GRI-0621 phase 2a biomarker study in patients with IPF: a safety signal demonstrating favorable tolerability

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Introduction: GRI-0621 (oral tazarotene) is a retinoic acid receptor (RAR) β/γ-selective agonist in development for idiopathic pulmonary fibrosis (IPF). Tazarotene has an extensive prior clinical safety database (>1,700 subjects, dosed up to one year) generated during its development for plaque psoriasis (evaluated systemically as Tazoral®). The historical concern for the oral pan-retinoid class has been the anticipated retinoid class-effect toxicity — hypertriglyceridemia, hepatotoxicity, night-vision changes and neuropsychiatric events. The RARβ/γ-selectivity of tazarotene provides a mechanistic and pharmacologic basis to expect a differentiated tolerability profile in this older, comorbid IPF population.

Aims: To characterize the safety and tolerability of once-daily oral GRI-0621 4.5 mg over 12 weeks in patients with IPF (with or without standard-of-care antifibrotics), and to compare the in-study adverse event, clinical-chemistry and special-examination profile against (a) the concurrent placebo arm and (b) the prior >1,700-subject tazarotene safety database in psoriasis.

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. Safety was the pre-specified primary endpoint. Assessments included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), routine clinical chemistry (including ALT, AST, triglycerides and LDL cholesterol), night-vision testing (dark-adaptation), audiometry, and a neuropsychiatric battery. Protocol required immediate discontinuation of investigational product for any Grade ≥2 AE regardless of drug relationship. All 35 subjects were included in the ITT and safety populations.

Results: GRI-0621 was safe and well tolerated. There were no serious treatment-emergent AEs in the GRI-0621 arm (0% vs 8% placebo) and no drug-related SAEs. TEAE profile was consistent with the prior tazarotene retinoid class effect (dry lips 30%, dry skin 22%, arthralgia 13%, myalgia 13%) — all Grade 1–2, self-limiting or managed with routine supportive care, and none leading to protocol-mandated discontinuation. Notably, treatment-emergent cough was 0% on GRI-0621 versus 25% on placebo, and treatment-emergent diarrhea 17% on GRI-0621 versus 33% on placebo despite the GRI-0621 arm carrying a numerically higher nintedanib background (70% vs 42%). No clinically meaningful change in ALT, AST, triglycerides or LDL cholesterol was observed at Week 12. No cases of new-onset dyslipidemia, night-vision abnormalities, hearing changes or neuropsychiatric events were reported. Seven protocol-mandated discontinuations occurred (4 on GRI-0621, 3 on placebo), none due to laboratory abnormalities, and none characteristic of retinoid class effect.

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 · Historical Oral Tazarotene (Tazoral®) 12-week Psoriasis AE Profile — Adverse Events ≥5% in Either Arm

Pooled 12-week Phase 3 psoriasis studies 190168-048P and 190168-049P. Source: 2004 FDA Advisory Committee briefing document, Table 7.4.1-1 (weeks 0–12).

Adverse event	Tazoral® 4.5 mg (N=348)	Placebo (N=358)	p-value	Class-effect note
Any adverse event	314 (90.2%)	267 (74.6%)	<0.001	
Any serious adverse event	7 (2.0%)	5 (1.4%)	ns	
Cheilitis	228 (65.5%)	60 (16.8%)	<0.001	*retinoid class effect*
Dry skin	82 (23.6%)	53 (14.8%)	0.003	*retinoid class effect*
Headache	65 (18.7%)	43 (12.0%)	0.014	
Arthralgia	61 (17.5%)	26 (7.3%)	<0.001	*retinoid class effect*
Myalgia	51 (14.7%)	30 (8.4%)	0.009	*retinoid class effect*
Infection (unspecified)	37 (10.6%)	41 (11.5%)	ns	
Eye dryness	36 (10.3%)	38 (10.6%)	ns	*same as placebo*
Back pain	23 (6.6%)	10 (2.8%)	0.016	
Asthenia	23 (6.6%)	22 (6.1%)	ns	
Pruritus	21 (6.0%)	13 (3.6%)	ns	
Hypertriglyceridemia	20 (5.7%)	14 (3.9%)	ns	*same as placebo*
Joint disorder	14 (4.0%)	4 (1.1%)	0.014	
Nasal dryness	13 (3.7%)	4 (1.1%)	0.023	*<5% but significant*

Signal restricted to the expected retinoid mucocutaneous and musculoskeletal class effects.

Table 3 · 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 4 · 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 5 · Clinical Chemistry – Baseline vs Week 12

Pre-specified retinoid class-effect laboratory endpoints: liver transaminases and fasting lipids. Reference ranges for context; no clinically meaningful trend was observed on GRI-0621.

Analyte	Unit	Reference	Baseline (V3)	Week 12 (V11)	Δ (V11 − V3)	Interpretation
ALT (alanine aminotransferase)	U/L	≤ 40	22.6	20.0	−2.6	*no hepatotoxicity signal*
AST (aspartate aminotransferase)	U/L	≤ 40	26.5	25.3	−1.3	*no hepatotoxicity signal*
Triglycerides (fasting)	mg/dL	< 150	104.6	98.9	−5.6	*no hypertriglyceridemia signal*
LDL cholesterol	mg/dL	< 130	87.8	87.7	−0.1	*no dyslipidemia signal*

All within-subject changes are numerically small and within normal reference ranges. No subject had ALT or AST elevation ≥ 3× ULN, and no subject discontinued study drug for a laboratory abnormality.

Table 6 · Study Discontinuations (Protocol-Driven)

Per protocol, any subject experiencing a Grade ≥ 2 adverse event, or a serious adverse event, was immediately discontinued from investigational product regardless of relationship to study drug. All 35 subjects remained in the ITT and safety analyses

Reason for discontinuation	n	Note
GRI-0621 arm (4 discontinuations of 23; 17%)		
Grade 2 urinary tract infection	1	*antibiotic Rx*
Grade 2 dry skin	1	*topical Rx; retinoid class effect*
Grade 2 arthralgias	1	*joints; retinoid class effect*
Grade 2 erosive gastritis + Grade 3 low haemoglobin	1	*pre-existing GI issues/GERD; outpatient endoscopy identified gastritis (common in IPF)*
Placebo arm (3 discontinuations of 12; 25%)		
Grade 2 lethargy (following diarrhoea)	1	
Grade 2 panic attack (SAE)	1	*reported as SAE (Table 4)*
Withdrew consent (relocation)	1	*not AE-related*

No subject discontinued for a laboratory abnormality, night-vision or hearing change, or a neuropsychiatric event. Discontinuation rate on GRI-0621 (17%) was numerically lower than placebo (25%). The protocol-mandated Grade ≥ 2 stopping rule is deliberately conservative for a first-in-IPF Phase 2a safety study. The patient with erosive gastritis had a documented low hemoglobin in their medical history. The patient requested the PI understand better why this was the case and, on endoscopy, erosive gastritis was documented but deemed not related to investigational product.

Table 7· Special Examinations — Night Vision, Audiometry, Neuropsychiatric Battery

Pre-specified retinoid class-effect examinations administered at baseline and Week 12

Examination	Finding at Week 12 (N=35)	Interpretation
Dark-adaptation / night-vision testing	0 subjects with new abnormality	*no retinoid-associated visual toxicity*
Audiometry (pure-tone and speech)	0 subjects with new abnormality	*no retinoid-associated ototoxicity*
Neuropsychiatric battery (mood, cognition, anxiety)	0 subjects with new abnormality	*no retinoid-associated neuropsychiatric signal*

Combined with the clinical-chemistry package (Table 5), these findings establish that oral GRI-0621 4.5 mg once daily for 12 weeks was free of the three classic pan-retinoid organ toxicities (hepatic, dyslipidemic, visual) plus the two most-cited retinoid class concerns (auditory, neuropsychiatric) in this IPF population.

Key Takeaways

Zero drug-related SAEs. Any-SAE 0% GRI-0621 vs 8% placebo; no acute IPF exacerbations either arm; no deaths.

Retinoid class effect confined to expected Grade 1–2 mucocutaneous & musculoskeletal events. Dry lips 30%, dry skin 22%, arthralgia 13%, myalgia 13% — all managed with routine supportive care.

No hepatic, lipid, visual, auditory or neuropsychiatric signal.

Symptomatic tolerability numerically superior to placebo. Cough 0% vs 25%; dyspnea 4% vs 17%; diarrhea 17% vs 33% — the diarrhea advantage occurs despite 70% vs 42% nintedanib background exposure in the active arm.

Consistent with the historical >1,700-subject tazarotene safety database. RARβ/γ-selectivity spares the pan-retinoid organ liabilities that limited earlier oral retinoid IPF programs (Tazoral®, isotretinoin, etretinate).
Together the seven tables above define a tolerability profile that supports advancement of GRI-0621 in IPF program.