Mereo BioPharma

Alvelestat (MPH966) R&D Day

March 14 2022

Mereo BioPharma Group plc

NASDAQ: MREO

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Mereo Biopharma Alvelestat R&D Day - Agenda

- Welcome, Introductions and Agenda – **Dr. Denise Scots-Knight, PhD, CEO Mereo BioPharma**
- AATD and ASTRAEUS Phase 2 update - **Dr. Jackie Parkin, MD, SVP and Therapeutic Head Mereo**
- ATALANTa Phase 2 update – **Dr. Mike Wells, MD, Division of Pulmonary, Allergy and Critical Care Medicine, Associate Professor of Medicine at the University of Alabama at Birmingham**
- ASTRAEUS biomarker strategy and end-points – **Dr. Jackie Parkin, MD, SVP and Therapeutic Head Mereo**
- Neutrophil Elastase specific breakdown marker - Aα-Val^{360} AATD - **Prof. Robert Stockley, Professor of Medicine at the University Hospital Birmingham (UK), Director of the Lung Immunobiochemical Research Program at the University Hospital Birmingham, Chief Investigator ASTRAEUS**
- COVID-19 (COSTA) – **Dr. Mike Wells, MD, Division of Pulmonary, Allergy and Critical Care Medicine, Associate Professor of Medicine at the University of Alabama at Birmingham**
- Bronchiolitis Obliterans Syndrome – **Dr. Steven Pavletic, MD, National Cancer Institute, National Institutes of Health, Bethesda, Adjunct Professor of Medicine at the Georgetown University, Lombardi Cancer Center, Division of Oncology & Dr. Annie Im, MD, Associate Professor, Division of Hematology/Oncology, University of Pittsburgh**
- Closing remarks followed by Q&A

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Today's Speakers

Dr. Mike Wells
Mike Wells, MD, Division of Pulmonary, Allergy and Critical Care Medicine, Associate Professor of Medicine at the University of Alabama at Birmingham

Prof. Robert Stockley
Professor of Medicine at the University Hospital Birmingham (UK), Director of the Lung Immunobiochemical Research Program at the University Hospital Birmingham, Chief Investigator ASTRAEUS

Dr. Steven Pavletic
MD, National Cancer Institute, National Institutes of Health, Bethesda, Adjunct Professor of Medicine at the Georgetown University, Lombardi Cancer Center, Division of Oncology

Dr. Annie Im
MD, Associate Professor, Division of Hematology / Oncology, University of Pittsburgh

Dr. Denise Scots-Knight
Chief Executive Officer

Dr. Jackie Parkin
Therapeutic Area Head, Respiratory and Endocrinology

Dr. John Lewicki
Chief Scientific Officer

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Introduction

Dr Denise Scots-Knight
Mereo BioPharma CEO

Upcoming Key Milestones & Opportunities

Upcoming Milestone For Core Programs						
Product Candidate	**Indication**	**2022**	**2023**	**2024**	**Partner**	**Next Milestone**
Etigilimab	**Solid tumors**	Phase 1b/2 basket study with potential cohort expansion				Phase 1b/2 full enrolment and data Phase 2 cohort expansion
Alvelestat	**AATD**	Phase 2 ASTRAEUS* Phase 2 ATALANTa				**AATD** Phase 2 top-line data
	BOS	Phase 1b	Phase 2			**BOS** Phase 2 initiation
Setrusumab	**Osteogenesis imperfecta**	Pediatric Phase 2b/3 fracture study	Pediatric Phase 2 children <5 years		ultragenyx pharmaceutical	Initiation of pivotal study pediatric & young adults (5-25yrs old) Initiation of Phase 2 children <5 yrs old)

**ASTRAEUS is a proof-of-concept phase 2 study*

Non-core Programs	
	Navicixizumab has been partnered with OncXerna for further development. **Received a $2M CMC milestone**
	Leflutrozole and acumapimod are currently under partnering discussions. **Next Milestone**: Partnership agreement

Projected milestone

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Alpha-1 Antitrypsin Deficiency- Associated Emphysema

Dr Jackie Parkin
SVP and Therapeutic Area Head

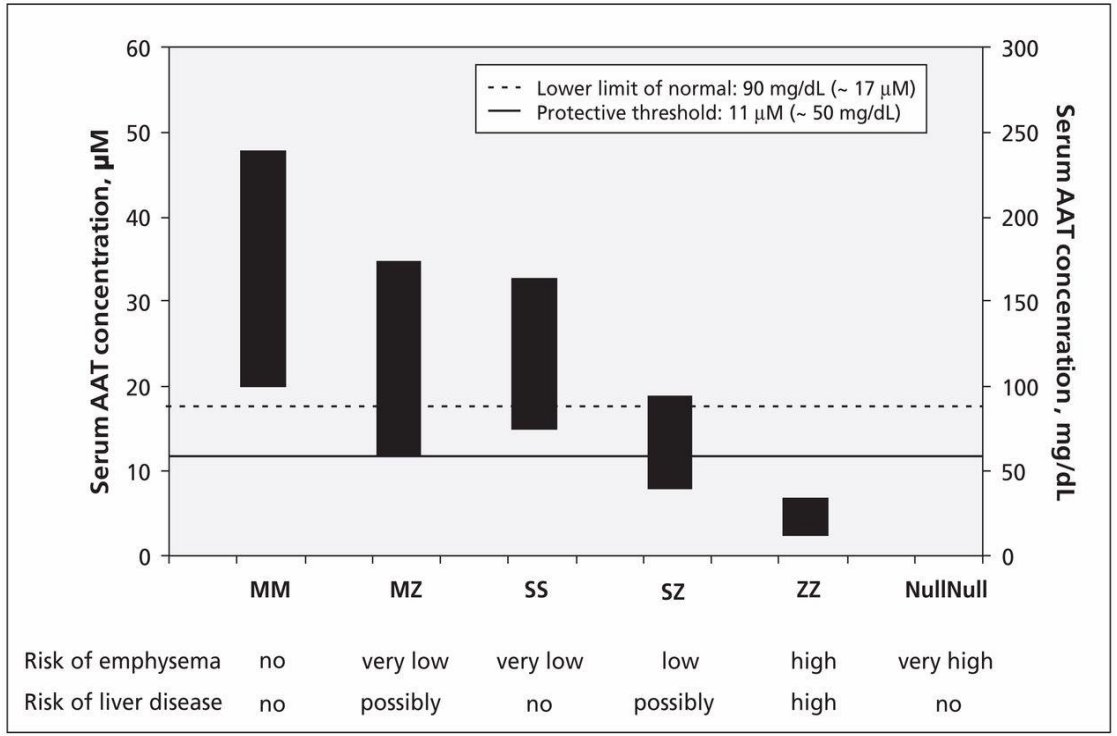
AATD-Associated Emphysema: A Disorder Of Physiological Protease Inhibitor Deficiency

Genetic condition

- Autosomal co-dominant inheritance – MM (normal), MZ, SZ, ZZ and null
- Severity of disease related to level of α1AT Homozygotes (ZZs) and nulls have most severe deficiency and disease
- PiZZs misfolded α1AT 'trapped' in liver – 'loss of function' mutation with systemic deficiency
- Liver disease in ~ 15% PiZZs, mainly children, due to accumulation of polymerised α1AT

AATD-Lung Disease

- Prevalence in US ~ 80-100,000, 90% undiagnosed
- Mean delay to diagnosis in US is 5 years.
- Presents age 20 to 50 – shortness of breath, cough and reduced exercise tolerance
- Unopposed proteases → progressive alveolar & structural damage → emphysema
- May progress to chronic oxygen therapy, lung surgery, transplant and death



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AATD-Associated Emphysema – Current Standard Of Care And Unmet Need

- **Treatment as for 'usual' COPD**, focus on personal lifestyle management (avoid smoking and pollution)
- Testing of family to enable lifestyle choices
- **Intravenous plasma-derived AAT "augmentation" only approved therapy,** weekly, clinical efficacy not uniformly recognized by physicians/payors
  - Limited penetration into lung
  - Inability to 'titrate' up to cover periods of acute lung inflammation, elastase activity and lung damage
  - Growing evidence that higher doses may be needed for clinical efficacy (cost and convenience)
- **Alvelestat highly differentiated from augmentation**
  - Oral inhibitor of neutrophil elastase (NE), pharmacodynamic profile demonstrates high levels NE suppression
  - Not susceptible to oxidative inactivation at sites of inflammation
  - Active against both soluble and cell-bound NE
  - Significant lung penetration

Alvelestat: Development In Severe AATD-Associated Emphysema

- Two complementary Phase 2 clinical trials (ASTRAEUS and ATALANTa) to deliver
  - Efficacy on biomarkers of pathogenesis
  - Characterisation dose response for progression to Phase 3
  - Safety and tolerability
- Biomarker assay development
- Further investigation of MoA (Ex vivo assay)

Ongoing AATD Trials

ATALANTa

Astraeus STUDY

Clinical Trials and Basic Research Partnerships

University of Birmingham

NIH National Center for Advancing Translational Sciences

UAB MEDICINE

ALPHA-1 FOUNDATION

ProAxsis a NetScientific portfolio company

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“ASTRAEUS”

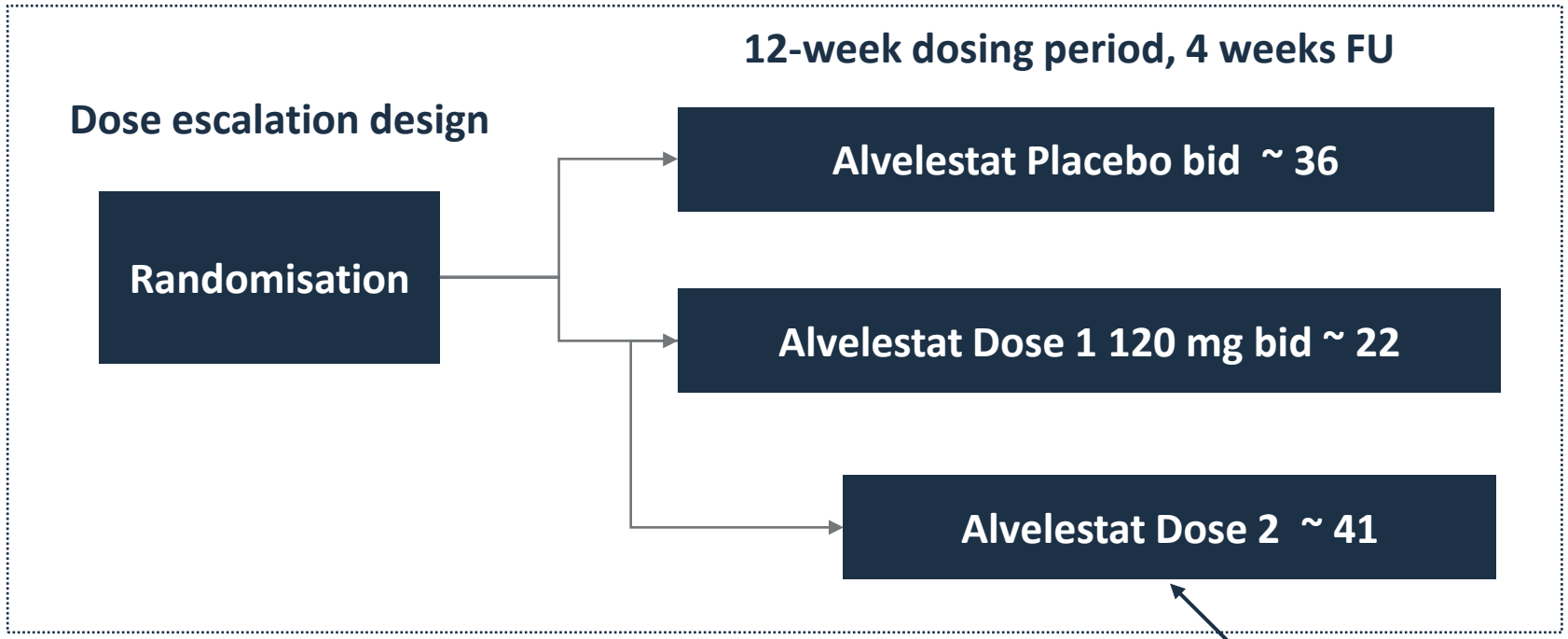
A Phase 2, Proof-of-concept, Multicentre, Double-blind, Randomised, Dose-ascending, Sequential Group, Placebo-controlled Study to Evaluate the Mechanistic Effect, Safety, and Tolerability of 12 Weeks Twice Daily Oral Administration of Alvelestat (MPH966) in Participants With Alpha-1 Antitrypsin Deficiency

ASTRAEUS Phase 2 Study in AATD-Associated Emphysema

A randomized double blind-placebo-controlled study in patients naïve to augmentation or following a 6-month wash-out period. **Total of 99 patients enrolled. Chief Investigator – Prof. Rob Stockley**

Trial Population

- Age ≥18 and ≤80 years
- Pi*ZZ, Pi*Z Null, Pi*Null genotype/phenotype, other rare types
- FEV1 ≥20% predicted



IDMC –both doses deemed safe to proceed
Preferential recruitment to highest dose per protocol

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ASTRAEUS Phase 2 Initial Endpoints

Primary Endpoints	Secondary and Exploratory Endpoints
• Within individual % change from baseline in plasma desmosine/isodesmosine at end of treatment compared to placebo to week 12	• Blood Neutrophil Elastase activity • Blood Aα-Val^{360} levels • Safety and tolerability • Lung damage and inflammation biomarkers • Pharmacokinetics • St. George's Respiratory Questionnaire • Spirometry including - Forced expiratory volume in 1 second (FEV_1), FVC and FEF25-75 • Exacerbations

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ASTRAEUS Demographics And Baseline AATD Characteristics

- Similar to other baseline data for randomized control trials in severe AATD patients[$]

	ASTRAEUS	RAPID*	
	All, (N=99)	A1PI(n=93)	Placebo (n=87)
Age years Mean ±SD (Range)	57.3 ±10.1 (26-75)	53.8±6.9	52.4±7.8
Sex Male (%) Female (%)	39(40%) 60(60%)	48(52%) 45(48%)	50(57%) 37(43%)
Race White (%)	95(96%)	93(100%)	87(100%)
FEV_1 % predicted Mean± SD	56.7±20.7	47.4±12.1	47.2±11.1
A1AP concentration µm Mean±SD (Range)	3.9 ±1.6 (0.04-9.0)	6.38±4.62	5.94±2.42
Mutation status	All ZZ	^NR	^NR
Time from AATD diagnosis years - Median (Range)	9 (1-42)	^NR	^NR

$ Preliminary uncleaned data

*Chapman et al. (2015) Lancet. 2015 Jul 25;386(9991):360-8

^NR- Not Reported

Note: Uncleaned data. Final values may differ from those presented here.

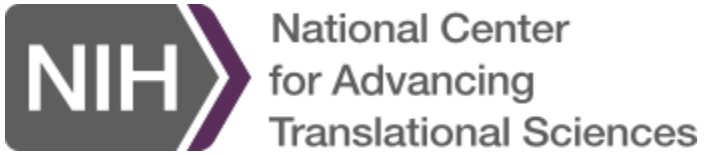
No Safety Signals Identified To-date In AATD Patients (Data Blinded To Mereo)

- Independent Data Monitoring Committee reviews unblinded safety data ~ quarterly.
- There have been no safety signals detected on adverse event or lab monitoring, including in infectious events, liver, hematology or ECG review.
- Most commonly reported treatment-emergent adverse event (TEAE) has been headache- considered a tolerability issue and not a safety issue for alvelestat.
- Headache is a known side effect of alvelestat and was most frequent in the highest dose arm. Dosing amended to include a within-participant dose escalation step which reduced the frequency/severity of headache

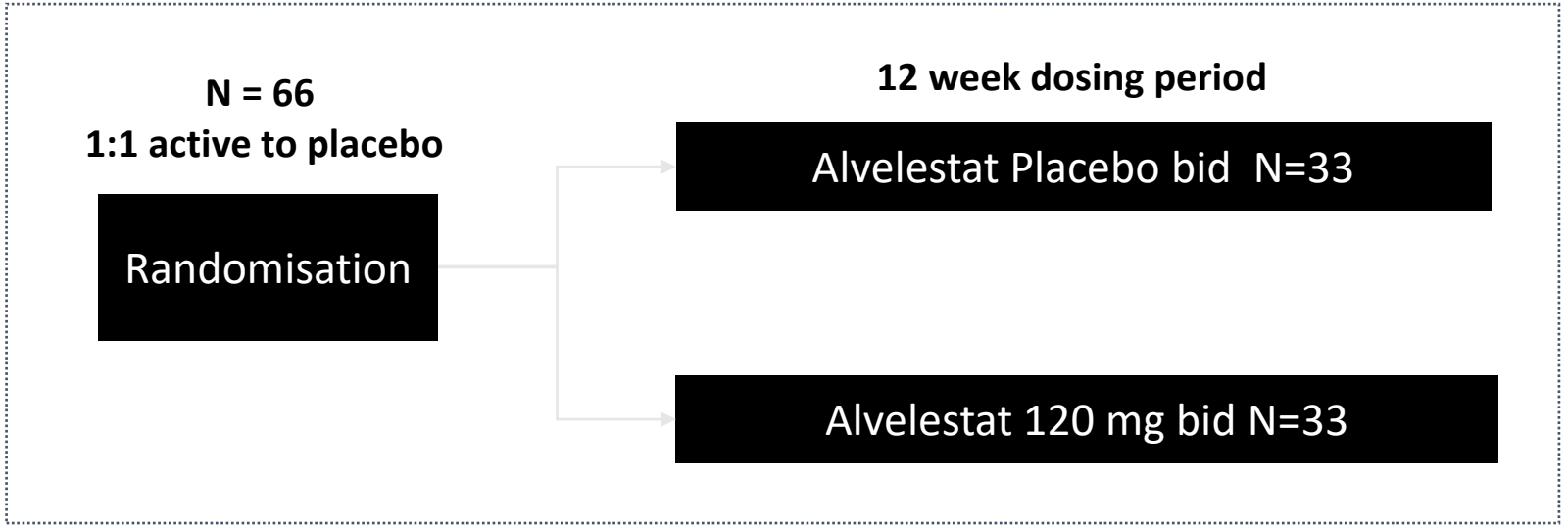
Note: Uncleaned data. Final values may differ from those presented here.

Alvelestat (MPH966) for the Treatment of ALpha-1 ANTitrypsin Deficiency "ATALANTa"

Dr Mike Wells



Alvelestat (MPH966) For The Treatment of ALpha-1 ANTitrypsin Deficiency "ATALANTa" (Investigator-initiated – Principal Investigator Prof Mark Dransfield, UAB)



Trial Population

- Age ≥18 and ≤80 years
- Pi*ZZ, Pi*SZ, Pi*Z Null, or Pi*Null genotype/phenotype
- Emphysema, FEV1 ≥25% predicted
- Not currently receiving augmentation OR on stable augmentation for at least 12 weeks prior to screening

Primary Endpoints

- Within-individual % change in plasma desmosine/isodesmosine (week 12)
- Safety and tolerability

Secondary Endpoints

- Blood Aα-Val^{360}, Neutrophil elastase
- Protease neo-epitopes
- Collagen peptides/chemoattractants
- Pro-inflammatory cytokines

Exploratory Endpoints

- PK/PD
- Spirometry
- PROMs

ATALANTa Extends Patient Population, Biomarkers Analysis Complementary To ASTRAEUS

Target Population

- Confirmed diagnosis of AATD (Pi*ZZ, Pi*SZ, Pi*null, or another rare phenotype/genotype known to be associated) with either low (serum AAT level <11 µM or <57.2 mg/dL) or functionally impaired AAT including “F” or “I” mutations.
- Patients are eligible regardless of previous or ongoing stable treatment with augmentation:
  - Patients either who have received weekly infusions of augmentation at 60 mg/kg for at least 12 weeks prior to screening and intend to continue augmentation through the study period).
- Dose 120 mg bid or placebo
- Focus on US sites

Biomarker Endpoints

- Biomarker intense (Protease pathway; extracellular matrix/collagen; inflammation, neutrophil activation and chemo attractants)
- Common biomarkers collected at same timepoints (consistent with ASTRAEUS) to support future bridging of analyses across both studies

ATALANTa - Consistent Supportive Safety Profile Of Alvelestat In Patients With AATD

10 active sites in USA

37 patients randomized

- No SAEs reported in the study to date
- No clinically important abnormalities in hematology and clinical chemistry reported to date
- 6 monthly DSMB meeting (last Dec 2 2021) “We reviewed AEs and safety data and noted no concerning trends”

Note: Uncleaned data. Final values may differ from those presented here.

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Biomarkers along the pathogenic pathway: Desmosine

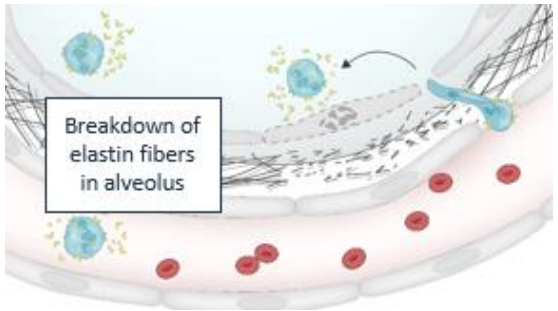
Dr Jackie Parkin
SVP and Therapeutic Area Head

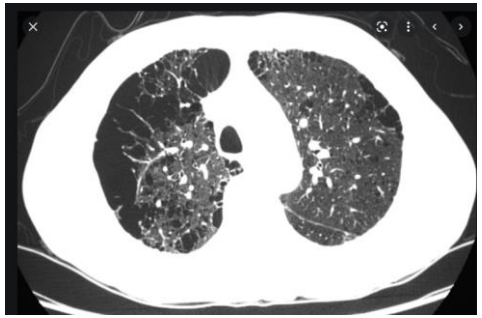
Linking Biomarkers Of The Pathological Pathway

AATD-Lung Disease Pathogenic Pathway

Blood NE	Aα-Val^{360}	Desmosine	CT Density/FEV$_1$
Neutrophil Elastase Activity	Unopposed NE	Alveolar Elastin Breakdown	Lung Tissue Loss/Emphysema
Increased neutrophil elastase activity	Increase in neutrophil elastase-driven target (fibrinogen) breakdown	Elastin breakdown fragments	

Alvelestat





Plasma Desmosine as a Biomarker of Proposed Pathogenic Mechanism (Elastosis)

Marker of Effect on Target Tissue

- Measure of elastolytic rate (desmosine/isodesmonsine = "desmosine“)
- Consistently increased in AATD-associated lung disease (emphysema)
- Addresses question of whether NE inhibition alone modifies a marker within the pathogenic pathway

Desmosine increased in diseases associated with increased NE and shows response to NE suppression with alvelestat in signal-seeking clinical studies

- Cystic Fibrosis: ~19% reduction alvelestat (n=26) compared to placebo (n=29) (p=0.105) by 4 weeks[$]
- Bronchiectasis: ~10% reduction in alvelestat compared to placebo (p= 0.120) by 4 weeks[#]
- Bronchiolitis Obliterans Syndrome (BOS): decrease of ~ 16% from baseline by week 8 (p=0.066)[^]

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$Elborn et al., (Log transformed data on file) 2012; #Stockley et al., 2013; ^ Im et al., 2021

Elevated Blinded Baseline Desmosine Levels In ASTRAEUS Consistent With Other Studies

Data, including therapeutic response, available in AATD

- Correlate with clinical measures of disease severity (FEV1), respiratory function (diffusion factor) and structure (lung density) in AATD population
- Elevated in AATD across different studies
- Responsive to AAT replacement (~ 6.5% reduction at 3 months) in RAPID study[$]

Elevated (blinded) baseline desmosine levels in ASTRAEUS, consistent with other studies of severe AATD

- **ASTRAEUS baseline = 0.386 ng/ml (SD 0.137)**
- RAPID study baseline = 0.365 ng/ml (SD 0.101)
- Healthy volunteers = 0.21ng/ml (SD 0.03)

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Note: Uncleaned data. Final values may differ from those presented here.

$ Ma et al *Chronic Obstr Pulm Dis*. 2017; 4(1): 34-44

** *Albarbarawi et al. (2013) Bioanalysis. 2013 Aug;5(16):1991-2001*

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Biomarkers along pathogenic pathway: Neutrophil Elastase Activity

Monitoring Neutrophil Elastase (NE) Levels In Patients With AATD

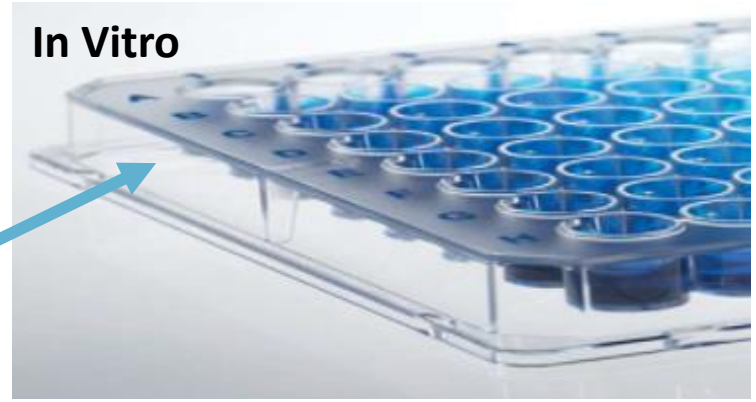
"Functional PK" assays used in AAT augmentation measure NE inhibiting capacity of serum to quantitate level of "biologically active" AAT

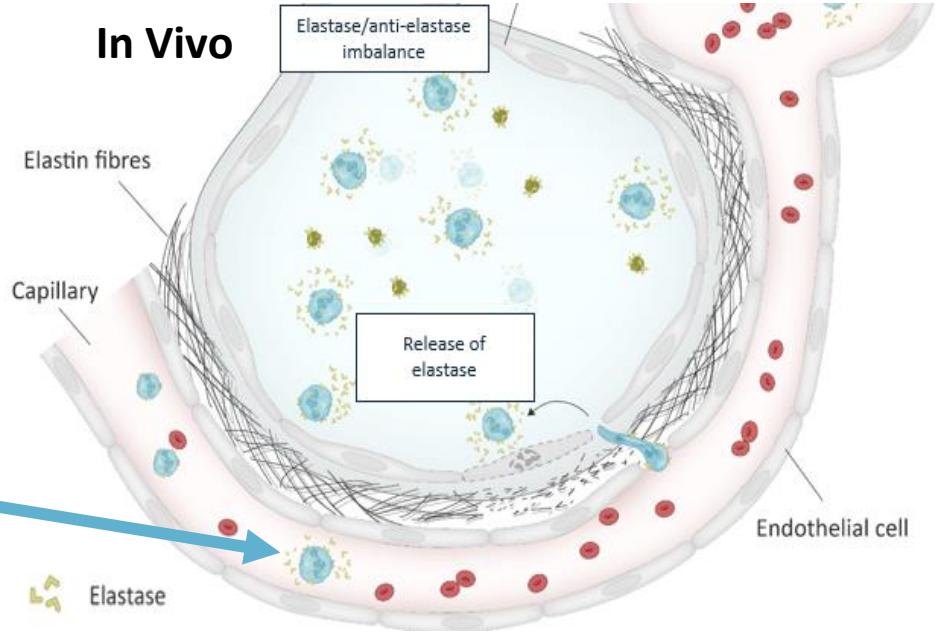
- Does not measure NE activity within a patient and cannot be used as a measure of ongoing *in vivo* suppression

Measurement of elastase in AATD to monitor therapeutic intervention is challenging:

- Limited sensitivity of assays for blood NE activity
- NE activity assays available for sputum, but minority with AATD produce sputum

Increased sensitivity of an established NE activity method (ProAxsis®) now enables measurement of blood elastase activity in patients enrolled in ASTRAEUS





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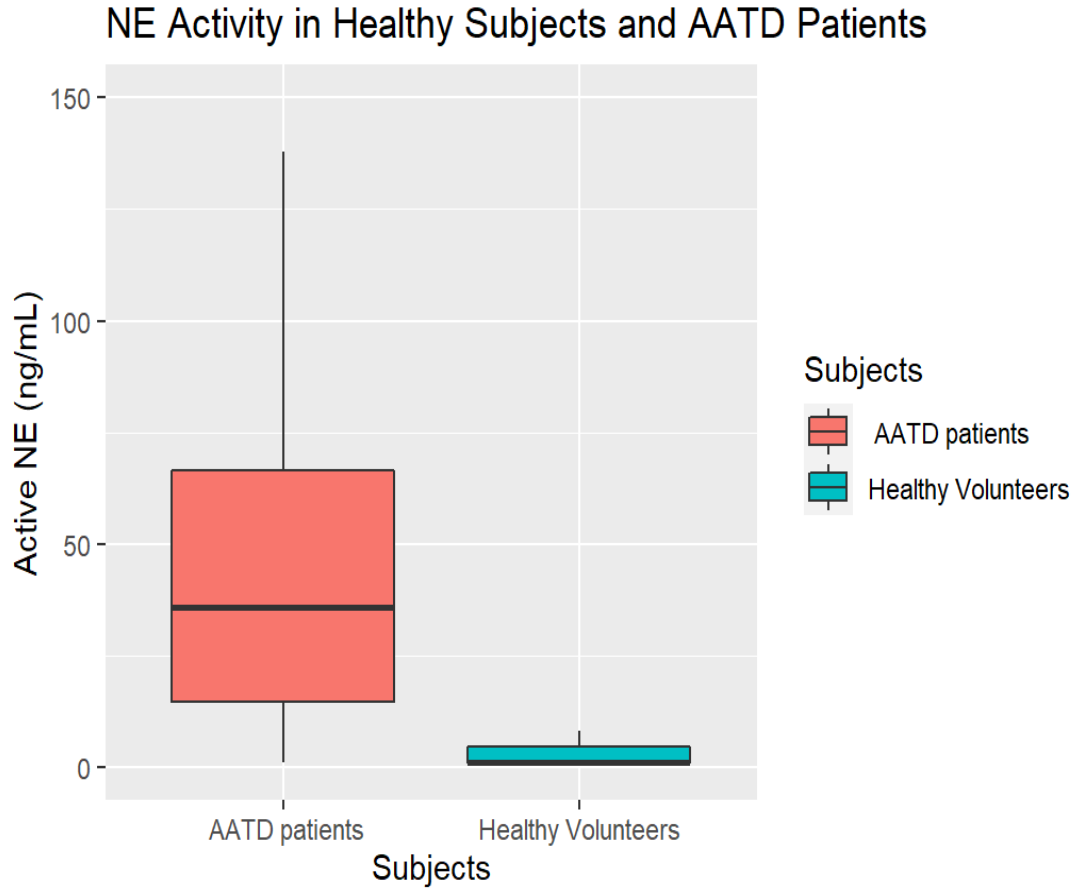
Measurement Of Target Engagement - Activity-based NE Immunoassay For In-vivo Blood Monitoring Of NE Suppression

- The ProteaseTag® activity-based immunoassay specifically measures active neutrophil elastase levels
- Improved sensitivity, enables detection in blood supports potential detection of therapeutic effect.

Active NE (ng/ml)		
	ASTRAEUS Baseline Blinded data (N=82)	Healthy Subjects Recent data (N=39)
Mean	63.6	9.6
Median	40.7	0
Range	0-685.6	0-104.2



Significant difference between the active NE concentrations in each group (p = <0.0001)

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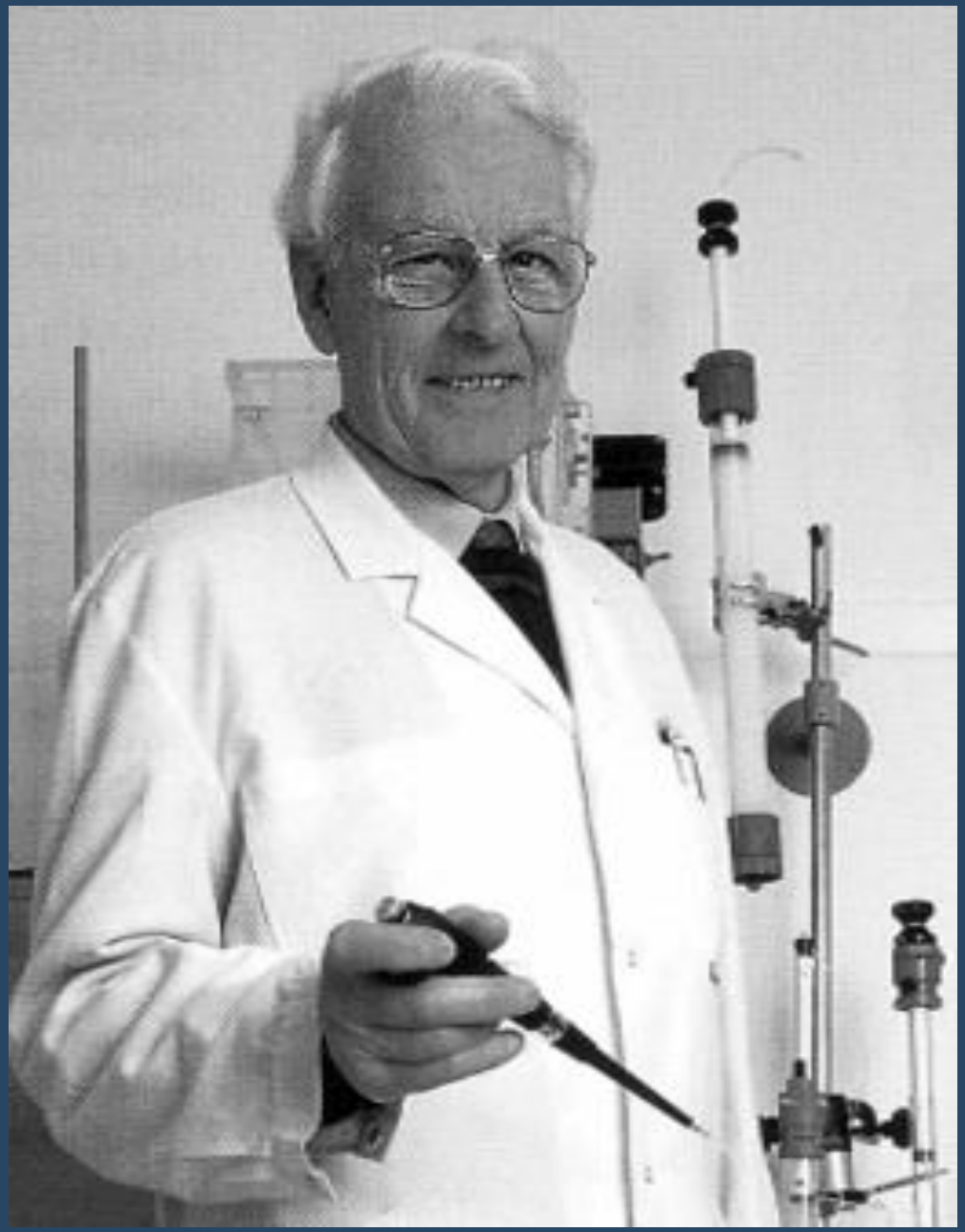
Note: Uncleaned data. Final values may differ from those presented here.

Biomarkers along the pathogenic pathway: Aα-Val^{360}

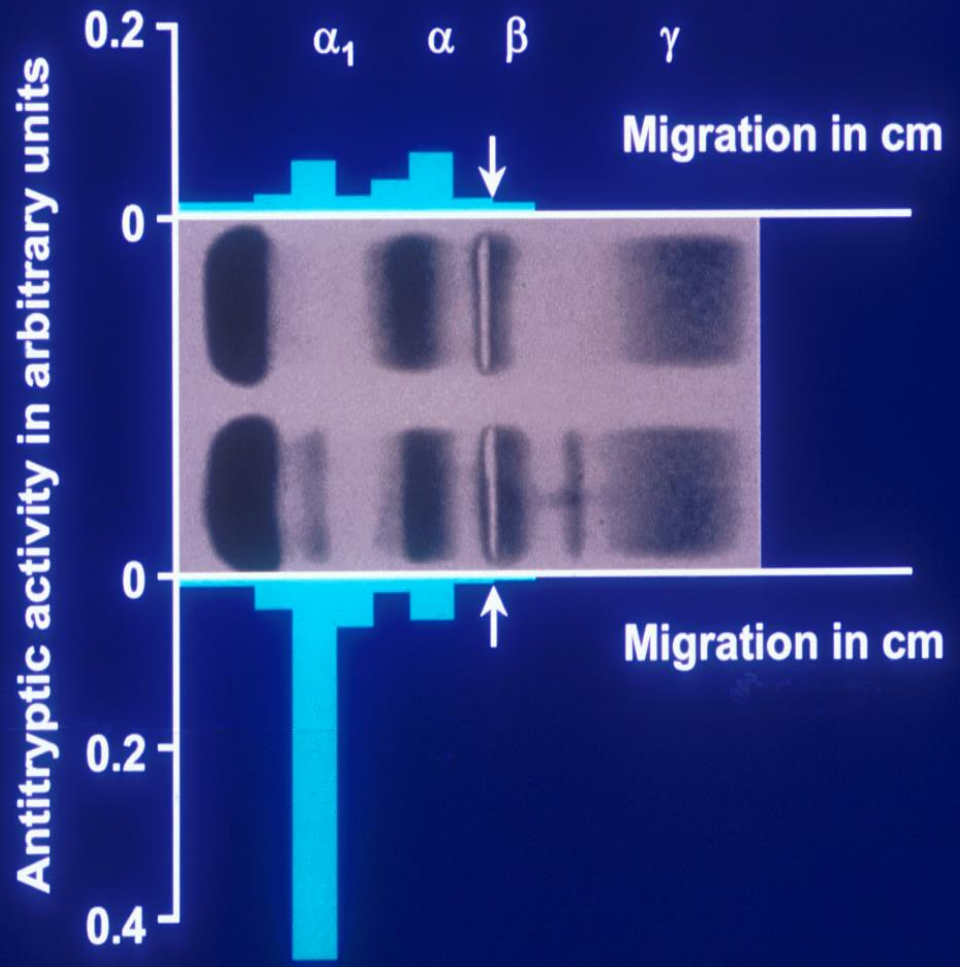
Professor Robert Stockley

Director of the Lung Immunobiochemical Research Program at the University Hospital Birmingham, Chief Investigator ASTRAEUS

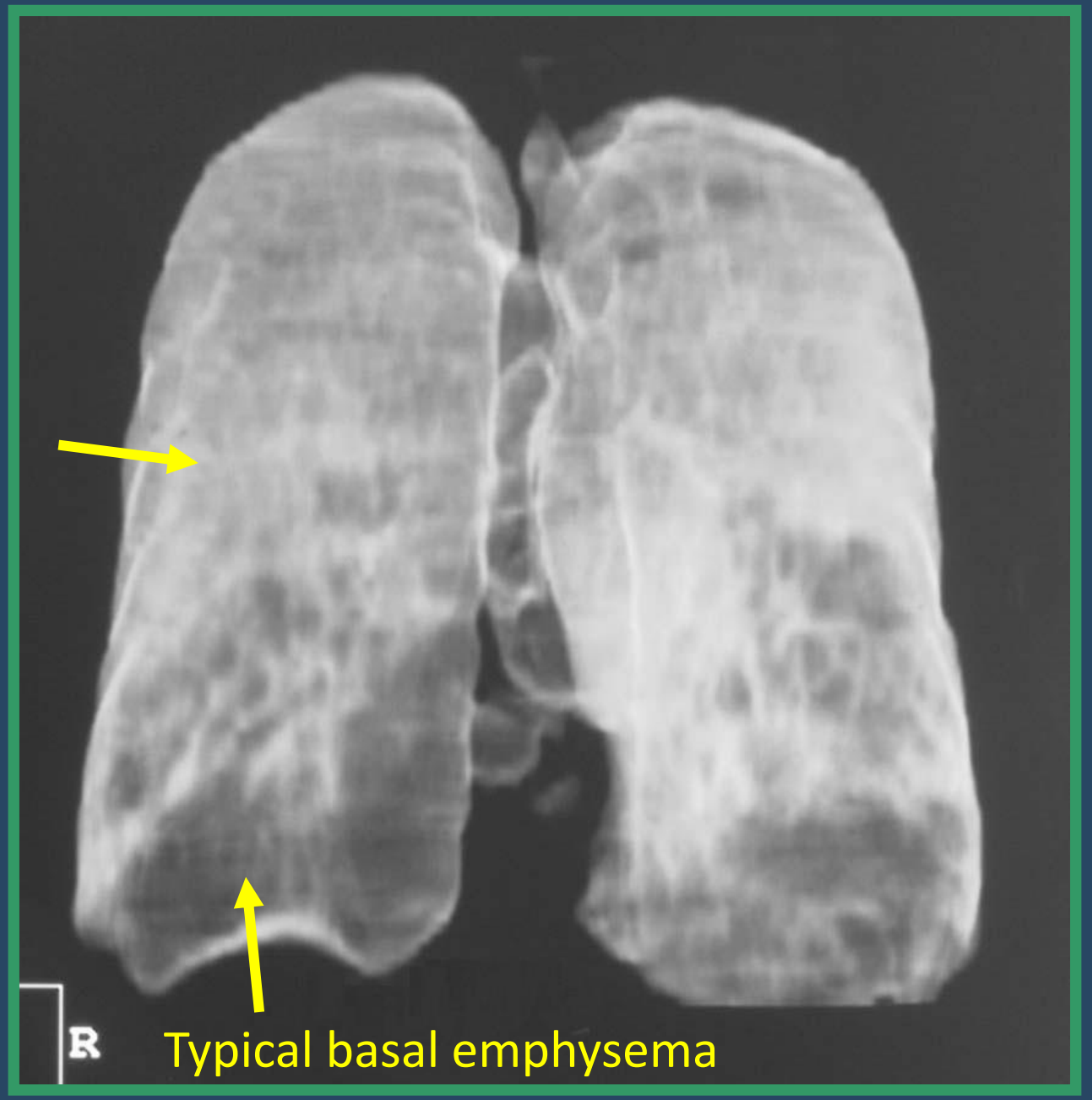


Carl-Bertil Laurell

α_1-antitrypsin deficiency



Laurell and Eriksson 1963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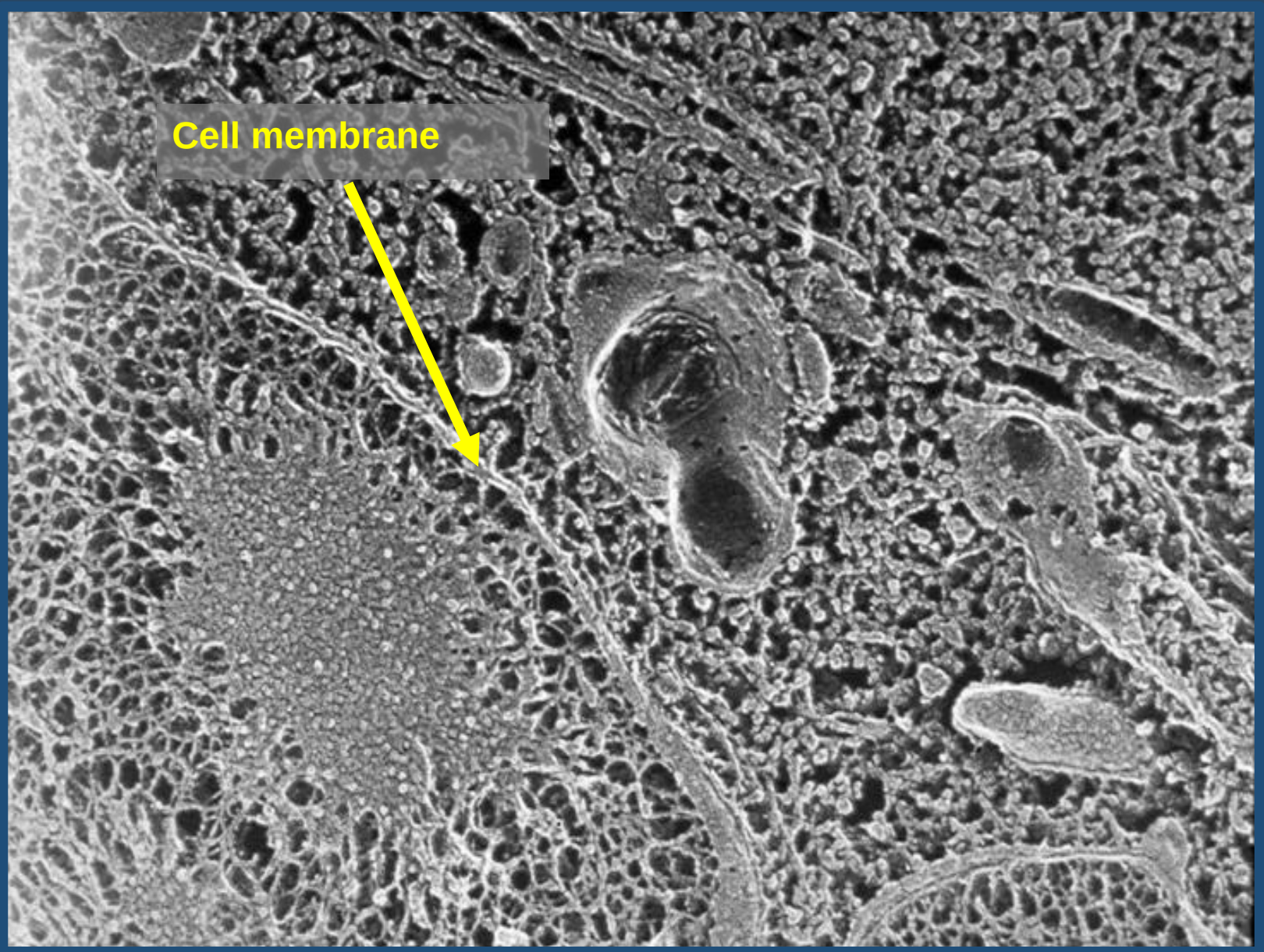
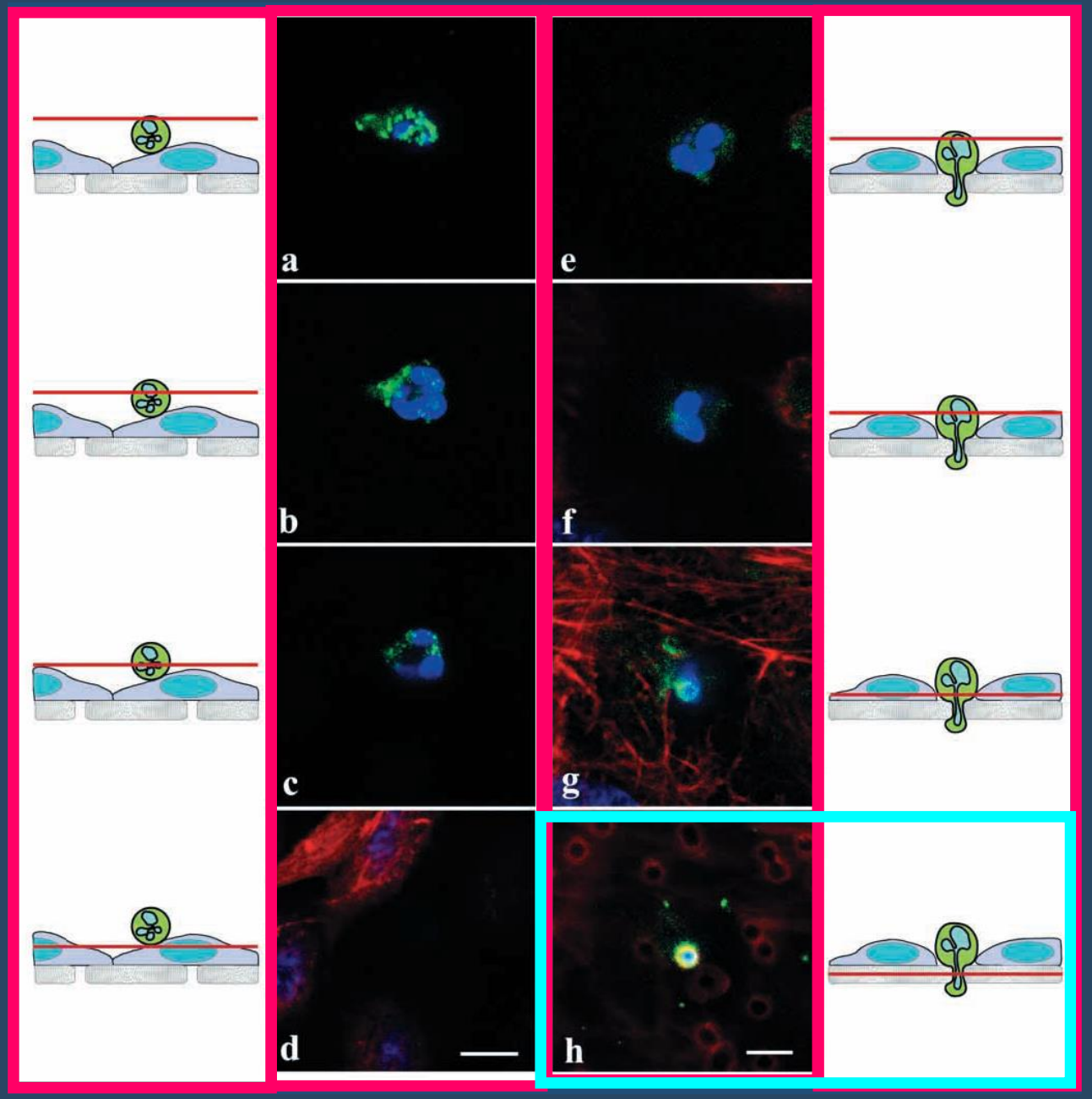
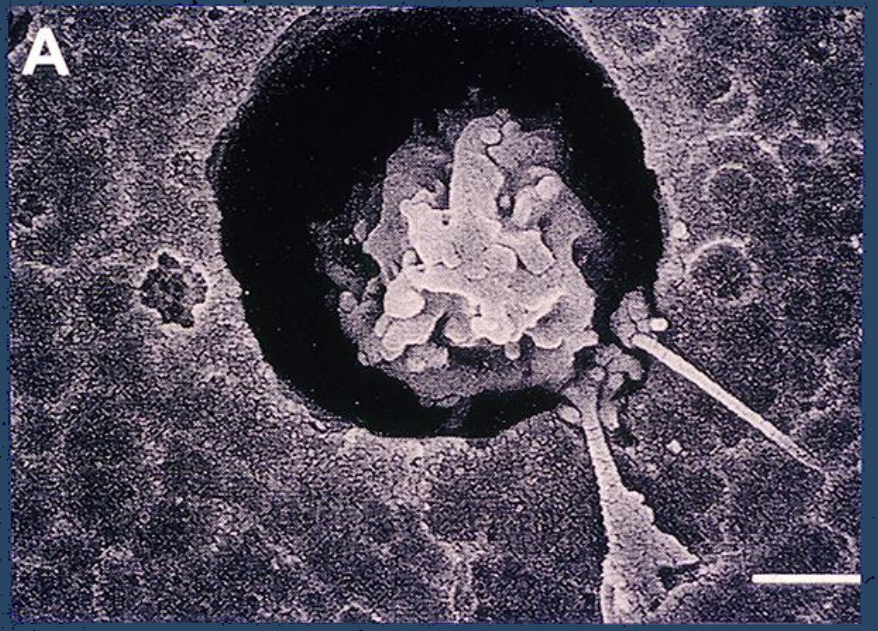
Typical basal emphysema



Courtesy of Robert Meacham, St. Louis USA



Cepinskas et al.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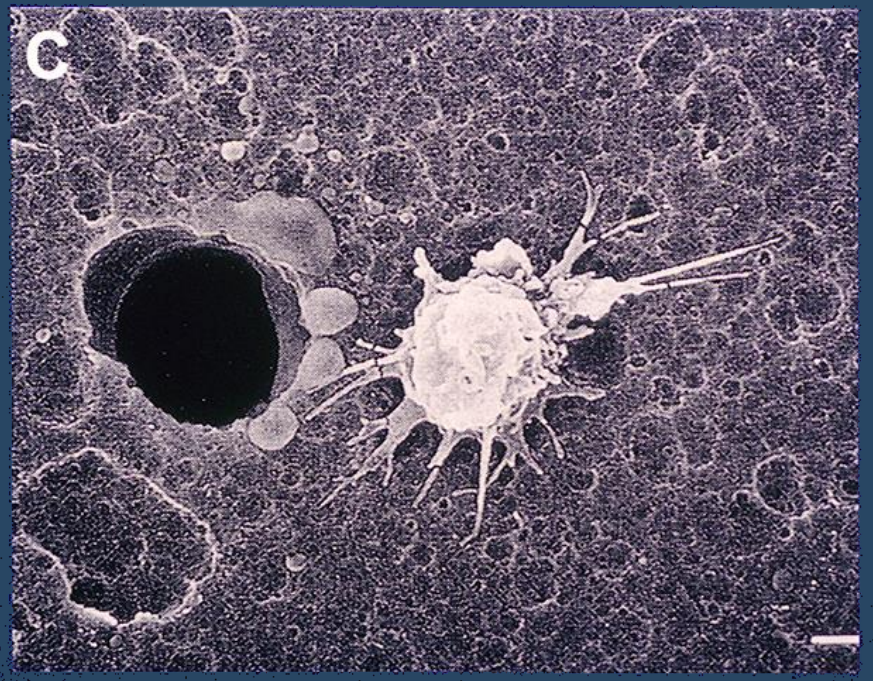
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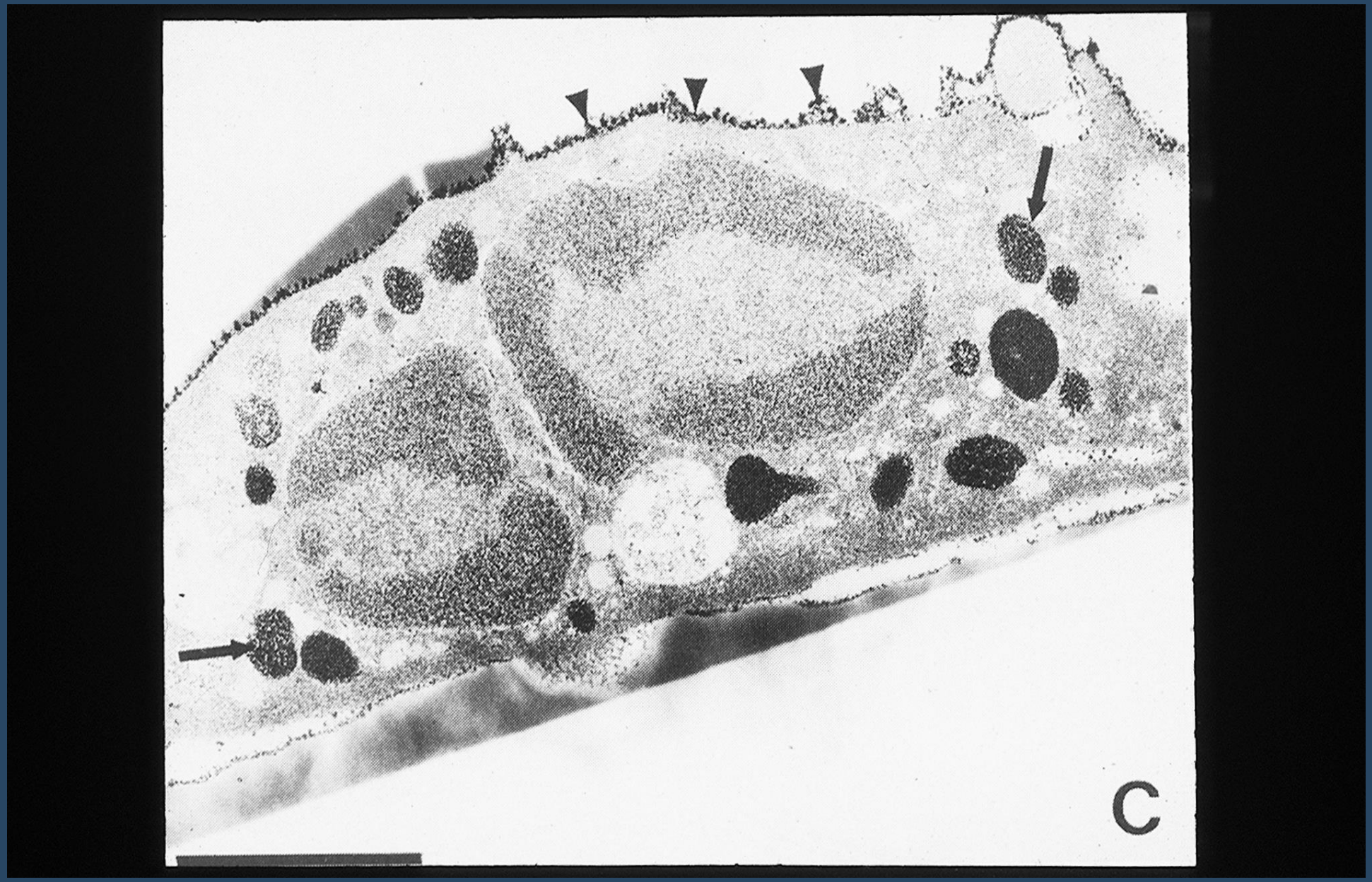
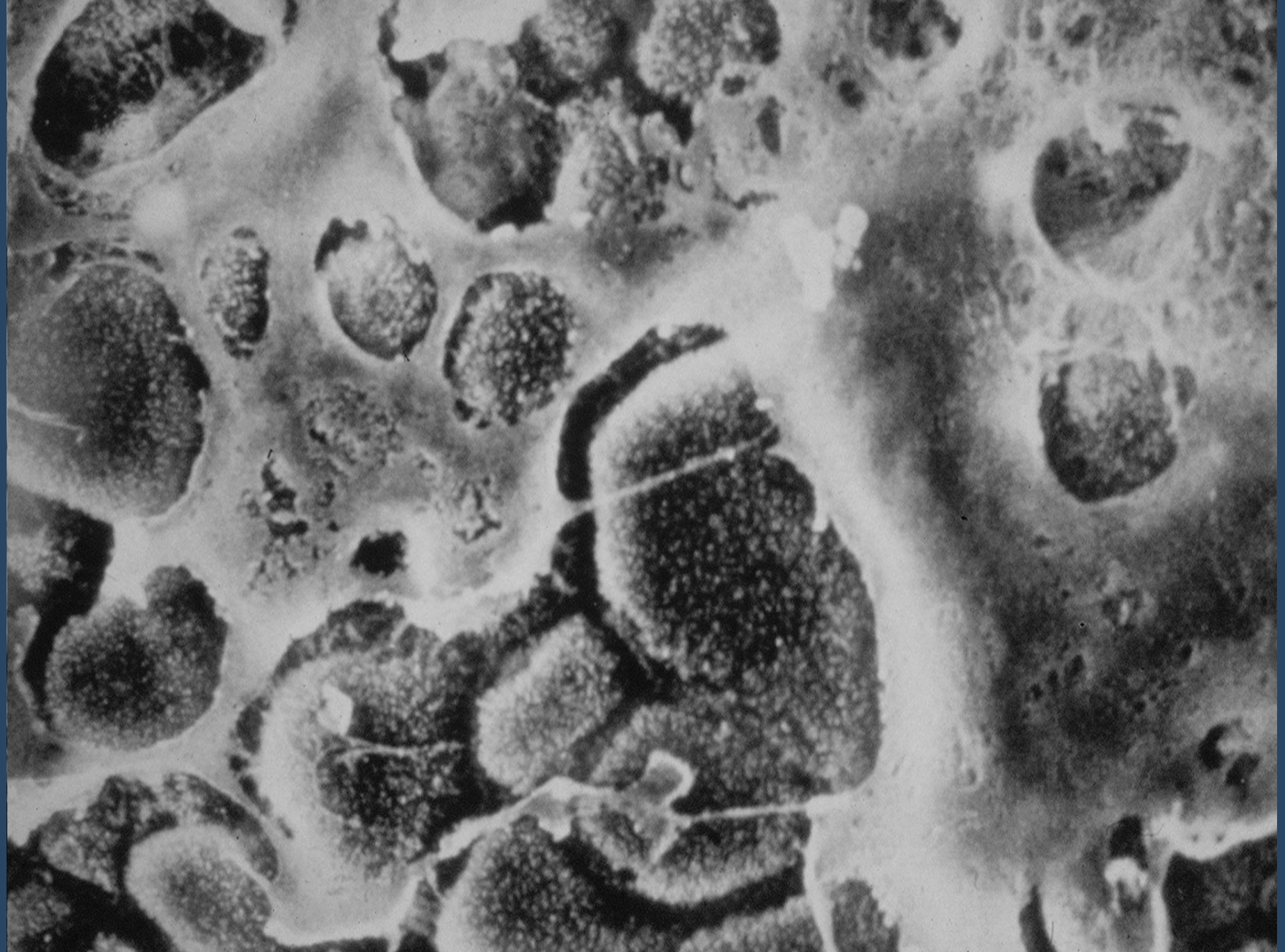
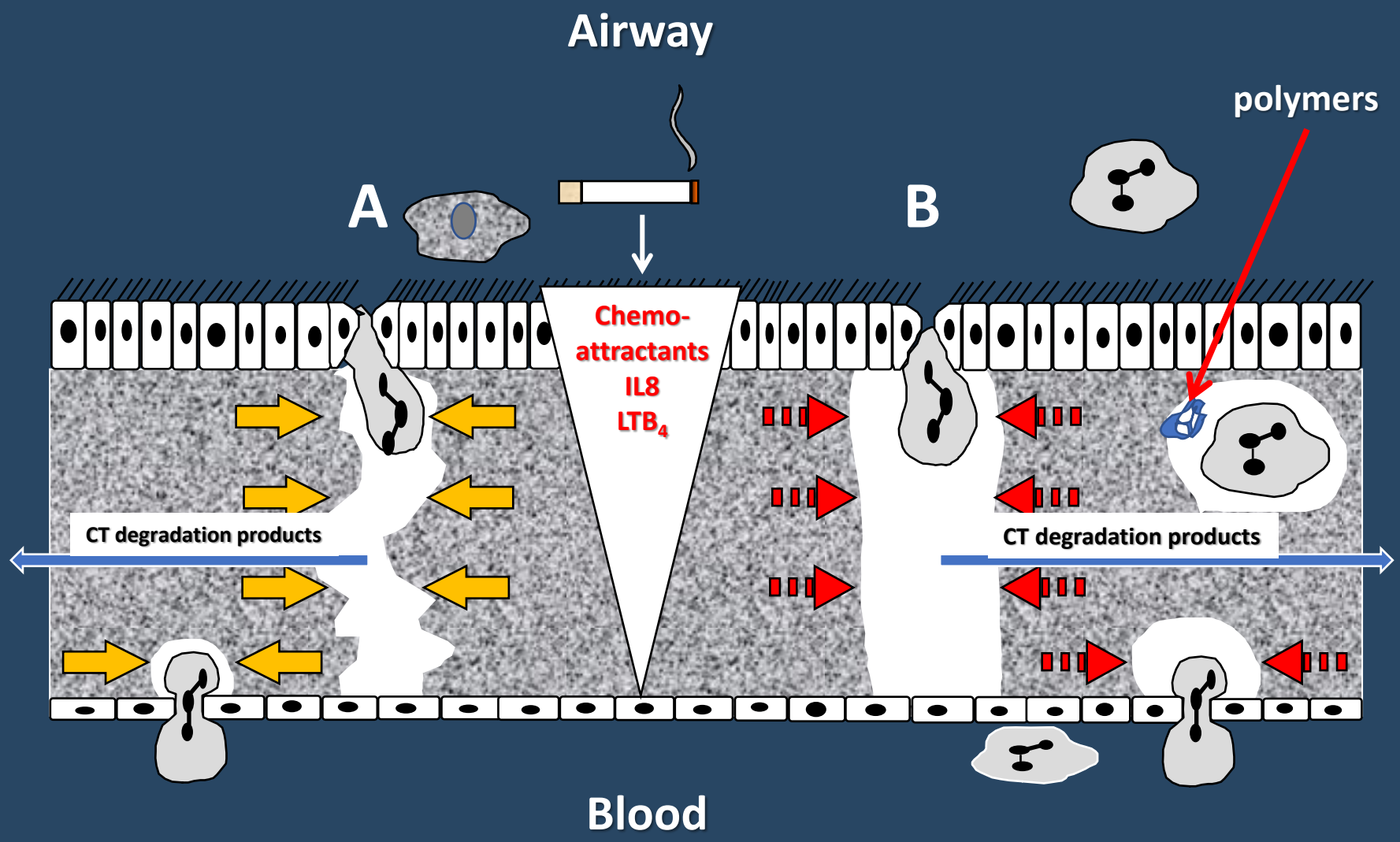


Courtesy of CA Owen

Effects of Neutrophil Elastase

- Emphysema
- Mucous gland hyperplasia
- Mucus secretion
- Reduce CBF
- Epithelial destruction and leakage
- Activation of complement
- Inactivation of Immunoglobulins and opsonophagocytic receptors

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Chemo-
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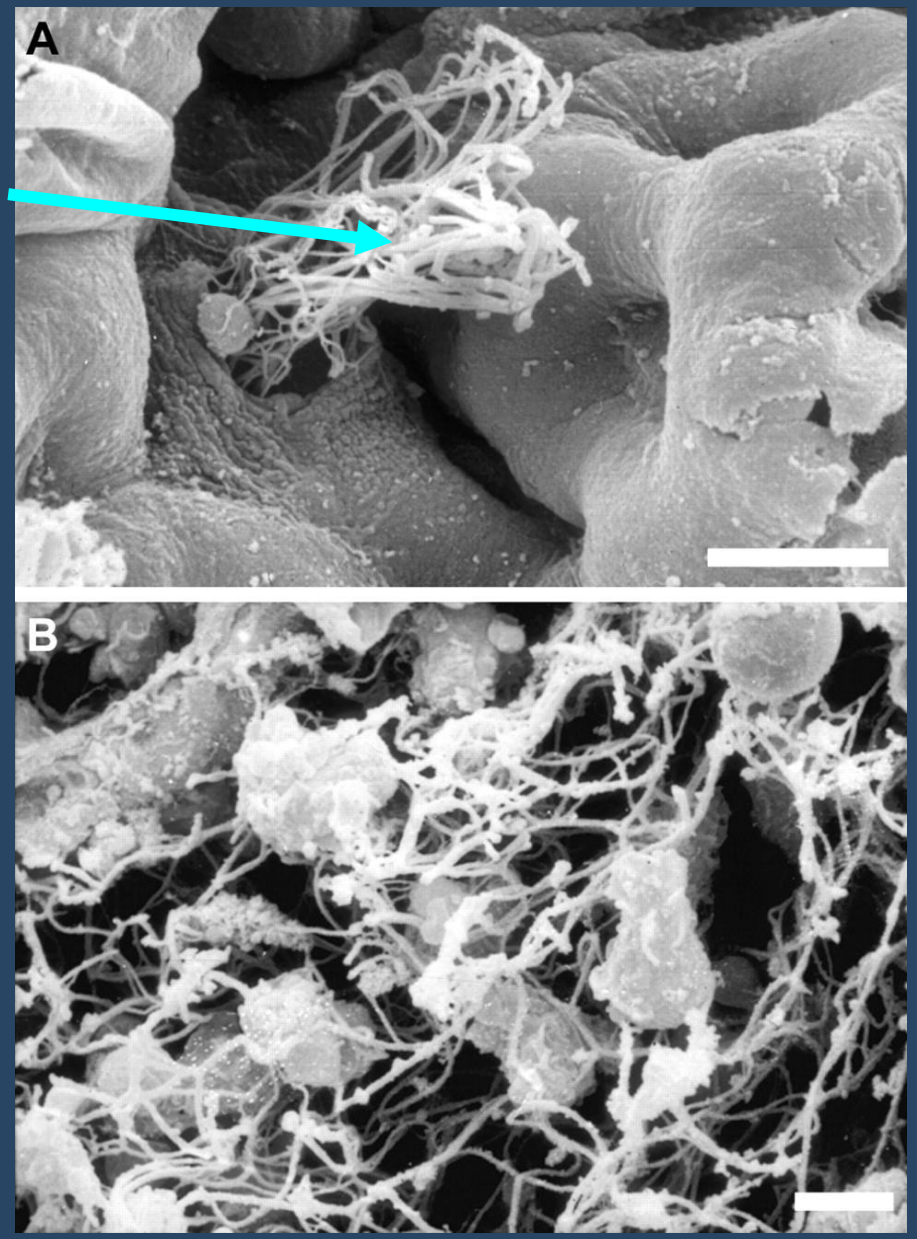
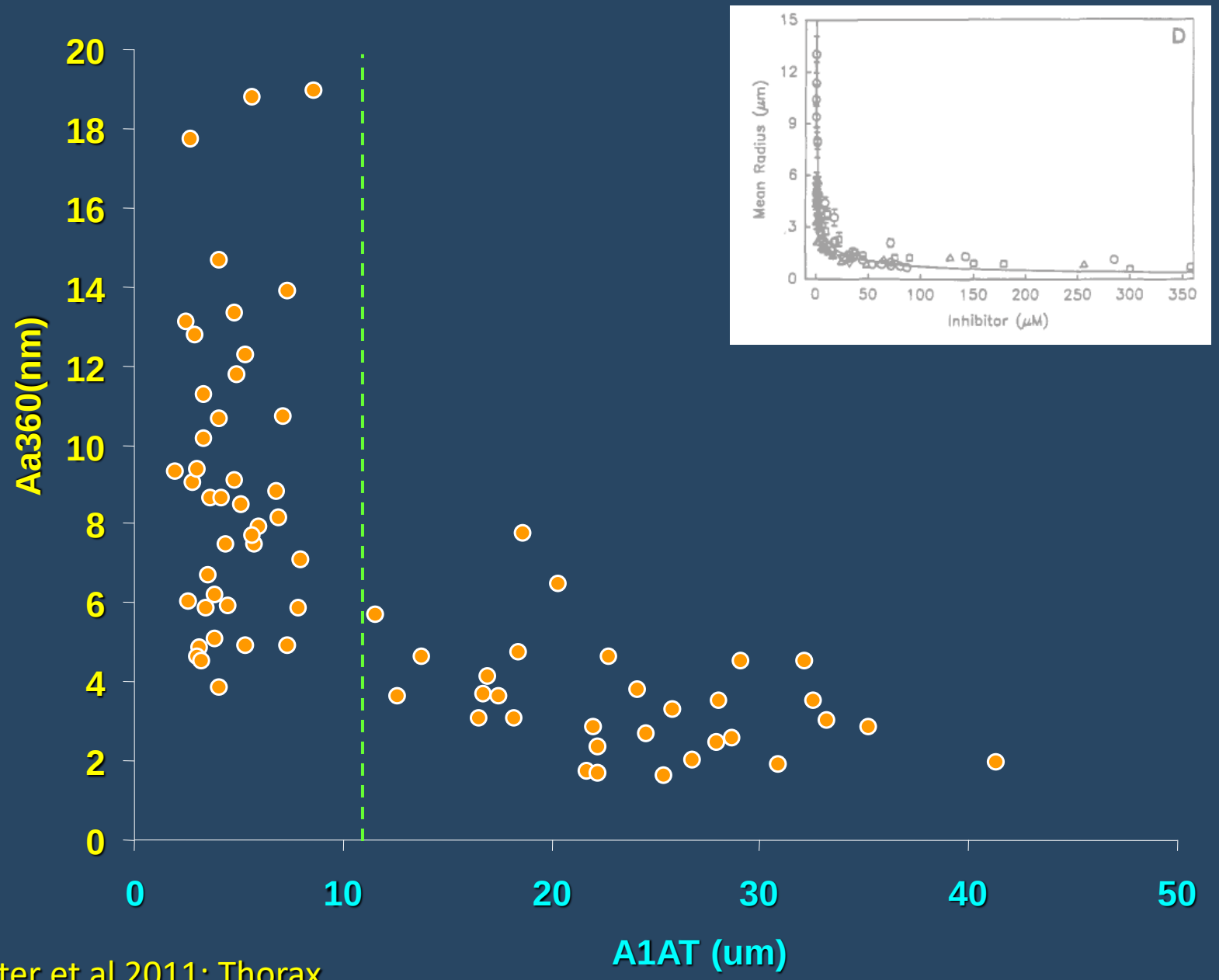
IL8
LTB4
CT degradation products
CT degradation products
Blood

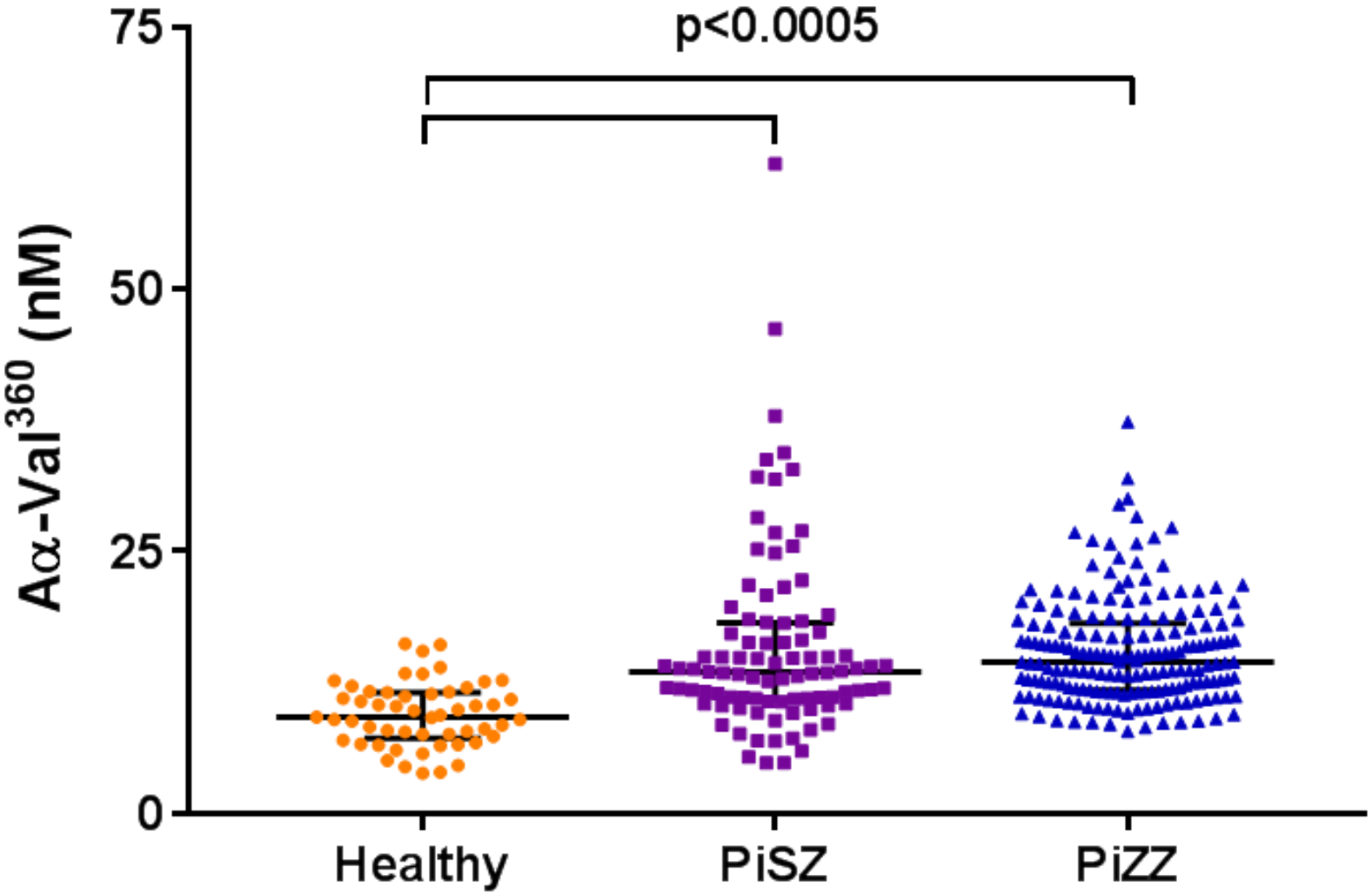
Fibrinogen



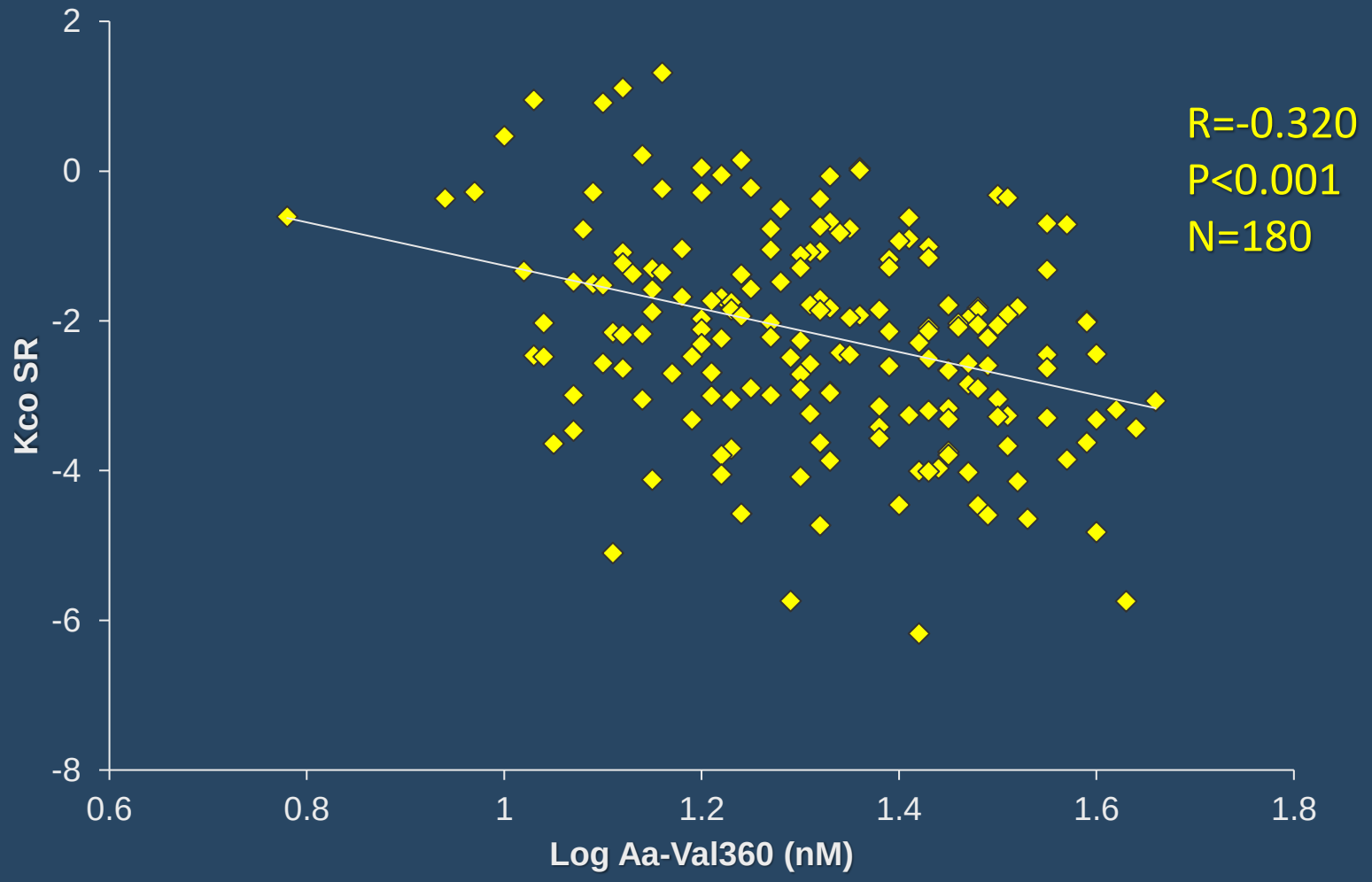
Burns, A. R. et al. Physiol. Rev. 83: 309-336 2003;
doi:10.1152/physrev.00023.2002



Carter et al 2011; Thorax

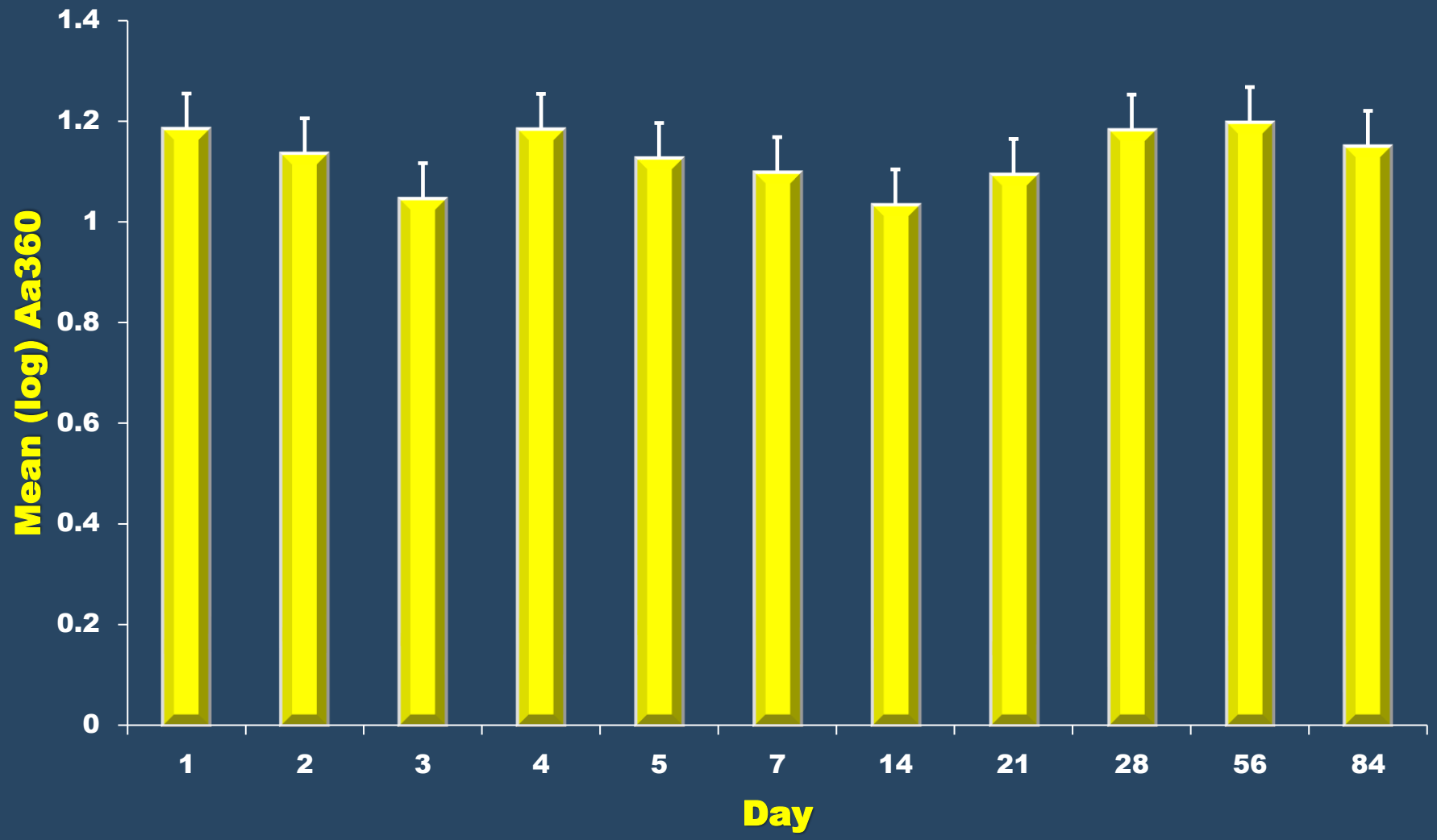

p<0.0005
75
50
25
0
Aα-Val360 (nM)
Healthy
PiSZ
PiZZ

The Relationship Between Aα-Val^{360} and Kco (SR) (PiZ A1AT deficient patients)



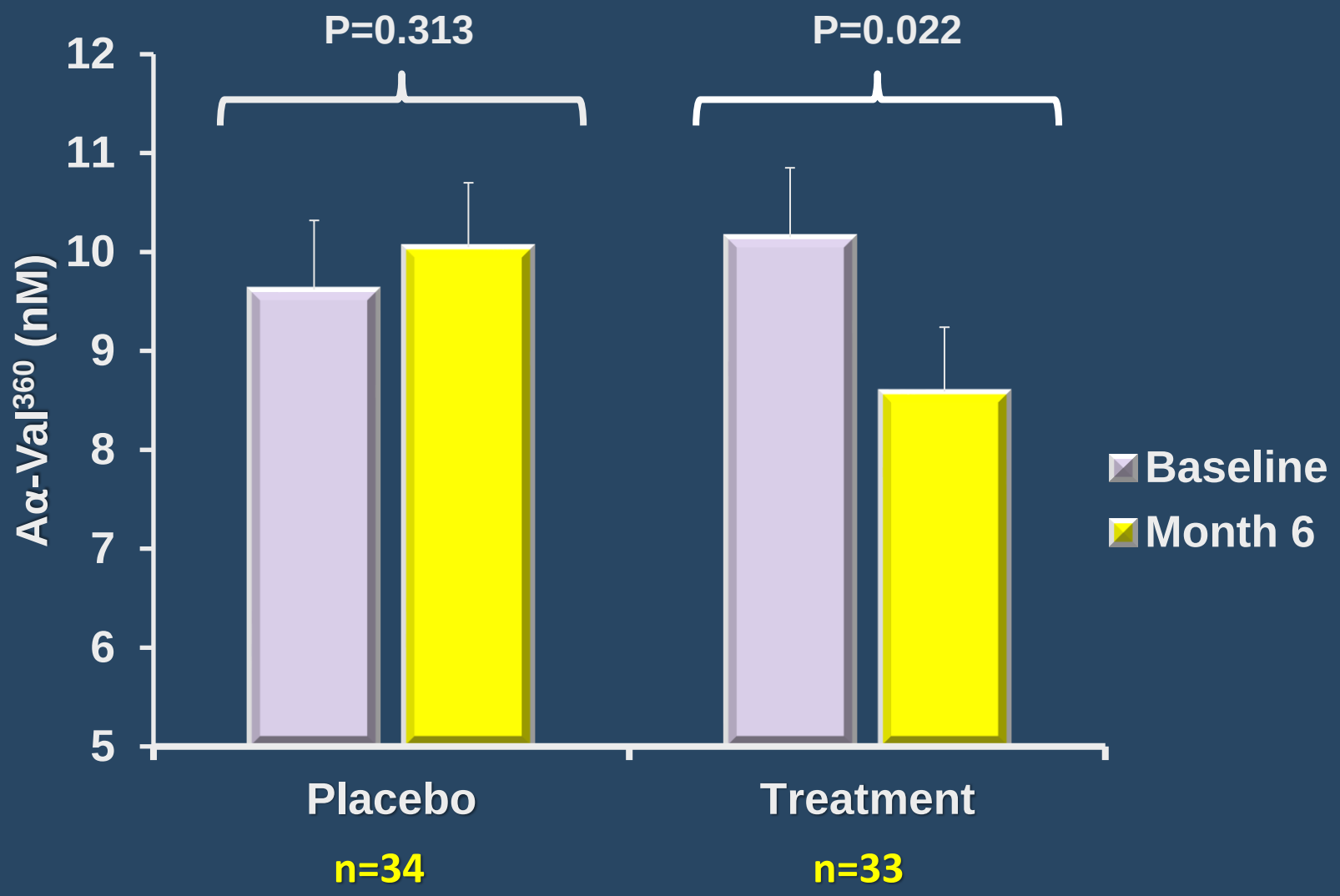
Kco: Carbon monoxide transfer coefficient

$A\alpha^{360}$ Levels in Stable State PiZ A1AT Deficient Subjects Over an 84 day Period



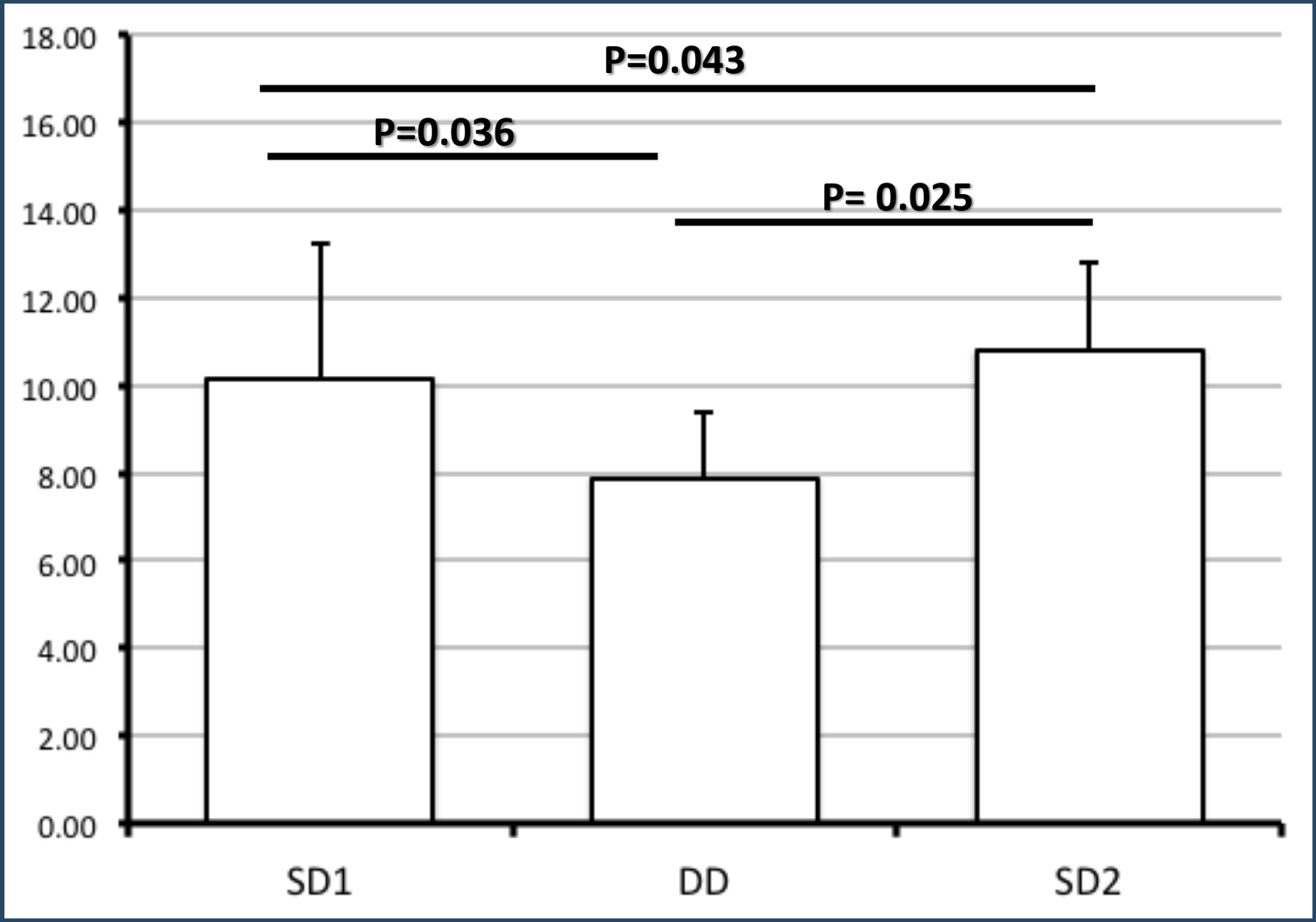
Aα-Val^{360} In Participants of EXACTLE

(A1AT replacement therapy versus Placebo in PiZ A1AT Deficient Subjects)



Aα-Val360 in plasma

Means ± SD

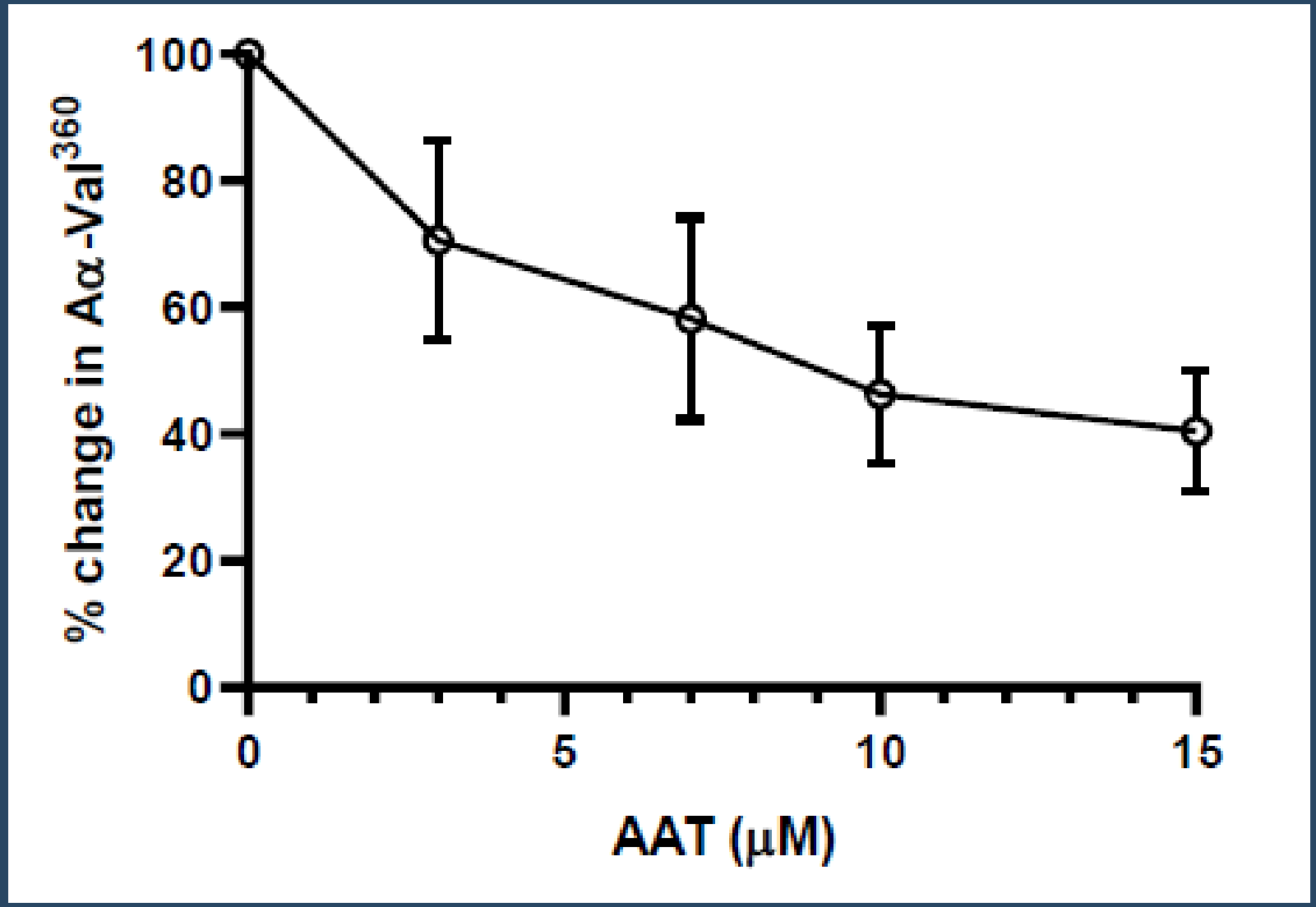


SD1: standard dose (60 mg/kg/week) phase 1

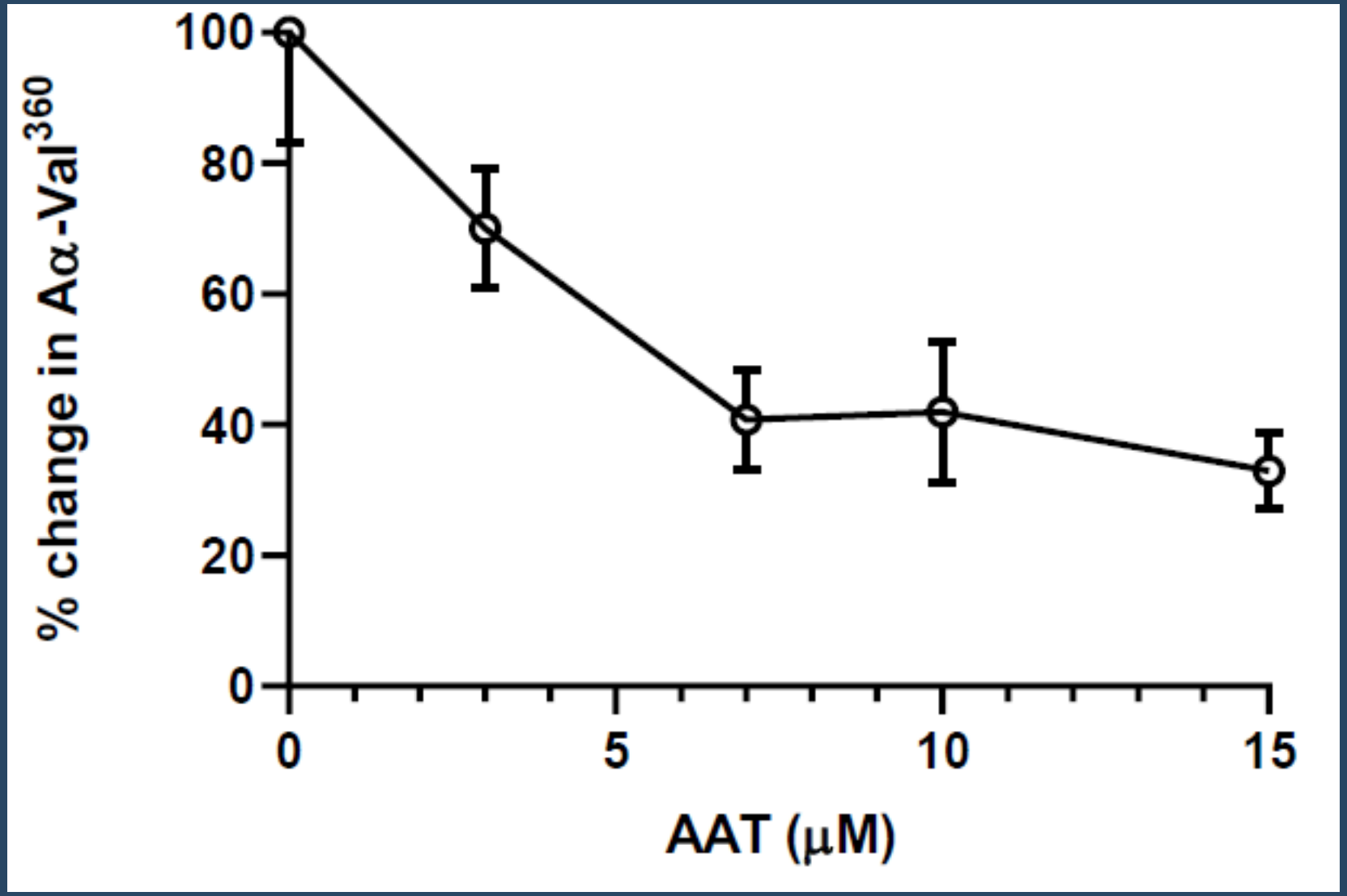
DD: double dose (120 mg/kg/week)

SD2: standard dose (60 mg/kg/week) phase 2

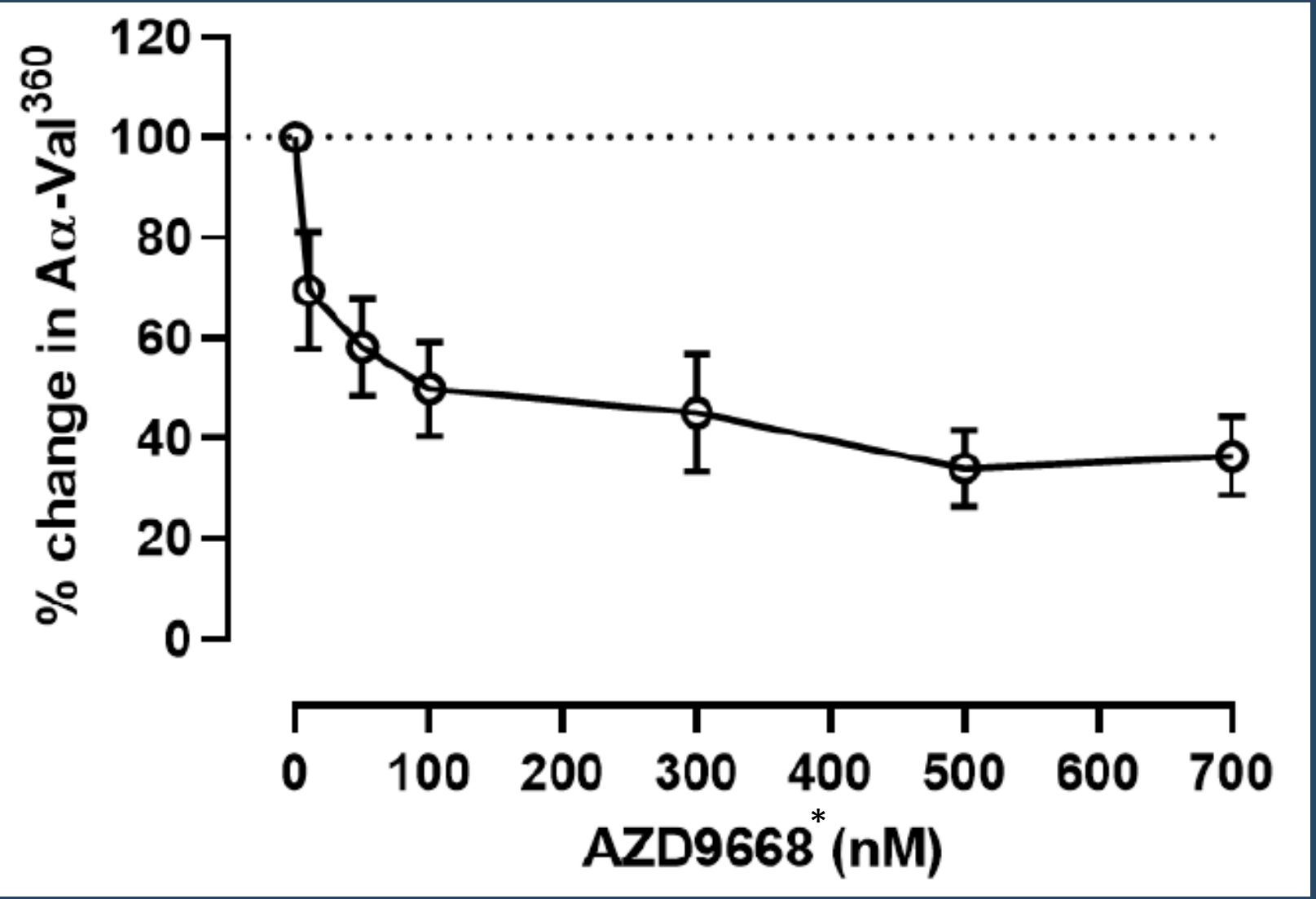
Simultaneous incubation



Preincubation



Alvelestat/elastase



*AZD9668: alvelestat

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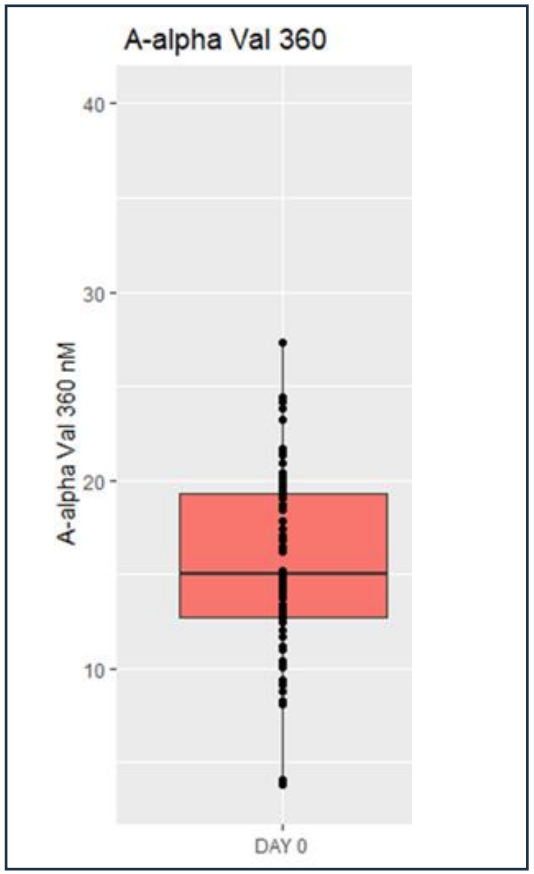
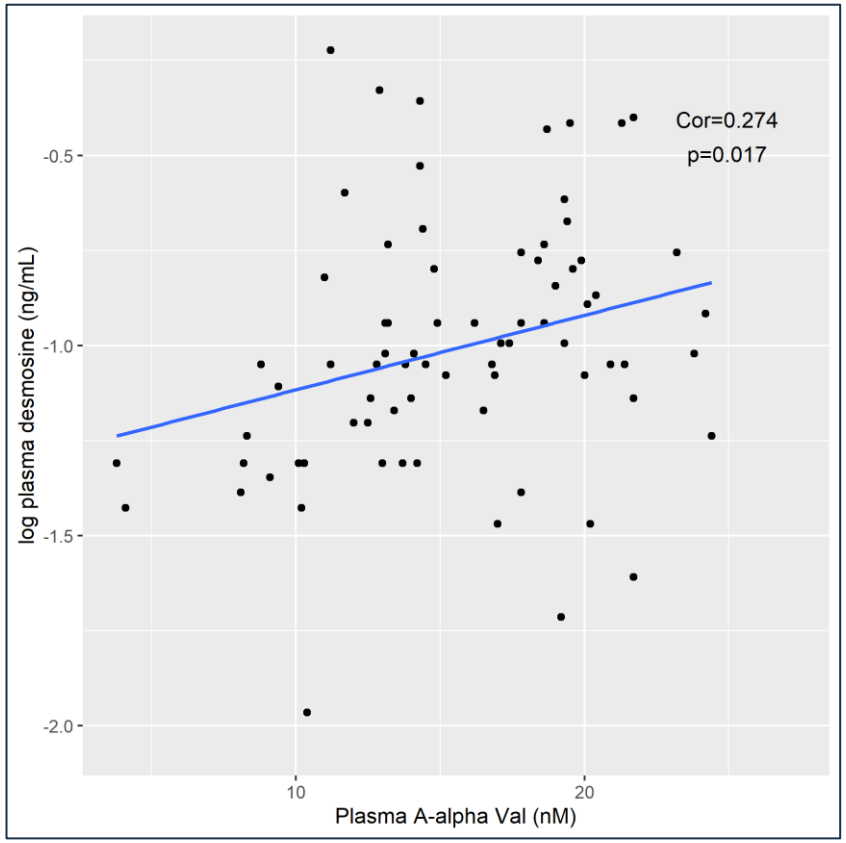
ASTRAEUS

Baseline Aα-Val^{360}

Plasma Aα-Val^{360} Blinded Baseline Levels Raised In ASTRAEUS AATD Population





- Blinded baseline level ASTRAEUS mean **15.05nM (SD 4.81)**
- Similar to levels in AATD Registry study in PiZZ (Carter et al 2013)

Positive correlation between desmosine and Aα-Val^{360} levels at baseline in ASTRAEUS

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Note: Uncleaned data. Final values may differ from those presented here.

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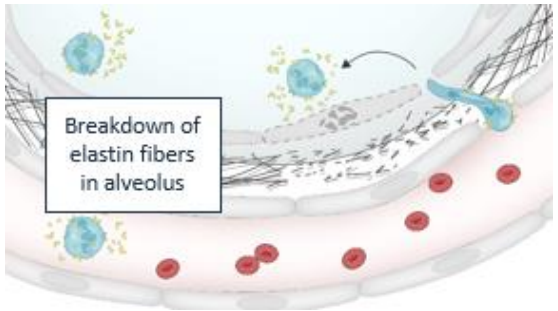
ASTRAEUS
Addition Of Primary Endpoints Along The Pathogenic Pathway

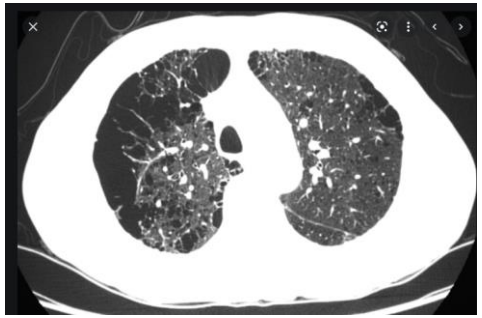
Linking Biomarkers To Pathological Pathway

AATD-Lung Disease Pathogenic Pathway

Blood NE	Aα-Val^{360}	Desmosine	CT Density/FEV$_1$
Neutrophil Elastase Activity	Unopposed NE	Alveolar Elastin Breakdown	Lung Tissue Loss/Emphysema
Increased neutrophil elastase activity	Increase in neutrophil elastase-driven target (fibrinogen) breakdown	Elastin breakdown fragments	

Alvelestat





ASTRAEUS Phase 2 Revised Endpoints

Primary Endpoints	Secondary and Exploratory Endpoints

• Within individual % change from baseline up to end of treatment **within treatment arm** and in comparison, to placebo up to week 12 in:
  ○ Plasma desmosine/isodesmosine levels
  ○ **Blood Neutrophil Elastase activity**
  ○ **Blood Aα-Val^{360} levels**
	• Safety and tolerability
	• Lung damage and inflammation biomarkers
	• Pharmacokinetics
	• St. George's Respiratory Questionnaire
	• Spirometry including - Forced expiratory volume in 1 second (FEV_1), FVC and FEF25-75
	• Exacerbations

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Summary - Development Of Alvelestat In AATD-associated Emphysema

The ASTRAEUS 12-week trial is on track to deliver top-line Phase 2 data in early Q2 2022

- Enrolled 99 patients, representative of the target population with severe AATD-associated emphysema
- Three biomarkers on the pathogenic pathway are elevated at baseline in-line with other AATD studies
- Clean safety profile to-date following regular IDMC reviews
  - Tendency for headaches at the high dose managed through dose escalation

- Type C meeting held with the FDA – valuable for planning and overall guidance
- Plan to engage in discussions on Registrational trial design in end of Phase 2 meeting
- Currently expect sufficient pharmacodynamic data to select single dose to take forward in a registrational trial

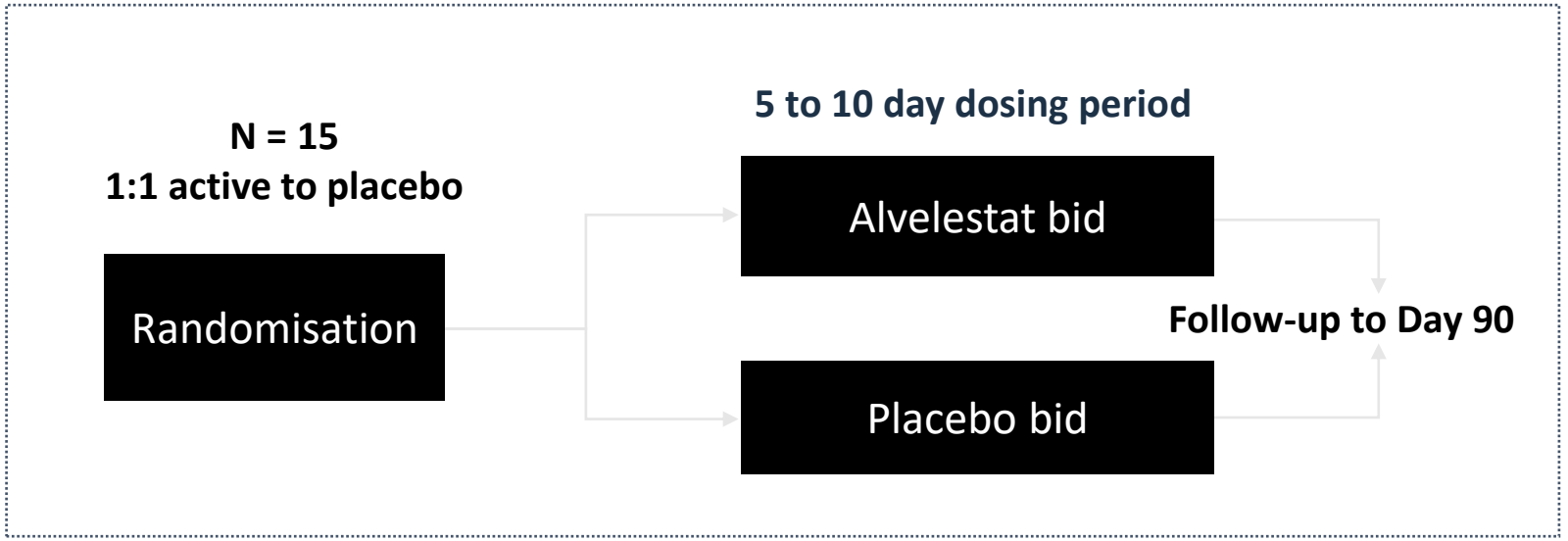
Note: Uncleaned data. Final values may differ from those presented here.

A Phase Ib/II, Single Center, Placebo-Controlled, Randomized, Blinded Study in Adult Patients (> 18 Years) With COVID-19 Respiratory Disease, to Evaluate, Safety, Tolerability and Mechanistic Effect of Alvelestat on Top of Standard of Care (COSTA)

Dr Mike Wells (Principal Investigator)

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

COVID-19 Phase 1b/2 Investigator-initiated Study “COSTA”



Trial Population

- > 18 years, hospitalized
- Proven moderate/Severe SARS-CoV-2 infection (WHO grade 3-5)
- Not on invasive ventilation

Primary Endpoint

- Safety and tolerability (Day 60)

Secondary Endpoints

Pharmacodynamic Biomarkers of:

- Inflammation
- Coagulopathy
- NETosis and elastase

Clinical outcomes

Mortality (Day 90)

COSTA COVID- 19 Patients Were Diagnosed With A Mild To Severe Disease And Received SOC Treatment At Enrolment

- 15 patients were randomized (10 male, 5 female), and all completed the Primary Endpoint Safety assessment to Day 60 and the Day 90 final study assessment.
- Common co-morbidities: hypertension, sleep apnea, hypercholesterolemia, and Type 2 diabetes.
- At entry to the study, patients were WHO severity score 4 or 5 requiring supplemental oxygen, all had initiated dexamethasone and 14 were on antiviral treatment with remdesivir at baseline or initiated after randomization (7/7 on placebo and 7/8 on alvelestat).
- The majority of patients were WHO COVID-19 Ordinal Severity Scale Score 4 (hospitalized mild disease requiring supplemental oxygen) or 5 (hospitalized severe disease, requiring non-invasive ventilation or high flow oxygen) at entry to the study.

COSTA COVID 19 Patients Were Diagnosed With A Mild To Severe Disease And Received SOC Treatment At Enrolment

Variables	All	Placebo (N =7)	Treatment (N =8)	p-value (2 sided)
Age	47.80 (20.34)	54.43 (14.33)	42.00 (23.86)	0.2520
Height	173.02 (10.42)	17.37 (13.89)	172.72 (7.18)	0.9099
Weight	111.42 (49.75)	116.16 (68.51)	107.26 (29.75)	0.7585
Ethnicity				
Hispanic or Latino	2 (13.33)	1 (14.29)	1 (12.50)	>0.9999
Not Hispanic or Latino	13 (86.67)	6 (85.71)	7 (87.50)	
Race				
Black or African American	7 (46.67)	3 (42.86)	4 (50.00)	>0.9999
White	6 (40.00)	3 (42.86)	3 (37.50)	
Other	2 (13.33)	1 (14.29)	1 (12.50)	
Sex				
Male	10 (66.67)	4 (57.14)	6 (75.00)	0.6084
Female	5 (33.33)	3 (42.86)	2 (25.00)	

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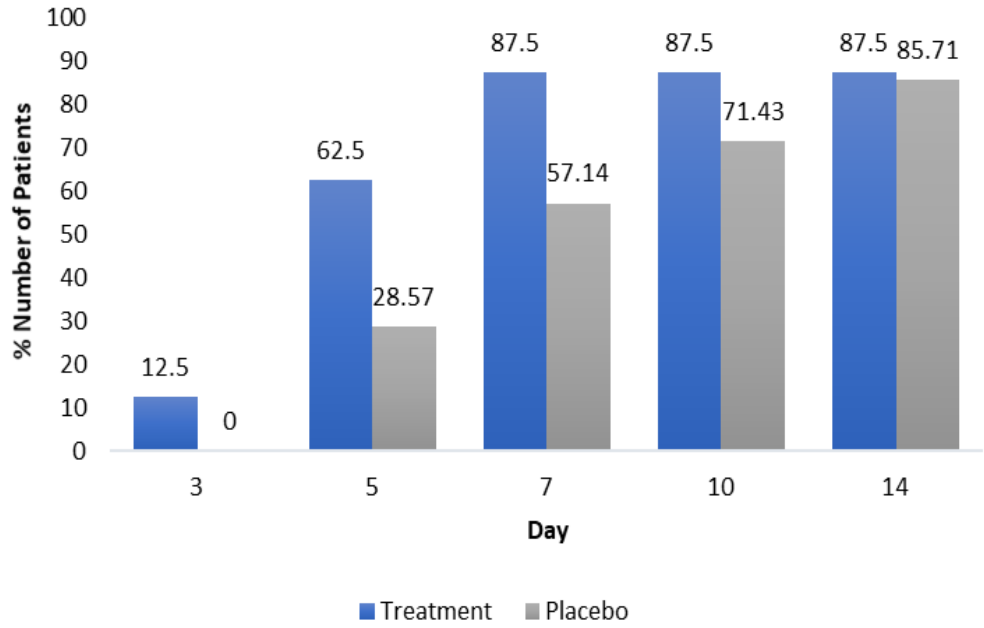
Early Results With Alvelestat Suggest A Potential For Clinical Benefit Over And Above Standard Of Care

Patients in the alvelestat arm 62.5% (5/8) showed a **more rapid and clinically meaningful improvement** (≥2-point decrease in the WHO Disease Severity score) than patients in the placebo arm.

WHO Disease Severity score

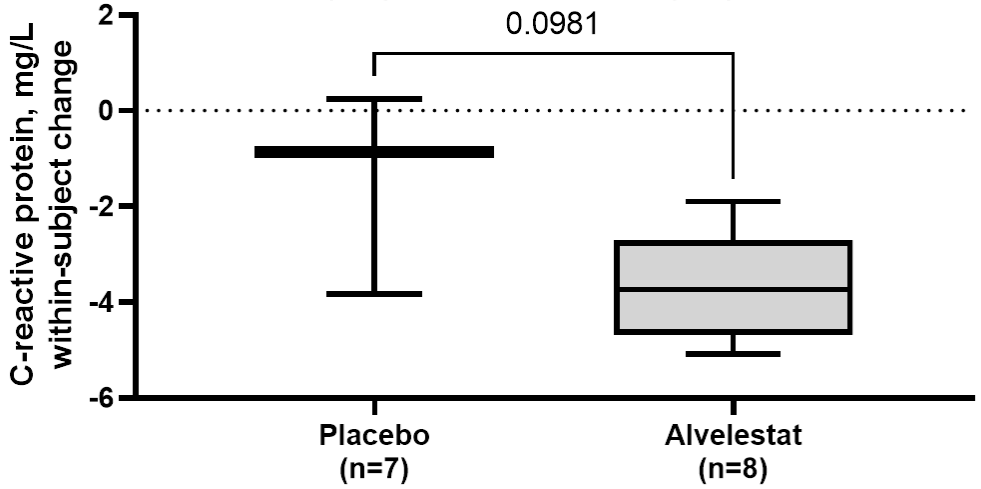
0. Uninfected, no clinical or virological evidence of infection
1. Ambulatory, no limitation of activities
2. Ambulatory, limitation of activities
3. Hospitalized – mild disease, no oxygen therapy*
4. Hospitalized – mild disease, oxygen by mask or nasal prongs*
5. Hospitalized – severe disease, noninvasive ventilation or high flow oxygen*
6. Hospitalized – severe disease, intubation and mechanical ventilation
7. Hospitalized – severe disease, ventilation and additional organ support – vasopressors, renal replacement therapy, extracorporeal membrane oxygenation
8. Death

% Subjects ≥ 2-point Improvement in WHO Score

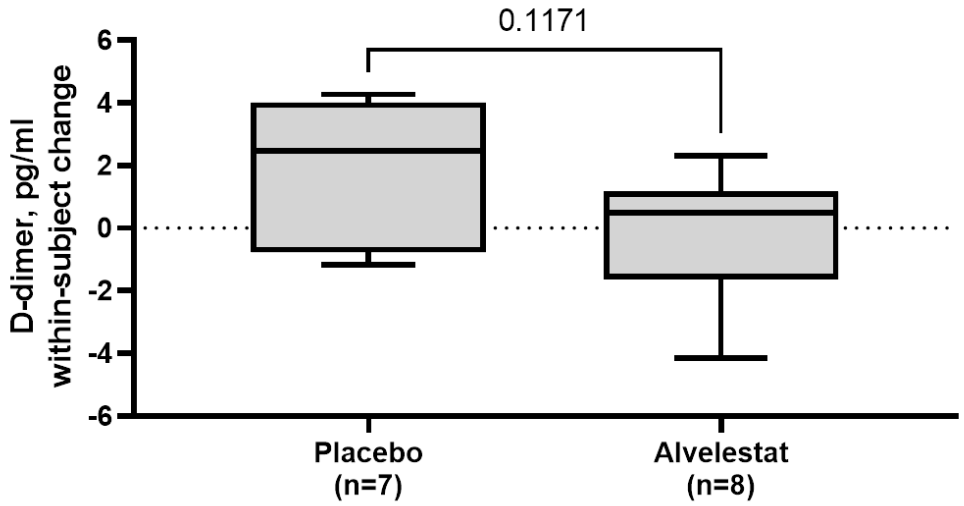


Effects On Blood Biomarkers Support The Clinical Data

Inflammation



Coagulopathy



- Biomarkers of NETosis, were generally within the normal range at baseline, potentially due to use of high dose systemic steroids and less severe disease than previous studies.

*P-value obtained by Fisher's exact test

Alvelestat Was Well Tolerated In Patients With Covid 19 And COSTA Safety Finding Consistent With The Known Safety Profile Of Alvelestat

- No safety signals were observed in lab safety monitoring, including none in liver, renal and vital sign parameters.
- Treatment emergent headaches were more frequent in the alvelestat arm (4/8 - all of moderate severity) compared to placebo (1/7 of mild severity). Three patients in the alvelestat arm were noted to also have headache in the screening period. None were considered study-drug related by the investigator.
- There was no difference in frequency of other adverse events between alvelestat and placebo arms to Day 60.
- There were no deaths on study (to end of study assessment at Day 90)

Conclusions

- A clinically meaningful effect in short term 5-10 day dosing in hospitalised COVID-19 was observed with alvelestat, supporting anti-inflammatory effects on top of those achieved by high dose corticosteroids
- No adverse safety signals were observed in an acutely sick population
- Further investigation to interrogate MoA /NETosis is under consideration

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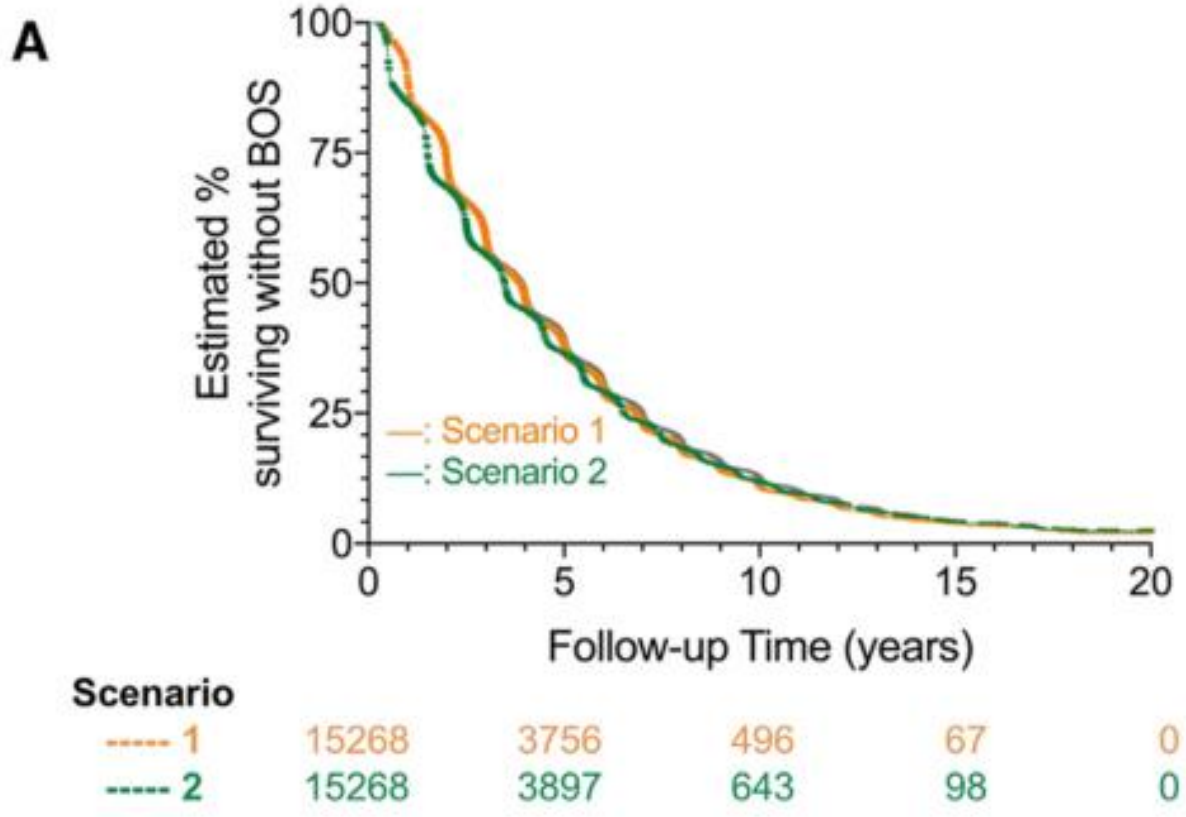
Bronchiolitis Obliterans Syndrome (BOS)

BOS – A Rare Disease With High Unmet Need In Patients Receiving Lung Transplant And Allogenic Stem Cell Transplant

- Allo-immune response - graft versus host or host-versus graft
- Pathology overlaps in LTx and SCT
- Most common cause of re-transplant and death in long term, with 50% LTx recipients developing BOS by 5 years
- Median survival 2.6 to 4.27 years post diagnosis



Kulkarni et al 2018, Bionchiolitis Obliterans Syndrome-free survival after lung transplantation: An International Society for Heart and lung Transplantation Thoracic Transplant Registry analysis

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Bronchiolitis Obliterans Syndrome following Allogeneic Stem Cell Transplant

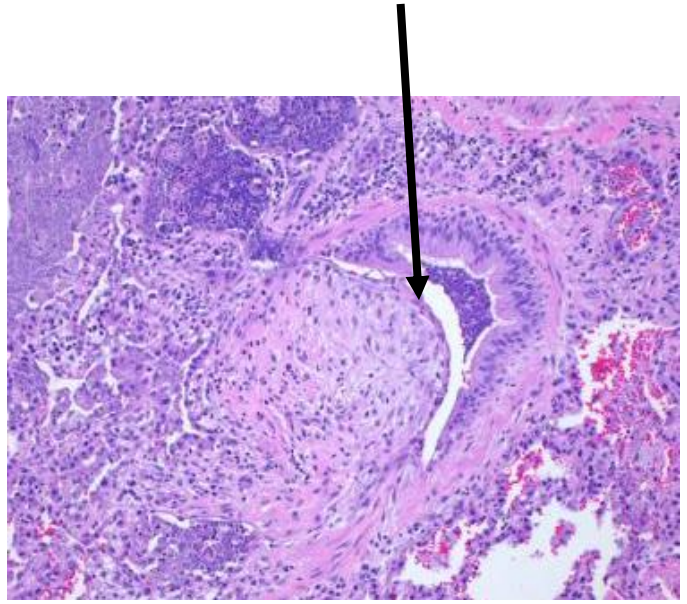
Dr Steve Pavletic and Dr Annie Im

NIH NATIONAL CANCER INSTITUTE
Center for Cancer Research

Background of BOS

- 12,000 allogeneic stem cell transplants (SCT) are performed in the United States each year
- BOS affects 6% of patients, leading to irreversible effects on pulmonary function, functional capacity, and increased risk of death
- Current treatment strategies are aimed at systemic immunosuppression for chronic GVHD, but < 20% have improvement
- 2-year overall survival rate in patients with BOS has been unchanged for over 20 years and 5-year survival is only 13%
- There are no FDA approved agents for the treatment of BOS

BOS characterised by excessive fibroproliferation of the small airways



Meyer et al 2014

Scientific Rationale Of Neutrophil Elastase Inhibition In BOS Associated With SCT And Lung Transplant

Although there is no single causative pathway in the pathogenesis of BOS, evidence suggests that neutrophil-mediated injury has a prominent role:

- Neutrophilia in bronchoalveolar lavage (BAL) fluid is considered a hallmark of BOS, and may even precede the diagnosis
- BOS is characterized by an imbalance between NE and inhibitors of NE:
    - NE is able to cleave a wide range of substrates including elastin and collagen, and also causes damage to lung endothelial and epithelial cells directly
    - Significantly elevated levels of free NE and decreased levels of endogenous inhibitors in BAL fluid of BOS patients compared to those without BOS (Hirsch et al 1999)
    - Although other proteases are present, neutrophil elastase is the predominant active protease in BOS (Stone et al 2013)

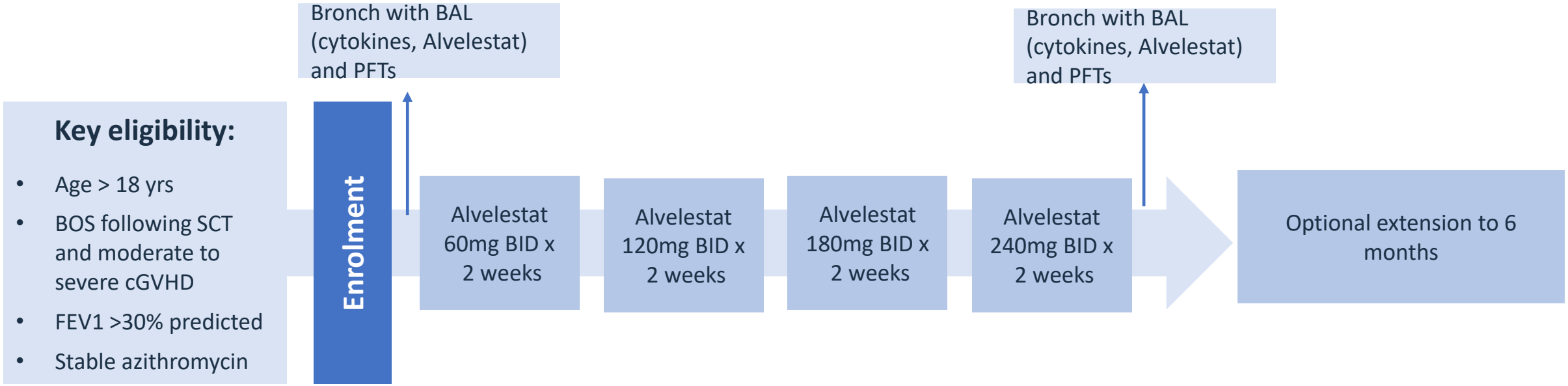
Alvelestat (MPH966), an Oral Neutrophil Elastase Inhibitor, in Bronchiolitis Obliterans Syndrome (BOS) After Allogeneic Hematopoietic Stem Cell Transplantation

Steven Pavletic, MD, Clinical Investigator and Head of the Graft versus-Host and Late Effects Section in the Immune Deficiency Cellular Therapy Program of the National Cancer Institute (NCI), National Institutes of Health (NIH), Adjunct Professor of Medicine at the Georgetown University, Lombardi Cancer Center, Division of Oncology

Annie Im, MD, Associate Professor, Division of Hematology/Oncology, University of Pittsburgh, UPMC Hillman Cancer Center, Pittsburgh, PA

The Phase 1b/2 Open Label Study Is Investigating Alvelestat, In BOS After Allogeneic Hematopoietic Stem Cell Transplantation - Phase 1b Design

- An open label, within patient 2 weekly dose-escalation design
- 60, 120, 180, 240 mg bid, 6 months at highest dose



BOS Study Design: Investigator IND, Dr Pavletic, NCI Intramural Funding

Study End Points

Primary Endpoint (N=10)
Identification of maximally tolerated dose to take into Phase 2 (additional 24 patients)

Exploratory measures / endpoints	
• FEV_1 • Toxicity assessment • Blood NE activity and plasma desmosine • Collagen synthesis/breakdown biomarkers	• Alvelestat concentration (blood & BAL*/induced sputum) • Inflammatory cytokines (blood and sputum) • Chronic GVHD scoring

Alvelestat Shows A Signal Of Stabilizing Disease In Patients With Advanced BOS

- The median duration of treatment was 6.4 months (First 9, one is ongoing in continuation phase)

- Based on NIH chronic GVHD consensus criteria, **8** patients had unchanged disease and 1 patient had progressive disease (decline in FEV1 after pneumonia).

- Although patients did not achieve the 10% improvement in FEV1 required for an organ response, 2 patients had improvement of 9% in FEV1 and 4 patients had improvement in the Lee chronic GVHD symptom scale lung score.

Alvelestat Shows A Signal Of Stabilizing Disease In Patients With Advanced BOS

Patient	Age	Gender	cGVHD severity	cGVHD involved organs	Baseline FEV1	End of treatment FEV_1 % predicted	LSS baseline / end of treatment
1	46	F	Moderate	Lungs, mouth	74%	73%	1/1
2	21	F	Severe	Lungs	38%	47%	**3/2**
3	50	M	Severe	Lungs, mouth , Esophagus, skin, skin, eyes, joints/fascia	46%	55%	1/1
4	44	M	Severe	Lungs, eyes	53%	40%	**2/2**
5	62	M	Severe	Lungs	52%	46%	2/2
6	59	F	Severe	Lungs, skin, eyes, genital	44%	38%	**2/3**
7	61	F	Severe	Lungs, skin	44%	41%	2/2
8	39	F	Severe	Lungs, eyes	39%	41%	3/3
9	28	F	Severe	Lungs. Eyes, genitals	37%	33%	3/3
10	69	M	Severe	Lungs, oral	43%	NA Ongoing in continuation phase	NA Ongoing in continuation phase

Alvelestat Is Well Tolerated In Patients With Advanced BOS And Show Similar Safety Profile To AATD

- 10 patients were enrolled (4 men and 6 women)
- All 10 patients were able to tolerate dose escalation of alvelestat up to the maximum dose 240mg twice daily; MTD was not reached
- The most common adverse events
    - Grade 2: increased creatinine, ALT or AST elevation, and upper respiratory infection and hearing impairment.
    - Grade 3: vomiting, anemia, acute kidney injury, inflammatory lung nodules, dyspnea, astrovirus gastroenteritis,
    - Grade 4: acute kidney injury and lung infection
- Four out of the ten subjects experienced Serious Adverse Events(SAEs) which are presented in the table. The SAEs of vomiting and inflammatory lung nodules were considered possibly related to treatment. All other SAEs were not related, and all SAEs have resolved
- Only one non-serious AE of headache has been reported in this study as moderate in severity that lasted approximately two weeks for which no change to study drug was taken

Alvelestat Is Well Tolerated In Patients With Advanced BOS And Show Similar Safety Profile To AATD

Reported SAEs			
Common Toxicity Criteria Term	Grades	# events	# Subjects with SAE (%)
Acute kidney injury	1, 3 and 4	4	20%
Hearing impaired	2	1	10%
Anemia	3	1	10%
Upper respiratory infection	2	1	10%
Lung infection	4	1	10%
Dyspnea	1	1	10%
Vomiting	3	1	10%
Astrovirus gastroenteritis	3	1	10%
Inflammatory lung nodules	3	1	10%

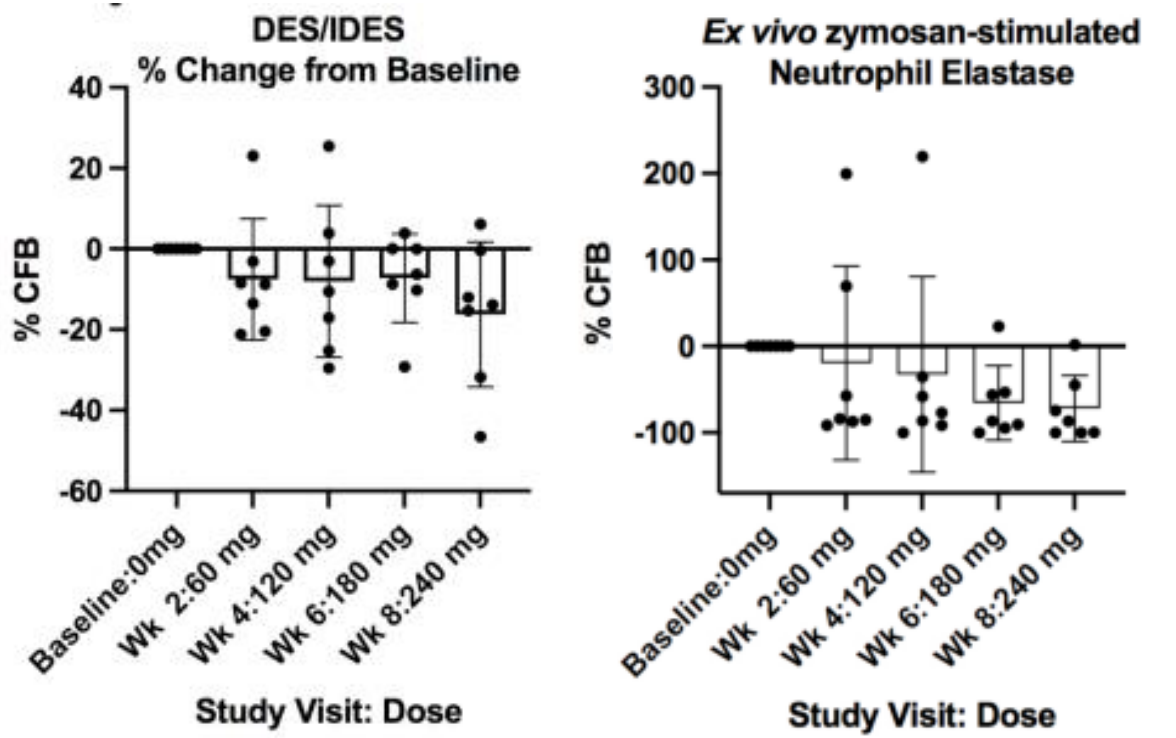
Im et al, Blood (2020) 136 (Supplement 1): 18–19.

Biomarker Data From Initial 7 Patients Analyses

- Mature elastin breakdown peptides desmosine/isodesmosine (DES/IDES)
- *Ex vivo* stimulated neutrophil elastase
- Neo-epitope by-products of collagen type 3 and 6 synthesis (PRO-C3 and PRO-C6) and degradation (C3M and C6M) as biomarkers of fibrosis/tissue modelling

Increased Elastin Breakdown In Patients With BOS And Consistency Of A Suppressive Effect On Biomarkers Of Elastase Activity By Alvelestat Supports NE Role

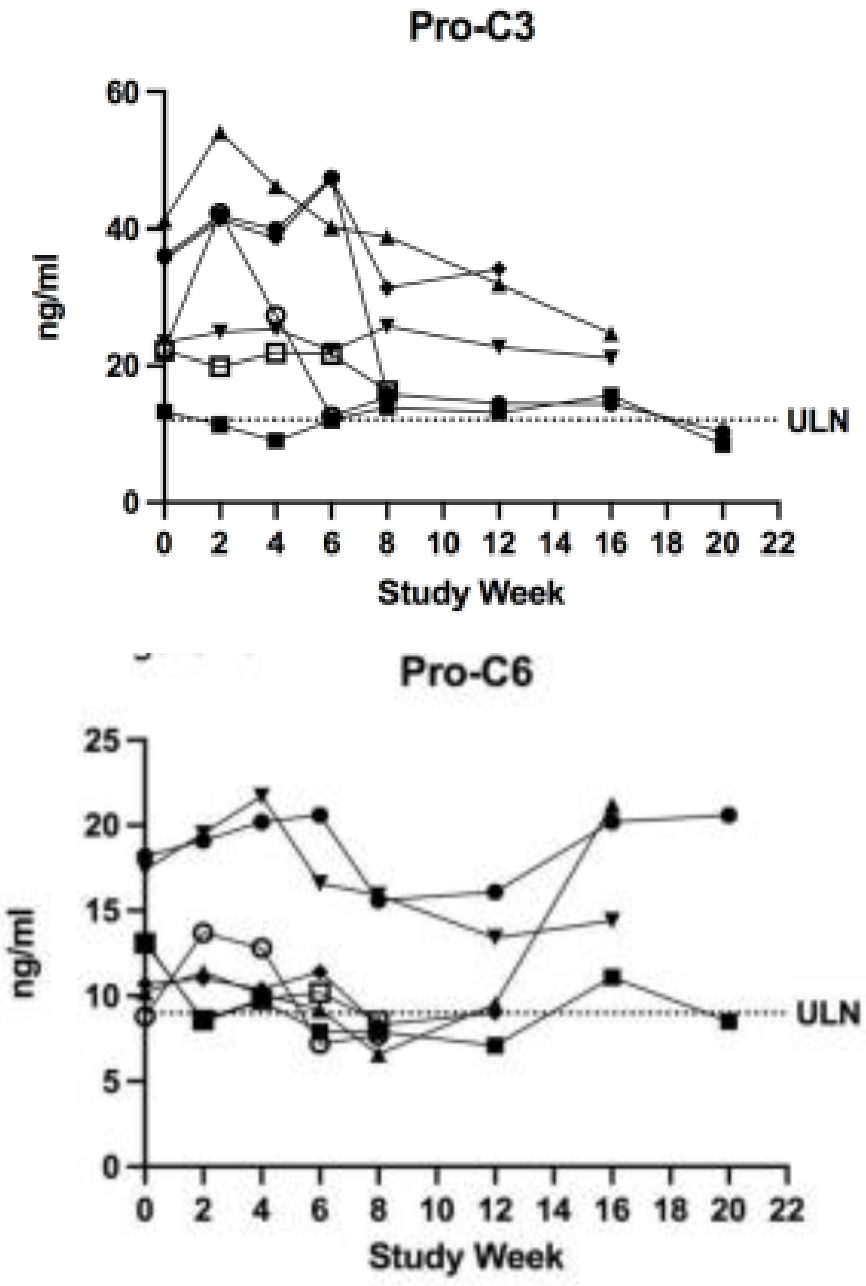
- Desmosine was elevated at baseline (mean± SEM, n=7 0.46± 0.05 ng/ml, ULN 0.280 ng/ml)
- Desmosine levels progressively declined during the dose escalation period to 0.38 ± 0.04ng/ml by week 8, representing a mean within subject % change from baseline (CFB) of -16.2%.
- *Ex vivo* zymosan stimulated elastase activity also showed progressive decrease over the dose escalation period, with some subjects demonstrating 100% suppression.



Im et al, Blood (2021) 138 (Supplement 1): 1815.

Collagen Turnover Analysis

- Collagen synthesis as measured by PRO-C3 and PRO-C6 was increased above ULN at baseline and declined with alvelestat treatment
- Collagen Type 3 and 6 Turnover (measured as the ratio of Synthesis to Degradation) generally decreased, particularly in patients with high baseline turnover
- There was consistency of a suppressive effect on biomarkers of elastase activity and collagen turnover in 6 of 7 treated patients, all of whom had improved or stable lung disease (ranging from change in FEV1 % predicted at end of treatment from +9% to -6%



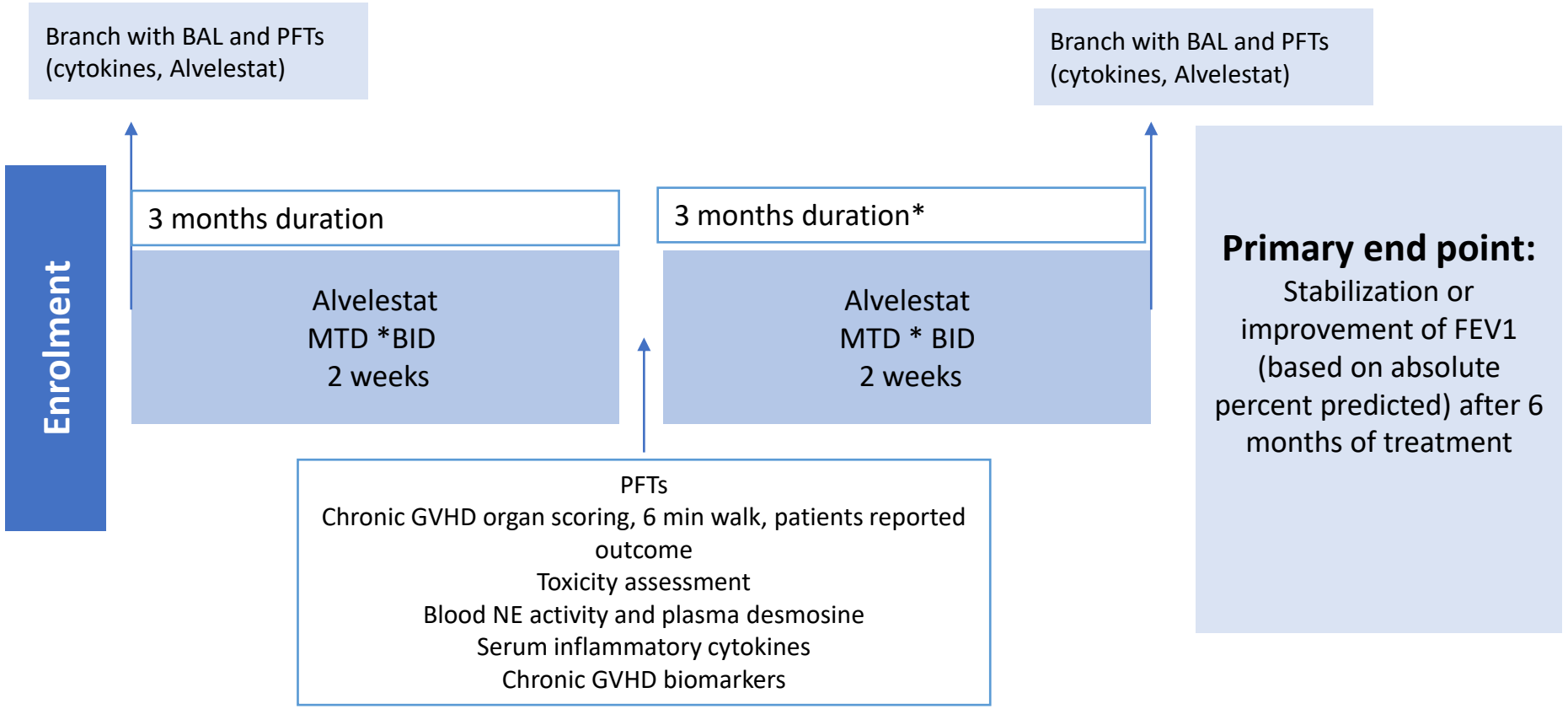
Conclusions From Biomarker Studies

- This is the first evidence of elevated elastase activity as detected by elastin breakdown in patients with BOS and chronic GVHD
- Treatment with the selective NE inhibitor, alvelestat was associated with progressive reduction of plasma desmosine levels over 8 weeks of within-subject dose escalation, and reduction in stimulated neutrophil elastase activity
- The consistent suppression of elastase and of collagen synthesis/turnover biomarkers following alvelestat treatment is encouraging for its potential to impact progressive lung fibrosis in BOS and chronic GVHD

Encouraging Results From Phase1b Study Trigger Initiation Of Phase 2 Study

Key eligibility:

- Age > 18 yrs
- BOS following SCT and must be within 2 years from diagnosis
- Patients may be at any time interval after SCT with moderate to severe chronic GVHD
- FEV1 >30% predicted
- Stable azithromycin



Primary end point:
Stabilization or improvement of FEV1 (based on absolute percent predicted) after 6 months of treatment

*Patients with stable or improved FEV1 after 6 months of treatment will be eligible for additional 6 months of treatment

PH2 study expected to strengthen clinical response data:

- Broader patient population
- Additional biomarker analysis will extend the knowledge for clinical efficacy in BOS

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Program Summary and Conclusions

Summary

- The ASTRAEUS 12-week trial is on track to deliver top-line Phase 2 data for alvelestat in AATD patients with lung emphysema in early Q2 2022*
  - Primary endpoints evolved to three key biomarkers on the pathogenic pathway of the lung disease including detection of neutrophil elastase levels in patients
    - More comprehensive - allows investigation of a number of causal pathway biomarkers for further development
    - In-vivo neutrophil elastase assay more akin to “functional PK” in-vitro assays used as a primary end-point in Phase 2 studies for AAT augmentation
    - Follows on from Mereo's development of the biomarker strategy and the Type C meeting held with the FDA
- The ATALANTa Phase 2 study will currently read-out in early 2023 and is complementary to ASTRAEUS
- Alvelestat has demonstrated a clean safety profile in all studies to-date with a tendency for headaches managed through dose escalation*
- Plan to engage in discussions with the FDA on Registrational trial design for AATD in end of Phase 2 meeting in 2H 2022
- Alvelestat has potential in other indications
  - Demonstrated impact on biomarkers of elastin breakdown and fibrosis in BOS following allogeneic hematopoietic stem cell transplantation, with encouraging pulmonary function outcomes. Phase 2 to be initiated in earlier stage patients, with clinical endpoints.
  - Demonstrated a clinically meaningful effect in short term 5-10 day dosing in hospitalised COVID-19 supports anti-inflammatory effects on top of those achieved by high dose corticosteroids

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***Note: Uncleaned data. Final values may differ from those presented here.**

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Q&A

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Thank You

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NASDAQ: MREO

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Q&A Session

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