POST-HOC BIOMARKER ANALYSIS IN PARTICIPANTS WITH IPF RECEIVING BEXOTEGRAST OVER 12-WEEKS IN INTEGRIS-IPF

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Abstract

Rationale

Biomarkers of early therapeutic response are needed to inform drug development in idiopathic pulmonary fibrosis (IPF). Here we used proteomic screening to assess longitudinal changes in plasma protein levels in participants with IPF receiving bexotegrast, a dual-selective inhibitor of TGF-β-activating integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$ shown to reduce forced vital capacity (FVC) decline compared to placebo in participants with IPF over 12 weeks[1], to identify candidate biomarkers of therapeutic response.

Methods

Plasma samples from INTEGRIS-IPF (NCT04396756) collected at baseline, Week 4 and Week 12 were analyzed by Olink Explore 384 Inflammation panel. Pairwise comparisons and mixed effects model for repeated measures (MMRM) were used to assess differences in protein levels at baseline, between treatment groups across time, and to correlate protein levels with % predicted FVC (FVCpp).

Results

Pairwise comparison of plasma proteins showed minimal differences between bexotegrast and placebo groups at baseline, with a downward shift in most proteins observed with bexotegrast relative to placebo at Weeks 4 and 12. MMRM analysis of a subset of 17 plasma proteins previously shown to predict outcome in patients with interstitial lung disease (ILD)[2] showed that 7 were significantly modulated in participants with IPF receiving bexotegrast (320 mg) vs placebo ($p<0.05$). MMRM analysis of the larger protein panel also showed significant differences in change from baseline for 13 proteins between groups receiving bexotegrast (320 mg QD) and placebo, along with 9 proteins found to significantly associate with longitudinal changes in FVCpp ($p\text{-adj}<0.05$).

INTEGRIS-IPF Study Design and FVC Results

- INTEGRIS-IPF, a Phase 2a clinical trial evaluating bexotegrast in participants with IPF (Fig 1A), previously showed a significant reduction in FVC decline (Fig 1B) in participants treated with bexotegrast vs placebo (320 mg QD vs placebo data shown here)[1]

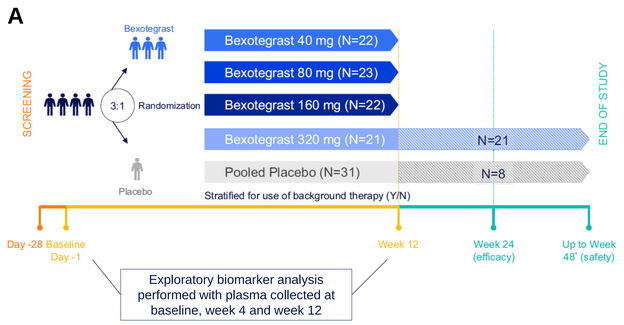


Figure 1:
A) Study design for INTEGRIS-IPF[1].
B) Change from Baseline in FVC through Week 12 in participants receiving 320 mg bexotegrast compared with placebo. FVC change from Baseline analyzed in efficacy mITT population by MMRM. *p<0.05 vs. placebo; **p<0.01 vs. placebo; FVC, forced vital capacity; LS, least squares; mITT, modified intent-to-treat; SE, standard error

Results from Targeted Analysis of 17 Previously Validated ILD Biomarkers

- Targeted analysis of 17 biomarkers previously shown to predict outcome in ILD[2] showed that 7 were reduced in participants receiving bexotegrast vs placebo over 12 weeks (example data from ITGB6, MMP10, PLAUR and SPON1 shown in Figure 3)
- Statistical significance (320 mg QD vs placebo; $p < 0.05$) for each of these proteins was confirmed by MMRM analysis (Table 3)

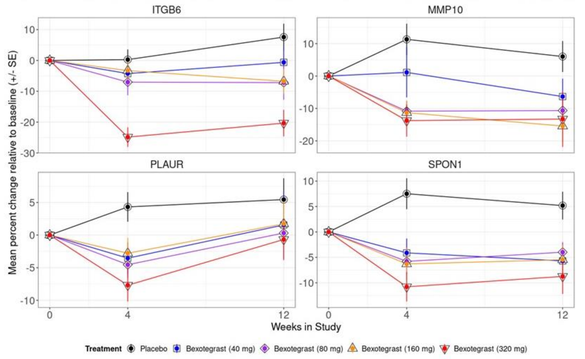


Figure 3: Mean percent change from baseline for plasma levels of ITGB6, MMP10, PLAUR, and SPON1 plotted at 4 and 12 weeks by treatment group. Percent changes calculated from protein expression units. Full protein names listed in Table 3. SE, standard error

Table 3: List of 17 plasma biomarkers previously shown to predict outcome in ILD[2] with subset reduced by treatment (bexotegrast 320mg vs placebo; $p < 0.05$) indicated

Protein ID	Name	p <0.05
AGER	**advanced glycosylation end-product specific receptor**	**Yes**
ITGB6	**integrin subunit beta 6**	**Yes**
MMP10	**matrix metallopeptidase 10**	**Yes**
SPON1	**spondin 1**	**Yes**
PLAUR	**plasminogen activator, urokinase receptor**	**Yes**
HGF	**hepatocyte growth factor**	**Yes**
SCGB3A2	**secretoglobin family 3A member 2**	**Yes**
ANGPTL4	*angiopoietin like 4*	*No*
CXCL17	*C-X-C motif chemokine ligand 17*	*No*
DPP10	*dipeptidyl peptidase like 10*	*No*
FASLG	*Fas ligand*	*No*
FCAR	*Fc alpha receptor*	*No*
IL17C	*interleukin 17C*	*No*
KRT19	*keratin 19*	*No*
PRSS8	*serine protease 8*	*No*
TGFA	*transforming growth factor alpha*	*No*
TNFRSF11B	*TNF receptor superfamily member 11b*	*No*

Results from Pairwise Comparison of All Proteins

- Pairwise comparison of all plasma proteins was performed between bexotegrast (320 mg QD) and placebo groups at baseline, week 4 and week 12 (Fig 2A-C)
- Minimal differences were observed between groups at baseline (Fig 2A), with a downward shift in most proteins observed with bexotegrast compared to placebo at Weeks 4 and 12 (Fig 2B,C)

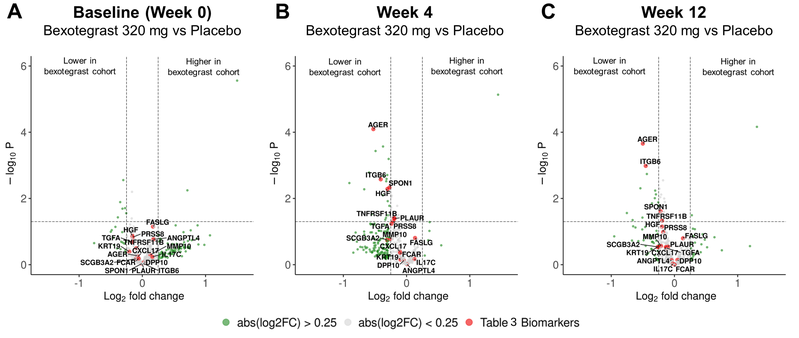
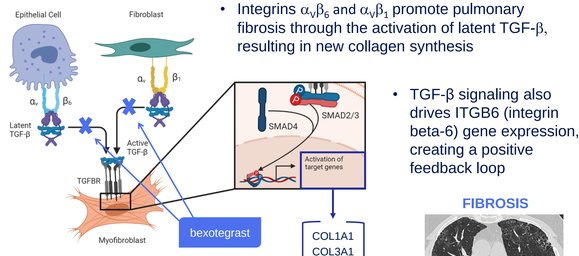


Figure 2. Cross-sectional pairwise comparison of plasma protein levels between participants receiving 320 mg QD bexotegrast or placebo was performed at (A) baseline, (B) 4 weeks and (C) 12 weeks. 365 proteins passing QC were included in the analysis.17 protein biomarkers previously shown to predict 1 year outcome in ILD[2] highlighted in red. Proteins with log2 fold change > 0.25 between groups indicated in green.

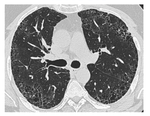
Mechanism of Action of Bexotegrast in IPF



- Integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$ promote pulmonary fibrosis through the activation of latent TGF-β, resulting in new collagen synthesis
- TGF-β signaling also drives ITGB6 (integrin beta-6) gene expression, creating a positive feedback loop
- Bexotegrast, a dual inhibitor of integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$, is undergoing late-stage evaluation in the BEACON-IPF study

COL1A1
COL3A1
TIMP1
CCN2
ITGB6
…

FIBROSIS



Results from Overall Protein Panel Analysis

Table 1: Plasma proteins reduced in pts receiving bexotegrast (320mg QD) vs placebo

Protein	Name	p-adj value
AGER	advanced glycosylation end-product specific receptor	<0.0001
ITGB6	integrin subunit beta 6	0.00245
ESM1	endothelial cell specific molecule 1	0.00245
SPON1	spondin 1	0.00245
MMP10	matrix metallopeptidase 10	0.0149
OMD	osteomodulin	0.0313
FSTL3	follistatin like 3	0.0372
LTO1	LTO1 maturation factor of ABCE1	0.0372
NELL2	neural EGFL like 2	0.0372
MATN2	matrilin 2	0.0372
COLEC12	collectin subfamily member 12	0.0392
GBP2	guanylate binding protein 2	0.0436
ROBO1	roundabout guidance receptor 1	0.0436

Table 2: Plasma proteins associated with longitudinal changes in FVCpp

Positive association with change in FVCpp

Protein	Name	p-adj value
IL10	interleukin 10	<0.0001

Negative association with change in FVCpp

Protein	Name	p-adj value
JUN	Jun proto-oncogene, AP-1 transcription factor subunit	<0.0001
NCLN	nicalin	0.000125
IL6	interleukin 6	0.00424
KRT19	keratin 19	0.00366
ITGB6	integrin subunit beta 6	0.0111
ARNT	aryl hydrocarbon receptor nuclear translocator	0.0257
FST	follistatin	0.0473
CXCL17	C-X-C motif chemokine ligand 17	0.0473

Table 1: Plasma proteins reduced over time in participants receiving bexotegrast (320mg QD) vs placebo; subset of panel n=254 proteins analyzed (MMRM; p-adj<0.05). Table 2: Plasma proteins found to correlate with FVCpp over time (MMRM; p-adj<0.05). p-values adjusted (p-adj) for false discovery rate using the Benjamini-Hochberg method. FVCpp - % predicted forced vital capacity; MMRM – Mixed model repeated measures; p-adj – adjusted p-value; pts - participants

CONCLUSIONS

- Proteomic analysis of plasma samples collected in INTEGRIS-IPF showed that ITGB6 (integrin beta-6) levels negatively correlate with changes in FVCpp and were reduced in participants receiving bexotegrast (320 mg) vs placebo, warranting its further study as a biomarker of therapeutic response
- Future analyses of plasma biomarkers are planned in the currently enrolling BEACON-IPF study (NCT06097260) to better understand their potential utility for early detection of therapeutic response

References: 1. Lancaster, L. et al. AJRCCM 2024 doi.org/10.1164/rccm.202403-0636OC
2. Bowman, W.S. et al. Lancet Respir Med 2022; Conference 2023

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