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GRI-0621 Phase 2a biomarker study in patients with : GRI-0621 has a positive effect on FVC after 12 weeks of treatment

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Introduction: Forced vital capacity (FVC) decline remains the physiological anchor for regulatory assessment of disease-modifying therapy in idiopathic pulmonary fibrosis (IPF). Approved antifibrotics (nintedanib, pirfenidone) attenuate the rate of FVC decline but do not stop or reverse it. GRI-0621 (oral tazarotene) is a retinoic acid receptor (RAR) β/γ-selective agonist that acts orthogonally to the approved antifibrotics.

Aims: To asses the effect of once-daily oral GRI-0621 4.5 mg on safety, translational biomarkers and exploratory lung function of GRI-0621, an oral RARβ/γ-selective agonist, in patients with IPF.

Methods: GRI-0621-IPF-02 (NCT06331624) was a Phase 2a, randomized, double-blind, placebo-controlled trial. Thirty-five patients with IPF were randomized 2:1 to oral GRI-0621 4.5 mg once daily (n=23) or placebo (n=12) for 12 weeks; 80% received background pirfenidone or nintedanib.

Results: Analyses reported here are the per-protocol population with paired baseline and Week 12 spirometry. Treatment-emergent dyspnea was 4% on GRI-0621 versus 17% on placebo (−76% relative), providing symptomatic concordance with the physiologic signal on the same restrictive-mechanics axis.

Figure 1 · GRI-0621-IPF-02 Study Design

Randomized, double-blind, placebo-controlled, 12-week Phase 2 study (ClinicalTrials.gov NCT06331624).

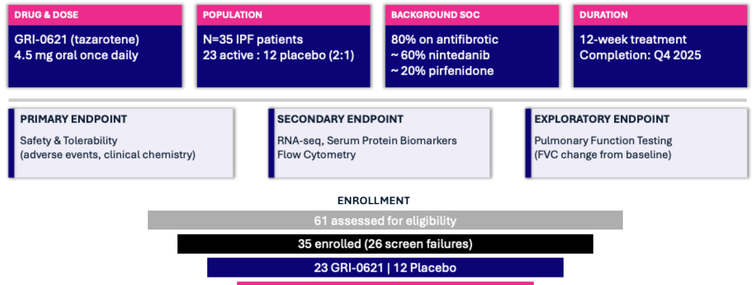


Table 2 · Baseline Characteristics

Characteristic	GRI-0621 (N=23)	Placebo (N=12)	Total (N=35)
Age at consent, years, mean (SD)	72.4 (7.34)	72.3 (8.38)	72.4 (7.59)
Male sex at birth, n (%)	19 (82.6)	8 (66.7)	27 (77.1)
White race, n (%)	23 (100.0)	12 (100.0)	35 (100.0)
Ethnicity			
Hispanic or Latino, n (%)	1 (4.3)	0 (0.0)	1 (2.9)
Not Hispanic or Latino, n (%)	22 (95.7)	12 (100.0)	34 (97.1)
Height, cm, mean (SD)	172.5 (8.85)	169.4 (9.46)	171.4 (9.05)
Weight, kg, mean (SD)	83.3 (16.81)	96.4 (32.89)	87.8 (23.93)
Body-mass index, kg/m², mean (SD)	27.95 (5.19)	33.67 (10.98)	29.91 (8.00)
Time since IPF diagnosis, months, mean (SD)	55 (35.6)	26 (18.0)	—
Baseline FVC, mL, mean (SD)	3,041 (734)	3,323 (1,190)	3,132 (896)
Baseline % predicted FVC, mean (SD)	79 (12.6)	93 (21.1)	—
Former smoker, n (%)	—	—	23 (66)
Background antifibrotic therapy			
Receiving standard-of-care, n (%)	19 (83)	9 (75)	28 (80)
Nintedanib, n (%)	16 (70)	5 (42)	21 (60)
Pirfenidone, n (%)	3 (13)	4 (33)	7 (20)
Neither treatment, n (%)	4 (17)	3 (25)	7 (20)

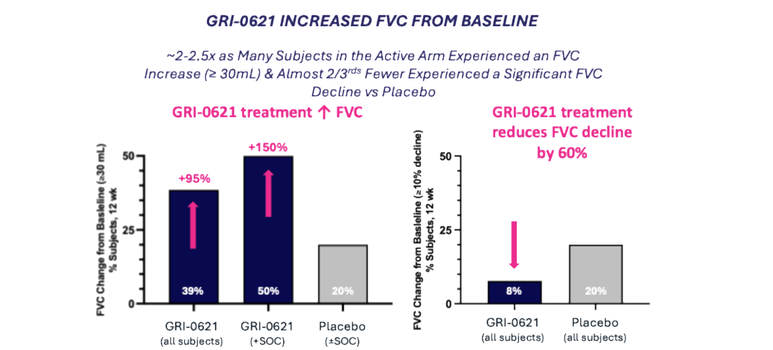
The subject-level responder / decliner analysis is the most robust categorical readout in a small Phase 2a population. Two definitions are used: (i) any FVC gain ≥ 30 mL from baseline over 12 weeks (FVC-preserved cohort), and (ii) FVC decline ≥ 10% from baseline (accelerated decliner cohort).

As shown in the Figure 2, subject-level FVC preservation was concordant with the mean-difference readout: 39% of GRI-0621 subjects (all-subjects cohort) and 50% of the +SOC subset gained FVC over 12 weeks, versus 20% on placebo — a +95% and +150% relative separation respectively. At the other end of the distribution, only 8% of GRI-0621 subjects experienced a ≥10% FVC decline versus 20% of placebo subjects — a 60% relative reduction.

Figure 2 · Subject-level FVC Responder And Decliner Rates At Week 12

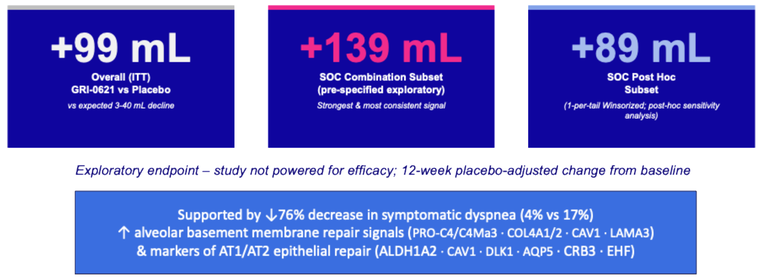
Left panel — FVC responders. Approximately 2x –2.5x as many GRI-0621 subjects experienced an FVC increase (≥ 30 mL) vs placebo. Right panel — FVC decliners (≥ 10% decline). 8% of GRI-0621 subjects met the accelerated-decline threshold vs 20% of placebo — a 60% relative reduction

GRI-0621-IPF-02: FVC Responders vs Decliners



In the pre-specified per-protocol analysis, the placebo-adjusted mean FVC change from baseline at Week 12 was +99 mL overall (95% CI −170 to +369) and +139 mL in the SOC-combination subset (95% CI −184, +462), set against an expected 30–40 mL of natural-history decline over 12 weeks (Table 3). All ten pre-specified robustness sensitivity variants remained directionally positive.

GRI-0621-IPF-02: FVC Exploratory Endpoint



Exploratory endpoint – study not powered for efficacy; 12-week placebo-adjusted change from baseline

Supported by ↓76% decrease in symptomatic dyspnea (4% vs 17%)
↑ alveolar basement membrane repair signals (PRO-C4/C4Ma3 · COL4A1/2 · CAV1 · LAMA3)
& markers of AT1/AT2 epithelial repair (ALDH1A2 · CAV1 · DLK1 · AQP5 · CRB3 · EHF)

Table 3. FVC Change From Baseline (Week 12) — Primary Analysis And Robustness Sensitivity Family

Endpoint	Pop.	GRI (mL)	GRI 95% CI	PBO (mL)	PBO 95% CI	Δ (mL)	Δ 95% CI	n
FVC change from baseline (mL), Week 12 — All-subjects cohort								
All PP (primary)	All subj.	13.1	[−190, +216]	−86.0	[−263, +91]	+99.1	[−170, +369]	13 / 5
MMRM	All subj.	1.1	[-167. +170]	-51.5	[-320, +217]	+52.5	[-265, +370]	16 / 7
10% Trimmed	All subj.	−46.4	[−121, +28]	−86.0	[−263, +91]	+39.6	[−152, +232]	11 / 5
20% Trimmed	All subj.	−56.7	[−115, +1]	−100.0	[−208, +8]	+43.3	[−80, +166]	9 / 3
1-per-tail Trimmed	All subj.	−46.4	[−121, +28]	−100.0	[−208, +8]	+53.6	[−78, +185]	11 / 3
10% Winsorized	All subj.	−39.2	[−117, +39]	−86.0	[−263, +91]	+46.8	[−147, +240]	13 / 5
20% Winsorized	All subj.	−60.8	[−112, −10]	−104.0	[−156, −52]	+43.2	[−30, +116]	13 / 5
1-per-tail Winsor.	All subj.	−39.2	[−117, +39]	−104.0	[−156, −52]	+64.8	[−29, +159]	13 / 5
Super-Responder Excluded	All subj.	−72.5	[−161, +16]	−86.0	[−263, +91]	+13.5	[−184, +211]	12 / 5
FVC change from baseline (mL), Week 12 — +SOC subset								
All PP (+SOC sub.)	+SOC sub.	+53.0	[−217, +323]	−86.0	[−263, +91]	+139.0	[−184, +462]	10 / 5
MMRM	+SOC sub.	+23.5	[-188, +235]	-57.6	[-360, +244]	+81.1	[-288, +450]	13 / 6
10% Trimmed	+SOC sub.	−18.8	[−116, +78]	−86.0	[−263, +91]	+67.3	[−135, +269]	8 / 5
20% Trimmed	+SOC sub.	−25.0	[−94, +44]	−100.0	[−208, +8]	+75.0	[−53, +203]	6 / 3
1-per-tail Trimmed	+SOC sub.	−18.8	[−116, +78]	−100.0	[−208, +8]	+81.3	[−64, +227]	8 / 3
10% Winsorized	+SOC sub.	−15.0	[−113, +83]	−86.0	[−263, +91]	+71.0	[−131, +273]	10 / 5
20% Winsorized	+SOC sub.	−33.0	[−83, +17]	−104.0	[−156, −52]	+71.0	[−2, +144]	10 / 5
1-per-tail Winsorized	+SOC sub.	−15.0	[−113, +83]	−104.0	[−156, −52]	+89.0	[−22, +200]	10 / 5
Super-Responder Excluded	+SOC sub.	−56.7	[−178, +64]	−86.0	[−263, +91]	+29.3	[−185, +244]	9 / 5
Other physiological / symptomatic read-outs								
Dyspnea (treat.-emergent)	Overall	4%	—	17%	—	−76% relative	—	—

Trimmed / Winsorized variants are post hoc robustness sensitivity analyses excluding or capping extreme values. SOC = standard of care (background nintedanib or pirfenidone); PP = per-protocol; PBO = placebo.

Table 4 · FVC-linked Concordant Signals — The Causal Cascade Converging On Lung Volume

Multi-modality readouts from the same 35-subject IPF-02 population. Signals are direction-consistent across serum neo-epitopes, transcriptomics (RNA-seq), spectral flow cytometry, and clinical FVC / dyspnea readouts.

Modality	Readout summary
Upstream driver · Myofibroblast inhibition (α-SMA / ROCK / TGF-β) and Fibrolysis	
Flow	TGF-β* MFI ↓ (direct in-human suppression of a profibrotic TGF-β source)
RNA-seq	TGF-β pathway: **ADAMTS1** ↓, **F2R** ↓, **TXNDC5** ↓, LTBP1 ↓ (tethers latent TGFβ to ECM), TGFBR2 ↓ → SMAD6/7 ↑, **PMEPA1** ↑ (TGF-β negative feedback via SAMD) → FN1 ↓, CCN2 (CTGF) ↓, TGFB1 ↓ (TGF-β-induced matrix protein), MMP1 ↓ ROCK2 pathway: RHOA/B ↓ (upstream Rho GTPase activates ROCK) → **ROCK2** ↓, **MYL12A** ↓ → ACTA2 ↓, LIMK1 ↓ (activated by ROCK; cytoskeletal stiffening), CFL1 ↓ (inactivated by LIMK1; sustains myofibroblast contractility), TLN1/VCL ↓ (stabilized actin filaments; transmits contractile force to the ECM), MRTFA (co-activates SRF-driven contractile genes) ↓ → SRF ↓ (drives contractile gene program (ACTA2/MYL9/CNN1) Collagen: **PLOD1** ↓ (matrix-remodeling enzymes rebalanced); COL1A2 ↓ COL3A1 ↓ COL6A2/A3 ↓ (new pathologic collagen ↓)
Serum	PRO-C3 / C6 ↓ (Type III & VI collagen formation / endotrophin); C3M, CTX-III, C6M turnover markers reported directionally PRO-C3/C3M ↓, PRO-C3/CTX-III ↓, PRO-C6/C6M ↓ (net synthesis/degradation shifts, fibrolysis-favoring)
Structural moat · Basement-membrane repair (net Type IV BM gain) and Re-epithelialization (AT2→AT1 alveolar repair)	
Serum	PRO-C4 ↑ (Type IV BM synthesis); C4Ma3 ↓ (MMP-12-mediated BM destruction); PRO-C4/C4Ma3 net + 13.6 units (net BM repair shift)
RNA-seq	BM repair → AT2/AT1 repair: **COL4A1/A2** ↑, LAMA3 ↑, COL17A1 ↑ → **CCN3** ↑ → **ALDH1A2** ↑, NAPSA ↑, SFTPB ↑ → **NUPR1** ↑, CRB3 ↑ **CAV1** ↑, **DLK1** ↑, AGER ↑ (AT1), AQP5 ↑ (AT1)
Clinical	FVC ↑ Dyspnea ↓ Cough ↓ as an epithelial-repair-consistent functional read-outs
Physiologic summation · FVC stabilization (this poster)	
Clinical (FVC)	FVC responder rate ↑; PBO-adjusted FVC ΔCFB +99 mL overall / +139 mL +SOC; All 10 sensitivity variants remain net-positive (+13.5 to +89.0 mL)
Clinical (event)	≥10% FVC decline event rate 8% vs 20% (−60% relative)
Symptomatic	Treatment-emergent dyspnea 4% vs 17% (−76% relative) — symptomatic concordance with the physiologic FVC signal

Conclusion

In this Phase 2a randomized, double-blind, placebo-controlled study, once-daily oral GRI-0621 produced a positive effect on FVC at Week 12 that persisted across all robustness sensitivity analyses, a 39% (all-subjects) to 50% (+SOC) responder rate versus 20% on placebo, and a 60% relative reduction in the ≥10% FVC decline event rate.
The FVC signal was directionally concordant with upstream molecular readouts on the same subjects across four independent modalities (serum ECM neo-epitopes, whole-blood transcriptomics, spectral flow cytometry, and patient-reported dyspnea), and is consistent with a mechanistically anchored — not stochastic — physiologic effect of the drug.

Together these data further strengthen the potential clinical proof of concept and reinforce the therapeutic differentiation of GRI-0621, supporting the planned pivotal adaptive Phase 2b/3 program (GRI-0621-IPF-03) in IPF.