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Developing Novel Treatments for Fibrotic Diseases

MAY 2024

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Pliant – Company Highlights

Industry-Leading Fibrosis Platform

- Inhibition of integrin-mediated TGF-β activation resulting in antifibrotic effect and shown to be well-tolerated
- Proprietary drug discovery platform - In-house compound library of integrin binders

Programs Targeting High Unmet Medical Need with High-Impact, Near-Term Catalysts

- Bexotegrast (PLN-74809) in development for the treatment of IPF (Phase 2b/3) and PSC (Phase 2a)
  - In IPF, well tolerated with clear treatment effect at 24 weeks on FVC, lung fibrosis (QLF) and symptoms (cough)
  - In PSC, well tolerated at all doses tested and showed reductions in ELF score and PRO-C3 levels relative to placebo at 12 weeks
- Phase 1 enrolling for PLN-101095 – potential first-in-class small molecule dual $\alpha_V\beta_8/\alpha_V\beta_1$ inhibitor overcoming ICI resistance

Strong Financial Position

- $150 million loan facility; amended March 2024
- $483.9 million cash[1] balance as of March 31, 2024
- Operations funded through 2026 together with loan agreement

1 – Includes cash, cash equivalents and short-term investments.

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Pliant Development Pipeline

Program	Indication	Preclinical	Clinical			Anticipated Milestone	Global Rights
			Phase I	Phase IIa	Phase IIb / III		
Bexotegrast (PLN-74809) Dual selective inhibitor of $\alpha_v\beta_6$ /$\alpha_v\beta_1$	Idiopathic Pulmonary Fibrosis					BEACON-IPF Phase 2b/3 trial underway	PLIANT
	Primary Sclerosing Cholangitis					24-Week 320 mg data Mid 2024	PLIANT
PLN-101095 Inhibitor of $\alpha_v\beta_8$ /$\alpha_v\beta_1$	Solid Tumors					Initial data 4Q 2024	PLIANT
PLN-101325 Anti-integrin mAb of $\alpha_7\beta_1$	DMD Other Muscular Dystrophies					Phase 1 ready	PLIANT

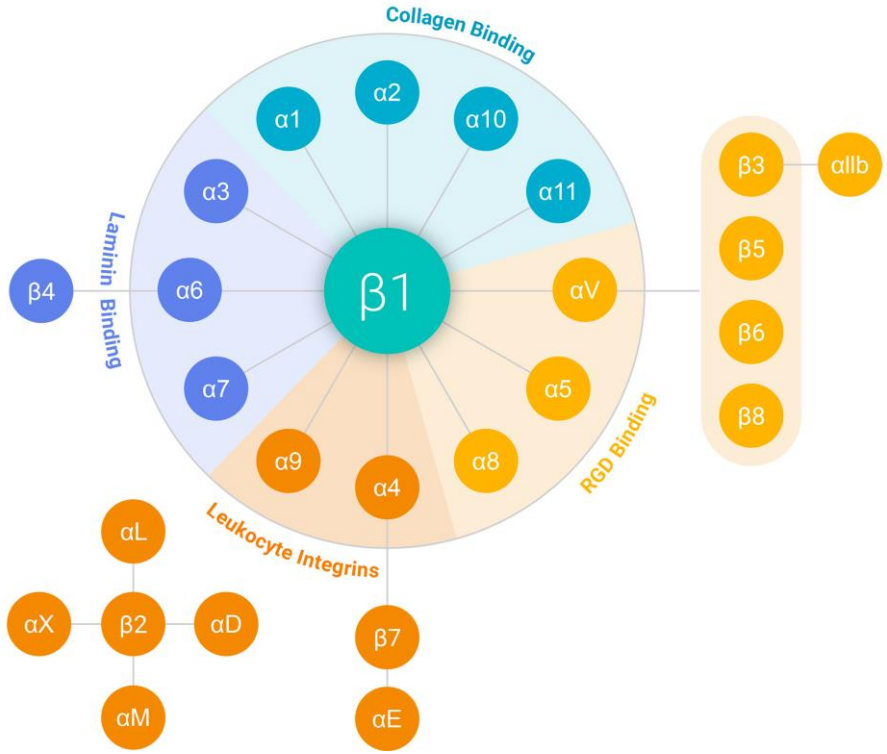
Pliant's Integrin Focused Library
Core Platform for Novel Pipeline and Partner Programs

Integrins

- Cell surface receptors that facilitate cell-cell and cell-extracellular matrix adhesion and interaction
- A major path of communication between the extracellular matrix, inflammatory cells, fibroblasts
- Closely involved in signaling processes governing tissue fibrosis

Pliant's Proprietary Library of 10,000+ Integrin Binding Compounds

- Emphasis on optimal pharmacokinetic and selectivity profile
- Broad spectrum of receptor subfamilies including α_V integrins, collagen and laminin binders



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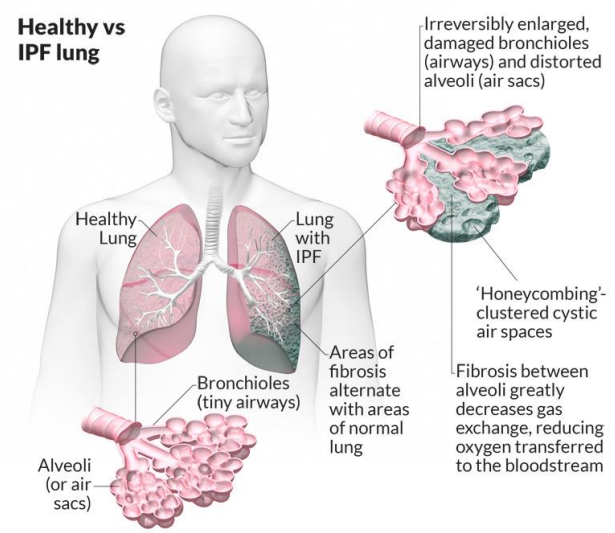
Fibrosis – A Silent Killer

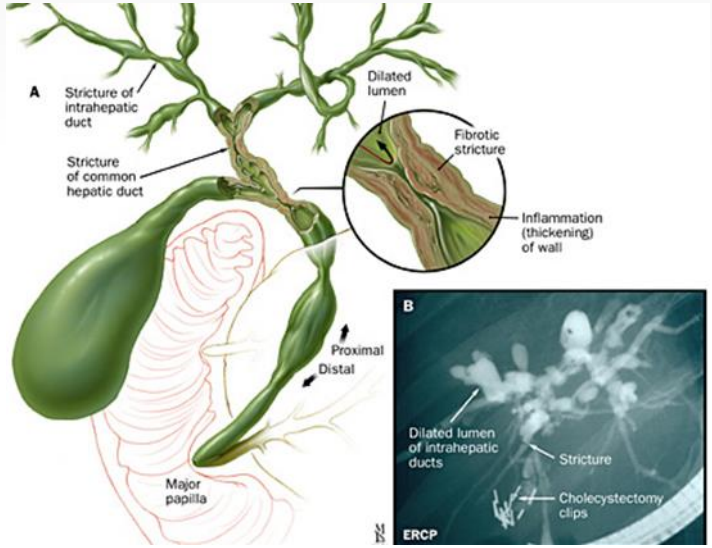
Idiopathic Pulmonary Fibrosis (IPF) is a lethal pathological process with limited therapeutic options

- 140k patients in the U.S.; 30k-40k new cases/year; 40k deaths/year
- **Median survival: 3–5 years -** Worse than some common cancers



Primary Sclerosing Cholangitis (PSC) is a progressive inflammatory liver disease resulting in scarring of bile ducts, and cirrhosis

- 30k-45k patients in the U.S.
- **Median survival: 10-12 years** without intervention
- Currently **no FDA approved therapeutics**



Bexotegrast
Understanding the IPF commercial opportunity

CURRENT COMMERCIAL LANDSCAPE IN IPF

- Two marketed agents – Esbriet® and Ofev® with **>$4 billion total global revenues** in 2022
- Growing market with positive tailwinds
  - Increasing incidence of IPF with aging population
  - New therapies expanding treatable population

CHANGING TREATMENT LANDSCAPE

- Near-term patent expiry of current treatments
  - Esbriet: First generic sold May 2022
  - Ofev: Loss of US market exclusivity projected in 2025

SIGNIFICANT NEED FOR NEW THERAPEUTIC OPTIONS

- Esbriet and Ofev display modest slowing of IPF progression
  - No improvement on patient quality of life or survival benefit
  - **Significant tolerability issues**

Esbriet® is a trademark of Genentech/Roche
Ofev® is a trademark of Boehringer Ingelheim International

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Bexotegrast
A Potentially Broadly Applicable Antifibrotic

Growing Evidence that Localized TGF-β Inhibition has Potential as Backbone Antifibrotic

- Tissue-specific TGF-β inhibition avoids systemic toxicity while maintaining the antifibrotic effect

Bexotegrast Continues to Demonstrate a Favorable Safety and Tolerability Profile

- Well tolerated in over 700 participants across different patient populations
- No drug-related serious adverse events observed across all trials

Bexotegrast Has Potential to Treat Multiple Fibrotic Diseases

- Clear antifibrotic effect across organ systems and indications
- Bexotegrast can expand into additional pulmonary and liver fibrosis indications

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Bexotegrast
A Potential Preferred Treatment Option

ANTI-FIBROTIC MoA

- Targeted inhibition of fibrotic process– tissue specific inhibition of TGF-β
- Dose-dependent FVC benefit in INTEGRIS-IPF study

MONO & COMBO TREATMENT

- Will be evaluated as backbone therapy to be used as monotherapy, and with current treatments
- Flexibility in optimizing therapy for each patient

ORAL 1X DAILY DOSING

- Improvement over current multi-pill, multiple times a day options
- No added burden of monthly liver function monitoring

SAFETY / TOLERABILITY

- Well tolerated
- Low frequency of GI-related AEs in monotherapy setting

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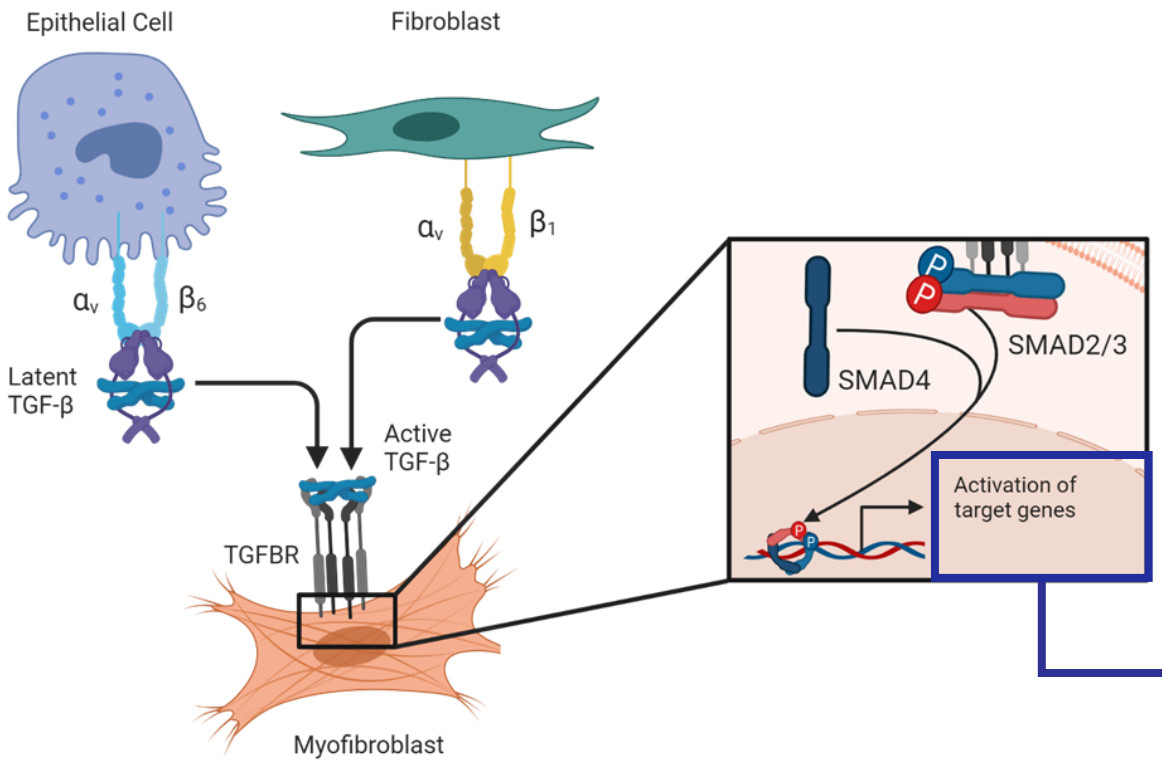
$\alpha_v\beta_6$ / $\alpha_v\beta_1$ Integrins Drive TGF-β Activation in Lung Fibrosis

$\alpha_v\beta_6$ / $\alpha_v\beta_1$ integrins promote fibrosis by activating TGF-β

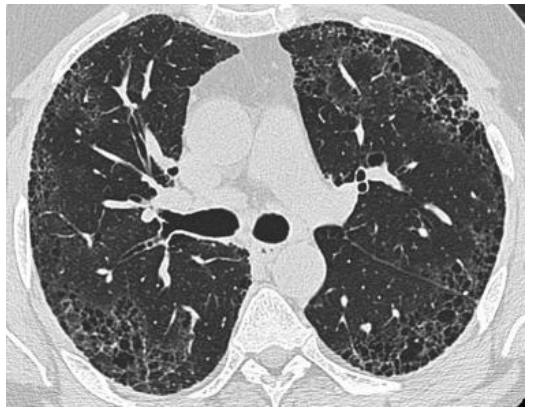


- TGF-β is a central mediator of fibrosis
- $\alpha_v\beta_6$ /$\alpha_v\beta_1$ integrins activate latent TGF-β in fibrotic tissue
- Systemic TGF-β blockade carries toxicity risks

Selectively blocking TGF-β in fibrotic tissues may provide a low risk, effective antifibrotic approach

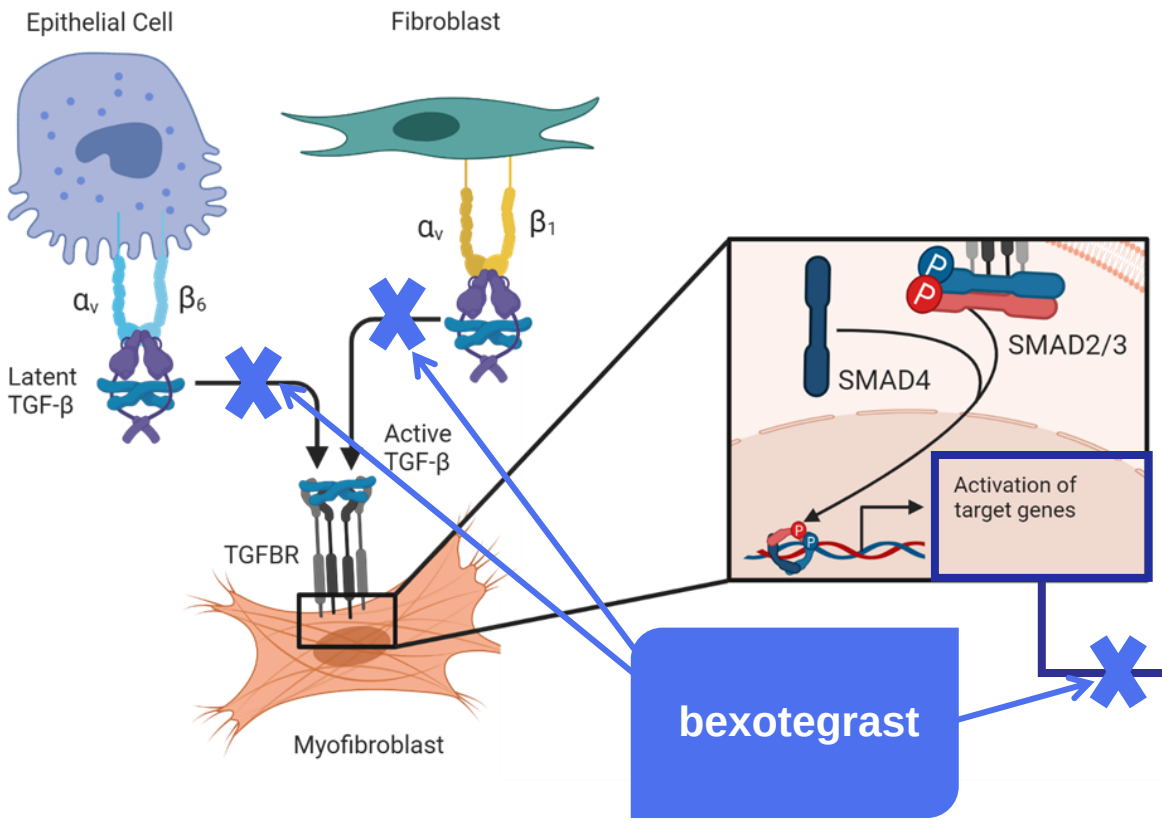
COL1A1
COL3A1
TIMP1
CCN2
ENPP2
…

FIBROSIS



Bexotegrast Reduces TGF-β Signaling and Downstream Profibrotic Pathways Through Inhibition of Integrins $\alpha_v\beta_6$ / $\alpha_v\beta_1$

$\alpha_v\beta_6$ / $\alpha_v\beta_1$ integrins promote fibrosis by activating TGF-β



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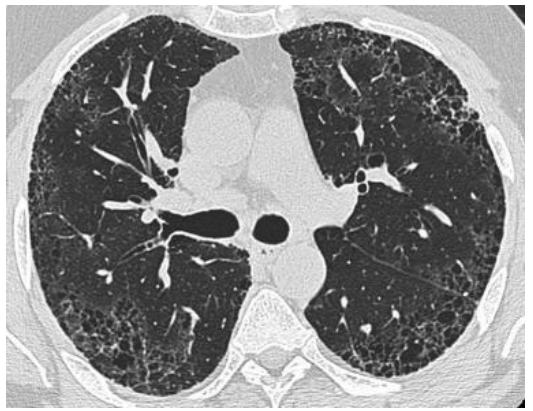

Pliant Compounds Have Not Shown Adverse Effects Typical of Systemic Inhibition of TGF-β Pathways[1]

By targeting integrins that are upregulated specifically in fibrotic tissues, Pliant's small molecule compounds may avoid toxicities associated with systemic TGF-β blockade[1]

Affected organ system	Systemic TGF-β blockade	Observed with Pliant compounds?[1]
Cardiovascular System	Cardiotoxicity	**NO**
Immune System	Autoimmunity/Inflammation	**NO**
GI System	Autoimmunity/Inflammation	**NO**
Skin	Keratoacanthomas/SCC	**NO**
Hematology	Thrombocytopenia/Anemia	**NO**

1 - Based on preclinical GLP tox studies as well as clinical trials to date.

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Bexotegrast - Nonclinical Toxicology Studies
No concerns for clinical advancement

GLP Study category	Studies completed	Findings with Bexotegrast (PLN-74809)
Repeat Dose Toxicology	• 1-Month IND-enabling NHP and mouse • 3-Month Sub-chronic NHP and mouse • 9-Month Chronic NHP • 6-Month Chronic Mouse	**No findings limiting clinical advancement including** • No pulmonary infiltrates • No bladder cancer NOAEL[1] in sub-chronic and chronic GLP tox studies at the highest dose tested in NHPs
Safety Pharmacology	• Standard cardiac ion channel panel • Cardiovascular/respiratory in telemetered NHP	**No findings:** • No effect on respiratory or cardiovascular parameters
Genetic Toxicology	• Ames • *In vitro* micronucleus • *In vivo* micronucleus	**No genotoxic findings:** • Ames negative • Micronucleus negative
Reproductive Toxicology	• Mouse Embryofetal Development • Rabbit Embryofetal Development • Mouse Fertility	**No findings:** • No embryofetal effects • No effects on fertility

700+ human subjects dosed to date with no safety concerns at doses up to 640 mg sd / 320 mg md

1 – No observed adverse effect level.

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INTEGRIS-IPF – Introduction

Purpose of Evaluating Long-Term Treatment with Bexotegrast 320 mg

- Evaluate long term safety of the top dose planned for late-stage development
- Evaluate durability of treatment effect (FVC) including symptomatic improvement (cough)
- Assess long-term effects on pulmonary fibrosis as measured through QLF imaging

Key Takeaways from the Trial

- Bexotegrast continues to demonstrate a favorable safety and tolerability profile
- Bexotegrast demonstrated durable improvements across physiologic (FVC), radiographic (QLF) and symptomatic (cough) assessments versus placebo
- Data provide strong support to advance bexotegrast into late-stage development

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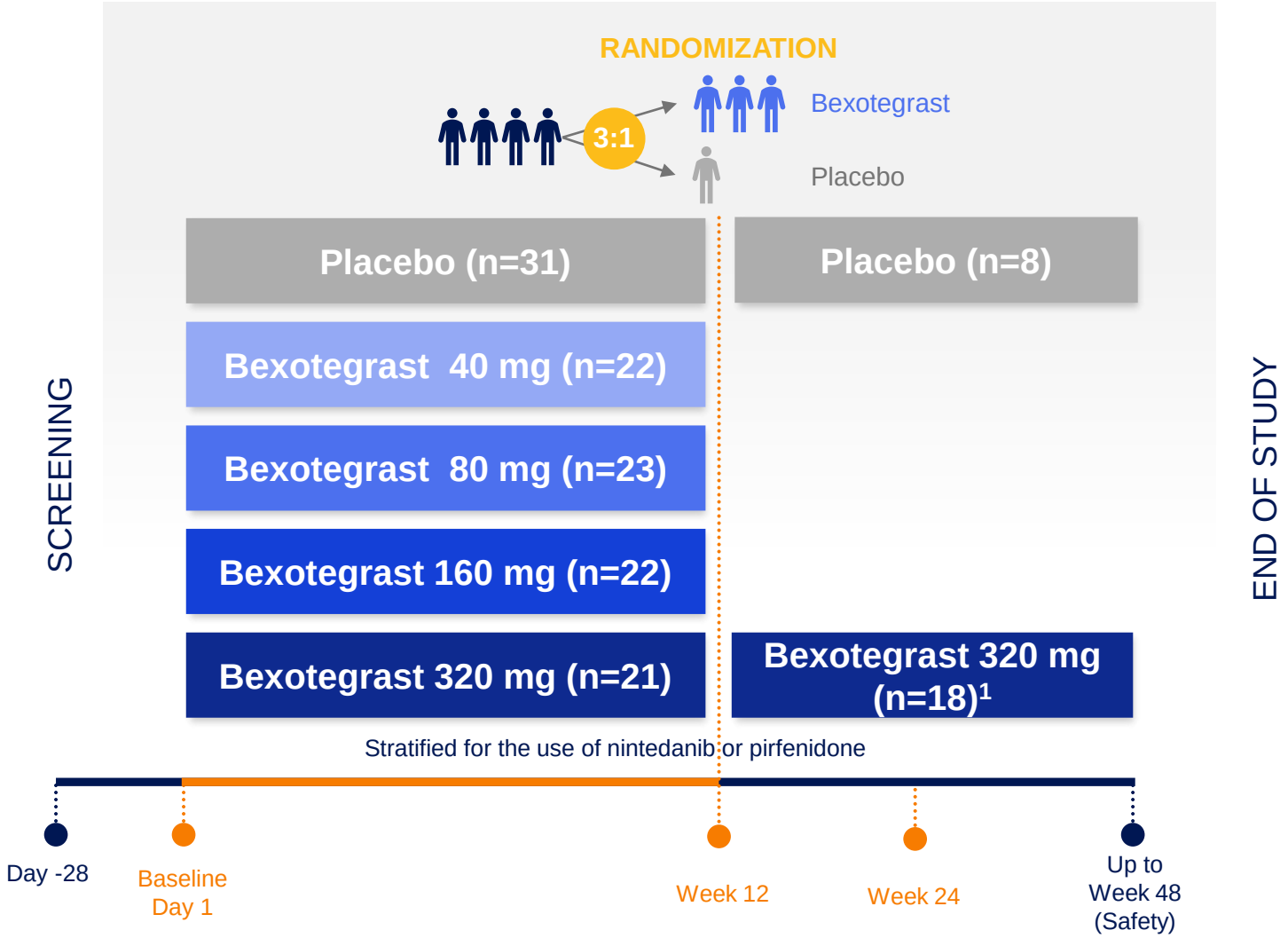
INTEGRIS-IPF Study Design and Objectives



PRIMARY AND SECONDARY ENDPOINTS

- Safety, tolerability, PK

EXPLORATORY ENDPOINTS

- Change in forced vital capacity (FVC) over 12 weeks and 24 weeks
- High resolution CT-based quantitative lung fibrosis (QLF) imaging
- Patient reported cough severity
- Effect on selected biomarkers

1 – Treatment duration per protocol: minimum of 24 weeks and a maximum of 48 weeks

Key Takeaways from the INTEGRIS-IPF Trial

Bexotegrast Demonstrated a Favorable Safety and Tolerability Profile up to 40 Weeks

Bexotegrast Demonstrated a Dose-dependent Treatment Effect on Registrational Endpoint

- Statistically significant increases from baseline in mean FVC at Week 12
- Treatment benefits were present at Week 24 across physiologic (FVC), radiographic (QLF) and symptomatic (cough) assessments versus placebo
- Bexotegrast treatment effect was observed with and without use of standard-of-care agents

Data Provide Strong Support to Advance Bexotegrast into Late-stage Development

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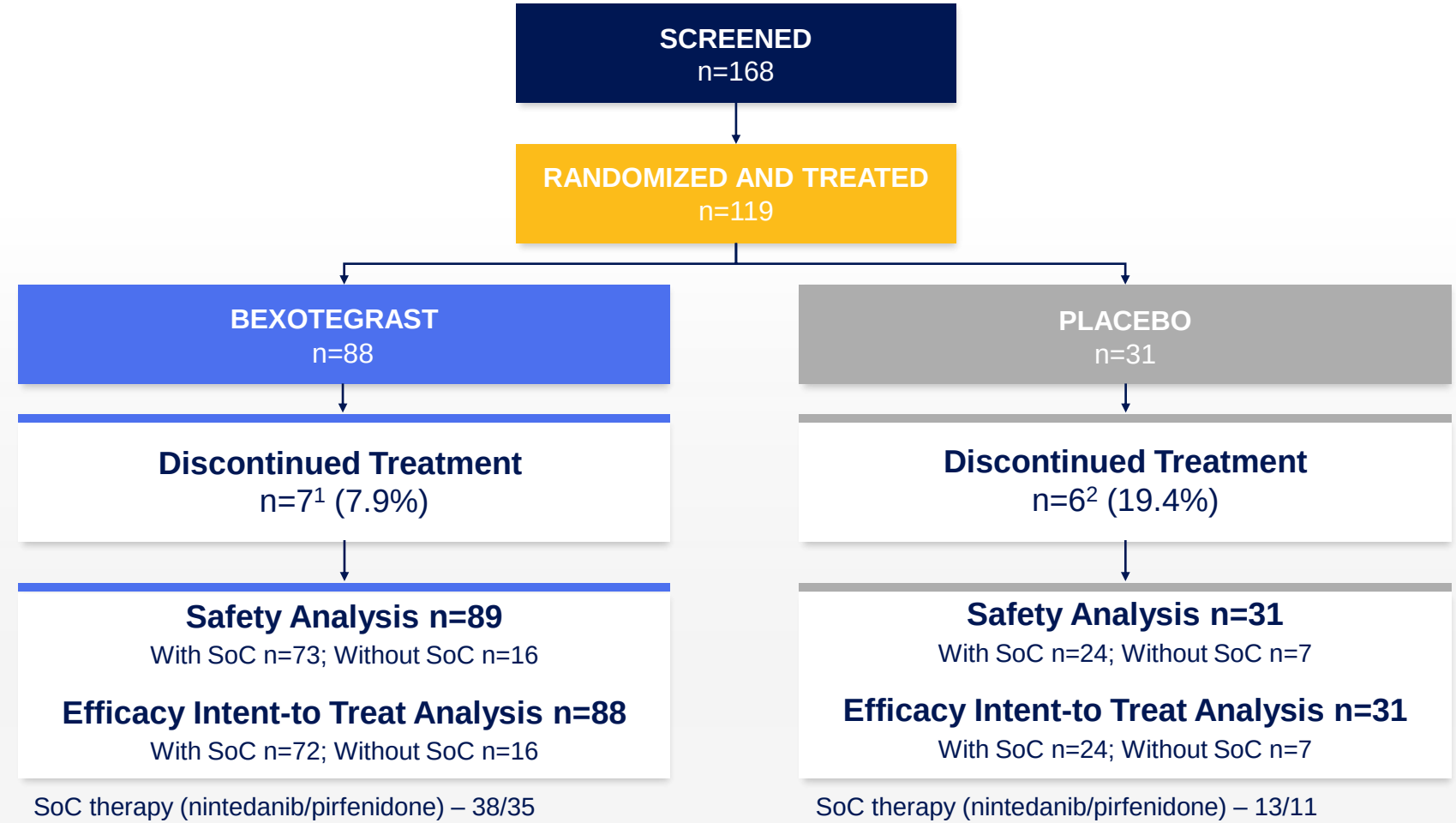
INTEGRIS-IPF – Final Participant Disposition



1- Adverse event (n=3); withdrawal of consent (n=3); physician decision (n=1); 2- Adverse event (n=2); withdrawal of consent (n=3); Lung transplant (n=1).
SoC = Standard of Care

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Baseline Demographics

Characteristic	Bexotegrast 320mg (n=22)	Placebo (n=8)
Male sex, n (%)	21 (95.5)	5 (62.5)
Female sex, n (%)	1 (4.5)	3 (37.5)
Age (yr), mean (SD)	70.5 (7.14)	73.3 (7.98)
Race, n (%)		
White	21 (95.5)	8 (100)
Other / Not Reported / Unknown	1 (4.5)	0
Weight (kg), mean (SD)	88.5 (15.61)	80.6 (13.18)
Body-mass index (kg/m^2), mean (SD)	28.1 (4.08)	27.1 (2.95)

SD = Standard deviation; BMI = Body Mass Index; FVC = Forced Vital Capacity; DLCO = Diffusing capacity for carbon monoxide.

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Baseline Disease Characteristics

Characteristic	Bexotegrast 40 mg (n=22)	Bexotegrast 80 mg (n=23)	Bexotegrast 160 mg (n=22)	Bexotegrast 320 mg (n=21)	Bexotegrast All (n=88)	Placebo (n=31)
Time since diagnosis of IPF (mo), mean (SD)	22.2 (12.44)	28.6 (17.08)	27.8 (12.43)	35.6 (29.06)	28.5 (19.11)	34.0 (21.62)
Standard of Care Use, n (%)	17 (77.3)	19 (82.6)	19 (86.4)	17 (81.0)	72 (81.8)	24 (77.4)
None	5 (22.72)	4 (17.39)	3 (13.63)	4 (19.0)	16 (18.2)	7 (22.6)
Nintedanib	12 (54.5)	9 (39.1)	7 (31.8)	9 (42.9)	37 (42.0)	13 (41.9)
Pirfenidone	5 (22.7)	10 (43.5)	12 (54.5)	8 (38.1)	35 (39.8)	11 (35.5)
Duration of Standard of Care at Randomization (mo), mean (SD)	19.5 (11.53)	20.2 (11.52)	20.1 (11.63)	24.4 (21.88)	21.0 (14.48)	22.6 (17.85)
FVC (mL)						
Mean (SD)	2,976.5 (861.01)	3,128.7 (814.20)	2,863.0 (725.39)	3,193.7 (674.01)	3,039.7 (771.20)	3,073.9 (773.54)
Median	2937.0	2929.0	2702.5	3256.0	2898.5	3179.0
Percent of predicted value (%), mean (SD)	74.8 (14.70)	82.7 (13.47)	78.8 (16.36)	77.7 (15.41)	78.5 (15.01)	77.7 (16.44)
Percent of predicted DLCO, corrected for the hemoglobin level (%), mean (SD)	57.2 (14.74)	51.8 (14.67)	48.6 (15.11)	47.9 (13.18)	51.5 (14.69)	50.1 (15.23)
GAP Stage, n (%)						
GAP Stage I	11 (50.0)	8 (34.8)	7 (31.8)	7 (33.3)	33 (37.5)	10 (32.3)
GAP Stage II	10 (45.5)	15 (65.2)	13 (59.1)	12 (57.1)	50 (56.8)	18 (58.1)
GAP Stage III	1 (4.5)	0	2 (9.1)	2 (9.5)	5 (5.7)	3 (9.7)

BMI = Body Mass Index; mo = Month; SD = Standard Deviation;
GAP Stage I = GAP Index 0-3; GAP Stage II = GAP Index 4-5; GAP Stage III = GAP Index 6-8.
GAP Index score (0-8) derived from Gender, Age, FVC, % Predicted and DLCO, % Predicted.

Well Tolerated Up to 40 Weeks

AE, n (%) of Participants Reporting	Through 12 weeks						Up to 40 weeks	
	Bexotegrast 40 mg (n=22)	Bexotegrast 80 mg (n=23)	Bexotegrast 160 mg (n=22)	Bexotegrast 320 mg (n=22)*	Bexotegrast All (n=88)	Placebo (n=31)	Bexotegrast 320 mg (n=22)*	Placebo (n=8)
Any AEs	16 (72.7)	15 (65.2)	15 (68.2)	18 (81.8)	64 (72.7)	21 (67.7)	20 (90.9)	7 (87.5)
TEAE	16 (72.7)	15 (65.2)	14 (63.6)	17 (77.3)	62 (70.5)	21 (67.7)	20 (90.9)	7 (87.5)
Related to study drug	**4 (18.2)**	**7 (30.4)**	**4 (18.2)**	**4 (18.2)**	**19 (21.6)**	**10 (32.3)**	**5 (22.7)**	**2 (25.0)**
Serious TEAE	1 (4.5)	0	2 (9.1)	1 (4.5)	4 (4.5)	3 (9.7)	2 (9.1)	1 (12.5)
Related to study drug	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
TEAE of CTCAE Grade 3 or Higher	2 (9.1)	0	2 (9.1)	2 (9.1)	6 (6.8)	2 (6.5)	5 (22.7)	1 (12.5)
Related to study drug	**0**	**0**	**1 (4.5)**	**0**	**1 (1.1)**	**0**	**1 (4.5) [1]**	**0**
TEAE Leading to Interruption of Study Drug	0	0	1 (4.5) [1]	1 (4.5) [2]	2 (2.3)	0	4 (18.2) [2]	0
TEAE Leading to Withdrawal of Study Drug	0	0	0	3 (13.6) [2,3,4]	3 (3.4)	3 (9.7)	3 (13.6) [2,3,4]	1 (12.5)
TEAE Leading to Early Termination from Study	0	0	0	3 (13.6) [2,3,4]	3 (3.4)	2 (6.5)	3 (13.6) [2,3,4]	0
TEAE Leading to Death	0	0	0	1 (4.5) [3]	1 (1.1)	0	1 (4.5) [3]	0

1 – COVID-19; 2 – Abdominal pain/Diarrhea in participant with pre-existing ulcerative colitis; 3 – Acute respiratory failure in a GAP Stage III participant with pre-existing atrial fibrillation 8 days following elective atrioventricular node ablation;
4 – Diarrhea in participant with concomitant use of nintedanib
* One placebo participant received 1 week of treatment with Bexotegrast 320 mg and is included in the 320 mg treatment groups. The participant did not have any AEs.

AE = Adverse Event; TEAE = Treatment Emergent Adverse Event; SAE = Serious Adverse Events. Adverse events coded using MedDRA v. 24.0.
TEAE is defined as any AE starting (or worsening) on or after the date of first dose.

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Most Frequent TEAEs

AE, n (%) of Participants Reporting	Bexotegrast 320 mg (N=22)	Placebo (N=8)
Most frequent TEAEs (>10% in at least one arm and n >1 participant)		
Diarrhea	7 (31.8)	3 (37.5)
Related to study drug	4 (18.2)	0
Dyspnea	5 (22.7)	1 (12.5)
Related to study drug	0	0
Idiopathic Pulmonary Fibrosis/Pulmonary Fibrosis	4 (18.2)	2 (25.0)
Related to study drug	0	0
Cough	3 (13.6)	2 (25.0)
Related to study drug	0	0
Upper respiratory tract infection	2 (9.1)	1 (12.5)
Related to study drug	0	0

Adverse events coded using MedDRA version 24.0
TEAE is defined as any AE starting (or worsening) on or after the date of first dose
AE, adverse event; TEAE, treatment-emergent AE

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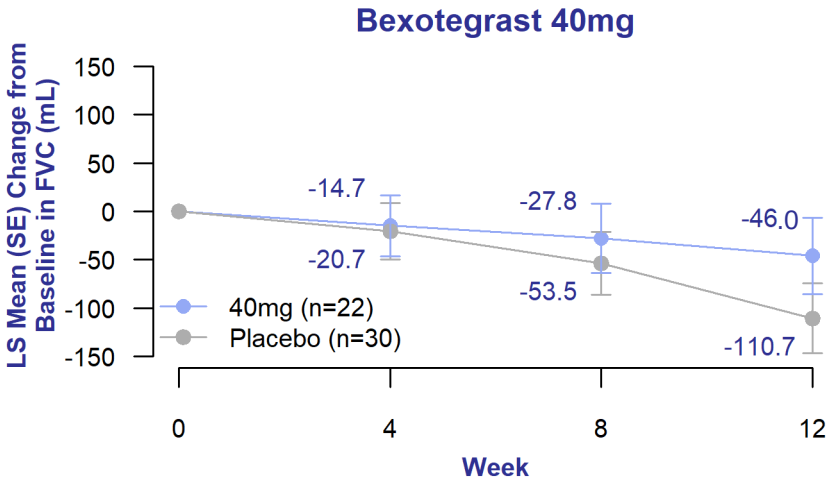
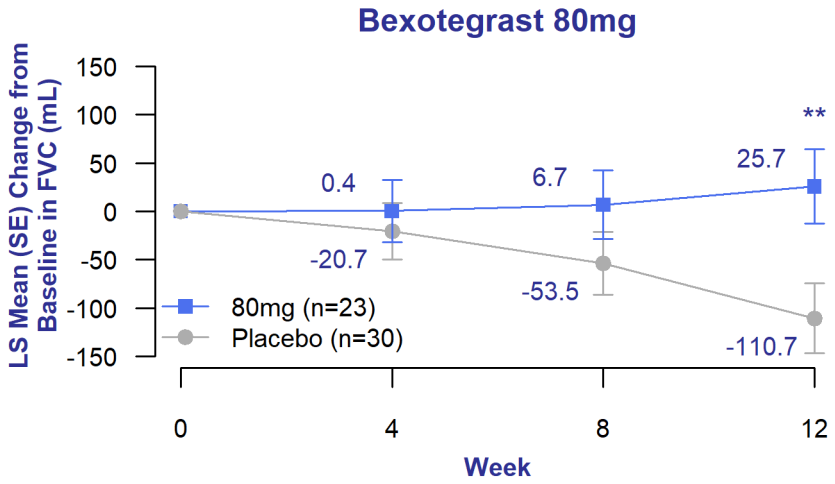
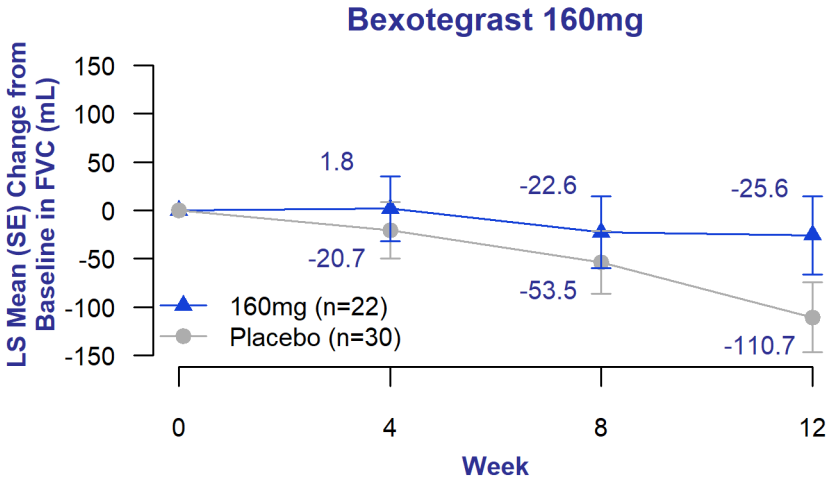
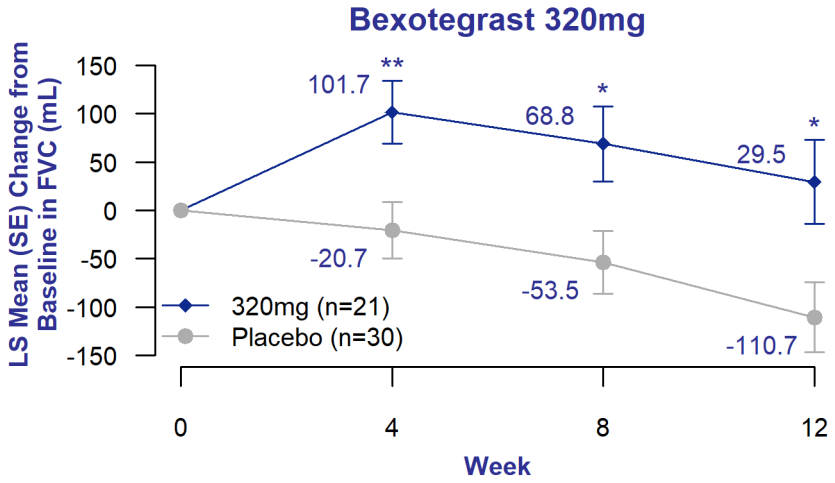
FVC Change from Baseline over 12 Weeks
mITT Population









* p < 0.05 vs placebo
** p < 0.01 vs placebo

FVC = forced vital capacity; mITT = modified intent to treat; 1 participant in the placebo group was identified as a statistical outlier across all treatment groups and excluded from the mITT analysis.

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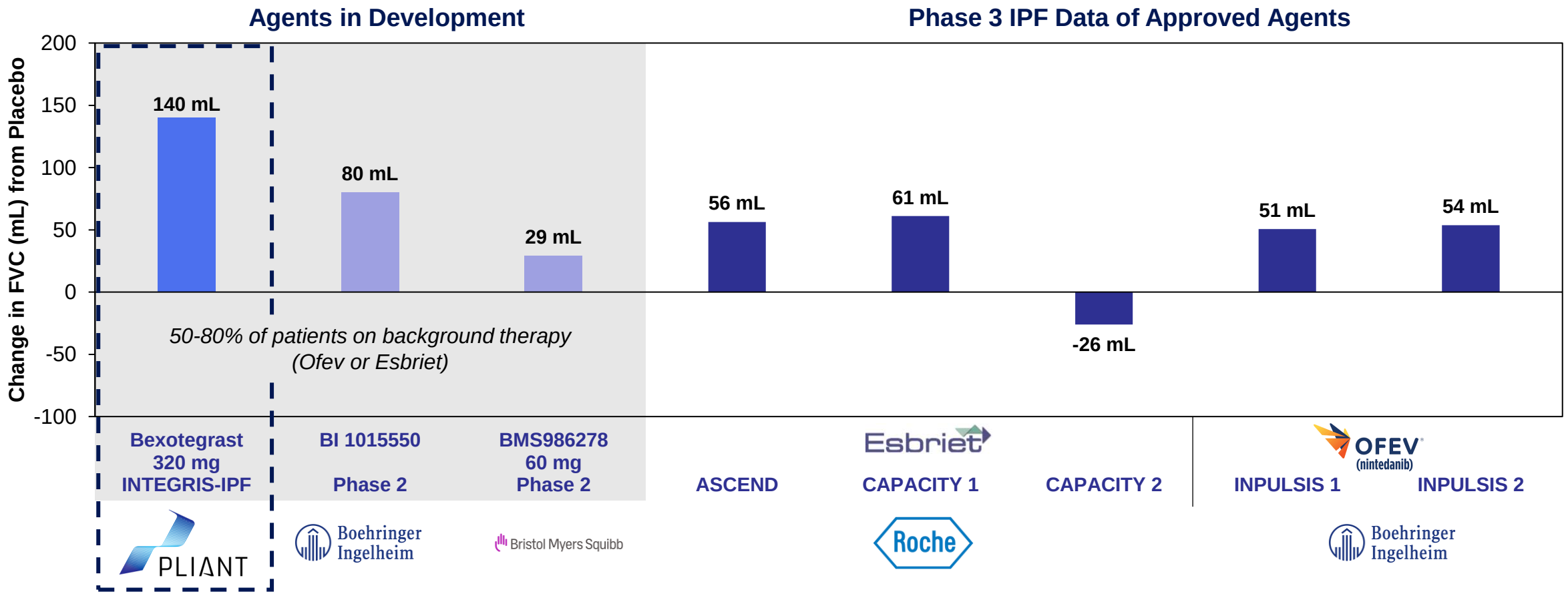
Absolute Change from Baseline Versus Placebo at 12-Weeks for Approved and Select Investigational Agents

Absolute Change from Baseline versus Placebo in FVC (mL) at 12 Weeks



Bexotegrast, BI-1015550 and BMS-986278 from Phase 2 trials. Graphic is not meant to represent a head-to-head study. Comparing the results from different trials may be unreliable due to different protocol designs, trial designs, patient selection and populations, number of patients, trial endpoints, trial objectives and other parameters that may not be the same across trials. Therefore, cross-study comparisons provide very limited information about the efficacy of safety of a drug. Bexotegrast INTEGRIS-IPF study consisted of n-22 subjects in the 320 mg arm, a significantly smaller number of patients than reflected in the other datasets represented on this slide. In larger trials of bexotegrast, the clinical activity suggested by our INTEGRIS-IPF trial may not be replicated

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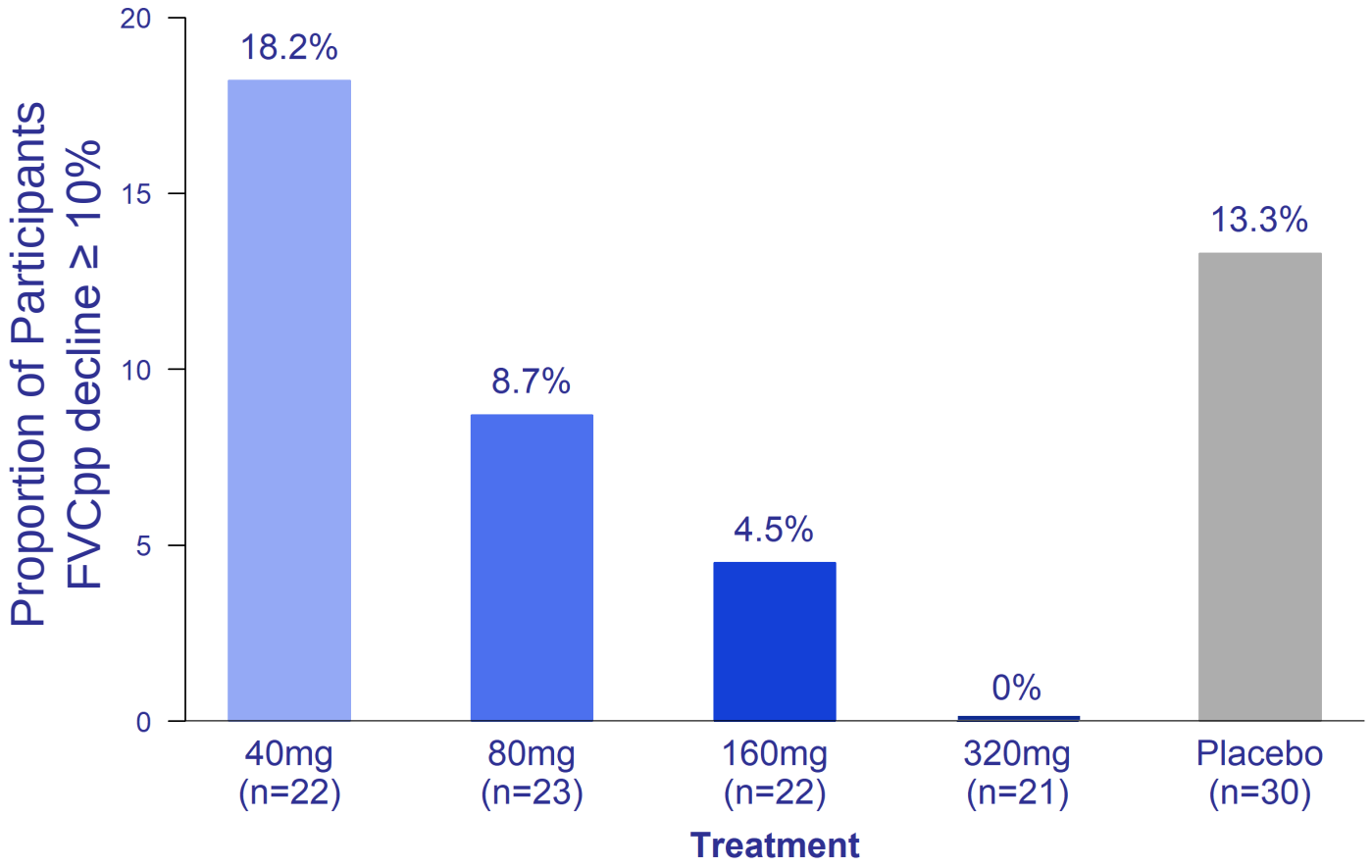
Proportion of Participants with Relative FVCpp Decline ≥ 10%
mITT Population

mITT Population at 12 Weeks



mITT Population at 24 Weeks

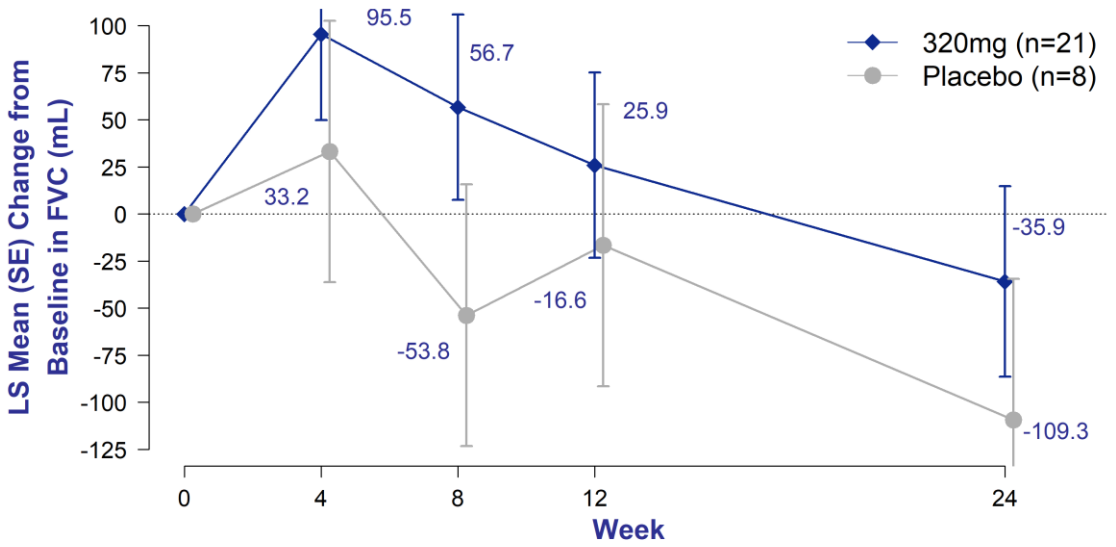
Bexotegrast reduced the decline in FVCpp by 68% relative to placebo from Baseline at Week 24

FVCpp = Forced vital capacity, percent predicted.

1- Ann Am Thorac Soc. 2017 Sep;14(9):1395-1402; 2- Am J Respir Crit Care Med. 2022 Apr 15;205(8):936-948.

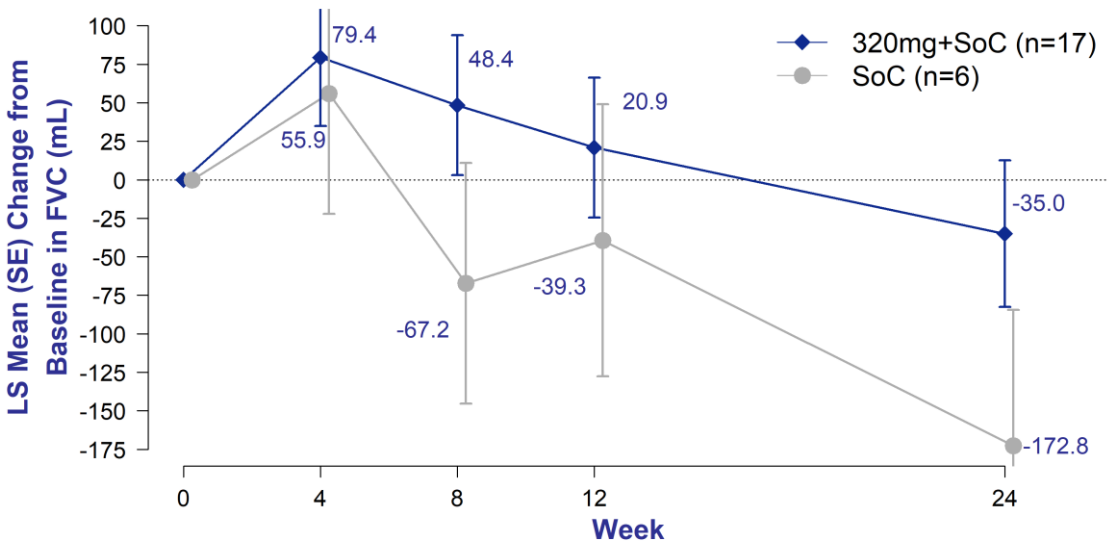
FVC Change from Baseline over 24 Weeks
ITT Population vs. SoC Sub-Group

ITT Population



Bexotegrast reduced FVC decline by 67% relative to placebo at Week 24

Standard-of-Care Sub-Group



Bexotegrast + SOC reduced FVC decline by 80% relative to SOC alone at Week 24

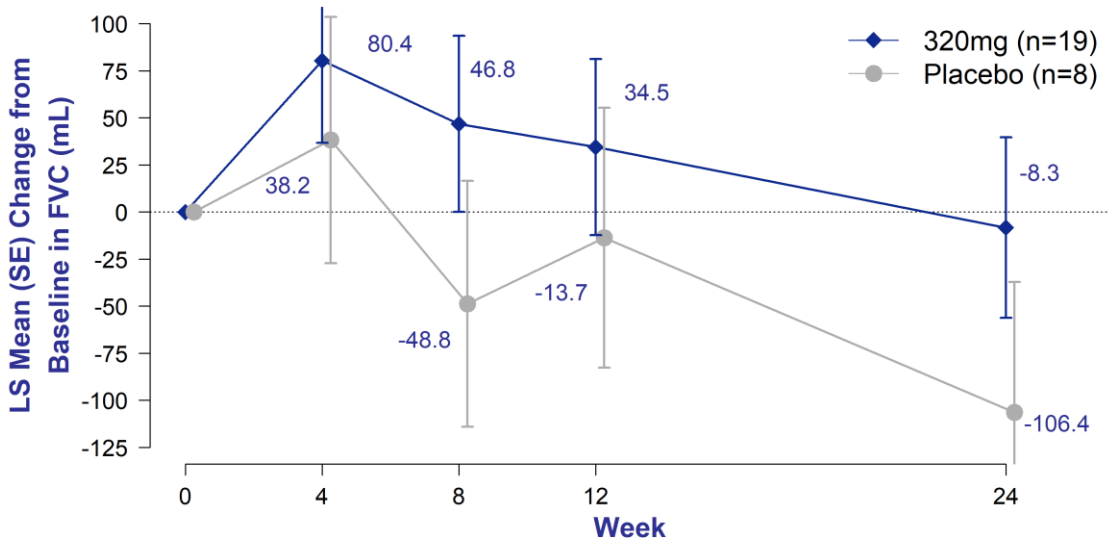
Participants not on SoC not shown due to small sample size, n=4 (320 mg) and n=2 (placebo)
FVC = forced vital capacity; ITT=intent to treat; SoC = standard of care (nintedanib or pirfenidone)

PLIANT

FVC Change from Baseline over 24 Weeks – Sensitivity Analysis

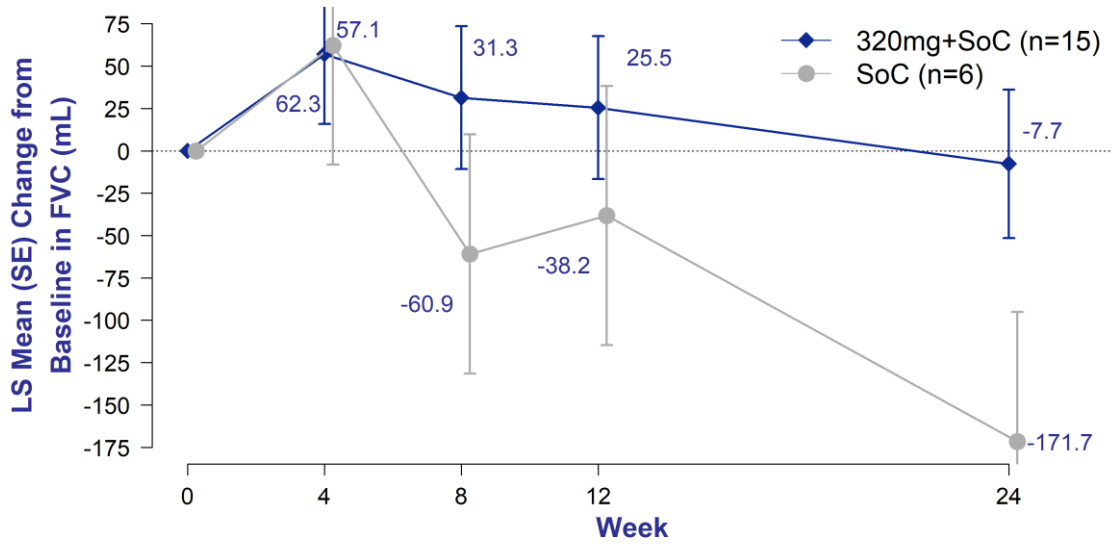
Trimmed Mean Sensitivity Analysis[1]

ITT Population



Bexotegrast reduced FVC decline by 92% relative to placebo at Week 24

Standard-of-Care Sub-Group

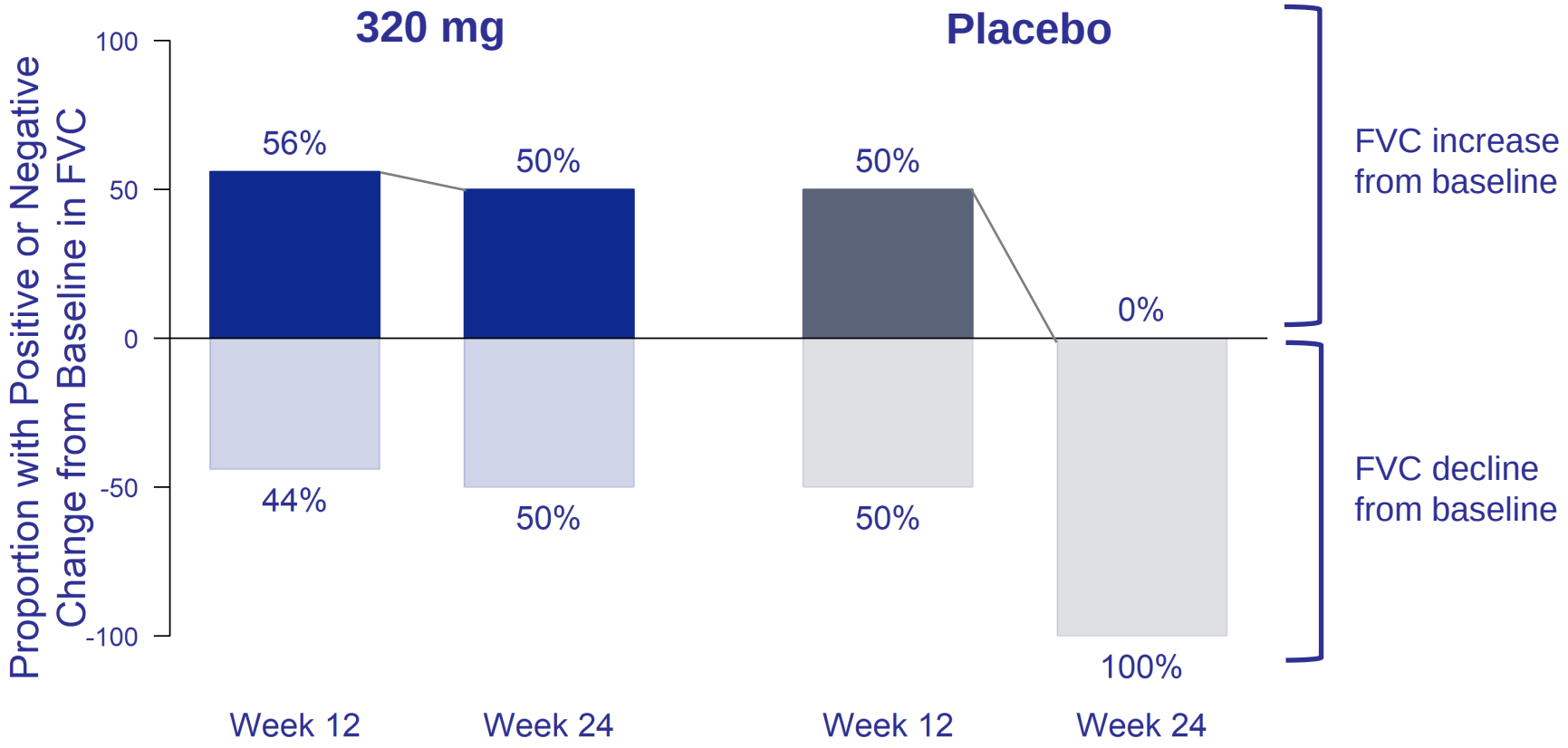


Bexotegrast + SOC reduced FVC decline by 96% relative to SOC alone at Week 24

1 – Trimmed Mean Sensitivity Analysis excludes the two bexotegrast-treated participants with the highest and lowest FVC values at Week 24.
Participants not on SoC not shown due to small sample size, n=4 (320 mg) and n=2 (placebo)
FVC = forced vital capacity; ITT = intent to treat; SoC = standard of care (nintedanib or pirfenidone)

PLIANT

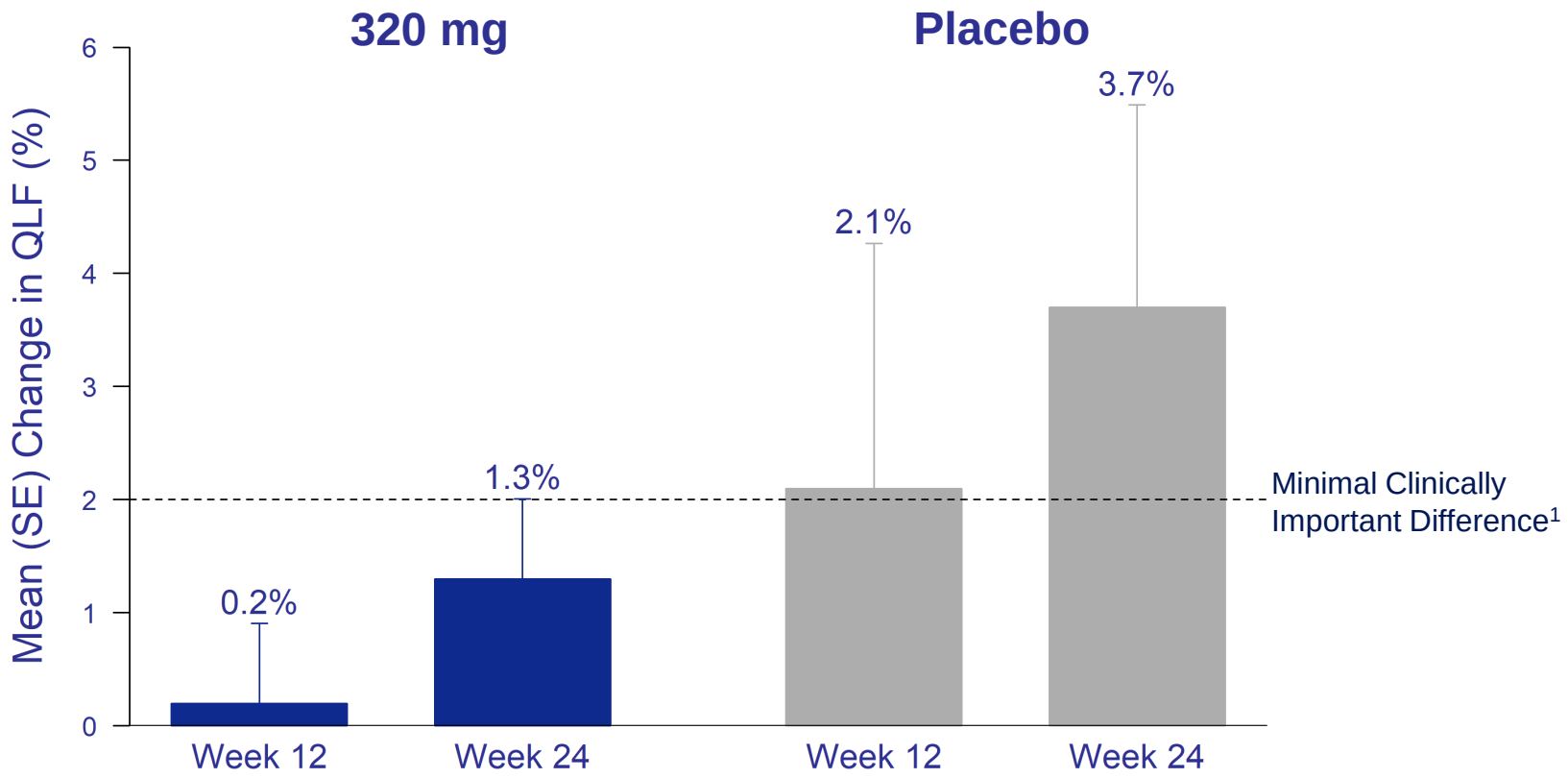
Bexotegrast Demonstrated Durable Increase in FVC at Week 24
ITT Population



89% of bexotegrast-treated participants with FVC increase at Week 12 maintained an increase at Week 24

FVC = forced vital capacity; ITT = intent to treat.
Participants with missing data not included

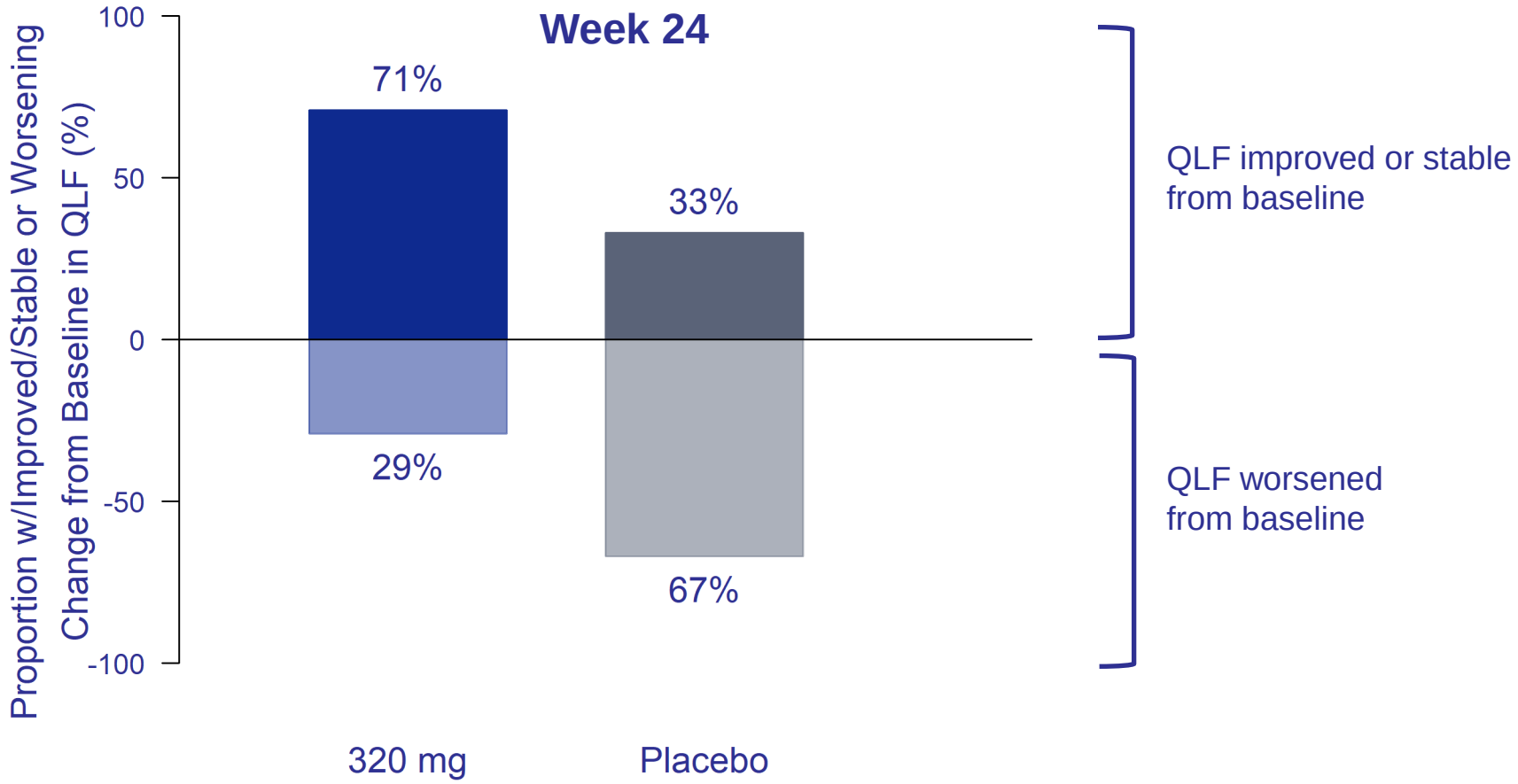
QLF Mean Percent Change from Baseline at Weeks 12 and 24
Per CT Protocol Population



Bexotegrast group demonstrated stabilization of fibrosis, in contrast to placebo group which showed clinically meaningful progression at Weeks 12 and 24

QLF = quantitative lung fibrosis; QLF Minimal Clinically Important Difference for whole lung: 2%; stable disease (-2%, 2%)
Per CT protocol population: Participants with both baseline and post baseline high resolution computed tomography (HRCT) scans meeting evaluability criteria per Imaging Charter
1 EU Radiology 2020 30:726-734

More Patients on Bexotegrast Showed Stabilization of Fibrosis at Week 24
Per CT Protocol Population

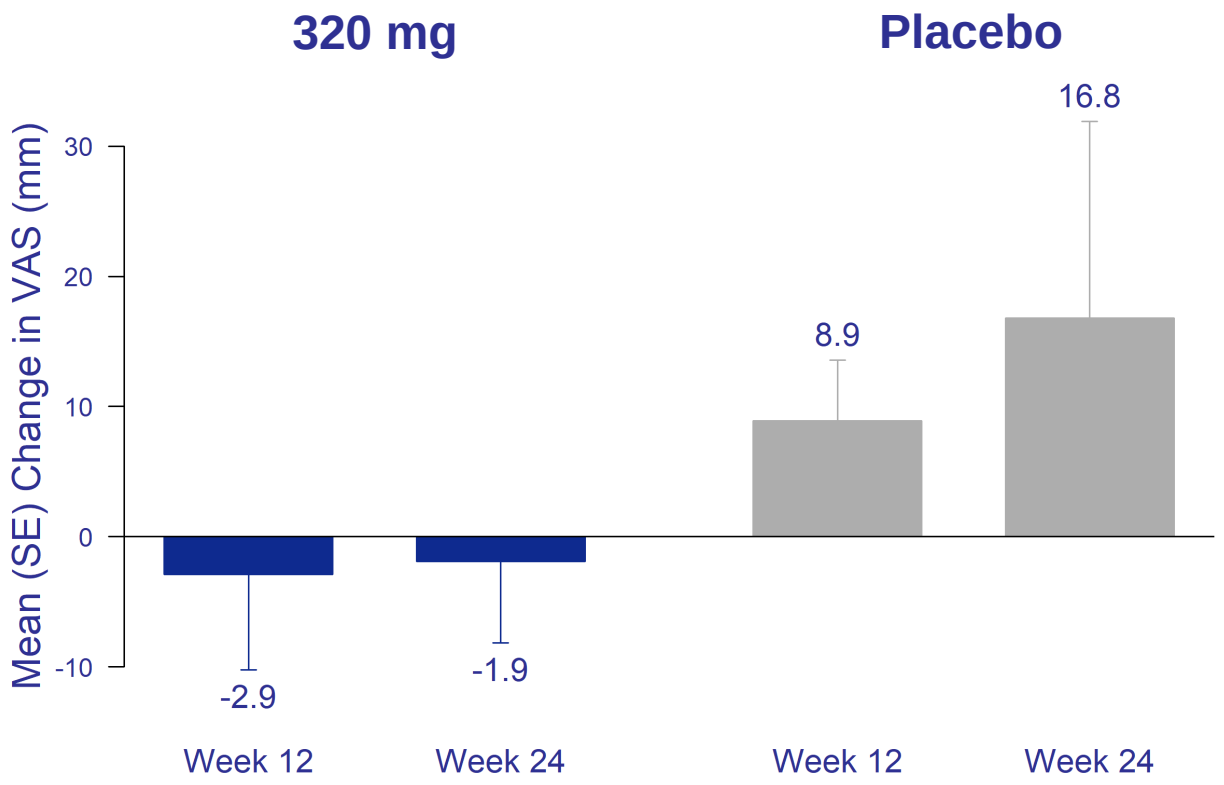


At Week 24, bexotegrast-treated participants were more than twice as likely to show stabilization or improvement of fibrosis relative to placebo

QLF = quantitative lung fibrosis; QLF Minimal Clinically Important Difference for whole lung: 2%; Improved disease <-2%, Stable disease (-2%, 2%), Worsened disease >2%
Per CT protocol population: Participants with both baseline and post baseline high resolution computed tomography (HRCT) scans meeting evaluability criteria per Imaging Charter

PLIANT

Cough Severity Visual Analog Scale (VAS) Change from Baseline
ITT Population

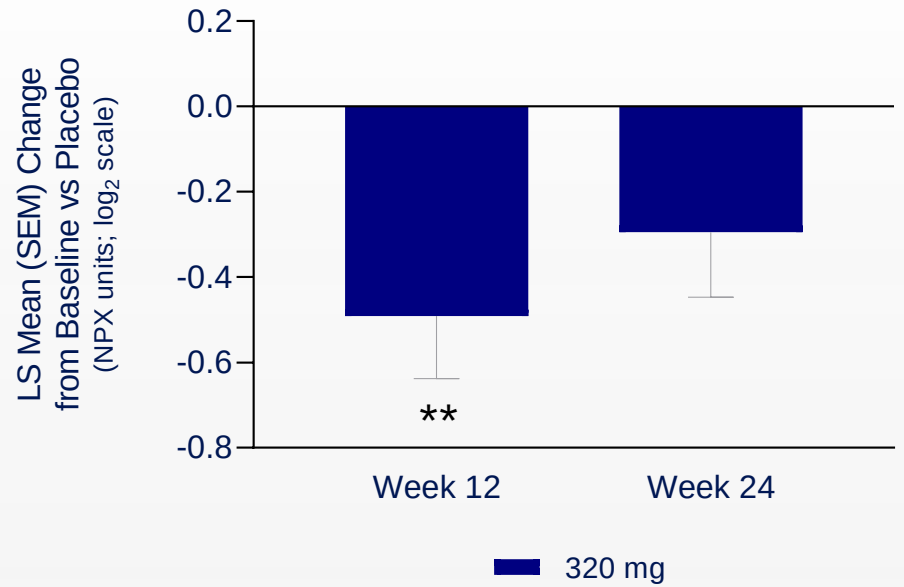


Chronic cough in IPF is an independent predictor of disease progression and mortality[1]

1 - *Respirology* 2011; 16: 969–975.
Cough VAS measures patient reported cough severity over last 2 weeks on scale of 0-100 mm

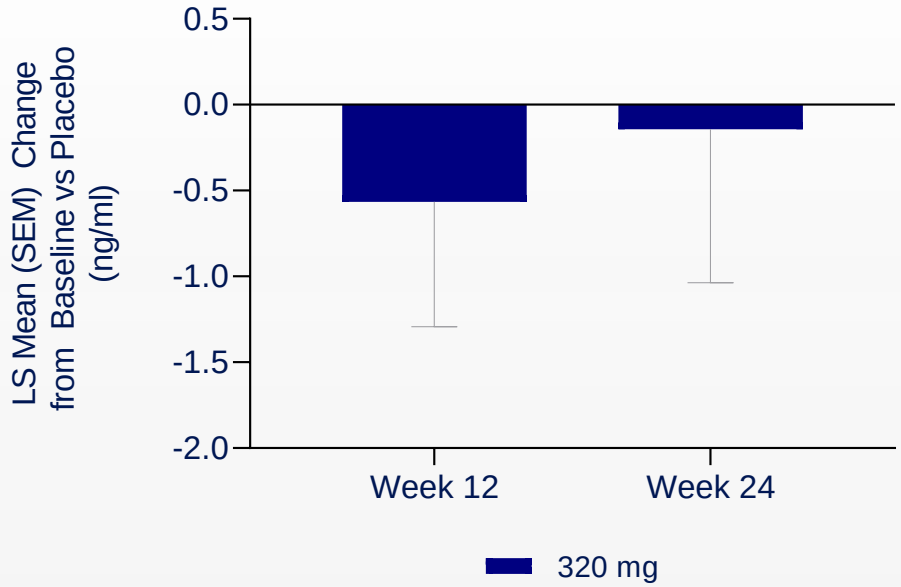
Bexotegrast Reduced Circulating Biomarkers ITGB6 and PRO-C3 Relative to Placebo

Plasma Integrin beta-6 (ITGB6)



** p < 0.01 vs placebo

Serum PRO-C3
Type III collagen synthesis neoepitope



Elevated integrin beta-6 plasma levels shown to be associated with ILD progression over 12 months[1]

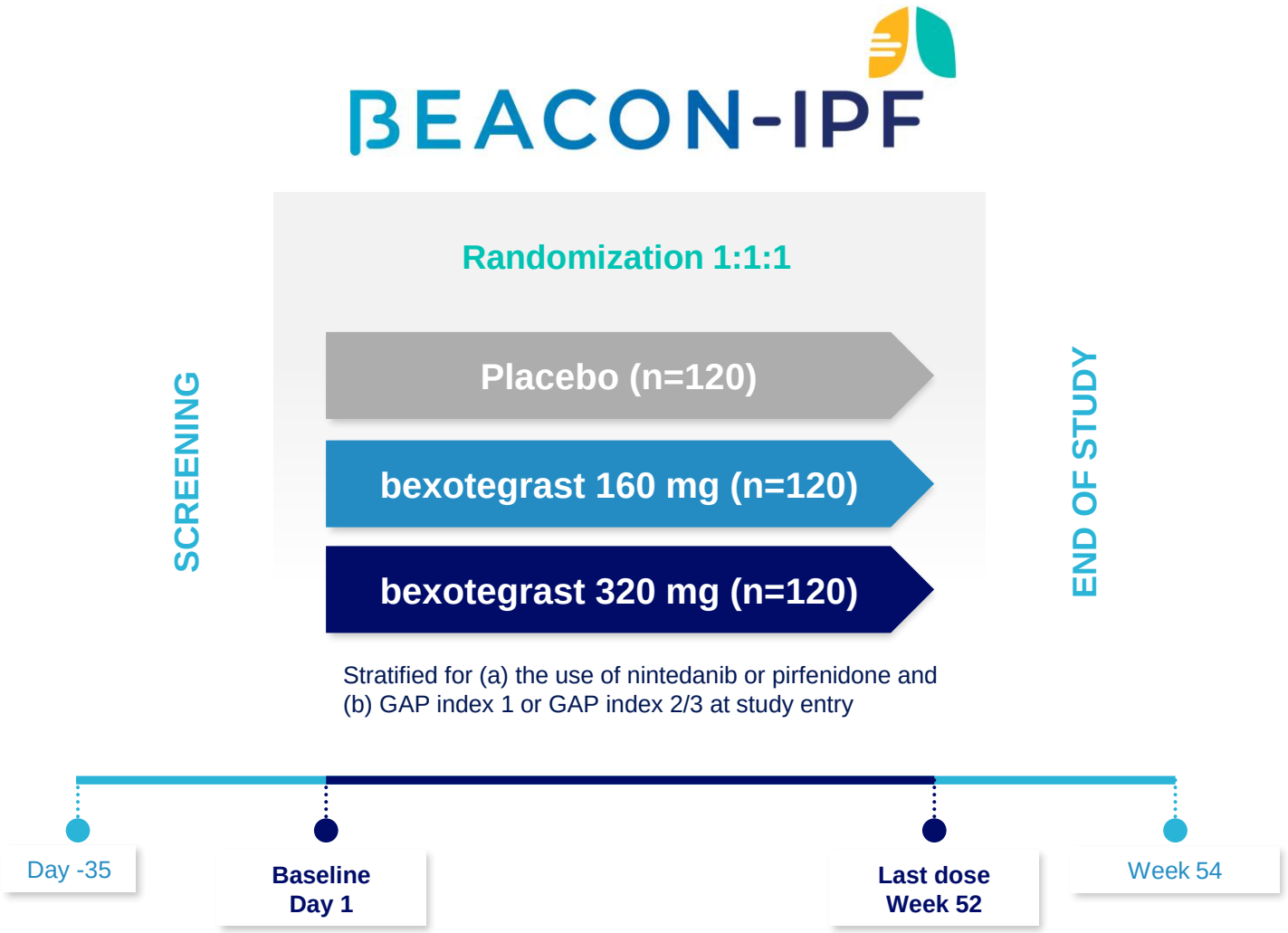
PRO-C3 shown to be elevated in patients with IPF and associated with progressive disease[2]

1- *Lancet Respir Med.* 2022 Jun;10(6):593-602; 2- *Respir Res*. 2019 Jul 12;20(1):148.

LS = Least Squares; SE = Standard Error; Integrin beta-6 data reported in relative quantitation log_2 scale

PLIANT

BEACON-IPF Phase 2b Study Design



Actively Enrolling

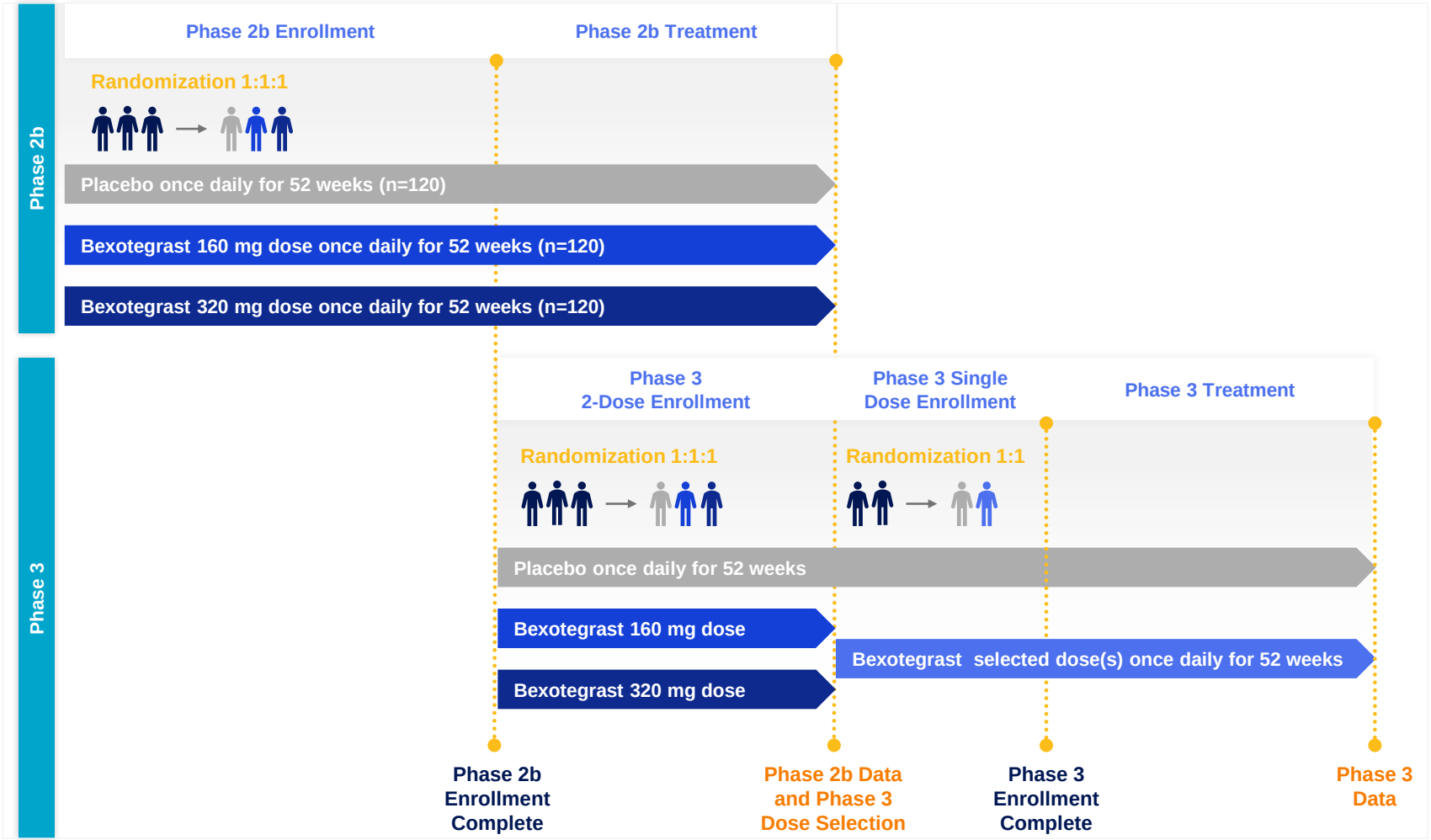
PRIMARY ENDPOINT

- Change from baseline in absolute FVC (mL) at Week 52

SECONDARY ENDPOINTS

- Time to disease progression (≥10% absolute decline from baseline in FVCpp, respiratory-related hospitalization, or all-cause mortality)
- Change from baseline in absolute FVC (mL) in participants on and off background therapy
- Quantitative Lung Fibrosis (QLF)
- Change from baseline in Living with Pulmonary Fibrosis total score at Week 52
- Safety and Tolerability

BEACON-IPF Phase 2b/3 Study Design – Endpoints



KEY PRIMARY ENDPOINT

- Change from baseline in absolute FVC (mL) at Week 52

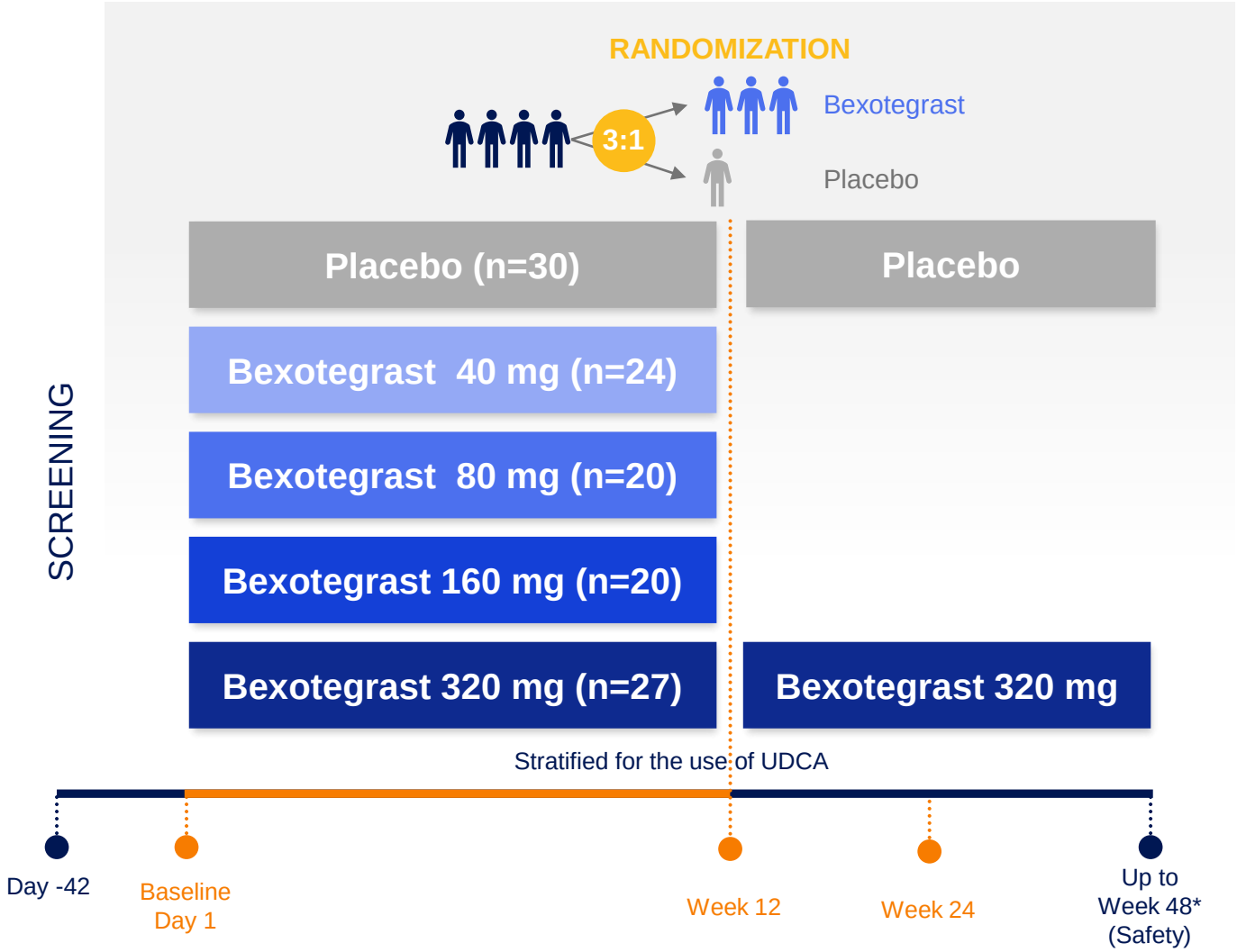
KEY SECONDARY ENDPOINTS

- Time to disease progression (≥ 10% absolute decline from baseline in FVCpp, respiratory-related hospitalization, or all cause mortality throughWeek 52)
- Change from baseline in absolute FVC (mL) at Week 52 in those ON and NOT on background therapy
- Change from baseline in Living with Pulmonary Fibrosis Dyspnea and Cough Domain scores at Week 52
- Safety and tolerability over 52 weeks

PLIANT

INTEGRIS-PSC Study Design and Objectives

First PSC Trial Enriched with Participants with Suspected Liver Fibrosis



PRIMARY AND SECONDARY ENDPOINTS

- Safety, tolerability, PK

EXPLORATORY ENDPOINTS

- Changes in liver fibrosis markers, ELF score and PRO-C3
- Changes in liver imaging
- Changes in liver biochemistry

INCLUSION CRITERIA

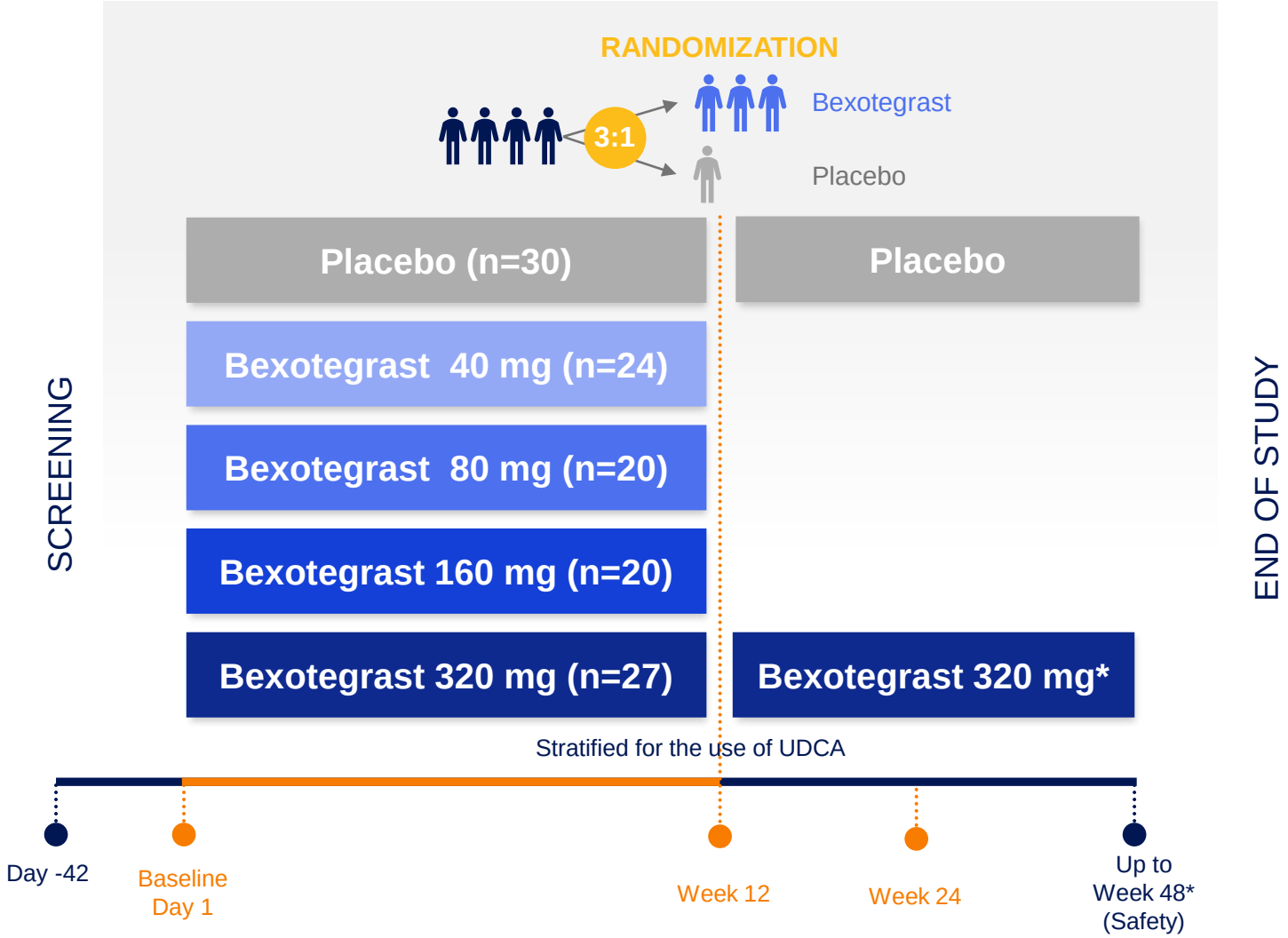
- At-risk for moderate/severe fibrosis defined by at least one criterion:
  - ELF ≥ 7.7
  - TE ≥ 8 but ≤ 14.4 kPa
  - MRE ≥ 2.4 but ≤ 4.9 kPa
  - Historical biopsy

UDCA = Ursodeoxycholic acid ; TE = Transient elastography; ELF = enhanced liver fibrosis

*Trial will complete once the last trial participant enrolled reaches 24 weeks of treatment

INTEGRIS-PSC Study Design and Objectives

First PSC Trial Enriched with Participants with Suspected Liver Fibrosis



PRIMARY AND SECONDARY ENDPOINTS

- Safety, tolerability, PK

EXPLORATORY ENDPOINTS

- Changes in liver fibrosis markers, ELF score and PRO-C3
- Changes in liver biochemistry
- Changes in liver imaging

INCLUSION CRITERIA

- Suspected moderate/severe fibrosis defined by at least one criterion:
  - ELF ≥ 7.7
  - TE ≥ 8 but ≤ 14.4 kPa
  - MRE ≥ 2.4 but ≤ 4.9 kPa
  - Historical biopsy

UDCA = Ursodeoxycholic acid; ELF = enhanced liver fibrosis

*Trial will complete once the last trial participant enrolled reaches 24 weeks of treatment

INTEGRIS-PSC – Key Findings at Week 12

Bexotegrast was Well Tolerated in Participants with PSC

- No safety concerns identified across all dose groups, including the 320 mg dose group
- The most common AEs were observed at lower rates in bexotegrast-treated patients vs. placebo
- No treatment-related SAEs on bexotegrast

Bexotegrast Demonstrated Antifibrotic Activity in a PSC Population with Suspected Liver Fibrosis

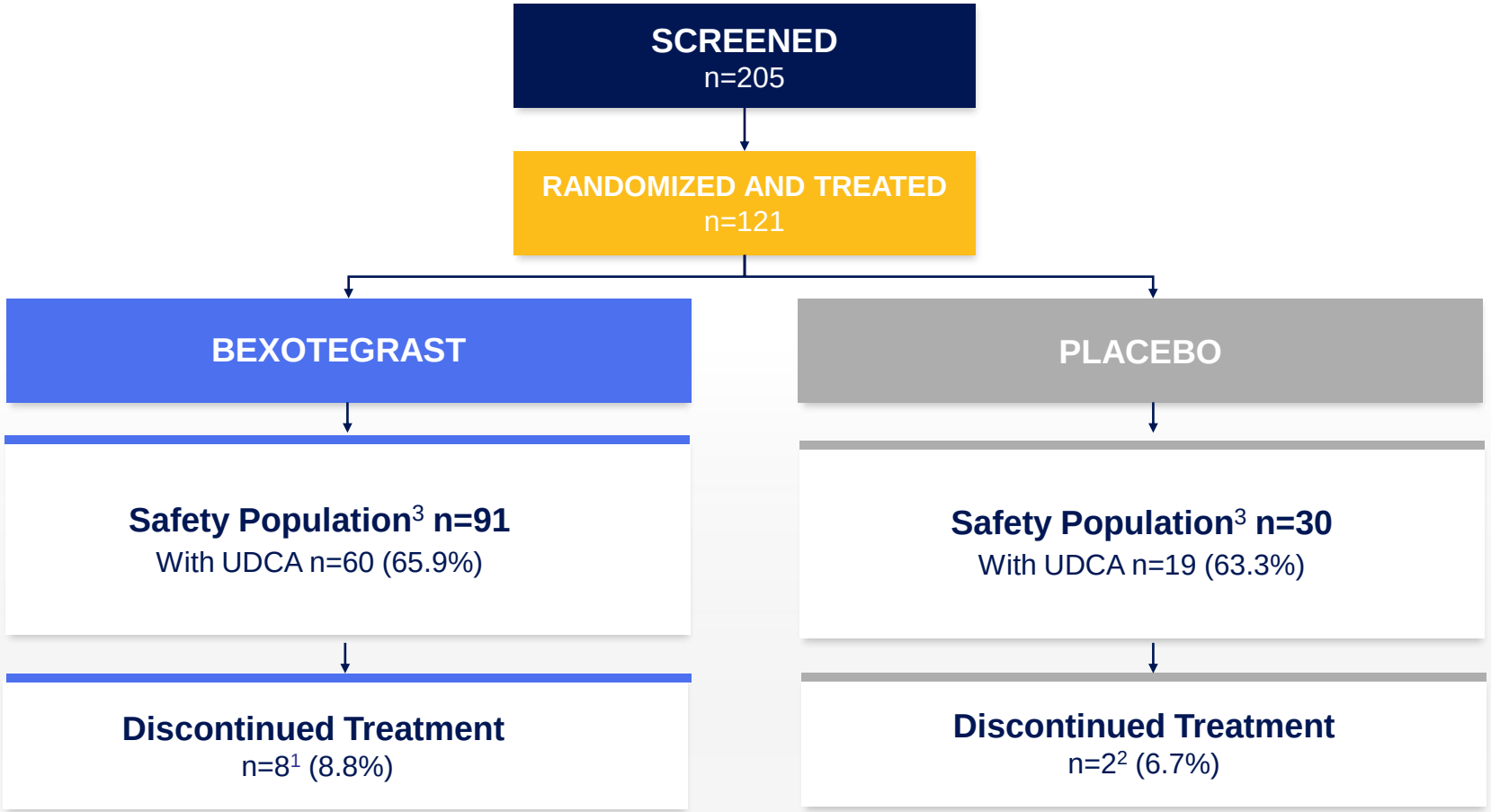
- Reduced liver fibrosis markers ELF and PRO-C3 at all doses relative to placebo over short-term treatment
- Contrast MRI suggested improved hepatocyte function and bile flow at all doses relative to placebo

Additional Findings

- Statistically significant reductions in itch relative to placebo for the 160 mg and 320 mg doses
- ALP remained stable at all doses relative to increases on placebo

PLIANT

INTEGRIS-PSC – Participant Disposition



1 – Adverse Event (n=4; 40 mg, 80 mg, 160 mg, 320 mg) Protocol Deviation (n=1; 40 mg) Withdrawal by subject (n=2, 320 mg) other (n=1 320 mg); 2 – Adverse Event (n=2); 3 – Safety population is the key population for both analysis of safety and efficacy

UDCA = Ursodeoxycholic acid

INTEGRIS-PSC – Baseline Demographics

Characteristic	Bexotegrast 40mg (n=24)*	Bexotegrast 80mg (n=20)*	Bexotegrast 160mg (n=20)*	Bexotegrast 320mg (n=27)	Bexotegrast All (n=91)	Placebo (n=30)
Male sex, n (%)	17 (70.8)	16 (80.0)	14 (70.0)	13 (48.1)	60 (65.9)	24 (80.0)
Age (yr), mean (SD)	46.9 (15.06)	40.5 (15.32)	45.1 (12.65)	47.1 (14.47)	45.2 (14.44)	45.2 (13.75)
Race, n (%)						
White	20 (83.3)	16 (80.0)	18 (90.0)	26 (96.3)	80 (87.9)	25 (83.3)
Black	2 (8.3)	2 (10.0)	1 (5.0)	0	5 (5.5)	2 (6.7)
Asian	2 (8.3)	1 (5.0)	1 (5.0)	1 (3.7)	5 (5.5)	1 (3.8)
Other / Not Reported / Unknown	0	1 (5.0)	0	0	1 (1.1)	2 (6.7)
Time since diagnosis of PSC (yr), mean (SD)	11.1 (8.15)	8.3 (7.97)	7.8 (6.78)	9.7 (11.56)	9.3 (8.89)	9.1 (7.45)
Concomitant UDCA use, n (%)	14 (58.3)	15 (75.0)	13 (65.0)	18 (66.7)	60 (65.9)	19 (63.3)
IBD, n (%)	18 (75.0)	12 (60.0)	11 (55.0)	13 (48.1)	54 (59.3)	17 (56.7)
Ulcerative colitis	11 (45.8)	6 (30.0)	7 (35.0)	6 (22.2)	30 (33.0)	10 (33.3)
Crohn’s disease	6 (25.0)	4 (20.0)	2 (10.0)	8 (29.6)	20 (22.0)	6 (20.0)
IBD Other	3 (12.5)	2 (10.0)	2 (10.0)	0	7 (7.7)	1 (3.3)
Partial Mayo Score, mean (SD)	0.7 (1.08)	1.6 (2.54)	1.1 (1.27)	0.8 (1.17)	1.0 (1.57)	0.5 (1.36)
Itch NRS, mean (SD)	1.8 (2.54)	2.1 (2.63)	1.4 (1.50)	0.9 (1.77)	1.5 (2.15)	1.0 (1.43)

Duration since diagnosis at screening is calculated from the first reported date for preferred terms of PSC.
Partial Mayo score only reported for those with active IBD at Baseline
BMI = Body Mass Index; IBD= inflammatory bowel diseases; NRS= numerical Rating scale;
SD = Standard deviation

* Two participants (80 mg and 160mg) were dispensed incorrect number of tablets and provided incorrect dosing instructions for the full treatment period due to an error at a single site. The participants’ daily dose corresponded to a ≤40 mg dose. These 2 participants are grouped in the 40 mg dose group for all summaries.

INTEGRIS-PSC – Baseline Disease Activity Markers

	Bexotegrast 40mg (n=24)	Bexotegrast 80mg (n=20)	Bexotegrast 160mg (n=20)	Bexotegrast 320mg (n=27)	Bexotegrast All (n=91)	Placebo (n=30)
Liver Biochemistry, mean (SD)						
Alkaline phosphatase (ALP) (U/L)	315.1 (140.26)	199.2 (81.03)	273.8 (165.63)	190.6 (91.29)	243.6 (132.13)	277.4 (215.88)
Alanine aminotransferase (ALT) (U/L)	91.5 (62.08)	67.6 (63.15)	98.4 (73.11)	60.4 (37.76)	78.5 (60.20)	73.1 (59.84)
Aspartate aminotransferase (AST) (U/L)	67.2 (49.34)	46.4 (30.12)	69.0 (39.62)	44.6 (24.69)	56.3 (38.10)	51.6 (37.13)
Total Bilirubin (mg/dL)	0.66 (0.307)	0.79 (0.493)	0.88 (0.396)	0.53 (0.208)	0.70 (0.373)	0.82 (0.373)
Direct bilirubin (mg/dL)	0.27 (0.164)	0.26 (0.188)	0.31 (0.166)	0.16 (0.062)	0.24 (0.156)	0.31 (0.238)
Markers of Fibrosis, mean (SD)						
ELF Score	9.6 (0.77)	9.2 (1.01)	9.4 (0.79)	9.0 (0.84)	9.3 (0.87)	9.3 (1.03)
PRO-C3 (ng/mL)	49.96 (13.844)	48.84 (42.790)	46.12 (11.670)	46.48 (19.536)	47.81 (24.058)	48.50 (24.329)
Transient Elastography (kPa)	10.1 (2.62)	9.1 (2.99)	8.2 (3.16)	8.7 (3.14)	9.0 (3.02)	8.6 (2.8)

ELF: Enhanced Liver Fibrosis; PROC-C3: neo-epitope pro-peptide of type III collagen formation.
PRO-C3 quantified using Roche COBAS platform (assay reports approximately 2x higher concentrations than previous generation PRO-C3 ELISA)

INTEGRIS-PSC – Safety Summary

AE, n (%) of Participants Reporting	Bexotegrast 40mg (n=24)	Bexotegrast 80mg (n=20)	Bexotegrast 160mg (n=20)	Bexotegrast 320mg (n=27)	Bexotegrast All (n=91)	Placebo (n=30)
TEAE	10 (41.7)	16 (80.0)	15 (75.0)	20 (74.1)	61 (67.0)	20 (66.7)
Related to study drug	**1 (4.2)**	**6 (30.0)**	**4 (20.0)**	**0**	**11 (12.1)**	**7 (23.3)**
Serious TEAE	1 (4.2)	1 (5.0)	0	0	2 (2.2)	0
Related to study drug	**0**	**0**	**0**	**0**	**0**	**0**
TEAE of CTCAE Grade 3 or Higher	1 (4.2)	2 (10.0)	1 (5.0)	1 (3.7)	5 (5.5)	3 (10.0)
Related to study drug	**0**	**0**	**0**	**0**	**0**	**2 (6.7)**
TEAE Leading to Interruption of Study Drug	1 (4.2)[1]	0	0	4 (14.8)[5]	5 (5.5)	1 (3.3)[7]
TEAE Leading to Withdrawal of Study Drug	1 (4.2)[2]	1 (5.0)[3]	1 (5.0)[4]	1 (3.7)[6]	4 (4.4)	2 (6.7)[8]
TEAE Leading to Early Termination from Study	0	0	1 (5.0)[4]	0	1 (1.1)	0
TEAE Leading to Death	0	0	0	0	0	0

1 – chills/constipation/fatigue/nausea/pyrexia/vomiting; 2 – COVID-19/dyspnoea/nasal congestion; 3 – Hepatic enzyme increase/Pruritus ; 4 – Fatigue; 5 – fatigue; cough; oropharyngeal pain; increased ALT; 6 – increased ALP, ALT and AST; 7 – abdominal pain upper/fatigue/ocular icterus/pruritus; 8 – cardiomegaly/dyspnoea/malaise; headache

AE = Adverse Event; TEAE = Treatment Emergent Adverse Event; SAE = Serious Adverse Events. Adverse events coded using MedDRA v. 24.0.
TEAE is defined as any AE starting (or worsening) on or after the date of first dose.

PLIANT

INTEGRIS-PSC – Most Frequent TEAEs

TEAE, n (%) of Participants Reporting	Bexotegrast 40mg (n=24)	Bexotegrast 80mg (n=20)	Bexotegrast 160mg (n=20)	Bexotegrast 320mg (n=27)	Bexotegrast All (n=91)	Placebo (n=30)
Most frequent TEAEs (n ≥ 3 in at least one arm)						
Fatigue	3 (12.5)	2 (10.0)	4 (20.0)	3 (11.1)	12 (13.2)	4 (13.3)
Pruritus[1]	2 (8.3)	4 (20.0)	3 (15.0)	2 (7.4)	11 (12.1)	6 (20.0)
Headache	1 (4.2)	2 (10.0)	3 (15.0)	2 (7.4)	8 (8.8)	4 (13.3)
COVID-19	2 (8.3)	1 (5.0)	0	4 (14.8)	7 (7.7)	3 (10.0)
Nausea	1 (4.2)	2 (10.0)	3 (15.0)	1 (3.7)	7 (7.7)	0
Frequent bowel movements	0	3 (15.0)	0	0	3 (3.3)	3 (10.0)
Cholangitis	0	1 (5.0)	1 (5.0)	0	2 (2.2)	4 (13.3)
Pyrexia	1 (4.2)	0	0	0	1 (1.1)	3 (10.0)
Dyspepsia	0	0	0	0	0	3 (10.0)
Ocular icterus	0	0	0	0	0	3 (10.0)

1- Pruritus includes preferred terms for pruritus and cholestatic pruritus

TEAE = Treatment Emergent Adverse Event; Adverse events coded using MedDRA version 24.0.
TEAE is defined as any AE starting (or worsening) on or after the date of first dose

PLIANT

INTEGRIS-PSC – Serious Adverse Events

No SAEs were Related to Study Drug

Treatment Group	SAE Preferred Term	Standard Toxicity Grade	Treatment Related	Any alternative cause or confounding factors?	Action Taken	Outcome
40 mg	Cholecystitis / Abdominal pain / Pancreatitis	Grade 3 (all) (Severe)	No	ERCP (post-procedure)	Hospitalization; **Event in follow-up Period (3-4 weeks post last dose)**	Recovered / Resolved
80 mg	Cholangitis	Grade 3 (Severe)	No	No [1]	Hospitalization; Dose not changed	Recovered / Resolved

1 – Patient has medical history of cholangitis.

SAE = Serious Adverse Events. Adverse events coded using MedDRA version 24.0.

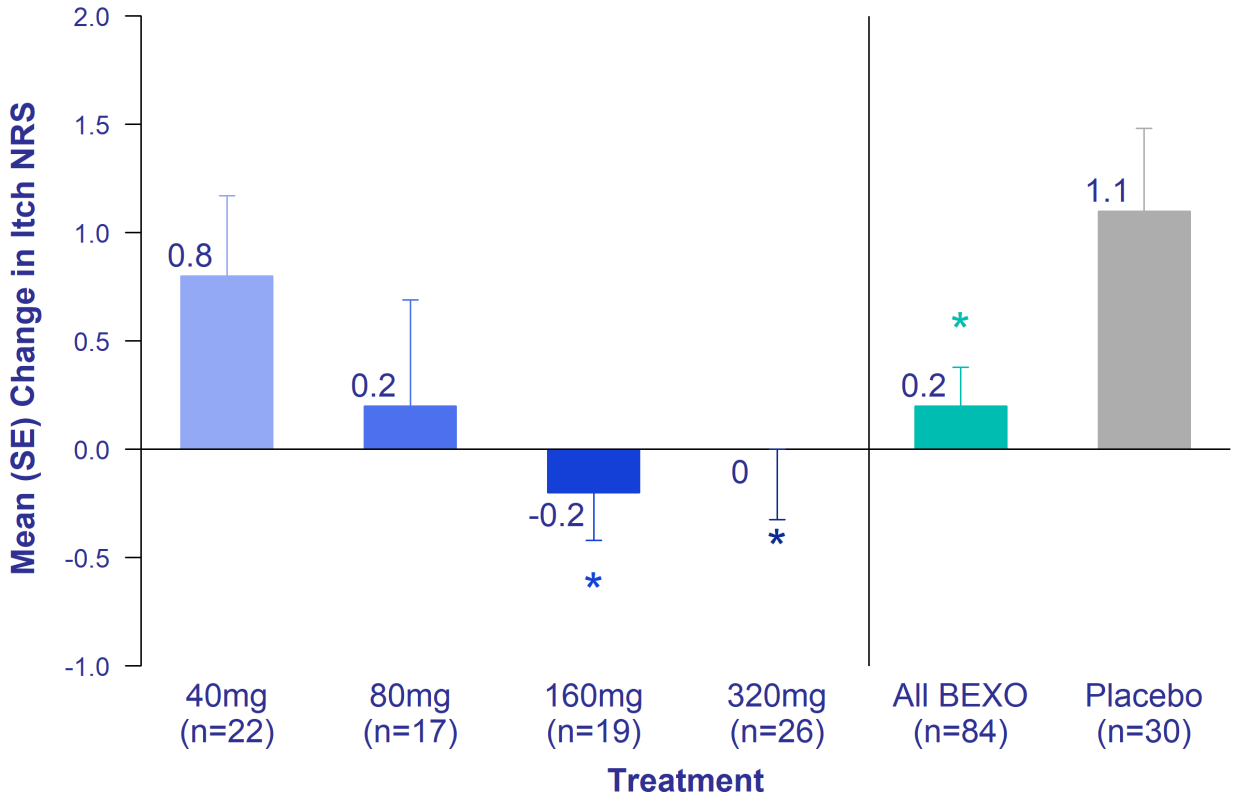
INTEGRIS-PSC – TEAEs Leading to Withdrawal of Study Drug

Treatment Group	AE Preferred Term (s)	Standard Toxicity Grade	Treatment Related	Any alternative cause or confounding factors?	Action Taken	Outcome
40 mg	COVID-19 / Nasal congestion / Dyspnoea	Grade 1 (Mild)	No	COVID-19	Drug withdrawn	Recovered / Resolved
80 mg	Hepatic enzyme increased / Pruritus	Grade 1 (Mild)	Yes	Variation in PSC / Aggravation of PSC	Drug withdrawn	Recovered / Resolved
160 mg	Fatigue	Grade 2 (Moderate)	Yes	No	Drug withdrawn	Recovered / Resolved
Placebo	Dyspnoea / Malaise / Cardiomegaly	Grade 2 (Moderate) / Grade 3 (Severe) / Grade 1 (Mild)	Yes	No	Drug withdrawn	Recovered / Resolved
Placebo	Headache	Grade 1 (Mild)	Yes	Fasting before drug administration	Drug withdrawn	Recovered / Resolved

TEAE = Treatment Emergent Adverse Event; Adverse events coded using MedDRA version 24.0.
TEAE is defined as any AE starting (or worsening) on or after the date of first dose

Itch Numerical Rating Scale – Change from Baseline at Week 12

Safety Population



* p < 0.05 vs placebo

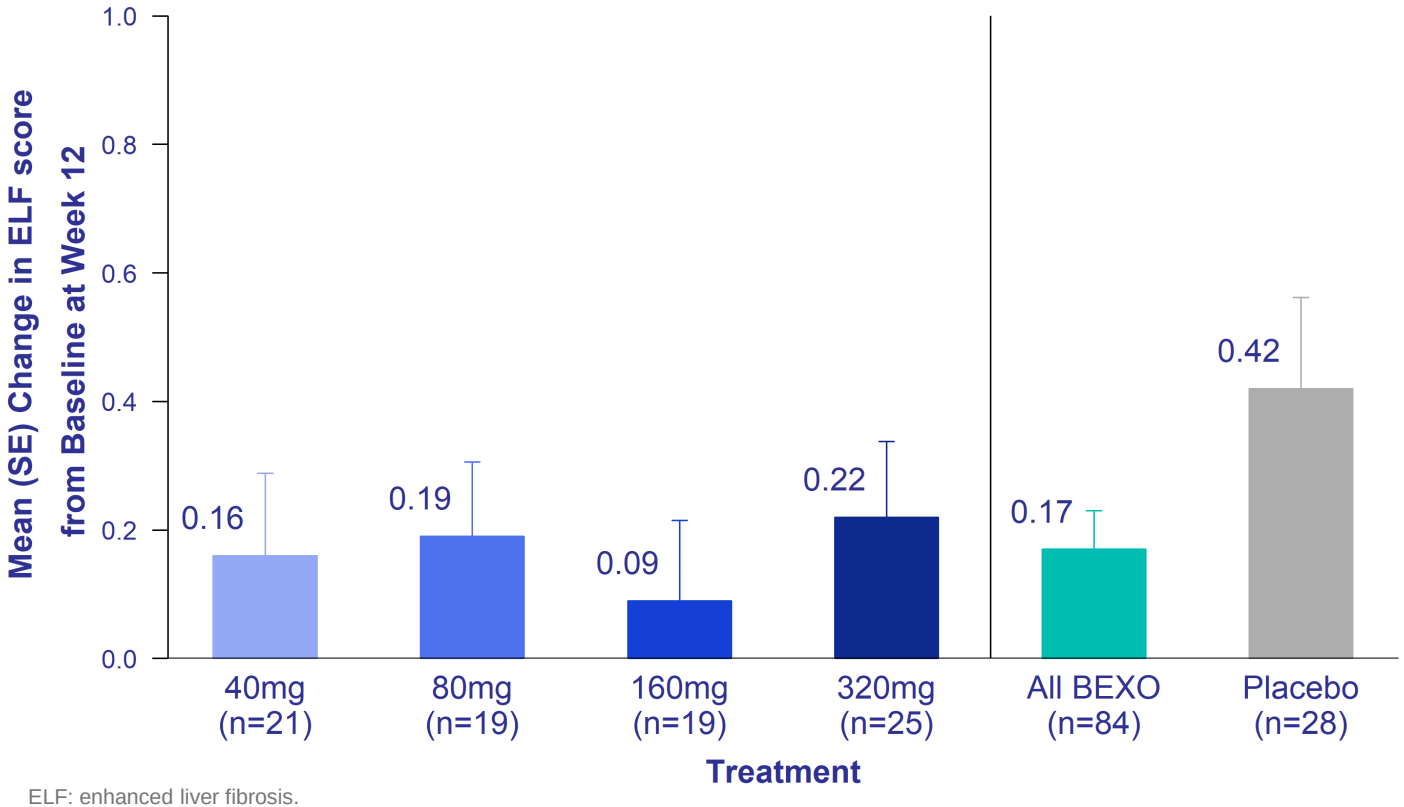
Bexotegrast showed statistically significant reductions in itch relative to placebo for the 160 mg and 320 doses

NRS: Numerical Rating scale; Itch NRS is a patient reported outcome which assesses severity of itch, over the last 24 hours, on a scale of 0 (no itch) to 10 (Worst imaginable itching).

PLIANT

ELF Score – Change from Baseline at Week 12

Safety Population



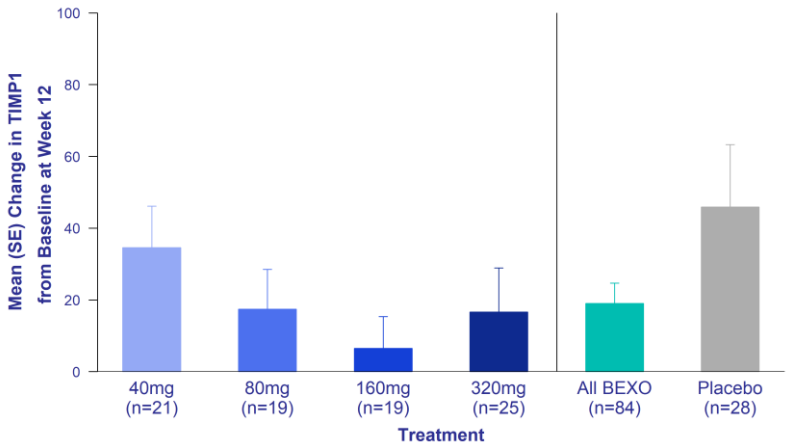
ELF: enhanced liver fibrosis.

Bexotegrast reduced ELF score relative to placebo at all doses

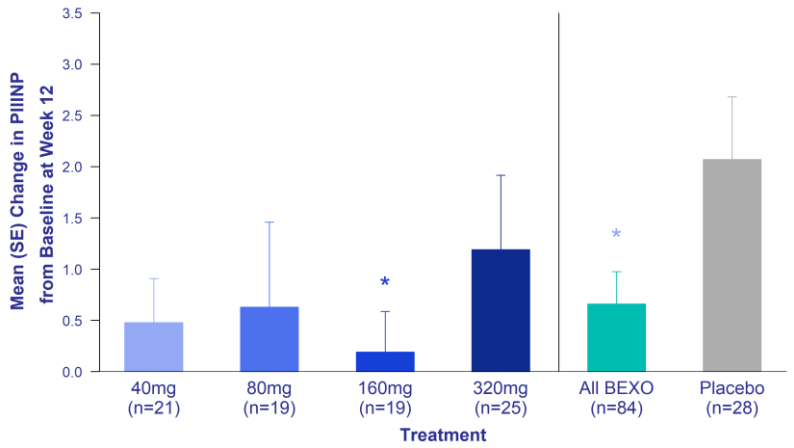
ELF Score Components - Change from Baseline at Week 12

Safety Population

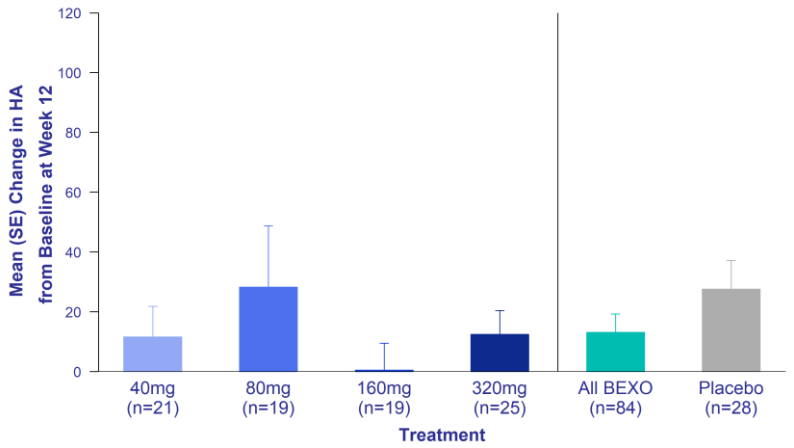
TIMP-1



PIIINP



HA

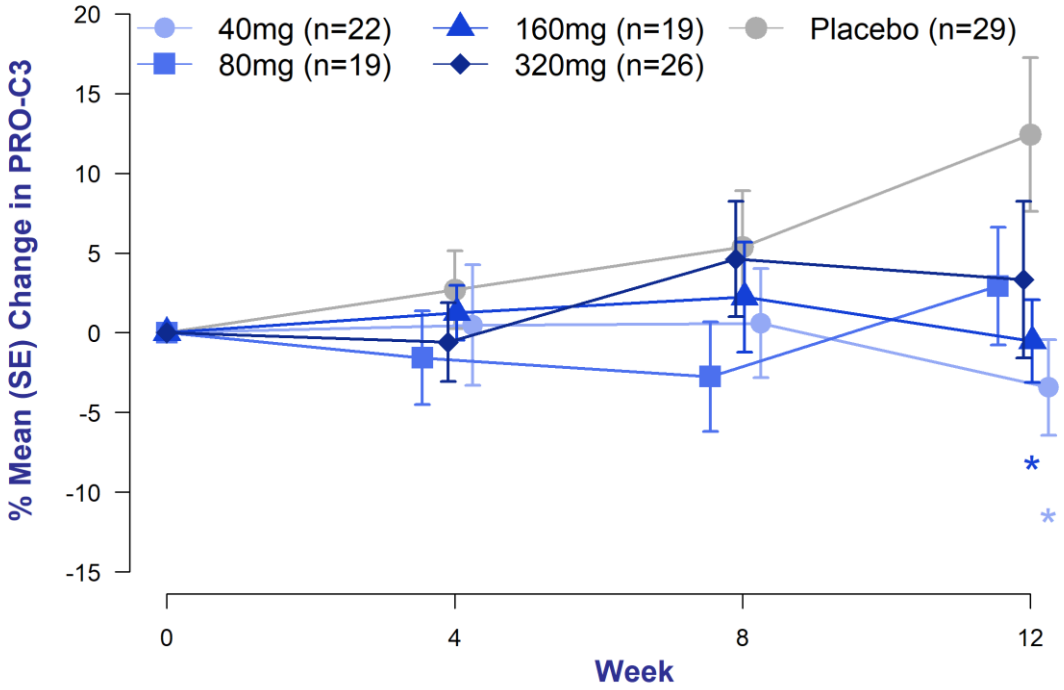


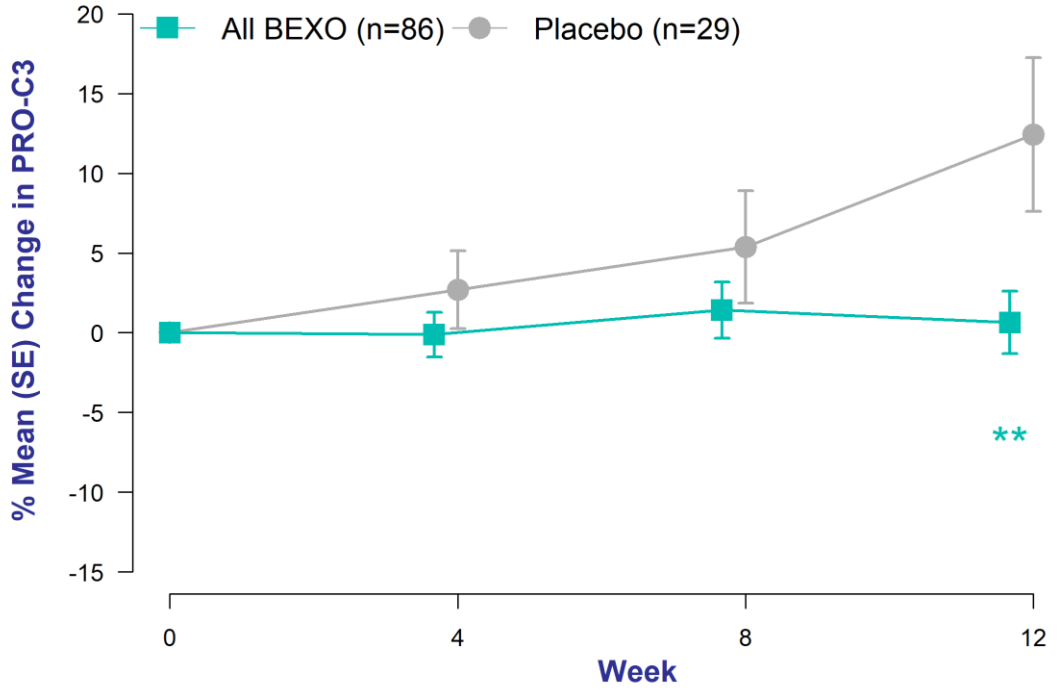
Bexotegrast reduced all components of ELF score compared to placebo

TIMP-1:Tissue inhibitor of metalloproteinases-1; HA: Hyaluronic acid ; PIIINP: Procollagen III, N-terminal propeptide

PRO-C3 – Percent Change from Baseline

Safety Population





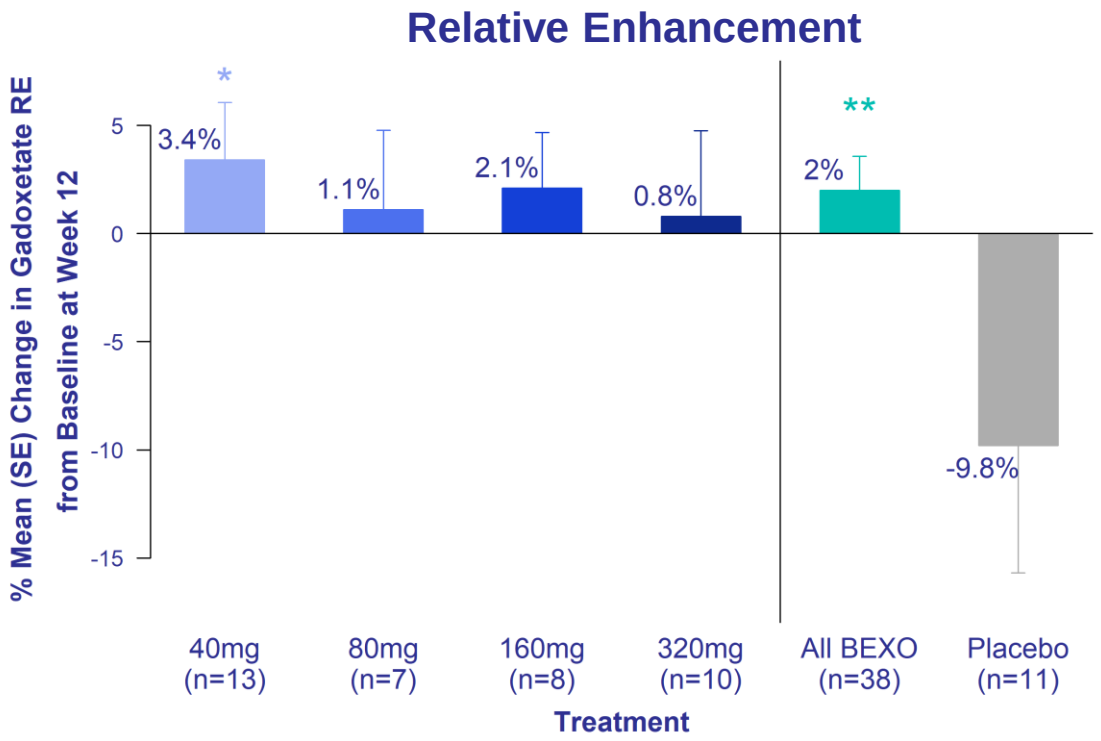
* p < 0.05 vs placebo
** p < 0.01 vs placebo

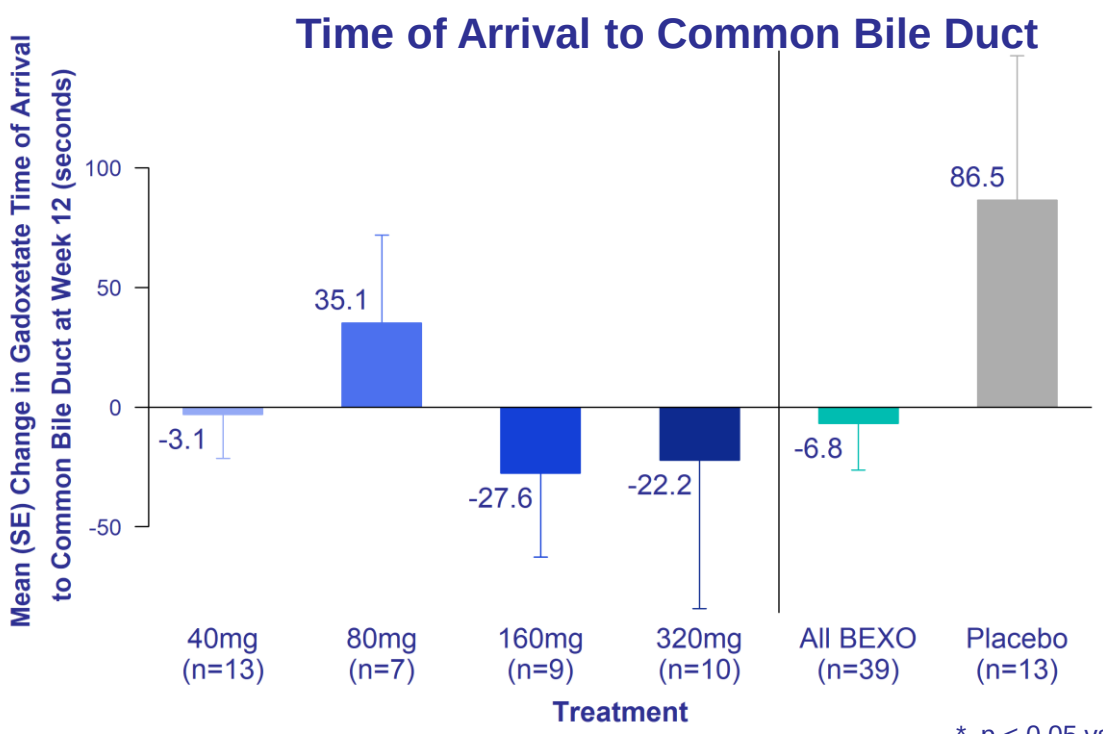
All doses reduced collagen synthesis (PRO-C3) relative to placebo with statistical significance at Week 12 for 40 mg and 160 mg doses

PROC-C3: neo-epitope pro-peptide of type III collagen formation.
Only participates with both a baseline and post baseline are summarized.

MRI Parameters – Change from Baseline at Week 12

Sub-Study Safety Population





* $p < 0.05$ vs placebo
** $p < 0.01$ vs placebo

All doses showed increased relative enhancement compared to placebo, suggesting improved hepatocyte function

All doses reduced time of arrival to the common bile duct compared to placebo, suggesting improved bile flow

Relative enhancement (RE), using the contrast agent gadoxetate, is a measure of hepatocyte function. Time of arrival of gadoxetate to bile duct is a measure of excretory function.
MRI was an optional sub study to main study.

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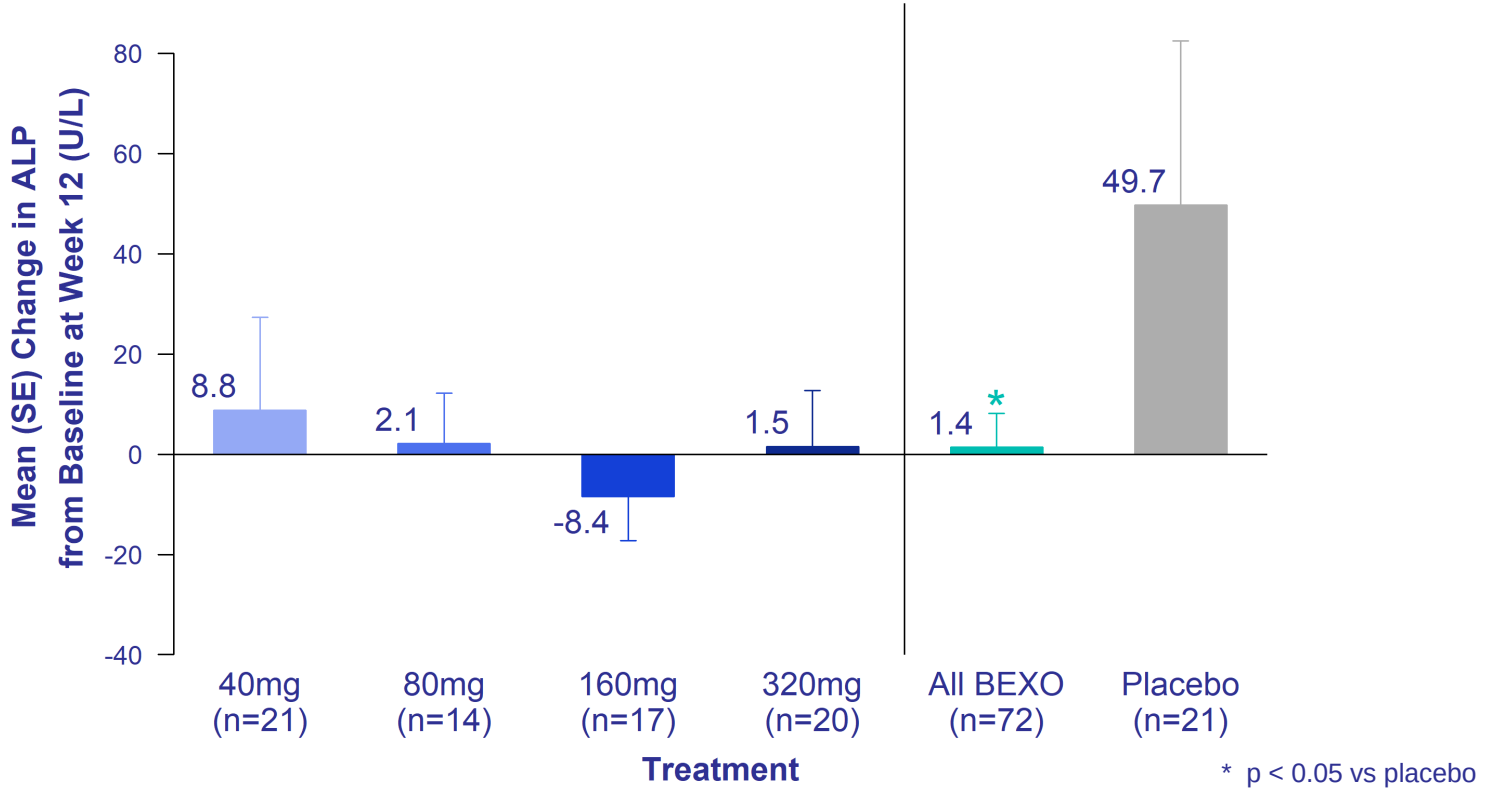
ALP – Change from Baseline at Week 12

Safety Population – Participants with ALP > ULN at Baseline



Bexotegrast improved ALP relative to placebo at all doses in subgroup with elevated ALP at baseline

ALP -Alkaline phosphatase.

INTEGRIS-PSC – Summary and Next Steps

- Bexotegrast continues to demonstrate a favorable safety and tolerability profile in a PSC patient population with suspected moderate to severe liver fibrosis
- All bexotegrast doses showed antifibrotic activity (ELF and PRO-C3) over short-term treatment duration
- Contrast MRI suggested improved hepatocyte function and bile flow with bexotegrast treatment
- All doses displayed improvement in Itch Numerical Rating Scale at Week 12 relative to placebo with statistical significance for the 160 mg and 320 mg doses
- Planning for regulatory interactions to discuss path to registration;
  320 mg 24-week data expected in mid-2024

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Bexotegrast – A Potentially Broadly Applicable Antifibrotic

Growing Evidence that Localized TGF-β Inhibition has Potential as Backbone Antifibrotic

- TGF-β inhibition is a potent antifibrotic pathway, but systemic toxicity has challenged drug development
- Tissue-specific TGF-β inhibition avoids systemic toxicity while maintaining the antifibrotic effect

Bexotegrast Continues to Demonstrate a Favorable Safety and Tolerability Profile

- Well tolerated in over 700 participants across multiple different patient populations
- No drug-related serious adverse events observed to date across all trials

Bexotegrast Shows Potential to Treat Fibrotic Diseases Across Multiple Organ Systems

- Clear antifibrotic effect across multiple organ systems and indications
- Effect has been observed across multiple exploratory endpoints and biomarkers
- Bexotegrast is positioned to expand into multiple indications across pulmonary and liver fibrosis

PLIANT

Bexotegrast Phase 2a 320 mg Dose Global Safety-PK-Exploratory Efficacy Trial in PSC

24-Week Data in Mid-2024

Randomization 3:1
(bexotegrast : placebo)

KEY INCLUSION/EXCLUSION CRITERIA

- Adults with large duct PSC
- Pre-cirrhotic
- Stable IBD, if present
- Stratified for UDCA use

Placebo (n=7)

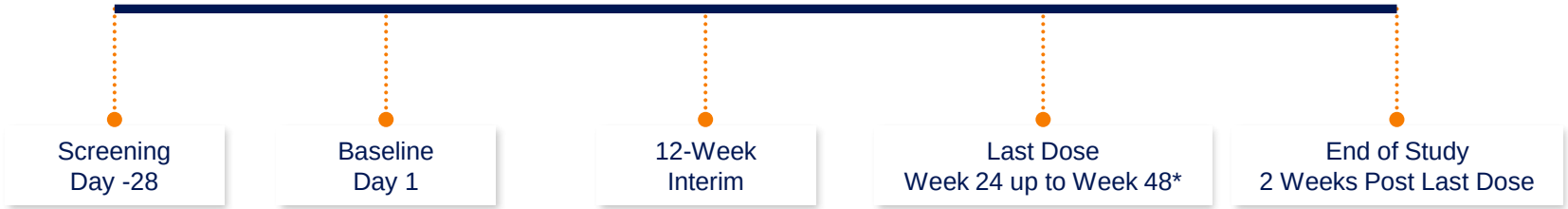
bexotegrast 320 mg (n=21)

PRIMARY AND SECONDARY ENDPOINTS

- Safety, tolerability, PK

EXPLORATORY ENDPOINTS

- Effect on fibrosis biomarkers (e.g., Pro-C3, ELF) at Wks 12 and 24
- Change in ALP at Wks 12 and 24



*Trial will complete once the last trial participant enrolled reaches 24 weeks of treatment

PLIANT

PLN-101095

Dual Selective $\alpha_V\beta_8$ / $\alpha_V\beta_1$ Integrin Inhibitor

Reprograming the Immunosuppressive Tumor Micro-Environment of Solid Tumors

Potential First-in-Class Small Molecule Dual $\alpha_V\beta_8$ / $\alpha_V\beta_1$ Inhibitor

$\alpha_V\beta_8$ Biology

$\alpha_V\beta_8$ regulates **TGFβ** activation with a central role in immune suppression in cancer

Pharmacology

Highly selective inhibitor of $\alpha_V\beta_8$ & $\alpha_V\beta_1$

Supports human dose projections and **high target coverage**

Compelling rationale for $\alpha_V\beta_8$ combination therapy with **PD-(L)1**

Differentiation

Dual mode of action targeting T cells $\alpha_V\beta_8$ & Fibroblasts $\alpha_V\beta_1$

PO Dosing

Development Status

No major findings in 28D GLP rat & dog toxicology studies

IND submitted Q4 2022

FIH study initiated 2Q 2023

Substantial opportunity for an oral medicine **targeting TGFβ activation** in ICI resistance **via $\alpha_V\beta_8$**

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Pliant's Approach to Addressing Immune Checkpoint Inhibitor Resistance

Common Mechanisms of I-O Resistance	Pliant's Approach
Tumor-specific IFNγ levels at baseline predict pembrolizumab responses [4,5]	Potently inhibit general immunosuppressive immune checkpoint to restore CD8 T cell IFNy secretion
Immunosuppressive stroma / myeloid compartment associated with active TGFβ signaling predicts atezolizumab responses [3]	Prevent both free and latent-TGFβ signaling from major integrin sources found in solid tumors
Tumor infiltrating lymphocytes highly sensitive to TGFβ immunosuppression [e.g.1,2]	Dual mechanism significantly increases quantity of TILs and increase resistance to exhaustion

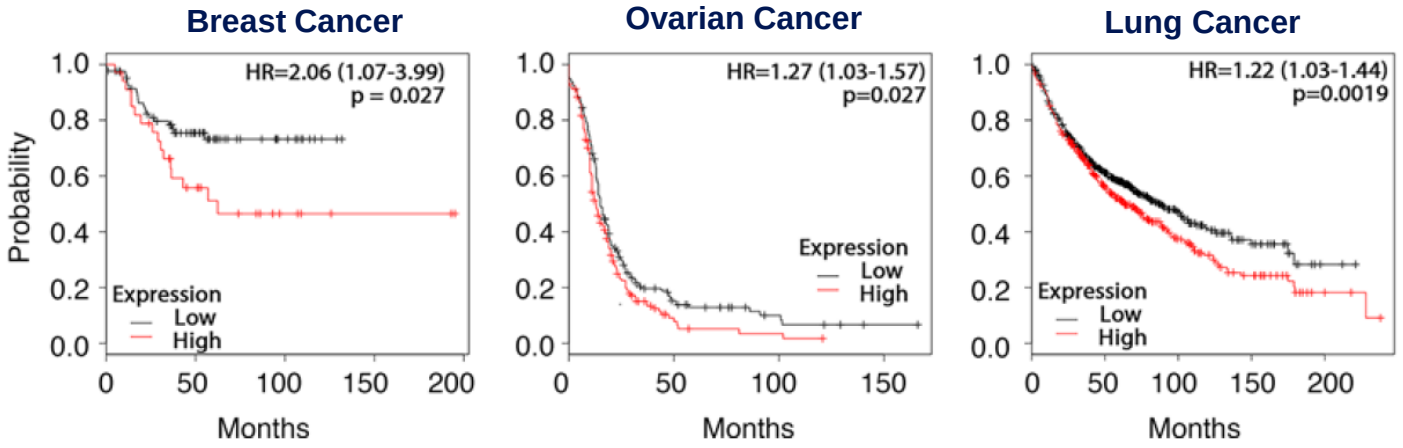
Dual inhibition of $\alpha_V\beta_8$ & PD-1 exploit unexpected synergistic pathways leading to enhanced tumor killing[6]

1- Thomas DA, et al. *Cancer Cell.* 2005 Nov;8(5):369-80. 2- Yang, ZZ. et al. *Leukemia*. 2014 28, 1872–1884. 3- Mariathasan, S. et al. 2018 *Nature* 554, 544–548.
4- Ayers, M et al. *J Clin Invest.* 2017 127(8):2930-2940. 5- Cindy Yang, S.Y. et al. *Nat Commun*. 2021 12, 5137. 6- Larrick J et al., DOI: https://doi.org/10.21203/rs.3.rs-1778271/v1

High ITGB8 on Tumor or T cells Has Poor Prognosis

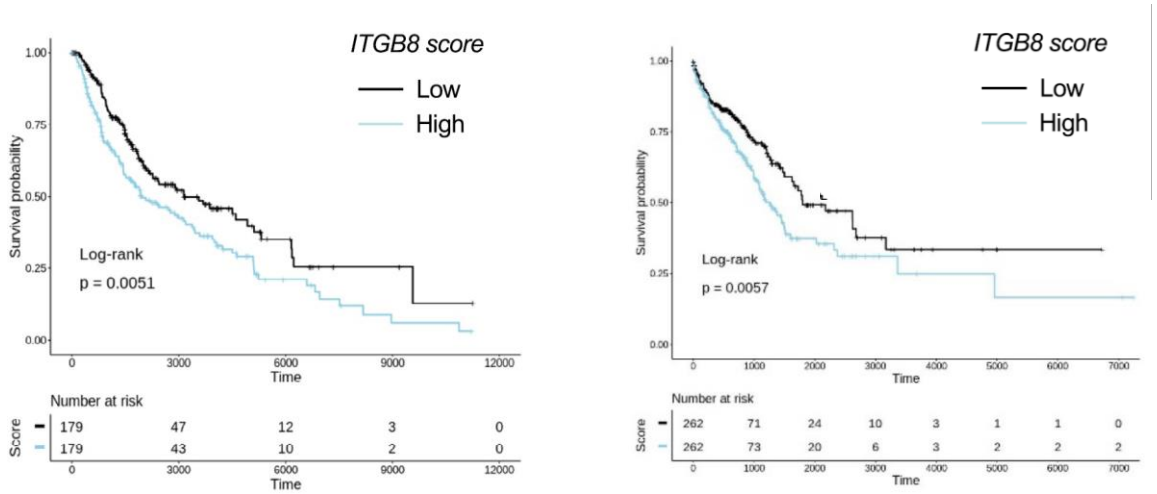
High ITGB8 expression on tumor cells has a worse clinical prognosis

Takasaka N. et al. *JCI Insight 2018;3*
doi 10.1172/jci.insight.122591



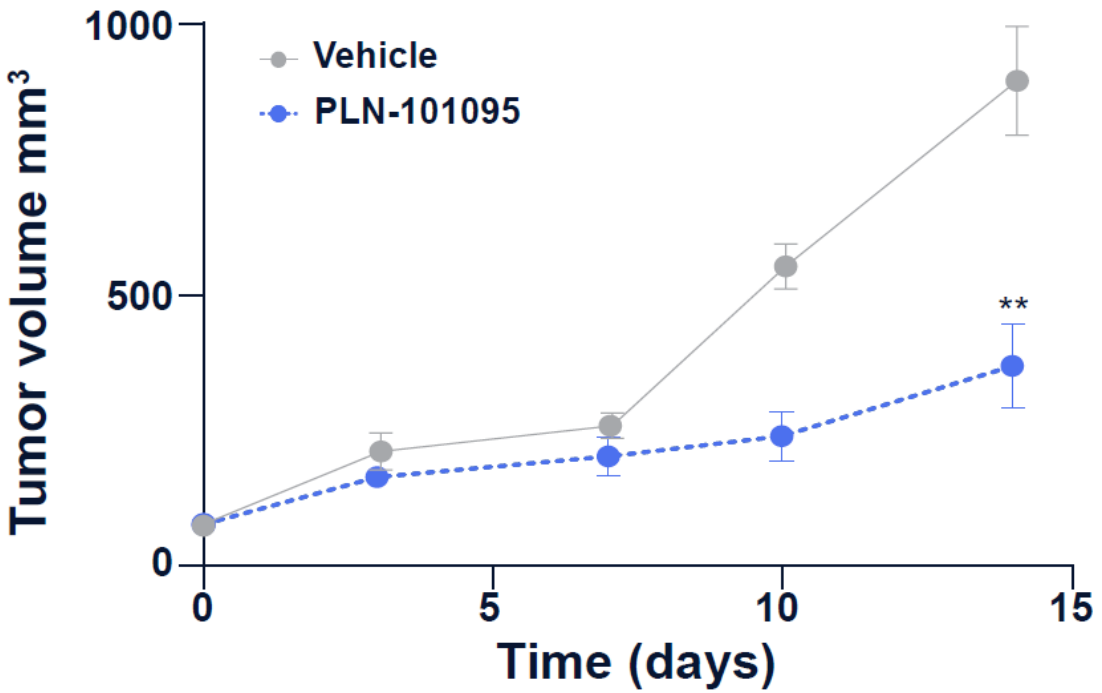
High ITGB8 score on infiltrating T cells correlates with worse prognosis

Lainé A., *Nat Commun* **12**, 6228 (2021)
doi: 10.1038/s41467-021-26352-2

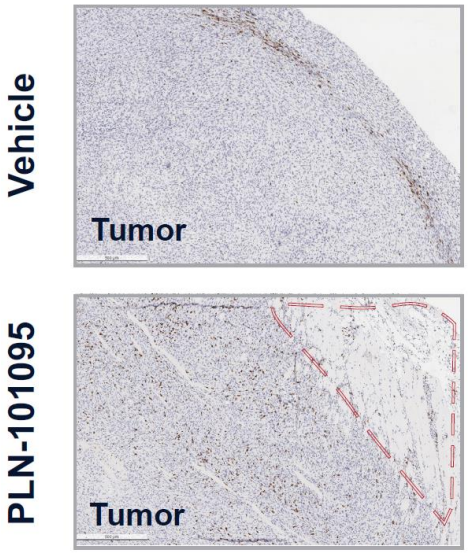


PLN-101095 Inhibited Tumor Growth and Promoted T cell Infiltration in the EMT6 Model

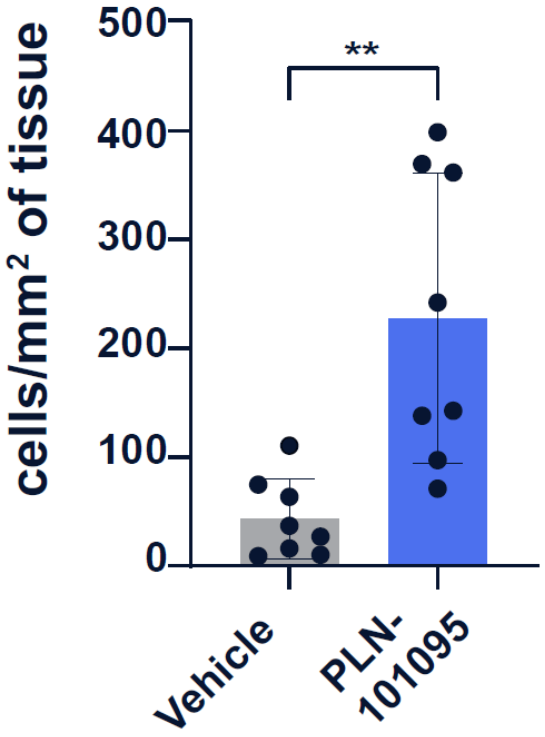
Tumor Growth Inhibition in EMT6 Tumors



CD8⁺ T Cells



CD8⁺ T Cells

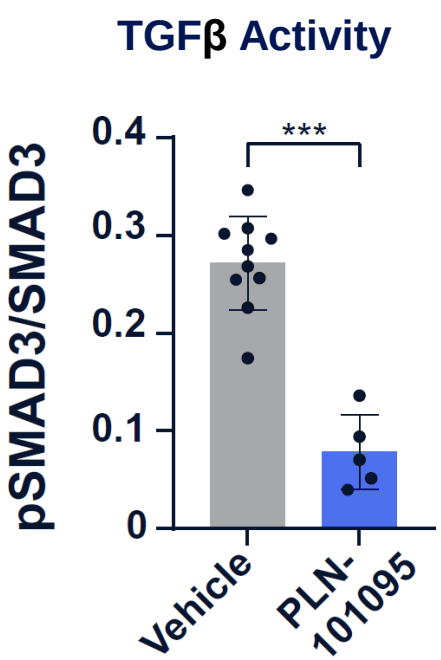


SITC 2022 Poster #1352

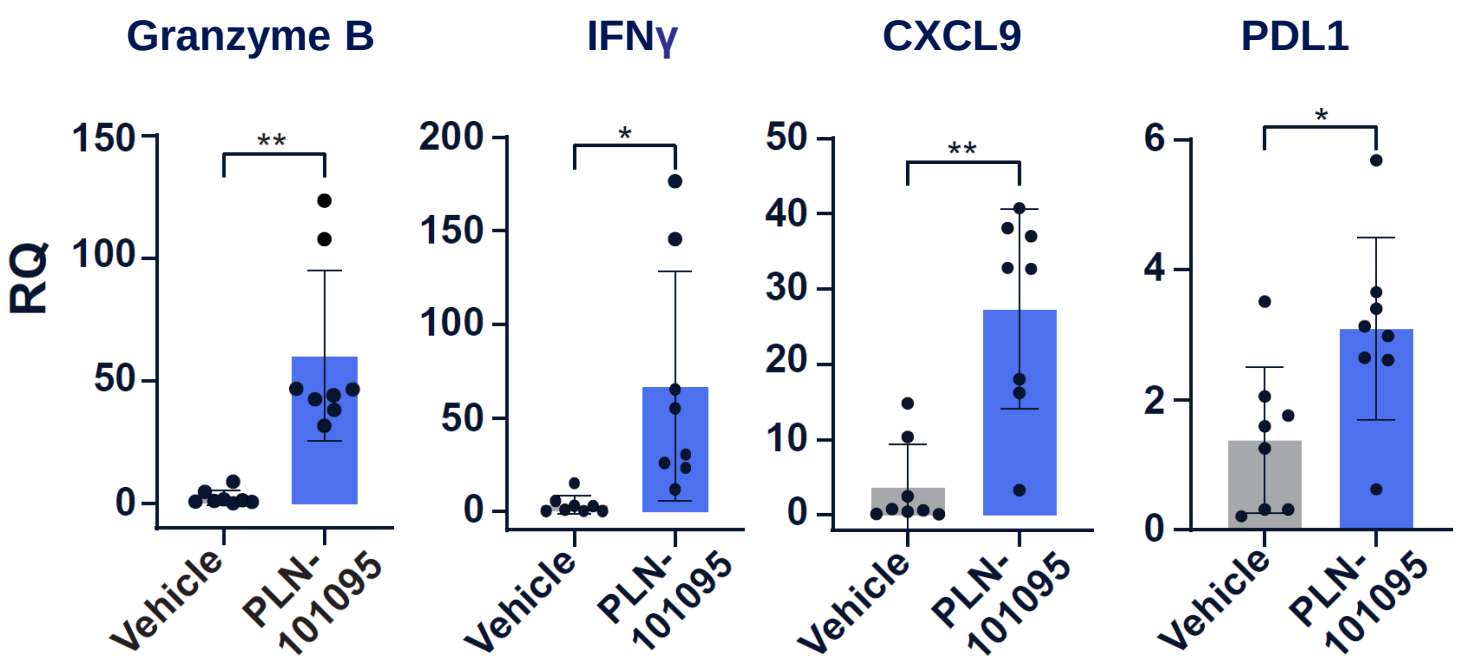
PLIANT

Single Agent PLN-101095 Promoted T Cell Infiltration

Reduced TGF-β Signaling



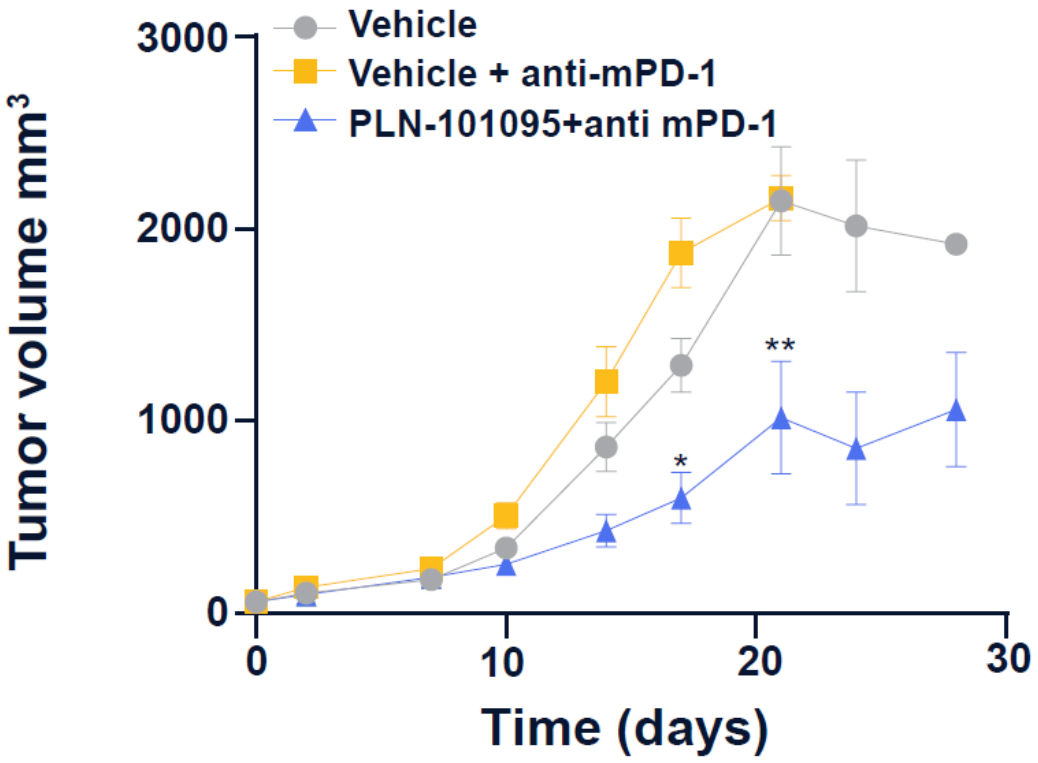
Increased Expression of IFNγ-Regulated Genes



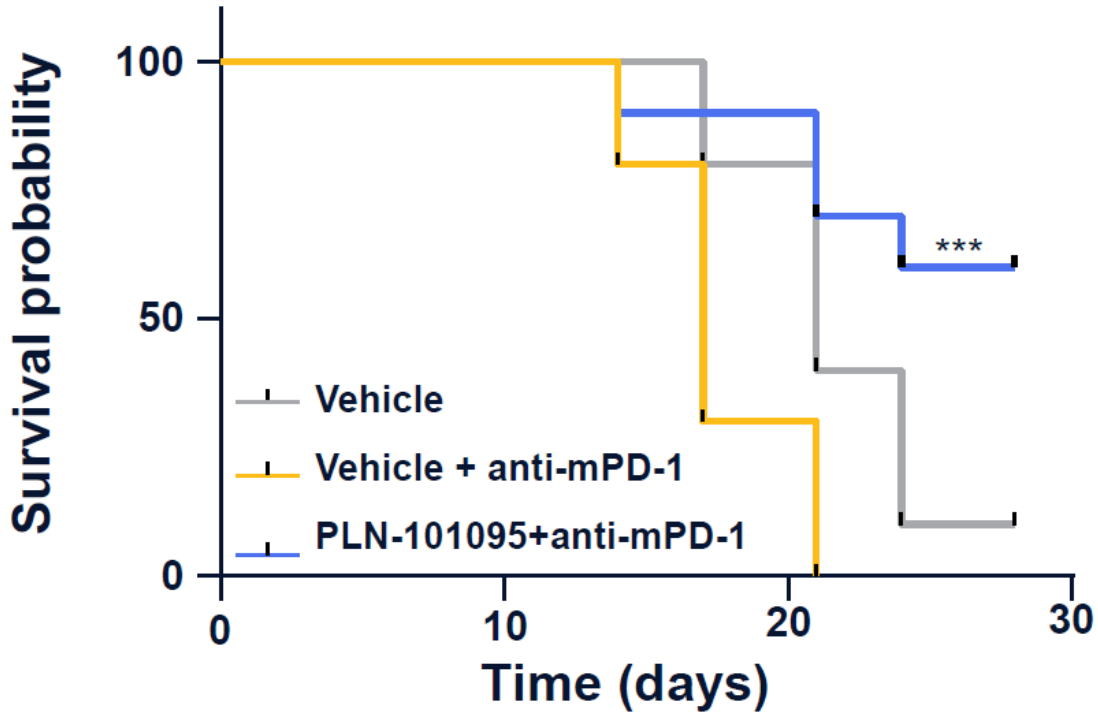
SITC 2022 Poster #1352

PLN-101095 Plus αPD-1 Demonstrated High Tumor Growth Inhibition in EMT6 Syngeneic Mouse Model

Tumor Growth Inhibition in EMT6 Tumors



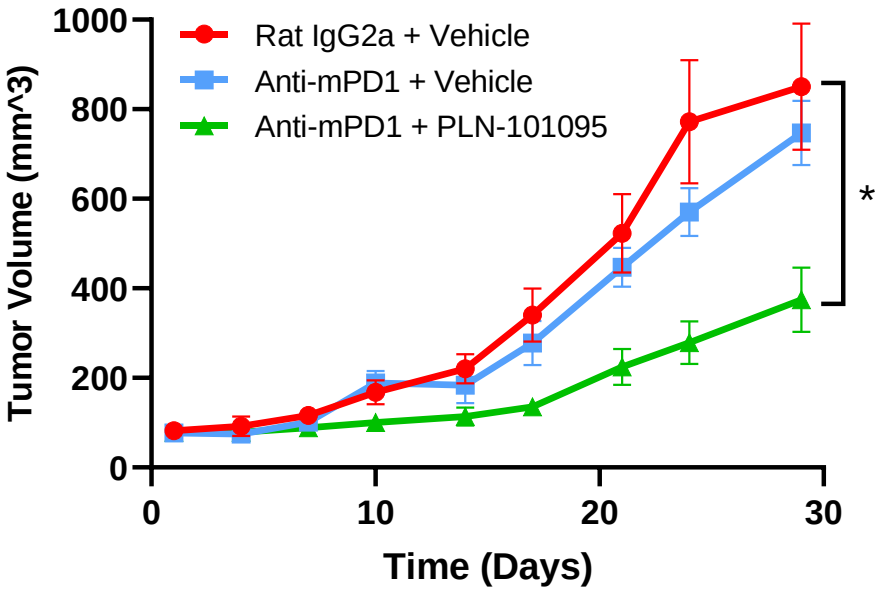
Survival



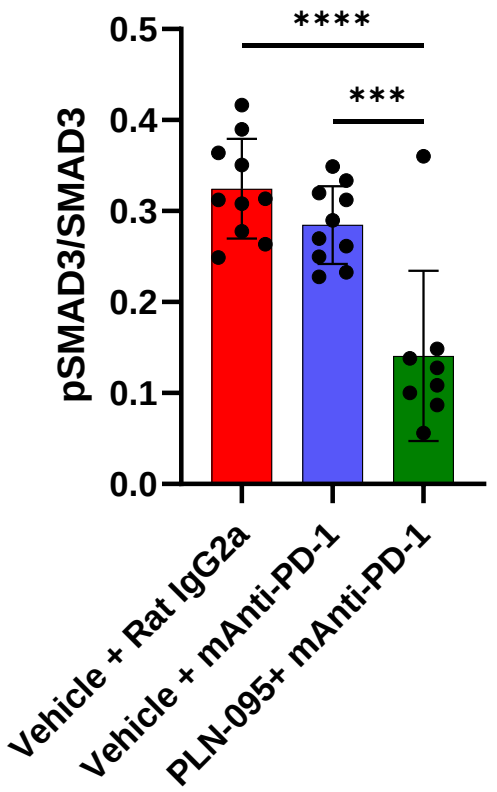
SITC 2022 Poster #1352

PLN-101095 Inhibited Pan02 Tumor Growth & Increases T cell Infiltration

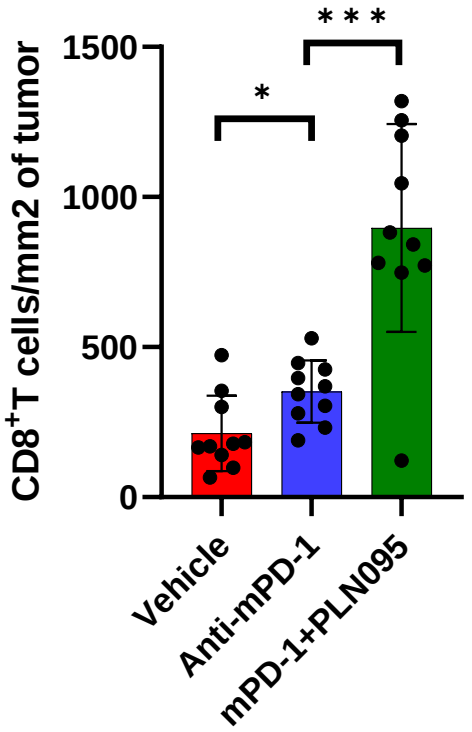
Tumor Growth Inhibition in Pan02 Tumors



TGFβ Signaling



CD8⁺ T Cells



SITC 2022 Poster #1352

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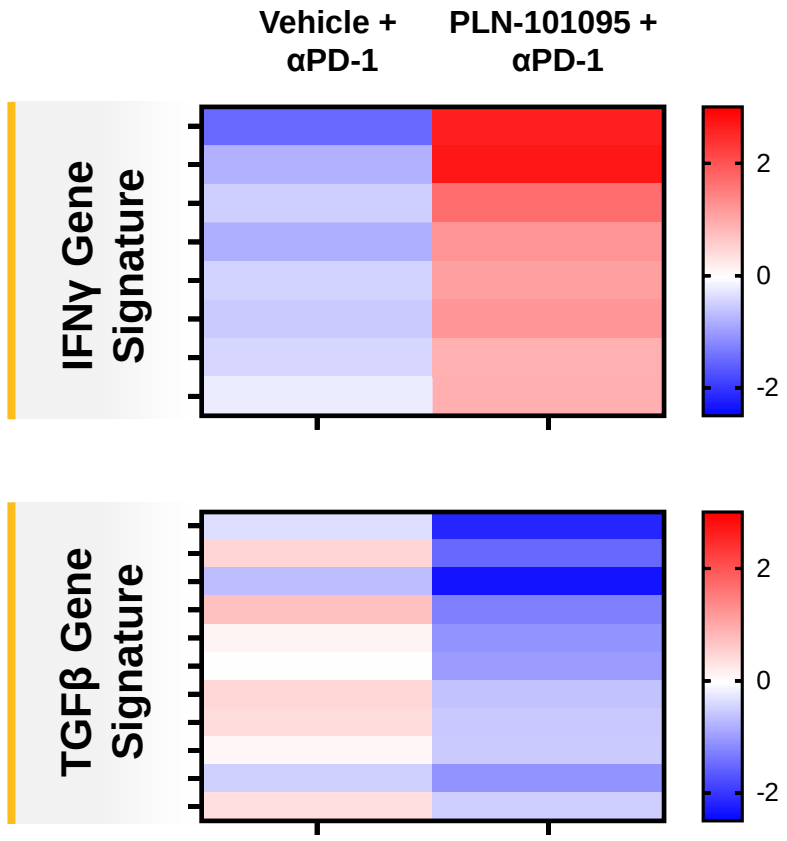
PLN-101095 Potently Increased IFNγ Signature & Reduces TGFβ Gene Signatures



Anti-PD-(L)1 Non-Responsive Baseline Gene Signature

High **TGFβ** Signature

Low **IFNγ** Signature

PLN-101095 Promotes ICI Responsiveness

Sensitized to Anti-PD-(L)1

High **IFNγ** Signature

Low **TGFβ** Signature

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PLN-101095 Nonclinical Safety Studies
No Effects of Concern for Clinical Advancement

Study Category	Studies Completed	Findings with PLN-101095
Repeat Dose Toxicology	• 14-day DRF in rat • 7-day DRF in dog • GLP 1-Month IND-enabling rat • GLP 1-Month IND-enabling dog	• **No adverse findings** in rat or dog DRF • All doses tolerated • **NOAEL[1] set at highest dose**
Safety Pharmacology	• GLP hERG • Safety44	• **No findings**
Genetic Toxicology	• GLP Ames • GLP In vitro micronucleus	• **No findings**

1 – No observed adverse effect level.

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Key Program Highlights

Oral route of administration of small molecule $\alpha_V\beta_8$ inhibitor

Highly potent dual inhibitor of $\alpha_V\beta_8$ / $\alpha_V\beta_1$ inhibitor

Activity demonstrated in multiple **PD-1 resistant** tumor models

Greater reduction in **TGF-β signaling** than either $\alpha_V\beta_8$ or TGF-$\beta_{1,2}$ mAb

Significant reduction in tumor **fibrogenesis**

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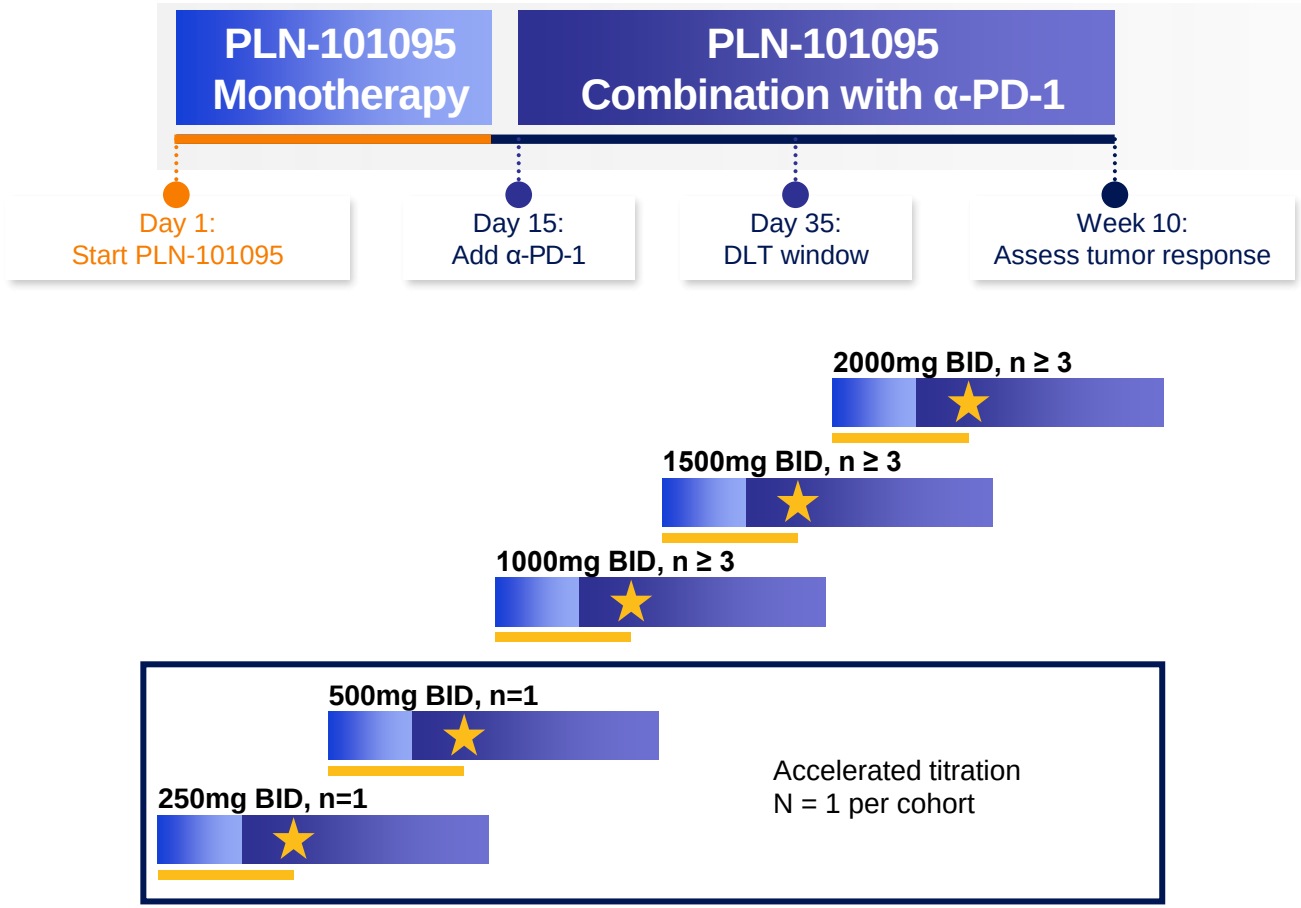
PLN-101095 Phase 1 Study in Patients Resistant to Immune Checkpoint Inhibitors



★ **Safety Review Committee (SCR) Meetings** will review safety data within the DLT windowed 35 days, including AEs, lab values, and DLTs for all participants enrolled in a dose cohort

STUDY POPULATION

- Advanced or metastatic solid tumors for which pembrolizumab is indicated & have received at least 2 doses pembrolizumab
- Pembrolizumab relapsed or refractory

ENDPOINTS

- Primary: safety & tolerability
- Secondary: mono- and combination therapy PK
- Exploratory:
  - PK & PD
  - Antitumor activity: ORR, TTR, DOR, PFS & OS

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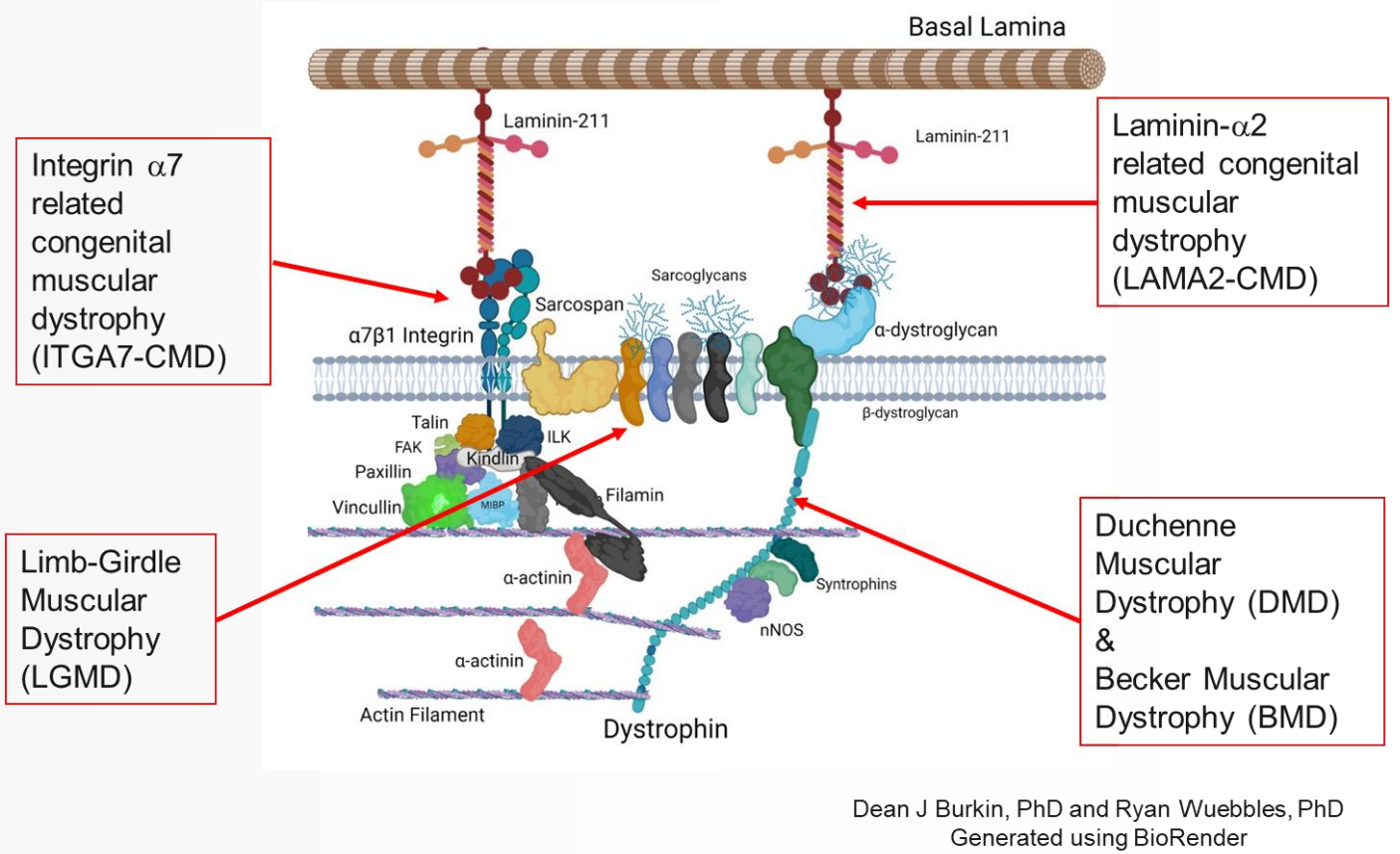
Selective Muscle Cell Integrin Agonism for the Treatment of Muscular Dystrophies

$\alpha_7\beta_1$: A Drug Target in Muscular Dystrophies

- Predominantly expressed in skeletal, heart and smooth muscle
- $\alpha_7\beta_1$ strong genetic modifier in MDX mice
  - Lack of $\alpha_7\beta_1$ worsens disease phenotype
  - Over expression increases survival and improves function
    - Pharmacological agents that increase expression show similar effects
- Human mutations in $\alpha_7\beta_1$ result in congenital MD
- ITGA7 frameshift (heterozygous, nonfunctional mutation is associated with lean muscle volume reduction (UK Biobank)



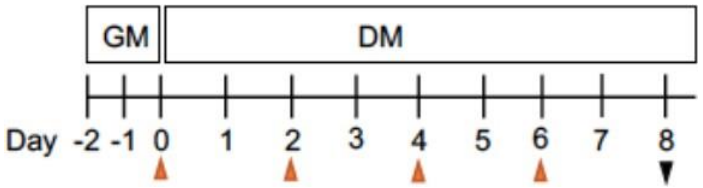
Dean J Burkin, PhD and Ryan Wuebbles, PhD
Generated using BioRender

J Cell Bio 2001, *Human Gen Ther* 2015, *Molecular Therapy* 2017

Integrin $\alpha_7\beta_1$ Agonist Antibody Promoted Muscle Maturation

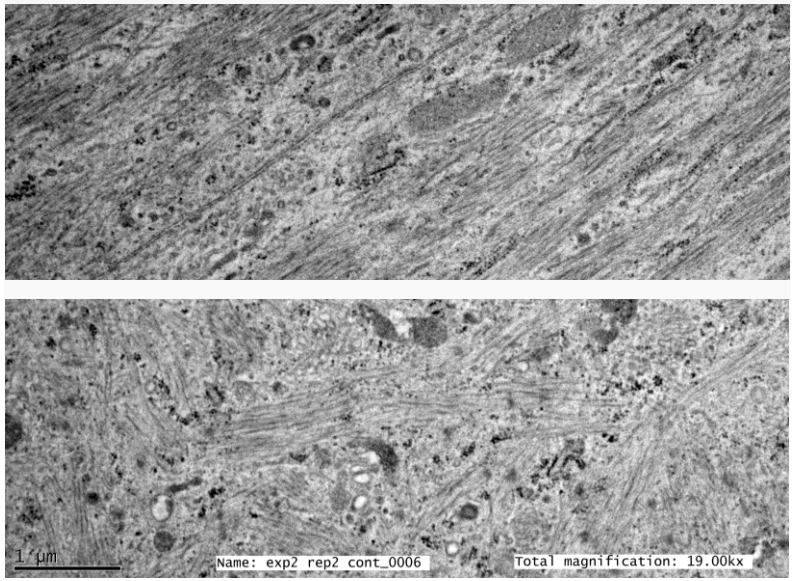
AB1071 hMMTs treated with 1 ug/ml or 10 ug/ml
Pliant antibody contain myotubes with substantially improved sarcomere organization that can withstand tetanic stimulation compared to IgG4 control

TREATMENT REGIME

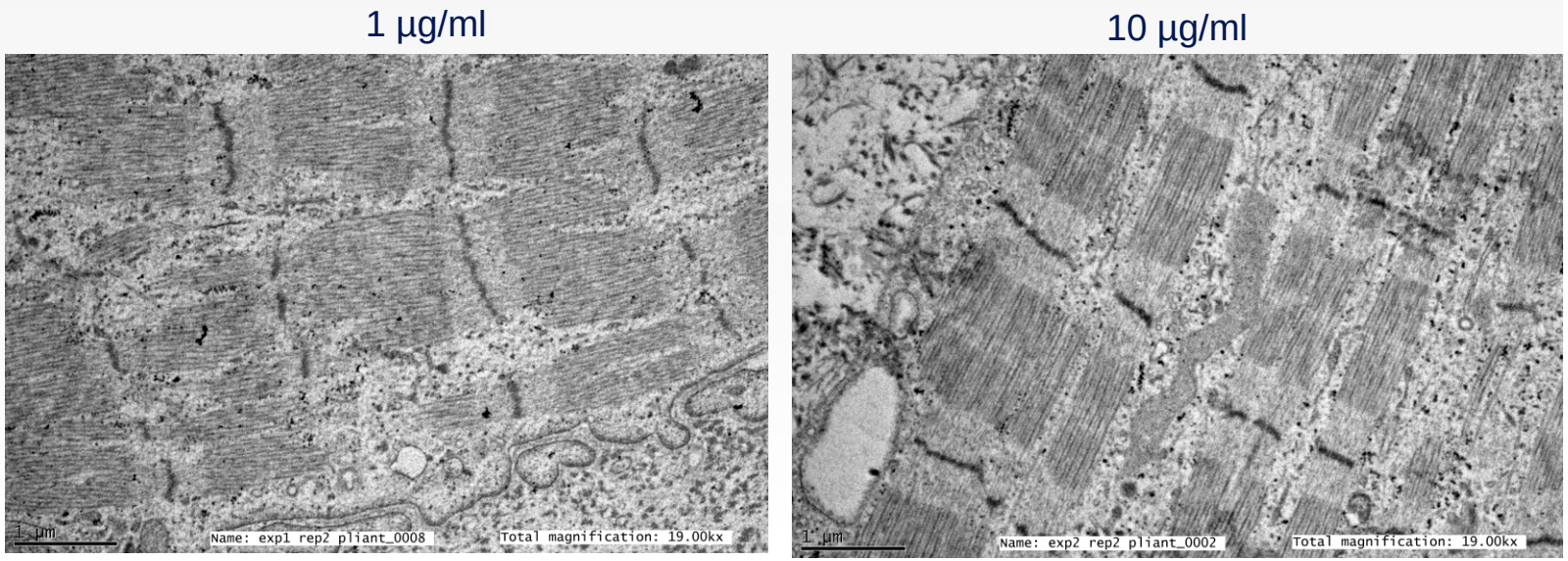


(+) “Exercise”

IgG4



α7β1 agonist



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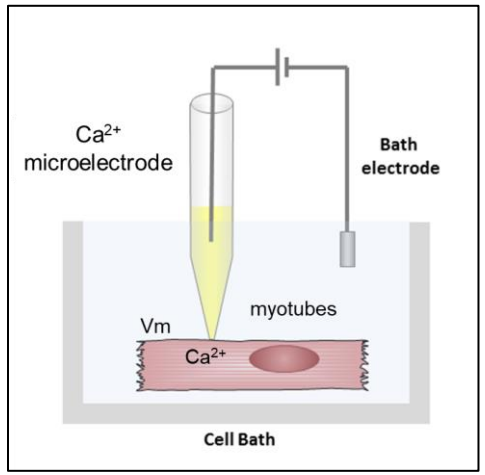
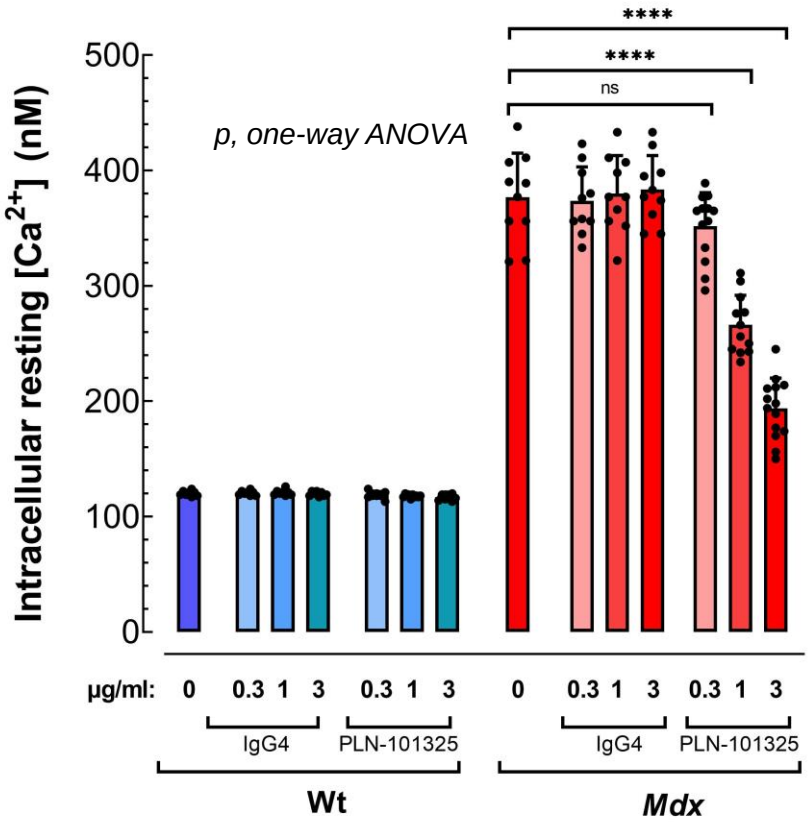
Institute of Biomedical Engineering
UNIVERSITY OF TORONTO

Effect of PLN-101325 in Ca2+ Homeostasis and Resting Membrane Potential of B10-mdx Myotubes

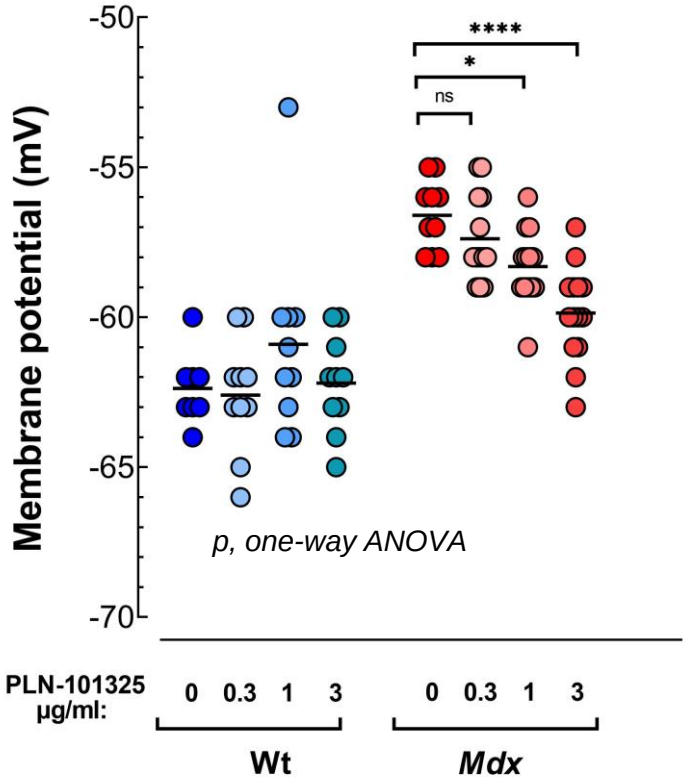
Reduced intracellular resting calcium and hyperpolarization of the membrane potentially support improved plasmalemmal integrity by PLN-101325



Intracellular resting Ca^{2+}



Resting membrane potential



Dr. Jose R. Lopez

Mount Sinai MEDICAL CENTER

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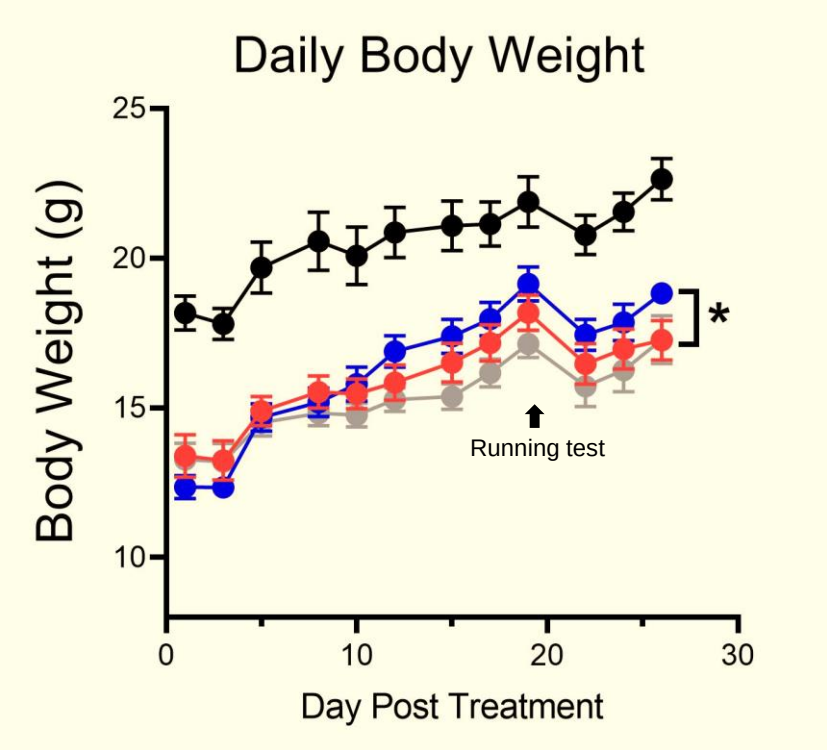
Body Weight Improvement at 4 and 12 Weeks of Treatment

- PLN-101325 3x/ wk IP
- 5-6 wk old D2-MDX mice

4-week

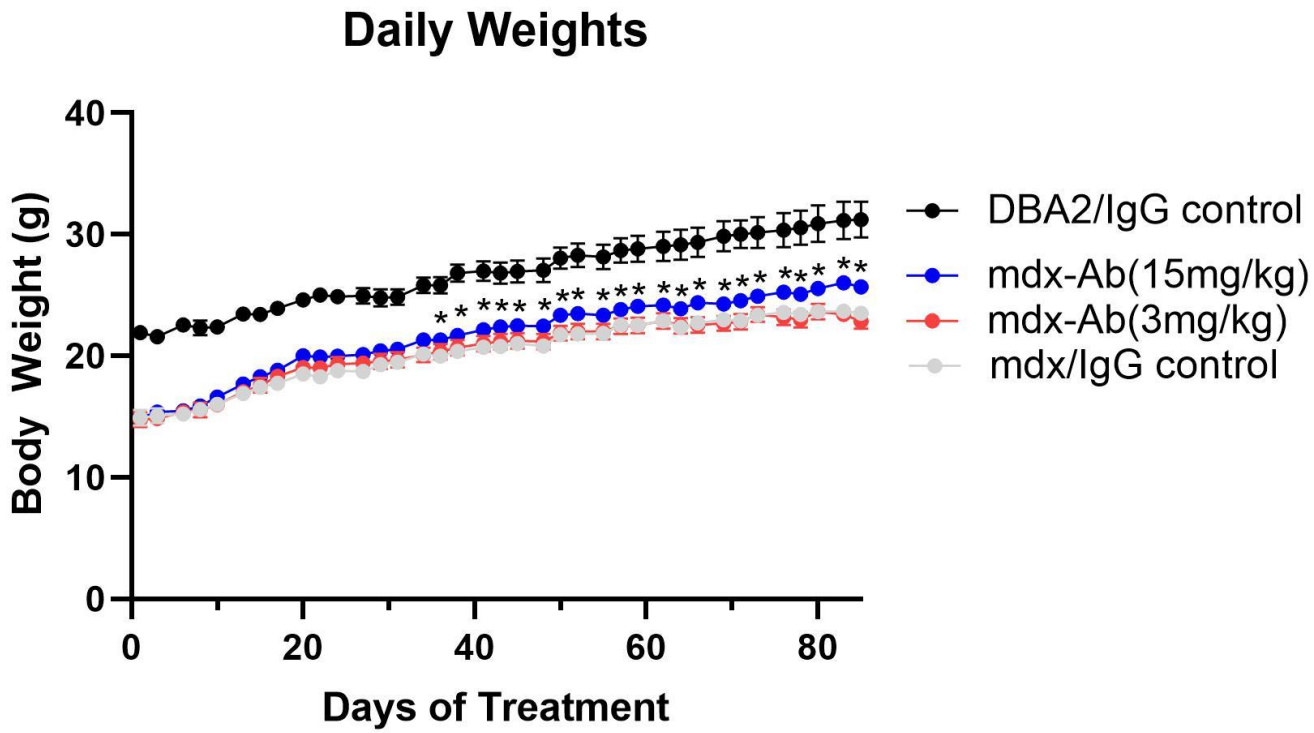
8 ± 3% Increase in Body Weight



12-week

9 ± 1% Increase in Body Weight

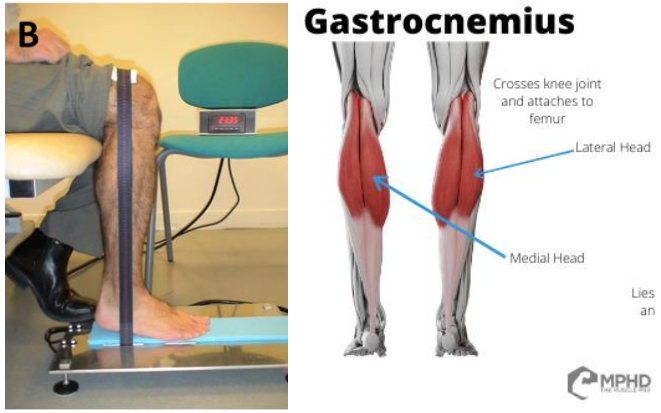
Weight Increase 9 ± 1%



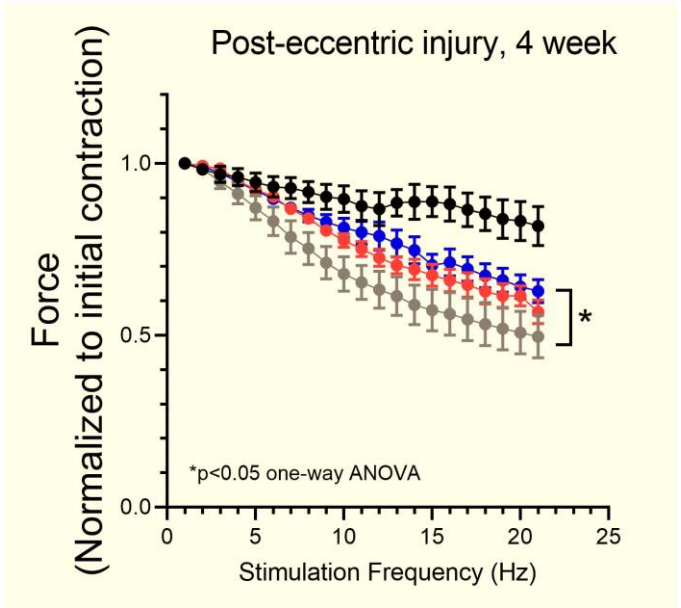
Improved Response to Post Eccentric Injury at 4 and 12 Weeks of Treatment

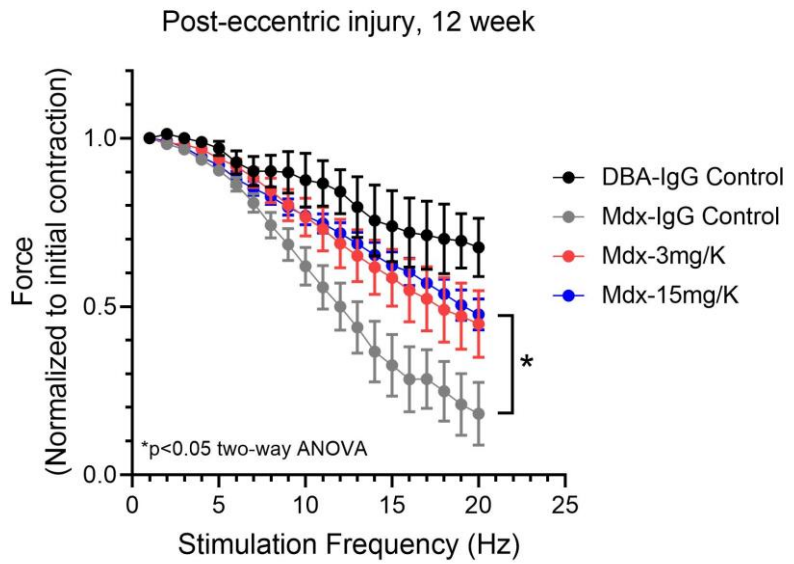
Plantar flexion test

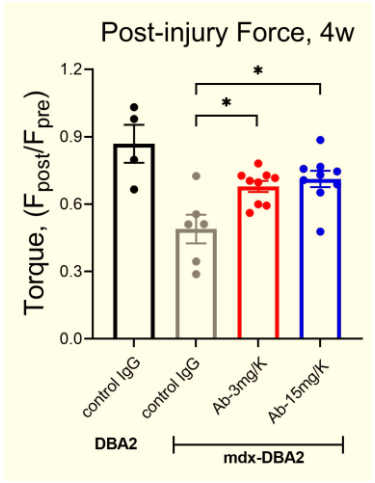
- Gastrocnemius (GC): Premier mover muscle for plantar flexion.
- GC only muscle to join both ankle and knee.

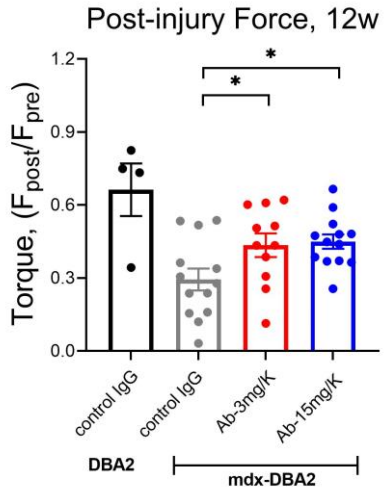


Eccentric muscle injury protocol: A series of 20 tetanic stimulations (80Hz, 0.2ms pulse, 500ms duration) are delivered at 0.1Hz frequency. The foot is rotated against the direction of contraction by 10° over 250ms, resulting in an eccentric contraction

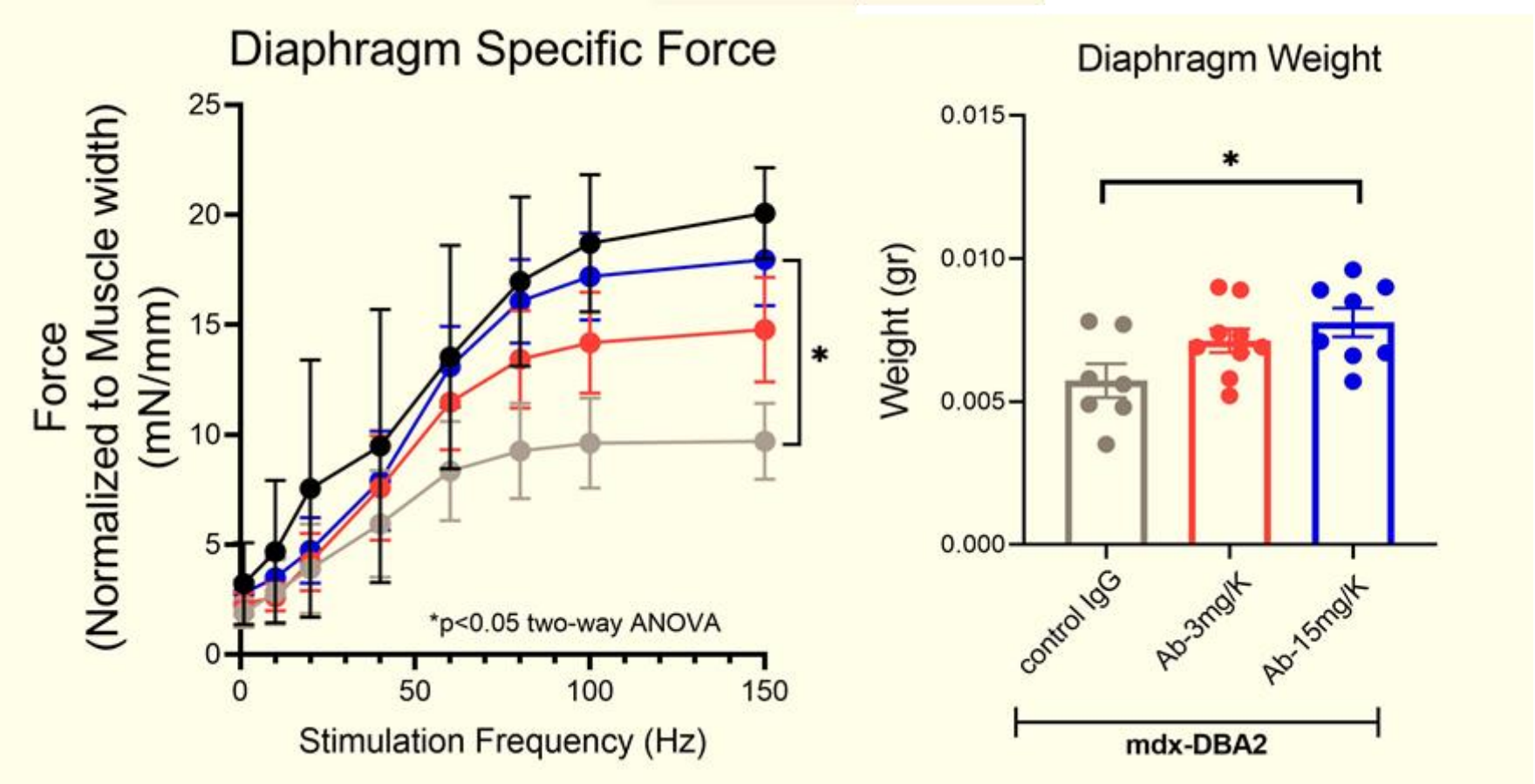








Diaphragm Force Significantly Improved at 4 Weeks of Treatment



MYOLOGICA

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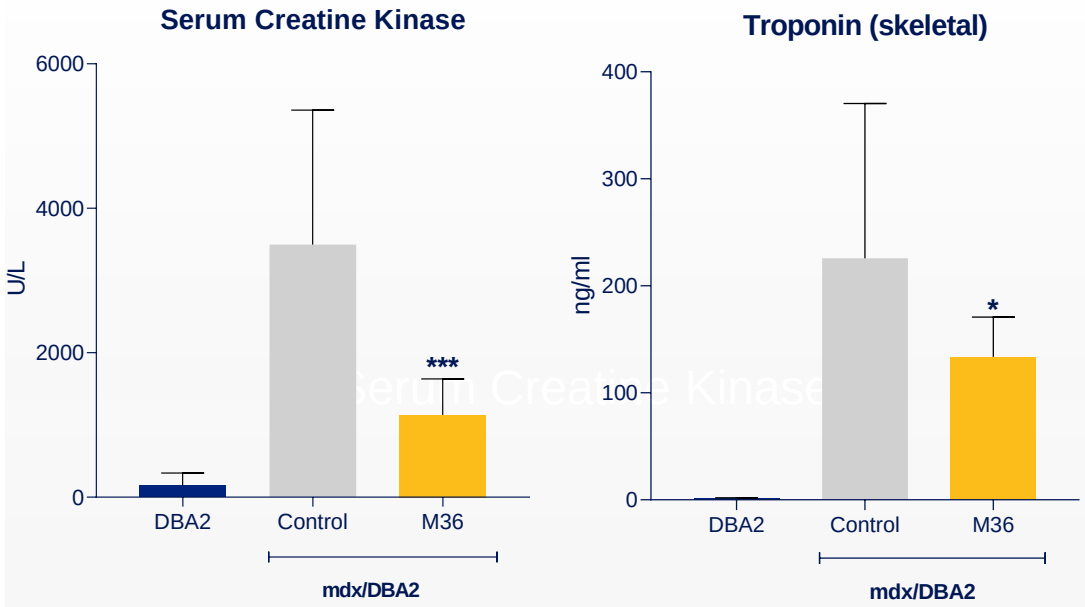
Pliant's $\alpha_7\beta_1$ mAb Demonstrated Improved Muscle Membrane Integrity and Diaphragm Function in Mouse DMD Model

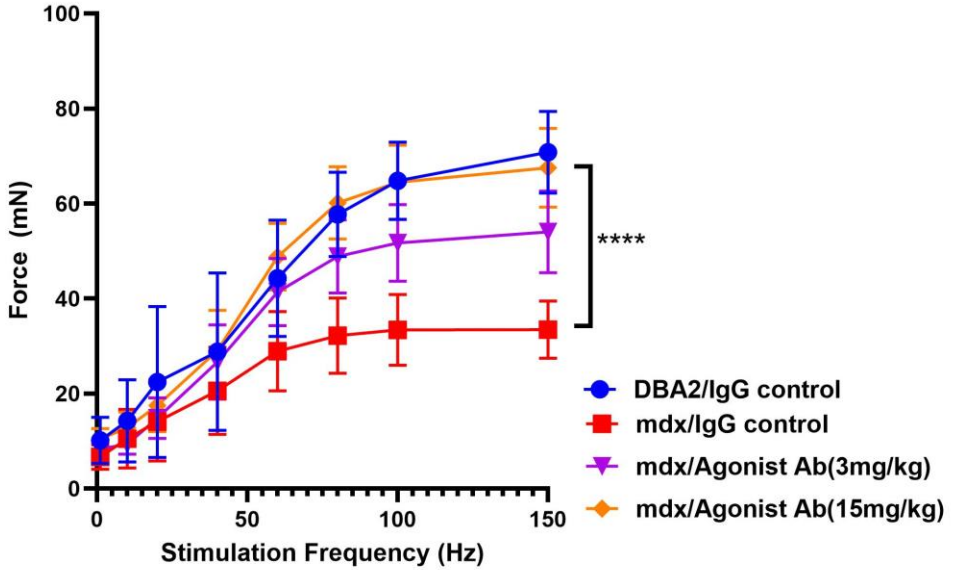
Antibody treatment protected against muscle damage



- Reduction of clinical biomarkers including serum creatine kinase and skeletal troponin

***p 0.001, *p<0.05, one-way ANOVA
Mean +/- SD n=10/group

Duchenne muscular dystrophy (DMD) causes progressive wasting of cardiac and respiratory muscles (main cause of death)



- Improvement in diaphragm function is expected to significantly improve patient pulmonary function

****p 0.0001, two-way ANOVA

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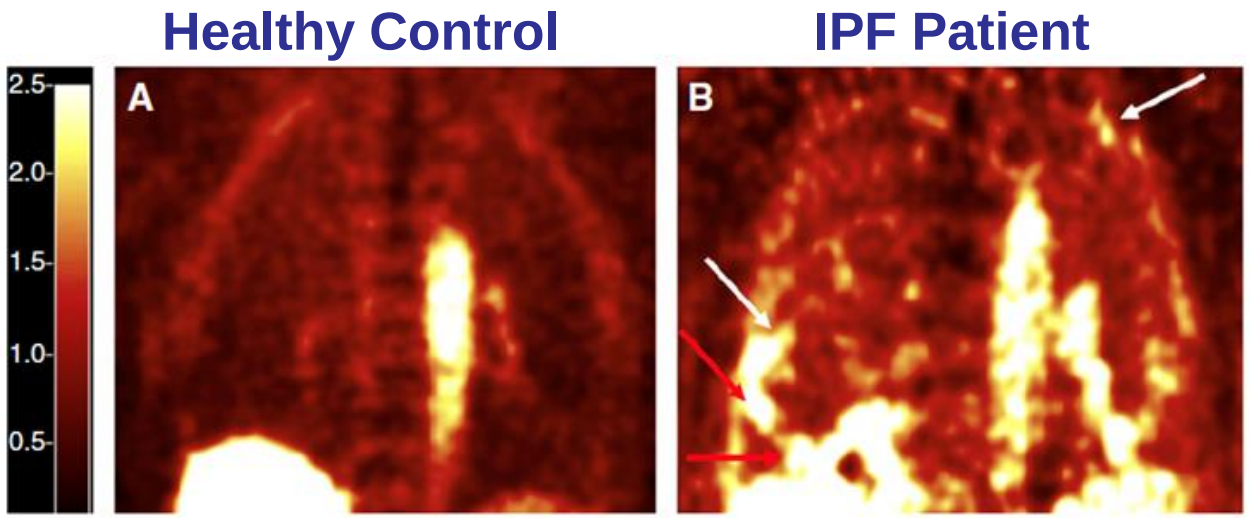
PLN-74809-205 – Phase 2a Collagen PET Study Topline Results

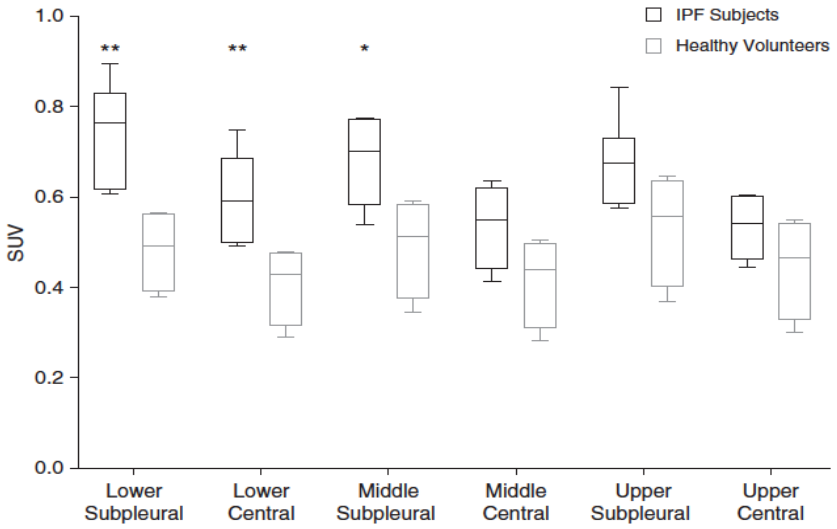
May 2024

Quantification of Collagen in the Lung using PET Imaging

- ^{68}Ga-CBP8 is a PET probe that binds type I collagen with high specificity[1]
- IPF patients have higher standardized uptake values (SUV) compared to healthy volunteers[2]
- The probe binds to both freshly synthesized and mature collagen
- ^{68}Ga-CBP8 previously detected treatment response to anti-fibrotic therapy in a mouse model of pulmonary fibrosis[1]



Note: Uptake in the heart and vasculature as well as in the liver is to be expected based on the probe's half-life and biodistribution



^{68}GA-CBP8: peptide-based collagen binding probe 8 tagged with Gallium-68 radioisotope
SUV: standardized uptake value; SUV measures the ratio of the uptake of a radiotracer in tissue
[1]Désogere et al, Sci Trans Med. 2017; [2]Montessi Am J Respir Crit Care Med 200:2 2019

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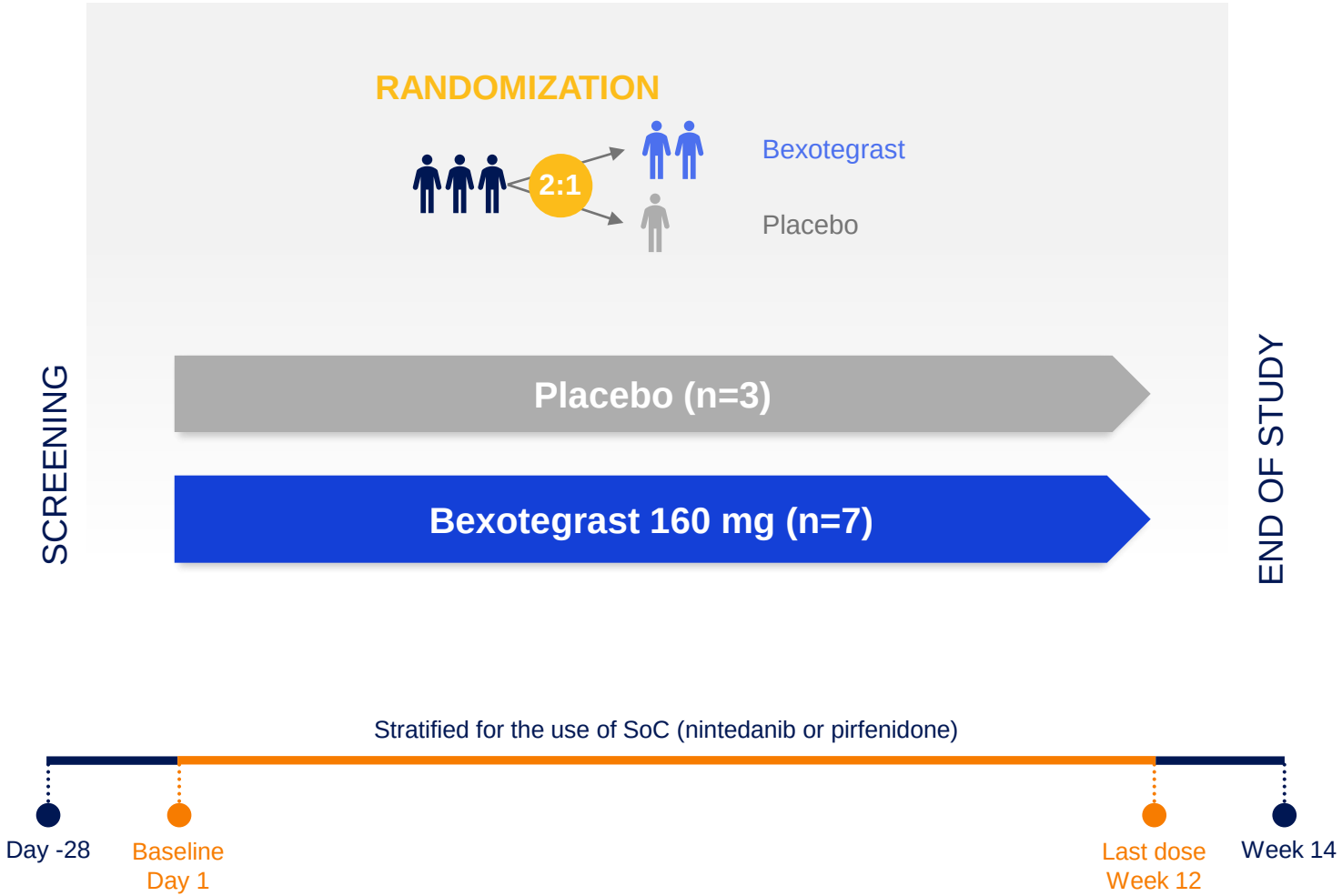
Study 205 Design and Objectives

Quantification of Type 1 Collagen in the Lung using PET Imaging



PRIMARY AND SECONDARY ENDPOINTS

- Change in whole lung standardized uptake value (SUV) of ^{68}GA-CBP8 (type-1 collagen probe)
- Safety and tolerability

EXPLORATORY ENDPOINTS

- Changes in FVC and FVCpp
- Change in VAS for cough severity
- Changes in fibrosis biomarkers

INCLUSION CRITERIA

- Diagnosis of IPF (within 8 years)
- FVC percent predicted ≥ 45%
- DLCO ≥ 30%
- Estimated glomerular filtration rate ≥ 50mL/min

FVC: forced vital capacity, FVCpp: forced vital capacity percent predicted; SoC = Standard of care; VAS: visual analog scale
^{68}GA-CBP8: peptide-based collagen binding probe 8 tagged with Gallium-68 radioisotope

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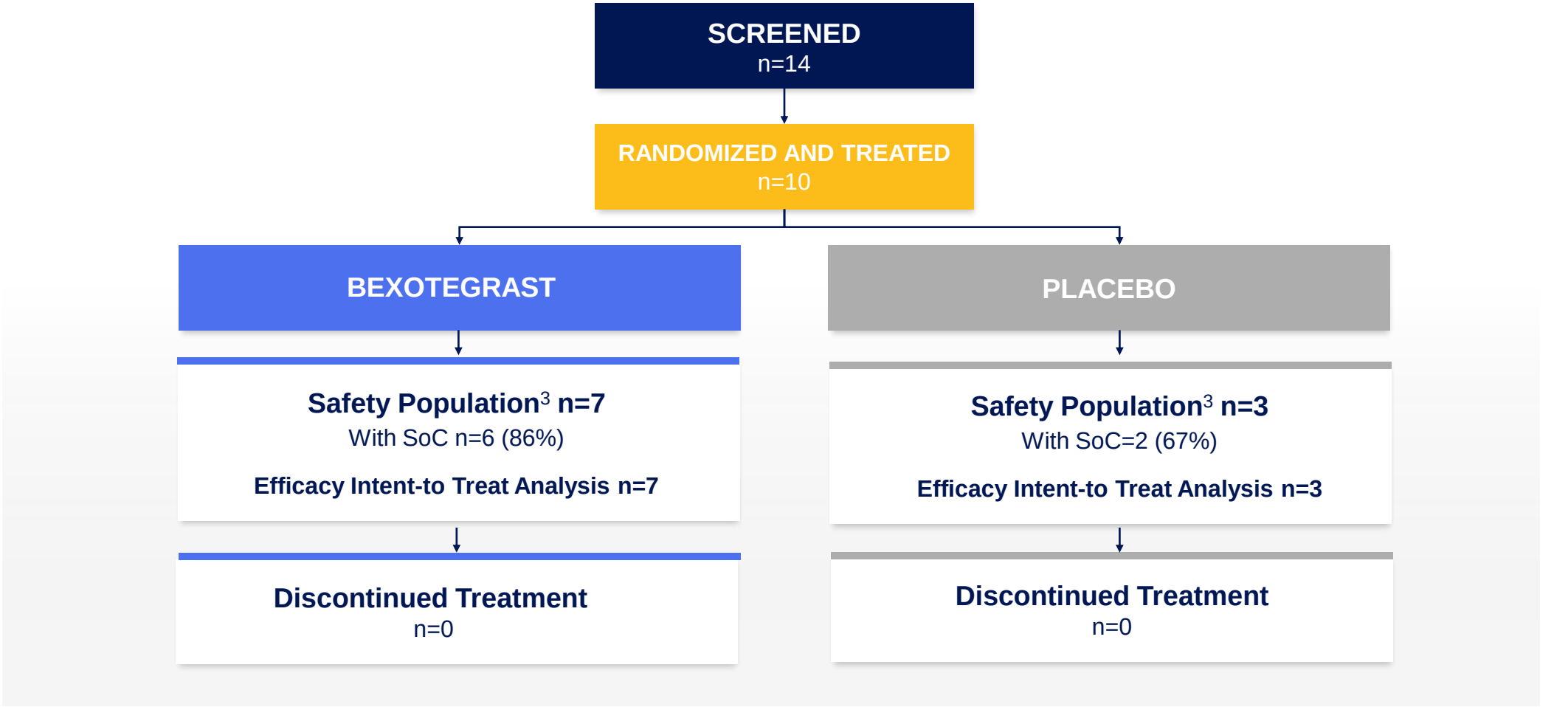
Participant Disposition



SoC = Standard of care

Baseline Demographics

Characteristic	Bexotegrast 160mg (n=7)	Placebo (n=3)
Male sex, n (%)	6 (85.7)	3 (100)
Age (yr), median (IQR)	70 (64 – 72)	74 (72 – 76)
Weight (kg), median (IQR)	81.2 (79.0 – 88.5)	78.0 (77.6 – 85.3)
BMI (kg/m^2), median (IQR)	25.7 (23.7 – 30.4)	26.4 (24.0 – 30.3)
Race, n (%)		
White	6 (85.7)	3 (100)
Black	0	0
Asian	1 (14.3)	0
Other / Not Reported / Unknown	0	0

IQR = Interquartile range (Q1, Q3); BMI = Body Mass Index

Baseline Disease Characteristics

Characteristic	Bexotegrast 160mg (n=7)	Placebo (n=3)
Time since diagnosis of IPF (mo), median (IQR)	50 (22 – 70)	9 (7 – 72)
Standard of Care Use, n (%)		
Nintedanib	5 (71.4)	1 (33.3)
Pirfenidone	1 (14.3)	1 (33.3)
Duration of Standard of Care at Randomization (mo), median (IQR)	34.5 (17 – 55)	40.0 (6 – 74)
FVC		
Absolute (mL), median (IQR)	2,750 (2,400 – 3,080)	2,250 (1,700 – 2,640)
Percent of predicted value (%), median (IQR)	66.0 (56.0 - 92.0)	58.0 (49.0 - 69.0)
Percent of predicted DLCO, corrected for the hemoglobin level (%), median (IQR)	49 (40.0 – 58.0)	43 (36.5 – 45.0)
GAP Stage, n (%)		
GAP Stage I	4 (57.1)	0
GAP Stage II	2 (28.6)	2 (66.7)
GAP Stage III	1 (14.3)	1 (33.3)

GAP Index score derived from Gender, Age, FVC, % Predicted and DLCO, % Predicted.
IQR = Interquartile range (Q1, Q3); DLCO= Diffusing Capacity for Carbon Monoxide; FVC = Forced Vital Capacity

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Study 205 – Key Findings

Bexotegrast cohort showed reduced PET ligand standardized uptake values (SUV) compared to placebo

- Reduction in SUV post-treatment indicates less total lung collagen, suggesting potential reversal of fibrosis
- Additional support of bexotegrast's antifibrotic mechanism of action

No new safety concerns identified over 12 weeks of treatment

- Most adverse events were mild with no study discontinuations observed
- No SAEs observed

Bexotegrast cohort showed improved lung function and decreased cough severity across all timepoints

- Positive FVC change compared to decline in placebo across all time points
- Decrease in cough severity observed at all time points compared to worsening seen on placebo

Biomarker results further support bexotegrast's antifibrotic mechanism

- Bexotegrast cohort showed reduced circulating PRO-C3 and Integrin Beta-6 levels at Weeks 4 and 12 compared to placebo

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Safety Overview

- No serious adverse events (SAEs) occurred in the trial
- Most treatment emergent adverse events (TEAEs) were mild in nature
- No study discontinuations occurred
- Bexotegrast continues to demonstrate a favorable safety and tolerability profile in the IPF patient population

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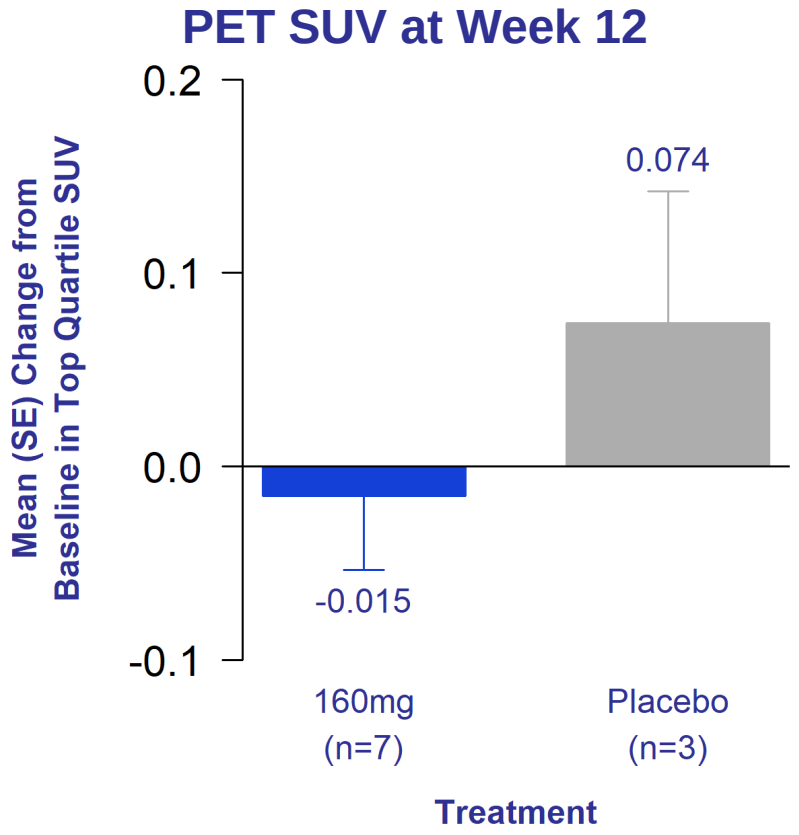
Bexotegrast Showed Reduced PET Tracer SUV Compared to Placebo

ITT Population



Reduction in post-treatment SUV indicates a reduction in total lung collagen

Reduced post-treatment total lung collagen suggests potential reversal of fibrosis

[2] Montessi AJRCCM 200:2 2019

SUV = Standardized Uptake Value; SE = Standard Error; ^{68}GA-CBP8: peptide-based collagen binding probe 8 tagged with Gallium-68 radioisotope
SUV measures the ratio of the uptake of a radiotracer in tissue; Top quartile SUV is the mean of SUVs within the top quartile for each lung section; Whole lung is the average of the left and right lungs

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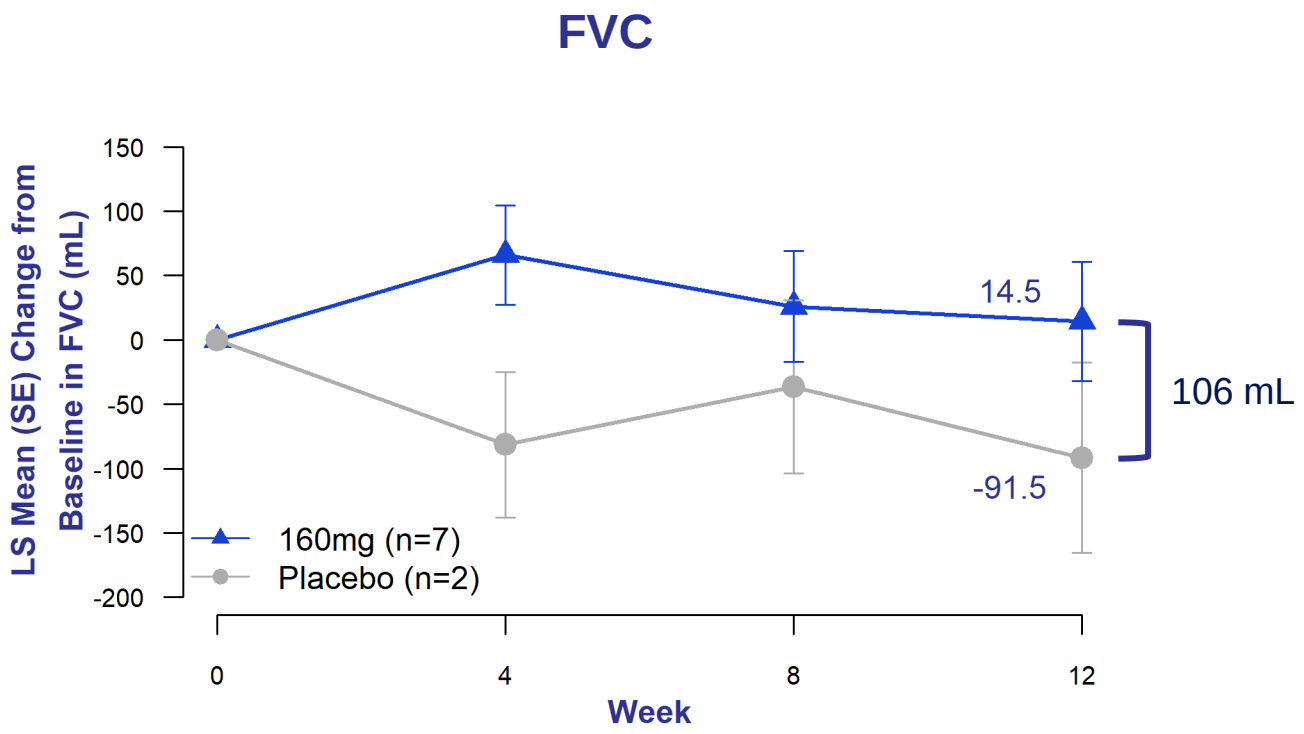
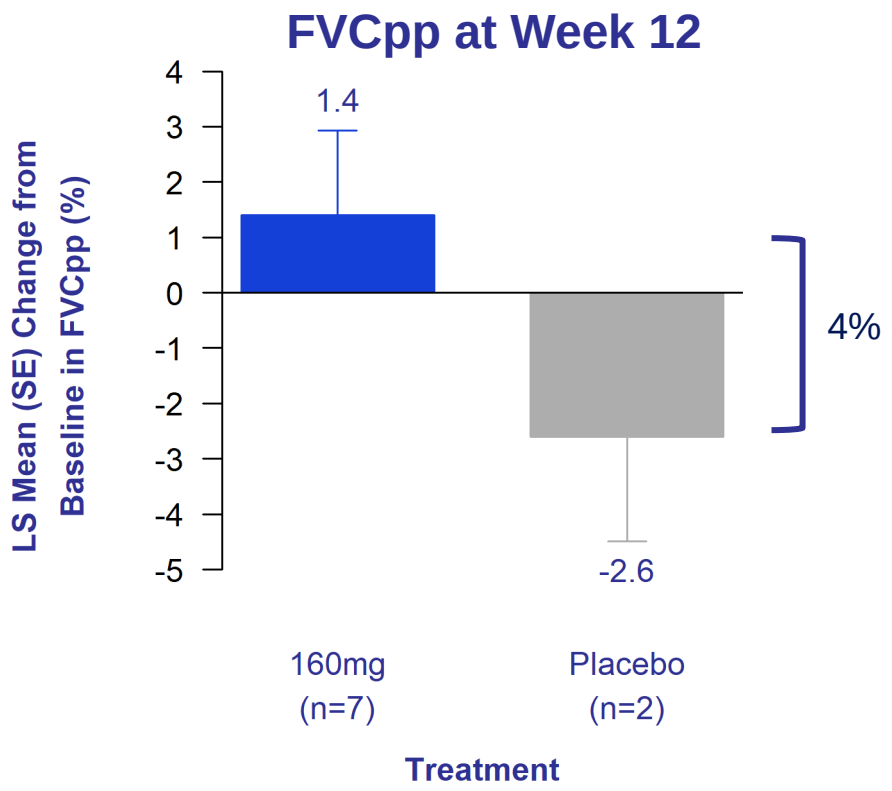
Bexotegrast Showed Improved Lung Function Compared to Placebo

ITT Population





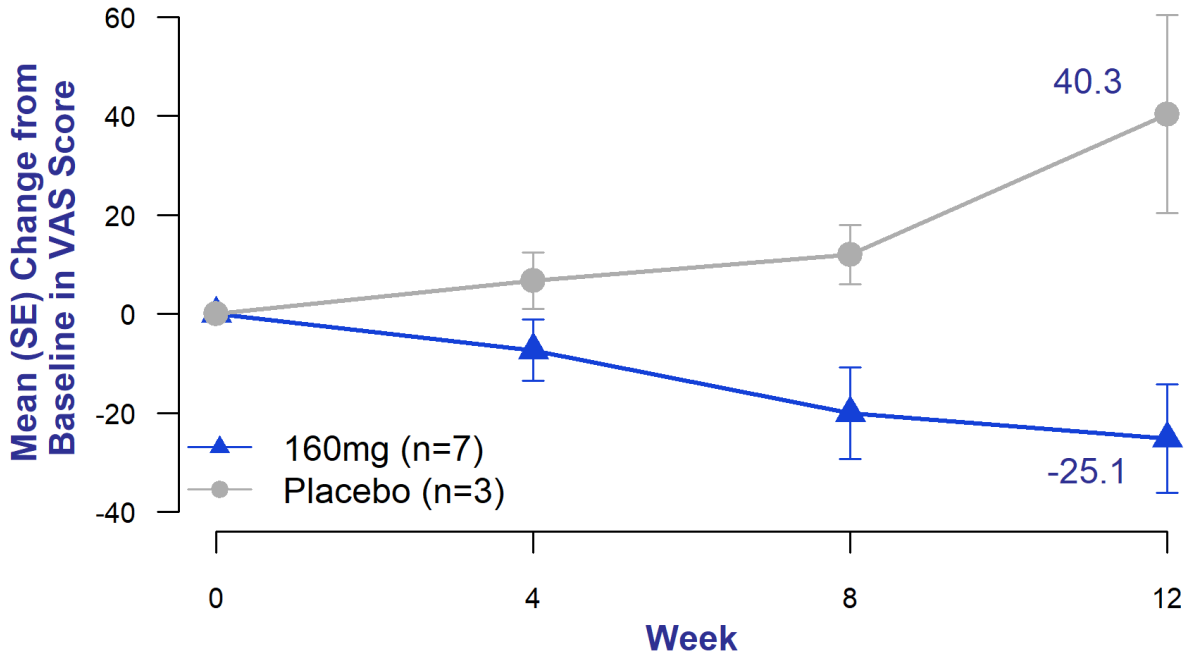
Bexotegrast cohort maintained a clear separation from placebo at all time points

Note: One placebo subject did not have FVC that meet quality standards per ATS guidelines at Weeks 4, 8 and 12
LS = Least Squares; SE = Standard Error; FVC = Forced Vital Capacity; FVCpp = Forced Vital Capacity Percent Predicted

Bexotegrast Showed Decreased Cough Severity Compared to Placebo

ITT Population

Cough Severity Over 12 Weeks of Treatment

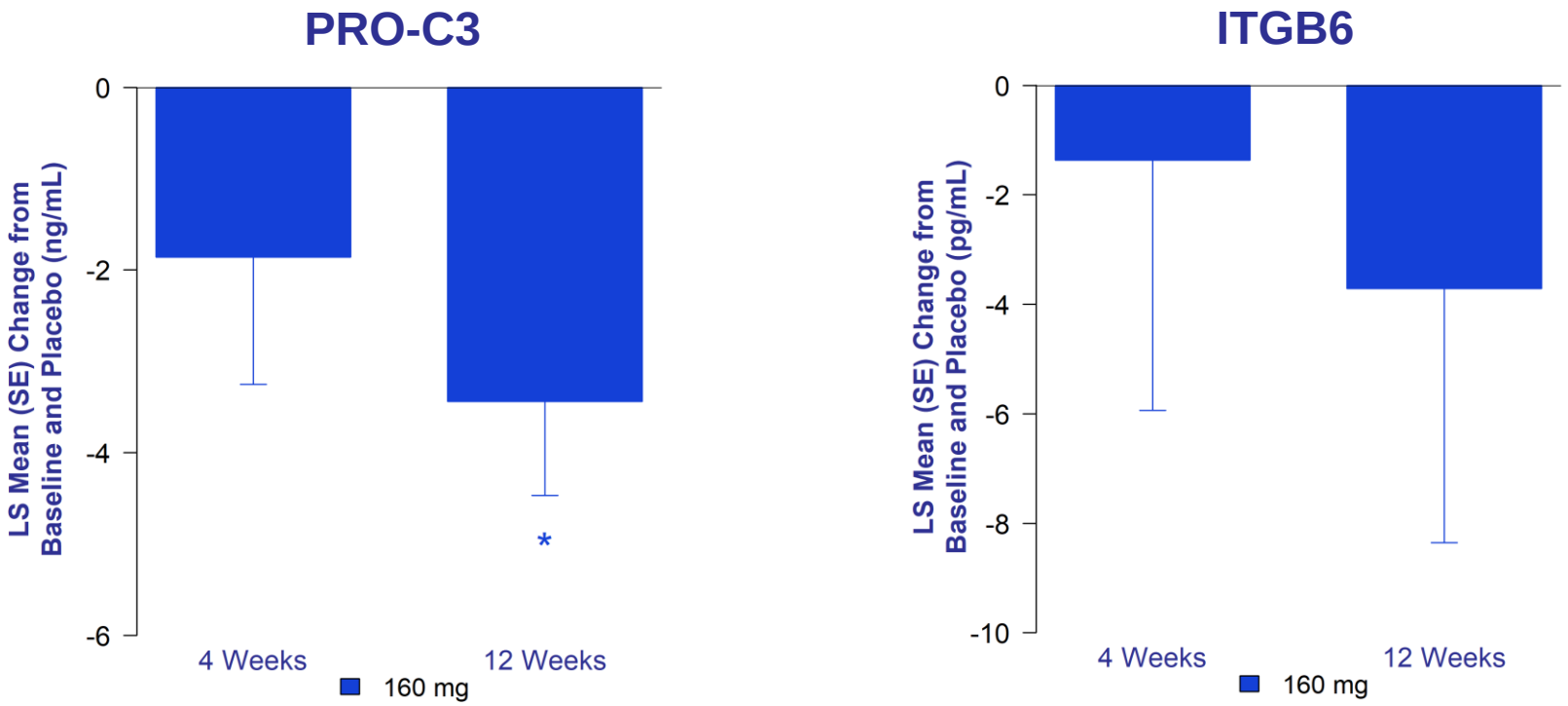


Bexotegrast cohort experienced decreased cough severity across all timepoints compared to increased severity on placebo

EOT: end of treatment; SE: standard error; VAS = Visual Analog Scale
Cough VAS measures patient reported cough severity over last 2 weeks on scale of 0-100 mm

Bexotegrast Showed Reduced Fibrosis Biomarkers Compared to Placebo

ITT Population



* $p < 0.05$ vs placebo

PRO-C3 has been shown to be elevated in patients with IPF and associated with progressive disease[3]

Elevated ITGB6 plasma levels have been shown to be associated with ILD progression[4]

[3]Respir Res. 2019 Jul 12;20(1):148. doi: 10.1186/s12931-019-1118-7; [4]Lancet Respir Med. 2022 Jun;10(6):593-602. doi: 10.1016/S2213-2600(21)00503-8. Epub 2022 Jan 18

ITGB6: Integrin Beta 6; LS = Least Squares; PRO-C3 = Type III Collagen Synthesis Neoepitope; SE = Standard Error

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Bexotegrast – Demonstrated Antifibrotic activity

- Bexotegrast continues to demonstrate antifibrotic activity as assessed using a novel PET tracer which measures total lung collagen, and with established serum biomarkers of fibrosis and ILD progression
- PET results build upon previous evidence of Bexotegrast's antifibrotic mechanism of action using quantitative lung imaging
- Bexotegrast cohort showed improvements in lung function and decreases in cough severity across all time points compared to placebo
- Bexotegrast continues to demonstrate a favorable safety and tolerability profile in the IPF patient population
- Bexotegrast 160 and 320 mg are currently being evaluated in a global Phase 2b/3 study

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