS-115 in patients with idiopathic pulmonary fibrosis

Yasuhiko Nishioka [a,*], Sakae Homma [b], Takashi Ogura [c], Seidai Sato [a], Naoki Arai [d], Keisuke Tomii [e], Koichiro Kamio [f], Susumu Sakamoto [b], Yasunari Miyazaki [g], Hiromi Tomioka [h], Shu Hisata [i], Tomohiro Handa [j], Arata Azuma [f]

[a] Department of Respiratory Medicine and Rheumatology, Graduate School of Biomedical Sciences, Tokushima University, Tokushima, Japan; 3-18-15, Kuramoto-cho, Tokushima, 770-8503, Japan
[b] Department of Respiratory Medicine, Toho University Omori Medical Center, Tokyo, Japan; 6-11-1 Omorinishi, Ota-ku, Tokyo, 143-8540, Japan
[c] Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan; 6-16-1 Tomiokahigashi, Kanazawa-ku, Yokohama, Kanagawa, 236-0051, Japan
[d] Department of Respiratory Medicine, National Hospital Organization, Ibaraki Higashi National Hospital, Ibaraki, Japan; 825 Terunuma, Tokaimura, Naka-gun, Ibaraki, 319-1113, Japan
[e] Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan; 2-1-1, Minatojimaminamimachi, Chuo-ku, Kobe-city, Hyogo, 650-0047, Japan
[f] Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School Tokyo, Japan; 1-1-5 Sendagi, Bunkyo-ku, Tokyo, 113-8603, Japan
[g] Department of Respiratory Medicine, Tokyo Medical and Dental University, Tokyo, Japan; 1-5-45 Yushima, Bunkyo-ku, Tokyo, 113-8510, Japan
[h] Department of Respiratory Medicine, Kobe City Medical Center West Hospital, Kobe, Japan; 2-4, Ichiban-cho, Nagata-ku, Kobe-city, Hyogo, 653-0013, Japan
[i] Division of Pulmonary Medicine, Department of Medicine, Jichi Medical University, Tochigi, Japan; 3311-1 Yakushiji, Shimotsuke-shi, Tochigi, 329-0498, Japan
[j] Department of Advanced Medicine for Respiratory Failure/Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan; 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan

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ABSTRACT

Background: TAS-115, a novel oral multi-kinase inhibitor, showed antifibrotic effects in *in vitro* and *in vivo* animal models of idiopathic pulmonary fibrosis (IPF).

Methods: In this exploratory phase 2 study, IPF patients with a percent predicted forced vital capacity (%FVC) decline ≥5% acquired within the previous 6 months were enrolled. Patients were divided into three pre-treatment cohorts, namely, treatment-naïve, pirfenidone, or nintedanib. TAS-115 was administered orally at 200 mg/day with a 5-day on and 2-day off regimen. After 13 weeks of treatment, patients entered a 13-week extension

* *Corresponding author*. Department of Respiratory Medicine and Rheumatology, Graduate School of Biomedical Sciences, Tokushima University, 3-18-15, Kuramoto-cho, Tokushima, 770-8503, Japan.
E-mail address: yasuhiko@tokushima-u.ac.jp (Y. Nishioka).

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treatment period where the efficacy was evaluated. The primary endpoint was the difference in slope of %FVC decline at Week 13 from baseline. Safety was also evaluated.

Results: Between June 2018 and July 2019, 46 patients were enrolled, and 30 (65.2%) patients completed the 13-week treatment. Of these, 22 (47.8%) proceeded to extension treatment. For the primary endpoint, TAS-115 treatment lowered the slope of the %FVC decline of 0.0750%/day (95% confidence interval: 0.0341–0.1158%/day) at Week 13. Efficacy was also demonstrated at Week 26. Treatment-related adverse events were reported in 40 (88.9%) patients, but most were manageable by dose reduction, dose interruption, or symptomatic treatment.

Conclusions: TAS-115 treatment was effective, assessed using intra-patient change in slope of %FVC decline as a surrogate endpoint in patients with IPF pre-treated with pirfenidone or nintedanib and treatment-naïve patients. TAS-115 showed acceptable tolerability and a manageable safety profile.

Trial registration: Japic-Clinical Trials Information, JapicCTI-183898 (first registered: March 15, 2018).

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common type of idiopathic interstitial pneumonia, showing chronic, progressive fibrogenesis in the lungs [1,2]. The incidence of IPF has been reported to be 2.8–18 per 100,000 worldwide [1–3]. Patients with IPF show gradual deterioration of respiratory function, leading to a poor prognosis and survival time of 33–51 months [1–3].

The cause of IPF is not clear, but persistent damage to alveolar epithelial cells, precipitated by a range of factors, contributes to the activation of profibrotic responses. These responses include enhanced production of platelet-derived growth factor (PDGF) and transforming growth factor-β by immune cells, such as macrophages or lymphocytes, injured alveolar epithelial cells, and fibrocytes [4,5]. Profibrotic responses activate lung fibroblast and myofibroblast differentiation, inducing the deposition of pathological matrixes in the lungs [5]. In Japan, pirfenidone and nintedanib are currently used for the treatment of IPF [6–8]. However, these antifibrotic drugs are not sufficiently effective; ≥40% of patients treated with pirfenidone or nintedanib had a ≥5% annual decline in forced vital capacity (FVC) [9–11]. Furthermore, treatment-related adverse events (TRAEs), including gastrointestinal intolerance, rash, and photosensitivity with pirfenidone and diarrhea and hepatic enzyme elevation with nintedanib, require dose reduction, drug suspension, or symptom management [12,13]. International guidelines on the treatment of IPF recommend the administration of pirfenidone and nintedanib; however, this recommendation is conditional due to less than moderate confidence in effect estimates [14]. In addition, no clinical studies of second line agents for use after pirfenidone and nintedanib have been evaluated, and no further drugs are available. Therefore, there is a clear need for treatment options for IPF following pirfenidone and nintedanib.

TAS-115 is an oral multi-kinase inhibitor that competes with adenosine triphosphate and exhibits an inhibitory effect on PDGF receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), colony stimulating factor-1 receptor (FMSR), and other receptors [15]. The potent inhibition of PDGFR and VEGFR blocks the proliferation and migration of fibroblasts, and FMSR inhibition suppresses macrophage activation that promotes fibrosis. Previous studies have shown that TAS-115 inhibition of PDGFR phosphorylation and profibrotic function of lung fibroblasts *in vitro* to a degree comparable or superior to nintedanib [15]. In a bleomycin-induced pulmonary fibrosis model in mice, TAS-115 significantly inhibited the development of pulmonary fibrosis and collagen deposition [15]. A phase 1 clinical trial of TAS-115 in patients with cancer reported that the most common TRAEs were laboratory abnormalities, gastrointestinal symptoms, general disorders and skin disorders [16], indicating a profile different from those of pirfenidone and nintedanib.

Based on these findings, we performed an exploratory phase 2 clinical trial of TAS-115 to evaluate its therapeutic effect and safety in patients with IPF [17].

2. Patients and methods

2.1. Study design and ethics

This open-label, non-randomized, multi-center, exploratory phase 2 study of TAS-115 was completed at ten sites in Japan from April 2018 to June 2020. The study protocol was based on a previously described method [17]. The study was conducted in accordance with ethical principles of or derived from the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol and informed consent form were approved by the institutional review board at each participating study site. All patients gave written informed consent before initiation of any study-specific procedures.

2.2. Patients

Eligibility was described in the previous report [17]. Briefly, we enrolled patients aged 40–80 years who were diagnosed with IPF within the preceding 5 years, based on the guidelines from the 2011 American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association. Other key inclusion criteria were IPF patients whose %FVC and diffusing capacity of the lungs for carbon monoxide (DLco) were ≥50% and ≥30% predicted, respectively. Patients met one or more of the following pre-treatment conditions: (1) monotherapy with either pirfenidone or nintedanib had been continued for ≥3 months as IPF treatment, and %FVC had declined ≥5% within the previous 6 months; (2) monotherapy with pirfenidone or nintedanib was discontinued due to safety concerns, and a %FVC decline was identified during the previous 3 months; or (3) the patient had not been treated with pirfenidone or nintedanib, did not request treatment with these drugs, and a %FVC decline ≥5% during the previous 6 months.

2.3. Procedures

The study consisted of three cohorts: patients previously treated with pirfenidone (Cohort P) or nintedanib (Cohort N), and pirfenidone–nintedanib treatment-naïve patients (Cohort U; Supplementary Fig. S1). A single oral dose of 200 mg TAS-115 was administered daily. The dosing regimen was 5-day on and 2-day off per week, repeated for 13 weeks. After the 13-week treatment period, patients entered a 13-week extension treatment period if the slope of %FVC decline at Week 13 was lower than that at baseline. The dosage of TAS-115 was reduced in the event of severe TRAEs that did not remit or resolve after symptomatic treatment.

The primary endpoint was the difference in the rate of change of %FVC (slope of %FVC decline) at Week 13 compared with the baseline (Supplementary Fig. S2). The treatment was considered effective when the slope of the decline in %FVC during the evaluation period was lower than that at baseline. Key secondary endpoints were: (1) difference in slope of %FVC decline at Week 6 and 26 compared with the baseline; (2) proportion of %FVC responders at Week 6, 13, and 26. Responders were defined as patients with an absolute reduction of %FVC ≤5% and ≤10%; and (3) change in %FVC, FVC, VC, and %DLco from baseline levels at Week 6, 13, and 26. As an exploratory endpoint, lung fibrosis scores were assessed based on high-resolution computed tomography (HRCT) using a data-driven texture analysis (DTA) with independent central radiological review. The extent of fibrotic abnormality was calculated as the percentage of total lung volume classified as fibrotic at baseline, Week 13, and Week 26 by DTA.

2.4. Statistical analysis

Analyses of the primary and secondary endpoints were performed on the per protocol set (PPS). Summary statistics of variables relative to baseline were calculated at Week 6, 13, and 26. The change in %FVC, FVC, VC, and %DLco were calculated using a simple regression model. Correlation coefficients between %FVC and DTA fibrosis score at baseline, Week 13, and Week 26 were analyzed by Pearson's method. Correlations were analyzed between the change from baseline in %FVC at Week 13 or Week 26, and the DTA fibrosis score. Safety was assessed in all treated patients who received at least one dose of TAS-115. All analyses were performed using SAS ver. 9.4 and SAS/STAT 15.1 for Windows (SAS Institute, Cary, NC, USA).

3. Results

Among the 46 enrolled patients, 30 (65.2%) patients completed the 13-week treatment with TAS-115, and 22 (47.8%) patients entered the extension treatment period. A total of 45 (97.8%) patients received TAS-115 and 31 (67.4%) patients were included in the PPS (Fig. 1). The demographics and other baseline characteristics were similar among the cohorts in the PPS population (Table 1). The reasons for discontinuation of prior pharmacotherapy were disease progression and adverse events (AEs). The mean adherence in the PPS was 90.2% at Week 13 and 89.0% at Week 26. The median relative dose intensities at Week 13 and 26 were 87.7% and 68.9%, respectively.

For the primary endpoint, the mean (standard deviation; SD) slope of %FVC decline at baseline and Week 13 were −0.0798 (0.0646) and −0.0049 (0.0665), respectively (Table 2). The mean (SD) difference in the slope of %FVC decline from baseline at Week 13 was 0.0750 (0.1113)%/day (95% CI: 0.0341, 0.1158%/day). The difference in the slope of %FVC decline from baseline at Week 13 was positive compared to that at baseline. The individual changes in the estimated %FVC during the 13-week treatment with TAS-115 are shown in Fig. 2(A). In patients who had three or more %FVC data at baseline, the mean (SD) estimated slope of %FVC decline at baseline was calculated using a simple regression model, and the difference between the estimated slope at baseline and at Week 13 was 0.047 (0.081)%/day. With respect to the secondary endpoints, an effect was observed in seven of eight patients at Week 13 and five of six patients at Week 26, who had an early dose reduction within 6 weeks (Fig. 2(B) and Supplementary Fig. S3). Changes in %FVC, FVC, VC, and %DLco from baseline at Week 6, 13, and 26 are shown in Table 3. The proportion of responders with %FVC ≤5% was 93.5% (29/31 patients) at Week 6, 80.6% (25/31 patients) at Week 13, and 80.0% (16/20 patients) at Week 26. The mean (SD) absolute change in FVC from baseline at Week 6, 13, and 26 were 37.3 (192.5), −8.1 (219.0), and −25.6 (119.7) mL, respectively.

Significant correlations between the %FVC and the DTA fibrosis score were observed at baseline, Week 13, and Week 26 (Pearson correlation: −0.720 at baseline [$p < 0.001$], −0.680 at Week 13 [$p < 0.001$], −0.813 at Week 26 [$p < 0.001$]). No significant correlation between the changes from baseline in %FVC and the DTA fibrosis score was observed (Supplementary Fig. S4).

Safety analyses were assessed in all treated patients ($n = 45$). The overall incidence of treatment-emergent AEs (TEAEs) was 97.8% (44/45 patients) and TRAEs was 88.9% (40/45 patients) (Table 4). Severe TEAEs and TRAEs were reported in 42.2% (19/45 patients) and 26.7% (12/45 patients), respectively. Most TEAEs and TRAEs occurred within the first treatment

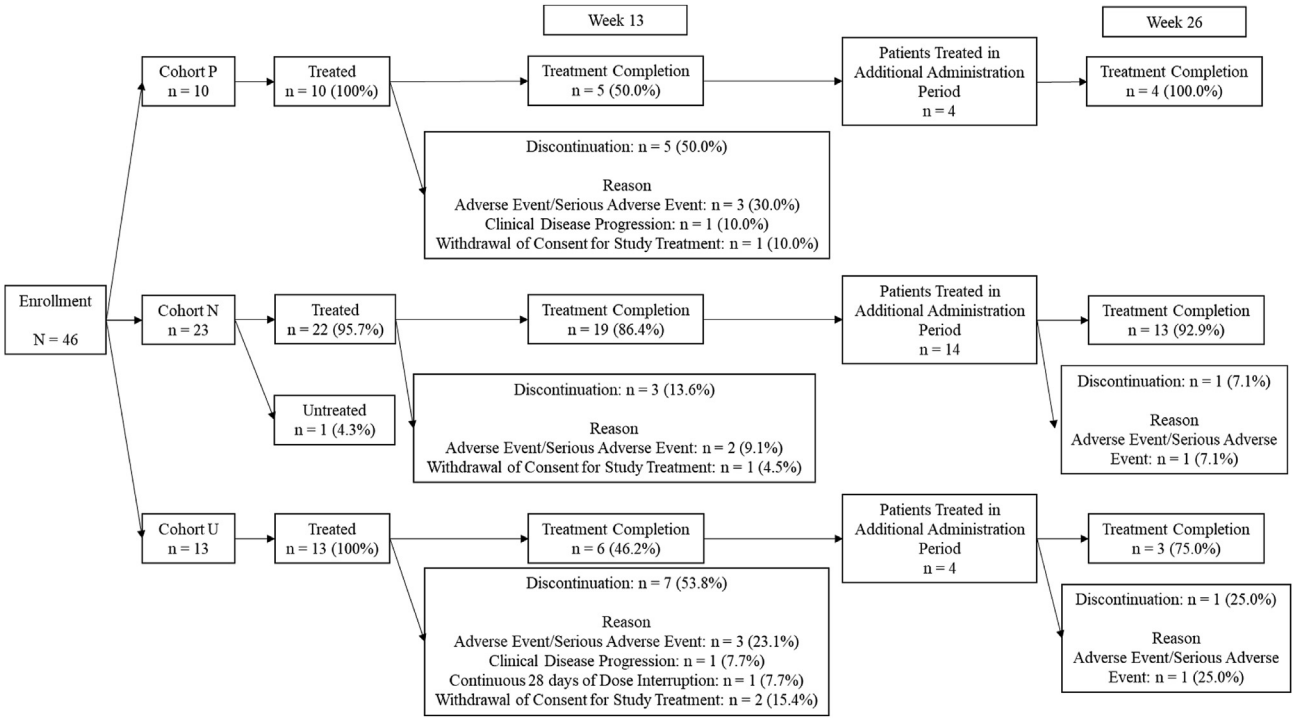

Fig. 1 – Patient disposition. Cohort P = patients previously treated with pirfenidone, Cohort N = patients previously treated with nintedanib, and Cohort U = treatment-naïve patients.

period (Supplementary Tables S1 and S2). TEAEs and TRAEs leading to discontinuation of TAS-115 treatment were reported in 22.2% (10/45 patients) and 17.8% (8/45 patients), respectively. During the study, a total of 3/45 patients (6.7%) died due to TEAEs; no deaths resulted from TRAEs. The most frequently reported TEAEs (≥20% of patients) were rash and eyelid oedema, which were also the most frequently reported TRAEs (≥20% of patients) (Table 4).

Table 1 – Demographic and other baseline characteristics in the per protocol set.

	Cohort P (N = 5)	Cohort N (N = 19)	Cohort U (N = 7)	Total (N = 31)
Gender				
Male	4 (80.0)	15 (78.9)	4 (57.1)	23 (74.2)
Female	1 (20.0)	4 (21.1)	3 (42.9)	8 (25.8)
Age (years)	71.0 (2.7)	68.3 (5.5)	68.3 (9.7)	68.7 (6.3)
BMI (kg/m^2)	25.2 (4.0)	22.5 (2.8)	26.1 (4.0)	23.7 (3.6)
Smoking history				
Never smoked	1 (20.0)	5 (26.3)	2 (28.6)	8 (25.8)
Former smoker	4 (80.0)	14 (73.7)	5 (71.4)	23 (74.2)
Duration of disease (days)[a]	1288.0 (491.5)	887.2 (541.4)	370.3 (352.4)	835.1 (565.0)
Duration of antifibrotic therapy (days)	N = 5	N = 19	N = 0	N = 24
	591.2 (556.9)	640.7 (434.9)	- (–)	630.4 (449.8)
FVC (mL)	2104.0 (494.7)	2238.9 (574.6)	2667.1 (1339.5)	2313.9 (793.5)
%FVC (%)	63.9 (10.1)	66.5 (15.1)	81.3 (21.7)	69.4 (17.0)
VC (mL)	2250.0 (539.9)	2242.6 (563.0)	2758.6 (1425.7)	2360.3 (826.7)
DLco (mL/min/mmHg)	8.576 (2.519)	8.938 (2.663)	11.499 (5.365)	9.458 (3.483)
%DLco (%)	51.3 (12.8)	56.5 (20.4)	64.4 (22.0)	57.4 (19.6)

Analysis set: Per protocol set.
Data are presented as n (%) or mean (SD).
BMI = body mass index, DLco = diffusing capacity of the lungs for carbon monoxide, FVC = forced vital capacity, and SD = standard deviation.
Cohort P = patients previously treated with pirfenidone, Cohort N = patients previously treated with nintedanib, and Cohort U = treatment-naïve patients.
[a] Date of enrolment - date of initial diagnosis +1.

Table 2 – Difference in slope of %FVC decline from baseline at Week 13.

		Cohort P (N = 5)	Cohort N (N = 19)	Cohort U (N = 7)	Total (N = 31)
Slope of %FVC					
Baseline	Mean (SD)	−0.0863 (0.0647)	−0.0884 (0.0740)	−0.0520 (0.0220)	−0.0798 (0.0646)
	Median	−0.059	−0.068	−0.048	−0.059
	min, max	[-0.195, −0.034]	[-0.325, −0.030]	[-0.092, −0.029]	[-0.325, −0.029]
Week 13	Mean (SD)	0.0201 (0.0395)	−0.0077 (0.0726)	−0.0150 (0.0678)	−0.0049 (0.0665)
	Median	0.025	0.000	−0.020	0.000
	min, max	[-0.041, 0.059]	[-0.120, 0.199]	[-0.134, 0.073]	[-0.134, 0.199]
Difference in slope of %FVC decline from baseline					
Week 13	Mean (SD)	0.1065 (0.0957)	0.0806 (0.1260)	0.0371 (0.0753)	0.0750 (0.1113)
	95% CI	[-0.0123, 0.2253]	[0.0199, 0.1414]	[-0.0325, 0.1067]	[0.0341, 0.1158]
	Median	0.0843	0.0517	0.038	0.0569
	min, max	[-0.007, 0.244]	[-0.045, 0.524]	[-0.086, 0.140]	[-0.086, 0.524]

Analysis set: Per protocol set.
CI = confidence interval, FVC = forced vital capacity, max = maximum, min = minimum, and SD = standard deviation.
Cohort P = patients previously treated with pirfenidone, Cohort N = patients previously treated with nintedanib, and Cohort U = treatment-naïve patients.

Serious TEAEs were reported in 26.7% (12/45 patients), including acute exacerbation of IPF in 6.7% (3/45 patients), and bacterial pneumonia in 4.4% (2/45 patients). Serious TRAEs were reported in 8.9% (4/45 patients), including pyrexia, acute exacerbation of IPF, interstitial lung disease (which did not meet the diagnostic criteria for acute exacerbation of IPF [18]), and rash in 2.2% (1/45 patient) each. There were no clinically significant abnormalities on 12-lead electrocardiogram (ECG) or in vital signs.

4. Discussion

This exploratory phase 2 study demonstrated that TAS-115 delayed IPF progression in patients with %FVC decline who had not responded adequately to pirfenidone or nintedanib treatment, as well as treatment-naïve patients. The safety and tolerability were acceptable, and most AEs of TAS-115 could be managed by dose reduction, drug interruption, or symptomatic treatment.

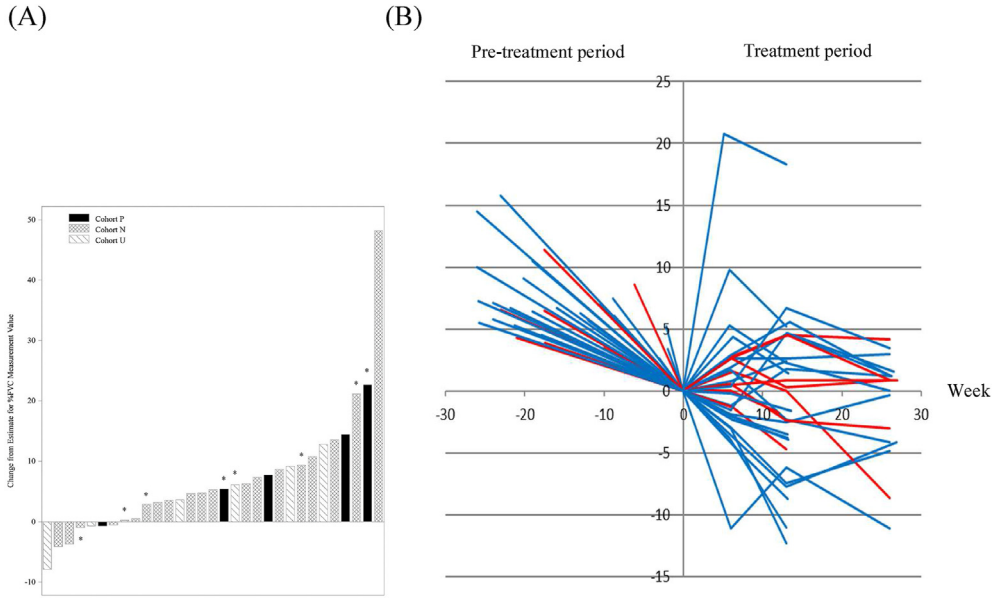

Fig. 2 – Individual change in (A) the estimated %FVC from baseline at Week 13 and (B) %FVC pre-treatment and after treatment with TAS-115. Analysis set: Per protocol set; ■ : Cohort P (patients previously treated with pirfenidone); ▨ : Cohort N (patients previously treated with nintedanib); and ▨ : Cohort U (treatment-naïve patients). FVC = forced vital capacity. * Patients experienced early dose reduction within 6 weeks.
The patients who experienced early dose reduction with TAS-115 in the first six weeks are indicated by the red line.

Table 3 – Summary of the secondary endpoints.

		Cohort P (N = 5)	Cohort N (N = 19)	Cohort U (N = 7)	Total (N = 31)
Difference in slope of %FVC decline (%/day) from baseline					
Week 6	n	5	18	7	30
	Mean	0.1303 (0.1063)	0.1028 (0.2151)	0.0714 (0.1003)	0.1001 (0.1764)
		[-0.0017, 0.2622]	[-0.0041, 0.2098]	[-0.0213, 0.1641]	[0.0342, 0.1659]
Week 13	n	5	19	7	31
	Mean	0.1065 (0.0957)	0.0806 (0.1260)	0.0371 (0.0753)	0.0750 (0.1113)
		[-0.0123, 0.2253]	[0.0199, 0.1414]	[-0.0325, 0.1067]	[0.0341, 0.1158]
Week 26	n	4	12	2	18
	Mean	0.1034 (0.0678)	0.0730 (0.0619)	0.0494 (0.0520)	0.0772 (0.0610)
		[-0.0045, 0.2113]	[0.0337, 0.1124]	[-0.4177, 0.5165]	[0.0468, 0.1075]
Proportion of %FVC responders (%)					
Week 6	n	5	19	7	31
	≤5% of %FVC response rate	5 (100.0)	17 (89.5)	7 (100.0)	29 (93.5)
		[47.8, 100.0]	[66.9, 98.7]	[59.0, 100.0]	[78.6, 99.2]
	≤10% of %FVC response rate	5 (100.0)	17 (89.5)	7 (100.0)	29 (93.5)
		[47.8, 100.0]	[66.9, 98.7]	[59.0, 100.0]	[78.6, 99.2]
Week 13	n	5	19	7	31
	≤5% of %FVC response rate	5 (100.0)	14 (73.7)	6 (85.7)	25 (80.6)
		[47.8, 100.0]	[48.8, 90.9]	[42.1, 99.6]	[62.5, 92.5]
	≤10% of %FVC response rate	5 (100.0)	18 (94.7)	6 (85.7)	29 (93.5)
		[47.8, 100.0]	[74.0, 99.9]	[42.1, 99.6]	[78.6, 99.2]
Week 26	n	4	13	3	20
	≤5% of %FVC response rate	4 (100.0)	10 (76.9)	2 (66.7)	16 (80.0)
		[39.8, 100.0]	[46.2, 95.0]	[9.4, 99.2]	[56.3, 94.3]
	≤10% of %FVC response rate	4 (100.0)	11 (84.6)	2 (66.7)	17 (85.0)
		[39.8, 100.0]	[54.6, 98.1]	[9.4, 99.2]	[62.1, 96.8]
%FVC (%)					
Week 6	n	5	18	7	30
	Mean	65.8 (9.9)	67.5 (16.2)	82.1 (24.5)	70.6 (18.3)
		[53.5, 78.1]	[59.5, 75.6]	[59.4, 104.7]	[63.8, 77.4]
	Mean change from baseline	1.9 (2.8)	0.5 (6.2)	0.8 (4.2)	0.8 (5.3)
		[-1.5, 5.3]	[-2.6, 3.6]	[-3.1, 4.7]	[-1.2, 2.8]
Week 13	n	5	19	7	31
	Mean	65.8 (8.2)	65.8 (16.8)	79.9 (25.2)	69.0 (18.5)
		[55.6, 76.0]	[57.7, 73.9]	[56.6, 103.2]	[62.2, 75.8]
	Mean change from baseline	1.9 (3.7)	−0.7 (6.7)	−1.4 (6.2)	−0.5 (6.1)
		[-2.7, 6.5]	[-3.9, 2.5]	[-7.1, 4.4]	[-2.7, 1.8]
Week 26	n	4	12	2	18
	Mean	63.6 (11.1)	68.4 (18.4)	66.5 (12.2)	67.1 (15.9)
		[45.9, 81.3]	[56.7, 80.1]	[-42.8, 175.8]	[59.2, 75.1]
	Mean change from baseline	0.8 (0.5)	−1.7 (4.8)	0.3 (4.6)	−1.0 (4.2)
		[-0.1, 1.6]	[-4.8, 1.3]	[-41.1, 41.6]	[-3.0, 1.1]
FVC (mL)					
Week 6	n	5	18	7	30
	Mean	2164.0 (472.3)	2283.9 (674.0)	2707.1 (1429.4)	2362.7 (871.2)
		[1577.5, 2750.5]	[1948.7, 2619.1]	[1385.2, 4029.1]	[2037.3, 2688.0]
	Mean change from baseline	60.0 (98.7)	30.0 (228.8)	40.0 (153.7)	37.3 (192.5)
		[-62.6, 182.6]	[-83.8, 143.8]	[-102.2, 182.2]	[-34.5, 109.2]
Week 13	n	5	19	7	31
	Mean	2160.0 (403.9)	2220.5 (655.4)	2641.4 (1421.5)	2305.8 (847.4)
		[1658.5, 2661.5]	[1904.6, 2536.4]	[1326.7, 3956.1]	[1995.0, 2616.6]
	Mean change from baseline	56.0 (137.2)	−18.4 (250.8)	−25.7 (185.1)	−8.1 (219.0)
		[-114.4, 226.4]	[-139.3, 102.5]	[-196.9, 145.5]	[-88.4, 72.3]
Week 26	n	4	12	2	18
	Mean	1947.5 (322.6)	2199.2 (669.1)	2055.0 (445.5)	2127.2 (575.8)
		[1434.1, 2460.9]	[1774.1, 2624.3]	[-1947.5, 6057.5]	[1840.9, 2413.6]
	Mean change from baseline	22.5 (17.1)	−47.5 (136.5)	10.0 (141.4)	−25.6 (119.7)
		[-4.7, 49.7]	[-134.2, 39.2]	[-1260.6, 1280.6]	[-85.1, 34.0]

(continued on next page)

Table 3 – (*continued*)

		Cohort P (N = 5)	Cohort N (N = 19)	Cohort U (N = 7)	Total (N = 31)
VC (mL)					
Week 6	n	5	18	7	30
	Mean	2210.0 (472.6) [1623.2, 2796.8]	2268.3 (634.5) [1952.8, 2583.9]	2722.9 (1395.6) [1432.1, 4013.6]	2364.7 (843.0) [2049.9, 2679.4]
	Mean change from baseline	−40.0 (70.0) [-126.9, 46.9]	10.6 (142.3) [-60.2, 81.3]	−35.7 (79.8) [-109.5, 38.1]	−8.7 (120.2) [-53.5, 36.2]
Week 13	n	5	19	7	31
	Mean	2238.0 (524.3) [1587.0, 2889.0]	2226.3 (649.2) [1913.4, 2539.2]	2645.7 (1411.0) [1340.8, 3950.7]	2322.9 (848.0) [2011.8, 2634.0]
	Mean change from baseline	−12.0 (55.4) [-80.8, 56.8]	−16.3 (245.3) [-134.5, 101.9]	−112.9 (145.6) [-247.5, 21.8]	−37.4 (206.1) [-113.0, 38.2]
Week 26	n	4	12	2	18
	Mean	2005.0 (375.7) [1407.1, 2602.9]	2163.3 (634.2) [1760.4, 2566.3]	2085.0 (431.3) [-1790.4, 5960.4]	2119.4 (548.4) [1846.7, 2392.1]
	Mean change from baseline	−100.0 (129.4) [-305.8, 105.8]	−83.3 (114.2) [-155.9, −10.8]	−25.0 (120.2) [-1105.0, 1055.0]	−80.6 (112.7) [-136.6, −24.5]
%DLco					
Week 6	n	5	18	7	30
	Mean	49.4 (9.7)	50.2 (17.4)	66.9 (18.2)	54.0 (17.7)
	Mean change from baseline	−1.8 (5.5)	−6.7 (9.3)	2.5 (6.4)	−3.8 (8.9)
Week 13	n	5	19	7	31
	Mean	49.1 (9.2)	49.4 (17.1)	64.9 (18.7)	52.8 (17.3)
	Mean change from baseline	−2.1 (6.2)	−7.1 (11.1)	0.5 (9.4)	−4.6 (10.4)
Week 26	n	4	11	2	17
	Mean	45.9 (7.1)	58.9 (22.6)	67.9 (39.9)	56.9 (21.8)
	Mean change from baseline	−3.5 (11.7)	−7.3 (8.9)	2.1 (5.2)	−5.3 (9.4)

Analysis set: Per protocol set.
Data presented as mean (SD) [95% CI] or n (%) [95% CI].
CI = confidence interval, DLco = diffusing capacity of the lungs for carbon monoxide, FVC = forced vital capacity, SD = standard deviation, and VC = vital capacity.
Cohort P = patients previously treated with pirfenidone, Cohort N = patients previously treated with nintedanib, and Cohort U = treatment-naïve patients.

For the primary endpoint, TAS-115 significantly slowed the slope of %FVC decline at Week 13 compared to that at baseline. The slope of %FVC decline was improved from −0.0798%/day at baseline to −0.0049%/day at Week 13; the mean (SD) change in %FVC from the estimated value was 4.11 (6.76)% at Week 6, 6.91 (10.27)% at Week 13, and 14.21 (11.19)% at Week 26. Treatment efficacy was observed from Week 6 and lasted until Week 26. It is noteworthy that efficacy was seen regardless of pre-treatment cohort (nintedanib, pirfenidone, or treatment-naïve) before starting TAS-115. Even in patients whose dose was reduced during the first six weeks of treatment, TAS-115 slowed the slope of %FVC decline, suggesting potential efficacy of TAS-115 at a dose of 100 mg.

In assessment of the primary endpoint, baseline slope of %FVC was calculated using two %FVC data points during the six months prior to treatment with TAS-115. As there were patients who had three or more %FVC data points prior to administration, we estimated the baseline slope using a simple regression model to obtain a similar result.

It is well recognized that slope of the decline in glomerular filtration rate is a strong surrogate endpoint and can be used as an endpoint for clinical trials of kidney disease progression in both early and late chronic kidney disease, instead of conventional composite endpoints [19,20]. Similarly, our study showed that the slope of %FVC decline can be used as an adequate surrogate endpoint in clinical trials of IPF within a short time. Meanwhile, it was reported that change in FVC over time was associated with IPF prognosis, and FVC and %FVC have been accepted as adequate surrogate endpoints in establishing a primary endpoint, even in phase 3 studies [21–23]. In a phase 3 study of nintedanib (INPULSIS study) [8], changes in FVC from baseline at Week 12 and 24 were −25.4 mL and −52.8 mL, respectively, among patients who took nintedanib [24]. Similarly, in our study, changes in FVC from baseline at Week 6, 13, and 26 were 37.3 mL, −8.1 mL, and −25.6 mL, respectively. These results suggested that TAS-115 is as effective as the approved drug nintedanib. There were no notable differences in patient characteristics between the two studies except body weight and BMI. The mean %FVC in the nintedanib and placebo groups was 79.8% and 79.3%, respectively, in the INPULSIS study, while it was only 69.4% in our study. It is noteworthy that most patients in our study were non-responders to nintedanib and pirfenidone; enrolled patients were at a more advanced stage of the disease. The favorable clinical outcomes we have described might be attributed to the potent inhibitory activity against PDGFR *in vitro* and better pharmacokinetic profiles than nintedanib [15,25]. No significant difference in the slope of DLco between baseline and Week 13 was observed in this study or previous studies with pirfenidone and nintedanib [26,27], suggesting DLco is not useful as an endpoint in clinical studies of IPF.

Table 4 – Most commonly reported treatment-emergent and treatment-related adverse events in all treated patients.

	Treatment-emergent adverse events (N = 45)		Treatment-related adverse events (N = 45)	
	Total	Severe	Total	Severe
Any Event	44 (97.8)	19 (42.2)	40 (88.9)	12 (26.7)
Eye disorders	19 (42.2)	0 (0.0)	19 (42.2)	0 (0.0)
Eyelid oedema	19 (42.2)	0 (0.0)	19 (42.2)	0 (0.0)
Gastrointestinal disorders	19 (42.2)	1 (2.2)	10 (22.2)	0 (0.0)
Constipation	5 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	24 (53.3)	1 (2.2)	22 (48.9)	0 (0.0)
Face oedema	6 (13.3)	0 (0.0)	6 (13.3)	0 (0.0)
Malaise	7 (15.6)	0 (0.0)	6 (13.3)	0 (0.0)
Oedema	5 (11.1)	0 (0.0)	5 (11.1)	0 (0.0)
Oedema peripheral	6 (13.3)	0 (0.0)	6 (13.3)	0 (0.0)
Pyrexia	6 (13.3)	0 (0.0)	6 (13.3)	0 (0.0)
Hepatobiliary disorders	8 (17.8)	0 (0.0)	8 (17.8)	0 (0.0)
Liver disorder	5 (11.1)	0 (0.0)	5 (11.1)	0 (0.0)
Infections and infestations	21 (46.7)	2 (4.4)	0 (0.0)	0 (0.0)
Bronchitis	5 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngitis	7 (15.6)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	18 (40.0)	4 (8.9)	15 (33.3)	3 (6.7)
Platelet count decreased	5 (11.1)	0 (0.0)	5 (11.1)	0 (0.0)
Metabolism and nutrition disorders	10 (22.2)	3 (6.7)	7 (15.6)	3 (6.7)
Hypophosphatemia	3 (6.7)	3 (6.7)	3 (6.7)	3 (6.7)
Decreased appetite	6 (13.3)	0 (0.0)	4 (8.9)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	9 (20.0)	4 (8.9)	2 (4.4)	2 (4.4)
Idiopathic pulmonary fibrosis	3 (6.7)	3 (6.7)	1 (2.2)	1 (2.2)
Skin and subcutaneous tissue disorders	29 (64.4)	5 (11.1)	28 (62.2)	5 (11.1)
Rash	22 (48.9)	1 (2.2)	21 (46.7)	1 (2.2)

MedDRA (ver. 22.1).
Data are presented as n (%).
Treatment-emergent and treatment-related adverse events were listed if reported in ≥10% of patients.
Severe treatment-emergent and treatment-related adverse events were listed if reported in ≥5% of patients.

Associations between the quantitative fibrosis score and the change in pulmonary function have been previously reported for nintedanib [28] and FG-3019 [29]. In this study, a significant correlation was found between the DTA fibrosis score and the %FVC at baseline, Week 13, and Week 26. However, there was no significant correlation between the DTA fibrosis score and the difference in %FVC from baseline at Week 13 and Week 26. Further studies with a large number of patients on long-term treatment may be required to confirm this association. The dose of TAS-115 in this study was 200 mg/day, which was the dose recommended for long-term continuous treatment without safety concerns based on a phase 1 study in patients with solid tumors [16]. This study was not intended to explore dose-response, rather one of our major objectives was to assess adherence to TAS-115 use in IPF patients over an extended period. However, efficacy was observed in the sub-group of patients whose dose was reduced to 100 mg/day. Although the number of patients was limited, the results suggest that TAS-115 has potential activity at a lower dose level.

Regarding safety, one of the most common AEs was a rash, which occurred in 50% of the patients, and was usually either mild or moderate in severity. AEs which led to dose reduction and interruption were mainly due to rashes. In three patients, the dose was reduced due to rashes, which were further managed using antihistamines, topical steroids, dose reduction, or drug interruption. The next most frequent AE was eyelid oedema; in most cases this was tolerable and did not require treatment or dose modification. Onset of reported AEs was most often within the first thirteen weeks of treatment, suggesting there were no safety concerns related to extension of the administration period. Four serious TRAEs were reported, but all recovered or improved during the study. In the combined data of the TOMORROW and INPULSIS studies, the most frequently reported AE in patients treated with nintedanib was diarrhea, which was reported in 61.5% of patients [30]. Other disorders such as nausea (24.3%), nasopharyngitis (12.9%), cough (12.9%), vomiting (11.8%), and hepatic enzyme elevations were common AEs with nintedanib [13,30]. In previous studies with pirfenidone, rashes (25.0%) and gastrointestinal events including nausea (37.6%), diarrhea (28.1%), dyspepsia (18.4%), and vomiting (15.9%) were common AEs [31]. Elevated liver enzymes and photosensitivity were also previously reported as AEs of pirfenidone. In contrast, the rate of diarrhea in this study was 6.7%, and other gastrointestinal disorders were rare, with no established causal relationship with TAS-115. These data suggest that the safety profile of TAS-115 is different from that of nintedanib, despite both being multi-kinase inhibitors. TAS-115 is a potential alternative to these drugs for treatment of patients with IPF who cannot tolerate nintedanib or pirfenidone.

This study has several limitations. First, the design of the study was open-label with no control group, a relatively short duration, and small number of patients. This limits the

conclusions able to be drawn. Second, only a dose of 200 mg/day was assessed. Although a dosage reduction to 100 mg/day was effective in patients whose dose was reduced due to AEs, no information was provided about the optimal dose. In order to evaluate the dose-response of TAS-115, a randomized, active-controlled, double-blind phase 2b study is planned, enrolling patients with chronic fibrosing interstitial lung diseases with a progressive phenotype who have been treated with pirfenidone or nintedanib.

5. Conclusions

This study demonstrated that TAS-115 was effective in delaying progression of IPF in patients pre-treated with pirfenidone or nintedanib, or in treatment-naïve patients, assessed using the intra-patient change in the slope of %FVC decline as a surrogate endpoint. The absolute change in FVC from baseline to Week 13 suggested that the efficacy of TAS-115 was similar to that of the approved drugs for IPF, considering that a majority of patients in this study had been treated with nintedanib or pirfenidone. The tolerability of TAS-115 was acceptable and the safety profile was manageable.

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Conflict of Interest

AA reports a research grant and honoraria from Boehringer Ingelheim, honoraria from Toray, Kyorin Pharma, and grant from Taiho during the conduct of the study. S Homma reports a grant from Taiho during the conduct of the study. TO reports honoraria from Taiho, Nippon Boehringer Ingelheim, Shionogi, Gilead Sciences, Fujifilm, Astellas, Chugai, Meiji Seika Pharma, and Toray. YN reports a research grant and honoraria from Nippon Boehringer Ingelheim, grant from Shionogi, and grants from Taiho during the conduct of the study. KT reports honoraria from Nippon Boehringer Ingelheim, Shionogi, and Taiho. S Hisata reports a honoraria for lectures from Boehringer Ingelheim. YM, NA, S Sato, S Sakamoto, TH, HT, and KK have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resinv.2023.04.008.

REFERENCES

[1] Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. Lancet 2017;389:1941–52.
[2] Glass DS, Grossfeld D, Renna HA, Agarwala P, Spiegler P, Kasselman LJ, et al. Idiopathic pulmonary fibrosis: molecular mechanisms and potential treatment approaches. Respir Investig 2020;58:320–35.
[3] Natsuizaka M, Chiba H, Kuronuma K, Otsuka M, Kudo K, Mori M, et al. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. Am J Respir Crit Care Med 2014;190:773–9.
[4] Yanagihara T, Sato S, Upagupta C, Kolb M. What have we learned from basic science studies on idiopathic pulmonary fibrosis? Eur Respir Rev 2019;28:190029.
[5] Wolters PJ, Blackwell TS, Eickelberg O, Loyd JE, Kaminski N, Jenkins G, et al. Time for a change: is idiopathic pulmonary fibrosis still idiopathic and only fibrotic? Lancet Respir Med 2018;6:154–60.
[6] Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010;35:821–9.
[7] King Jr TE, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2083–92.
[8] Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071–82.
[9] Tzouvelekis A, Karampitsakos T, Ntolios P, Tzilas V, Bouros E, Markozannes E, et al. Longitudinal "real-world" outcomes of pirfenidone in idiopathic pulmonary fibrosis in Greece. Front Med 2017;4:213.
[10] Flaherty KR, Kolb M, Vancheri C, Tang W, Conoscenti CS, Richeldi L. Stability or improvement in forced vital capacity with nintedanib in patients with idiopathic pulmonary fibrosis. Eur Respir J 2018;52:1702593.
[11] Kropski JA. Biomarkers and early treatment of idiopathic pulmonary fibrosis. Lancet Respir Med 2019;7:725–7.
[12] Cottin V, Maher T. Long-term clinical and real-world experience with pirfenidone in the treatment of idiopathic pulmonary fibrosis. Eur Respir Rev 2015;24:58–64.
[13] Corte T, Bonella F, Crestani B, Demedts MG, Richeldi L, Coeck C, et al. Safety, tolerability and appropriate use of nintedanib in idiopathic pulmonary fibrosis. Respir Res 2015;16:116.
[14] Raghu G, Rochwerg B, Zhang Y, Garcia CAC, Azuma A, Behr J, et al. An official ATS/ERS/JRS/ALAT clinical Practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical Practice guideline. Am J Respir Crit Care Med 2015;192:e3–19.
[15] Koyama K, Goto H, Morizumi S, Kagawa K, Nishimura H, Sato S, et al. The tyrosine kinase inhibitor TAS-115 attenuates bleomycin-induced lung fibrosis in mice. Am J Respir Cell Mol Biol 2019;60:478–87.
[16] Doi T, Matsubara N, Kawai A, Naka N, Takahashi S, Uemura H, et al. Phase I study of TAS-115, a novel oral multikinase inhibitor, in patients with advanced solid tumors. Invest N Drugs 2020;38:1175–85.

[17] Nishioka Y, Homma S, Okubo T, Azuma A. Design of phase 2 study of TAS-115, a novel oral multi-kinase inhibitor, in patients with idiopathic pulmonary fibrosis. Contemp Clin Trials Commun 2021;23:100832.
[18] Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. Am J Respir Crit Care Med 2016;194:265–75.
[19] Inker LA, Heerspink HJL, Tighiouart H, Levey AS, Coresh J, Gansevoort RT, et al. GFR Slope as a surrogate end point for kidney disease progression in clinical trials: a meta-analysis of treatment effects of randomized controlled trials. J Am Soc Nephrol 2019;30:1735–45.
[20] Grams ME, Sang Y, Ballew SH, Matsushita K, Astor BC, Carrero JJ, et al. Evaluating glomerular filtration rate slope as a surrogate end point for ESKD in clinical trials: an individual participant meta-analysis of observational data. J Am Soc Nephrol 2019;30:1746–55.
[21] Latsi PI, du Bois RM, Nicholson AG, Colby TV, Bisirtzoglou D, Nikolakopoulou A, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. Am J Respir Crit Care Med 2003;168:531–7.
[22] Collard HR, King Jr TE, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003;168:538–42.
[23] Flaherty KR, Mumford JA, Murray S, Kazerooni EA, Gross BH, Colby TV, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003;168:543–8.
[24] Richeldi L, Kolb M, Jouneau S, Wuyts WA, Schinzel B, Stowasser S, et al. Efficacy and safety of nintedanib in patients with advanced idiopathic pulmonary fibrosis. BMC Pulm Med 2020;20:3.
[25] Yamada S, Imura Y, Nakai T, Nakai S, Yasuda N, Kaneko K, et al. Therapeutic potential of TAS-115 via c-MET and PDGFRα signal inhibition for synovial sarcoma. BMC Cancer 2017;17:334.
[26] Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Respir Med 2020;8:147–57.
[27] Brown KK, Flaherty KR, Cottin V, Raghu G, Inoue Y, Azuma A, et al. Lung function outcomes in the INPULSIS® trials of nintedanib in idiopathic pulmonary fibrosis. Respir Med 2019;146:42–8.
[28] Lancaster L, Goldin J, Trampisch M, Kim GH, Ilowite J, Homik L, et al. Effects of nintedanib on quantitative lung fibrosis score in idiopathic pulmonary fibrosis. Open Respir Med J 2020;14:22–31.
[29] Raghu G, Scholand MB, de Andrade J, Lancaster L, Mageto Y, Goldin J, et al. FG-3019 anti-connective tissue growth factor monoclonal antibody: results of an open-label clinical trial in idiopathic pulmonary fibrosis. Eur Respir J 2016;47:1481–91.
[30] Richeldi L, Cottin V, du Bois RM, Selman M, Kimura T, Bailes Z, et al. Nintedanib in patients with idiopathic pulmonary fibrosis: combined evidence from the TOMORROW and INPULSIS® trials. Respir Med 2016;113:74–9.
[31] Lancaster L, Albera C, Bradford WZ, Costabel U, du Bois RM, Fagan EA, et al. Safety of pirfenidone in patients with idiopathic pulmonary fibrosis: integrated analysis of cumulative data from 5 clinical trials. BMJ Open Respir Res 2016;3:e000105.