Navigating the Landscape of COPD Clinical Trials:
From Diagnosis Criteria to Pivotal Endpoints

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory lung disease that obstructs airflow from the lungs, making it increasingly difficult to breath.

COPD is an umbrella term primarily used to describe chronic bronchitis and emphysema, conditions that are commonly associated with each other. This disease is a significant cause of morbidity and mortality worldwide, particularly affecting middle-aged and older adults. COPD ranks as the third leading cause of death globally, emphasizing the critical need for effective treatment and management strategies.

The understanding of COPD has significantly evolved over the past century. Initially, the term was used interchangeably with chronic bronchitis and emphysema, focusing on the clinical symptoms without a clear understanding of the underlying pathophysiology. In the mid-20th century, advancements in pulmonary medicine began to distinguish COPD from other respiratory diseases. The use of spirometry to measure airflow obstruction provided a more objective diagnosis, leading to better-defined diagnostic criteria and treatment protocols.

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Characteristics and Contributing Factors

COPD is characterized by persistent respiratory symptoms and airflow limitation that is not fully reversible. The obstruction is due to airway and/or alveolar abnormalities typically caused by significant exposure to harmful particles or gases. Key characteristics of COPD include chronic cough, sputum production, and dyspnea (shortness of breath). These symptoms often worsen over time and can severely impact a patient's quality of life.

Key Characteristics

1. **Airflow Limitation:**
   - Persistent and progressive airflow limitation is a hallmark of COPD.
2. **Inflammatory Response:**
   - An abnormal inflammatory response in the lungs to noxious particles or gases.
3. **Chronic Symptoms:**
   - Chronic cough, mucus production, and dyspnea.

Contributing Factors

The development and progression of COPD are influenced by a combination of biological, psychological, and environmental factors:

1. **Biological Factors:**
   - Genetic predisposition, such as alpha-1 antitrypsin deficiency, plays a crucial role. Aging also contributes to the natural decline in lung function, exacerbating COPD symptoms.
2. **Psychological Factors:**
   - Patients with COPD often experience anxiety and depression due to chronic illness and reduced physical capabilities. This psychological burden can affect their overall well-being and adherence to treatment regimens.
3. **Environmental Factors:**
   - Long-term exposure to tobacco smoke is the leading cause of COPD. Other significant contributors include occupational dust, chemicals, and air pollution. In developing countries, indoor air pollution from biomass fuel used in cooking and heating is also a major risk factor.

Prevalence and Future Trends

Prevalence

The prevalence of COPD has been increasing globally, with significant variations across different regions. In the United States, approximately 16 million adults have been diagnosed with COPD, but millions more may have the disease without knowing it. The trend analysis over the past decade shows a steady increase in COPD cases, due to the aging population and continuous exposure to risk factors like smoking and air pollution. According to the CDC, the number of COPD cases has risen by about 13% from 2011 to 2021.

Key Statistics

- According to a systematic review published in the European Respiratory Journal, the global burden of COPD was quantified through numerous studies, highlighting significant prevalence rates across multiple regions.
- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) reports that COPD is the third leading cause of death worldwide.

Trend Analysis for the Past 10 Years (2013-23)

The CDC data shows a consistent increase in COPD prevalence, attributed to both improved diagnosis and aging demographics. The American Lung Association reports that over 16 million Americans have been diagnosed with COPD, but the actual number may be higher as many cases remain undiagnosed. The projected trend suggests that without significant changes in prevention and treatment strategies, COPD prevalence will continue to rise over the next decade.

Future Projections for the COPD Treatment Market

Projected Market Growth

The COPD treatment market is projected to grow at a compound annual growth rate (CAGR) of approximately 4.5% from 2023 to 2030. This growth is driven by several key factors:

1. Increasing Disease Prevalence

- As the prevalence of COPD continues to rise, the demand for effective treatment options will increase correspondingly. According to the WHO, COPD is the third leading cause of death worldwide, and its incidence is expected to rise in coming years.

2. Advancements in Therapeutic Options

- Ongoing research and development are leading to the introduction of new and more effective treatments. Innovations such as combination inhalers, biologics, and personalized medicine approaches are expanding the therapeutic landscape. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) provides guidelines that highlight these advancements.

3. Development of Novel Drugs

- Pharmaceutical companies are investing heavily in development of novel drugs aimed at improving lung function, reducing exacerbations, and managing symptoms more effectively. These drugs are expected to drive market growth as they receive regulatory approval and enter the market.

Market for Treatment

The global market for COPD treatment is substantial, with an estimated market value of over $15 billion in 2022. This market is projected to grow at a compound annual growth rate (CAGR) of approximately 4.5% from 2023 to 2030. Factors driving this growth include increasing disease prevalence, advancements in therapeutic options, and the development of novel drugs.

Key Drugs with Highest Earning Potential in the US

Drug Name	Company	Annual Revenue (USD)
Spiriva	Boehringer Ingelheim	4.6 billion
Symbicort	AstraZeneca	3.5 billion
Advair	GlaxoSmithKline	2.8 billion
Trelegy Ellipta	GlaxoSmithKline	1.5 billion
Breo Ellipta	GlaxoSmithKline	1.2 billion

Diagnostic Criteria According to ICD-11

ICD-11 Code for COPD: CA22.0

Diagnostic criteria according to ICD-11::

1. Spirometry:

The diagnosis of COPD requires spirometry to confirm the presence of persistent airflow limitation. This is considered the gold standard for diagnosing COPD and involves measuring lung function to assess the severity of airflow obstruction. Exacerbations and comorbidities contribute to the overall severity in individual patients.

- **FEV1/FVC Ratio:** A post-bronchodilator FEV1/FVC ratio of less than 0.70 is a key diagnostic criterion for COPD. This ratio indicates the proportion of a person's vital capacity they can exhale in the first second of a forced breath.
- **Assessment of Severity:**
  - GOLD 1 - mild: FEV1≥ 80% predicted
  - GOLD 2 - moderate: 50% ≤FEV1 <80% predicted
  - GOLD 3 - severe: 30% ≤FEV1 <50% predicted
  - GOLD 4 - very severe: FEV1 <30% predicted

2. Symptoms and Risk Factors:

In addition to spirometry, a diagnosis of COPD is based on the presence of characteristic symptoms and a history of exposure to risk factors:

- **Chronic Symptoms:** These include chronic cough, sputum production, and dyspnea (shortness of breath).
- **Risk Factors:** A significant history of exposure to risk factors such as tobacco smoke, occupational dust, chemicals, and significant air pollution.

3. Exclusion of Other Conditions:

Differential Diagnosis: Ensuring that the symptoms are not due to other conditions such as;

- Emphysema
- Chronic Tracheobronchitis
- Chronic Tracheitis
- Simple Or Mucopurulent Chronic Bronchitis
- Asthmatic Bronchitis NOS
- Bronchiectasis
- Asthma
- Chronic Bronchitis NOS

Diagnostic Tools for COPD

1. Spirometry

Spirometry is the gold standard for diagnosing COPD. This test measures the amount and speed of air a person can inhale and exhale. Key spirometric indices include:

- Forced Expiratory Volume in one second (FEV1): The amount of air a person can forcefully exhale in one second.
- Forced Vital Capacity (FVC): The total amount of air exhaled during the spirometry test.
- FEV1/FVC Ratio: This ratio is used to diagnose airflow obstruction. A post-bronchodilator FEV1/FVC ratio of less than 0.70 confirms the presence of airflow limitation.

2. Imaging Studies

Chest X-rays and CT Scans are commonly used to support the diagnosis of COPD and exclude other conditions that can present with similar symptoms, such as lung cancer or tuberculosis.

- Chest X-ray: While not definitive for COPD, it can show signs of hyperinflation, flattened diaphragm, and other structural changes in the lungs.
- Computed Tomography (CT) Scan: Provides detailed images of the lung structure and is more sensitive than X-rays in detecting emphysema and other lung abnormalities.

3. Arterial Blood Gas Analysis

Arterial Blood Gas (ABG) Analysis is used to assess the levels of oxygen and carbon dioxide in the blood. This test is particularly important in patients with severe COPD to determine the need for oxygen therapy.

- PaO2: Partial pressure of oxygen in arterial blood. Lower values indicate hypoxemia.
- PaCO2: Partial pressure of carbon dioxide in arterial blood. Higher values may indicate hypercapnia.

4. Pulse Oximetry

Pulse Oximetry is a non-invasive method to monitor the oxygen saturation of the blood. This tool is useful for quick assessments in both outpatient and inpatient settings.

- SpO2: Oxygen saturation measured by pulse oximetry. Values below 90% may indicate the need for further investigation and potential oxygen therapy.

5. Six-Minute Walk Test (6MWT)

The 6MWT measures the distance a patient can walk quickly on a flat, firm surface in a period of six minutes. This test assesses the functional status and exercise tolerance of COPD patients.

- Distance Walked: The total distance walked in six minutes is recorded. Lower distances are indicative of greater disability.

Epidemiology

1. Age

- The prevalence of COPD increases significantly with age, particularly among individuals aged ≥65. According to the Centers for Disease Control and Prevention (CDC), the prevalence of COPD is highest among adults aged ≥65, at approximately 14%, compared to 6.6% among those aged 45-64, and 2% among those aged 18-44. Aging contributes to the decline in lung function and increases the susceptibility to COPD due to long-term exposure to risk factors.

2. Gender

- Historically, COPD has been more prevalent in men due to higher smoking rates. However, the gap is narrowing as women's smoking rates have increased and occupational exposures have diversified.

3. Racial Group

- In the US, Non-Hispanic white individuals have the highest prevalence, followed by non-Hispanic Black individuals, Hispanic individuals, and Asian/Pacific Islanders. According to a study published in the American Journal of Respiratory and Critical Care Medicine, non-Hispanic white individuals have a COPD prevalence rate of approximately 7.6%, compared to 6.8% among non-Hispanic Black individuals and 3.2% among Hispanic individuals.

4. Global Prevalence

- Globally, COPD is a leading cause of morbidity and mortality. The WHO estimates that >251 million people worldwide suffer from COPD, and it is projected to become the third leading cause of death globally by 2030.

5. Geographic Location

- Higher rates of COPD are observed in areas with increased exposure to risk factors such as air pollution, smoking, and occupational hazards. In the US, COPD prevalence is higher in rural areas compared to urban areas. According to the CDC, the prevalence of COPD in rural areas is approximately 8.3%, compared to 5.4% in urban areas.
- Additionally, certain states in the Southeastern United States, often referred to as the "COPD Belt," have higher COPD prevalence rates due to higher smoking rates and exposure to pollutants.

6. Genetic Predisposition

- One well-known genetic risk factor is alpha-1 antitrypsin deficiency, a hereditary condition that can lead to severe COPD at a younger age. According to the American Thoracic Society, individuals with alpha-1 antitrypsin deficiency are at a significantly higher risk of developing COPD, especially if they smoke. This deficiency leads to early-onset emphysema, even in non-smokers .

7. Impact on Healthcare and Economy

- COPD is a leading cause of hospitalizations and emergency department visits in the US. According to the National Heart, Lung, and Blood Institute, the annual economic burden of COPD in the US is estimated to be around $49 billion. The rising prevalence of COPD poses a challenge to healthcare systems, emphasizing the need for effective prevention and management strategies to reduce the disease burden.

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Pivotal Endpoints for COPD Clinical Trials, Key Challenges and Solutions

1. Lung Function (FEV1 and FVC)
2. Exacerbation Rate
3. Symptom Scores (CAT, SGRQ, mMRC)
4. Mortality (All-Cause and COPD-Related)
5. Quality of Life
6. Exercise Capacity (6MWT, ISWT)
7. Biomarkers
8. Healthcare Utilization
9. Safety and Adverse Events

1. Endpoint: Lung Function (FEV1 and FVC)

- **FEV1 (Forced Expiratory Volume in 1 second)** is a critical measure of lung function that quantifies the amount of air a person can forcefully exhale in one second. It is commonly used to assess the severity of airflow obstruction in COPD.
- **FVC (Forced Vital Capacity)** refers to the total volume of air that can be forcibly exhaled after taking a deep breath. This measurement provides additional context to FEV1, helping to differentiate between obstructive and restrictive lung diseases.

"By quantifying the respiratory volumes and flows, such as forced vital capacity (FVC) or forced expiratory volume in six seconds (FEV6), forced expiratory volume in the first second (FEV1), and the relationship between these parameters (FEV1/FVC or FEV1/FEV6 ratio), obstruction can be detected with high sensitivity and specificity." – Rivero Yeverino, 2019.

Challenges:

- **Variability:** Lung function tests are highly dependent on patient effort, technician skill, and environmental conditions. This variability can result in inconsistent measurements across different testing sessions.
- **Progression Detection:** COPD progression is typically slow, making it difficult to observe significant changes in FEV1 or FVC over short periods, particularly in early-phase trials.

Solutions:

- **Standardized Protocols:** Implementing rigorous, standardized protocols for spirometry can minimize variability. Technicians should be well-trained, and testing should be performed under controlled conditions.
- **Baseline Adjustments:** Employ statistical methods to adjust for baseline lung function and other confounding variables, thereby improving the precision of the results.
  - **Baseline Adjustment Method:**
    - **Analysis of Covariance (ANCOVA):** A common statistical method used in such trials is ANCOVA. This method adjusts for baseline differences by including the baseline FEV1 as a covariate in the analysis.
    - **How It Works:** ANCOVA models the post-treatment FEV1 (outcome) while controlling for the baseline FEV1. The model then estimates the treatment effect after accounting for the baseline lung function, thereby reducing the influence of initial differences between groups.
    - **Outcome:** By adjusting for baseline FEV1, researchers can isolate the true effect of the bronchodilator, improving the precision and validity of the trial results.
- **Longitudinal Monitoring:** Regular and frequent lung function testing can help capture subtle trends and reduce the impact of day-to-day variability.

2. Endpoint: Exacerbation Rate

- Exacerbation Rate refers to the frequency of acute worsening of COPD symptoms, often requiring additional treatment or hospitalization. This endpoint is crucial as exacerbations significantly impact patient quality of life and healthcare utilization.

Challenges:

- **Subjective Reporting:** Exacerbations are often based on patient self-reports, which can be influenced by recall bias or varying perceptions of what constitutes an exacerbation.
- **Heterogeneity:** The severity and triggers of exacerbations can vary widely between patients, making it difficult to standardize this endpoint.

Solutions:

- **Clear Definitions:** Providing clear, standardized definitions of what constitutes an exacerbation can help ensure consistency in reporting. Educating patients and clinicians on these definitions is also crucial.
- **Use of Objective Measures:** Incorporating objective criteria, such as medication changes or hospitalizations, can help to standardize the classification of exacerbations.
- **Electronic Monitoring:** Utilizing electronic diaries or mobile apps can facilitate real-time symptom tracking, reducing recall bias and improving data accuracy.

3. Endpoint: Symptom Scores

- Symptom Scores like the COPD Assessment Test (CAT), St. George's Respiratory Questionnaire (SGRQ), and Modified Medical Research Council (mMRC) Dyspnea Scale assess the impact of COPD on daily life, including symptoms, physical functioning, and overall QoL.

Challenges:

- **Subjectivity:** Symptom scores are subjective and can be influenced by external factors such as mood or stress, which may not relate to COPD.
- **Recall Bias:** Patients may have difficulty accurately recalling symptoms over extended periods, leading to potential inaccuracies in reporting.

Solutions:

- **Frequent Assessments:** Conducting regular symptom assessments can capture a more accurate picture of the patient's experience and reduce the impact of transient external factors.
- **Use of Multiple Instruments:** Employing a combination of validated symptom scores can provide a more comprehensive understanding of the patient's condition and help mitigate the limitations of any single tool.
- **Patient Training:** Providing patients with clear instructions and training on how to accurately complete symptom questionnaires can help reduce subjectivity and improve data reliability.

4. Endpoint: Mortality

- Mortality endpoints, both all-cause and COPD-related, measure the rate of death among trial participants. These endpoints are critical in evaluating the ultimate impact of a treatment on survival.

Challenges:

- **Low Event Rate:** Mortality rates in COPD trials, especially over short durations, tend to be low, necessitating large sample sizes or long follow-up periods to detect meaningful differences.
- **Cause Attribution:** Accurately determining whether a death is related to COPD can be complex, especially in populations with multiple comorbidities.

Solutions:

- **Long-Term Follow-Up:** Extending the trial duration or follow-up period increases the likelihood of capturing mortality events, enhancing the power of the analysis.
- **Independent Adjudication:** Using independent adjudication committees to review and classify the causes of death can improve accuracy and reduce bias in cause attribution.
- **Composite Endpoints:** Consider using composite endpoints that include mortality along with other significant clinical events (e.g., hospitalizations), providing a broader assessment of treatment impact.

5. Endpoint: Quality of Life

- Quality of Life (QoL) measures assess the broader impact of COPD on a patient's daily living, emotional well-being, and social functioning. These endpoints provide insights into how a treatment affects overall patient health beyond clinical measures.

Challenges:

- **Subjectivity and Variability:** QoL assessments are inherently subjective and can vary significantly based on subjective experiences, making it difficult to achieve consistent results across a diverse patient population.
- **Sensitivity to Change:** Some QoL instruments may not be sensitive enough to detect small but clinically meaningful improvements, particularly in trials with shorter durations.

Solutions:

- **Validated Instruments:** Utilize well-validated and disease-specific QoL measures, such as the SGRQ, to ensure that the instruments used are appropriate and reliable for the COPD population.
- **Frequent Monitoring:** Increasing the frequency of QoL assessments can help capture changes over time and provide a more dynamic understanding of treatment impact.
- **Patient Education:** Educating patients on the importance of accurately reporting their QoL can help minimize external influences and improve the reliability of the data.

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6. Endpoint Exercise Capacity

- Exercise Capacity is typically assessed using tests like the 6-Minute Walk Test (6MWT) or Incremental Shuttle Walk Test (ISWT). These endpoints measure how far a patient can walk in a set time or under increasing difficulty, providing a practical assessment of functional capacity in COPD patients.

Challenges:

- **Variability in Performance:** Patient motivation, physical fitness, and comorbid conditions can all influence performance on exercise tests, leading to variability in results.
- **Reproducibility:** The reproducibility of exercise capacity tests can be challenging if conditions (e.g., room temperature, time of day) differ between testing sessions.

Solutions:

- **Standardized Testing Conditions:** Conducting tests under controlled and standardized conditions can minimize variability and improve reproducibility.
- **Practice Runs:** Incorporating practice tests can help patients become familiar with the procedures, reducing the impact of anxiety or unfamiliarity on performance.
- **Objective Metrics:** Pairing exercise tests with objective physiological measures (e.g.,heart rate, oxygen saturation) can provide additional insights into patient status and improve the endpoint reliability.

7. Endpoint: Biomarkers

- Biomarkers are biological indicators that provide objective data on disease processes, inflammation, and treatment response in COPD.

Challenges:

- **Variability:** Biomarker levels can fluctuate due to factors unrelated to COPD, such as infections, stress, or other comorbid conditions, leading to potential variability in the data.
- **Lack of Standardization:** Some biomarkers may lack standardized assays or reference ranges, complicating their use in clinical trials.

Solutions:

- **Frequent Sampling:** Collecting biomarkers at multiple time points can account for day-to-day variability and provide a more accurate representation of changes over time.
- **Established Biomarkers:** Focus on well-established biomarkers with standardized testing methods to ensure consistency and reliability of results.
  - Examples of Established Biomarkers in COPD: Blood Eosinophil Count; C-Reactive Protein (CRP); Fibrinogen; Nitric Oxide (FeNO); Interleukin-6 (IL-6).
- **Combined Endpoints:** Using biomarkers in conjunction with clinical endpoints (e.g., exacerbation rate, lung function) can enhance the understanding of treatment effects and disease progression.

8. Endpoint: Healthcare Utilization

- Healthcare Utilization endpoints track the frequency and duration of hospitalizations, as well as the use of rescue medications, to evaluate the real-world impact of COPD on healthcare resources.

Challenges:

- **Data Collection:** Accurate collection of healthcare utilization data can be challenging, especially in trials involving multiple centers or international sites, where practices and standards of care may vary.
- **Healthcare System Variability:** Differences in healthcare systems, such as accessibility of care and local guidelines, can lead to variability in how healthcare utilization endpoints are recorded and interpreted.

Solutions:

- **Standardized Data Collection:** Using standardized forms and protocols for collecting healthcare utilization data across sites ensures consistency and improves data quality.
- **Harmonization Across Sites:** Harmonizing data collection practices across different countries or regions can help minimize variability due to local healthcare practices.
- **Electronic Health Records (EHRs):** Integrating EHRs into the data collection process can provide real-time, accurate data on hospitalizations and medication use, improving the reliability of these endpoints.

9. Endpoint: Safety & Adverse Events

- Safety and Adverse Events endpoints monitor the frequency, severity, and type of adverse events experienced by patients during the trial. These endpoints are essential for evaluating the safety profile of a treatment.

Challenges:

- **Underreporting:** Mild or expected adverse events may be underreported by both patients and investigators, leading to incomplete safety data.
- **Variability in Reporting:** Differences in how adverse events are reported and classified can create inconsistencies, making it difficult to compare safety profiles across studies.

Solutions:

- **Training and Monitoring:** Providing thorough training for investigators on how to report adverse events accurately, coupled with regular monitoring, can improve the completeness and accuracy of safety data.
- **Standardized Criteria:** Implementing standardized criteria and terminology (e.g., using the Common Terminology Criteria for Adverse Events) can help ensure consistency in reporting.
- **Centralized Reporting System:** Utilizing a centralized system for reporting and analyzing adverse events can enhance data quality and facilitate the identification of safety signals.

Top Five Most Commonly Prescribed COPD Drugs in the US

Drug Name	Sponsor	Mechanism of Action	Therapeutic Effects
Albuterol	Various (ProAir - Teva, Ventolin - GSK, Proventil - Merck)	Short-Acting Beta-Agonist (SABA)	Relaxes muscles in the airways and increases airflow to the lungs. Provides quick relief of acute COPD symptoms.
Spiriva (Tiotropium)	Boehringer Ingelheim	Anticholinergic bronchodilator	Improves airflow, reduces exacerbations
Symbicort (Budesonide/ Formoterol)	AstraZeneca	Combination of corticosteroid and long-acting beta-agonist	Reduces inflammation and relaxes airway muscles
Advair (Fluticasone/ Salmeterol)	GlaxoSmithKline	Combination of corticosteroid and long-acting beta-agonist	Reduces inflammation and relaxes airway muscles
Roflumilast (Daliresp)	AstraZeneca	Phosphodiesterase-4 inhibitor	Reduces inflammation and prevents COPD exacerbations

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Pivotal Trials that Demonstrated the efficacy of these FDA Approved Drugs

Drug Name	Clinical Trial Identifier	Sample Size	Key Findings and Statistical Data
Albuterol (ProAir, Ventolin, Proventil)	NCT01857323	318 participants	• Overall rate of discrepancies for dose cycle "not counted" was approximately 2.1 per 200 dose cycles. Most of subjects (83%) were somewhat or very satisfied, and >90% of subjects were satisfied with ease of holding and handling, using and taking, and inhaling a dose from the device. • Findings suggested that albuterol spiromax with dose counter was effective in functioning reliably and accurately with high degree of subject satisfaction.
Spiriva (Tiotropium)	NCT02172482	63127 participants	• Change from baseline in breathlessness when walking/climbing stairs was found to be 86.7% and 88.9%.
Symbicort (Budesonide/ Formoterol)	NCT02766608	2361 participants	• BGF MDI demonstrated significant improvements in morning pre-dose trough FEV1 and FEV1 AUC0-4 compared to FF MDI and BD MDI, with highly significant p-values ($p < 0.001$). • BGF MDI significantly reduced the time to first moderate or severe COPD exacerbation compared to FF MDI ($p = 0.0017$) and Symbicort TBH ($p = 0.0310$).
Advair (Fluticasone/ Salmeterol)	NCT01607398	52 participants	• This study investigated the anti-inflammatory effects of salmeterol/fluticasone propionate 50/250 mcg combination therapy in Japanese patients with chronic obstructive pulmonary disease. • Findings suggested that Advair did not show statistical difference in neutrophil count, IL-8, MPO, SP-D in induced sputum and IL-6, IL-8, hsCRP, SP-D in serum when compared with placebo group.
Roflumilast (Daliresp)	NCT00297102	1523 participants	• Compared to placebo, pre-bronchodilator FEV1 was statistically significantly ($p<0.0005$) increased with roflumilast by 39 mL in the ITT analysis and 47 mL in the PP analysis. • At all treatment visits there were increases in pre- and post-bronchodilator FEV1 from baseline in the Rof500 group and clearly smaller increases or decreases in FEV1 from baseline in the placebo group. • Statistically significant differences in LSMeans between Rof500 od and placebo ranging from 36 mL to 46 mL (pre-bronchodilator) and from 46 mL to 56 mL (post bronchodilator) were seen at all visits (ITT).

Approved Product Analysis: Albuterol

14.1 Bronchospasm Associated with Asthma - Adult and Adolescent Patients 12 Years of Age and Older

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Asthmatic patients 12 to 76 years of age	Improvement in FEV1 % (Forced Expiratory Volume)	Percent change in FEV1	Day 1 and Day 43 (out of 6 weeks)	PROAIR HFA Inhalation Aerosol (N=58 Day 1, N=52 Day 43)	Significant improvement in FEV1 on both Day 1 and Day 43 compared to placebo, and comparable to active comparator.
Asthmatic patients 12 to 76 years of age	Improvement in FEV1 % (Forced Expiratory Volume)	Percent change in FEV1	Day 1 and Day 43 (out of 6 weeks)	Matched Placebo (N=58 Day 1, N=49 Day 43)	Lower FEV1 improvement compared to PROAIR HFA.
Asthmatic patients 12 to 76 years of age	Improvement in FEV1 % (Forced Expiratory Volume)	Percent change in FEV1	Day 1 and Day 43 (out of 6 weeks)	Active Comparator HFA-134a (N=56 Day 1, N=49 Day 43)	FEV1 improvement comparable to PROAIR HFA.
Asthmatic patients 12 to 76 years of age	Bronchodilator Response	Time to onset, peak, duration	Day 1 (out of 6 weeks)	PROAIR HFA Inhalation Aerosol (N=31 of 58 patients)	15% increase in FEV1 within 30 minutes, with a median onset of 8.2 minutes, peak effect at 47 minutes, and duration of 3 hours, up to 6 hours in some patients.

Approved Product Analysis: Albuterol (cont.)

14.1 Bronchospasm Associated with Asthma - Pediatric Patients 4 to 11 Years of Age

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Asthmatic children 4 to 11 years of age	Improvement in FEV1 % (Forced Expiratory Volume)	Percent predicted FEV1	Day 1 and Day 22 (out of 3 weeks)	PROAIR HFA Inhalation Aerosol (N=50)	Significant improvement in FEV1 compared to placebo on both Day 1 and Day 22.
Asthmatic children 4 to 11 years of age	Improvement in FEV1 % (Forced Expiratory Volume)	Percent predicted FEV1	Day 1 and Day 22 (out of 3 weeks)	Matched Placebo (N=45)	Lower FEV1 improvement compared to PROAIR HFA.
Asthmatic children 4 to 11 years of age	Bronchodilator Response	Time to onset, peak, duration	Day 1 (out of 3 weeks)	PROAIR HFA Inhalation Aerosol (N=21 of 50 patients)	15% increase in FEV1 within 30 minutes, with a median onset of 10 minutes, peak effect at 31 minutes, and duration of 4 hours, up to 6 hours in some patients.
Crossover Study Asthmatic children 4 to 11 years of age	Bronchodilator Response	Percent predicted FEV1	Single-dose, 6 hours post-dose	PROAIR HFA Inhalation Aerosol (N=55)	One and two inhalations produced significantly greater bronchodilator responses compared to placebo.

14.2 Exercise-Induced Bronchospasm

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Adults and adolescents with exercise-induced bronchospasm (EIB)	Prevention of EIB (exercise-induced bronchospasm)	FEV1 maintenance within 80% of post-dose, pre-exercise baseline values	30 minutes before exercise, effects measured for 1-hour post-exercise	PROAIR HFA Inhalation Aerosol (N=24)	83% (20 of 24) of patients maintained FEV1 within 80% of baseline values after exercise compared to 25% (6 of 24) on placebo.
Adults and adolescents with exercise-induced bronchospasm (EIB)	Prevention of EIB (exercise-induced bronchospasm)	FEV1 maintenance within 80% of post-dose, pre-exercise baseline values	30 minutes before exercise, effects measured for 1-hour post-exercise	Placebo (N=24)	Only 25% (6 of 24) of patients maintained FEV1 within 80% of baseline values after exercise.

Approved Product Analysis: Spiriva

- The SPIRIVA HandiHaler (tiotropium bromide inhalation powder) clinical development program included six Phase 3 studies.
- A total of 2663 patients with COPD were enrolled, with 1308 receiving SPIRIVA HandiHaler.
- The program consisted of:
  - Two 1-year, placebo-controlled studies
  - Two 6-month, placebo-controlled studies
  - Two 1-year, ipratropium-controlled studies
- The studies included patients aged 40 years or older with a history of smoking greater than 10 pack-years.
- Participants had a clinical diagnosis of COPD, FEV1 ≤ 60% or 65% of predicted, and an FEV1/FVC ratio ≤ 0.7.

Additional trial to evaluate exacerbation – 1-year placebo-controlled trials

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with COPD	Improvement in lung function (FEV1 and FVC)	FEV1 and FVC measurements	Day 1, Day 8, and steady state maintained over 1 year	1-year placebo-controlled trials: N-Not Specified	Mean FEV1 improvement at 30 minutes was 0.13 L (13%) with a peak improvement of 0.24 L (24%) on Day 1. Further improvement to 0.28-0.31 L (28%-31%) after 1 week, maintained over 1 year with no tolerance.

Additional trial to evaluate exacerbation – 6-month placebo-controlled trial

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
6-Month, Placebo-Controlled Trial A	Improvement in lung function (FEV1)	Serial spirometric evaluations over 12 hours	Day 1 and Day 169	SPIRIVA (n=202), Placebo (n=179)	Significant and sustained improvement in FEV1 compared to placebo, maintained over 24 hours post-dose.
6-Month, Placebo-Controlled Trial B	Improvement in lung function (FEV1)	Serial spirometric evaluations over 3 hours	Throughout 6 months	Not specified	Improvement in FEV1 similar to Trial A, supporting the efficacy of SPIRIVA HandiHaler.
1-Year, Ipratropium-Controlled Trial	Improvement in lung function (FEV1)	Serial spirometric evaluations over 6 hours	Day 1 and Day 92	SPIRIVA (n=153), Ipratropium (n=72)	Results of each of the 1-year ipratropium-controlled trials were similar to the results of the 1-year placebo-controlled trials

Approved Product Analysis: Spiriva (cont.)

4-Year Effects on Lung Function

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
COPD patients, aged 40 to 88 years, mean pre-bronchodilator FEV1 of 39% predicted	Long-term effects on lung function (FEV1) and disease progression	Trough (pre-dose) FEV1 and rate of decline in FEV1	Baseline and monthly assessments over 4 years	SPIRIVA HandiHaler (n=2494), Control (n=2363)	No significant difference in the yearly rate of decline in FEV1 between groups. SPIRIVA HandiHaler maintained improvements in trough FEV1 by 87 to 103 mL over 4 years compared to control.

Exacerbations

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
COPD patients, aged 40 to 90 years, mean pre-bronchodilator FEV1 of 36% predicted	Reduction in COPD exacerbations and hospitalization due to COPD exacerbations	Proportion of patients with COPD exacerbations and hospitalization due to COPD exacerbations	6 months	SPIRIVA HandiHaler (n=1829)	SPIRIVA reduced the proportion of patients with exacerbations to 27.9% vs. 32.3% on placebo (OR = 0.81; 95% CI = 0.66, 0.99; p = 0.037). Hospitalization was reduced to 7.0% vs. 9.5% on placebo (OR = 0.72; 95% CI = 0.51, 1.01; p = 0.056).
COPD patients, aged 40 to 88 years, mean pre-bronchodilator FEV1 of 39% predicted	Reduction in COPD exacerbations and exacerbation-related hospitalizations	Hazard Ratio for exacerbations and hospitalizations	4 years	SPIRIVA HandiHaler (n=2494)	SPIRIVA reduced the risk of exacerbation by 14% (HR = 0.86; 95% CI = 0.81, 0.91; p<0.001) and the risk of exacerbation-related hospitalizations by 14% (HR = 0.86; 95% CI = 0.78, 0.95; p<0.002). Median time to first exacerbation was delayed from 12.5 months to 16.7 months.

Approved Product Analysis: Symbicort

14.1 Asthma - Study 1: Clinical Study with SYMBICORT 160/4.5

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with asthma, 12 years and older	Asthma worsening and withdrawals due to asthma events	Predefined asthma-worsening criteria (FEV1, PEF, rescue medication use, nighttime awakenings)	Over 12 weeks	SYMBICORT 160/4.5 mcg (n=124), Budesonide 160 mcg plus Formoterol 4.5 mcg (n=115), Budesonide 160 mcg (n=109), Formoterol 4.5 mcg (n=123), Placebo (n=125)	SYMBICORT: 13 (10.5%), Budesonide + Formoterol: 13 (11.3%), Budesonide: 22 (20.2%), Formoterol: 44 (35.8%), Placebo: 62 (49.6%)
Patients with asthma, 12 years and older	Improvement in lung function (FEV1)	Predose FEV1 (L)	Week 2	SYMBICORT 160/4.5 mcg (n=124), Budesonide 160 mcg plus Formoterol 4.5 mcg (n=115), Budesonide 160 mcg (n=109), Formoterol 4.5 mcg (n=123), Placebo (n=125)	SYMBICORT showed the greatest mean improvement in predose FEV1 (0.19 L, 9.4%) compared to placebo (-0.17 L, -6.9%).
Patients with asthma, 12 years and older	Improvement in secondary efficacy variables	AM PEF, PM PEF, Albuterol rescue use, Average symptom score	Baseline and end of treatment	SYMBICORT 160/4.5 mcg (n=124), Budesonide 160 mcg plus Formoterol 4.5 mcg (n=115), Budesonide 160 mcg (n=109), Formoterol 4.5 mcg (n=123), Placebo (n=125)	SYMBICORT improved AM PEF by 35 L/min and PM PEF by 34 L/min. Albuterol rescue use decreased by 1.0 puffs/day, and average symptom score improved by 0.28 points.
Patients with asthma, 12 years and older	Improvement in quality of life	Asthma Quality of Life Questionnaire (AQLQ(S))	Over 12 weeks	SYMBICORT 80/4.5 mcg vs. Placebo	SYMBICORT improved AQLQ score by 0.70 points compared to placebo, indicating a clinically meaningful improvement in asthma-specific quality of life.

Approved Product Analysis: Symbicort (cont.)

Study 2: Clinical Study with SYMBICORT 80/4.5

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with mild to moderate asthma, 12 years and older	Asthma worsening and withdrawals due to asthma events	Predefined asthma-worsening criteria (FEV1, PEF, rescue medication use, nighttime awakenings)	Over 12 weeks	SYMBICORT 80/4.5 mcg (n=123), Budesonide 80 mcg (n=121), Formoterol 4.5 mcg (n=114), Placebo (n=122)	SYMBICORT had the lowest withdrawal rate due to predefined asthma events (7.3%) compared to placebo (32.8%). SYMBICORT significantly reduced the number of patients with predefined asthma events (18.7% vs. 56.6% for placebo).
Patients with mild to moderate asthma, 12 years and older	Improvement in lung function (FEV1)	Predose FEV1 (L)	Over 12 weeks	SYMBICORT 80/4.5 mcg (n=123), Budesonide 80 mcg (n=121), Formoterol 4.5 mcg (n=114), Placebo (n=122)	SYMBICORT showed the greatest mean improvement in predose FEV1 compared to other treatments, with significant gains maintained through the study period.
Patients with mild to moderate asthma, 12 years and older	Improvement in secondary efficacy variables	AM PEF, PM PEF, Albuterol rescue use, Average symptom score	Baseline and end of treatment	SYMBICORT 80/4.5 mcg vs. Placebo	SYMBICORT showed improvements in AM and PM PEF, reduced albuterol rescue use, and improved average symptom scores, similar to results observed in Study 1.

Onset and Duration of Action and Progression of Improvement in Asthma Control

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with moderate to severe asthma, 12 years and older	Onset of bronchodilation and sustained FEV1 improvement	Percent change from baseline in FEV1	On the day of randomization (Day 1) and last day of treatment (Week 12)	SYMBICORT 160/4.5 mcg (n=124), Budesonide 160 mcg (n=109), Formoterol 4.5 mcg (n=123), Budesonide 160 mcg + Formoterol 4.5 mcg (n=115), Placebo (n=125)	SYMBICORT showed a median time to onset of bronchodilation (>15% improvement in FEV1) within 15 minutes. Maximum improvement occurred within 3 hours and was sustained over 12 hours.
Patients with moderate to severe asthma, 12 years and older	Sustained bronchodilation over 12 hours	Percent change from baseline in FEV1	12 hours post-dose on Day 1 and at Week 12	SYMBICORT 160/4.5 mcg (n=124), Budesonide 160 mcg (n=109), Formoterol 4.5 mcg (n=123), Budesonide 160 mcg + Formoterol 4.5 mcg (n=115), Placebo (n=125)	SYMBICORT maintained clinically significant bronchodilation over 12 hours without diminution of effect through 12 weeks of therapy.
Patients with moderate to severe asthma, 12 years and older	Improvement in asthma symptoms and rescue medication use	Symptom scores and albuterol rescue use	From Day 1 through Week 12	SYMBICORT 160/4.5 mcg	Reduction in asthma symptoms and albuterol rescue use, improvement in morning and evening PEF observed within 1 day of treatment and sustained over 12 weeks.

Approved Product Analysis: Symbicort (cont.)

14.2 Chronic Obstructive Pulmonary Disease (COPD) – Study 1

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
COPD patients, aged 40 years and older, FEV1 ≤ 50% predicted	Improvement in lung function (Pre-dose FEV1)	Percent change from baseline in pre-dose FEV1	Over 6 months	SYMBICORT 160/4.5 mcg (n=275), SYMBICORT 80/4.5 mcg (n=281), Budesonide 160 mcg + Formoterol 4.5 mcg (n=287), Budesonide 160 mcg (n=275), Formoterol 4.5 mcg (n=284), Placebo (n=299)	SYMBICORT 160/4.5 mcg showed a significant improvement in pre-dose FEV1 (10.7% from baseline) compared to Formoterol 4.5 mcg (6.9%) and placebo (2.2%). SYMBICORT 80/4.5 mcg did not show a significant difference compared to Formoterol 4.5 mcg.
COPD patients, aged 40 years and older, FEV1 ≤ 50% predicted	Improvement in lung function (1-hour post-dose FEV1)	Percent change from baseline in 1-hour post-dose FEV1	Over 6 months	SYMBICORT 160/4.5 mcg (n=275), SYMBICORT 80/4.5 mcg (n=281), Budesonide 160 mcg + Formoterol 4.5 mcg (n=287), Budesonide 160 mcg (n=275), Formoterol 4.5 mcg (n=284), Placebo (n=299)	SYMBICORT 160/4.5 mcg demonstrated a significant improvement in 1-hour post-dose FEV1 (22.6% from baseline) compared to Budesonide 160 mcg (4.9%) and placebo (4.1%).

Onset and Duration of Action and Progression of Improvement in Asthma Control

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
COPD patients, aged 40 years and older, FEV1 ≤ 50% predicted	Improvement in lung function (Pre-dose FEV1)	Percent change from baseline in pre-dose FEV1	Over 12 months	SYMBICORT 160/4.5 mcg (n=494), SYMBICORT 80/4.5 mcg (n=494), Formoterol 4.5 mcg (n=495), Placebo (n=481)	SYMBICORT 160/4.5 mcg showed significant improvement in pre-dose FEV1 (10.8% from baseline) compared to Formoterol 4.5 mcg (7.2%) & placebo (2.8%). SYMBICORT 80/4.5 mcg did not show significant diff. compared to Formoterol 4.5 mcg.
COPD patients, aged 40 years and older, FEV1 ≤ 50% predicted	Improvement in lung function (1-hr post-dose FEV1)	Percent change from baseline in 1-hour post-dose FEV1	Over 12 months	SYMBICORT 160/4.5 mcg (n=494), SYMBICORT 80/4.5 mcg (n=494), Formoterol 4.5 mcg (n=495), Placebo (n=481)	SYMBICORT 160/4.5 mcg showed a significant improvement in 1-hour post-dose FEV1 (24.0% from baseline) compared to placebo (5.2%).
COPD patients, aged 40 years and older, FEV1 ≤ 50% predicted	Onset of bronchodilation	FEV1 increase of 15% or greater from baseline	Serial measure-ments over 12 hrs (subset)	Study 1 (n=99), Study 2 (n=121)	Median time to onset of bronchodilation was 5 minutes post-dose. Maximum improvement in FEV1 occurred approximately 2 hours post-dose.
COPD patients, aged 40 years and older, FEV1 ≤ 50% predicted	Improvement in secondary endpoints	Morning and evening peak expiratory flow, reduction in rescue medication use	Over 12 months	SYMBICORT 160/4.5 mcg	Improvements in morning and evening PEF and reduction in rescue medication use supported the efficacy of SYMBICORT 160/4.5 mcg.

Approved Product Analysis: Advair

14.1 Study 1: Clinical Trial With ADVAIR DISKUS 100/50

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with asthma, 12 years and older	Withdrawals due to worsening asthma	Predefined withdrawal criteria (FEV1, PEF, rescue medication use, nighttime awakenings)	Over 12 weeks	ADVAIR DISKUS 100/50 (n=87), Fluticasone 100 mcg (n=85), Salmeterol 50 mcg (n=86), Placebo (n=77)	ADVAIR DISKUS had the lowest withdrawal rate due to worsening asthma (3%) compared to fluticasone (11%), salmeterol (35%), and placebo (49%).
Patients with asthma, 12 years and older	Improvement in lung function (FEV1)	Percent change from baseline in FEV1	Over 12 weeks	ADVAIR DISKUS 100/50 (n=87), Fluticasone 100 mcg (n=85), Salmeterol 50 mcg (n=86), Placebo (n=77)	ADVAIR DISKUS significantly improved FEV1 by 0.51 L (25%) compared to fluticasone (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L, 1%).
Patients with asthma, 12 years and older	Improvement in peak expiratory flow (PEF)	AM PEF, PM PEF	Baseline and endpoint (last available data)	ADVAIR DISKUS 100/50 (n=87), Fluticasone 100 mcg (n=85), Salmeterol 50 mcg (n=86), Placebo (n=77)	ADVAIR DISKUS improved AM PEF by 53 L/min and PM PEF by 35 L/min compared to baseline. Other treatments showed lesser or negative changes.
Patients with asthma, 12 years and older	Improvement in quality of life	Asthma Quality of Life Questionnaire (AQLQ)	Over 12 weeks	ADVAIR DISKUS 100/50 vs. Placebo	ADVAIR DISKUS improved AQLQ score by 1.25 points compared to placebo, indicating a clinically meaningful improvement in asthma-specific quality of life.

Approved Product Analysis: Advair (cont.)

Study 2: Clinical Trial With ADVAIR DISKUS 250/50

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with asthma, previously using inhaled corticosteroids	Withdrawals due to worsening asthma	Predefined withdrawal criteria (FEV1, PEF, rescue medication use, nighttime awakenings)	Over 12 weeks	ADVAIR DISKUS 250/50 (n=87), Fluticasone 250 mcg (n=87), Salmeterol 50 mcg (n=87), Placebo (n=88)	ADVAIR DISKUS had the lowest withdrawal rate due to worsening asthma (4%) compared to fluticasone (22%), salmeterol (38%), and placebo (62%).
Patients with asthma, previously using inhaled corticosteroids	Improvement in lung function (FEV1)	Percent change from baseline in FEV1	Over 12 weeks	ADVAIR DISKUS 250/50 (n=87), Fluticasone 250 mcg (n=87), Salmeterol 50 mcg (n=87), Placebo (n=88)	ADVAIR DISKUS significantly improved FEV1 by 0.48 L (23%) compared to fluticasone (0.25 L, 13%), salmeterol (0.05 L, 4%), and placebo (decrease of 0.11 L, decrease of 5%).
Patients with asthma, previously using inhaled corticosteroids	Improvement in peak expiratory flow (PEF)	AM PEF, PM PEF	Baseline and endpoint (last avail. data)	ADVAIR DISKUS 250/50 (n=87), Fluticasone 250 mcg (n=87), Salmeterol 50 mcg (n=87), Placebo (n=88)	ADVAIR DISKUS was superior to fluticasone, salmeterol, and placebo in improving both morning and evening PEF.
Patients with asthma, previously using inhaled corticosteroids	Improvement in quality of life	Asthma Quality of Life Questionnaire (AQLQ)	Over 12 weeks	ADVAIR DISKUS 250/50 vs. Placebo	ADVAIR DISKUS improved AQLQ score by 1.29 points compared to placebo, indicating a clinically meaningful improvement in asthma-specific quality of life.

Study 3: Clinical Trial With ADVAIR DISKUS 500/50

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with asthma, previously using inhaled corticosteroids	Improvement in morning peak expiratory flow (PEF)	Morning PEF (L/min)	12 weeks	N=503	Baseline PEF: ADVAIR DISKUS: 359 L/min, Fluticasone: 351 L/min, Concurrent therapy: 345 L/min

Approved Product Analysis: Advair (cont.)

Onset of Action and Progression of Improvement in Asthma Control

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with asthma, previously using inhaled corticosteroids or salmeterol	Onset of bronchodilation and improvement in asthma control	Percent change in FEV1 over 12 hours	First treatment day (Day 1)-out of 12 weeks	ADVAIR DISKUS 100/50 (n=87), Fluticasone 100 mcg (n=85), Salmeterol 50 mcg (n=86), Placebo (n=77)	Median time to onset of bronchodilation (≥15% improvement in FEV1) was within 30-60 minutes. Maximum improvement occurred within 3 hours, maintained for 12 hours.
Patients with asthma, previously using inhaled corticosteroids or salmeterol	Sustained bronchodilation effect over time	Percent change in FEV1 over 12 hours	Last treatment day (Week 12)-out of 12 weeks	ADVAIR DISKUS 100/50 (n=73), Fluticasone 100 mcg (n=65), Salmeterol 50 mcg (n=49), Placebo (n=26)	ADVAIR DISKUS showed sustained improvement in FEV1 over 12 hours on the last treatment day, with no diminution of effect over the 12 weeks.

Pediatric Patients

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Children with asthma, aged 4 to 11 years, symptomatic on low doses of inhaled corticosteroids	Improvement in lung function (FEV1)	Morning predose FEV1 (L)	Baseline and Endpoint (12 weeks)	ADVAIR DISKUS 100/50 (n=79 at baseline, n=69 at Endpoint), Fluticasone propionate 100 mcg (n=83 at baseline, n=75 at Endpoint)	ADVAIR DISKUS: FEV1 increased from 1.70 L to 1.88 L. Fluticasone: FEV1 increased from 1.65 L to 1.77 L. The findings support the efficacy of ADVAIR DISKUS in this age group.

Approved Product Analysis: Symbicort (cont.)

14.2 Chronic Obstructive Pulmonary Disease – Lung Function

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with COPD associated with chronic bronchitis	Improvement in lung function (predose FEV1)	Percent change in predose FEV1 from baseline	Over 24 weeks	ADVAIR DISKUS 250/50 (n=178), Salmeterol 50 mcg (n=177), Placebo (n=185)	ADVAIR DISKUS 250/50 showed a 165 mL (17%) improvement in predose FEV1 at Endpoint compared to salmeterol (91 mL, 9%) and placebo (1 mL, 1%).
Patients with COPD associated with chronic bronchitis	Improvement in lung function (2-hour postdose FEV1)	Percent change in 2-hour postdose FEV1 from baseline	Over 24 weeks	ADVAIR DISKUS 250/50 (n=178), Fluticasone 250 mcg (n=177), Placebo (n=185)	ADVAIR DISKUS 250/50 showed a 281 mL (27%) improvement in postdose FEV1 at Endpoint compared to fluticasone (147 mL, 14%) and placebo (58 mL, 6%).
Patients with COPD with history of exacerbations, pre-bronchodilator FEV1 <70% of predicted	Improvement in lung function (pre-bronchodilator FEV1)	Change in pre-bronchodilator FEV1 from baseline	Over 1 year	ADVAIR DISKUS 500/50 (n=1465), Fluticasone 500 mcg, Salmeterol 50 mcg, Placebo	ADVAIR DISKUS 500/50 showed a 113 mL (10%) improvement in pre-bronchodilator FEV1 compared to fluticasone (7 mL, 2%), salmeterol (15 mL, 2%), and placebo (-60 mL, -3%).

– Survival

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with COPD, aged 40-80 years, pre-bronchodilator FEV1 <60% of predicted	All-cause mortality (Primary Outcome)	Mortality rate (%)	Over 3 years	ADVAIR DISKUS 500/50 (n=6,112), Fluticasone 500 mcg, Salmeterol 50 mcg, Placebo	ADVAIR DISKUS 500/50: 12.6% mortality rate; Placebo: 15.2%; Salmeterol: 13.5%; Fluticasone: 16.0%. No significant improvement in survival with ADVAIR DISKUS 500/50 compared to placebo or individual components.
Patients with COPD, aged 40-80 years, pre-bronchodilator FEV1 <60% of predicted	Improvement in pulmonary function (Secondary Outcome)	Post-bronchodilator FEV1	Over 3 years	ADVAIR DISKUS 500/50 vs. Placebo, Fluticasone 500 mcg, Salmeterol 50 mcg	Pulmonary function (post-bronchodilator FEV1) improved with ADVAIR DISKUS 500/50, salmeterol, and fluticasone compared to placebo.

Approved Product Analysis: Symbicort (cont.)

– Exacerbations

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with COPD and history of exacerbations, pre-bronchodilator FEV1 of 33% predicted	Reduction in moderate/severe COPD exacerbations	Annual rate of exacerbations	Over 12 months	ADVAIR DISKUS 250/50 vs. Salmeterol 50 mcg	ADVAIR DISKUS 250/50 showed a 30.5% and 30.4% reduction in annual rate of moderate/severe exacerbations in two identical studies compared to salmeterol ($p<0.001$).
Patients with COPD and history of exacerbations, pre-bronchodilator FEV1 of 33% predicted	Reduction in exacerbations requiring oral corticosteroids	Annual rate of exacerbations requiring oral corticosteroids	Over 12 months	ADVAIR DISKUS 250/50 vs. Salmeterol 50 mcg	ADVAIR DISKUS 250/50 showed a 39.7% and 34.3% reduction in annual rate of exacerbations requiring oral corticosteroids in two identical studies compared to salmeterol ($p<0.001$).
Patients with COPD and history of exacerbations, pre-bronchodilator FEV1 <70% predicted	Reduction in moderate/severe COPD exacerbations	Rate of exacerbations	Over 1 year	ADVAIR DISKUS 500/50 vs. Placebo	ADVAIR DISKUS 500/50 showed a 25.4% reduction in moderate/severe exacerbations compared to placebo ($p<0.001$), but not significantly different when compared to fluticasone propionate or salmeterol.
Patients with COPD and history of exacerbations, pre-bronchodilator FEV1 <70% predicted	Reduction in moderate/severe COPD exacerbations	Rate of exacerbations	Over 3 years	ADVAIR DISKUS 500/50 vs. Placebo, Fluticasone 500 mcg, Salmeterol 50 mcg	ADVAIR DISKUS 500/50 showed a 25.1% reduction in moderate/severe exacerbations compared to placebo ($p<0.001$), and 9.0% and 12.2% reduction compared to fluticasone propionate and salmeterol, respectively.

Approved Product Analysis: Roflumilast

14.1 Chronic Obstructive Pulmonary Disease (COPD)

Study	Population	Primary Endpoint	Outcome Measures	Sample Size (N)	Results
Trial 5	Patients with severe COPD associated with chronic bronchitis and a history of exacerbations	Rate of moderate or severe exacerbations	Exacerbations per patient-year	DALIRESP (n=765), Placebo (n=760)	DALIRESP reduced exacerbations by 0.2 per patient-year (15% reduction), RR = 0.85 (95% CI: 0.74, 0.98)
Trial 6	Patients with severe COPD associated with chronic bronchitis and a history of exacerbations	Rate of moderate or severe exacerbations	Exacerbations per patient-year	DALIRESP (n=772), Placebo (n=799)	DALIRESP reduced exacerbations by 0.3 per patient-year (18% reduction), RR = 0.82 (95% CI: 0.71, 0.94)
Trial 5	Patients with severe COPD	Lung function	Change in FEV1 from baseline	DALIRESP (n=765), Placebo (n=760)	DALIRESP improved FEV1 by 39 mL compared to placebo (95% CI: 18, 60)
Trial 6	Patients with severe COPD	Lung function	Change in FEV1 from baseline	DALIRESP (n=772), Placebo (n=799)	DALIRESP improved FEV1 by 58 mL compared to placebo (95% CI: 41, 75)
Additional Data	Patients with severe COPD	Lung function	Change in FEV1 from baseline	Trial 5: DALIRESP (n=765), Placebo (n=760) Trial 6: DALIRESP (n=772), Placebo (n=799)	Trial 5: DALIRESP improved FEV1 by 39 mL (95% CI: 18, 60) | Trial 6: DALIRESP improved FEV1 by 58 mL (95% CI: 41, 75)

Summary of Failed Drug Candidates for COPD

Name of Drug	Clinical Trial Identifier	Reason for Termination / Drug Failure	Trend Analysis
Tezepelumab	NCT02555683	• Fevipiprant did not reduce the exacerbation compared to placebo over a 52-week period though is well tolerated in the treatment of subjects with uncontrolled severe asthma.	• This failure suggests that while Tezepelumab may have had an acceptable safety profile, its efficacy in reducing COPD exacerbations was not sufficient. The outcome emphasizes the challenge in translating positive asthma outcomes to COPD due to the different underlying disease mechanisms.
Lebrikizumab	NCT02546700	• It was inconclusive whether this trial achieved its endpoint reflecting the challenging path towards FDA approval.	• The inconclusive results highlight the difficulties in demonstrating clear, consistent efficacy in COPD trials, particularly for novel biologics. While lebrikizumab is effective in other respiratory conditions, its benefit in COPD, particularly for reducing exacerbations, may be limited.
Sildenafil	NCT01055405	• Concomitant treatment with sildenafil did not showed improvement on the results of pulmonary rehabilitation on exercise tolerance in patients with COPD.	• This outcome indicates that Sildenafil, effective for pulmonary arterial hypertension, may not translate its benefits to COPD-related exercise intolerance. It underscores the importance of targeting the right patient groups and ensuring the therapeutic mechanism aligns with disease pathology.
Roflumilast	NCT01630200	• This trial conducted in 80 participants failed to reach its endpoint as roflumilast did not show an atheroprotective effect in subjects with subclinical atherosclerosis in COPD.	• Roflumilast's failure in this trial suggests that its anti-inflammatory effects may not extend to cardiovascular protection in COPD patients. This underscores the complexity of addressing comorbid conditions in COPD and suggests a need for combination therapies or more targeted approaches.
Ferric carboxymaltose	GDCT0284728	• Although FCM did not improve oxygenation over 8 weeks in subjects with COPD, however this treatment is well tolerated and produced improvements in exercise capacity and functional limitation caused by breathlessness.	• Although FCM showed some functional benefits, the lack of improvement in oxygenation was critical to its failure. This highlights the importance of selecting primary endpoints that reflect the most significant and meaningful outcomes for COPD patients.

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Common Failure Points in COPD Clinical Trials

1. Heterogeneity of the Disease:

• Variation in Symptoms: COPD presents with a wide range of symptoms and severity, making it difficult to standardize trial criteria.

• Comorbidities: Many patients with COPD have other chronic conditions like cardiovascular diseases, which can complicate trial outcomes and data interpretation.

2. Patient Recruitment and Retention:

• Eligibility Criteria: Strict inclusion and exclusion criteria often limit the pool of eligible participants.

• Patient Burden: COPD patients often experience significant physical limitations, which can make frequent clinic visits and participation in lengthy trials difficult.

3. Long-Term Trials:

• Slow Disease Progression: COPD progresses slowly, requiring long-term trials to observe meaningful changes, increasing costs and logistical challenges.

• Compliance: Ensuring patient adherence to treatment protocols over extended periods can be difficult, affecting the reliability of the trial data.

4. Endpoints and Outcome Measures:

• Diverse Outcome Measures: The selection of appropriate and meaningful endpoints is challenging due to COPD's multifaceted nature.

• Regulatory Expectations: Different regulatory agencies may have varying requirements for primary and secondary endpoints.

5. Biomarker Development:

• Lack of Robust Biomarkers: Identifying reliable biomarkers for disease progression and treatment response remains an ongoing challenge, limiting personalized treatment approaches in trials.

6. Environmental and Behavioral Factors:

• Impact of Smoking: As smoking is a major risk factor for COPD, trials must account for smoking status, cessation, and relapse, which can confound results.

• Environmental Exposures: Variability in patients' exposure to environmental pollutants can also affect trial outcomes.

7. Technological and Methodological Challenges:

• Use of Advanced Imaging: Advanced imaging is costly and may not be widely available or standardized across trial sites.

• Remote Monitoring: Incorporating telemedicine and remote monitoring technologies requires overcoming challenges in data integration and patient compliance.

8. Ethical Considerations:

• Placebo Control: In severe cases, it may be unethical to withhold standard treatments, complicating trial design.

• Informed Consent: Given the potential severity of COPD and its impact on cognitive function, obtaining informed consent can sometimes be challenging.

Safety Concerns and Standard of Care Treatment Options for COPD

Safety Concerns in COPD

1. **Exacerbations:** A major safety concern, exacerbations are often triggered by respiratory infections or environmental pollutants and can lead to significant morbidity, hospitalizations, and increased healthcare costs. Frequent exacerbations accelerate lung function decline and are associated with higher mortality rates.
2. **Cardiovascular Complications:** COPD is often associated with an increased risk of cardiovascular diseases. The chronic systemic inflammation present in COPD patients contributes to the development and progression of these cardiovascular conditions.
3. **Respiratory Infections:** COPD patients are more susceptible to respiratory infections due to compromised lung function and immune response. These infections can trigger exacerbations and lead to severe complications. Preventive measures, including vaccinations and prompt treatment, are critical.
4. **Osteoporosis:** The use of systemic corticosteroids in COPD treatment, along with the chronic inflammation and reduced physical activity associated with the disease, can lead to osteoporosis. This increases the risk of fractures in COPD patients.
5. **Muscle Wasting and Weakness:** COPD is associated with muscle wasting and weakness, partly due to chronic inflammation, reduced physical activity, and the use of certain medications. This can lead to decreased exercise capacity and increased disability.

Standard of Care Treatment Options

1. **Pharmacological Treatments:**
   - Bronchodilators (Short-Acting and Long-Acting)
   - Inhaled Corticosteroids (ICS)
   - Phosphodiesterase-4 Inhibitors
   - Oral Corticosteroids
2. **Non-Pharmacological Treatments:**
   - Pulmonary Rehabilitation
   - Smoking Cessation
   - Vaccinations
   - Oxygen Therapy
3. **Surgical Interventions:**
   - Lung Volume Reduction Surgery (LVRS)
   - Lung Transplantation
   - Bronchial Rheoplasty
4. **Experimental and Emerging Therapies:**
   - Monoclonal Antibodies
   - Stem Cell Therapy and Genetic Therapies
5. **Lifestyle Modifications:**
   - Nutritional Support and Physical Activity
6. **Psychosocial Support:**
   - Mental Health and Support Groups

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Strategies to Improve Clinical Trial Protocols for FDA Approval

1. Patient Selection Criteria:

- Include patients who reflect the real-world diversity of COPD while excluding those with severe comorbidities that might confound results.
- Incorporate biomarkers to identify subgroups of patients more likely to respond to specific treatments.

2. Standardized Definitions and Endpoints:

- Utilize standardized definitions and endpoints as outlined by international bodies such as the GOLD and the FDA.
- Use composite endpoints that combine multiple measures to provide a more comprehensive assessment of efficacy.

3. Enhanced Trial Design and Methodology:

- Use adaptive trial designs that allow for modifications based on interim results, improving efficiency and ethical management.
- Implement robust support systems to keep patients engaged.

4. Improved Data Collection and Management:

- Use Electronic Data Capture systems to streamline data collection, ensure consistency, and facilitate real-time data monitoring.
- Utilize telemedicine and remote monitoring tech to gather continuous data on patient health and adherence.

5. Regulatory Insights and Compliance:

- Engage with the FDA early and throughout the trial process to ensure alignment with regulatory expectations.
- Maintain meticulous records of trial protocols, amendments, adverse events, and patient outcomes.

6. Incorporating Real-World Evidence (RWE):

- Use RWD from electronic health records to complement clinical trial data, providing insights into treatment effectiveness and safety in diverse populations.
- Design hybrid trials that merge randomized controlled trials with RWD to enhance generalizability.

7. Addressing Patient-Centered Outcomes:

- Establish patient advisory boards to provide input on trial design, endpoints, and recruitment strategies.
- Incorporate Patient-Reported Outcomes to capture patient perspectives on symptoms, treatment satisfaction, and quality of life.

8. Advanced Statistical Methods:

- Implement Bayesian statistical methods to incorporate prior knowledge and adaptively update trial results, enhancing the robustness of findings.
- Use multiplicity adjustments to control for the increased risk of false positives when evaluating multiple endpoints.

Notable Key Opinion Leaders in COPD Research

Name	Specialty	Designation	Location	Brief Bio
Philip G Bardin (MBBCh, MRCP, FRACP)	Pulmonology/ Pneumology; Sleep Medicine	Professor, Monash University	Victoria, Australia	Philip G. Bardin is a distinguished Professor of Respiratory Medicine at Monash University and serves as the Director of Respiratory and Sleep Medicine at Monash Health in Melbourne, Australia. Additionally, he holds an adjunct professorship at the University of Melbourne. Professor Bardin has been the recipient of several prestigious awards and grants like National Health and Medical Research Council (NHMRC) Grants, Asthma Foundation Awards and Monash Health Excellence Awards. He is recognised for investigation of obstructive lung diseases (particularly virusasthma-COPD exacerbations) and has conducted extensive research of new asthma and COPD therapies.
Christine R Jenkins (MBBS, MD, FRACP)	Thoracic Surgery; Pulmonology/ Pneumology	Clinical Professor, University of Sydney	New South Wales, Australia	Professor Jenkins is a globally respected expert in asthma and COPD. As a Professor of Respiratory Medicine, Christine R. Jenkins has been instrumental in shaping the academic and research landscape in respiratory health. Additionally, at the George Institute, she leads the Respiratory Group, focusing on global respiratory health challenges, particularly in low and middle-income countries. Professor Jenkins has received numerous awards amongst which are TSANZ Society Medal. She is involved with the American Thoracic Society (ATS) and the European Respiratory Society (ERS) and has published peer-reviewed articles.
Gregory G King (MB ChB, PhD, FRACP)	Pulmonology/ Pneumology	Professor, University of Sydney	New South Wales, Australia	Gregory G. King is a highly respected Professor of Respiratory Medicine at the University of Sydney. He also holds a Senior Staff Specialist position at Royal North Shore Hospital and is an Associate Investigator at the Woolcock Institute of Medical Research, where he leads cutting-edge research in respiratory diseases. Professor King is renowned for his work in lung imaging, particularly using hyperpolarized gas MRI, which has provided new insights into how structural changes in the lungs impact respiratory function in diseases like asthma and COPD. His research has had a significant impact on understanding how these diseases develop and how they can be better managed. Professor King is actively involved with TSANZ, where he has received the Society's Research Medal for his outstanding contributions to the field. His publications includes works titled "New Physiological measurements in COPD".
Christine F McDonald (MBBS, MD, FRACP)	Internal Medicine; Pulmonology/ Pneumology	Medical Director, Institute for Breathing and Sleep	Victoria, Australia	Christine F. McDonald is a leading respiratory physician and the Director of the Institute for Breathing and Sleep at Austin Health in Melbourne, Australia. She is also a Clinical Professor in the Department of Medicine at the University of Melbourne. Her work is internationally recognized, particularly in the areas of chronic obstructive pulmonary disease (COPD) and sleep-related breathing disorders. She has served as the president of TSANZ, reflecting her leadership and influence in the field of respiratory medicine. Professor McDonald has been involved in numerous global health initiatives aimed at improving respiratory care and sleep medicine practices worldwide including authoring articles focusing on asthma, COPD and oxygen therapy.
Peter G Gibson (MBBS, D Med)	Pulmonology/ Pneumology; Sleep Medicine	Professor of Medicine, the University of Newcastle and Senior Respiratory Physician, John Hunter Hospital	New South Wales, Australia	Peter G. Gibson is a highly esteemed Professor of Medicine at the University of Newcastle and a senior respiratory physician at John Hunter Hospital. With a medical degree from the University of Sydney and a Ph.D. focused on airway inflammation, Professor Gibson is recognized globally for his pioneering research in asthma and chronic obstructive pulmonary disease (COPD). His work has led to significant advancements in understanding airway inflammation and its management, influencing clinical practices worldwide. Professor Gibson has received numerous accolades, including the Thoracic Society of Australia and New Zealand (TSANZ) Society Medal and multiple fellowships from the National Health and Medical Research Council (NHMRC). He has also contributed to over 200 peer-reviewed publications, including influential studies on biomarkers like Fractional Exhaled Nitric Oxide (FeNO) in asthma management. His ongoing work at the University of Newcastle and John Hunter Hospital focuses on translating research into improved patient care.

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If you would like further information on how iNGENū CRO can assist you to conduct your clinical trial, please contact Dr Sud Agarwal or Adam Moodie:

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