Biologic Therapies for Treatment of Moderate-To-Severe Uncontrolled Asthma Associated with Type 2 Inflammation

Modeling Analysis Plan

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Institute for Clinical and Economic Review

Table of Contents

Overview

This analysis plan details our modeling approach and outcomes to be assessed for the economic evaluation of biologic agents for the treatment of moderate-to-severe uncontrolled asthma with evidence of Type 2 inflammation. Refer to the research protocol for details on the systematic review of the clinical evidence on this topic.

2. Approach

The primary aim of this analysis is to estimate the cost-effectiveness of five biologic agents (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) for the treatment of moderate-to-severe uncontrolled asthma with evidence of Type 2 inflammation in adults and in children six years and older. This analysis is an update of our prior analysis on this topic.[1] The population for this updated review is designated with a broad intention to capture the United States' indications for all the relevant biologics, though not all of the therapies are indicated for use in younger children or patients with moderate asthma. Quality-adjusted survival and health care costs will be estimated for each biologic and its relevant comparators using the health care sector perspective. Costs and outcomes will be discounted at 3% per year. Incremental costs and outcomes will be calculated comparing each intervention to its comparator. The model will be developed in Microsoft Excel 2016 (Redmond, WA) and will follow the general structure of the Institute for Clinical and Economic Review (ICER) 2016 mepolizumab review with updates to accommodate best-available evidence and the additional agents.[1] The model framework and assumptions are described in detail below.

3. Methods

3.1 Overview and Model Structure

The decision analytic model structure will be informed by the primary aim, previous modeling evidence, the evidence review, and stakeholder input. The model structure will be based on formerly developed models assessing the cost-effectiveness of asthma biologics including mepolizumab and omalizumab.[1-3]

The Markov model will include three primary health states: 1) an asthma non-exacerbation state (i.e., day-to-day asthma symptoms), 2) an asthma exacerbation state (including three mutually exclusive subcategories: asthma-related event that requires an oral corticosteroid burst, asthma-related emergency department [ED] visit, or asthma-related hospitalization), and 3) death (including asthma-related mortality and other cause mortality) (Figure 1). The model structure is similar to

Biologic Therapies for Treatment of Moderate-To-Severe Uncontrolled Asthma Associated with Type 2 Inflammation – Modeling Analysis Plan 08/08/2018

other published asthma cost-effectiveness analysis (CEA) models, including ICER's 2016 report on mepolizumab and related peer-reviewed manuscript[1,3] and the omalizumab model for patients with severe uncontrolled asthma described in the National Institute for Health and Clinical Excellence (NICE) appraisal determination in 2013 and elsewhere.[2,4-8] Of note, compared to ICER's 2016 initial report on mepolizumab, this update's model structure allows for one evaluation of treatment response and a separate set of inputs for those who achieve treatment response. Non-responders are assumed to revert to standard of care with its associated average costs and outcomes. This inclusion of treatment response is consistent with NICE's mepolizumab 2017 technology appraisal guidance.[9]

Figure 1. Model Framework
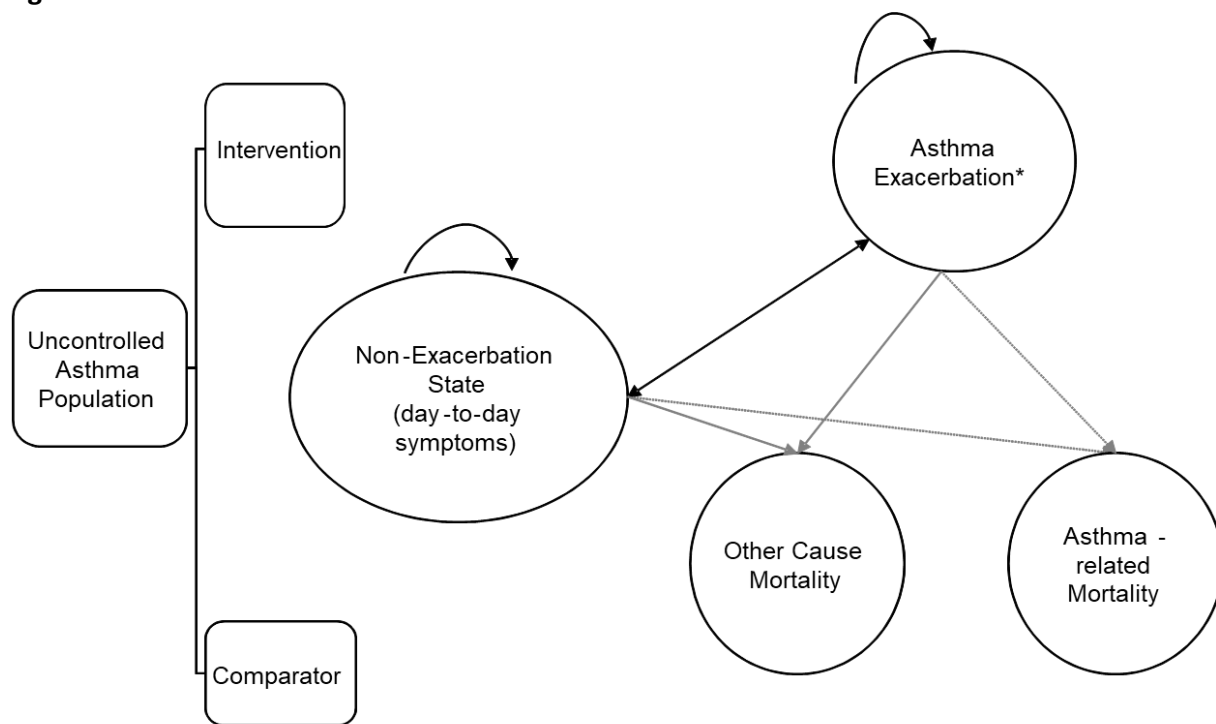
*Exacerbation could be defined into different subcategories:
1. Asthma related event that requires an oral steroid burst (but not emergency department or hospitalization)
2. Asthma related event that requires admittance to the emergency department (but not a hospitalization)
3. Asthma related event that requires a hospitalization

A lifetime horizon will be assumed in the base case, consistent with the ICER Value Framework and other asthma cost-effectiveness models.[8,10,11] Given uncertainty around duration of treatment with the asthma biologics, and the relatively limited incremental impact of mortality on the costs and outcomes in this population, we will evaluate shorter treatment time horizons in sensitivity analyses. The discount rate for all future costs and outcomes will be 3% per year.

Biologic Therapies for Treatment of Moderate-To-Severe Uncontrolled Asthma Associated with Type 2 Inflammation – Modeling Analysis Plan 08/08/2018

We will use a cycle length of two weeks to reflect the average length of time for an asthma exacerbation, and to be consistent with prior published cost-effectiveness analyses[2,5] and asthma guidelines that suggest exacerbation events should only be considered new after at least a 7-day period.[12]

Key clinical inputs for the model, informed by the evidence review, will include exacerbation rates (including oral steroid bursts, ED visits, and hospitalizations), chronic oral steroid use, asthma-related mortality, asthma control, biologic treatment response, and adverse events.

Model outcomes for each intervention will include total drug and non-drug health care costs, life years (LY) gained, quality-adjusted life years (QALYs) gained, and asthma exacerbations.

3.2 Treatments

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. Each intervention of interest, represented in the list of asthma biologics below, will be added on to a standard of care (SoC) comparator.

- Omalizumab 75-375 mg by subcutaneous injection once every 2 or 4 weeks
- Mepolizumab 100 mg by subcutaneous injection once every 4 weeks
- Reslizumab 3 mg/kg by intravenous infusion once every 4 weeks
- Benralizumab 30 mg by subcutaneous injection once every 4 weeks x 3; then every 8 weeks
- Dupilumab 300 mg by subcutaneous injection once every 2 weeks

Comparators

The comparators of interest will be SoC, typically defined as daily inhaled corticosteroids plus at least one additional controller therapy. SoC comparators will be flexible across each evaluated biologic intervention to mirror the control arms in randomized controlled trials.

Consistent with ICER's long-term value voting, pairwise comparisons between the interventions of interest will be performed only if the clinical evidence review finds sufficient evidence on relevant outcomes suggesting clinical separation.

3.3 Target Populations

The population of focus for the updated review will be adults and children ages six years and older with moderate to severe, uncontrolled asthma and evidence of Type 2 inflammation. The population is intentionally broad to capture the indicated populations for all of the biologics, though not all of the therapies are indicated for younger children or patients with moderate asthma. Severe asthma is defined as asthma that requires either oral corticosteroids for >50% of the year or the combination of high dose inhaled corticosteroids and a long acting beta agonist or other controller medication (leukotriene inhibitor/theophylline) to maintain control.[13] We recognize the definition of severe asthma has evolved over time. Uncontrolled asthma is defined by at least one of the following: frequent exacerbations (2+ bursts of oral steroid therapy lasting at least four days); serious exacerbations (hospitalization, ICU stay or mechanical ventilation); airflow limitation (forced expiratory volume in one second (FEV1) <80% predicted); or poor symptom control (Asthma Control Questionnaire >1.5; Asthma Control Test < 20).[13] Similarly, we recognize that the definition of an asthma exacerbation varies across the trials.[14] All individuals should be treated with high-dose inhaled corticosteroid therapy and at least one additional controller medication (e.g., long-acting beta agonists, leukotriene agonists, theophylline, or oral corticosteroids).

Table 1 presents the base-case model cohort characteristics for the five interventions of interest in this review (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab). Best-available evidence for Table 1 will be derived from the clinical review averaged across the included clinical review studies and biologics. Placeholder values are included from a mepolizumab trial for age and % female[15] and average weight from a recent omalizumab trial.[16] Only characteristics that are used within the economic model are displayed in Table 1. See the clinical review for further patient cohort characteristics.

Table 1. Base-Case Model Cohort Characteristics

Characteristic	Across All Biologic Agents*
Mean (SD) age	50[15]
Mean (SD) weight (kg)	85.4 (24.2)[16]
Percent female (%)	57%[15]

* placeholder values are displayed prior to evidence informed from the clinical review

3.4 Key Model Choices and Assumptions

Model assumptions are described in Table 2.

Biologic Therapies for Treatment of Moderate-To-Severe Uncontrolled Asthma Associated with
Type 2 Inflammation – Modeling Analysis Plan 08/08/2018

Table 2. Key Model Assumptions

Assumption	Rationale
Base-case utility for the non-exacerbation health state will be allowed to be different for biologic plus SoC versus SoC alone due to potential improvements in day-to-day symptoms.	Without direct elicitation of utilities in trials comparing biologic plus SoC versus SoC alone, we will rely on evidence of patient reported outcome instruments with known utility mappings. From the prior review, mepolizumab utility estimates were used through the SGRQ mapping algorithm.[17] Although other utility relationships are known for the Asthma Quality of Life Questionnaire, using different mapping algorithms across different instruments will not be explored unless evidence suggests differences across biologics on the same patient-reported outcome. NICE used the same approach for estimating the utility for mepolizumab and omalizumab.[9]
Treatment response will be included in the base-case for biologics with known evidence on treatment response and its associated clinical outcomes. Treatment response will not be included for those without treatment response evidence.	This structural inclusion in the updated review is consistent with recent asthma biologic health technology assessments and allows for treatment response to impact costs and outcomes.[9]
Additional risks of death given oral steroid burst will not impact mortality over and above the severe asthma-related mortality rate for all living health states in the model.	Increased mortality rates are included for exacerbations requiring emergency care (hospitalizations or ED visits) consistent with United Kingdom evidence. No added mortality is included for oral steroid burst exacerbations given the risk of death found from the United Kingdom evidence was similar to the annual U.S. risk of severe asthma-related mortality conditioned on age.[9,18]
Reduction in daily chronic oral glucocorticoid dose to a level of less than 5 mg is not harmful in terms of adverse events or disutility.	5 mg is a typical literature cutoff with chronic doses at or above 5mg being considered harmful.[19]
Asthma Control Questionnaire produces similar results for the 5, 6, and 7 versions.	Supporting literature[20]
Disutilities for hospitalizations, ED visits, and oral steroid bursts are assumed to be for two weeks.	Disutility is comparable to the NICE omalizumab and mepolizumab assessment groups' reference-case.[8,9]
In order to eliminate differences across baseline characteristics, such as age, that may impact lifetime costs and outcomes, we will average over baseline characteristics to estimate the same model cohort's age, gender, weight, and SoC annualized exacerbation rates.	The comparative clinical evidence will be allowed to be unique for each biologic plus SoC versus SoC alone; differences in SoC cohort characteristics across evidence sources should be normed as we do not suspect such characteristics to have a significant effect modification impact on the incremental lifetime findings. The normed characteristic ranges will be tested using sensitivity analyses.

2.5 Input Parameters

Model inputs were estimated from the clinical review, as well as from published literature and information provided by stakeholders. The inputs that informed the model are described below.

Clinical Inputs

Treatment Regimen

Table 3 indicates the inputs corresponding to the regimen for the specified interventions. Further, Table 3 includes the findings for each regimen as compared to SoC alone on the proportion of patients who are on oral corticosteroids at the end of study, generally from oral steroid sparing studies. Consistent with NICE reports, we assumed 100% compliance and adherence for those who respond to biologic add-on therapy.[8,9]

Table 3. Treatment Regimen

Characteristic	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Treatment dose	75-375 mg every 2 to 4 weeks (assumed 36 vials per year with wastage)[2]	100 mg every 4 weeks	3.0 mg/kg every 4 weeks (assumed 3 single-use 100mg/ml vials per administration or 39 per year with wastage)	30 mg every 4 weeks (first 3 doses) then every 8 weeks[21]	300 mg every 2 weeks[22]
Route of administration	Subcutaneous injection	Subcutaneous injection	Intravenous infusion	Subcutaneous injection	Subcutaneous injection
Chronic oral corticosteroid use post trial (%)	Not reported*	46% vs. 68% SoC[23]	Not reported*	Not reported*	31% vs. 67% SoC[24]

* For evidence "Not reported," by the time of the draft report, no difference will be assumed between biologic plus SoC versus SoC alone.

Exacerbation-Related Inputs

Inputs related to exacerbations are detailed in Tables 4 and 5. Until the ICER clinical evidence is available, we provided placeholder values from the largest randomized controlled trial or pooled trials to populate the exacerbation-related inputs needed for the model.

Biologic Therapies for Treatment of Moderate-To-Severe Uncontrolled Asthma Associated with Type 2 Inflammation – Modeling Analysis Plan 08/08/2018

Table 4. Exacerbation-Related Inputs: Interventions

Characteristic	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Rate Ratio for Exacerbations Resulting in Steroid Burst (without ED visit or hospitalization)*	0.62 (0.54, 0.71)[25]	0.45 (0.36-0.55)[14]	0.43 (0.33-0.55)[14]	0.59 (0.51-0.68)[14]	Not reported; assumed 0.54 (0.43-0.68)[22]
Rate Ratio for Exacerbations Resulting in ED visit (without hospitalization)*	0.40 (0.19, 0.82)[25]	0.36 (0.20-0.66)[14]	0.67 (0.39-1.17)[14]	0.68 (0.47-0.98)[14]	Not reported; assumed 0.54 (0.43-0.68)[22]
Rate Ratio for Exacerbations Resulting in Hospitalization*	0.49 (0.25, 0.97)[25]	0.31 (0.13-0.73)[14]	0.67 (0.39-1.17)[14]	0.68 (0.47-0.98)[14]	Not reported; assumed 0.54 (0.43-0.68)[22]

* Until the ICER clinical evidence is available, we provided placeholder values from the largest randomized controlled trial or pooled trials to populate the exacerbation-related inputs needed for the model.

Table 5. Exacerbation Related Inputs: Standard of Care

Characteristic	Standard of Care Across All Biologics
Annualized Exacerbation Rate, end of study (95% CI)*	1.74 (plausible range: 1.x -2.x)[15]
Proportion of Exacerbations Resulting in Steroid Burst (without ED visit or hospitalization)**	90%[15,25,26]
Proportion of Exacerbations Resulting in ED visit (without hospitalization)**	5%[15,25,26]
Proportion of Exacerbations Resulting in Hospitalization**	5%[15,25,26]

*Placeholder value based on mepolizumab trial[15]; this finding will be averaged across evidence sources and biologics with the minimum and maximum evidence source rate informing the plausible range.
** Placeholder proportions assumed based off of values from Ortega et al. 2014[15], Bousquet et al. 2005[25], and Castro et al. 2015[28].

Adverse Events

The evidence suggests no differences in costs or disutilities associated with biologics plus SoC versus SoC alone. This evidence may be replaced by any signals found from the ICER clinical review that is

deemed to significantly impact the long-run costs and outcomes. Note that chronic oral steroid use and its associated long-run costs and disutility is included within this updated review.

Asthma-related Mortality

Asthma-related mortality and other cause mortality will be modeled for all living health states (non-exacerbation and exacerbation).[9,18,27,28] There is a known increased risk of death linked with asthma-related hospitalizations as described by Watson and colleagues, who analyzed a United Kingdom database including 250,043 asthma-related hospital admissions to determine the mortality rate following hospitalizations.[27] For the asthma-related hospitalization exacerbation subcategory, the relationship of increased death, consistent with Watson et al., will be added to the background of asthma-related mortality and other cause mortality. Further, the NICE mepolizumab report suggested there may be an increased risk of death for other exacerbation-related subcategories.[9] The National Review of Asthma Deaths report is the first United Kingdom-wide investigation into asthma deaths and the largest worldwide study of this kind to date.[28] They used "death by location" to show indications for death at home, on the way to the hospital, and in the hospital. Due to this evidence, the NICE mepolizumab report suggested that the risk of death for those over age 45 years was 1.79% for those who experienced an asthma-related ED visit. They also suggested the risk of death for those over age 45 years was 0.38% for those who experienced an asthma-related oral steroid burst exacerbation. Given the annual risk of death for those with severe asthma from de Vries et al. was 0.4% per year and due to potential differences in death rates in the US,[20] we assumed no increased risk of death over that of severe asthma for the oral steroid burst asthma exacerbation sub category (see assumptions Table 2).

Utility Inputs

Model Health States

To adjust for potential quality of life differences, utilities will be applied for each model health state. Health state utilities will be derived from publicly available literature and applied to the disease states. The utilities for the non-exacerbation health state are presented in Table 6. The disutilities for other health states or events are displayed in Table 7.

The non-exacerbation health state utility value will be specific to the evidence for the biologic plus SoC versus SoC. For the non-exacerbation health state, the clinical evidence from Ortega et al. and Chupp et al. reported on the St George's Respiratory Questionnaire (SGRQ) for mepolizumab plus SoC versus SoC alone.[14] There is a published mapping between mean total SGRQ scores and the EQ-5D. The mean total SGRQ score of 38.9 for SoC[15] and 31.5 for mepolizumab plus SoC based on the pooled study mean difference[14] provided the required inputs for the aggregate mapping algorithm (EQ-5D utility = 0.9617 - 0.0013*SGRQ score - 0.0001*(SGRQ score)^2 + 0.0231* male).[17]

Without direct elicitation of utilities in trials comparing biologic plus SoC versus SoC alone, we relied on evidence of patient reported outcome instruments with known utility mappings. From the prior review, mepolizumab utility estimates were used through the SGRQ mapping algorithm.[17] Although other utility relationships are published for the Asthma Quality of Life Questionnaire and to a lesser extent, the Asthma Control Questionnaire, implementation of mapping algorithms across different instruments will not be explored unless evidence suggests differences across biologics on the same patient-reported outcome. Of note, the NICE mepolizumab report suggested that despite some studies showing significant omalizumab improvements in the Asthma Quality of Life Questionnaire, the base case when comparing mepolizumab to omalizumab used the mepolizumab utility signals for both products, similar to the approach described above.[9]

Table 6 shows the associated asthma patient-reported outcome responses for each respective biologic, the mean change difference in Asthma Control Questionnaire and the non-exacerbation mean health state utility for biologic plus SoC versus SoC alone. The values for patient-reported outcome responses are planned to be updated based on the clinical review.

Table 6. Asthma Patient-Reported Outcome Response and Corresponding Non-Exacerbation Utility

Characteristic	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Asthma Patient-Reported Outcome Measure	ACQ[29]	ACQ[14] SGRQ[14]	ACQ[14]	ACQ[14]	ACQ[22]
Asthma Patient-Reported Outcome Mean Change Difference versus SoC (95% CI)	-0.87 (-1.09, -0.65)[29]	**ACQ:** -0.42 (-0.56 to -0.28)[14] **SGRQ:** -7.4 (-9.5 to -5.3)[14]	-0.25 (-0.33 to -0.17)[14]	-0.20 (-0.29 to -0.11)[14]	-0.22 (-0.36, -0.08)[22]
Non-Exacerbation Mean Health State Utility for biologic plus SoC vs. SoC alone (SE)*	Biologic plus SoC 0.830 (0.010) SoC 0.768 (0.015)	Biologic plus SoC 0.830 (0.010) SoC 0.768 (0.015)	Biologic plus SoC 0.830 (0.010) SoC 0.768 (0.015)	Biologic plus SoC 0.830 (0.010) SoC 0.768 (0.015)	Biologic plus SoC 0.830 (0.010) SoC 0.768 (0.015)

*Utility mapping based on mepolizumab plus SoC versus SoC alone for the St. George's Respiratory Questionnaire; mepolizumab utility values for the non-exacerbation health state were assumed similar for the other biologics plus SoC so long as the clinical review suggests comparable Asthma Control Questionnaire mean change differences versus SoC alone.

Biologic Therapies for Treatment of Moderate-To-Severe Uncontrolled Asthma Associated with Type 2 Inflammation – Modeling Analysis Plan 08/08/2018

Treatment Disutilities

Disutilities for the exacerbation health states will be assumed to be the same across treatment strategies (i.e. the same for biologic plus SoC versus SoC alone).[30] Given a dearth of data on the utility associated with an asthma-related ED visit, we will assume the mid-point between the values for hospitalization and oral steroid burst events. We will assign the pre-post decrement in utilities observed in Lloyd et al.[30] for exacerbation-related events. Two weeks duration was assumed for all exacerbation health states, consistent with the model cycle. Although an oral steroid burst or ED visit does not typically last two weeks, the stress and anxiety related to these events may remain over a two-week period.

Severe asthma flare-ups are commonly treated through prescribed bursts of oral corticosteroids (OCS), ranging in intensive treatment periods from five days to two weeks. While consistent use of OCS is associated with a greater likelihood of side effects, we'd like to clarify that there is a clear-cut distinction between chronic OCS use and a steroid burst.[31,32]

The disutility of chronic OCS for the proportion of patients using >5 mg daily (-0.023)[7] will be assumed to be equivalent to the disability-adjusted life years (DALYs) that were weighted by the proportion of chronic oral corticosteroid user who developed the following adverse events: type 2 diabetes, myocardial infarction, glaucoma, cataracts, ulcer, osteoporosis, and stroke. Table 7 displays the disutilities present in the model.

Table 7. Disutilities

Characteristic	Disutility	Source
Steroid Burst*	-0.1	Lloyd et al. 2006[30]
ED Visit*	-0.15	Lloyd et al. 2006[30] and assumption
Hospitalization*	-0.20	Lloyd et al. 2006[30]
Chronic Oral Corticosteroid Use**	-0.023	Norman et al. 2013[7]

* 2-week duration
** Lifetime duration

Treatment Response Inputs

Treatment response is allowed at one time point within the base-case model framework. Without known evidence related to a biologic's treatment response, we will assume that the trial efficacy signals persist, and biologic treatment continues for the duration of the model outside the trial period. Evidence needs for including treatment response within the analysis are the following:

- Treatment response definition
- Evaluation time of response (weeks after initiation)

Biologic Therapies for Treatment of Moderate-To-Severe Uncontrolled Asthma Associated with Type 2 Inflammation – Modeling Analysis Plan 08/08/2018

- Proportion who respond
- Exacerbation rate ratio for responders (by subcategory if available)
- Response utility for non-exacerbation health state.

According to the NICE mepolizumab response evidence,[9] treatment response evidence needs were presented for mepolizumab and for omalizumab (Table 8). Treatment response was associated with an increase in utility of 0.01 for those who responded and remained on mepolizumab compared to the overall trial-based mepolizumab non-exacerbation utility mapping.[9] Unless stronger evidence emerges by biologic response, we will assume a comparable increase in utility of 0.01 for other biologics with evidence of treatment response. We will assume the percentage who respond will continue on biologic plus SoC with the remaining percentage who do not respond reverting back to SoC alone (with SoC average costs and outcomes).

Table 8. Response

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Definition	The definition of response was based on the physician global evaluation of treatment effectiveness (complete or marked improvement in control)[9,33]	Patients with a decrease or no increase in annualized exacerbation rate from that observed at baseline are considered responders[9,34]	Clinically meaningful reduction in the number of severe exacerbations needing systemic corticosteroids or a clinically significant reduction in continuous oral corticosteroid use while maintaining improving asthma control.[35]	Not known	Not known
Time Point	16 weeks	12 months	12 months	Not known	Not known
Proportion Responding	60.5%[9]	90.9%[9,14]	Not known	Not known	Not known
Exacerbation Relative Risk versus SoC and 95% CI	0.360 (0.204, 0.507)	0.550[9,14]	Not known	Not known	Not known
Non-Exacerbation Mean Health State Utility for biologic plus SoC responders*	0.840 (0.009)[9]	0.840 (0.009)[9]	Not known	Not known	Not known

*Utility mapping based on mepolizumab plus SoC responders versus SoC alone for the St. George's Respiratory Questionnaire; utility values for biologic responders within the non-exacerbation health state will be assumed similar for the other biologics plus SoC unless biologic specific evidence is available.

Cost Inputs

Treatment Costs and Details

The unit cost for each intervention is reported in Table 9. We did not find estimates of net price for all biologics in the SSR Health database and will thus rely on the Federal Supply Schedule (FSS) prices for these interventions unless manufacturers provide us with a net price for their respective biologic for this review. Further, threshold prices will be calculated at the three cost-effectiveness thresholds ($50,000, $100,000 and $150,000 per QALY gained).

Treatment-related costs (SoC and asthma biologics) will be assigned by treatment scenario for all living health states (exacerbation and non-exacerbation states).

Table 9. Treatment Costs and Details: Interventions

Characteristic	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Federal Supply Schedule (units)	$965.76 (150 mg vial)	$2,553.97 (100 mg)	$847.04 (100mg/ml vial)	$4,728.23 (30 mg)	$2,774.65 (2 x 300 mg)
Manufacturer Net Price					

Healthcare Utilization Inputs

Health Care Utilization Costs

Table 10 details the healthcare utilization unit costs that will be used in the model. Unit costs for healthcare utilization were the same across different treatments and populations.

Unit costs for asthma-related hospital stays, emergency department visits, and oral steroid asthma-related exacerbations were estimated using a cohort of 222,817 US patients with asthma from the Clinformatics DataMart Multiplan dataset. Costs were estimated for 30-day periods after an exacerbation and were summarized as mean healthcare cost per exacerbation and inflated to 2018 US Dollars.[36]

There are likely standard of care differences within and across biologic therapies. Given that the biologic interventions are indicated as add-on therapies to standard of care, the annual cost of standard of care in an incremental analysis compared to standard of care alone will cancel out to an

Biologic Therapies for Treatment of Moderate-To-Severe Uncontrolled Asthma Associated with Type 2 Inflammation – Modeling Analysis Plan 08/08/2018

approximate incremental difference of $0. Therefore, we assumed the same annualized cost of standard of care from the prior mepolizumab ICER review and consistent with Whittington et al. 2018.[3]

The chronic use of oral corticosteroids likely results in adverse clinical events and their associated costs. We will assume that doses of daily oral corticosteroids above 5 mg were potentially harmful to the patient in terms of adverse events and could impact day-to-day living. Annual US costs associated with an individual who uses oral corticosteroids chronically above the 5mg dose level or uses oral steroids for more than six months was $7439.[19] This annual estimate compared chronic oral steroid users to asthma patients who did not use oral steroids.

Finally, costs associated with biologic administration are also displayed in Table 10.

Table 10. Healthcare Utilization Cost Inputs

Healthcare Unit Costs	Unit Cost (2018 USD)	Source
Exacerbation-Related Steroid Burst (SD)	$1,297 (2,214)	Suruki RY et al. 2017[36]
Exacerbation-Related ED Visit (SD)	$1,747 (2,320)	Suruki RY et al. 2017[36]
Exacerbation-Related Hospitalization (SD)	$7,632 (6,118)	Suruki RY et al. 2017[36]
Annual cost for standard of care (95% interval)	$6,105 ($4,967, $7,358)	Whittington et al. 2018[3]
Annual cost of long-term oral corticosteroid use with adverse events	$7439	Lefebvre et al. 2017[19]
Intravenous treatment administration (1st hour) for reslizumab	$136.41 per administration	Physicians' Fee and Coding Guide, 2016 (HCPCS code 96413)[37]
Office visit treatment administration for subcutaneous office-administered biologics	$74.16 per administration	Physicians' Fee and Coding Guide, 2016 (HCPCS code 99213)[37]

3.6 Model Outcomes

Health outcomes and costs will be dependent on time spent in each health state, clinical events, and direct medical costs. The health outcomes of each intervention will be evaluated in terms of life years gained and QALYs gained. Quality of life weights will be applied to each health state, including potential quality of life decrements associated with chronic oral steroid use. The model will include direct medical costs, including but not limited to costs related to the interventions and their administration, condition-related care including treatment of exacerbations, and serious adverse events.

The primary model outcome will be expressed in terms of the incremental cost per QALY gained and incremental cost per life year gained. Other model outcomes will include exacerbations and deaths summarized as average per person year rates.

3.7 Analysis

Each model cycle will last two weeks. Patient quality-adjusted survival and health care costs will be estimated for each model cycle and then summarized over the model time horizon for each treatment option. Differences in quality-adjusted survival and costs between each treatment and comparator will be used to calculate incremental cost-effectiveness ratios.

Sensitivity Analysis

We will conduct one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses will also be performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Additionally, we will perform a threshold analysis by systematically altering the price of the acquisition cost for each treatment option to estimate the maximum prices that would correspond to given willingness to pay (WTP) thresholds.

Scenario Analyses

Given available evidence on patient health-state level costs and lost productivity to the patient and caregiver, the perspective will be expanded to a modified societal one. If data are available that accurately define other populations across all therapies, then selected populations may be analyzed as a separate scenario including high eosinophilic asthma.

Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using reviewers. Finally, we will compare results to other cost-effectiveness models in this therapy area.

3.8 Acknowledgements

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Biologic Therapies for Treatment of Moderate-To-Severe Uncontrolled Asthma Associated with Type 2 Inflammation – Modeling Analysis Plan 08/08/2018

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