Supplementary material

for

Zinpentraxin Alfa for Idiopathic Pulmonary Fibrosis: The Randomized Phase III STARSCAPE Trial

Luca Richeldi, Courtney Schiffman, Jürgen Behr, Yoshikazu Inoue, Tamera J. Corte, Vincent Cottin, R. Gisli Jenkins, Steven D. Nathan, Ganesh Raghu, Simon L. F. Walsh, Parminderjit K. Jayia, Nikhil Kamath, Fernando J. Martinez

Supplementary Methods

Diagnosis of IPF

Patients were diagnosed with IPF in accordance with the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guideline (1). To confirm eligibility, patients were required to have a chest HRCT pattern consistent with a subsequent diagnosis of IPF (confirmed by central review of chest HRCT) within 12 months of screening or during the screening period, along with central review of histopathology features in any available lung biopsy. When a biopsy was not available, patients with clinical characteristics suggestive of IPF and with a HRCT pattern of UIP or probable UIP were considered to have a diagnosis of IPF.

Concomitant Medications

Permitted concomitant medications included standard-of-care antifibrotic therapy (pirfenidone or nintedanib); systemic corticosteroids for acute exacerbations of IPF; chronic maintenance, low-dose oral corticosteroids equivalent to prednisone ≤10 mg/day; inhaled bronchodilator agents with restricted use before efficacy assessment measures; initiation/change of supplemental oxygen except when performing the 6MWT; and approved vaccinations including COVID-19 vaccinations.

Randomization and Masking

The enrollment target for STARSCAPE was 658 patients. Eligible patients were randomized 1:1 to receive placebo or zinpentraxin alfa. Patients were randomized using an interactive voice or web-based response system (IxRS, Almac) and a permuted block randomization method. A production randomization list was created, fixed within each cell, where the cells were determined by crossing the

randomization strata. Randomization was stratified by 1) use of concurrent nintedanib versus concurrent pirfenidone versus no concurrent treatment and 2) geographical region (China, Hong Kong, and Taiwan; North America; Europe; Latin America; and Rest of World). The randomization list was managed by the IxRS vendor; the trial sponsor and trial staff did not have access to this list.

Patients and trial investigators were blinded to treatment assignment during the trial. The trial sponsor was also blinded to treatment assignment, with the exception of individuals who required access to patient treatment assignments to fulfill their job roles during the trial.

Study Drug Preparation

The first-generation zinpentraxin alfa, which was used initially, was found to contain Chinese hamster ovary (CHO) Gal-1 and CHO Gal-3 from the production process. No new safety risks and no evidence of impact of efficacy due to the presence of CHO Gal-1 and CHO Gal-3 were identified. However, an additional purification step was applied and second-generation zinpentraxin alfa was administered to patients who enrolled in the trial after June 1, 2022, and randomized to the zinpentraxin alfa treatment arm. Patients enrolled before this date continued to receive first-generation zinpentraxin alfa.

Trial Visits and Assessments

Trial visits were conducted during the screening period, on dosing Days 1, 3, and 5, then every 4 weeks from Week 4 to Week 52. For patients not entering the OLE phase, an end-of-study visit was scheduled for Week 56. AEs and serious adverse events were assessed at every trial visit from Day 1 onwards. AEs of special interest included potential drug-induced liver injury with an elevated ALT or AST in

combination with either an elevated bilirubin or clinical jaundice; suspected transmission of an infectious agent by the trial drug; suspected infusion-related reaction with NCI CTCAE Grade ≥2; suspected anaphylactic or hypersensitivity reactions; and acute or suspected exacerbation of IPF. Laboratory assessments, vital signs, physical examination, weight, prior/concomitant medication, and oxygen use were assessed at prespecified trial visits. Spirometry assessments were performed according to the ATS/ERS guidelines (1) and 6MWT according to du Bois *et al*. (2) with additional control measures suggested by the ERS/ATS guideline for field walking tests (3), and were performed during screening, on Day 1 and then every 4 weeks from Week 4 to 52.

More specifically, the 6MWT was performed once and according to the guidance (2, 3):

- The test was performed indoors on a flat, straight corridor with a hard surface of at least 30 m in length.
- An oxygen titration procedure was performed during screening of patients who required supplemental oxygen during the 6MWT (up to 6 L/min of oxygen at sea level, and up to 8 L/min at altitude of >5000 ft) to establish a baseline flow rate. The oxygen titration procedure was conducted as per local standard practice.
- Before each 6MWT, patients were required to have resting oxygen saturation as measured by pulse oximetry of at least 89% after 10 minutes of rest, breathing room air, or at the baseline oxygen flow rate as established during the titration procedure.

- Patients were instructed to walk as far as they could without jogging or running; if they needed to slow down or stop to rest, they were permitted to do so and encouraged to resume walking as soon as they were able.
- The test was stopped if the patient experienced chest pain, intolerable dyspnea, leg cramps, diaphoresis, or desaturation below 83% for at least 10 seconds.
- The pre-test conditions for oxygen use were maintained throughout the study as much as possible, as noted at the Day 1 visit prior to first dose.
- Assessment of 6MWT was performed after completion of PRO questionnaires and after PFTs, allowing for a short recovery period from the PFTs. In the rare instance that it was not possible to complete the 6MWT last, 30–60 minute recovery time was allowed before proceeding to the next efficacy assessment.

Assessment of IPF exacerbations, as previously defined by Collard et al. (4), were evaluated at all trial visits.

Secondary Endpoints

The key secondary efficacy endpoint was absolute change from baseline to Week 52 in 6MWD (m). Additional secondary endpoints included change from baseline to Week 52 in %FVC, time to disease progression, defined as time to first occurrence of either ≥10% absolute decline in %FVC, ≥15% relative decline in 6MWD, or death, change from baseline to Week 52 in UCSD SOBQ, SGRQ and DLco, time to first respiratory-related hospitalization (defined as non-elective hospitalization due to any respiratory cause, including acute exacerbations of IPF, or suspected acute exacerbations of IPF, as determined by the Clinical Adjudication Committee), time to

first acute or suspected acute exacerbation of IPF (as determined by the Clinical Adjudication Committee), and time to all-cause mortality.

Statistical Analyses

The safety evaluable population included all randomized patients who received at least one full or partial dose of trial drug and was analyzed according to treatment received. Unless specified otherwise, all baseline and efficacy analyses were based on the Full Analysis Set, defined as all randomized patients who received at least one full or partial dose of trial drug, analyzed according to treatment assigned.

With a planned sample size of 658 patients and using a two-sided type I error level of 0.05, the trial had a nominal power of 0.89 to detect a standardized effect size of 0.25 on difference in change from baseline to Week 52 in absolute FVC (mL) and FVC%, and a nominal power of 0.97 to detect a standardized effect size of 0.30 on 6MWD.

The primary efficacy endpoint of demonstrating superiority of zinpentraxin alfa over placebo was analyzed using a linear mixed-effect model with random intercept and random slope, with FVC mL measured at each timepoint as the dependent variable, stratification factors (concurrent antifibrotic therapy and geographic region), age, sex, height, and treatment by time interaction as fixed effects, and subject and time as random effects. The comparison of zinpentraxin alfa with placebo was conducted by computing the estimate of the difference in absolute change from baseline at Week 52 between the two treatment arms. If the primary efficacy test on FVC (mL) was found to be significant at the alpha level of 0.05 two-sided, then the fixed-sequence testing procedure was planned to continue by testing the key secondary endpoint of 6MWD at the alpha level of 0.05 two-sided using the same

methodology as the primary endpoint. For time-to-event endpoints, the log-rank test was used for the comparison between the two treatment arms and the hazard ratios were estimated using a Cox regression model.

An interim futility analysis was prespecified for when ≥40% of patients were expected to have completed their Week 28 visit. The futility analysis sought to determine if there was at least a 10 mL benefit in FVC in the zinpentraxin group versus the placebo group. The futility boundary for this analysis was calculated to correspond to approximately 25% Bayesian predictive power, assuming a linear extrapolation between the Week 28 and Week 52 visits.

Post-Hoc Analysis of Phase II FVC Data

In the post-hoc analysis of the FVC data from the phase II trial we assessed the impact of extreme FVC decline observed in a small number of patients on the efficacy results. We refer to the FVC trajectories of these patients as “influential data points,” or “outliers” relative to the distribution of FVC decline for this population. There was no reason to suspect that these influential data points were a result of errors in the pulmonary function tests, but rather appeared to be reflective of rapid disease progression in these patients. The impact on linear mixed effects model estimates of within-treatment-arm FVC changes and the differences in change between arms were assessed using two models based on the prespecified model for the STARSCAPE analysis.

- Pre-specified STARSCAPE model A included a random intercept and slope with baseline FVC in outcome vector.

- Pre-specified STARSCAPE model B included a random intercept and slope, with baseline FVC in outcome vector, and excluded data from patients with extreme FVC decline.

Boxplots with individual data points were used to visualize the distribution of FVC slopes by treatment arm, and the unadjusted mean and median FVC changes from baseline to Week 28 were compared.

Table E1. Random coefficient regression model analysis for FVC, %FVC, and 6MWD (Full Analysis Set)

	Mean change (SE) from baseline at Week 52, mL [95% CI]		Difference in mean change (SE) from baseline at Week 52, mL [95% CI]	*P* value
	Placebo (*n* = 330)	**Zinpentraxin alfa (*n* = 330)**		
FVC	–214.89 (24.168)	–235.72 (24.071)	–20.83 (34.114)	0.5420
	[–262.44, –167.3]	[–283.07, –188.4]	[–87.94, 46.29]	
%FVC	–5.72 (0.633)	–6.22 (0.630)	–0.51 (0.894)	0.5707
	[–6.96, –4.47]	[–7.46, –4.98]	[–2.27, 1.25]	
6MWD	–24.19 (7.673)	–33.64 (7.655)	–9.44 (10.836)	0.3842
	[–39.29, –9.10]	[–48.71, –18.57]	[–30.77, 11.88]	

[a]Estimates are from analyses with a random coefficient regression model using unstructured covariance matrix of random intercept and random slope. The following terms are included in the model: age, sex, height, time, treatment × time, concurrent IPF treatment, and region for FVC and 6MWD; time, treatment × time, concurrent IPF treatment, and region for %FVC.

Definition of abbreviations: %FVC = percent predicted forced vital capacity; 6MWD = 6-minute walk distance; CI = confidence interval; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; SE = standard error.

Table E2. Summary of additional secondary endpoints (Full Analysis Set)

	Placebo (*n* = 330)	**Zinpentraxin alfa (*n* = 330)**
Change from baseline to Week 52 in UCSD SOBQ		
n	35	37
Mean (SD)	4.8 (14.8)	11.1 (21.2)
Median	4.0	5.0
Change from baseline to Week 52 in SGRQ		
n (%)	43	46
Mean (SD)	3.09 (11.51)	6.15 (13.87)
Median	1.18	5.53
Change from baseline to Week 52 in DLco[a]		
n (%)	36	32
Mean (SD)	–6.68 (9.28)	–6.30 (9.56)
Median	–6.50	–7.81
Time to first respiratory-related hospitalization[b]		
Patients with event, *n* (%)	17 (5.2)	17 (5.2)
Median time to event (months)	NA	NA
HR (95% CI)	1.01 (0.51, 1.97)	
P value	0.9833	
Time to first acute or suspected exacerbation of IPF[c]		
Patients with event, *n* (%)	14 (4.2)	12 (3.6)
Median time to event (months)	NA	NA
HR (95% CI)	0.86 (0.40, 1.86)	
P value	0.7005	
Time to all-cause mortality		
Patients with event, *n* (%)	4 (1.2)	4 (1.2)
Median time to event (months)	NA	NA
HR (95% CI)	1.00 (0.25, 3.98)	
P value	0.9962	

[a]Corrected to hemoglobin; [b]Defined as non-elective hospitalization due to any respiratory cause, including acute exacerbations of IPF, or suspected acute exacerbations of IPF, as determined by the Clinical Adjudication Committee; [c]As determined by the Clinical Adjudication Committee.

Definition of abbreviations: CI = confidence interval; DLco = carbon monoxide diffusing capacity; HR = hazard ratio; IPF = idiopathic pulmonary fibrosis; SGRQ = St. George Respiratory Questionnaire; UCSD SOBQ = University of California, San Diego Shortness of Breath Questionnaire.

Table E3. Futility analysis: change from baseline to Week 28 in FVC (mL)[a]

Visit	Comparison	Point estimate (95% CI) for difference in change from baseline
Week 28	Zinpentraxin alfa versus placebo	–15.70 (–57.20, 25.81)

[a]The pre-specified futility threshold for FVC was 10 mL.

Definition of abbreviations: CI = confidence interval; FVC = forced vital capacity.

Table E4. Reanalysis of phase II FVC data: mean change from baseline to Week 28 in absolute FVC

	Mean change in FVC from baseline to Week 28, mL		Difference in mean change from baseline at Week 28, mL	
	Placebo (*n* = 39) (90% CI)	**Zinpentraxin alfa (*n* = 77) (90% CI)**	**(90% CI)**	***P* value**
Pre-specified phase II model[a]	–206.46 (–247.25, –165.68)	–124.74 (–154.09, –95.39)	81.72 (31.47, 131.97)	0.0076
Pre-specified phase III model[b]	–213.04 (–283.07, –143.01)	–129.92 (–180.87, –78.96)	83.1 (–2.61, 168.86)	0.1106
Pre-specified phase III model, excluding outliers[c]	–135.37 (–175.33, –95.40)	–117.15 (–145.82, –88.49)	18.2 (–30.30, 66.73)	0.5346

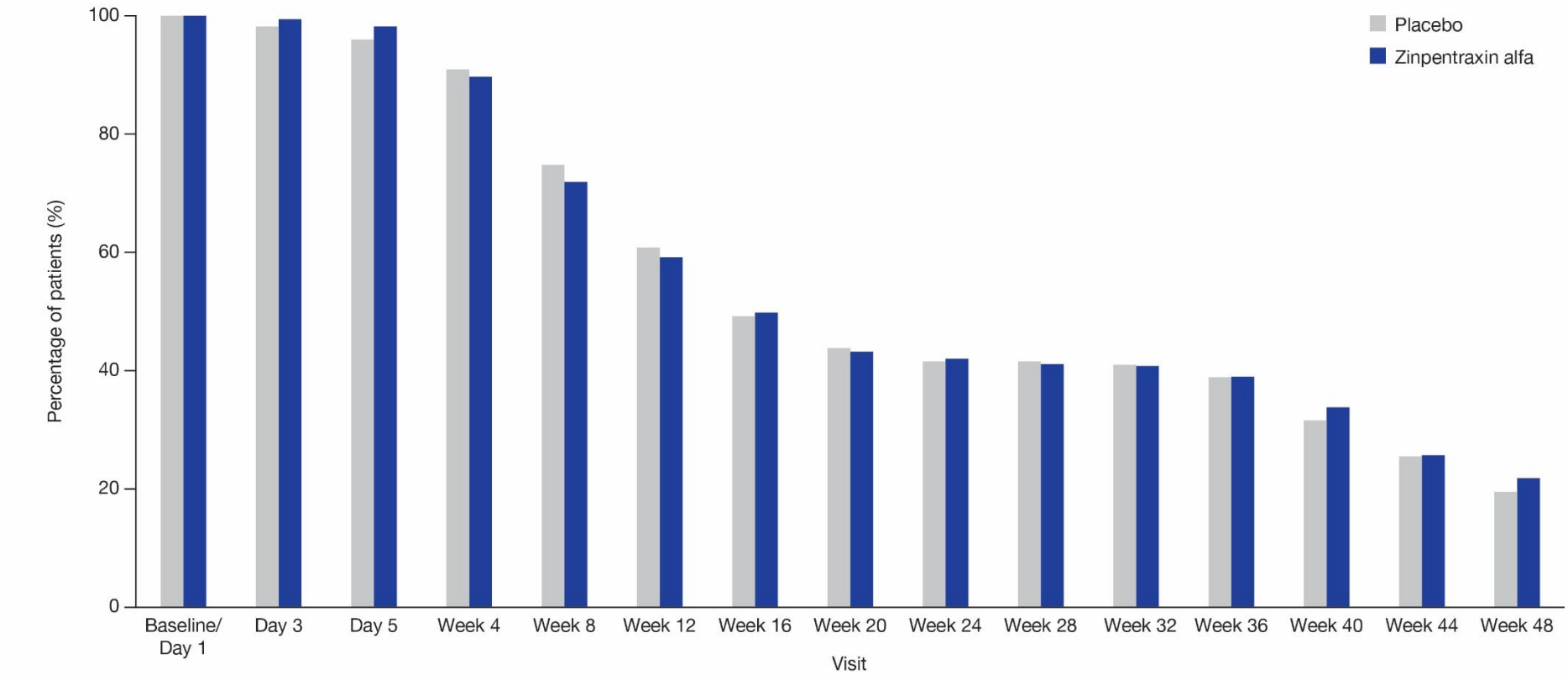
[a]Pre-specified phase II model: random intercept; baseline FVC as covariate (not in outcome vector).

[b]Pre-specified phase III model: random intercept and slope; baseline FVC in outcome vector.

[c]Pre-specified phase III model: random intercept and slope; baseline FVC in outcome vector; excluding two patients in the placebo arm and one patient in the zinpentraxin alfa with extreme FVC decline.

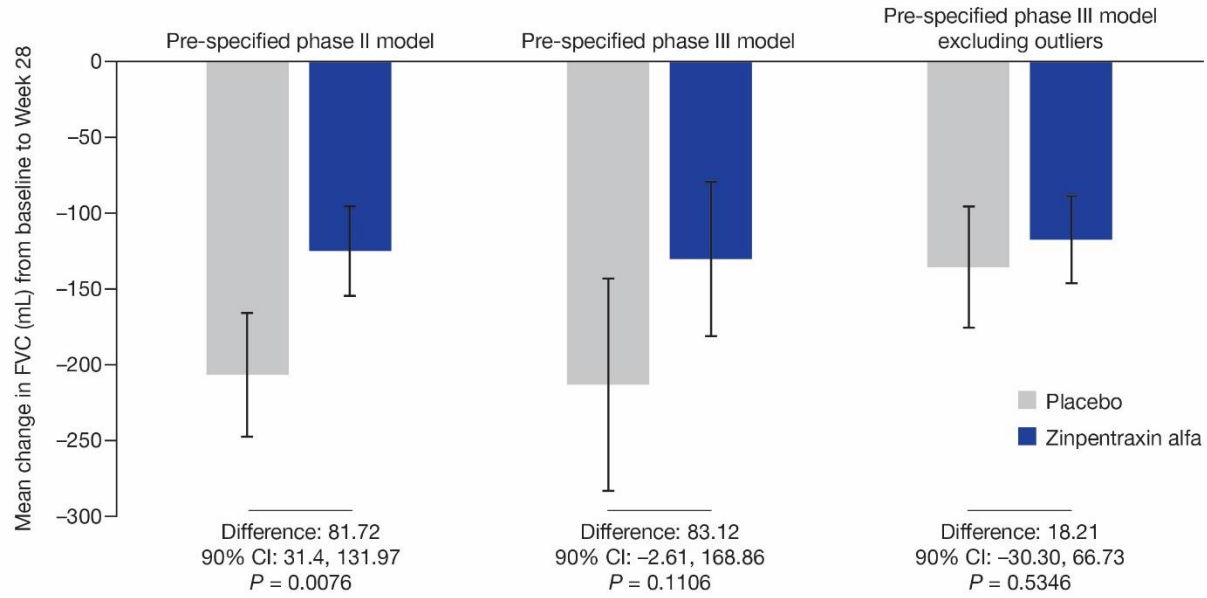
Definition of abbreviations: CI = confidence interval; FVC = forced vital capacity.

Figure E1. Treatment received by visit (Safety Population)



Zinpentraxin alfa	331	329	325	297	238	196	165	143	139	136	135	129	112	85	72
Placebo	329	323	316	299	246	200	162	144	137	137	135	128	104	84	64

Figure E2. Post-hoc analysis of phase II FVC data: mean change in FVC (mL) from baseline to Week 28 in the two arms, using the pre-specified phase II model or phase III model, with and without outliers



Definition of abbreviations: CI = confidence interval; FVC = forced vital capacity.

REFERENCES

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