Public Meeting on Patient-Focused Drug Development for Alpha-1 Antitrypsin Deficiency

September 29, 2015

Welcome

Donna Lipscomb
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

September 29, 2015

Agenda

- **Setting the Context**
  - Opening Remarks
  - Overview of FDA's Patient-Focused Drug Development Initiative
  - Background on Alpha-1 Antitrypsin Deficiency
  - Overview of Discussion Format
- **Discussion Topic 1:** The effects of Alpha-1 Antitrypsin Deficiency that matter most to you
- **Discussion Topic 2:** Patients' perspectives on current approaches to treatment
- **Discussion Topic 3:** Patients' perspectives on participating in a clinical trial
- **Open Public Comment**
- **Closing Remarks**

Opening Remarks

Ginette Michaud, MD
Deputy Director, Office of Blood Research and Review
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

September 29, 2015

FDA's Patient-Focused Drug Development Initiative

Pujita Vaidya, MPH
Office of Strategic Program
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

September 29, 2015

Patient-Focused Drug Development under PDUFA V

- **FDA is developing a more systematic way of gathering patient perspective on their condition and available treatment options**
  - Patient perspective helps inform our understanding of the context for the assessment of benefit-risk and decision making for new drugs
  - Input can inform FDA's oversight both during drug development and during our review of a marketing application

- **Patient-Focused Drug Development is part of FDA commitments under the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA V)**
  - FDA will convene at least 20 meetings on specific disease areas over the next five years
  - CDER will convene at least 16 meetings and CBER will convene 3 meetings
  - Meetings will help develop a systematic approach to gathering patient input

Identifying Disease Areas for the Patient-Focused Meetings

- **In September 2012, FDA announced a preliminary set of diseases as potential meeting candidates**
  - Public input on these nominations was collected. FDA carefully considered these public comments and the perspectives of our drug review divisions at FDA

- **FDA identified a set of 16 diseases to be the focus of meetings for fiscal years 2013-2015**
  - Another public process was initiated and 8 diseases were determined as the disease set for fiscal years 2016-2017

Disease Areas to be the focus of meetings for FY 2013-2017

Fiscal Year 2013	Fiscal Year 2014	Fiscal Year 2015	Fiscal Year 2016-2017
• Chronic fatigue syndrome/ myalgic encephalomyelitis • HIV • Lung cancer • Narcolepsy	• Sickle cell disease • Fibromyalgia • Pulmonary arterial hypertension • Inborn errors of metabolism • Hemophilia A, B, and other heritable bleeding disorders • Idiopathic pulmonary fibrosis	• Female sexual dysfunction • Breast cancer • Chagas disease • Functional gastrointestinal disorders • Huntington's disease and Parkinson's disease • **Alpha-1 antitrypsin deficiency (September 29)**	• Non-tuberculous mycobacterial lung infections (October 15) *To be announced* • Alopecia areata • Autism • Hereditary angioedema • Patients who have received an organ transplant • Psoriasis • Neuropathic pain associated with peripheral neuropathy • Sarcopenia

Tailoring Each Patient-Focused Meeting

- **Each meeting focuses on a set of questions that aim to elicit patients' perspectives on their disease and on treatment approaches**
  - We start with a set of questions that could apply to any disease area; these questions are taken from FDA's benefit-risk framework and represent important considerations in our decision-making
  - We then further tailor the questions to the disease area of the meeting (e.g., current state of drug development, specific interests of the FDA review division, and the needs of the patient population)
- **Focus on relevant current topics in drug development for the disease at each meeting**
  - E.g., focus on HIV patient perspectives on potential "cure research"
- **We've learned that active patient involvement and participation is key to the success of these meetings.**

"Voice of the Patient" Reports

- Following each meeting, FDA publishes a Voice of the Patient report that summarizes the patient testimony at the meeting, perspectives shared in written docket comments, as well as any unique views provided by those who joined the meeting webcast.

- These reports serve an important function in communicating to both FDA review staff and the regulated industry what improvements patients would most like to see in their daily life.

- FDA believes that the long run impact of this program will be a better, more informed understanding of how we might find ways to develop new treatments for these diseases.

$Alpha_1$-Antitrypsin Deficiency Disease Overview

Ross Pierce, MD
Medical Officer, Office of Blood Research and Review
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

September 29, 2015

$Alpha_1$-Antitrypsin Deficiency (AATD)

- Autosomal co-dominant genetic disorder with over 100 different genetic mutations
- Reduced serum and lung levels of $Alpha_1$ Antitrypsin (AAT)
- Highly variable clinical presentation
  - Lung Disease (emphysema) in many but not all with severe deficiency
  - Liver disease much less common than lung disease

Prevalence of AATD

- Between 60,000 and 120,000 individuals in the U.S. have severe AATD (1 in 2000 to 5000 live births)
- Vast majority of individuals with AATD are undiagnosed
- Doctors in the U.S. do not routinely screen patients with emphysema or chronic obstructive pulmonary disease for AATD

What does Alpha 1 Antitrypsin (AAT) do?

- Key inhibitor of Neutrophil Elastase (NE), an enzyme that can break down proteins in lung tissue
  - In normal lungs, NE is present in low levels
  - In the lungs of patients with severe AATD, NE is present at higher levels

- Various poorly understood anti-inflammatory properties

Mechanism of AATD Lung Disease

- Lack of AAT to inhibit Neutrophil Elastase results in faster breakdown of lung tissue with development of emphysema
- In emphysema, the peripheral air sacs (alveoli) become enlarged as their walls are destroyed, resulting in:
  - Over-inflated lungs
  - Partial airway collapse with airflow obstruction
  - Decline in lung density (mass/volume)

Symptoms of AATD Lung Disease

- Emphysema, a form of chronic obstructive pulmonary disease including:
  - Shortness of breath
  - Reduced exercise tolerance
  - Exacerbations resulting in increased:
    - Shortness of breath
    - Sputum
    - Pus in the sputum
- Asthma in some patients
- Wasting/malnutrition

Highly Variable Clinical Presentation

- Many individuals with severe AATD do not develop emphysema during their lifetimes.
- Age of onset
  - Smokers: 30's or 40's, or earlier
  - Non-smokers: 50's or 60's

- 15% of patients develop liver disease

Mechanism of AATD Liver Disease

- Abnormally folded mutant AAT molecules remain and accumulate in liver cells causing liver inflammation, cell death, scarring, and sometimes cirrhosis.

- This chronic inflammation may also predispose to liver cancer.

Childhood AATD Liver Disease

- Infants may have poor feeding, poor weight gain, hepatitis, jaundice
- Signs and symptoms such as failure to thrive, elevated liver enzymes in up to 50% of affected children
- Majority recover and remain healthy throughout childhood, but some progress to cirrhosis
- Risk of liver cancer

Adult AATD Liver Disease

- Scant published data
- Liver disease in adults may occur without history of childhood liver disease.
- Liver disease probably increases with advancing age
- Presence of cirrhosis as high as 40%

Management of AATD Liver Disease (1)

- No specific therapy approved.
- Standard supportive care for liver disease to prevent/treat bleeding, abdominal fluid accumulation, itching, malnutrition, fat soluble vitamin deficiency, infection, slowed growth, and liver cancer
- Avoid smoking and secondhand smoke.
- Avoid alcohol

Management of AATD Liver Disease (2)

- May require lower doses/frequency or avoidance of some medicines broken down by the liver, such as acetaminophen
- Screening for liver cancer with ultrasound recommended every 6 -12 months if scarring, cirrhosis, or liver enzymes are elevated
- <25% of patients with liver disease require liver transplantation

Management of AATD Lung Disease (1)

- A_1-PI augmentation therapy administered intravenously weekly
  - Inhaled A_1-PI remains experimental
- Avoid smoking
- Inhaled bronchodilators, corticosteroids
- Influenza and pneumococcal (pneumonia) vaccination
- Supplemental oxygen

Management of AATD Lung Disease (2)

- Pulmonary rehabilitation
- Management of acute exacerbations
  - Brief courses of corticosteroids
  - Early antibiotic therapy
  - Temporary respirator support
- Lung transplantation

Rationale for A_1-PI Augmentation Therapy

- **Theory** predicts that achieving AAT: Neutrophil Elastase balance by increasing lung levels of AAT would stop destruction of lung tissue and slow the progression of emphysema

- Currently recommended doses of approved **alpha-1 protease inhibitors (A_1-PI)** may not be sufficient to completely inhibit excess NE in severe AATD

What we know about A_1-PI Augmentation Therapy

- Increases blood and lung levels of AAT
- Generally well tolerated
- Very low risk of viral transmission
- Inconvenient requiring regular weekly intravenous administration

What we do *not* know about A_1-PI Augmentation Therapy

- Optimal dose/blood level
- Effects at different stages of lung disease
- Long-term effects on lung function
- Effects on exacerbation frequency and severity
- Effects on symptoms and quality of life
- Effect on mortality

Conclusions (1)

- AATD can be a serious disease characterized by progressive lung and/or liver disease that may ultimately require lung or liver transplantation.
- There is no specific treatment for liver disease.
- Augmentation therapy with A1-PI is the only specific therapy for lung disease, but at the currently recommended dose, its effects on symptoms, exacerbations, quality of life, and mortality are uncertain.

Conclusions (2)

- Ongoing studies provide opportunities to determine whether higher doses of A_1-PI administered intravenously and/or by inhalation improve symptoms and function.
- Additional therapies need to be developed to address the unmet medical needs of patients with AATD lung and liver disease.

Overview of Discussion Format

Donna Lipscomb
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

Discussion Overview

Topic 1: The effects of Alpha-1 Antitrypsin Deficiency

- Of all of the symptoms that you experience because of your condition, which one to three symptoms have the most significant impact on your life?
- Are there specific activities that are important to you, but that you cannot do at all, or as well as you would like, because of your condition?
- How have your condition and its symptoms changed over time?
- What worries you most about your condition?

Discussion Overview

Topic 2: Current approaches to treatment

- What are you currently doing to treat your condition or its symptoms?
  - How well do these treatments work for you?
  - What are the most significant disadvantages or complications of your current treatments, and how do they affect your daily life?
  - How has your treatment changed over time and why?
  - What aspects of your condition are not improved by your current treatment regimen?
  - What treatment has had the most positive impact on your life?

- If you could create your ideal treatment, what would it do for you (i.e., what specific things would you look for in an ideal treatment)?

Discussion Overview

Topic 3: Perspectives on participating in a clinical trial

- If you had the opportunity to consider participating in a clinical trial studying experimental treatments, what things would you consider when deciding whether or not to participate?

Discussion Format

- **We will first hear from a panel of patients**
  - The purpose is to set a good foundation for our discussion
  - The panelists reflect a range of experiences with AATD

- **Presentation of survey results**
  - The Alpha-1 Foundation will present survey data on the discussion questions

- **We will then broaden the dialogue to include patients and patient representatives in the audience**
  - The purpose is to build on the experiences shared by the panel
  - We will ask questions and invite you to raise your hand to respond
  - Please state your name before answering

Discussion Format

- **You will have a chance to answer "polling" questions**
  - Their purpose is to aid our discussion
  - In-person participants, please use the "clickers" to respond
  - Web participants, please answer the questions through the webcast
  - Patients and patient representatives only, please

- **Web participants can add comments through the webcast**
  - Although they may not all be read or summarized today, your comments will incorporated into our summary report

Send us your comments!

You can send us comments through the "public docket"

- The docket will be open until November 30, 2015
- Share your experience, or expand upon something discussed today
- Comments will be incorporated into our summary report
- Anyone is welcome to comment

Visit:
http://www.regulations.gov/#!docketDetail;D=FDA-2015-N-1798

Click Comment Now!

Discussion Ground Rules

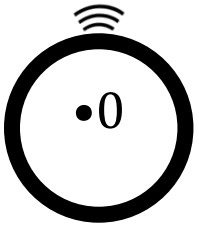
- We encourage patients, caregivers, and advocates to contribute to the dialogue
- FDA is here to listen
- Discussion will focus on symptoms and treatments
  - Open Public Comment Period is available to comment on other topics
- The views expressed today are personal opinions
- Respect for one another is paramount

1. Where do you live?

33% A. Within the Washington, D.C. area (including the Virginia and Maryland suburbs)

33% B. Outside of the Washington, D.C. metropolitan area, but within the U.S.

33% C. Outside of the U.S.



2. Which of the following best describes you?

Check all that apply

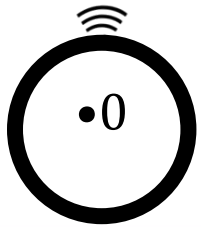
20% A. I have Alpha1 Antitrypsin Deficiency (AATD) but no active disease

20% B. I have emphysema because of AATD

20% C. I have liver disease because of AATD

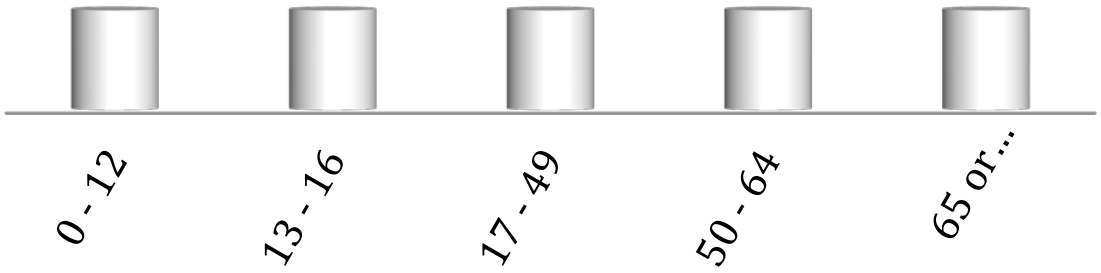
20% D. I have both liver disease and emphysema because of AATD

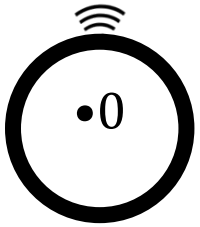
20% E. I am a family member or caregiver of someone with AATD



3. What is your/your loved one's age in years?

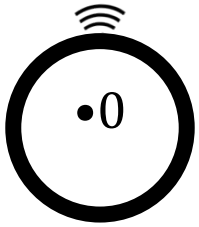
A. 0 - 12
B. 13 - 16
C. 17 - 49
D. 50 - 64
E. 65 or older

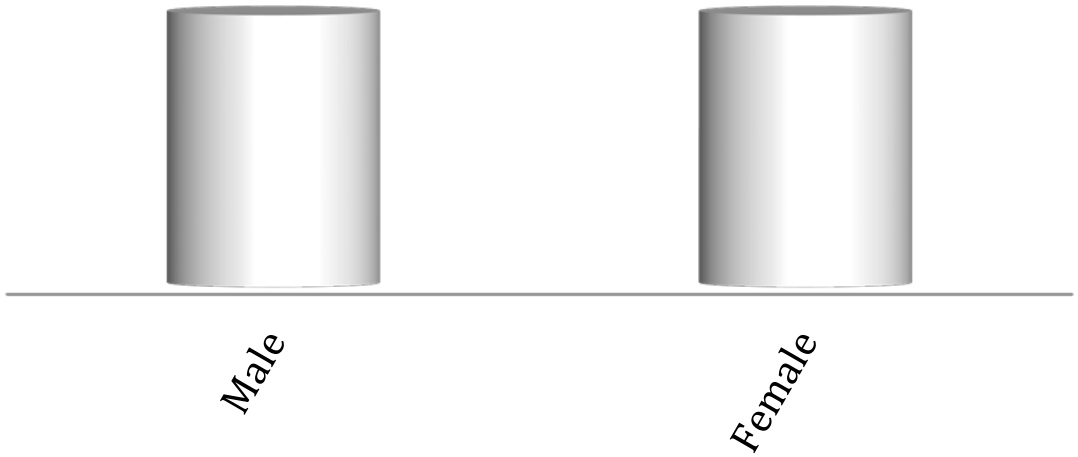




4. Are you/Is your loved one:

A. Male
B. Female





Discussion Topic 1

The effects of Alpha-1 Antitrypsin Deficiency that matter most to you

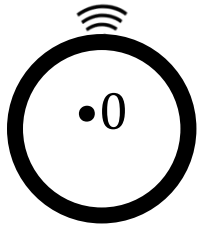
Donna Lipscomb
Facilitator

Discussion Topic 1: The effects of Alpha-1 Antitrypsin Deficiency that matter most to you

- Of all of the symptoms that you experience because of your condition, which one to three symptoms have the most significant impact on your life?
- Are there specific activities that are important to you, but that you cannot do at all, or as well as you would like, because of your condition?
- How have your condition and its symptoms changed over time?
- What worries you most about your condition?

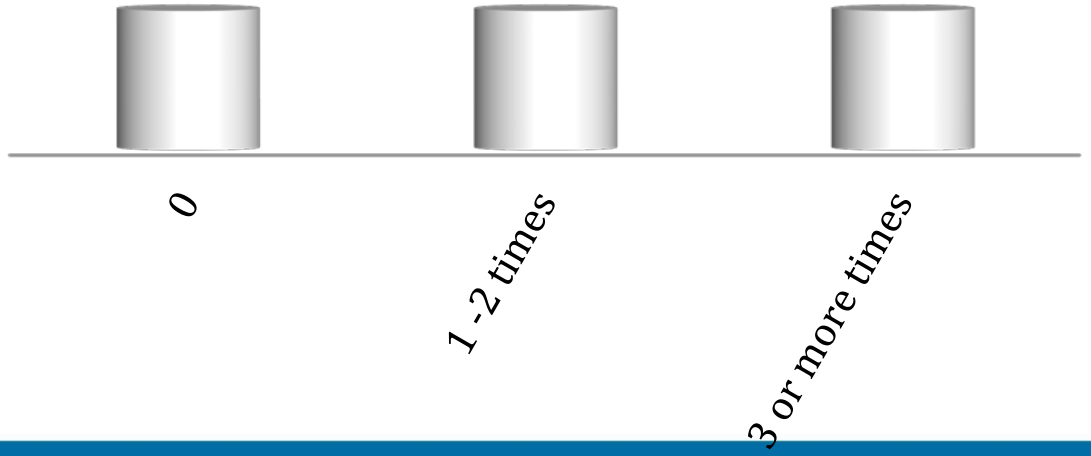
5. Which of the following symptoms currently have a significant impact on you/your loved one's daily life? Check all that apply

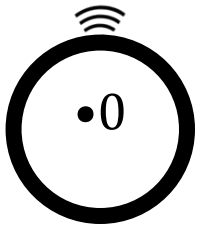
10% A. Shortness of breath
10% B. Chronic cough
10% C. Production of phlegm
10% D. Poor appetite
10% E. Weight loss
10% F. Weight gain when taking steroids like prednisone
10% G. Weight gain not related to steroids
10% H. Anxiety and/or depression
10% I. Jaundice
10% J. Chronic itching



6. If you have liver disease because of AATD, how many times in the past year did you/your loved one experience a bleeding episode that required medical attention?

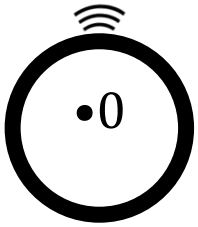
A. 0
B. 1 -2 times
C. 3 or more times

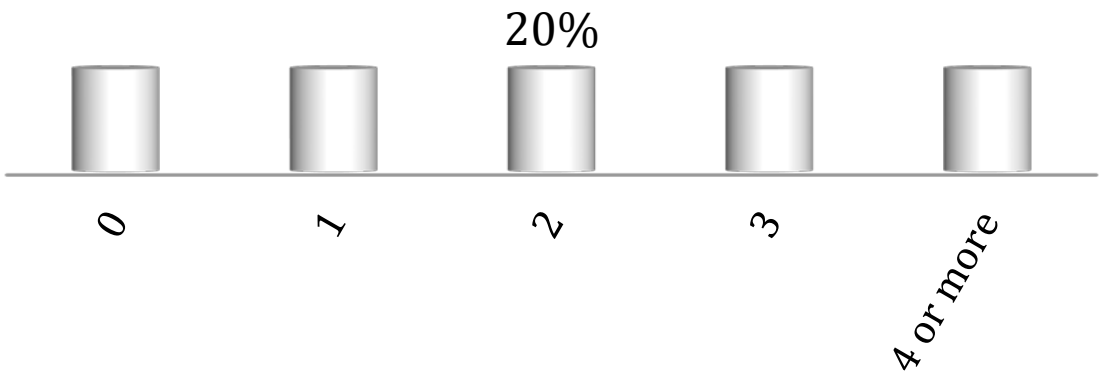




7. How many exacerbations of lung symptoms (shortness of breath, increase in sputum volume or pus content) have you/your loved one had *in the past year*?

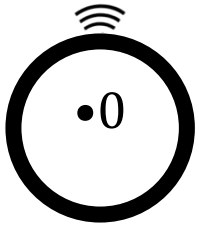
A. 0
B. 1
C. 2
D. 3
E. 4 or more

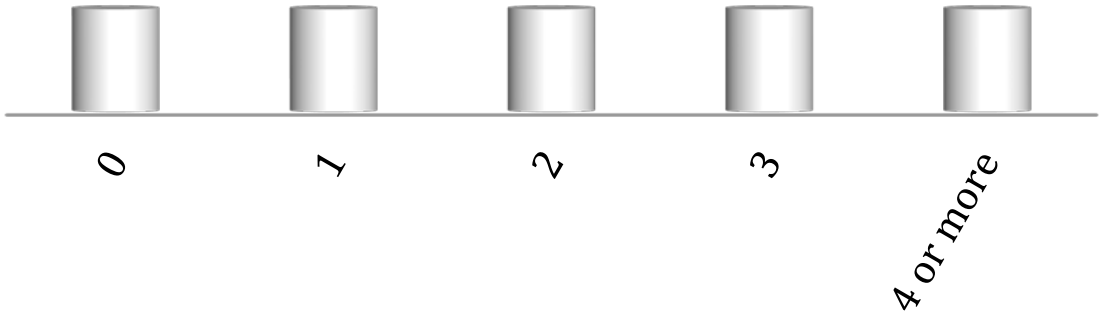




8. Of your/your loved one's exacerbations of lung symptoms in the past year, how many required hospitalization?

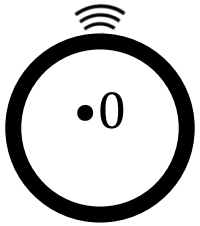
A. 0
B. 1
C. 2
D. 3
E. 4 or more

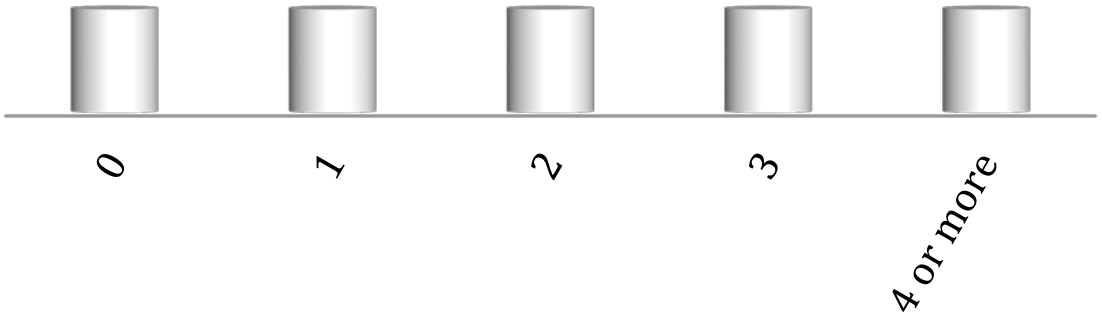




9. Of your/your loved one's exacerbations of lung symptoms in the past year, how many required an emergency room visit or a doctor's visit without hospitalization?

A. 0
B. 1
C. 2
D. 3
E. 4 or more





Discussion Topic 1: The effects of Alpha-1 Antitrypsin Deficiency that matter most to you

- Of all of the symptoms that you experience because of your condition, which one to three symptoms have the most significant impact on your life?
- Are there specific activities that are important to you, but that you cannot do at all, or as well as you would like, because of your condition?
- How have your condition and its symptoms changed over time?
- What worries you most about your condition?

LUNCH

Discussion Topic 2

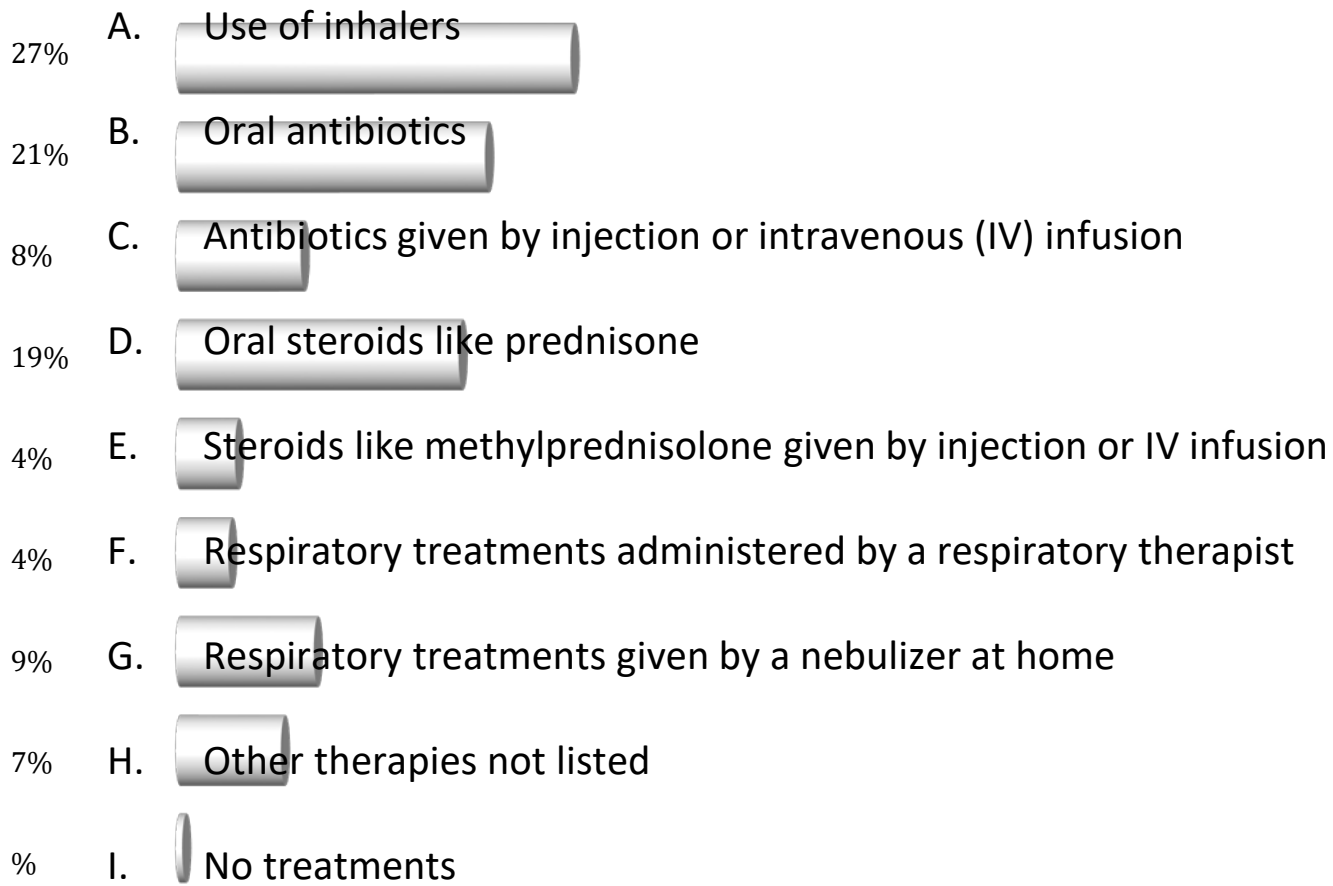
Patients' perspectives on current approaches to treatment for Alpha-1 Antitrypsin Deficiency

Donna Lipscomb
Facilitator

Discussion Topic 2: Patients' perspectives on current approaches to treatment for Alpha-1 Antitrypsin Deficiency

- What are you currently doing to treat your condition or its symptoms?
  - How well do these treatments work for you?
  - What are the most significant disadvantages or complications of your current treatments, and how do they affect your daily life?
  - How has your treatment changed over time and why?
  - What aspects of your condition are not improved by your current treatment regimen?
  - What treatment has had the most positive impact on your life?
- If you could create your ideal treatment, what would it do for you (i.e., what specific things would you look for in an ideal treatment)?

10. In the past year, what therapies have you/your loved used to manage exacerbations of lung symptoms? Check all that apply



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11. Have you/your loved one undergone lung transplantation for emphysema because of AATD?

A. Yes
B. No

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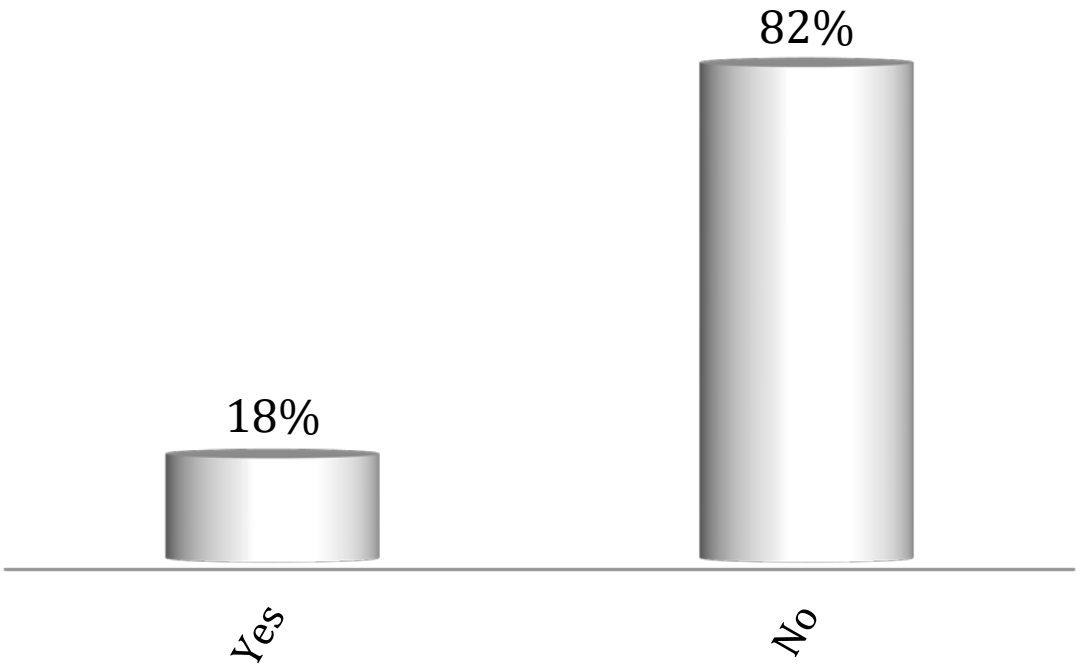
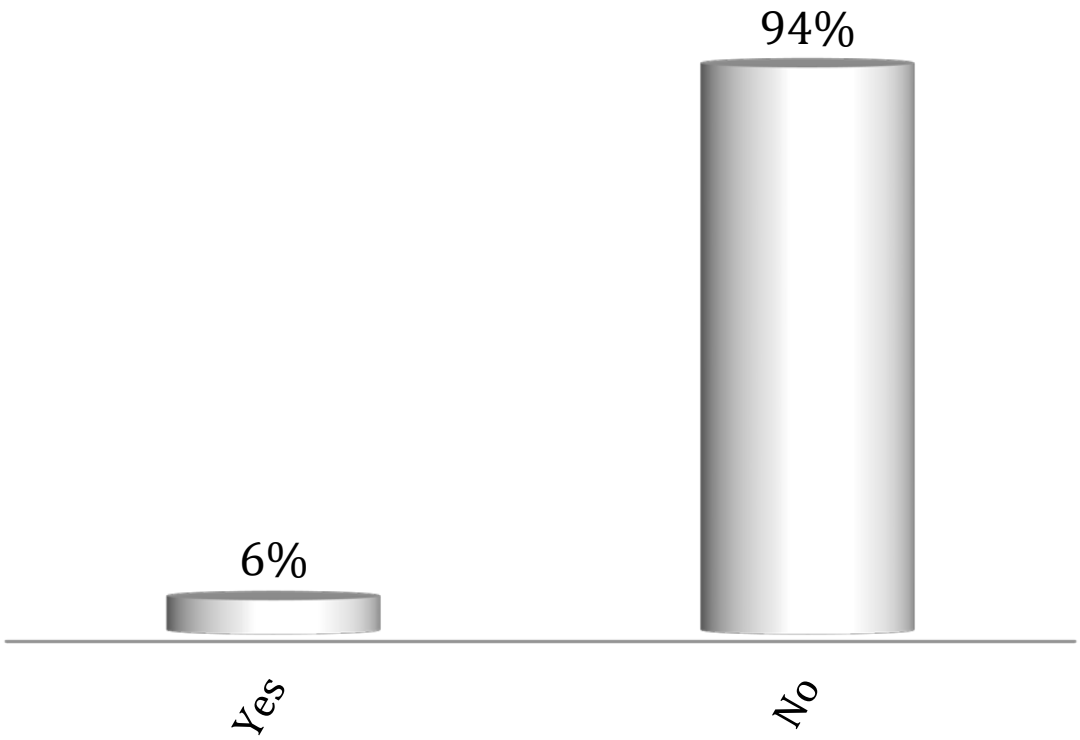


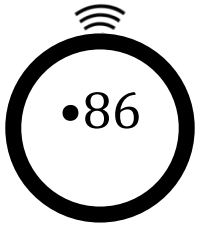
12. Have you undergone liver transplantation because of AATD?

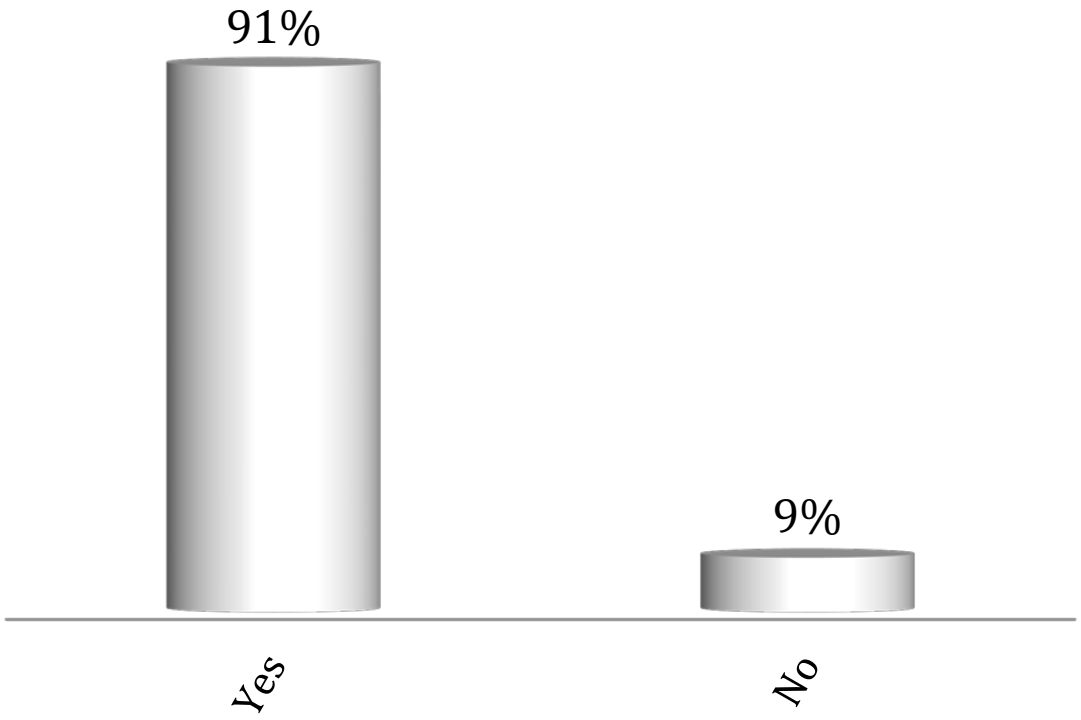
A. Yes
B. No



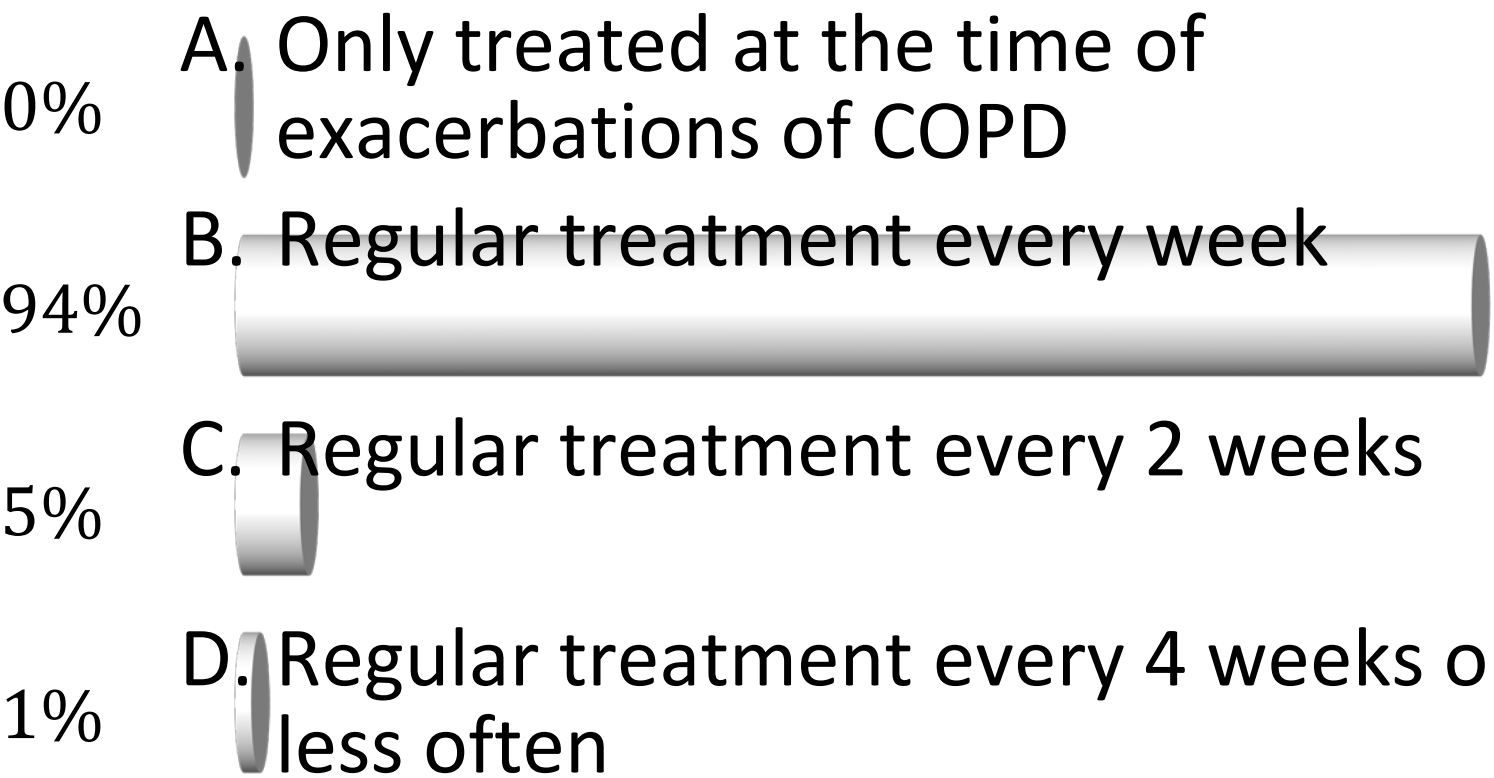
13. Are you/your loved one currently receiving augmentation therapy with Alpha1-Proteinase Inhibitor (Aralast NP, Glassia, Prolastin-C, or Zemaira)?

A. Yes
B. No





14. If you/your loved one are being treated with augmentation therapy with Alpha$_1$-Proteinase Inhibitor (Aralast NP, Glassia, Prolastin-C, or Zemaira), what is the current frequency of your treatment regimen?



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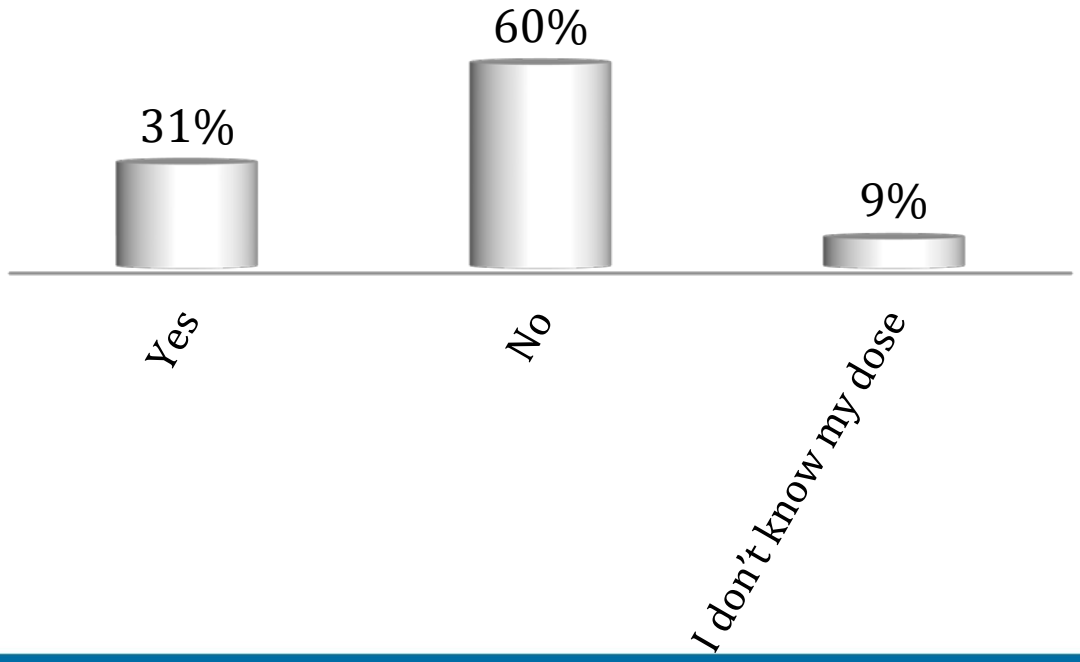
15. If you know your Alpha$_1$-Proteinase Inhibitor dose, do you receive a dose higher than 60 mg/kg/week (FDA labeled dose)?

A. Yes
B. No
C. I don't know my dose



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16. Which of the following best describes how you/your loved one feel about your current treatment regimen?

11% A. I am satisfied with my current treatment regimen and do not want to change it

76% B. I am satisfied with my current treatment regimen, but am willing to consider new options

13% C. I am not satisfied with my current regimen

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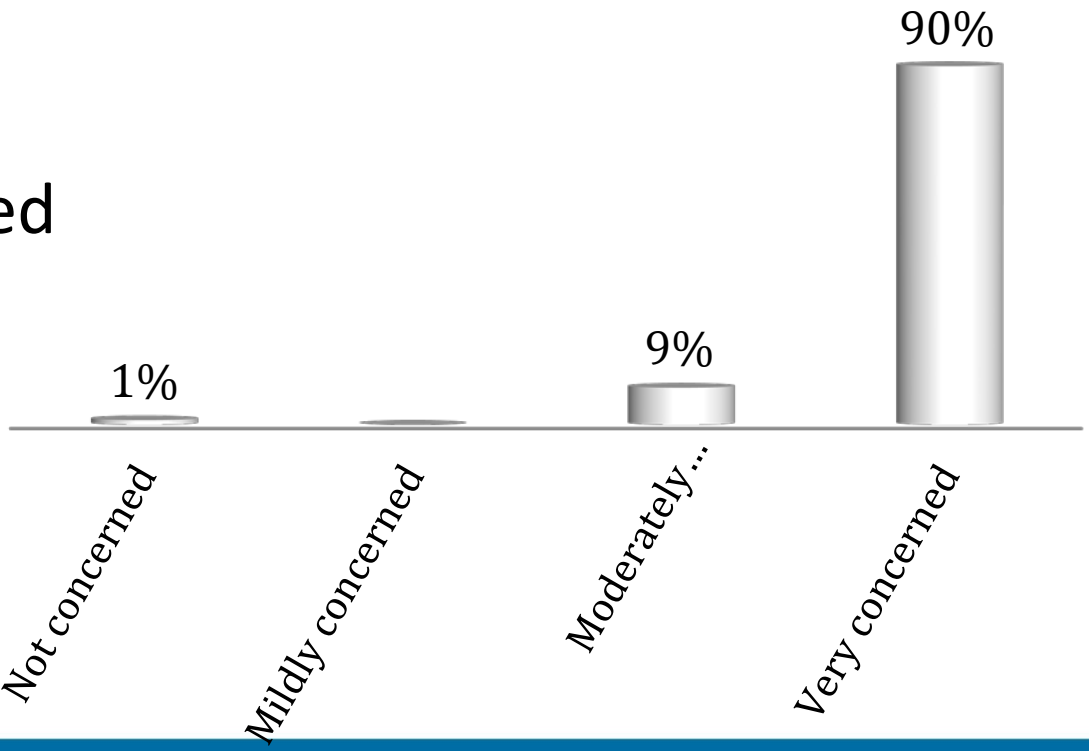
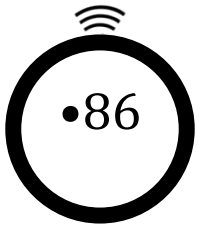
17. What is your level of concern regarding the cost of augmentation therapy with Alpha$_1$-Proteinase Inhibitor?

A. Not concerned
B. Mildly concerned
C. Moderately concerned
D. Very concerned





18. If you are not currently on augmentation therapy with Alpha$_1$-Proteinase Inhibitor would you start therapy with an inhaled formulation if one were approved by the FDA?

A. Yes
B. No

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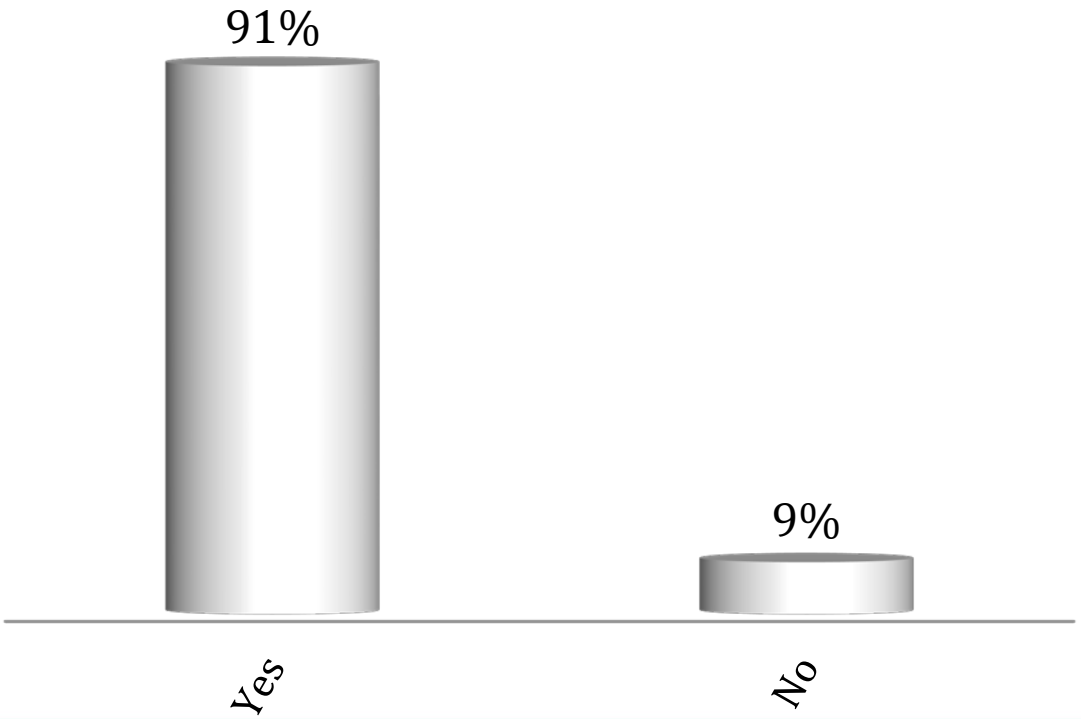


19. If you are currently receiving augmentation therapy with Alpha$_1$-Proteinase Inhibitor, what factors would influence a decision to possibly switch to an inhaled formulation if one were approved by the FDA? *Check all that apply.*

62% A. Convenience

0% B. Tolerability/less discomfort

31% C. Efficacy as compared to IV A_1-PI on the progression of emphysema

8% D. Cost

•26

Discussion Topic 2: Patients' perspectives on current approaches to treatment for Alpha-1 Antitrypsin Deficiency

- What are you currently doing to treat your condition or its symptoms?
  - How well do these treatments work for you?
  - What are the most significant disadvantages or complications of your current treatments, and how do they affect your daily life?
  - How has your treatment changed over time and why?
  - What aspects of your condition are not improved by your current treatment regimen?
  - What treatment has had the most positive impact on your life?
- If you could create your ideal treatment, what would it do for you (i.e., what specific things would you look for in an ideal treatment)?

Discussion Topic 3

Patients' perspectives on participating in a clinical trial to study experimental treatments

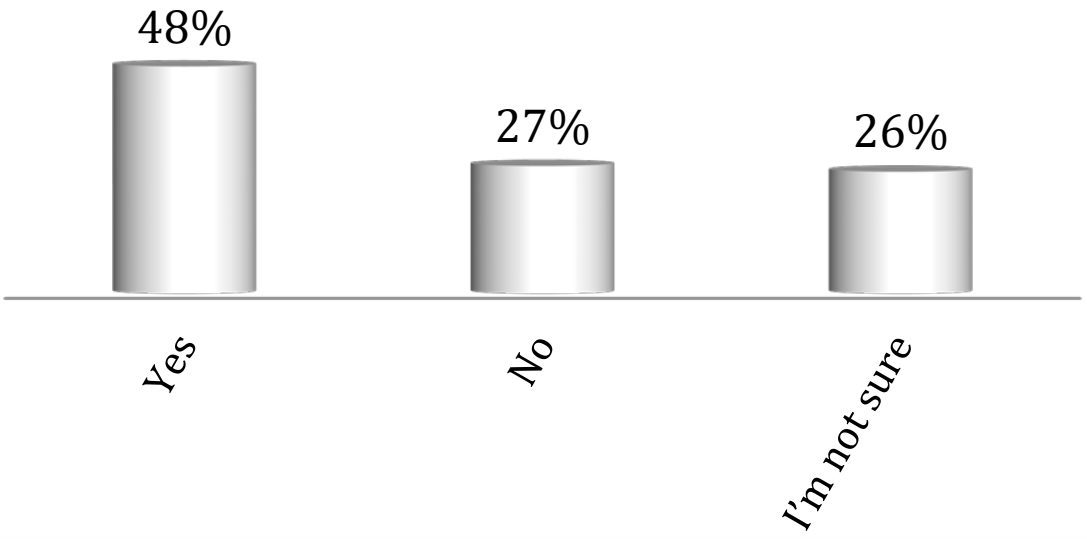
Donna Lipscomb
Facilitator

Discussion Topic 3: Patients' perspectives on participating in a clinical trial to study experimental treatments

- If you had the opportunity to consider participating in a clinical trial studying experimental treatments, what things would you consider when deciding whether or not to participate?

20. Have you/your loved one ever participated in any type of clinical trial studying investigational treatments for AATD?

A. Yes
B. No
C. I'm not sure



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21. If you/your loved one had the opportunity to participate in a clinical trial to study an investigational treatment, which of the following best describes your thoughts?

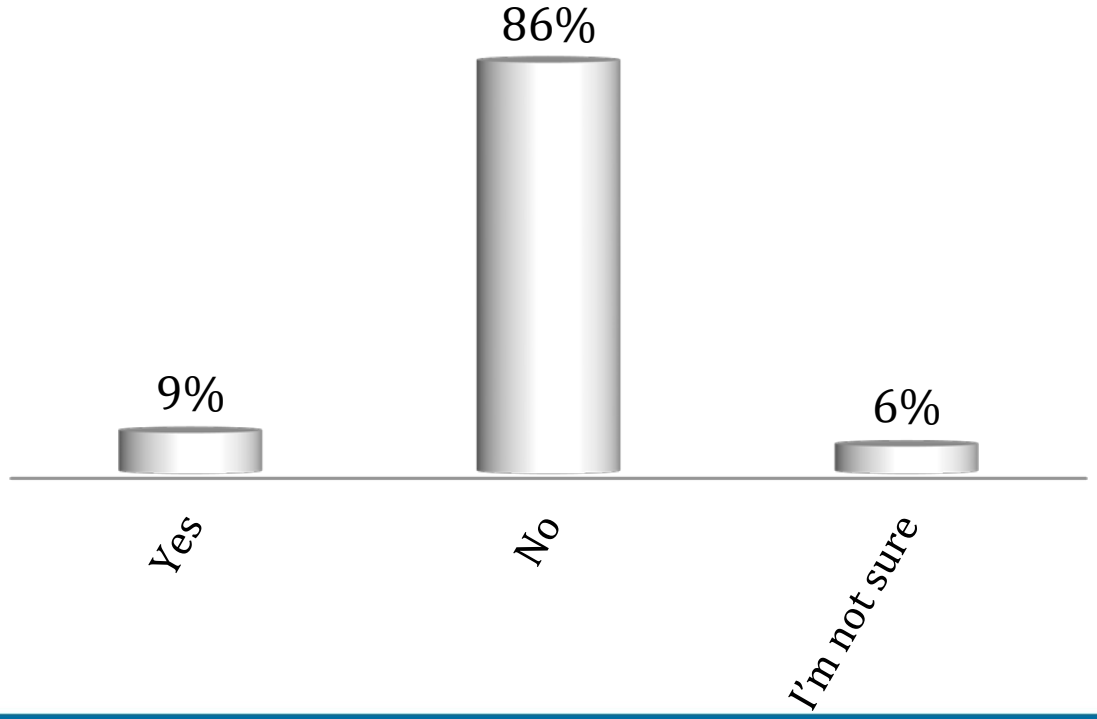
55% A. Yes: I am generally willing to consider participating

4% B. No: I would not consider participating

41% C. Maybe: My participation would depend on various factors.

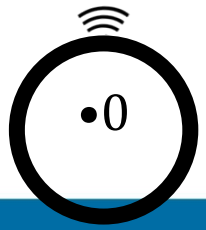
22. Would you be willing to participate in a placebo-controlled clinical trial conducted in patients with AATD-related lung disease?

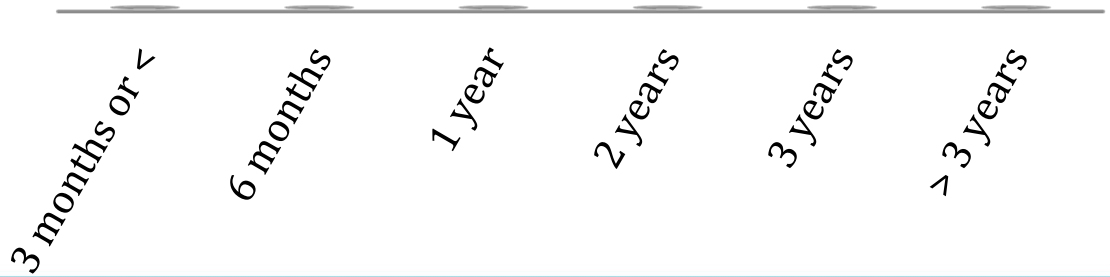
A. Yes
B. No
C. I'm not sure



23. If you were willing to participate in a placebo-controlled clinical trial conducted in patients with AATD-related lung disease, how long would you consider receiving a blinded active test product or placebo?

A. 3 months or <
B. 6 months
C. 1 year
D. 2 years
E. 3 years
F. > 3 years





Discussion Topic 3: Patients' perspectives on participating in a clinical trial to study experimental treatments

- If you had the opportunity to consider participating in a clinical trial studying experimental treatments, what things would you consider when deciding whether or not to participate?

Open Public Comment Period

Closing Remarks

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