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Modeling severe uncontrolled asthma: Transitioning away from health states

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ABSTRACT

Background: Models developed to date to simulate long-term outcomes of asthma have been criticized for lacking granularity and ignoring disease heterogeneity.
Objective: To propose an alternative approach to modeling asthma and apply it to model long-term outcomes in a population with moderate-to-severe type 2 asthma (patients with raised fractional exhaled nitric oxide or eosinophils) and treated with conventional therapy.
Methods: A discretely integrated condition event (DICE) approach was adopted, simulating individual profiles with asthma over patients' lifetime in terms of exacerbations, asthma-related death, and death unrelated to asthma. The timing of these events is dependent on profile characteristics including lung function, asthma control, exacerbation history, and other baseline characteristics or contextual factors. Predictive equations were derived from a clinical trial to model time to exacerbation, change in asthma control, lung function, and utility. Real-world studies were used to supplement data gaps. Outcomes evaluated included life expectancy, quality-adjusted life-years (QALY), number of exacerbations, and lung function over time.
Results: Average annual rates of severe and moderate exacerbations were 1.82 and 3.08 respectively, with rates increasing over time. Lung function declined at a higher rate compared with the general population. Average life expectancy was 75.2 years, compared with 82.4 years in a matched general population. The majority of life-years were spent with uncontrolled asthma and impaired lung function.
Conclusion: Patients with moderate-to-severe type 2 asthma and a history of exacerbations suffer from frequent exacerbations and reduced lung function and life expectancy. Capturing multiple conditions to simulate long-term outcomes in patients with asthma may provide more realistic projections of exacerbation rates.

1. Introduction

The use of mathematical modeling as a tool to support drug discovery [1], drug development [2], disease prediction [3], and healthcare decision-making [4,5] has become common practice. Model-based solutions provide insights from early stages of drug discovery to public health interventions and are often motivated by the requirement to confront complex questions related to molecular mechanisms, etiology, pathogenesis, and decisions surrounding a drug, disease, or intervention. For example, appropriate public health planning and

Abbreviations: ACQ-7, 7-item asthma control questionnaire; AM, ante meridiem; DICE, discretely integrated condition event; EOS, elevated blood eosinophils; ER, emergency room; EQ-5D, EuroQol 5-dimensions questionnaire; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; HRQOL, health-related quality of life; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; PM, post meridiem; $ppFEV_1$, percent predicted forced expiratory volume in 1 s; QALY, quality-adjusted life-years; SCS, systemic corticosteroids; TSLE, time since last exacerbation; US, United States.

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policy-making necessitate an understanding of the burden of a disease, commonly measured using indicators of long-term mortality and morbidity [6]. However, longitudinal studies following up large samples of heterogeneous patient populations over their lifetime are rare, so analysts and decision-makers generally rely upon models to synthesize evidence from different sources, extend findings to alternative populations, and fill in the data gaps [7]. This reliance becomes more prominent when evaluating the impact of a new intervention, as clinical trials are performed over a finite period, often shorter than an intervention's intended duration.

Modeling is commonly used to extrapolate outcomes from clinical trials over longer timespans [8], ultimately to inform policies aimed at maximizing the health of the population.

The use of modeling to inform therapeutic selection and resource allocation for high-burden diseases, such as asthma, is on the rise [9]. Asthma is the most common chronic respiratory disease, affecting over 339 million individuals [10], causing an estimated 1150 deaths daily, and 10.5 million years of life lost were attributed to asthma-related premature deaths in 2016, worldwide [11]. The economic burden of asthma is also significant, with the total cost of asthma in the United States (US) estimated at $81.9 billion in 2013 [12]. Despite existing standard of care, many patients with asthma continue to have uncontrolled disease, leading to an impacted health-related quality of life (HRQOL) [13] and a higher risk of asthma exacerbations [14], which can sometimes be fatal [15]. As asthma exacerbations cause a decline in lung function [16], with declined lung function contributing to a further increase in risk of recurrent exacerbations [14], therapy is necessary to break this circle. Several new biological drug treatments targeting patients with moderate-to-severe type 2, eosinophilic, and/or allergic asthma have been launched in recent years [17] to address both the unmet therapeutic needs, as approximately half of patients in the general asthma population still need systemic corticosteroids (SCS) [18], and the large impact of asthma on public health.

Although the arrival of these treatments has been coupled with the creation of models to simulate long-term outcomes and ascertain the added "value" of these treatments, the models developed to date have been criticized for lacking granularity and ignoring disease heterogeneity [9]. A semi-Markov cohort approach has most often been adopted to model moderate-to-severe asthma, separating an assumed homogeneous cohort of patients into mutually exclusive health states defined by the occurrence of asthma exacerbations and, in some models, by the level of asthma control [9]. The limitations and simplifications associated with this approach [19] do not take into account contemporary asthma management, which advocates a personalized treatment approach based on an individual patient's risk factors [9,20]. In addition, the requirement with this approach for a finite number of mutually exclusive health states limits the number of asthma outcomes considered, with the side effects, level of asthma control, lung function, and their interaction with exacerbations often overlooked. There is a need, therefore, for a more granular model in asthma that overcomes these limitations.

In this paper, we propose an alternative approach to modeling asthma, which can be used as a framework to evaluate its long-term burden and assess the value of alternative approaches to its management. We then apply this approach to model long-term outcomes in a population of patients with moderate-to-severe asthma treated with conventional therapy (medium-to high-dose inhaled corticosteroids [ICS] plus long-acting beta agonists [LABAs] and possibly a third controller medication), as data on the long-term trajectory of asthma outcomes in this population are limited. Specifically, we assess the long-term occurrence of exacerbations, the trajectories of lung function, asthma control, HRQOL, and life expectancy in a moderate-to-severe type 2 asthma population (ie, patients with elevated fractional exhaled nitric oxide [FeNO] or elevated blood eosinophils [EOS] who experienced at least one severe exacerbation in the year before baseline).

2. Patients and methods

A conceptualization exercise was conducted [21], drawing upon a review of published literature on moderate-to-severe asthma (asthma management guidelines, clinical trials, and observational studies of natural history) to create an influence diagram to guide the development of the model. This involved scoping out elements of the course of asthma, its clinical manifestations and underlying mechanisms, and the dynamic relationship between asthma outcomes (see Supplemental Section 1.0).

2.1. Model structure

Given the heterogeneity of the asthma population, an individual-based simulation was considered most appropriate to capture the relationship between exacerbations, asthma control, and lung function identified from the conceptualization exercise. A DICE approach was adopted, conceptualizing asthma and its management in terms of "conditions" (aspects that persist over time) discretely integrated with "events" (incidents that happen at particular points in time) [22].

The model simulates the course of individual profiles of patients with asthma in terms of occurrence of the following "real events": exacerbations, asthma-related death, and death unrelated to asthma. Exacerbations are separated into moderate and severe exacerbations. Moderate exacerbations are defined as loss of asthma control events that do not meet the criteria for severe exacerbations and that meet any of the following criteria: $\geq$6 additional reliever puffs in a 24-h period compared with baseline on 2 consecutive days; $\geq$20 % decrease in prebronchodilator forced expiratory volume in 1 s (FEV_1) compared with baseline; increase in ICS dose $\geq$4 times the dose at baseline; or a decrease in ante meridiem (AM) or post meridiem (PM) peak flow of $\geq$30% on 2 consecutive days of treatment [23]. Severe exacerbations are defined as those exacerbations requiring use of SCS for $\geq$3 days or requiring a hospitalization or emergency room (ER) visit because of asthma, requiring SCS [23]. To reflect differing consequences on mortality and HRQOL, severe exacerbations are further separated into those requiring only a SCS burst, those requiring an ER visit but no hospitalization, and those requiring hospitalization. Following a severe exacerbation, asthma-related death may occur, with the risk of death depending on the age of the profile and severity of the exacerbation (ie, depending on the setting of treatment of the severe exacerbation). If the exacerbation is nonfatal, the profile is at risk for a subsequent exacerbation once the current one resolves. Death unrelated to asthma may occur at any time, dependent on the age, gender, and lung function of the profile.

The timing in which events occur is dependent on characteristics of the profile, defined as "conditions". These conditions include lung function (based on prebronchodilator FEV_1 in liters), asthma control (based on the 7-item asthma control questionnaire [ACQ-7]) [24], exacerbation history (number of exacerbations in preceding year and time since last exacerbation [TSLE]), other characteristics (eg, age, gender, and biomarker levels) and contextual factors (eg, time and season).

Due to their strong interlinked relationship with exacerbations, lung function, asthma control, and exacerbation history are explicitly modeled as "dynamic conditions," evolving over time, with changes in the level of these conditions in turn affecting event times (Fig. 1 and Supplemental Section 2.0). Updates to these conditions are made using modeling events (referred to as "update events"), which occur at predefined discrete intervals. Updates in the levels of lung function and asthma control (and consequently event times) occur every 2 weeks for the first 12 weeks, and after every season change and every exacerbation thereafter. Biomarkers and other demographic (except age) and disease characteristics are treated as "static conditions" (ie, their values do not change over time, either because they are static in nature [eg, race] or because only their baseline value [eg, biomarkers] was considered as a

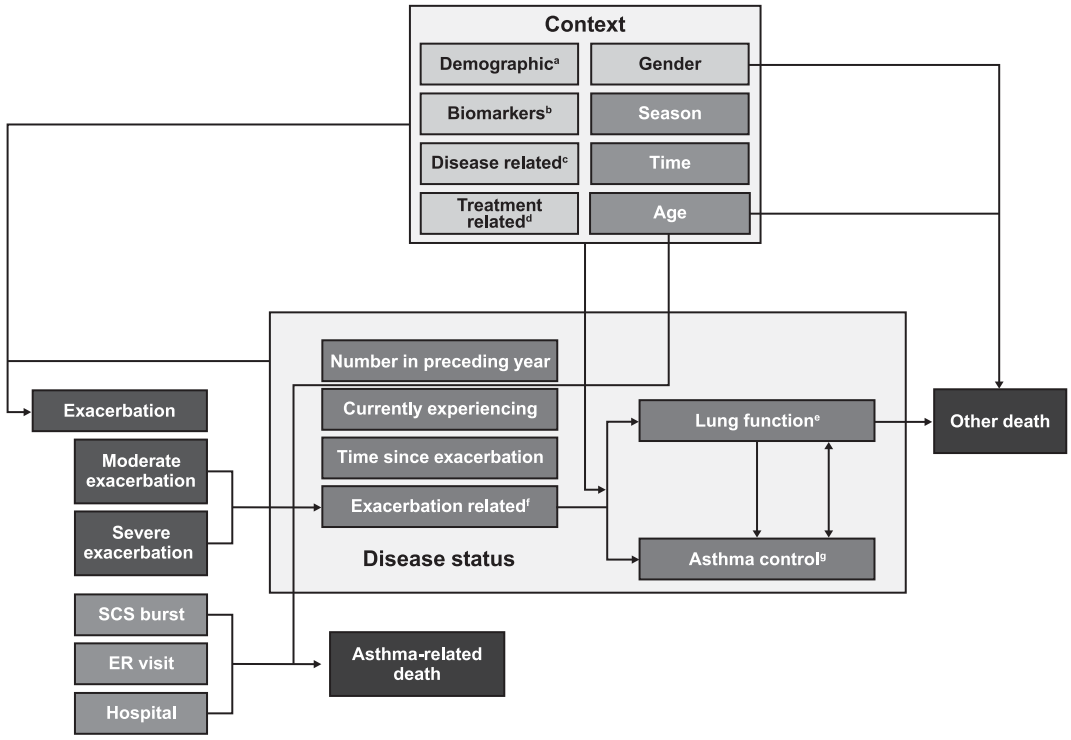

Fig. 1. Relationship between conditions and events
Abbreviation: ER, emergency room.
Events are denoted in black, conditions in gray. Conditions in dark gray are explicitly modeled as dynamic conditions; conditions in light gray are static.
[a]Height, weight, body mass index, race, ethnicity, region.
[b]Baseline values of eosinophils, fractional exhaled nitric oxide, immunoglobulin E.
[c]Evening peak expiratory flow, history of nasal polyposis, time since asthma diagnosis/age at onset.
[d]Inhaled corticosteroids dose at baseline (medium vs high), number of daily reliever puffs at baseline.
[e]Measured based on forced expiratory volume in 1 s (FEV_1) in liters and percent predicted FEV_1.
[f]The exacerbation-related conditions are duplicated for moderate and severe exacerbations.
[g]Measured using the 7-item asthma control questionnaire.

predictor of events or other conditions).

The model processes individual patient profiles (comprising a set of conditions) sequentially. Once a profile is selected and baseline values of conditions are defined for this profile, the initial time to the occurrence of an exacerbation and time to death unrelated to asthma are predicted depending on the profile's baseline condition values, and the time to update dynamic conditions is set to 2 weeks after baseline. Events and their consequences are then processed in the sequence of their occurrence. The model moves on to the next event (ie, the event with the closest time of occurrence), updates time-dependent profile characteristics, accumulates time-dependent outcomes, and processes the consequences associated with the event.

Time-dependent outcomes include life-years in total and time spent with uncontrolled asthma (ACQ-7 $\geq$1.5) as well as QALYs. QALYs are accumulated from utilities measured using the EuroQol 5-dimensions questionnaire (EQ-5D) utility index dependent on age, gender, asthma control, and exacerbation occurrence, among others. Further details on the model process and each event are provided in Supplemental Section 2.0.

In summary, the key process simulated involves the following dynamic relationships between lung function, asthma control, and exacerbations:

- Lung function is a predictor of exacerbations [14] and mortality [25] and is a component of asthma control [20].
- Asthma control is a predictor of exacerbations [14] and HRQOL [13].
- Occurrence of exacerbations affects HRQOL [26], lung function [27], asthma control [20], and the subsequent risk of exacerbations [14] and may also lead to asthma-related death [15].

2.2. Model inputs

To model time to exacerbation, change in asthma control, lung function, and HRQOL, predictive equations were derived using patient-level data from the LIBERTY ASTHMA QUEST (NCT02414854) clinical trial [23]. Standard parametric and parametric frailty survival models with time-dependent covariates were used to model time to first exacerbation and time to subsequent exacerbation, respectively. A gamma-distributed frailty term was incorporated in the time to subsequent exacerbation model to account for recurrent events and patient heterogeneity. Repeated measures mixed-effect regression models with random intercept and slope (ie, time since randomization) were used to predict the changes in asthma control, lung function and HRQOL (measured using the EQ-5D). Beyond the first year of the model, change in lung function was modeled using data from retrospective studies [27, 28], given that short-term trial data could not capture the long-term decline in lung function adequately. In a similar context, to capture the decline in HRQOL due to aging, decrements derived from the US EQ-5D catalog [29] were applied beyond the first year (ie, the duration of the clinical trial). Further details on these analyses are provided in Supplemental Section 3.0 and parameter estimates for each equation are displayed in Table 1.

Data on the distribution between severe and moderate exacerbations and the duration of the exacerbations were obtained from the LIBERTY

Table 1
Predictive equations.

	Time to first exacerbation[a]	Time to subsequent exacerbations[a]	ACQ-7	FEV_1 (L)	EQ-5D utility
Log-normal shape parameter	1.4918	0.4547	–	–	–
Intercept	4.1210	2.2320	0.5423	−1.0240	0.6982
Time since randomization (months^(-0.5))	–	–	0.5211	−0.0235	0.0171
Value at baseline	–	–	−0.6057	−0.2583	−0.6427
Age: <18 years at baseline	−0.4695	−0.3650	−0.2374	0.2143	−0.0052
Gender: Male	–	–	0.1707	−0.0275	0.0224
Height (cm) at baseline	–	–	–	0.0081	–
Weight (kg) at baseline (reference: <50 kg)					
≥100 kg	–	–	–	0.0679	–
50≤ – <100 kg	–	–	–	0.1114	–
Region (reference: Asia)					
East Europe	0.4260	0.1430	0.3127	−0.0387	−0.0026
Latin America	−0.1088	0.4199	0.0099	0.0058	−0.0003
Western countries	0.3710	0.7544	0.2352	−0.1193	0.0072
Current $ppFEV_1$	1.3197	0.6751	–	–	–
Current ACQ-7	−0.4743	−0.2449	–	–	−0.0709
Current season (reference: winter)					
Spring	0.1338	0.0637	−0.0540	0.0163	–
Summer	0.2784	−0.0304	−0.0913	0.0342	–
Fall	−0.1666	−0.2541	−0.0242	0.0056	–
Number of previous severe exacerbations at baseline					
1	0.4121	Reference	Reference	Reference	Reference
2	0.4007	−0.1637	0.0221	−0.0466	−0.0020
3	0.3273	0.0810	−0.0929	−0.0204	0.0061
4+	Reference	−0.5235	0.0014	−0.0305	0.0089
Number of exacerbation events during follow-up (reference: 4+); because these coefficients were derived based on exacerbation events observed within a period of 1 year, to extrapolate beyond the duration of the trial, this covariate was treated as the number of exacerbations experienced in the simulation within the preceding year.					
3	–	0.4634	–	–	–
2	–	0.7180	–	–	–
1	–	1.3351	–	–	–
Time (days) from last exacerbation (log)	0.0990	–	–	–	–
Eosinophils group at baseline (reference: <0.15 Giga/L)					
0.15≤ – <0.3 Giga/L	−0.2111	0.1121	−0.0128	0.0113	−0.0053
0.3≤ – <0.4 Giga/L	−0.3542	−0.2461	−0.0070	0.1191	0.0078
≥0.4 Giga/L		0.1033	−0.0987	0.0855	0.0022
Eosinophils (time since randomization [months^(-0.5)]) interaction					
0.15≤ – <0.3 Giga/L	–	–	–	−0.0211	–
0.3≤ – <0.4 Giga/L	–	–	–	−0.0535	–
≥0.4 Giga/L	–	–	–	−0.0838	–
Body mass index at baseline (reference: <25 kg/m^2)					
25≤ – <30 kg/m2	–	−0.0614	−0.0224	–	–
≥30 kg/m2	–	0.1280	0.0815	–	–
Time (years) since diagnosis at baseline	–	0.0063	–	−0.0023	–
Age (years) at asthma onset	–	–	–	–	−0.0006
History of nasal polyposis at baseline	–	0.1535	−0.0667	–	–
Evening peak expiratory flow (L/min) at baseline	–	–	−0.0010	0.0010	−0.0001
Reliever puffs (per day) at baseline	–	–	0.0336	–	0.0014
FeNO (parts per billion) at baseline	–	–	−0.0009	−0.0004	0.0001
Immunoglobin E ≥100 IU/mL at baseline	–	–	–	0.0328	–
Inhaled corticosteroid dose at baseline: medium	−0.1649	0.0367	−0.0085	0.0092	−0.0055
Days since end of last moderate exacerbation (reference: >28 days)					
0 days: currently experiencing moderate exacerbation	–	–	0.3732	−0.2118	–
1–28 days since end of moderate exacerbation	–	–	0.1329	−0.0239	–
Days since end of last severe exacerbation (reference: >28 days [except for EQ-5D utility equation, for which the reference is "Not currently experiencing a severe exacerbation"])					
0 days: currently experiencing severe exacerbation	–	–	0.8061	−0.2279	−0.0197
1–28 days since end of severe exacerbation	–	–	0.1384	0.0179	–

Abbreviations: ACQ-7, 7-item asthma control questionnaire; EQ-5D, EuroQol 5-dimensions questionnaire; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; IU, international units; $ppFEV_1$, percent predicted FEV_1.

[a] Coefficients interpreted as an increase/decrease in time to first/subsequent exacerbation per unit increase for continuous predictors or for one group vs reference category.

ASTHMA QUEST trial, while the distribution across treatment settings for the severe exacerbations [30] and age-dependent fatality rates following severe exacerbations leading to hospitalization [15] were obtained from retrospective studies (Table 2). Fatality rates following severe exacerbations leading to SCS burst or ER visit were deduced based on data on the location of asthma-related deaths [31], the treatment setting of severe exacerbations [30] and fatality rates following a hospitalized exacerbation [15], using methods adopted in previous models [32,33].

Time to death unrelated to asthma was estimated using a Gompertz distribution [34] fitted to US general population life tables by age and gender [35], which were adjusted to exclude asthma-related deaths [36]. Time to death was further adjusted depending on the lung function of each profile. Specifically, FEV_1 in liters was transformed into percent predicted FEV_1 ($ppFEV_1$) using the NHANES III predicted set [37], and hazard ratios of death depending on the level of $ppFEV_1$ were applied as derived from a retrospective analysis of the Clinical Practice Research Datalink (Table 2) [38]. Further details on inputs derived from

Table 2
Other model inputs.

	Mean	SE/N/CI	Source
Duration of exacerbation (days):			
Moderate exacerbation	16.56	0.51	Post hoc analysis of
Severe exacerbation leading to SCS burst	17.95	0.83	LIBERTY ASTHMA QUEST
Severe exacerbation leading to ER visit	20.20	2.92	
Severe exacerbation leading to hospitalization	29.4	6.18	
Proportion of exacerbations that are severe:			
First exacerbation	64.7 %	170	Post hoc analysis of
Subsequent exacerbations	62.8 %	479	LIBERTY ASTHMA QUEST
Proportion of severe exacerbations leading to:			
SCS burst	73.56 %	5698	[30]
ER visit	7.79 %	1404	
Hospitalization	18.65 %	508	
Proportion of severe exacerbations leading to hospitalization that are fatal, by age:			
12–14 years	0.080 %	114,834	[15]
15–33 years	0.260 %	101,905	
34–54 years	0.490 %	238,033	
55–74 years	1.350 %	200,008	
75+ years	3.020 %	105,708	
Proportion of severe exacerbations leading to SCS burst that are fatal, by age:			
12–14 years	0.012 %	NA	[15,30–32]
15–33 years	0.039 %	NA	
34–54 years	0.073 %	NA	
55–74 years	0.202 %	NA	
75+ years	0.453 %	NA	
Proportion of severe exacerbations leading to ER visit that are fatal, by age:			
12–14 years	0.01 %	NA	[15,30–32]
15–33 years	0.03 %	NA	
34–54 years	0.06 %	NA	
55–74 years	0.16 %	NA	
75+ years	0.35 %	NA	
Hazard ratio for excess mortality unrelated to asthma, by level of lung function ($ppFEV_1$)			
≥80 %	1.0000		
≥50 % and <80 %	1.8620	1.6060–2.1590	[38]
<50 %	2.9190	2.4680–3.4520	

Abbreviations: ER, emergency room; NA, not applicable; $ppFEV_1$, percent predicted forced expiratory volume in 1 s; SCS, systemic corticosteroids.

real-world studies and how these are operationalized in the model are provided in Supplemental Section 4.0. A summary of the sources for all inputs utilized in the model as described in the sections above is provided in Table 3.

To validate the model, various exercises were conducted, including examining face, technical, and predictive validity. This included reviewing the model concept, structure and modelling of asthma outcomes with external practicing clinicians and external modelers, verifying the mathematical sequence of calculations, and comparing model predictions versus observed data (Supplemental Section 5.0).

2.3. Analyses

Before running the analyses, the predictive ability of the model was verified by setting the model settings equivalent to that of the trial informing the model and comparing model predicted outcomes with observed outcomes (ie, exacerbations, lung function, and asthma control). This included setting the model to a 1-year time horizon, restricting exacerbation occurrence, such that no exacerbations could occur within 28 days of a previous exacerbation, and simulating only profiles randomized to the placebo arm.

Following the verification of the model's predictive ability, the base-case analysis was performed. This evaluated the long-term trajectory of patients aged 12 years or older, treated with medium-to high-dose ICS plus LABAs and possibly a third controller medication, with either raised EOS (≥150 cells/μL) or FeNO (≥25 parts per billion) and ≥1 severe exacerbation in the year before baseline. All profiles meeting the above-mentioned criteria at baseline, regardless of the treatment they were eventually randomized to, were included in the analysis. Exacerbations were allowed to occur following resolution of a previous exacerbation, and the time horizon was set to lifetime.

As the simulation uses random numbers to determine each profile's trajectories, each profile was run over 3 replications to ensure results were not driven by sampling variability (Supplemental Section 6.0). Outcomes evaluated included life expectancy, QALYs, number of exacerbations, and lung function over time. Various scenario analyses were conducted to explore the main areas of structural uncertainty and input uncertainty within the model, including the source used to inform the long-term change in lung function [16,27,28,39] and the source of asthma-related mortality data [15,40], as well as assumptions on the influence of prior exacerbation history.

Table 3
Summary of sources used to inform model inputs.

Input	Study	Reference
Time to first and subsequent exacerbation	LIBERTY ASTHMA QUEST	Supplemental Section 3.0
Change in asthma control	LIBERTY ASTHMA QUEST	Supplemental Section 3.0
Change in lung function (First Year)	LIBERTY ASTHMA QUEST	Supplemental Section 3.0
Change in lung function (Subsequent Years)	Retrospective studies	[27,28]
Proportion of exacerbations that are severe	LIBERTY ASTHMA QUEST	Supplemental Section 3.0
Duration of exacerbations	LIBERTY ASTHMA QUEST	Supplemental Section 3.0
Distribution of severe exacerbations across resource use settings	US claims data	[30]
Proportion of severe exacerbations leading to hospitalization that are fatal, by age	HCUP Nationwide Inpatient Sample (NIS)	[15]
Proportion of severe exacerbations leading to SCS burst or ER visit that are fatal, by age	HCUP NIS, US claims data, Multiple Cause of Death Files	[15,30–32] Supplemental Section 4.0
Mortality unrelated to severe exacerbations by age and gender	US Life tables, US cause of death statistics	[35,36]
Hazard ratios of death by $ppFEV_1$	Clinical Practice Research Datalink	Supplemental Section 4.0.
Change in EQ-5D	LIBERTY ASTHMA QUEST	Supplemental Section 3.0

3. Results

3.1. Predictive validation

The model predicted time to first and subsequent exacerbations, change in ACQ-7 and change in FEV_1 observed in the LIBERTY ASTHMA QUEST trial [23] at different time points very well, replicating the observed curves (Supplemental Section 5.0). The severe exacerbation rate predicted by the model was 1.086 as compared with the rate of 1.042 observed in the trial for patients treated with placebo.

3.2. Base-case analysis

A total of 1484 individual records of patients matching the criteria for the modeled population and with complete information on the baseline characteristics required were identified from LIBERTY ASTHMA QUEST. Average baseline characteristics feeding into the simulation are displayed in Table 4. The model predicted that over a lifetime horizon, each patient experienced 135 exacerbations on average, of which 50 were severe (Table 5). Average undiscounted life-years were 27.6 (average age at baseline: 47.6 years), with 21% of deaths occurring because of a severe exacerbation. Considering these outcomes, the average annual severe and moderate exacerbation rates were 1.82 and 3.08, respectively.

Considerably lower exacerbation rates were predicted in the first year of the time horizon (Fig. 2), with these rates increasing steadily over time. Matching a priori expectations, lung function (FEV_1 in liters) declined over time by an average of 28 mL per year after the first year. The decline was higher compared with what would be expected in a population without respiratory disease (ie, $ppFEV_1$ declined as opposed to remaining stable).

When considering asthma control and quality of life, patients spent most of the time with uncontrolled asthma (ACQ-7 $\geq$1.5), with 17.6 years spent with uncontrolled asthma vs 9.97 with controlled asthma. Average undiscounted QALYs were 21.37, while QALYs discounted at a rate of 3% annually were 13.81.

Table 4
Baseline characteristics of population modeled.

	Mean (SD)	Min–Max
Demographic characteristics		
Gender: female (%)	61.10 %	0–1
Age (years)	47.63 (15.24)	12–84
Weight (kg)	79.55 (19.98)	30–227
Height (meters)	1.65 (0.10)	1.37–1.98
Region		
Western	36.30 %	
Latin America	27.70 %	
Asia	10.50 %	
Eastern Europe	25.50 %	
Race		
Caucasian/White	83.4 %	
Asian/Oriental	11.8 %	
Black	3.8 %	
American Indian or Alaskan Native	0.1 %	
Native Hawaiian or other Pacific Islander	0.1 %	
Other	1.0 %	
Ethnicity		
Hispanic/Latino	25.9 %	
Non-Hispanic/Latino	74.1 %	
Disease characteristics		
Blood eosinophil count (cells/uL)	430 (380)	0–4330
Number of severe exacerbations in preceding year	2.12 (2.24)	1–50
TSLE (days)	169.95 (88.73)	52–412
Immunoglobin E (IU/mL)	472.84 (779.43)	1–5000
Prebronchodilator FEV_1 (L)	1.78 (0.61)	0.42–4.24
$ppFEV_1$	58.34 (13.39)	0.08–89
History of nasal polyposis	18.93 %	
ACQ-7 score	2.87 (0.7)	0.43–6
EQ-5D utility index score	0.74 (0.18)	−0.09 to 1
AM symptoms score	1.13 (0.84)	0–4
PM symptoms score	1.26 (0.83)	0–4
Baseline inhaled corticosteroids use		
Medium-dose inhaled corticosteroids	48.30 %	
High-dose inhaled corticosteroids	51.70 %	

Abbreviations: ACQ-7, 7-item asthma control questionnaire; AM, ante meridiem; EQ-5D, EuroQol 5-dimensions questionnaire; FEV_1, forced expiratory volume in 1 s; IU, international units; PM, post meridiem; $ppFEV_1$, percent predicted FEV_1; TSLE, time since last exacerbation.

Table 5
Base-case results.

Outcome	Result
Number of exacerbations	135.33
Number of moderate exacerbations	85.13
Number of severe exacerbations	50.21
Requiring SCS burst	36.93
Requiring ER visit	3.90
Requiring hospitalization	9.38
Life-years (undiscounted)	27.6
Life-years with controlled asthma	9.97
Life-years with uncontrolled asthma	17.63
Life-years with $ppFEV_1$ $\geq$80%	4.26
Life-years with $ppFEV_1$ $\geq$50% and <80%	12.82
Life-years with $ppFEV_1$ <50%	10.52
QALYs (undiscounted)	21.37
QALYs (discounted at 3 % per year)	13.81

Abbreviations: ER, emergency room; $ppFEV_1$, percent predicted forced expiratory volume in 1 s; QALY, quality-adjusted life-year; SCS, systemic corticosteroids.

3.3. Scenario analysis

Results from the scenario analyses are displayed in Table 6 with severe exacerbation rates over time across scenarios plotted in Fig. 3. Severe exacerbation rates varied between 1.74 and 2.05 annually, while life-years varied between 25.99 and 28.72 across the different scenarios. Assuming a slower decline in lung function [16] resulted in a slightly lower annual severe exacerbation rate (1.74 vs 1.82) and slightly longer life expectancy (28.44 vs 27.6) compared with the base case. Assuming a higher decline in lung function [39] resulted in an increased annual severe exacerbation rate of 2.05 and lower life-years (25.99) compared with the base case. Assuming that not only recent exacerbation history (ie, in the preceding year) affects the risk of future exacerbations but that all exacerbations experienced in the past will contribute to increasing the risk also resulted in a higher severe exacerbation rate (2.03 per year) and lower life expectancy (27.13 years). Similar results were obtained when the improvement in lung function observed in the first year (trial period) was removed.

4. Discussion

Our analyses predicted that patients with moderate-to-severe type 2 asthma and a history of exacerbations in the preceding year suffer from reduced life expectancy and HRQOL. Our model predicted an average age at death of 75.2 years compared with the average age of 82.4 years [35] expected in a general population matched on age and gender to our modeled population. Discounted QALYs were 13.8, which is 3.6 lower than would be expected in a matched general population [29,35]. This, coupled with the healthcare resource requirements to manage an estimated average of 1.82 severe exacerbations annually and to manage uncontrolled asthma (in which patients spent 65 % of their time), highlights the need for alternative treatment strategies beyond ICS, LABAs, and other conventional controller medications in this population. The recent launch of several biologic therapies with demonstrated efficacy in moderate-to-severe type 2 asthma, eosinophilic, and/or allergic asthma [17,23,41–43] brings hope for this patient population.

To our knowledge, this model is the first to use an individual-based approach to model the course of asthma over a lifetime. This enabled capturing multiple conditions, such as asthma control, lung function, and exacerbation risk without imposing restrictions on the number of conditions modeled, thereby allowing them to be captured on continuous scales. The ability to retain memory means that this approach overcomes multiple assumptions and simplifications adopted in previous models [9].

Previous models have assumed that the risk of exacerbations remains constant over time, often informing estimates from clinical trials [9],

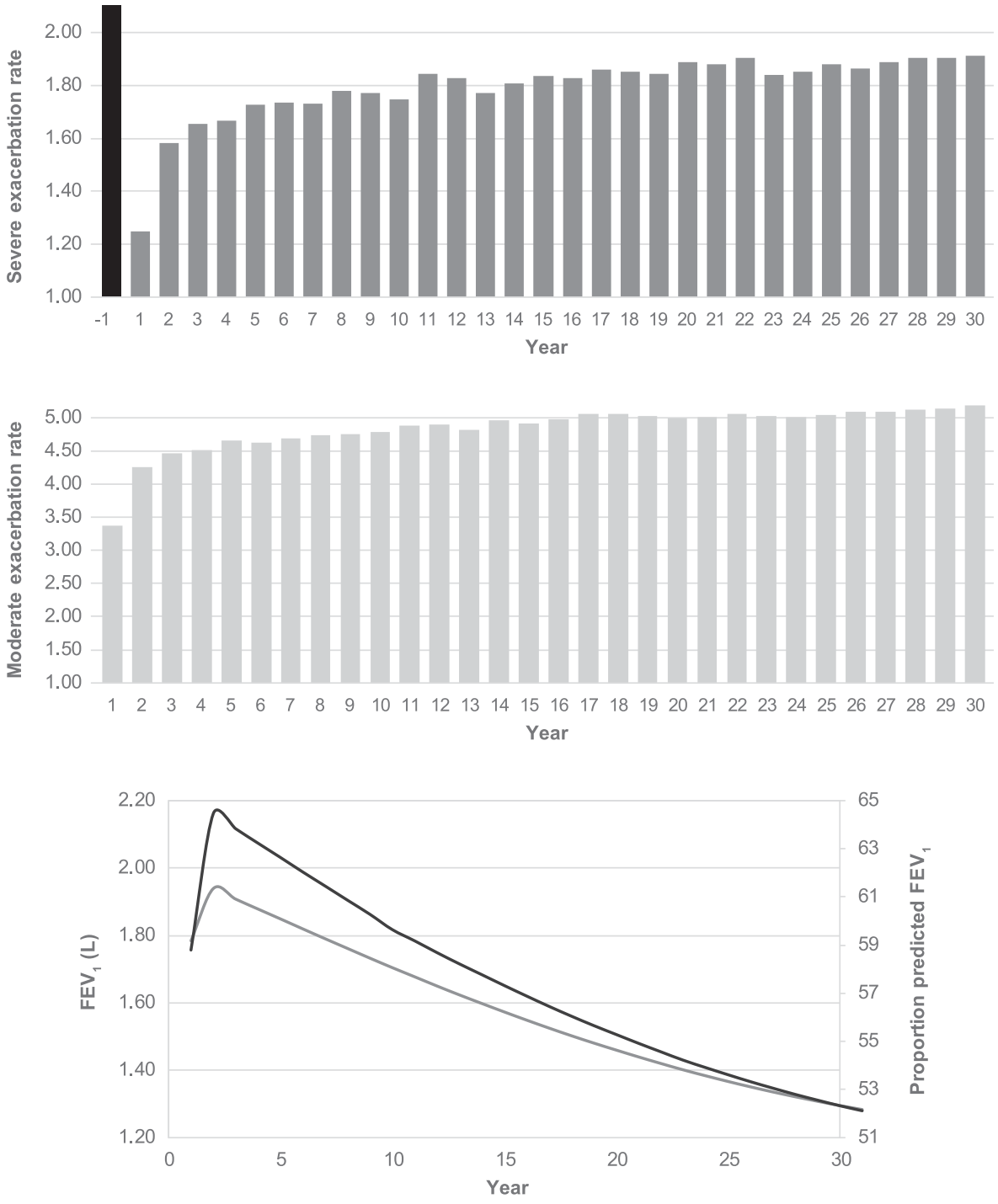

Fig. 2. Simulated asthma outcomes over time
Abbreviations: FEV_1, forced expiratory volume in 1 s; L, liters.
The black bar reflects the severe exacerbation rate in the year preceding the LIBERTY ASTHMA QUEST trial.
The dark line reflects $ppFEV_1$; light gray line reflects FEV_1 in liters.

which may underestimate the risk in the real world. This is because clinical trials are designed to evaluate treatment efficacy in relative terms rather than absolute risk levels of events. This necessitates the adoption of strict exclusion criteria (eg, exclusion of patients who experienced a recent asthma exacerbation) and idealistic definitions on the frequency of events (eg, considering 2 exacerbation events occurring within 28 days to be a single event) [23]. These factors, coupled with improved treatment adherence and monitoring of patients under clinical trial conditions, undoubtedly result in lower absolute exacerbation rates being observed in trials compared with what would be observed in the real world [44].

The impact of these factors can be observed to a certain extent when assessing exacerbation rates over time in our analyses. The simulation predicted 1.25 severe exacerbations in the first year of the time horizon, higher than the rate of 1.042 observed in the placebo arm of the trial informing the analysis [23]. While this is partly because the simulation considered all profiles matching the criteria for the defined population as opposed to just those randomized to the placebo arm, an important

Table 6
Scenario analyses.

Scenario name	Number of severe exacerbations	Number of moderate exacerbations	Life-years	Age at death (years)	Severe exacerbation rate (annual)	Moderate exacerbation rate (annual)	Undiscounted QALYs
1. Base case	50.21	85.13	27.60	75.20	1.82	3.08	21.37
2. Covariates on exacerbations experienced during follow-up treated as number of exacerbations experienced during simulation	55.14	93.48	27.13	74.76	2.03	3.45	20.95
3. No improvement in lung function in the first year, decline in lung function dependent only on occurrence of severe exacerbations	50.70	85.88	25.77	73.40	1.97	3.33	19.95
4. Decline in lung function sourced from Newby et al, 2014, [39] considering time, age, and count of severe exacerbations experienced	53.14	90.07	25.99	73.62	2.05	3.47	19.97
5. Decline in lung function sourced from Matsunaga et al, 2015, [28] considering occurrence of 0, 1, or 2+ severe exacerbations in preceding year	50.97	86.39	26.98	74.61	1.89	3.20	20.83
6. Decline in lung function sourced from Bai et al, 2007, [16] considering occurrence of 0–1 or 2+ severe exacerbations in preceding year	49.53	84.03	28.44	76.07	1.74	2.95	22.08
7. Decline in lung function sourced from O'Byrne et al, 2009, [27] considering occurrence of 0 or 1+ severe exacerbations in preceding year	50.12	84.97	26.97	74.60	1.86	3.15	20.83
8. Fatality after hospitalized exacerbation reflecting lower-end estimates based on Krishnan et al, 2006 [40]	52.84	89.56	28.72	76.35	1.84	3.12	22.16

Abbreviation: QALY, quality-adjusted life-year.

differentiator is the removal of artifacts of clinical trial design in the simulation. Profiles were exposed to the risk of experiencing subsequent exacerbations following resolution of their preceding exacerbation, rather than following 28 days from the start of the preceding exacerbation as dictated by trial definitions [23]. This removed a period of "immunity" for the profiles and resulted in slightly higher rates.

In the second year, the model predicted a higher severe exacerbation rate of 1.58, increasing steadily in the subsequent years to reach an average of 1.82 annually. One of the factors contributing to this increase is the relationship between TSLE and the risk of subsequent exacerbations. As demonstrated in previous analyses [45] and in analyses of the trial used to inform our model, the risk of experiencing an exacerbation is highest in the first month following an exacerbation and declines, yet remains high, in the next couple of months, before decreasing. As the profiles used in our analysis involved patients enrolled in a clinical trial that had "passed" specified exclusion criteria, patients with a recent exacerbation were excluded. This meant that the modeled population could not have experienced a severe exacerbation within at least 50 days before baseline (the average TSLE was 170 days). Therefore, the population modeled starts off at a reduced risk of experiencing a severe exacerbation in the near future. Over time, as the profiles exacerbate, their lung function decreases, asthma control worsens, and their risk of experiencing subsequent exacerbations increases. Since memory is retained in our model for longer than a commonly adopted cycle duration of 1 month [9], this results in an increasing exacerbation rate over time, diluting the effect of any exclusion criteria over time.

As our model explicitly considered lung function and its decline over time, lower levels of lung function caused an increased risk of experiencing exacerbations [14]. To capture the decline in lung function over time, the model considered use of external data based on literature. Extensive scenario analyses were conducted evaluating results across different sources identified to model long-term change in lung function. Although use of either of the studies resulted in alternative long-term trajectories, exacerbation rates increased over time across all scenarios.

Explicit modeling of lung function, TSLE, exacerbation history, asthma control, and their relationships contribute to more realistic projections of exacerbation rates, more reflective of the trajectory asthma patients follow in the real world. Nonetheless, our analysis is not immune to limitations arising from informing estimates from clinical trials. In the year preceding the LIBERTY ASTHMA QUEST trial, the population modeled experienced, on average, 2.12 severe exacerbations, whereas much lower estimates were observed during the simulation, with first-year estimates closer to those observed in the trial [23]. This is because predictive equations were derived using clinical trial data and, for the features outlined above to take on "full effect," a first exacerbation during the simulation is necessary. After several years in the simulation, estimated exacerbation rates were closer to the average number of severe exacerbations in the year before randomization, although they remained slightly lower. Therefore, the projected exacerbation rates in the model are considered to be lower than those expected in the real world.

A recent systematic review of decision-analytic models for asthma interventions concluded that current models generally do not adequately model the disease heterogeneity [9]. A key advantage of our approach is that the characteristics of each profile are considered in order to model their trajectory, therefore accounting for disease heterogeneity. Our analysis identified that lower ACQ-7 scores, lower number of exacerbation events prior to baseline or during follow-up, higher $ppFEV_1$, lower level of eosinophils at baseline, older age (≥18 years) and Western Countries were associated with a longer time to exacerbation. These predictors are consistent with those identified by earlier analyses [46], [-51] with a multivariate model used to consider the added 'impact' of each characteristic and different combinations of various characteristics in this study.

Use of predictive equations with covariates also eliminates the need for subgroup analyses, which are often required to model alternative populations. In addition, predictive equations may be more appropriate for modeling rare outcomes, such as severe exacerbations, than for deriving transition probabilities between health states from very few observations.

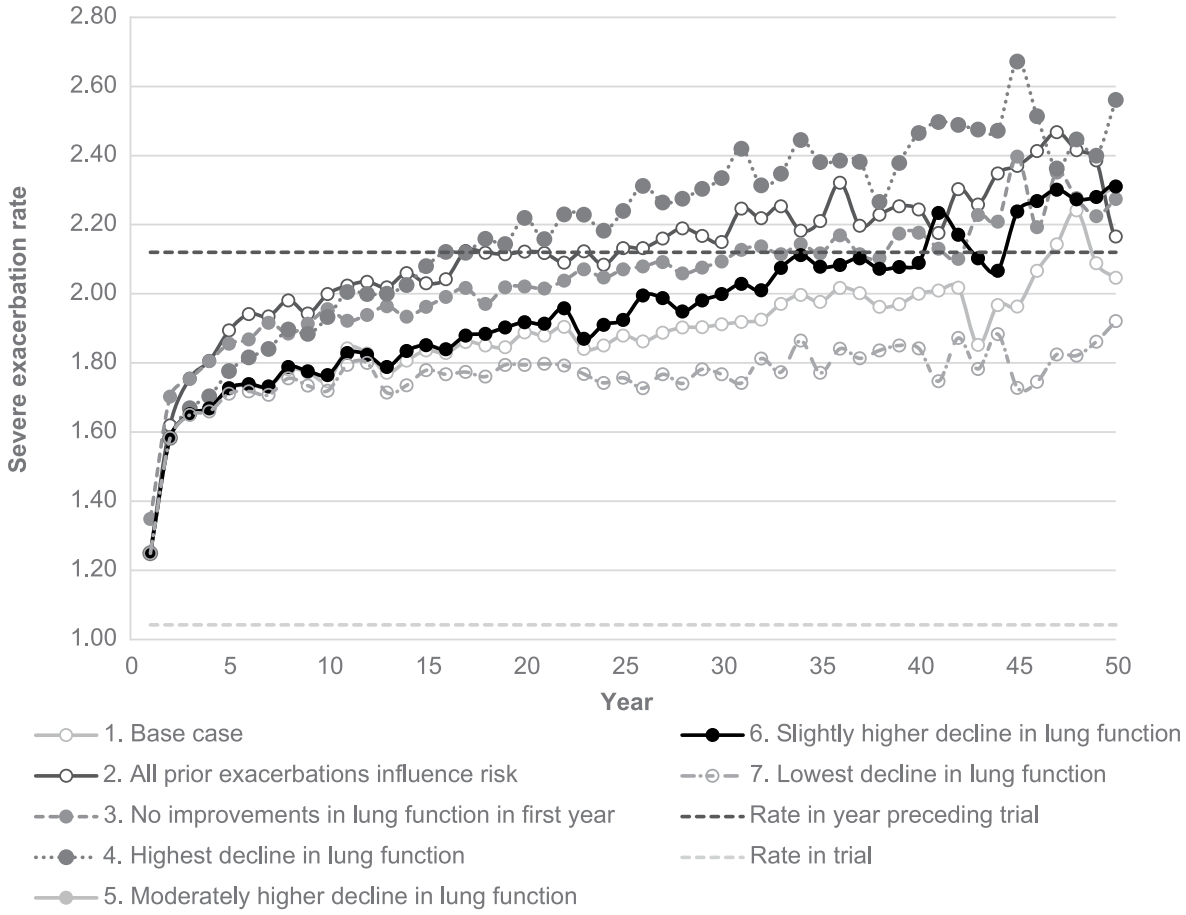

Fig. 3. Severe exacerbation rates across various scenario analyses.

The refinements outlined above allow capture of the complexity of asthma in a more granular manner, as compared with conventional cohort models. Nonetheless, this complexity can often challenge the ease of communicating the model because of the multitude of relationships being considered. In addition, capturing these dynamic relationships necessitates sophisticated statistical analyses and availability of detailed granular baseline data to assess the impact of multiple patient characteristics, which may not be available in a real-world setting. One other limitation of our approach is the added cost of run time, which may be burdensome when several analyses are needed.

While the analyses presented here focused on assessing outcomes among patients treated with ICS plus LABAs (and possibly a third standard controller medication), the model can be expanded and used as a framework to assess alternative therapies including biologic treatments. This would enable an assessment of differences between treatments on important domains in asthma management – such as lung function, asthma control, and exacerbations –on long-term patient outcomes and quality of life. This could then aid in identifying the optimal therapy for a given set of patient characteristics. Further enhancements may involve considering the chronic use of SCS (where relevant) and its impact on the risk of adverse events, as well as informing predictive equations from real-world longitudinal studies.

5. Conclusions

Patients with moderate-to-severe type 2 asthma and a history of exacerbations suffer from frequent exacerbations and reduced lung function and life expectancy. Capturing multiple conditions to simulate long-term outcomes in patients with asthma may provide more realistic projections of exacerbation rates, explicitly capturing the heterogeneity in this patient population.

CRediT authorship contribution statement

Tereza Lanitis: Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Asif H. Khan:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Irina Proskorovsky:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Ivan Houisse:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Andreas Kuznik:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Siddhesh Kamat:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Conrado Franco-Villalobos:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Florence Joulain:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Author declaration of individual contribution

All authors made substantial contributions to the conception, design and implementation of the model, manuscript drafting and approval for submission.

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Declaration of competing interest

IP, IH, and CF-V are employees of Evidera, which has received funding from Regeneron Pharmaceuticals, Inc and Sanofi for this analysis. TL was an employee of Evidera at the time the study was conducted. AHK and FJ are employees and stockholders of Sanofi. AK and SK are employees and stockholders of Regeneron Pharmaceuticals, Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2024.101390.

Data availability

The authors do not have permission to share data.

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