Cohort Two Biomarker Data

LTI-03 Ph1b

November 13, 2024

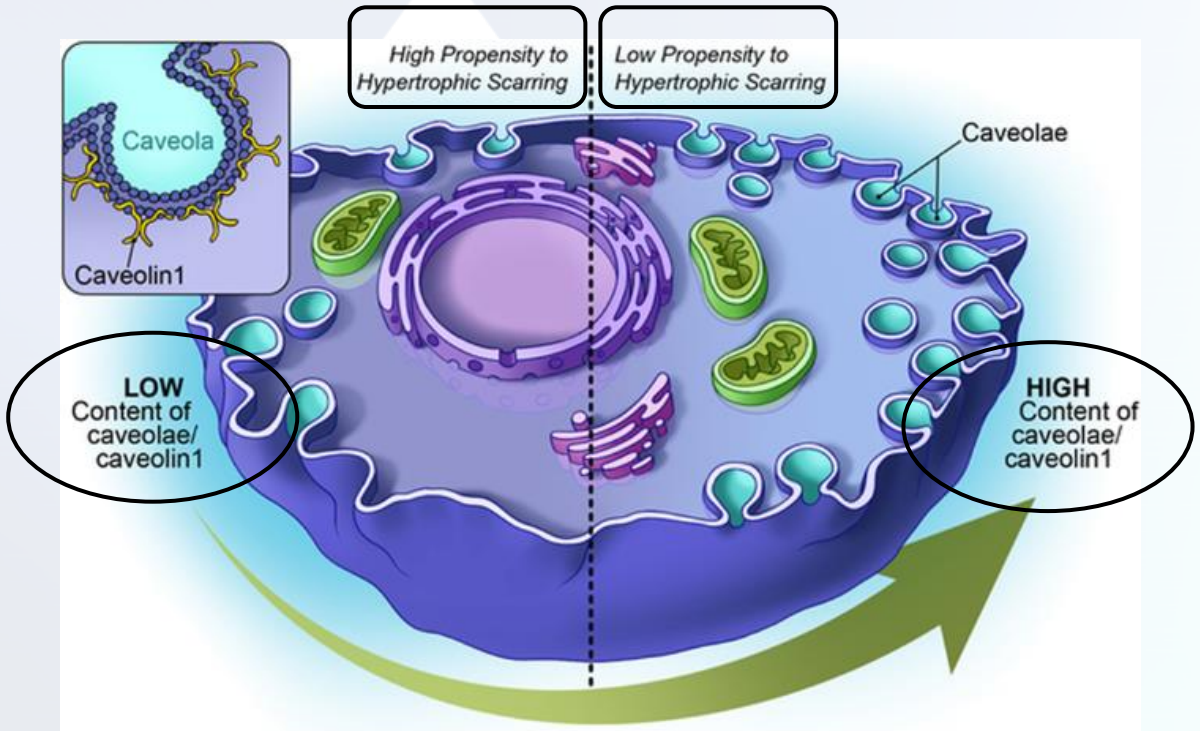
Forward-Looking Statements

This presentation release may contain forward-looking statements of Aileron Therapeutics, Inc. (“Aileron”, the “Company”, “we”, “our” or “us”) within the meaning of the Private Securities Litigation Reform Act of 1995, including statements with respect to: the timing and expectation of a Phase 2 trial of LTI-03; future expectations, plans and prospects for the Company, the sufficiency of the Company’s cash resources; and the potential commercial opportunity of LTI-03 and LTI-01. We use words such as "anticipate," "believe," "estimate," "expect," "hope," "intend," "may," "plan," "predict," "project," "target," "potential," "would," "can," "could," "should," "continue," and other words and terms of similar meaning to help identify forward-looking statements, although not all forward-looking statements contain these identifying words. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including risks and uncertainties related to changes in applicable laws or regulations, the possibility that the Company may be adversely affected by other economic, business, and/or competitive factors, including risks inherent in pharmaceutical research and development, such as: adverse results in the Company’s drug discovery, preclinical and clinical development activities, the risk that the results of preclinical studies and early clinical trials may not be replicated in later clinical trials, including in a Phase 2 trial of LTI-03, or that partial results of a trial will be indicative of the full results of the trial, the Company’s ability to enroll patients in its clinical trials, and the risk that any of its clinical trials may not commence, continue or be completed on time, or at all; decisions made by the U.S. Food and Drug Administration and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies with respect to our development candidates; our ability to obtain, maintain and enforce intellectual property rights for our platform and development candidates; competition; uncertainties as to the sufficiency of the Company’s cash resources to fund its planned activities for the periods anticipated and the Company’s ability to manage unplanned cash requirements; and general economic and market conditions; as well as the risks and uncertainties discussed in the "Risk Factors" section of the Company’s Annual Report on Form 10-K for the year ended December 31, 2023 and the Quarterly Report on Form 10-Q for the quarter ended June 30, 2024, which are on file with the United States Securities and Exchange Commission (the “SEC”), and in subsequent filings that the Company files with the SEC. These forward-looking statements should not be relied upon as representing the Company’s view as of any date subsequent to the date of this press release, and we expressly disclaim any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

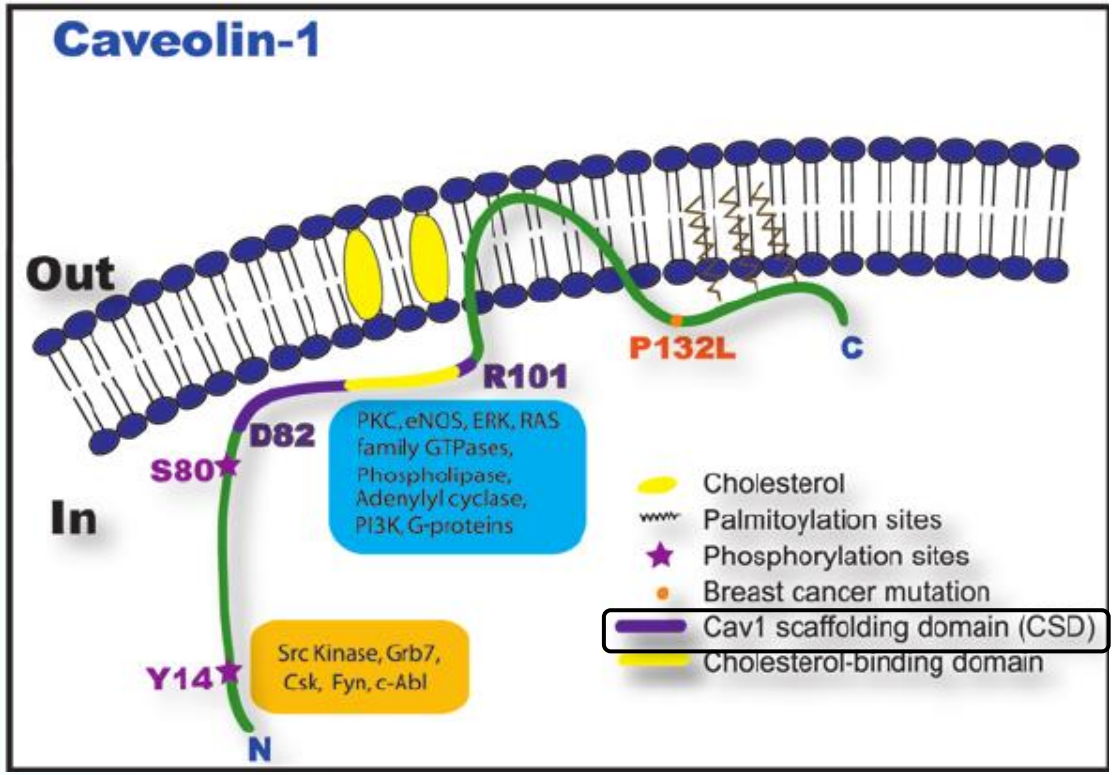
Summary

- Dose dependent movement of 5 biomarkers indicate active LTI-03 pharmacodynamics (COL1A1, CXCL7, TSLP, GAL7, SPD)
- Statistical significance of three biomarkers in cohort 2, and statistical significance of four in the combined data set
- Surfactant protein D, indicator of epithelial cell health was decreased by 5% in cohort 2; the same biomarker was decreased by OFEV® by 4% at 12 weeks in the INMARK clinical trial
    - Linked to decline in lung function
- pAKT (safety biomarker) was not activated in PBMCs in either cohort

Caveolin-1: a Key Regulator in Fibrosis



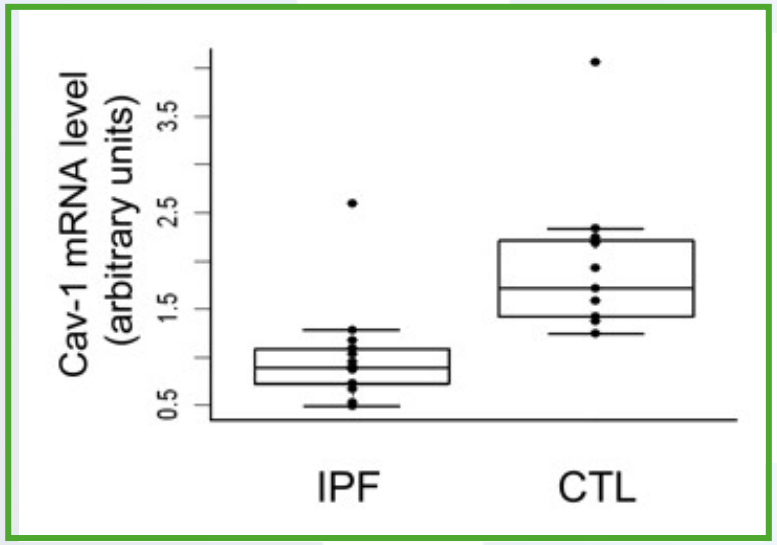
Fibroblasts, epithelial cells, endothelial cells, myocytes, adipocytes, & immune cells.



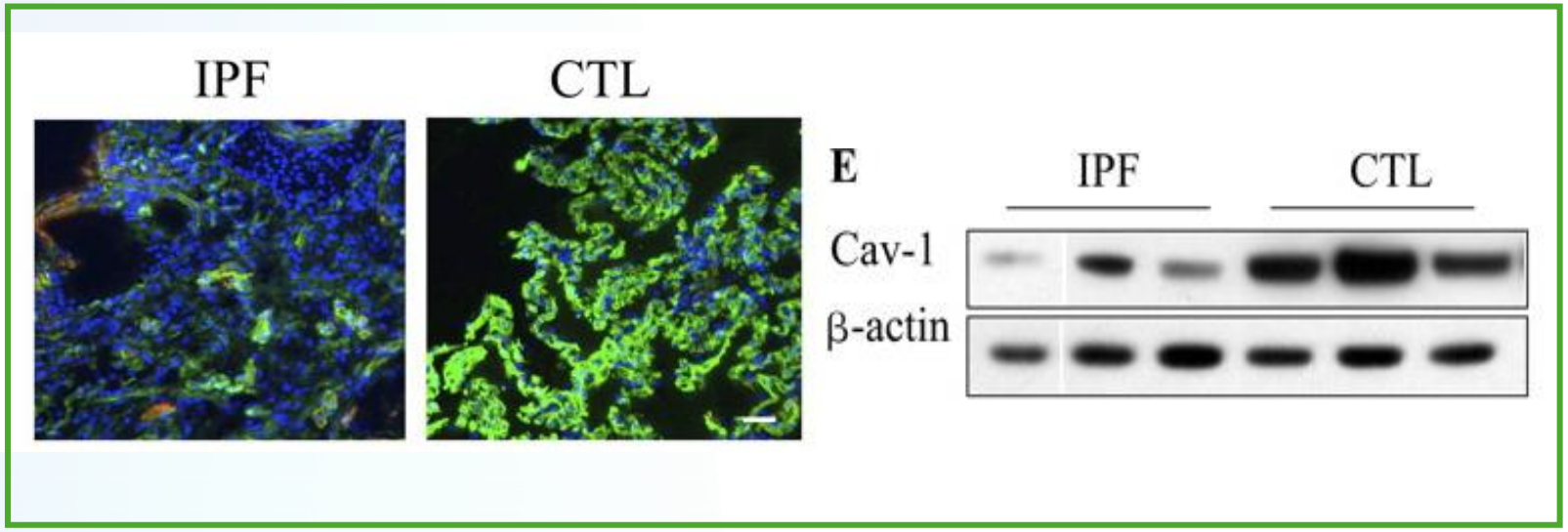
Caveolin-1 is Downregulated in IPF

Caveolin-1: a critical regulator of lung fibrosis in idiopathic pulmonary fibrosis

Xiao Mei Wang,[1] Yingze Zhang,[1] Hong Pyo Kim,[1] Zhihong Zhou,[1] Carol A. Feghali-Bostwick,[1] Fang Liu,[1] Emeka Ifedigbo,[1] Xiaohui Xu,[2] Tim D. Oury,[3] Naftali Kaminski,[1] and Augustine M.K. Choi[1]



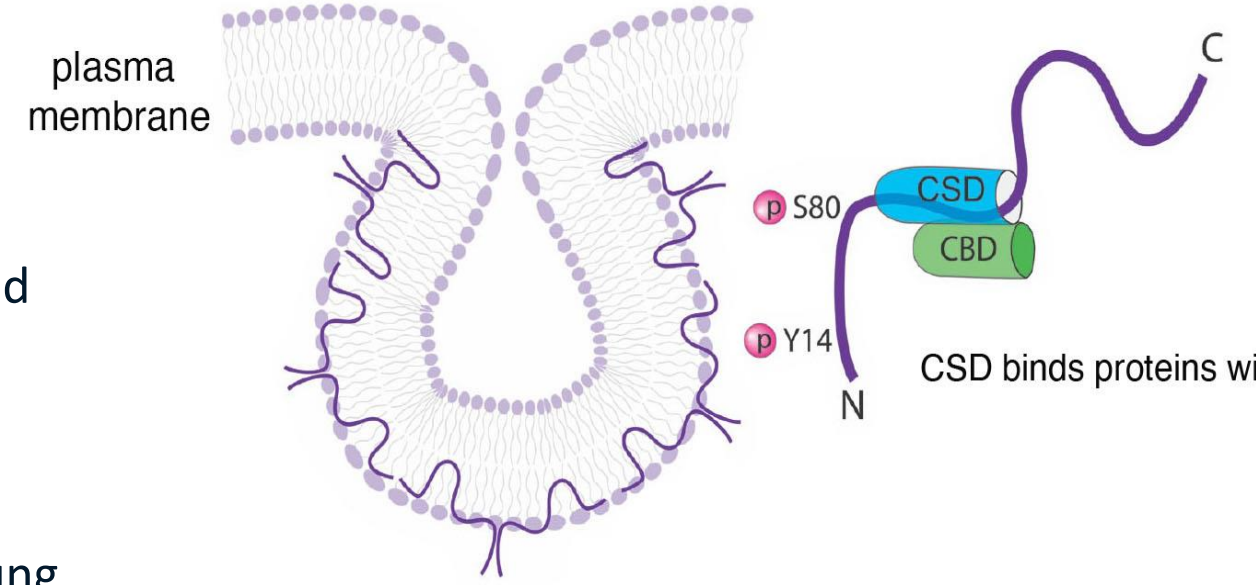
mRNA levels



Protein expression

Simulation of Caveolin-1 Activity via CSD Peptide

- LTI-03 is a seven amino acid peptide encompassing a portion of the Cav1 CSD
- LTI-03 is dosed direct-to-lung by dry powder inhaler



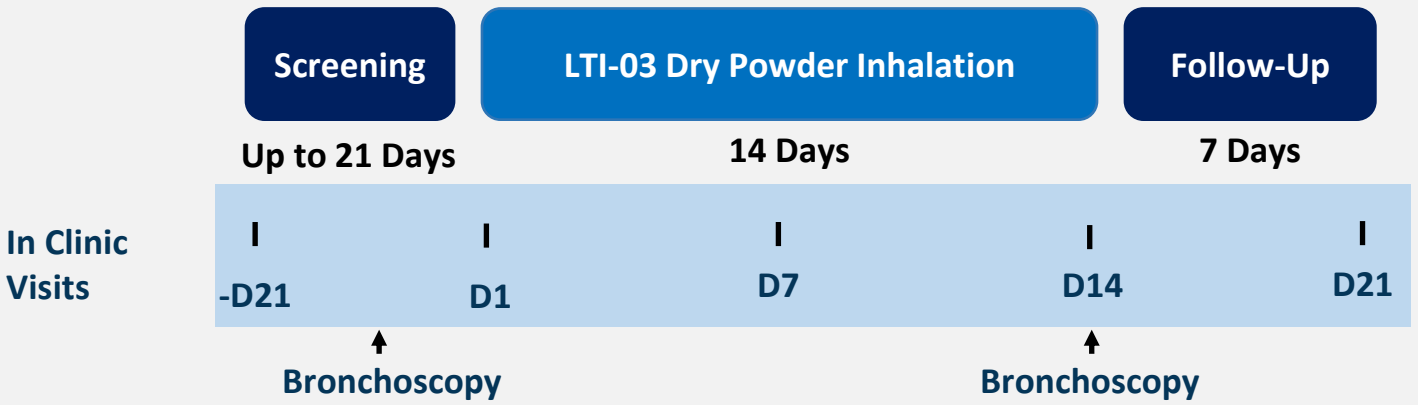
full CSD (20-mer): N-DGIWKAS**FTTFTVT**KYWFYR-C

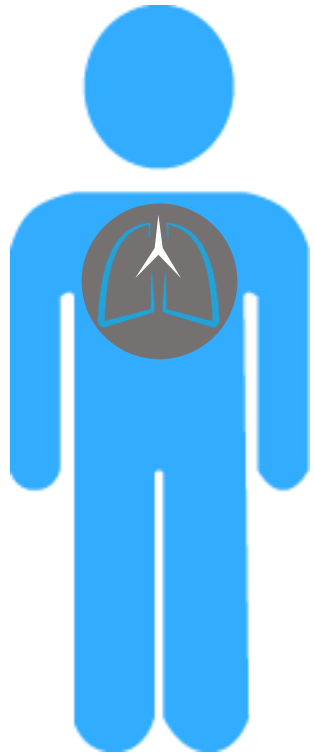
LTI-03 (7-mer): **FTTFTVT**

predicted molecular weight: 815.92 kDa

For a review on CSD/CBD binding domain list, see: Byrne et. al. PLOS One 2012

Phase 1b Clinical Trial Design (Status: In Process)





Study Design

- IPF diagnosis ≤ 3 years; no previous antifibrotic therapy w/in 2 months of baseline
- 24 patients total (18 active, 6 placebo)
  - Low (2.5mg BID) and high (5mg BID) dose cohorts, sequential daily dosing for 14 days
- Bronchoscopy at screening and Day 14
- Primary endpoint: Safety/tolerability
- Key exploratory endpoint: Biomarkers (blood, BAL, brushings)
- Statistical significance determined as p <0.05

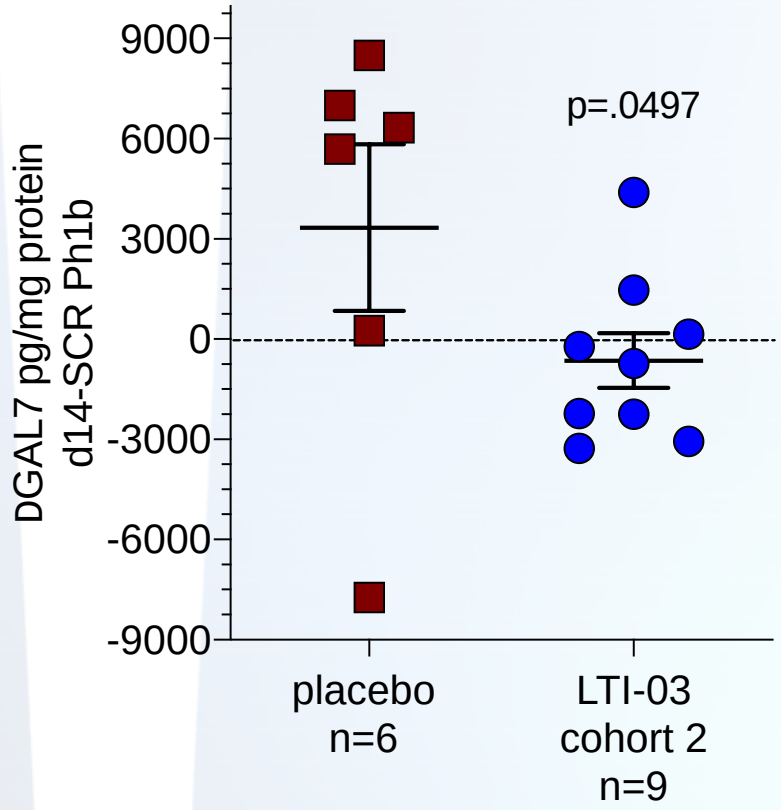
Summary

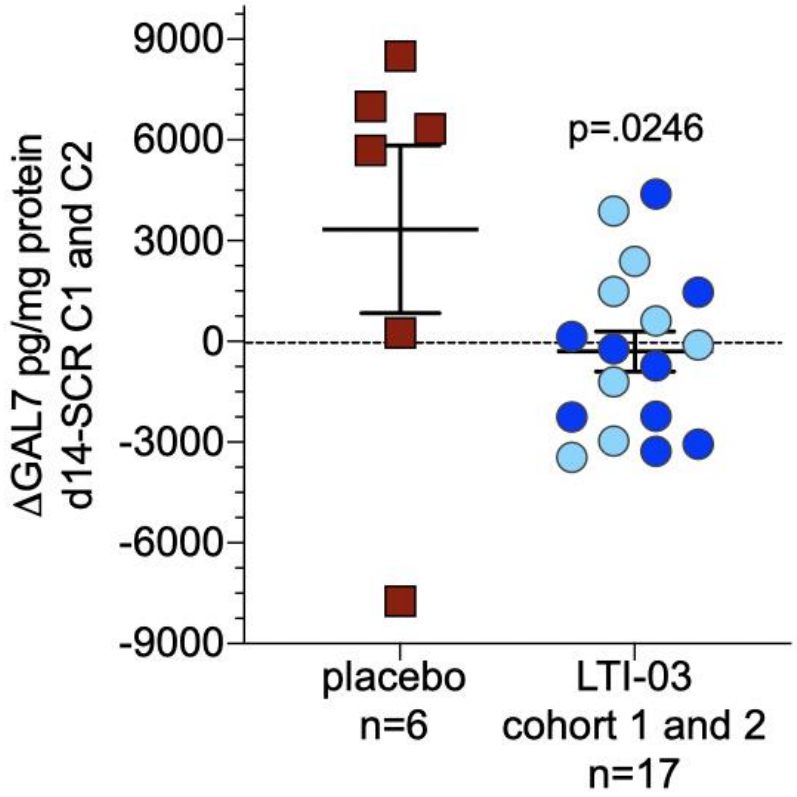
- Dose dependent movement of 5 biomarkers indicate active LTI-03 pharmacodynamics (COL1A1, CXCL7, TSLP, GAL7, SPD)
- Statistical significance of three biomarkers in cohort 2, and statistical significance of four in the combined data set
- Surfactant protein D, indicator of epithelial cell health was decreased by 5% in cohort 2; the same biomarker was decreased by OFEV® by 4% at 12 weeks in the INMARK clinical trial
    - Linked to decline in lung function
- pAKT (safety biomarker) was not activated in PBMCs in either cohort

Biomarker	Positive Trend C2	Statistically Significant (p<0.05) C2	Positive Trend C1+C2	Statistically Significant (p<0.05) C1+C2	dose dependency
Fibroblasts/ myofibroblasts					
COL1A1	✓		✓		✓
IL-11	✓		✓	✓	
CXCL7	✓	✓	✓	✓	✓
pSMAD/ tSMAD					
Basal-like cells					
TSLP	✓	✓	✓	✓	✓
GAL7	✓	✓	✓	✓	✓
Alveolar epithelial health					
SPD	✓		✓		✓
Inflammation/ safety					
%pAKT	✓	N/A	✓	N/A	N/A

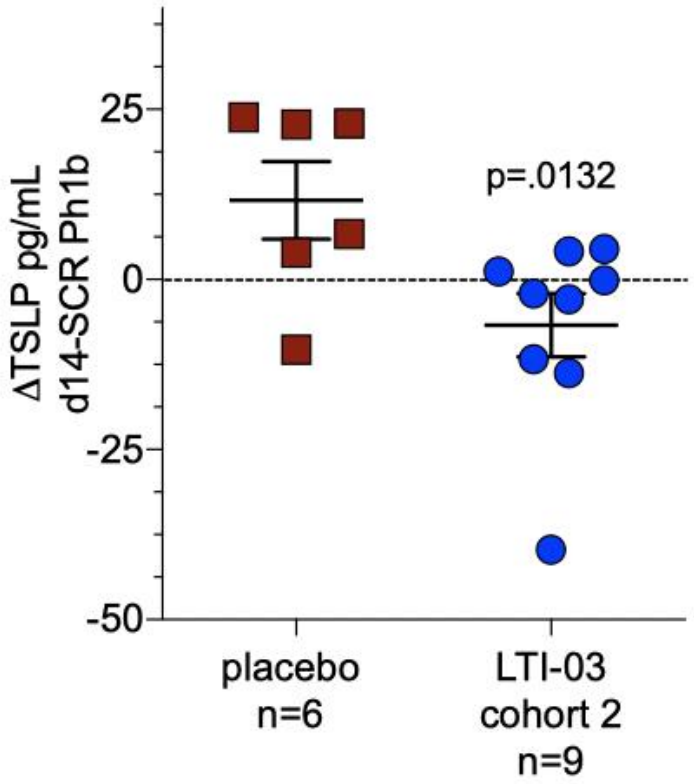
sRAGE, which was evaluated in cohort one, was not able to be evaluated in cohort two due to multiple protocol violations

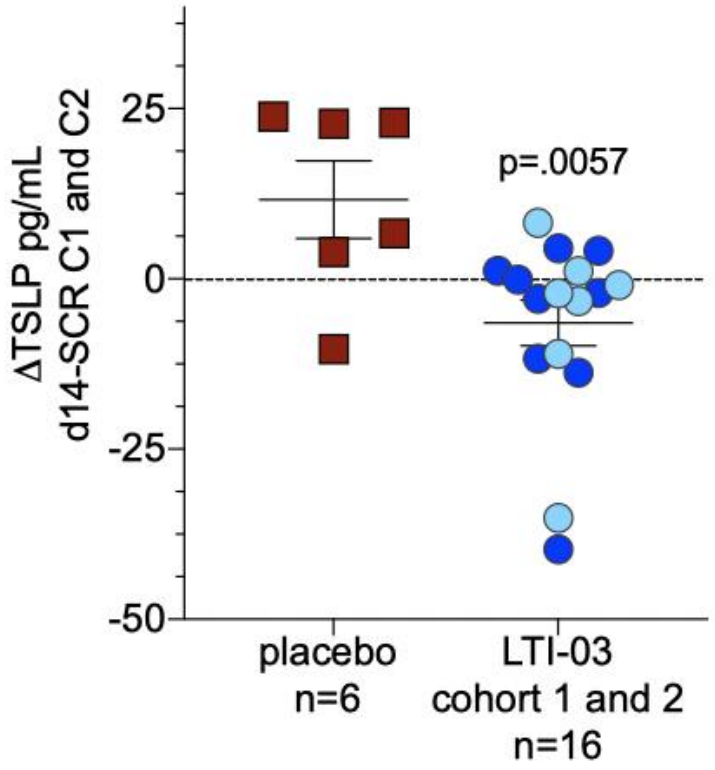
GAL7 – significant and dose dependent decrease



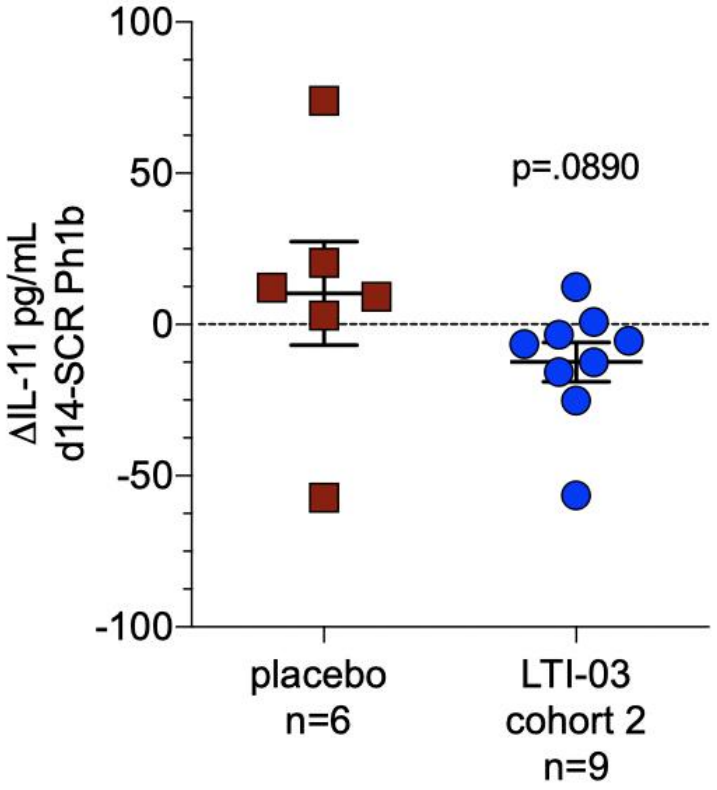


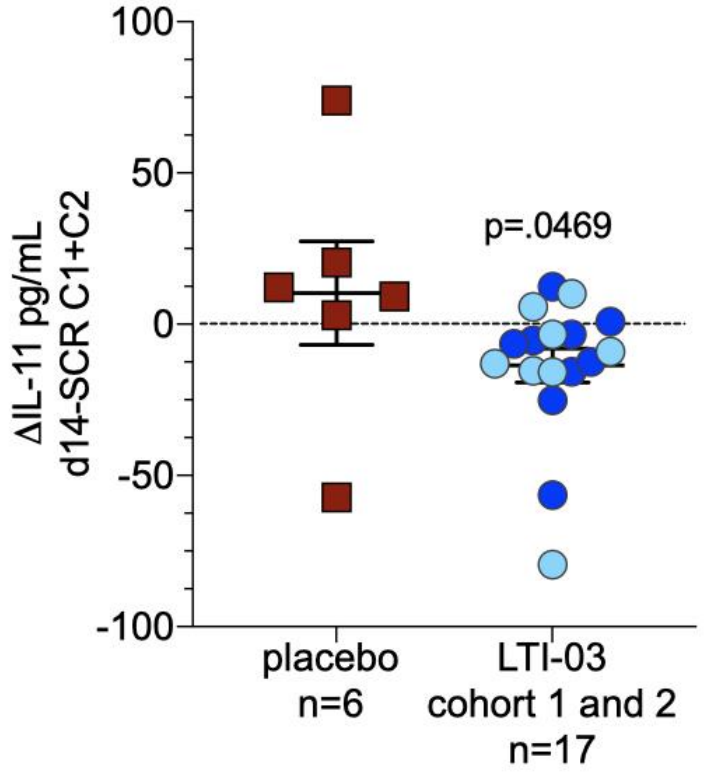
TSLP – significant and dose dependent decrease



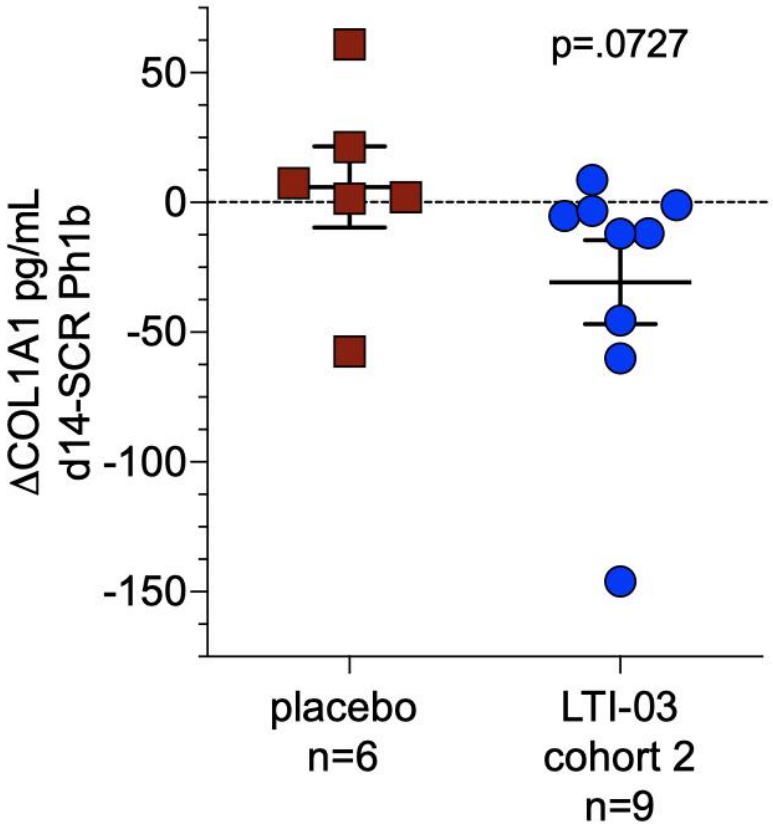


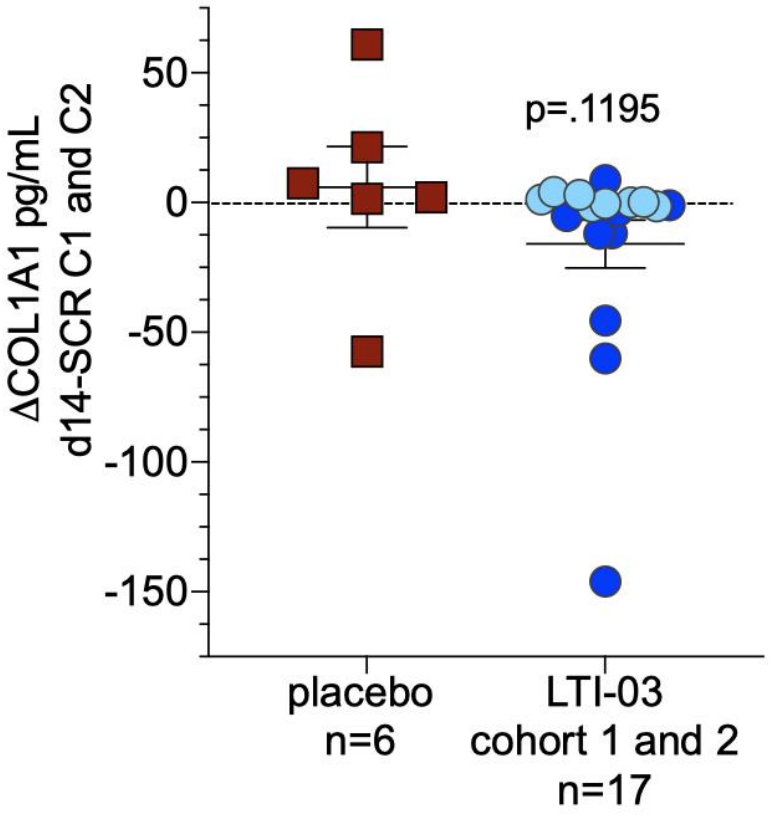
IL-11 significant decrease in combined data set



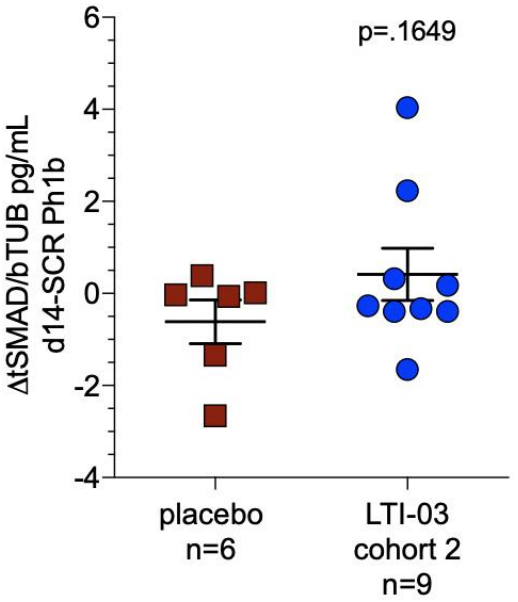


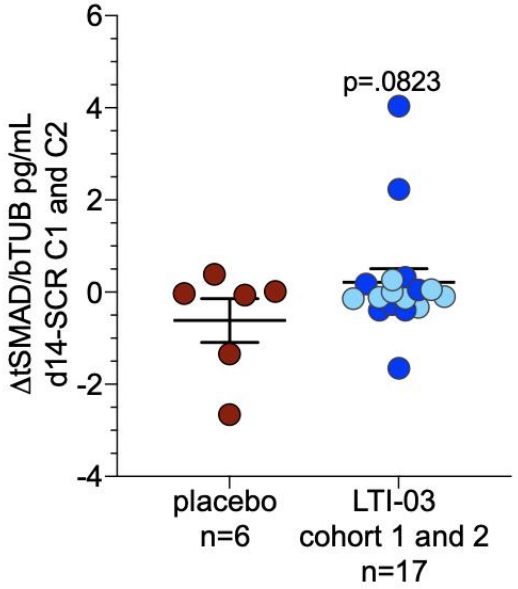
COL1A1 dose dependent decrease

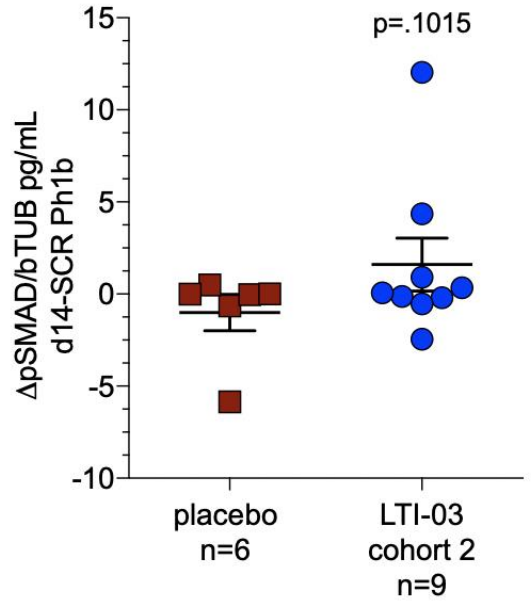


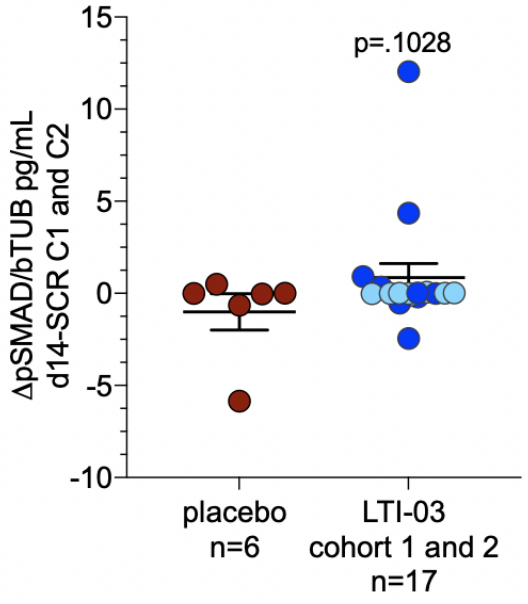


SMAD

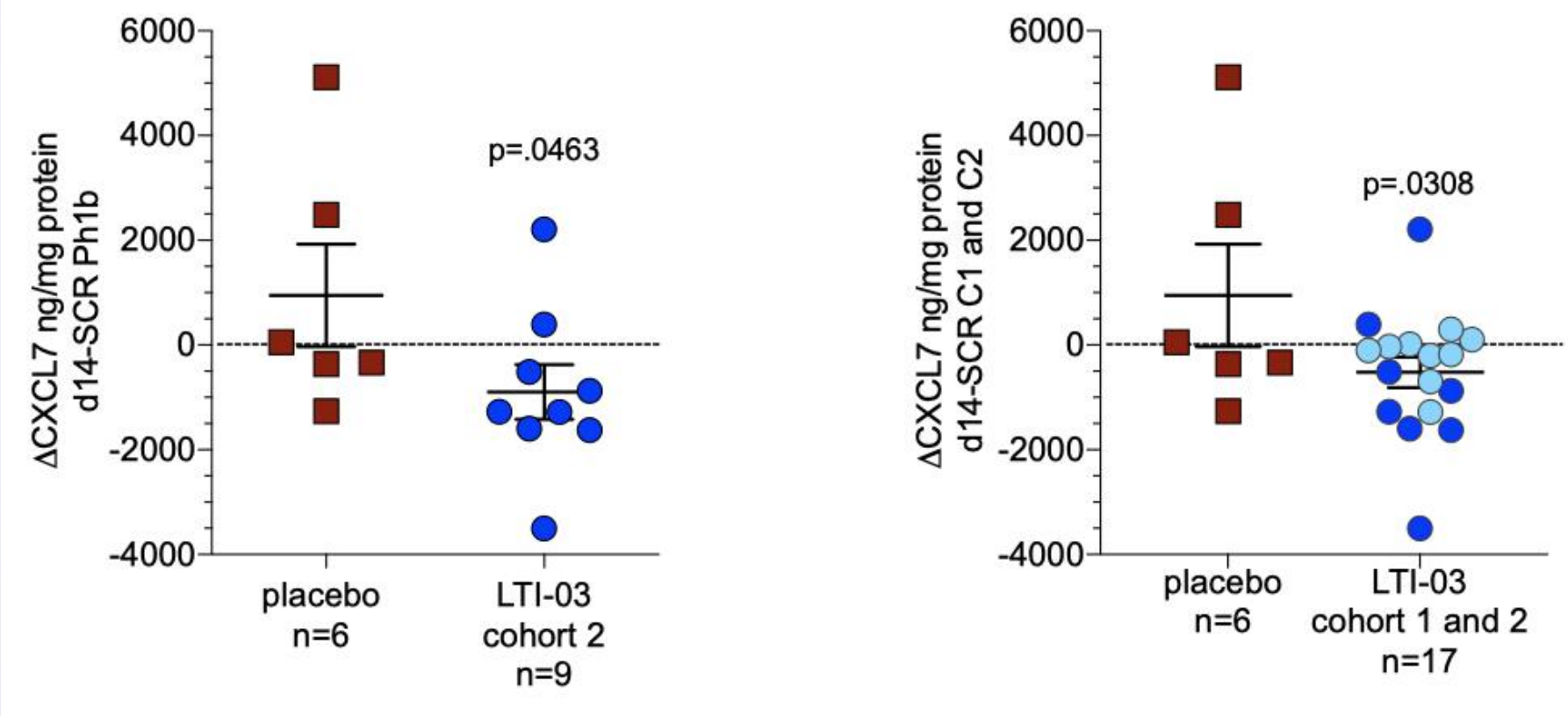

p=.1649
ΔtSMAD/bTUB pg/mL
d14-SCR Ph1b
6
4
2
0
-2
-4
placebo
n=6
LTI-03
cohort 2
n=9


p=.0823
ΔtSMAD/bTUB pg/mL
d14-SCR C1 and C2
6
4
2
0
-2
-4
placebo
n=6
LTI-03
cohort 1 and 2
n=17

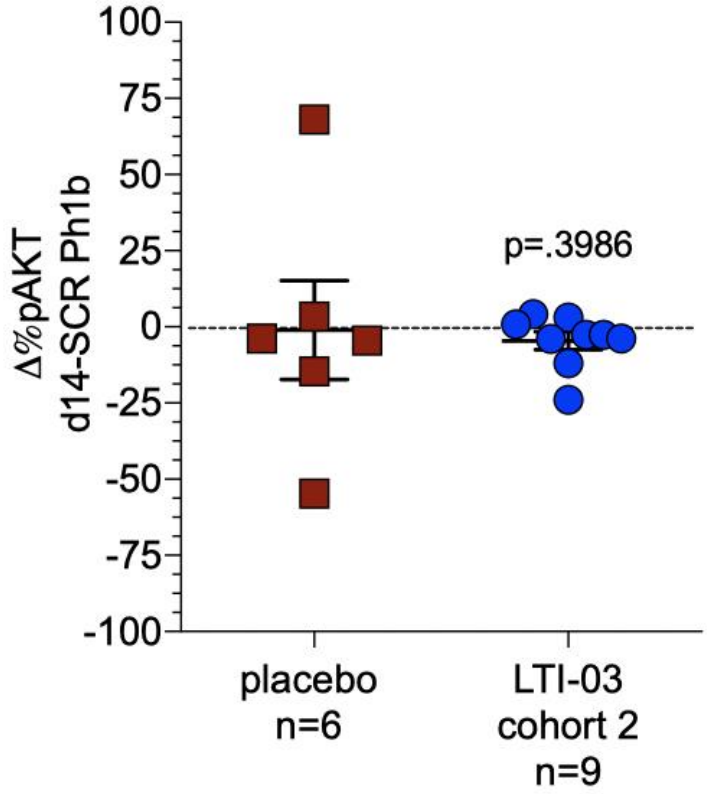

p=.1015
ΔpSMAD/bTUB pg/mL
d14-SCR Ph1b
15
10
5
0
-5
-10
placebo
n=6
LTI-03
cohort 2
n=9

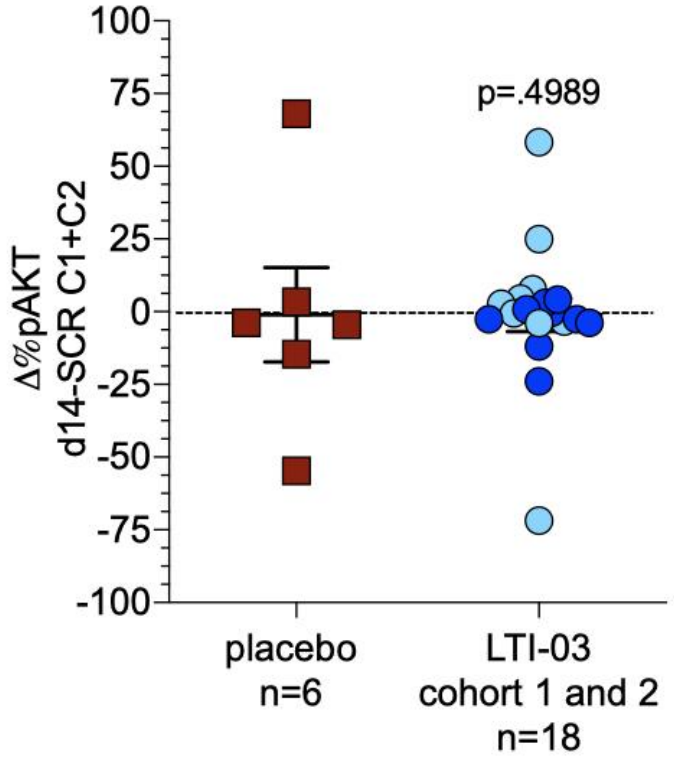

p=.1028
ΔpSMAD/bTUB pg/mL
d14-SCR C1 and C2
15
10
5
0
-5
-10
placebo
n=6
LTI-03
cohort 1 and 2
n=17

CXCL7 – significant and dose dependent decrease

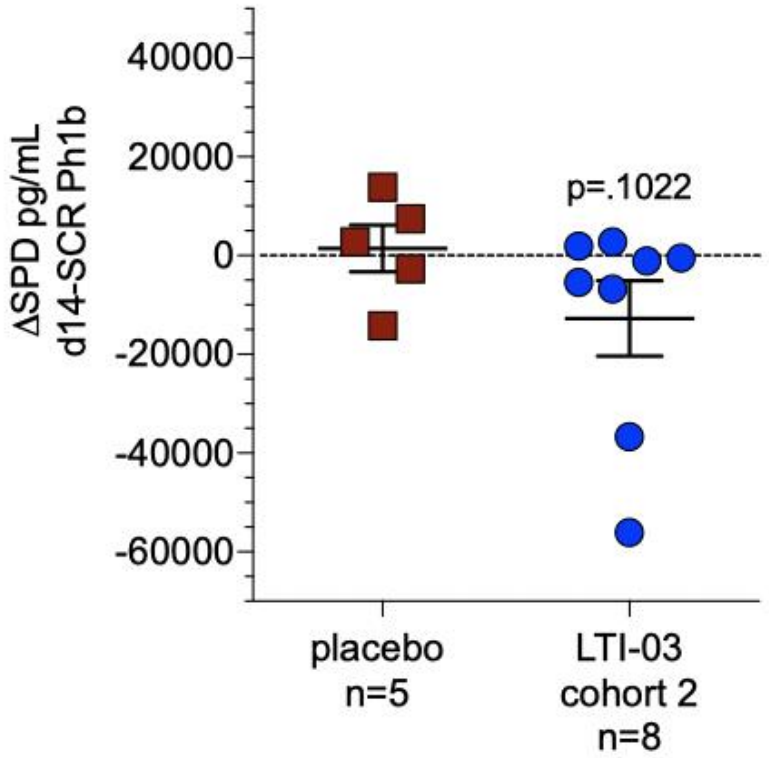


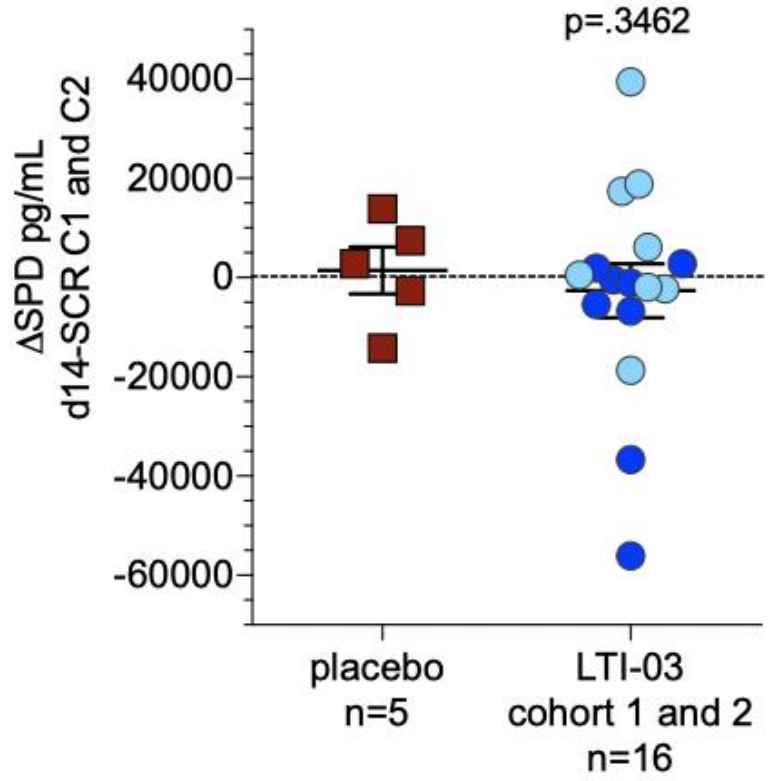
pAKT- PBMC


100
75
50
25
0
-25
-50
-75
-100
Δ%pAKT
d14-SCR Ph1b
p=.3986
placebo
n=6
LTI-03
cohort 2
n=9


100
75
50
25
0
-25
-50
-75
-100
Δ%pAKT
d14-SCR C1+C2
p=.4989
placebo
n=6
LTI-03
cohort 1 and 2
n=18

SPD – measured in plasma – dose dependent decrease





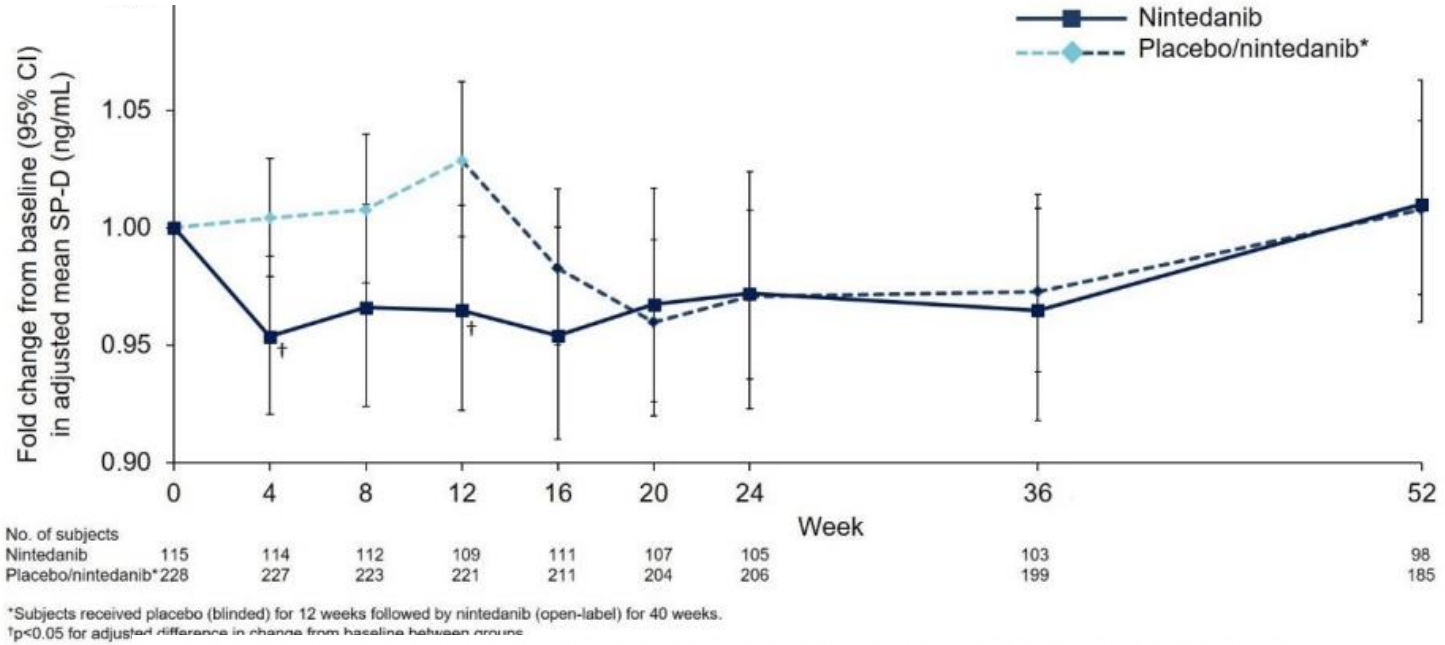
SPD was also decreased by OFEV® in clinical trial

Effects of nintedanib on circulating biomarkers of idiopathic pulmonary fibrosis

R Gisli Jenkins, Vincent Cottin, Yasuhiko Nishioka, Imre Noth, Eric S White, Carina Ittrich, Claudia Diefenbach, Klaus B Rohr, Moisés Selman, Toby M Maher, on behalf of the INMARK trial investigators

C3M, ng/mL	12.1 (3.1)	12.7 (4.0)
BGM, ng/mL	14.0 (7.0)	15.0 (8.4)
C3A, ng/mL	59.4 (14.5)	58.2 (13.7)
C5M, ng/mL	7.4 (3.2)	6.9 (2.3)
C6M, ng/mL	19.9 (14.9)	21.6 (27.0)
VICM, ng/mL	7.5 (7.3)	6.7 (6.2)
Pro-C3, ng/mL	15.5 (8.8)	14.7 (6.6)
Pro-C6, ng/mL	10.2 (6.4)	9.4 (5.0)
LOXL-2, ng/mL	187.8 (142.4)	182.9 (139.4)
NE-EL, ng/mL	8.9 (5.7)	9.7 (8.3)
KL-6, U/mL	1144.2 (983.5)	1087.5 (760.8)
SP-D, ng/mL	725.6 (556.3)	690.2 (441.2)
CA-125, U/mL	14.9 (8.8)	15.1 (10.2)
CA19-9, U/mL	19.5 (26.3)	34.1 (95.8)
ICAM-1, ng/mL	649.3 (164.5)	651.0 (180.1)

Data are mean (SD). All biomarkers were measured in serum except for KL-6, SP-D



nintedanib versus placebo. Fold changes from baseline in SP-D at week 12 corresponded to a 4% decrease and 3% increase in the nintedanib and placebo groups, respectively (ratio 0.94 [95% CI: 0.89, 0.99]; p=0.024). Fold changes in CA-

Just baseline values reported

The biomarker data regarding change in SPD in this trial and the data from the INMARK trial of nintedanib compares two clinical trials with different trial designs, patient enrollment criteria and treatment regimens. In addition, the applicable measurements were observed over different time periods and using different assays. As a result, the data from these trials may not be directly comparable.

Biomarker	Positive Trend C2	Statistically Significant (p<0.05) C2	Positive Trend C1+C2	Statistically Significant (p<0.05) C1+C2	dose dependency
Fibroblasts/ myofibroblasts					
COL1A1	✓		✓		✓
IL-11	✓		✓	✓	
CXCL7	✓	✓	✓	✓	✓
pSMAD/ tSMAD					
Basal-like cells					
TSLP	✓	✓	✓	✓	✓
GAL7	✓	✓	✓	✓	✓
Alveolar epithelial health					
SPD	✓		✓		✓
Inflammation/ safety					
%pAKT	✓	N/A	✓	N/A	N/A

sRAGE, which was evaluated in cohort one, was not able to be evaluated in cohort two due to multiple protocol violations