OA2380 *ERS Congress 2026 | Session 12.04 — Rare ILD/DPLD | Abstract #63931*

Safety, translational biomarkers and lung function with the oral RARβ/γ-selective agonist GRI-0621 in idiopathic pulmonary fibrosis: a Phase 2a randomised, double-blind, placebo controlled trial (GRI-0621-IPF-02)

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Conflict of interest: *Action for Pulmonary Fibrosis trustee; Honorarium fee (investigators meeting) from GRI Bio* · **Acknowledgment:** *This work was supported by the National Institute for Health and Care Research (NIHR) Respiratory Translational Research Collaboration (TRC)* · **Trial registration:** *ClinicalTrials.gov NCT06331624*

Introduction: Idiopathic pulmonary fibrosis (IPF) is driven by epithelial injury, immune dysregulation and excess extracellular matrix; approved antifibrotics slow decline but do not restore lung architecture. Retinoic acid receptor β/γ (RARβ/γ) signalling regulates immune homeostasis, epithelial differentiation, collagen turnover and repair.

Aims: To assess safety, translational biomarkers and exploratory lung function of GRI-0621, an oral RARβ/γ-selective agonist, in IPF.

Methods: GRI-0621-IPF-02 (NCT06331624) was a Phase 2a, randomised, double-blind, placebo-controlled trial. 35 patients with IPF were randomised 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. Endpoints included adverse events (AEs), RNA sequencing, serum collagen and injury biomarkers, flow-cytometry immune phenotyping and forced vital capacity (FVC).

Results: GRI-0621 was well tolerated; common AEs were mild dry lips (30%), dry skin (22%) and musculoskeletal symptoms (13%). Versus placebo, treated patients reported less cough (0% vs 25%), dyspnoea (4% vs 17%) and diarrhoea (13% vs 33%), with no weight loss (vs 17%). Biomarkers showed reduced type III/VI collagen formation with increased degradation, increased type IV collagen formation, and lower neutrophil, macrophage and pro-fibrotic Th2 activity. Placebo-adjusted FVC change was +99 mL overall and +139 mL with background therapy; subjects with no FVC decline rose to 39% (vs 20%) and 50% and ≥10% decline fell to 8% (vs 20%).

Table 1 · GRI-0621-IPF-02 Baseline Characteristics

N = 35 (safety population, GRI-0621 4.5 mg once daily n=23 vs placebo n=12). Mean (SD) unless otherwise noted.

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 SOC, 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)

Arms were well balanced for age, sex and race; the placebo arm carried numerically higher BMI, shorter time since IPF diagnosis, and lower nintedanib background. Baseline % predicted FVC was mildly lower in the GRI-0621 arm.

Table 2 · GRI-0621-IPF-02 Treatment-Emergent Adverse Events (Safety Population N=35)

Reported here: TEAEs pre-specified for safety-endpoint analysis plus retinoid class-effect events at any incidence.

Adverse event	GRI-0621 (N=23)	Placebo (N=12)	Interpretation
Overall summary			
Any TEAE	19 (83%)	11 (92%)	
Any serious TEAE	0 (0%)	1 (8%)	
Grade ≥ 2 TEAE	4 (17%)	2 (17%)	
Discont. due to TEAE	4 (17%)	3 (25%)	*protocol-mandated at Grade ≥2*
Symptomatic tolerability (respiratory, GI, weight)			
Cough	0 (0%)	3 (25%)	*GRI < placebo (pbo)*
Dyspnea	1 (4%)	2 (17%)	*GRI < placebo*
Diarrhea	4 (17%)	4 (33%)	*GRI < pbo despite 70% vs 42% nintedanib*
Weight loss	0 (0%)	2 (17%)	*GRI < placebo*
Retinoid class effects (mucocutaneous and musculoskeletal)			
Dry lips *	7 (30%)	0 (0%)	*retinoid class effect (Grade 1–2)*
Dry skin *	5 (22%)	0 (0%)	*retinoid class effect (Grade 1–2)*
Arthralgia *	3 (13%)	1 (8%)	*retinoid class effect (Grade 1–2)*
Myalgia *	3 (13%)	0 (0%)	*retinoid class effect (Grade 1–2)*

** Retinoid class-effect events reported at any incidence (below the 5% pre-specified threshold for other TEAEs). All Grade 1–2; all responded to standard supportive care (emollients, lip balm, ibuprofen).*

Table 3. Serious Adverse Events (SAEs)

All treatment-emergent serious adverse events captured over the 12-week randomized period. Investigator adjudication of relationship to study drug is reported.

Category	GRI-0621 (N=23)	Placebo (N=12)	Note
Any SAE	0 (0%)	1 (8%)	
Treatment-related SAE	0 (0%)	0 (0%)	*no drug-related SAEs in either arm*
SAE leading to discontinuation	0 (0%)	1 (8%)	*placebo — Grade 2 panic attack*
Death	0 (0%)	0 (0%)	

No treatment-related SAEs occurred on GRI-0621. The single SAE was a placebo-arm Grade 2 panic attack judged by the investigator to be unrelated to study drug.

Table 3. Serum ECM Biomarkers Of Matrix Turnover

Expanded 12-biomarker panel (collagen formation and degradation neo-epitopes plus inflammation/turnover markers).

Biomarker	Fav. dir.	Type	All subjects (n=19 GRI / 9 PBO)[a] GRI %CFB (mean ±SEM)	PBO %CFB (mean ±SEM)	PBO-adj Δ%CFB	HL Δ [95% CI]	+SOC subset (n=16 GRI / 6 PBO)[a] GRI %CFB (mean ±SEM)	PBO %CFB (mean ±SEM)	PBO-adj Δ%CFB	HL Δ [95% CI]
PRO-C3	↓ (yes)	Formation	+10.1±4.9%	+12.2±5.8%	−2.2%	−4.0 [−19.1,+10.5]	+9.0±5.3%	+12.6±8.3%	−3.6%	−5.6 [−28.3,+17.5]
PRO-C6	↑ (yes)	Formation	−4.1±5.5%	+8.2±23.6%	−12.3%	+0.0 [−20.6, +21.4]	−5.9±5.7%	+25.8±32.9%	−31.7%	−7.7 [−42.2, +19.4]
PRO-C4	↑ (yes)	Formation	+7.9±2.6%	+0.2±4.4%	+7.7%	+7.8 [−3.7, +17.5]	+5.4±2.5%	+2.4±5.0%	+2.9%	+2.0 [−9.3, +15.0]
PRO-C5	↔	Formation	+0.2±3.5%	−4.7±6.8%	+4.8%	+0.8 [−13.1, +21.5]	−2.7±3.2%	−1.5±7.5%	−1.2%	−0.4 [−18.7, +20.0]
C1M	↑ (yes)	Degradation	+33.4±16.2%	+50.5±39.4%	−17.1%	+1.4 [−63.2, +60.3]	+25.5±16.6%	+20.8±26.4%	+4.7%	+0.7 [−69.1, +72.6]
C3M	↑ (yes)	Degradation	−0.2±2.5%	−5.9±7.6%	+5.7%	+5.6 [−9.9, +23.3]	−1.9±2.8%	−1.3±9.5%	−0.6%	+3.5 [−24.1, +21.0]
CTX-III	↑ (yes)	Degradation	+6.8±6.8%	−2.8±8.3%	+9.6%	+3.6 [−7.3, +24.4]	+11.7±7.2%	+5.7±7.3%	+6.0%	+1.4 [−7.3, +17.8]
C6M	↑ (yes)	Degradation	+5.2±2.5%	−3.2±7.2%	+8.4%	+8.5 [−7.5, +23.4]	+5.2±2.4%	−0.4±8.1%	+5.6%	+8.4 [−11.4, +24.6]
C4Ma3	↓ (yes)	Degradation	+7.6±3.8%	+18.6±9.7%	−10.9%	−5.2 [−31.8, +13.0]	+5.1±4.1%	+9.8±9.3%	−4.7%	−1.4 [−26.0, +17.1]
VICM	↓ (yes)	MØ activity	+18.1±11.2%	+42.9±28.0%	−24.8%	−20.8 [−57.3, +31.3]	+18.2±13.2%	+56.7±40.4%	−38.5%	−25.6 [−89.0, +39.7]
CPa9-HNE	↓ (yes)	Neutrophil act.	−0.9±3.7%	+3.7±5.4%	−4.5%	−3.4 [−16.2, +10.5]	−2.7±4.2%	+2.0±5.4%	−4.7%	−2.0 [−15.2, +11.6]
ELP-3	↓ (yes)	Lung injury	−5.0±2.7%	−7.0±6.7%	+2.0%	−0.3 [−12.2, +13.0]	−6.7±2.9%	−1.9±5.5%	−4.8%	−2.4 [−18.1, +10.4]

a n = evaluable subjects per arm. b PBO-adj Δ %CFB = GRI mean − PBO mean. c HL Δ = Hodges-Lehmann median difference (GRI − PBO); 95% CI = distribution-free Wilcoxon–Mann-Whitney interval. d Fav. dir. = direction of change considered biologically favorable (↑ = increase beneficial; ↓ = decrease beneficial; ↔ = stabilization beneficial).

Table 4. Collagen Synthesis-vs-Degradation Balance Ratios

Ratios of collagen formation neo-epitopes to their matched degradation neo-epitopes quantify net matrix balance shifts.

Ratio	Fav. dir.	Biological meaning	All subjects (n=19 GRI / 9 PBO)[b] GRI %CFB (mean ±SEM)	PBO %CFB (mean ±SEM)	PBO-adj Δ%CFB	HL Δ [95% CI]	+SOC subset (n=16 GRI / 6 PBO)[b] GRI %CFB (mean ±SEM)	PBO %CFB (mean ±SEM)	PBO-adj Δ%CFB	HL Δ [95% CI]
PRO-C3 / C3M	↓ (yes)	↑ degradation (fibrolysis)	+11.1±5.2%	+24.7±12.1%	−13.6%	−10.5 [−22.7, +5.8]	+11.8±5.6%	+15.6±4.6%	−3.8%	−12.0 [−20.5, +10.6]
PRO-C3 / CTX-III	↓ (yes)	↑ degradation (fibrolysis)	+9.8±8.0%	+25.8±18.2%	−15.9%	−8.7 [−33.7, +16.0]	+1.7±6.3%	+7.6±7.3%	−5.9%	−8.6 [−32.1, +16.1]
PRO-C6 / C6M	↓ (yes)	↑ degradation (fibrolysis)	−7.5±6.0%	+6.5±15.8%	−14.0%	+0.0 [−33.6, +18.7]	−9.9±5.6%	+20.9±21.5%	−30.9%	−21.4 [−58.0, +11.7]
PRO-C4 / C4Ma3	↑ (yes)	↑ formation (BM repair)	+2.2±4.0%	−11.3±6.9%	+13.6%	+8.4 [−4.2, +26.4]	+2.5±4.7%	−4.9±5.3%	+7.4%	+5.2 [−9.4, +22.0]

a %CFB (ratio = mean percent change from baseline of the (numerator / denominator) unitless ratio. b n = evaluable subjects per arm. c PBO-adj Δ %CFB = GRI mean − PBO mean. HL Δ = Hodges-Lehmann median difference (GRI − PBO); 95% CI = distribution-free Wilcoxon-Mann-Whitney interval. d Fav. dir. = beneficial for all four ratios. All four ratios are exploratory context-only endpoints — hypothesis-

Table 5. Whole-Blood RNA-seq Anchor Genes Supporting The Nine Mechanistic Pillars

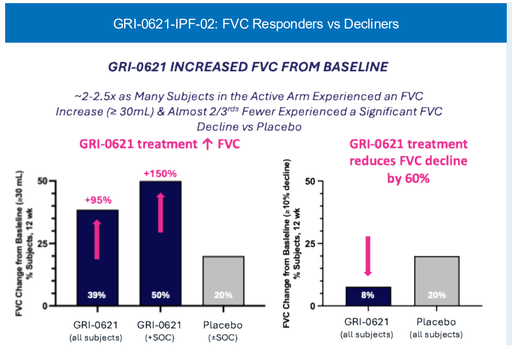
Curated anchor genes show coordinated, direction-consistent transcriptional change on GRI-0621.

Gene	Pillar	Dir.	|LogFC|[a]	p / FDR[b]	Biological role
ALDH1A2	Pharmacodynamic	↑	15.30	**0.011**	RAR pharmacodynamic target engagement (retinaldehyde dehydrogenase 2)
IL4	Immune re-balancing	↓	10.63	0.463	Th2 cytokine; corroborates flow CCR4↓ signal
IL13	Immune re-balancing	↓	3.09	0.857	Th2 cytokine; pro-fibrotic mediator
STAT6	Immune re-balancing	↓	1.54	0.095	TF M2/Th2 gene programs. STAT6-KO mice show attenuated fibrosis across models
CCR4	Immune re-balancing	↓	3.26	0.397	Th2/Treg homing receptor; concordant with protein flow signal
CCR8	Immune re-balancing	↓	6.67	0.182	Tissue-resident Treg/Th2 chemokine receptor. Blockade attenuates fibrosis in models
P2RY12	Reduced lung injury	↓	11.80	0.082	Tissue-resident macrophage receptor; active-disease anchor
FOLR2	Reduced lung injury	↓	6.76	0.082	Pro-fibrotic tissue-resident macrophage marker
Pi3 (elafin)	Reduced lung injury	↑	19.19	**0.047**	Restrains neutrophil-elastase injury; connects to CPa9-HNE and ELP-3 serum biomarkers
E2F3	Myofibroblast inhibition	↓	3.70	**0.024**	Drives fibroblast differentiation into myofibroblasts
F2R	Myofibroblast inhibition	↓	2.14	**1e-4**	Activates of thrombotic injury fibrotic signaling cascade
TXNDC5	Myofibroblast inhibition	↓	2.97	**0.028**	Folds 7 stabilizes TGFBR1, augmenting TGF-β receptor signaling amplitude
SMAD7	Myofibroblast inhibition	↑	2.02	0.111	Inhibitory Smad; endogenous negative feedback on Smad2/3
ACTA2	Myofibroblast inhibition	↓	10.81	0.089	α-SMA; core myofibroblast contractile marker
ROCK2	Myofibroblast inhibition	↓	2.61	**0.035**	Rho-kinase 2; actin-cytoskeletal contractility
MYL12A	Myofibroblast inhibition	↓	2.25	**0.006**	Myosin regulatory light chain 12A; contractile machinery downstream of ROCK2
CCN3	Myofibroblast inhibition	↑	15.68	**0.047**	Anti-fibrotic matricellular protein; opposes CCN2/CTGF activity
PLOD1	Fibrolysis	↓	2.58	**0.042**	Hydroxylates lysyl on procollagen, a prerequisite for crosslink maturation and matrix rigidity. Elevated in IPF
COL6A3	Fibrolysis	↓	6.43	0.174	Largest type VI collagen α-chain elevated in fibrotic lung and co-localized with COLI/III
ADAMTS1	Fibrolysis	↓	15.13	**0.034**	Metalloproteinase; strongest fibrolysis transcript signal
MMP1	Fibrolysis	↓	18.32	0.095	Interstitial collagenase; connects to serum PRO-C3/C3M turnover
LAMA3	Basement-membrane repair	↑	11.73	0.115	Laminin α3; principal alveolar-epithelial BM protein, IPF-deficient
COL4A1/A2	Basement-membrane repair	↑	5.4 / 3.9	**0.053 / 0.058**	Type IV collagen α1/α2;; transcript concordance with serum PRO-C4
COL17A1	Basement-membrane repair	↑	11.48	0.090	Type XVII collagen (BP180); hemidesmosome anchor restoring epithelial-BM adhesion
DLK1	Re-epithelialization (AT1/AT2)	↑	9.62	**0.003**	Notch-family transmembrane protein required for AT2→AT1 differentiation during repair
CAV1	Re-epithelialization (AT1/AT2)	↑	5.89	**0.015**	Caveolin-1; anti-fibrotic membrane-scaffolding protein reduced in IPF fibroblasts
NUPR1	Re-epithelialization (AT1/AT2)	↑	10.50	**0.043**	AT2 stress-resilience transcription factor (p8/COM1); reduced in IPF whole-lung baseline
CRB3	Re-epithelialization (AT1/AT2)	↑	7.62	**0.046**	Restored epithelial polarity
NAPSA	Re-epithelialization (AT1/AT2)	↑	8.84	0.075	Supports AT2 functional recovery; loss causes AT2 injury and fibrosis
ALDH1A2	Re-epithelialization (AT1/AT2)	↑	9.47	**0.011**	RALDH2, the rate-limiting enzyme for RA synthesis (impaired in IPF); supportive of AT2 identity and re-epithelialization.
FGF2	GI-protection	↑	5.83	**0.008**	AFT GI-toxicity mitigation; promotes epithelial repair in injured gut & counteracts AFT mucosal-vascular injury
FLT1	GI-protection	↑	4.28	**0.015**	AFT GI-toxicity mitigation; supports epithelial cell survival & counteracts AFT mucosal-vascular injury

a \|LogFC\| = absolute log fold-change, GRI-0621 vs. placebo, from the pillar evidence-summary transcriptomics. b Minimum FDR-adjusted p-value reported for that gene's strongest bucket contrast. c n = 19 GRI / 9 PBO evaluable for whole-cohort Phase 2a transcriptomics; per-bucket n are not separately itemized here. d TF = transcription factor; BM = basement membrane; ER = endoplasmic reticulum.

Seventy-two curated anchor genes were interrogated in whole-blood RNA-seq at baseline and Week 12. Eighteen transcripts reached FDR<0.05 with large-magnitude, direction-consistent change: **ALDH1A2** ↑ (retinaldehyde dehydrogenase 2; RAR pharmacodynamic target engagement); **ARG2** ↓; **PI3(elafin)** ↑; **E2F3** ↓; **F2R/PAR-1** ↓; **TXNDC5** ↓; **ROCK2** ↓; **MYL12A** ↓; **CCN3** ↑; **PLOD1** ↓; **ADAMTS1** ↓ (strongest fibrolysis transcript); **COL4A1/A2** ↑; **DLK1** ↑; **CAV1** ↑ (anti-fibrotic membrane scaffold, deficient in IPF fibroblasts); **NUPR1** ↑ (AT2 stress-resilience TF); and **CRB3** ↑ (apical epithelial polarity complex); **FGF2** ↑; **FLT1** ↑.The transcript pattern is coherent across pillars.

Figure 1 · 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.

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 robustness sensitivity variants remained directionally positive.

Table 6 · 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

FVC is the physiological summation of the four upstream matrix and epithelial pillars, not an independent readout. The dyspnea reduction is the symptomatic readout of the same restrictive-mechanics axis.

Conclusion

Selective RARβ/γ agonism produced convergent molecular, biomarker, immune and functional signals of attenuated fibrotic remodelling and epithelial/basement-membrane repair, with early FVC stabilisation, supporting larger adequately powered trials.