International Journal of Chronic Obstructive Pulmonary Disease

Dovepress
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ORIGINAL RESEARCH

# Impact of Increased Use of Single-Inhaler Triple Therapies on COPD Exacerbation Rates, Mortality, and Total Costs: PROMETHEUS France

Gaëtan Deslee[1], Héloïse Russo[2], Caroline Fabry-Vendrand[2], David Koskas[2], Gabriel Thabut[2], John P Bell[3], Melissa Caplen[4], Prachi Devendra Bhatt[4], Jennifer Carioto[4], Bruce Pyenson[4], Pierre-Régis Burgel[5]

[1]Service de Pneumologie, INSERM UMRS-1250, Hospital Universitaire de Reims, Reims, France; [2]Astrazeneca, Medical Department, Courbevoie, France; [3]AstraZeneca, Global Respiratory & Immunology, BioPharmaceuticals Medical, Cambridge, UK; [4]Milliman,New York, NY, USA; [5]Service de Pneumologie, Hôpital Cochin, Assistance Publique Hôpitaux de Paris et Université Paris Cité, Institut Cochin, INSERM U1016, Paris, France

Correspondence: Pierre-Régis Burgel, Service de Pneumologie, Hôpital Cochin, 27 rue du Faubourg Saint Jacques, Paris, 75014, France, Email pierre-regis.burgel@aphp.fr



**Background:** COPD is the seventh-leading cause of death in France. The randomized controlled trials ETHOS (NCT02465567) and IMPACT (NCT02164513) have demonstrated a reduction in exacerbations (primary endpoint) and suggest a decrease in mortality (secondary endpoint) with single-inhaler triple therapy (SITT)—containing a long-acting beta-2 agonist, long-acting anticholinergics, and an inhaled corticosteroid—in patients with COPD. No study has evaluated the potential impact of increased SITT use in France.

**Objective:** To evaluate the impact of increased SITT use in COPD on exacerbations, mortality, and medical costs in France.

**Methods:** A stochastic model was constructed using GOLD therapeutic recommendations and literature data on patient characteristics, prevalence, incidence, treatment distribution, COPD severity and treatment changes, mortality, and exacerbations to model the French COPD population. Two scenarios were studied: Status Quo (no increase in SITT use) and Increased SITT, using the GOLD stage and exacerbation history to initiate SITT treatment in modeled patients, considering the annual probabilities of transitioning from one GOLD stage to another over a 10-year period.

**Results:** Increased SITT use compared to the Status Quo over a 10-year period could reduce severe and moderate exacerbations by 8.0% and 9.2%, respectively, all-cause mortality by 8.5%, and medical costs by 875 million euros (excluding additional SITT costs), and extend the life of patients by 0.6 years per patient with COPD.

**Conclusion:** The model shows that increased SITT use in France, in line with recent recommendations, could be associated with a reduction in exacerbation rates, mortality, and costs in patients with COPD.

**Keywords:** COPD, single-inhaler triple therapy, population model

## Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition resulting from gene-environment interactions leading to airways (bronchitis, bronchiolitis) and/or alveolar damage causing persistent airflow obstruction and chronic respiratory symptoms (dyspnea, cough, sputum and/or exacerbation).[1] The main environmental exposure associated with COPD is tobacco smoking, but other toxic particles and gases from air pollution can be involved. COPD is a progressive disease where patients gradually experience a worsening in lung function. Patients with COPD are also at an increased risk of comorbid diseases including cardiovascular events, metabolic diseases, anemia, mental health issues, changes in sleep, and osteoporosis.[2] Importantly, in 2021, COPD was the seventh-leading cause of death in France, and rates are expected to increase, with a concomitant increase in more severe cases or those with GOLD stage 3 and 4.[3,4]

Received: 8 May 2025
Accepted: 15 October 2025
Published: 17 November 2025

Pharmacological treatment in COPD relies mainly on inhaled therapies, including rescue therapy provided by short-acting beta-2 agonists (SABA) and short-acting anticholinergics (SAMA), and maintenance therapies including long-acting beta-2 agonists (LABA), long-acting anticholinergics (LAMA), and inhaled corticosteroids (ICS).[5,6]

In 2023, the GOLD guidelines were updated to place an increased focus on exacerbations, which are defined as an acute worsening of COPD symptoms. Previously, patients were categorized into four types—A, B, C, and D—and in 2023 this was modified to combine C and D into a new type, GOLD E, representing patients with two or more moderate exacerbations or at least one severe (leading to hospitalization) exacerbation per year.[5,6] For newly diagnosed patients who are classified as GOLD E, the guidelines recommend initiating treatment with LABA/LAMA dual therapy. Patients who have concomitant asthma or a blood eosinophil count of 300 cells/μL or higher may benefit from the addition of an ICS. If an escalation of therapy is recommended in patients on LAMA/LABA dual therapy due to exacerbations or a blood eosinophil count of 100 cells/μL or higher, GOLD recommends to use triple therapy via the addition of an ICS.[5,6] While the GOLD document recommends use of triple therapy with either multiple inhaler triple therapy (MITT) or single inhaler triple therapy (SITT), there is data to suggest that compliance is improved when patients are prescribed a single inhaler.[7,8] Accordingly, the GOLD document states that SITT may be more convenient and effective.[5,6]

Exacerbations are important to the pathogenesis of COPD, as they contribute to an increased rate of lung function decline as well as a decline in the patient's functional health status, and an increased cost and healthcare resource burden.[5] A study that evaluated COPD hospitalizations between 2010 and 2012 in France observed that more than 8% of hospitalizations resulted in patient death.[9] A study specifically evaluating French patients that required intensive care unit (ICU) admission and mechanical ventilation for management of their exacerbation found that 23% of the patients died in the ICU, while 41% died within one year of admission.[10] In a prospective French cohort including 1824 patients, mortality rate during the four years following hospital admission for acute exacerbation of COPD was 45%.[11]

The healthcare resource burden of COPD is significant as well. A study that evaluated patients hospitalized due to COPD exacerbations from 2007 to 2012 found a 15.5% increase in the number of admissions over the six years, along with an increase in costs from €602 million to €678 million.[12] In addition to direct costs associated with hospitalization, a 2003 study estimated that patients with COPD also incurred an average indirect annual cost of €1,078.[13]

The ETHOS and IMPACT studies both evaluated the benefits of SITT and demonstrated that patients who were placed on SITT showed a reduction in exacerbation rates compared to those on dual therapy and suggested a reduction in mortality.[14,15] To date, there have not been any studies performed that evaluate the impact of increased SITT utilization on the French COPD population. In this study, we aim to estimate the impact of broader SITT utilization by using a 10-year stochastic microsimulation model based on the French COPD population.

# Methods

## Model Approach

This model was developed based on the US PROMETHEUS study, which modeled the impact of increased SITT use in the United States COPD population.[16] This was a multi-year stochastic microsimulation model that projected outcomes for patients with COPD over 10 years, from 2025 to 2034. Our model incorporates new entrants into the model annually and allows for multiple scenarios. The goal was to estimate the impact of increased SITT utilization on the number of moderate and severe exacerbations as well as costs. The model was developed to approximate the French COPD population using assumptions from literature-based sources. These sources were used to assign patient characteristics such as sex at birth, age, COPD incidence rates, baseline treatment distributions, changes in COPD severity/GOLD stage, mortality rates in the general and COPD populations, and exacerbation rates. We describe the sources used for each assumption in the supplementary materials. Patients were assigned a GOLD severity stage at the start of modeling and were eligible for stage progression annually. The baseline model also incorporated the projected annual population growth in the French population over the modeled 10-year timeframe.

## Simulation Overview, Model Populations, and Simulation Scenarios

This projection model was conducted over a 10-year timeframe, from 2025 to 2034, and it modeled 1,000 simulations with annual probabilistic changes made to the baseline patient characteristics. This allowed us to model a natural progression of COPD severity as well as annual exacerbations (both moderate and severe). Patients who experienced an exacerbation were modeled with a higher probability of COPD disease progression, and we also changed the probabilistic modeling based on the COPD therapies that the patient was receiving (whereby patients on double therapies would be more likely to progress than those on single therapies). Newly diagnosed patients with COPD were introduced to the model yearly, and patients exited the model if they died or if they reached 100 years of age.

There were two scenarios modeled, the Status Quo and the Increased SITT models:

- Status Quo (Baseline): This model simulated the current French COPD population under current prescribing patterns with no anticipated changes in SITT prescribing habits, assuming that any new triple therapy users would be prescribed SITT rather than MITT (Figure 1). After a change in GOLD stage or an emergency department or inpatient visit, treatment transition probabilities were determined using data from the AVOIDEx trial each year.[17]
- Increased SITT: This model simulated the impact of an increase in SITT utilization over our study timeframe, which was modeled based on prescribing recommendations in both GOLD 2023 and 2025 guidelines (Figure 2). While this model was originally developed utilizing GOLD 2023 guidelines, the model and its outputs are also valid when utilizing the most recent 2025 guidelines, as prescribing recommendations have not changed. Baseline assumptions used to develop patient characteristics were the same as what was used in the Status Quo model, with the key exception of medication transitions as this model transitions additional patients to SITT therapy.

In addition to reporting results for these two modeled scenarios, we also define two subsets of the population: the total and flagged populations. The flagged population is the subset of the total population that qualifies for SITT therapy according to GOLD recommendations (regardless of actual modeled medication use). The flagged and total population were sampled and simulated separately, leading to variations in patient counts and outcomes for the non-flagged population.

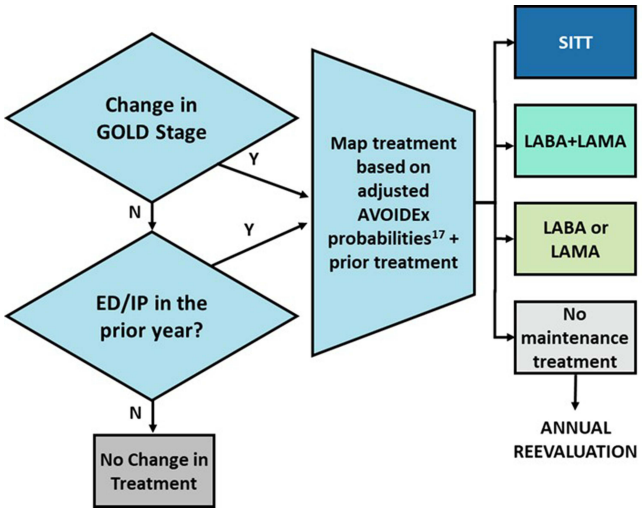


**Figure 1** Status Quo Medication Transition.
**Note**: If a patient started on SITT, no further transitions were made.
**Abbreviations**: N, No; Y, Yes; ED, emergency department; IP, inpatient admission; SITT, single-inhaler triple therapy; LABA, long-acting beta-2 agonist; LAMA, long-acting anticholinergic.


https://doi.org/10.2147/COPD.S539055

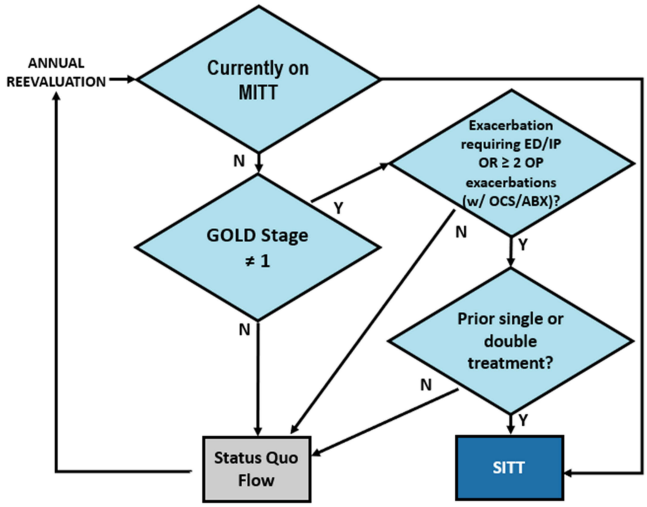


**Figure 2** Increased SITT Medication Transition.
**Note**: If a patient started on SITT, no further transitions were made.
**Abbreviations**: N, No; Y, Yes; ED, emergency department; IP, inpatient admission; OP, outpatient visit; SITT, single inhaler triple therapy; LABA, long-acting beta-2 agonist; LAMA, long-acting anticholinergic.

We also determined the number of years of life extended for both the total and flagged populations under the Increased SITT model compared to the Status Quo model. This was done by first utilizing standard mortality tables to determine the years of life expected by age and sex. We then adjusted these rates to adjust for the higher mortality rates associated with patients with COPD and used this to determine the expected years of life remaining.

## Statistical Analyses

We estimated the number and rate of projected deaths as well as the moderate and severe exacerbations for both the total and flagged populations under both models (Status Quo and Increased SITT). We determined the modeled changes in mortality, life-years, and exacerbations for the flagged and total populations separately. Last, we determined the number needed to treat (NNT) required for the Increased SITT model to increase life expectancy by one year.

# Results

At the start of our model, our study population was 46.7% female and had an average age of 69.6 years old. In terms of COPD severity, 26.0% of patients were in GOLD Stage 1 (mild), 49.4% were in GOLD Stage 2, 17.1% were in GOLD Stage 3, and 7.6% were in GOLD Stage 4 (very severe). Demographic information for the total and flagged populations across all 10 years of this study for both the Status Quo and Increased SITT models is shown in Table 1. Regarding medication therapy distribution at baseline, the largest group of patients with COPD were receiving no maintenance therapy at 27.6%, 16.5% of patients received LABA or LAMA, 8.3% received ICS + LABA or ICS + LAMA, 23.3% received LABA + LAMA, 14.7% received MITT, and 9.7% received SITT.

Figure 3 displays the medication therapy distribution at baseline through end of year 10 for the total population under the Status Quo model and Figure 4 displays the distribution for the Increased SITT model. At the end of the 10 years, 27% of patient years used SITT in the Status Quo model compared to 42% in the Increased SITT model, where the SITT use increased significantly from 6% at the beginning of our modeling.

**Table 1** Study Population Demographics, COPD Severity and Medication Therapy by Scenario

| | Baseline | Across All 10 Years | | | |
|---|---|---|---|---|---|
| | Total Population | Total Population | | Flagged Population | |
| | | Status Quo | Increased SITT | Status Quo | Increased SITT |
| Total years of life | 2.7M | 28.1M | 28.3M | 7.6M | 7.8M |
| Female, % | 46.7% | 46.5% | 46.5% | 41.8% | 41.7% |
| Average age | 69.6 | 70.5 | 70.5 | 71.4 | 71.6 |
| **GOLD Stage Distribution** | | | | | |
| GOLD Stage 1 | 26.0% | 13.0% | 12.9% | 1.7% | 1.7% |
| GOLD Stage 2 | 49.4% | 48.5% | 48.3% | 40.0% | 39.9% |
| GOLD Stage 3 | 17.1% | 30.1% | 30.2% | 40.7% | 40.6% |
| GOLD Stage 4 | 7.6% | 8.5% | 8.6% | 17.5% | 17.8% |
| **Medication Distribution** | | | | | |
| No Maintenance | 27.6% | 24.8% | 24.7% | 0.0% | 0.0% |
| LABA or LAMA | 16.5% | 14.3% | 13.2% | 3.7% | 0.0% |
| ICS+LABA or ICS+LAMA | 8.3% | 4.1% | 3.6% | 2.0% | 0.0% |
| LABA+LAMA | 23.3% | 27.1% | 20.5% | 25.1% | 0.0% |
| MITT | 14.7% | 6.3% | 0.0% | 23.8% | 0.0% |
| SITT | 9.7% | 23.3% | 38.0% | 45.4% | 100.0% |

**Notes**: Total years of life represents the sum of all life years that patients contribute to the 10-year time frame modeled.
**Abbreviations**: SITT, single inhaler triple therapy; LABA, long-acting beta-2 agonist; LAMA, long-acting anticholinergic; ICS, inhaled corticosteroids; MITT, multiple inhaler triple therapy.

Figure 5 shows the annual moderate and severe exacerbation rates for the Status Quo and Increased SITT models over the 10 years. For the flagged population, increased SITT utilization reduced the moderate exacerbation count by about 505,700 (a 9.2% reduction) and the severe exacerbation count by about 65,700 (an 8.0% reduction). This results in a total reduction in exacerbations of 571,400 (a 9.0% reduction). Over the 10 years, the flagged population would experience total savings of €874.74 million, €97.61 million in moderate exacerbation costs and €777.13 million in severe exacerbation costs due to reductions in severe and moderate exacerbations (Table 2). Additionally, all-cause mortality would decrease by 8.5% or a reduction of 39,000 deaths.

Under the Increased SITT model, the flagged population is also expected to have an increase in the number of years of life remaining. Figure 6 describes the impact of increased SITT utilization for the flagged and total populations. Increased SITT use led to extended life-years for all age groups, with an overall increase in patient life by 0.5 years per flagged COPD patient. The greatest benefit was seen in patients aged 46 to 54, with an increase of 0.9 years in the flagged population and 0.3 years in the total population. In addition, the number needed to treat to extend the average life of a patient with COPD by one year was 70 in the total population and 20 in the flagged population.

## Sensitivity Testing

In order to determine the impact of varying the baseline assumptions on the modeled results, we conducted sensitivity testing on three variables. We tested variations of: 1) the base case GOLD stage distribution, 2) the exacerbation rates,

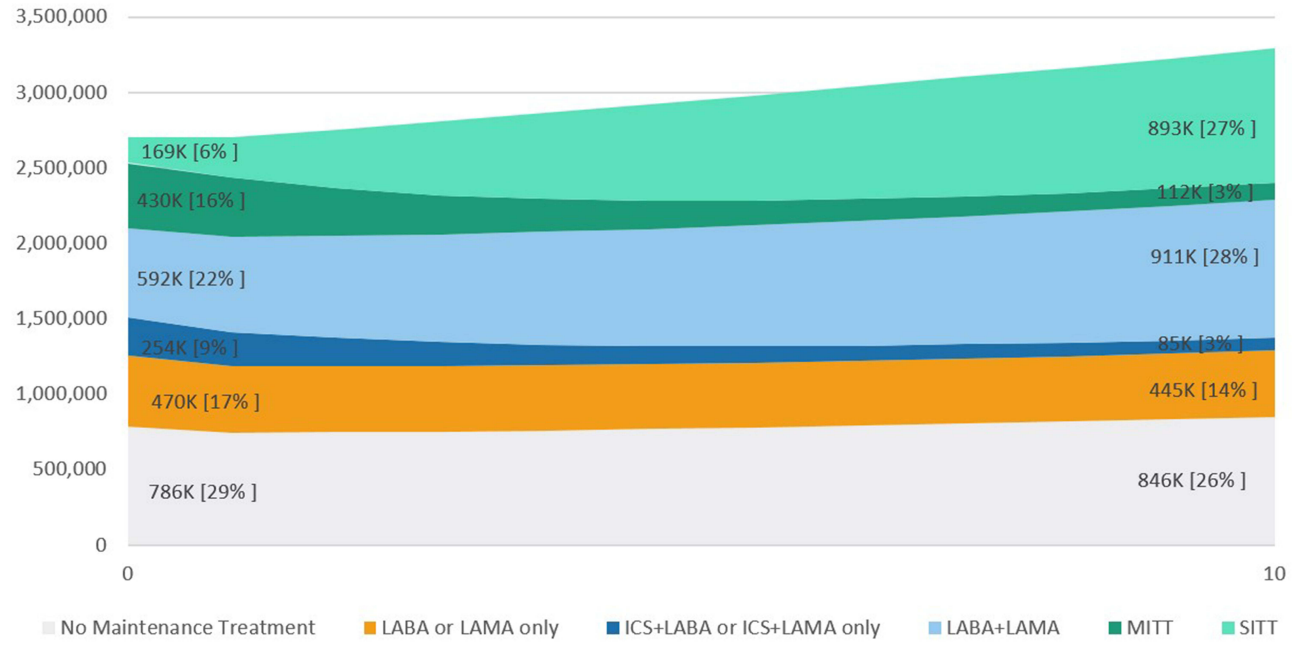


**Figure 3** Status Quo Patient Years by Treatment for the Total Population – Over 10 Years.

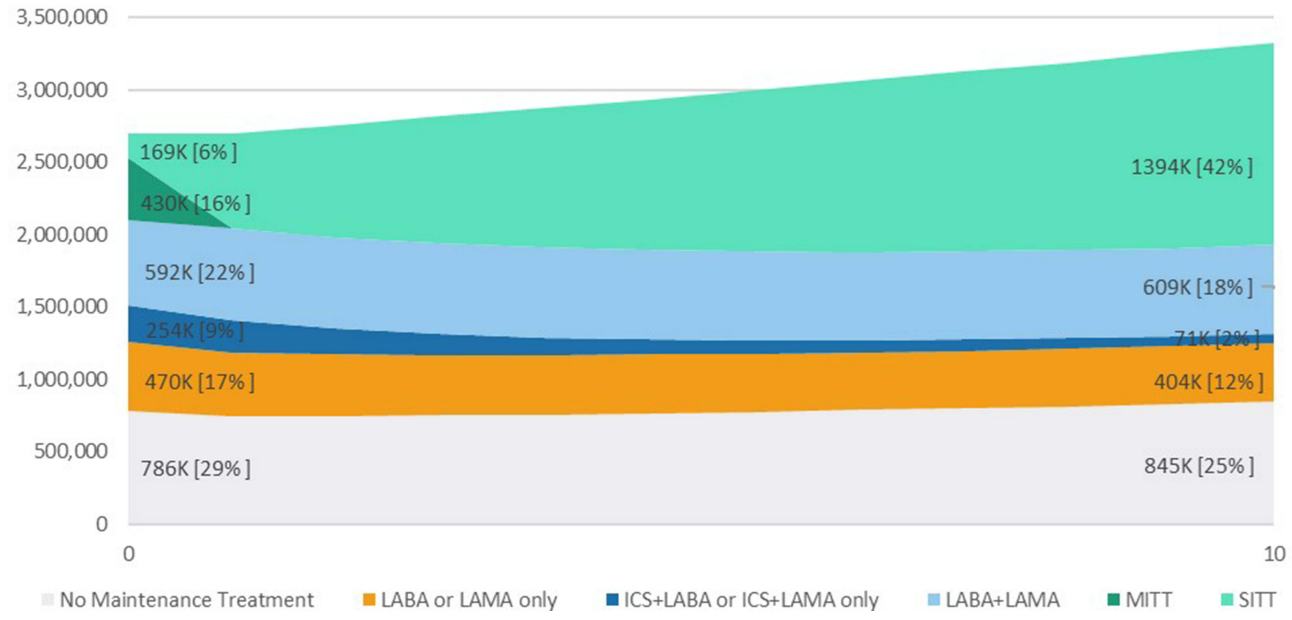


**Figure 4** Increased SITT Patient Years by Treatment for the Total Population – Over 10 Years.

and 3) the COPD population growth, to determine their impact on Increased SITT deaths and exacerbation counts, and exacerbation cost outcomes.

We sensitivity tested the GOLD stage distribution by assuming that the GOLD stage distributions were 10% more or 10% less severe than the current assumption by shifting more/less patients to a higher or lower GOLD stage, respectively. This was achieved by shifting patients modeled GOLD stage at the beginning of the 10-year model. We also evaluated the impact

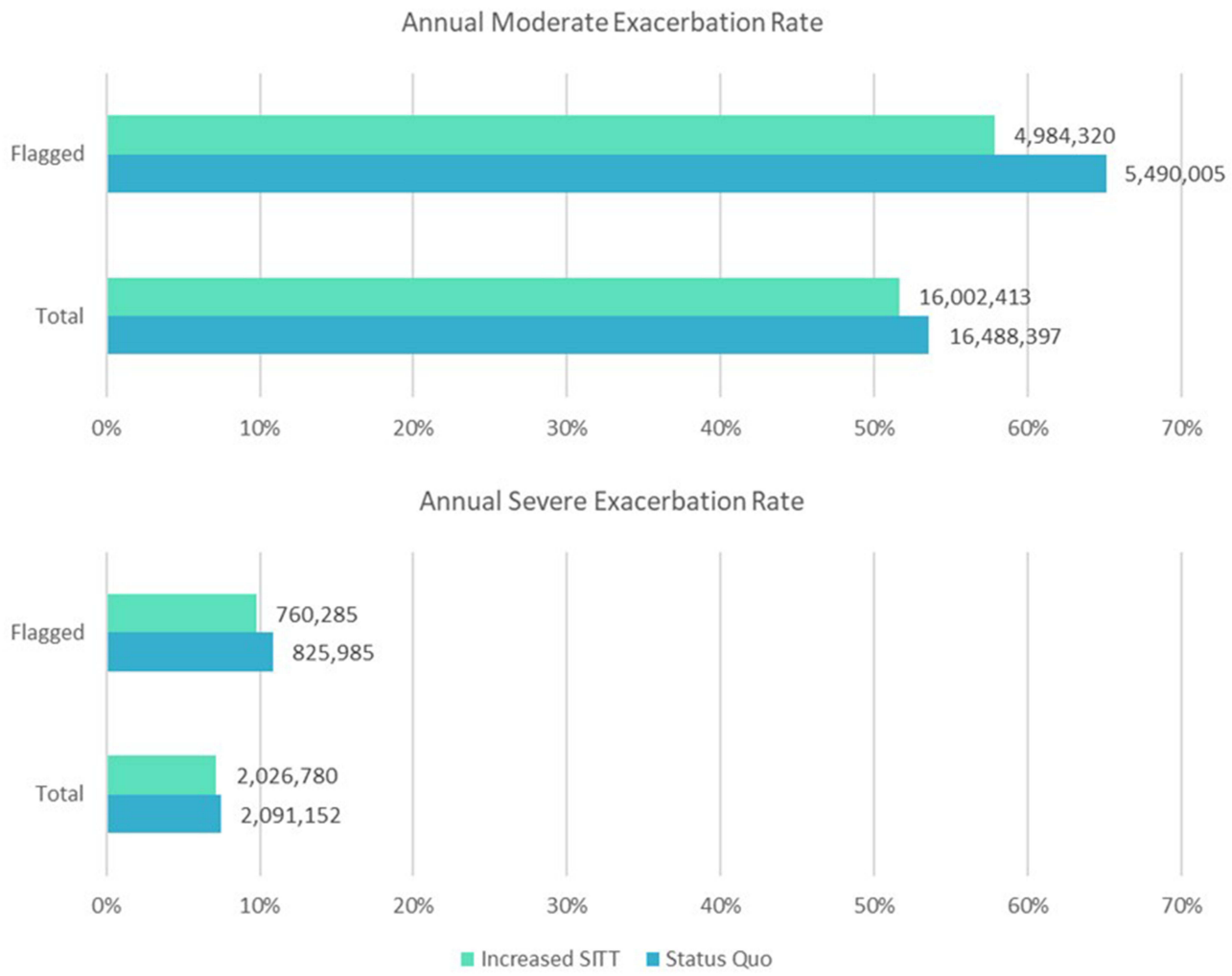


**Figure 5** Annual COPD Moderate and Severe Exacerbation Rates (%) – Over 10 years.

of increasing or decreasing the exacerbation rates (both moderate and severe) by 10%, which was a numerical change in rates. Last, we modeled a 1% higher or lower COPD population growth rate to determine its impact on outcomes as well.

In Figure 7, we display the results of these sensitivity tests for the comparison of the Increased SITT and Status Quo models for the flagged population. We found that modifying the exacerbation rates had the largest impact on the

**Table 2** Mortality, Life Years, and Exacerbation Outcomes by Population – Over 10 years

| | Total Population | | | | Flagged Population | | | |
|---|---|---|---|---|---|---|---|---|
| | Status Quo | Increased SITT | Absolute Difference | Percent Change | Status Quo | Increased SITT | Absolute Difference | Percent Change |
| Total patient years | 28.11M | 28.3M | 195.38K | 0.7% | 7.6M | 7.77M | 167.65K | 2.2% |
| Death counts | 1.8M | 1.76M | 36.98K | −2.1% | 574.09K | 535.06K | −39.03K | −6.8% |

(*Continued*)

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**Table 2** (Continued).

| | Total Population | | | | Flagged Population | | | |
|---|---|---|---|---|---|---|---|---|
| | **Status Quo** | **Increased SITT** | **Absolute Difference** | **Percent Change** | **Status Quo** | **Increased SITT** | **Absolute Difference** | **Percent Change** |
| **Clinical Outcomes** | | | | | | | | |
| All-cause mortality rate (%) | 6.2% | 6.0% | −0.2% | 2.7% | 7.3% | 6.7% | −0.6% | −8.5% |
| Severe exacerbation counts | 2.09M | 2.03M | 64.37K | −3.1% | 825.99K | 760.29K | −65.7K | −8.0% |
| ≥1 severe exacerbation rate (%) | 7.4% | 7.2% | −0.3% | −3.7% | 10.9% | 9.8% | −1.1% | −9.9% |
| Moderate exacerbation counts | 16.49M | 16M | 485.98K | −2.9% | 5.49M | 4.98M | −505.69K | −9.2% |
| ≥1 moderate exacerbation rate (%) | 53.6% | 51.7% | −1.9% | −3.6% | 65.1% | 57.8% | −7.3% | −11.2% |
| **Cost Outcomes** | | | | | | | | |
| Severe exacerbation cost, € | 25.09B | 24.33B | 760.84M | −3.0% | 9.97B | 9.19B | −777.13M | −7.8 |
| Moderate exacerbation cost, € | 3.22B | 3.12B | 93.74M | −2.9% | 1.08B | 980.74M | −97.61M | −9.1% |

**Notes**: Each scenario was simulated separately, and therefore there may be slight variation in the outcomes for the non-flagged population. B = billions (1000 millions), M = millions (1000 thousands), K = thousands (10 hundreds).

reductions to death counts, exacerbation counts, and costs. Conversely, increasing the COPD population growth rates by 1% from the base case generally had the smallest impact on the results across all populations and modeled scenarios. Additional details on the sensitivity testing are also provided in Supplemental Table 1.

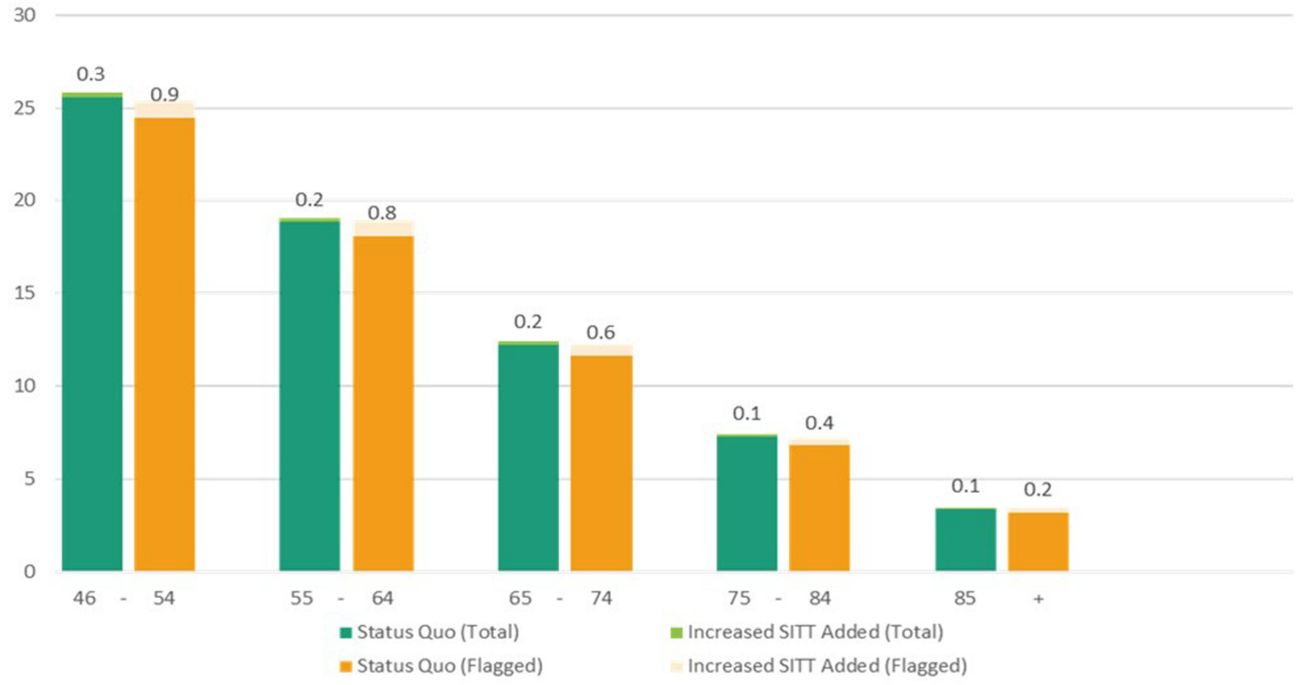


**Figure 6** Average Years of Life Remaining and Extended Life-years per Flagged COPD Patient, by Age Band – Over 10 Years.

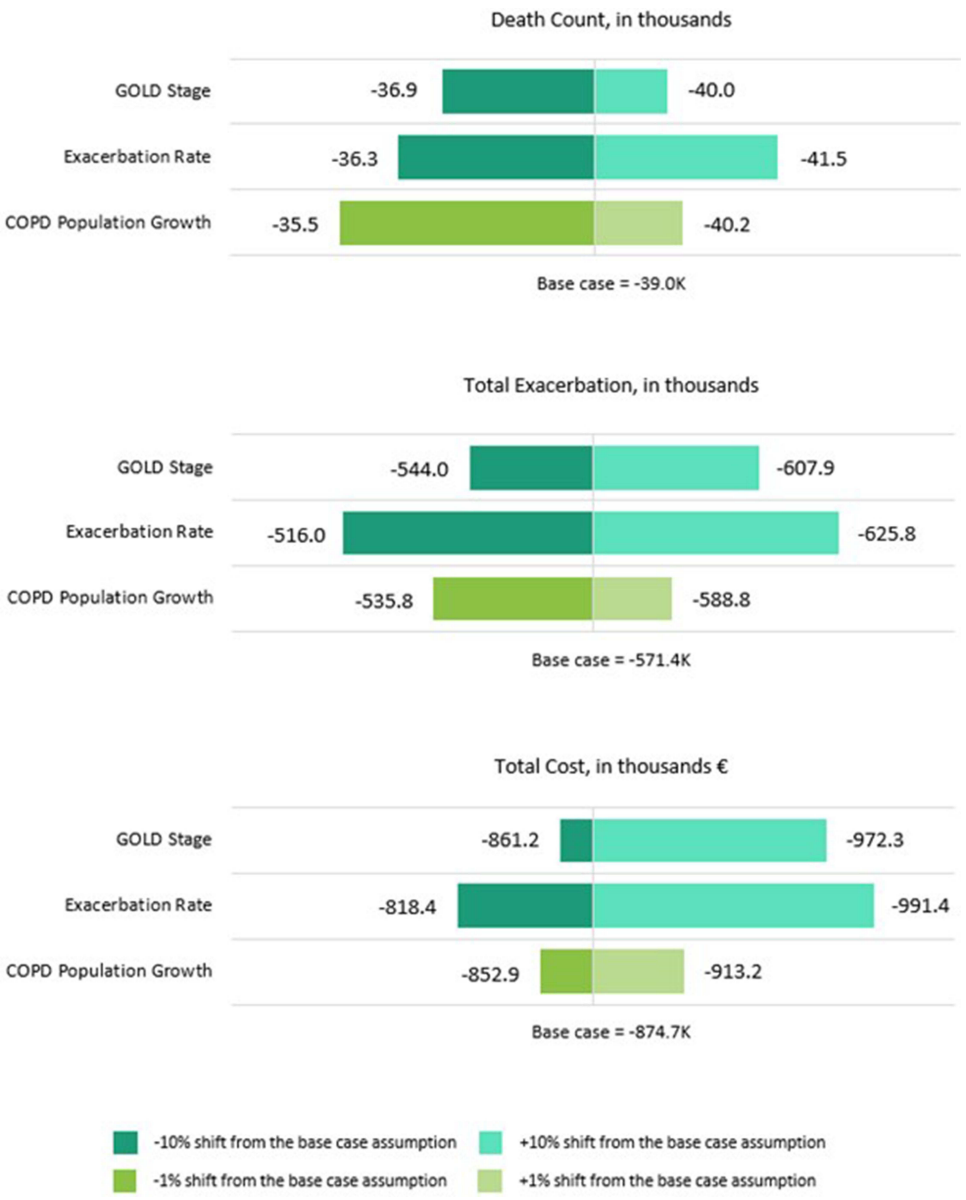


**Figure 7** Change in Status Quo and Increased SITT From Base Case Results Under the Sensitivity Testing Scenarios for the Flagged Population.

## Discussion

In the present study, we modeled the impact of Increased SITT utilization compared to Status Quo (current pattern of SITT utilization) in the French population of patients with COPD. Our data suggest that increasing the use of SITT would result in significant reduction in exacerbation rates (including severe exacerbation leading to hospitalization), mortality, and costs in patients with COPD.

While no prospective studies have been conducted evaluating the broad impact of increased SITT utilization, work has been done in other countries that demonstrates the interest of SITT. In the US population, the PROMETHEUS study also modeled improvements in outcomes in those with higher SITT utilization [15].

While historically, SITT has been reserved as an option for more severe patients, this work demonstrates the potential benefits of use in those with milder disease. Notably, we demonstrate a reduction in exacerbation count. In COPD, exacerbations have been shown to increase mortality and increase healthcare resource utilization and costs. In the flagged population, we modeled a reduction in the mortality rate by 8.5%, a reduction in moderate and severe exacerbation rates

by 8.0% and 9.2%, respectively. In addition, an increase in life-years expected of 0.6 years in the Increased SITT model as well as the NNT to extend the average life of a patient with COPD by one year was 20 in the flagged population. These clinical benefits would also translate to a 10-year savings of €875 million due to avoiding a total of 505,700 moderate and 65,700 severe exacerbations for the flagged population. The results of our sensitivity analysis demonstrate that alterations in the baseline assumptions would still result in clinical and cost benefits with the Increased SITT model. This strengthens the credibility of the assumptions used in this modeling.

In this model, we simulated direct shifts in GOLD stage, as we did not have data on clinical and biological markers of disease severity such as symptomatology scores like the CAT score or blood eosinophil count. Using these tools in clinical practice would change the annual movement of patients and may have an impact on modeled results. Additionally, we did not determine therapy-specific medication costs in this analysis. Exacerbation costs were derived from the literature and assumed inclusion of inpatient medications, but not any outpatient medications or changes in inhaler therapy. Moreover, we did not include in our analyses the rate of persistence of inhaled treatments and its potential impact on the results.[18]

Of note, our assumptions were limited by the lack of epidemiological data on French patients with COPD. Additionally, we assume that patients remain on SITT once initiated and there is no discontinuation due to adverse events or treatment failure. Other limitations of this model include a lack of modeling of other therapies for COPD. Of note, roflumilast is not used in France as it is not reimbursed and azithromycin is not labeled for COPD. Costs of maintenance COPD drugs were not included in our model. Less or more expensive therapies may represent an increased or decreased savings, respectively, to what is described here.

Taken in conjunction with the ETHOS and IMPACT studies, this model highlights the potential impact of SITT on patient outcomes. As in countries such as Canada that have modified their prescribing guidance to recommend SITT therapy in a more progressive manner, changes in national guidelines for pharmacological treatment in COPD in France could also be of interest.

## Conclusions

Higher than baseline SITT utilization is predicted to result in lower rates of mortality, moderate and severe exacerbations, and their corresponding medical costs in the French COPD population. Strategies that prioritize SITT therapy in patients that meet prescribing recommendations may lead to a decreased burden of illness in France.

## Data Sharing Statement

Published literature was utilized for this modeling study. Details on the sources utilized for each assumption are described in the supplementary materials.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This study was sponsored by AstraZeneca.

## Disclosure

Gaëtan Deslee reports personal fees from AstraZeneca during the conduct of the study and personal fees from Chiesi, GSK and Sanofi outside the submitted work; Héloïse Russo, Caroline Fabry-Vendrand, David Koskas, Gabriel Thabut and John P Bell are employees at AstraZeneca; Melissa Caplen, Prachi Devendra Bhatt, Jennifer Carioto, and Bruce Pyenson are employees of Milliman and report consulting fees from AstraZeneca; and Pierre-Régis Burgel reports personal fees from Astra-Zeneca, Boehringer Ingelheim, Chiesi, GSK, Insmed, MSD, Sanofi, Vertex and Viatris. AstraZeneca was involved in

the review of selected literature sources for inclusion in the modeling but had no role in the data analysis. AstraZeneca was also involved in paper review. The authors declare no other conflicts of interest. The abstract of this paper was presented at the Congrès de Pneumologie de Langue Française as a poster presentation with interim findings. The poster's abstract was published in "Poster Abstracts" in Revue des Maladies Respiratoires Actualités (volume 17, issue 1, pages 75-76 January 2025): https://doi.org/10.1016/j.rmra.2024.11.150. Additionally, this poster was accepted for an encore poster presentation at the Colloque des Données de Santé en Vie Réelle and was presented on July 3rd 2025.

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