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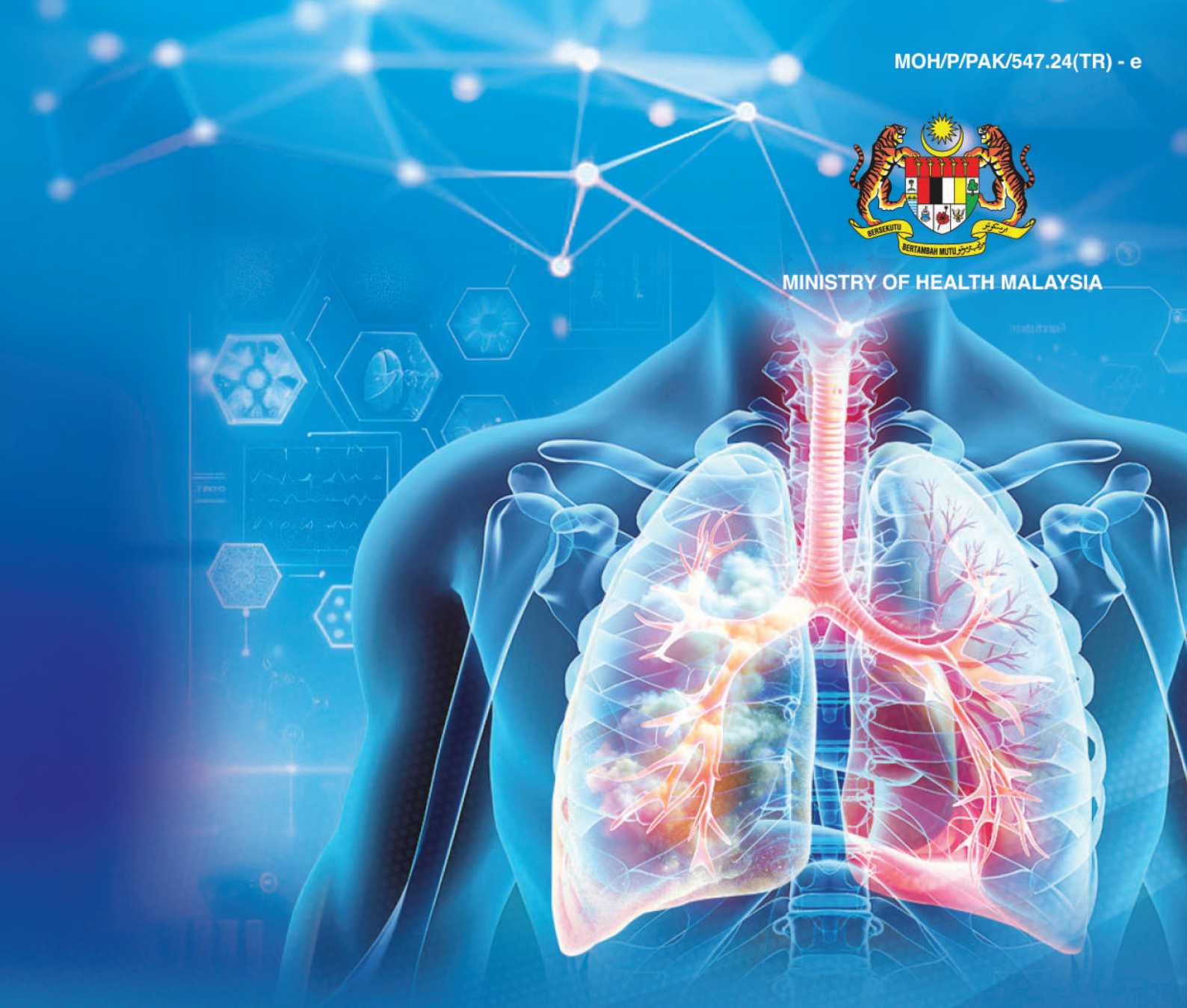

BIOLOGICS IN SEVERE ASTHMA

MAHTAS
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA

KEMENTERIAN KESIHATAN MALAYSIA

HEALTH TECHNOLOGY ASSESSMENT REPORT

BIOLOGICS IN SEVERE ASTHMA

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

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HTA Report
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EXECUTIVE SUMMARY

BACKGROUND

Asthma affects more than 300 million people worldwide. In Malaysia, the asthma prevalence was estimated between 8.9% and 13.0% in children and 6.3% in adults (National Health Morbidity Survey 2011). According to Global Initiative for Asthma (GINA) 2024, global severe asthma prevalence was approximately 3% to 10% of people with asthma have severe asthma.

According to GINA 2024, severe asthma is asthma that is uncontrolled despite adherence with optimised high-dose ICS-LABA therapy and treatment of contributory factors or that worsens when high-dose treatment is decreased. Type 2-inflammation of asthma (T2-asthma) is found in majority of patients with severe asthma and characterised by cytokines production such as interleukin-4 (IL-4), IL-5 and IL-13 as an adaptation process towards immune system on recognition of allergens. The immune system also triggered production of other cytokines including thymic stromal lymphopoeitin (TSLP).

Biologics therapies for severe asthma that are currently in the market target the key mediators of the T2-asthma to reduce the severity of the asthma. These biologics are anti-IL5 (mepolizumab), anti-IL5α (benralizumab), anti-IL4α (dupilumab) and anti-TSLP (tezepelumab).

Technical features

i. Mepolizumab – anti-IL5
Mepolizumab has a marketing authorisation in United Kingdom (UK) as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescent and children aged 6 years and older. The usual paediatric (6 – 12 years) dose is 40mg subcutaneous (SC) every 4 weeks (Q4W) and 100mg SC every 4 weeks for 12 years and older.

ii. Benralizumab – anti-IL5 receptor α
Benralizumab received marketing approval as an add-on therapy in adult patients with severe eosinophilic asthma who were inadequately controlled despite high-dose inhaled corticosteroids (ICS) plus long-acting beta-agonists (LABA). Benralizumab is approved for patients as young as 6-years old. The recommended dose for adult (12 years and older) is 30mg Q4W for the first 3 doses then once every 8-weeks (Q8W), given by subcutaneous injection using auto-injector. Meanwhile for children 6 – 11 years, the dose is based on bodyweight. For weight ≥35 kg the dose is 30 mg Q4W for the first 3 doses and then once Q8W. For weight <35kg the dose is 10 mg Q4W for the first 3 doses, then once Q8W.

iii. Dupilumab – anti-IL4 receptor α
Dupilumab is approved as an add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO [fractional exhaled nitric oxide] who are inadequately controlled with high dose ICS [inhaled corticosteroid] plus another maintenance treatment. Dupilumab is approved for patients ≥6-years old. The initial loading dose is 600 mg subcutaneously, followed by a subsequent dose of 300 mg every 2 weeks (Q2W).

iv. Tezepelumab - anti-TSLP
Tezepelumab is first approved biologics that targets thymic stromal lymphopoietin (TSLP). Received regulatory approval from USFDA in 2021 for treatment of severe asthma in patients over 12 years of age. Unlike other biologic therapies, it is not restricted to patients with allergic or refractory eosinophilic asthma. The recommended dose is 210mg Q4W, given by subcutaneous.

POLICY QUESTIONS

1. Should biologics be used to treat severe asthma?
2. Which biologics should be used to treat different severe asthma phenotypes?

OBJECTIVES

1. To assess the effectiveness and safety of biologics in treatment of severe asthma with regards to patient outcomes such as asthma control (exacerbation, spirometry, symptoms, quality of life [QoL], oral corticosteroid [OCS] sparing effects, hospital admission, Emergency Department ([ED] visit etc), mortality and adverse events or complications.

2. To assess the economic implication, social, ethical, and organisational aspects related to the biologics in treatment of severe asthma.

   The following **research questions** will be addressed:

   i. What is the best option for severe asthma?
   ii. Does the different types of biologics affect different types of severe asthma?
   iii. Is biologics in treatment of severe asthma cost-effective?
   iv. Which is the best type of biologics for treatment of severe asthma in terms of efficacy and cost-effective?
   v. What is the social, ethical, and organisational implication/ impact related to the use of biologics in treatment of severe asthma?

METHODS

Literature search was developed by the main author and an Information Specialist who searched for published articles pertaining to biologics treatment in severe asthma. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to June 2023, EBM Reviews - Health Technology Assessment, EBM Reviews - Cochrane Database of Systematic Review, EBM Reviews - Cochrane Central Register of Controlled Trials, and EBM Reviews - NHS Economic Evaluation Database. Parallel searches were run in PubMed, US FDA and INAHTA database. Search was limited to articles in English and in human.

RESULTS
PART A: SYSTEMATIC REVIEW

A total of **643** records were identified through the Ovid interface and PubMed while **5** were identified from other sources (references of retrieved articles). Following the removal of **594** duplicates and irrelevant titles, **53** titles were found to be potentially relevant, and abstracts were screened using the inclusion and exclusion criteria. Of these, **52** relevant abstracts were retrieved in full text. After reading, appraising, and applying the inclusion and exclusion criteria to the **52** full text articles, **30** full text articles were included in this report. **Twenty-seven (27)** articles were excluded as those primary studies were already included in systematic review and NMA / MA (n = 7) narrative reviews (n = 11) and overlapped with other included studies (n = 9).

The 30 full text articles which were finally selected in this review comprised of **three** systematic reviews with NMA, **seven** systematic reviews with MA, **five** systematic review, **eleven** RCTs, **one** observational study and **three** economic evaluation studies of individual biologics (dupilumab, mepolizumab and benralizumab).

All studies included were published in English language between **2018** and **2024** and were conducted in the United States, United Kingdom, Canada, Japan, Turkey, Singapore, Spain etc.

EFFECTIVENESS

Asthma exacerbations

All four biologics (mepolizumab, benralizumab, dupilumab and tezepelumab) showed consistent improvement in asthma exacerbation rate (AER) as well as in annual asthma exacerbation rate (AAER) compared to placebo. The pooled analysis study showed that the biologics significantly reduced the AAER by 44% (rate ratio [95% CI 0.52 to 0.62]; I^2 = 58.4%).

In term of subgroup analysis based on baseline blood eosinophils count (BEC), all four biologics showed consistent greater reductions in asthma exacerbation among patients with high BEC level (≥300 cells/uL) compared to low BEC count (<300 cells/uL). The pooled rate ratio was 0.38 (95% CI 0.29 to 0.49) versus 0.67 (95% CI 0.55 to 0.83); $P_{subgroup\_heterogeneity}$ = 0.001.

Asthma control

The most common tool reported involving all four biologics was Asthma Control Questionnaire (ACQ) score. All four biologics showed a positive effect in reducing the ACQ score when compared to placebo. Meta-analysis of mepolizumab, benralizumab, dupilumab and tezepelumab reported a reduction in the ACQ score by -0.34 points (95% CI -0.46 to -0.23, I^2 = 89.5%). However, the reduction did not reach the minimal clinically important difference (MCID) for the ACQ score (-0.50 points). The biologics were also found to improve the ACQ score in patients with high BEC level (≥300 cells/uL) compared to low BEC level (<300 cells/uL).

Lung function

Assessment of lung function in all four biologics was an improvement in forced expiratory volume in 1 second (FEV1). Studies retrieved showed that mepolizumab, benralizumab, tezepelumab and dupilumab significantly increased the FEV1 when compared to placebo. The pooled analysis of all four biologics reported 0.11L (95% CI 0.09 to 0.14); I^2 = 50.1% improvement.

In subgroup analysis of high (≥300 cells/uL) and low (<300 cells/uL) BEC level, all four biologics showed greater and significant improvement in high BEC level compared to low BEC level. The recent pooled result was available for benralizumab, dupilumab and tezepelumab; 0.18L (95% CI 0.14 to 0.22) versus 0.07L (95% CI 0.04 to 0.10); $P_{subgroup\_heterogeneity}$ <0.001. Meanwhile, for mepolizumab when compared to placebo, the result was 0.1L (95% CI 0.04 to 0.15) among patients with high BEC level.

Hospital admission and Emergency Department (ED) visit

Reduction in hospital admission and ED visit due to exacerbation was observed in all biologics. The pooled result of mepolizumab, benralizumab and tezepelumab showed 60% reduction with rate ratio 0.40 [95% 0.27 to 0.60], I^2 = 32%). According to network meta-analysis, reduction in hospitalisation and ED visit due to exacerbation showed no significant difference between mepolizumab, benralizumab, dupilumab and tezepelumab as the tezepelumab leads other biologic in SUCRA ranked at 95%.

In subgroup analysis of BEC level, tezepelumab, dupilumab, benralizumab and mepolizumab reduced the hospitalisation and ED visit in patients with high BEC level (≥300 cells/uL) where greatest reduction was observed in tezepelumab (90% reduction).

Reduction in oral corticosteroid intake (OCS)

Based on the included studies, benralizumab, mepolizumab, dupilumab and tezepelumab increased the probability of OCS dose reduction to <5mg/day. In a meta-analysis of all four biologics, 74% reduction was reported with a risk ratio of 1.74 (95% CI 1.23 to 2.46); I^2 = 44.1%. The results also showed high probability of the biologics to reduce more than 50% of OCS which was 68% (95% CI 1.29 to 2.19; I^2 = 27.2%. The probability of OCS discontinuation also increased with biologics compared to placebo; the pooled rate ratio between benralizumab, dupilumab and tezepelumab was 1.63 (95% CI 1.29 to 2.19; I^2 = 27.2%) and for mepolizumab the rate ratio was 1.61 (95% CI 1.07 to 2.41). The reduction in OCS occurred as early as four weeks of biologics treatment.

One benralizumab extension study reported on sustained reduction of OCS used in high BEC level subgroup ranging from 17% to 29% with median dose reduction of 10mg – 15mg to 5mg – 10mg.

Other outcomes

Reduction in blood eosinophils (bEos)

Many studies reported that mepolizumab, benralizumab, and tezepelumab reduced blood eosinophils in severe asthma. The pooled bEos reduction reported for mepolizumab, benralizumab, and tezepelumab were -609.19 cell/uL (95% CI -793.20 to -425.68), -518.68 cell/uL (95% CI -820.24 to -217.12), and (-151.05 cells/uL (95% CI -165.99 to -136.12), respectively.

Reduction in Fractional Exhale Nitric Oxide (FeNO) level

Significant reduction in FeNO level was reported in mepolizumab (-14.23 ppb [95% CI -19.71 to -8.75], tezepelumab (-12.41 ppb [95% CI -14.28 to -10.53]) and dupilumab compared to placebo. The FeNO reduction concentration with tezepelumab was observed as early as week-2 and the reduction were sustained up to 52- to 104-weeks.

Reduction in Serum IgE

Reduction in serum IgE was reported in dupilumab and tezepelumab compared to placebo. The extension studies of both biologics reported a sustained reduction of serum IgE up to 104-weeks; -122.90 IU/mL (95% CI -167.80 to -78.01), p = 0.00, I2 = 9.40% reduction in tezepelumab and 80% to 90% reduction with dupilumab.

SAFETY

According to the included studies, a few adverse events lead to the discontinuation of biologics treatment. Different biologics showed different risk of discontinuation such as RR 1.65 (95% CI 0.79 to 3.45) in benralizumab, RR 1.03 (95% CI 0.46 to 2.30) in dupilumab, RR 0.65 (95% CI 0.36 to 1.16) and RR 0.68 (95% CI 0.34 to 1.35) in tezepelumab. The reasons of the discontinuation were anaphylactic reaction, malignancy, live function abnormality, asthma-related event requiring intubation, pulmonary TB, non-asthma related events, no clinical improvement, severe headache, severe arthralgia, allergic rash, and conjunctivitis, persistent eczematous (on face, trunk and upper limb) and pruritis. Death during study period showed no difference between biologics and control groups (risk ratio 0.91 [95% CI 0.39 to 2.09], I^2 = 0%).

On the other hand, the most common adverse events reported in both biologics and placebo were nasopharyngitis, upper respiratory infection, headache, and injection-site reaction.

ECONOMIC EVALUATIONS

Overall, most of the included studies reported an ICER/QALY gained was higher than Willingness-to-Pay (WTP) threshold. According to the studies, the potential saving was related to decrease rate of hospitalisation, ED care, primary care visits and the management of clinically significant exacerbations. In economic evaluation study of mepolizumab in Singapore, the ICER/QALY was SGD335,486 (US$238,195) and the ICER/LY gained was SGD208,238 (US$147,846) with average of five exacerbations were avoided per patient over a lifetime. However, the ICER was above Singapore WTP threshold (SGD250,00). Meanwhile, an economic evaluation study of benralizumab in Spain reported that benralizumab was within Spain WTP (€24,000) as the ICUR obtained was €18,177/QALY with Net Monetary Benefit obtained with benralizumab was €813. Another economic evaluation was on dupilumab in Japan. The study compared dupilumab with benralizumab, mepolizumab and omalizumab where the study reported that dupilumab was cost-effective compared to benralizumab and mepolizumab but not cost-effective compared to omalizumab. One of the key drivers for this analysis was price of each biologic per vial.

ORGANISATIONAL

One study assessed the effects of tezepelumab on healthcare utilisation (HCU) among patients with severe asthma. The study showed that, tezepelumab showed fewer asthma-related unscheduled specialist visits, fewer telephone calls with a healthcare provider, lesser ambulance transports due to asthma, and fewer home visits from a healthcare provider than placebo.

SOCIAL

The included studies reported that mepolizumab, benralizumab, dupilumab and tezepelumab improved quality of life (QoL) by improving the Asthma Quality of Life Questionnaire (AQLQ), and St George's Respiratory Questionnaire (SGRQ). One dupilumab extension study assessed the quality of life among paediatric patients as well as their caregivers. The LS mean difference (LSMD) in dupilumab versus placebo showed significant improvement since week-24 onwards and at week-52 the LSMD was 0.34 (95% CI 0.16 to 0.52); p = 0.0002 in Paediatric Asthma Quality of Life Questionnaire Interviewer-Administered (PAQLQ(S)-IA), and 0.25 (95% CI 0.00 to 0.50; p = 0.0531) at week-24 and 0.47 (95% CI 0.22 to 0.72; p = 0.0003) at week-52 in Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ-IA) global score. According to the checklist, the improvements was observed in individual domain scores of emotional functions, activity limitation and symptoms.

PART B: ECONOMIC EVALUATION

A cost-effectiveness analysis (CEA) from the perspective of MOH was conducted.

Objectives

The objective of this CEA is to assess the incremental cost-effectiveness ratio (ICER) between asthma biologics (tezepelumab, benralizumab, mepolizumab and dupilumab) and Standard of Care (SoC) for the treatment of severe asthma.

Methods and Model Structure

Five-health states Markov model with a four-week cycle and a lifetime horizon was constructed and analysed using Microsoft Excel Workbook 2021.

The primary outcomes included total cost and quality-adjusted life years (QALYs) gained for each intervention in consideration. An annual discount rate of three per cent was applied to both costs and outcomes estimated.

The input on the treatment effects was drawn from the systematic review carried out in Section A of this report. Meanwhile, costs for drug acquisition and disease management were based on available local data. Health utility values for asthma health states and other key parameters applied to the model were sourced from previously published studies. This analysis also was based on one time of the Malaysian per capita gross domestic product (GDP) in 2022 (MYR 54,863 /QALY).

Results

The model indicated that adding biologics to the SoC improves QALYs but incurred higher costs. The ICERs for tezepelumab, benralizumab, mepolizumab, and dupilumab were RM 759,126, RM623,901.46, RM 1,543,407, and RM 883,807 per QALY gained, respectively. All ICERs exceeded the Malaysian Willingness to Pay (WTP) or cost-effectiveness threshold of one GDP per capita per QALY gained.

In addition, three scenario analyses were performed in which the provision of shorter treatment duration, the extension of dose treatment frequency and hypothetical percentage reduction of drug costs were explored. All the interventions showed reductions in the ICERs but were not cost-effective. Moreover, all drugs required more than 90% cost reduction, except for benralizumab which requires 81% cost reduction for the ICERs to be cost-effective.

One-way sensitivity analysis was performed to assess key drivers that impacted the estimated ICERs the most. Health utility value for long-term OCS use and drug cost were noted to show a remarkable impact on the ICERs. Meanwhile, a probabilistic sensitivity analysis was conducted to assess the robustness of model results. A Monte Carlo simulation of 1000 iterations was performed and the model results were shown to be consistent and robust.

CONCLUSION

Based on the above review, mepolizumab, benralizumab, dupilumab and tezepelumab significantly reduced exacerbations, ED visits and hospitalisation, improved lung function, asthma control, quality of life and reduced the use of oral corticosteroids especially among patients with high level of BEC (≥300 cells/uL).

In terms of economic implications, these biologics are effective but at a higher cost as the ICER/QALY are higher than the WTP threshold.

RECOMMENDATION

Biologics (mepolizumab, benralizumab, dupilumab or tezepelumab) may be used as an add-on therapy for severe asthma in patients with these criteria; high BEC level (≥300 cells/uL) and unresponsive to the optimal therapy. Taking into consideration the economic implications, effective price negotiations may improve the cost-effectiveness of this treatment.

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ABBREVIATIONS

AEs	Adverse events
AAER	Annual asthma exacerbation rate
ACT	Asthma control test
ACQ	Asthma control questionnaire
ADA	Anti-drugs antibodies
AER	Asthma exacerbation rate
AQLQ	Asthma Quality of Life Questionnaire
CRS	Chronic Rhinosinusitis
ED	Emergency department
FEV1	Forced Expiratory Volume
ICS	Inhale corticosteroid
LABA	Long-acting beta agonist
MA	Meta-analysis
mOCS	Maintenance oral corticosteroid
NMA	Network Meta-analysis
NP	Nasal polyps
OCS	Oral corticosteroid
ICER	Incremental Cost-Effectiveness Ratio
ICUR	Incremental Cost-Utility Ratio
Ig-E	Immunoglobulin-E
IL-4/5/13	Interleukin-4/5/13
IL-4α/5α	Interleukin-4/5 alpha receptor
PACQLQ	Paediatric Asthma Caregiver's Quality of Life Questionnaire
PAQLQ	Paediatric Asthma Caregiver's Quality of Life Questionnaire
PSA	Probabilistic Sensitivity Analysis
QoL	Quality of Life
RCT	Randomise Controlled Trial
SAEs	Serious adverse events
SGRQ	St George's Respiratory Questionnaire
SoC	Standard of Care
SR	Systematic Review
TEAE	Treatment-emergent adverse events
TSLP	Thymic stromal lymphopoietin
USFDA	United State Food and Drugs Administration
WTP	Willingness to Pay

1.0

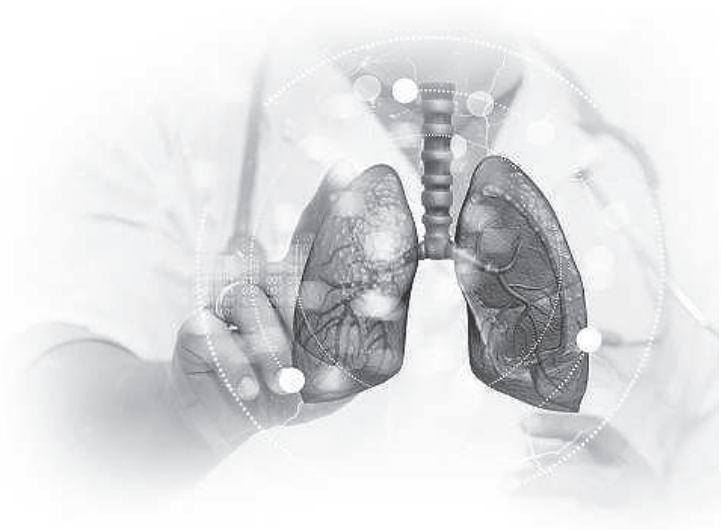
BACKGROUND

1.0 BACKGROUND

Asthma affects more than 300 million people worldwide.[1] In Malaysia, the prevalence is estimated between 3.4% in children (ages 6 - 17 years old) and 6.2% in adults.[2] According to World Health Organization (WHO), up to 10% of adults and 2.5% of children with asthma have severe asthma, with a reduced quality of life and an increased risk.[1]

According to GINA 2024, severe asthma is asthma that is uncontrolled despite adherence with optimised high-dose ICS-LABA therapy and treatment of contributory factors or that worsens when high-dose treatment is decreased.[3] Meanwhile, severe childhood asthma (SCA) is defined as asthma that remains uncontrolled even after adherence to optimise combination of high-dose inhaled corticosteroid and long-acting beta-agonist (ICS-LABA) and despite management of contributory factors and comorbidities, or asthma that worsens when high dose treatment is decreased.[4]

Despite evidence-based asthma management recommendations and treatments, asthma control is still suboptimal.[5] A local study on asthma control reported that 37% patients had well-controlled asthma, 36% were partly controlled and 27% uncontrolled.[5] Patients with severe, uncontrolled asthma are at risk of recurrent asthma exacerbations and hospitalisations even with standard treatment and consequently experience poor health-related quality of life. Additional treatment options for these patients include biologic therapies.[6,7]



Generally, there are two main types of severe asthma which are categorised based on the individual's response to treatment; Type 2 inflammation and Non-Type 2 inflammation.[8] Type 2-inflammation of asthma (T2-asthma) is found in majority of severe asthma and characterised by cytokines production such as interleukin (IL)-4, IL-5 and IL-13 as an adaptation process towards immune system on recognition of allergens. The immune system also triggered production of other cytokines included thymic stromal lymphopoeitin (TSLP).[3]

Current approved biologic therapies for severe asthma target key mediators of type 2 (T2) inflammation in eosinophilic or allergic asthma, including interleukin (IL)-5, IL-4, IL-13 and immunoglobulin E (IgE), and are prescribed based on indicators of these phenotypes, including dependence on oral corticosteroids (OCS) for disease control. The biologics reduce asthma exacerbations, improve lung function, reduce oral corticosteroid use and improve quality of life in appropriately selected patients.[9] At the moment, there are five approved biologics (monoclonal antibody) available for severe asthma **omalizumab, mepolizumab, reslizumab, benralizumab** and **dupilumab**.[6,7] Another biologic is **tezepelumab**, the anti-thymic stromal lymphopoietin.[4] For this HTA, only four monoclonal antibodies will be reviewed which are mepolizumab, benralizumab, dupilumab and tezepelumab.

Reasons for request

1. Severe asthma in spite of globally showing 3-14% of all asthma but recent local studies have shown that prevalence of uncontrolled asthma including severe asthma is about 20%.

2. In spite of low percentage but they consume much of health care facilities once they are admitted and seen in hospital facilities.

3. To review and assess the cost effectiveness of biologics systematically as they have been shown to have good response and able to reduce the morbidity and hospitalisation in this group of patients.

2.0

TECHNICAL FEATURES

2.0 TECHNICAL FEATURES

Technical features of reviewed biologics in severe asthma.

a. Mepolizumab – anti-IL5

Has a marketing authorisation in UK as an add-on treatment for severe eosinophilic asthma in adults, adolescent and children aged 6 years and older.[10] The usual paediatric (6 – 12 years) dose is 40mg subcutaneous (SC) every 4 weeks (Q4W) and 100mg SC every 4 weeks for 12 years and older.

b. Reslizumab – anti-IL5

As an add-on therapy for the treatment of severe eosinophilic asthma that is inadequately controlled in adults (≥18-years old).[11]

c. Benralizumab – anti-IL5 receptor α

As add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists. Benralizumab is approved for patients as young as 6-years old.[12] The recommended dose for adult (12 years and older) is 30mg Q4W for the first 3 doses then once Q8W, given by subcutaneous injection using auto-injector.[12] Meanwhile for children 6 – 11 years, the dose is based on bodyweight. For weight ≥35 kg the dose is 30 mg Q4W for the first 3 doses and then once Q8W. For weight <35kg the dose is 10 mg Q4W for the first 3 doses, then once Q8W.

d. Dupilumab – anti-IL4 receptor α

As an add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO [fractional exhaled nitric oxide] who are inadequately controlled with high dose ICS [inhaled corticosteroid] plus another medicinal product for maintenance treatment. Dupilumab is approved for patients ≥6-years old.[13] The initial loading dose is 600 mg subcutaneously, followed by a subsequent dose of 300 mg every 2 weeks (Q2W).

e. Tezepelumab - anti-thymic stromal lymphopoietin

First approved biologics that targets thymic stromal lymphopoietin (TSLP). It received regulatory approval from USFDA in 2021 for treatment of severe asthma in patients over 12 years of age.[4,14] Unlike other biologic therapies, it is not restricted to patients with allergic or eosinophilic asthma.[4] The recommended dose is 210mg Q4W, given by subcutaneous.

3.0

POLICY QUESTIONS

3.0 POLICY QUESTIONS

3.1 Should biologics be used to treat severe asthma?

3.2 Which biologics should be used to treat different severe asthma phenotypes?

4.0

OBJECTIVES

4.0 OBJECTIVES

4.1 To assess the effectiveness and safety of biologics in treatment of severe asthma with regards to patient outcomes such as asthma control (exacerbation, spirometry, symptoms, quality of life [QoL], oral corticosteroid [OCS] sparing effects, hospital admission, Emergency Department ([ED] visit etc), mortality and adverse events or complications.

4.2 To assess the economic implication, social, ethical, and organisational aspects related to the biologics in treatment of severe asthma.

The following **research questions** will be addressed:

4.1.1 What is the best option for severe asthma?

4.1.2 Does different types of biologics affect different types of severe asthma?

4.1.3 Is biologics in treatment of severe asthma cost-effective?

4.1.4 Which is the best type of biologics for treatment of severe asthma in terms of efficacy and cost-effective?

4.1.5 What is the social, ethical, and organisational implication/ impact related to the use of biologics in treatment of severe asthma?

5.0

PART A: SYSTEMATIC REVIEW

5.0 PART A: SYSTEMATIC REVIEW

5.1 METHODS

5.1.1 Literature Search strategy

Literature search was developed by the main author and co-author with help from Information Specialists who also searched for published articles pertaining to biologics in severe asthma. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to June 2023, EBM Reviews - Health Technology Assessment, EBM Reviews - Cochrane Database of Systematic Review, EBM Reviews - Cochrane Central Register of Controlled Trials, and EBM Reviews - NHS Economic Evaluation Database. Parallel searches were run in PubMed, US FDA and INAHTA database. There was no limitation in language, however, in the end only full text articles in English were included. Year of publication was limited from year 2018 to 2024 and only human study were included. Detailed search strategy is as in **Appendix 2**. The last search was performed in Mac 2024. Additional articles were identified from reviewing the references of retrieved articles as well as from the expert committees.

5.1.2 Study selection

Two dedicated reviewers independently screened the titles and abstracts against the inclusion and exclusion criteria as shown below and evaluated the selected full-text articles for final article selection. Disagreement was resolved by discussion as well as through expert opinion.

Inclusion Criteria:

a.	**Population**	Patient with severe asthma
b.	**Intervention**	Biologics (mepolizumab, benralizumab, dupilumab and tezepelumab)
c.	**Comparator**	i. Standard treatment ii. Between biologics
d.	**Outcomes**	• Effectiveness: Exacerbation rate, asthma control (exacerbation, spirometry, symptoms, quality of life (QoL), OCS sparing effects, hospital admission, ED visit etc), mortality, FEV1, FeNO and eosinophil count • Safety: adverse events, complications (OCS burst) • Economic implications: cost-effectiveness, cost-utility, cost-benefit analysis • Potential psychological and behavioural harms and benefits of the biologics • Training requirements or learning curve
e.	**Study design**	HTA reports, systematic reviews (SRs) with/out meta-analysis (MA) / network MA, randomised controlled trials (RCTs), cohort studies, and economic evaluation
f.	Full text articles published in English	

Exclusion Criteria:

a.	**Study design**	Animal study, laboratory study, case report, case series, narrative review
b.	Non-English full text articles	

5.1.3 Critical appraisal of literature/ assessment of risk of bias

The risk of bias or quality assessment (methodology quality) of all retrieved literatures was assessed depending on the type of the study design; using the relevant checklist of National Collaborating Centre for Methods and Tools (ROBIS)[15] for Systematic Review and Meta-analysis, a revised Cochrane Risk of Bias Tool (RoB 2) for Randomised Controlled Trials[16], and Critical Appraisal Skill Programme (CASP)[17] for Observational and Economic Studies.

5.1.4 Analysis and synthesis of evidence

Data extraction strategy

Data were extracted from included studies by a reviewer using a pre-designed data extraction form (*Evidence* Table in **Appendix 3**) and checked by another reviewer. Disagreements were resolved by discussion and the extracted data was also presented and discussed with the *Expert Committee*. The data extracted was as follows:

- Details of methods and study population characteristics
- Detail of intervention and comparators
- Details of individual outcomes specified.

Methods of data synthesis

Data on the effectiveness, and cost-effectiveness associated with biologics in treatment of severe asthma were presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review due to high heterogeneity especially the characteristics of the reviewed biologics.

5.2 RESULTS

5.2.1 Selection of Included articles

An overview of the systematic search and selection of the studies are illustrated in **Figure 1**. A total of **643** records were identified through the Ovid interface and PubMed while **5** were identified from other sources (references of retrieved articles). Following the removal of **594** duplicates and irrelevant titles, **53** titles were found to be potentially relevant, and abstracts were screened using the inclusion and exclusion criteria. Of these, **52** relevant abstracts were retrieved in full text. After reading, appraising, and applying the inclusion and exclusion criteria to the **52** full text articles, **30** full text articles were included. **Twenty-seven (27)** articles were excluded as those primary studies were already included in systematic review and NMA / MA (n = 7) narrative reviews (n = 11) and overlap with other included studies (n = 9). The excluded articles were listed as in **Appendix 4**.

The 30 full text articles which were finally selected in this review comprised of **seven** systematic reviews with MA,[18-24] **three** systematic reviews with NMA,[25-27] **five** systematic review,[28-32] **eight** RCTs,[33-40] **three** non-RCTs,[41-43] **one** cross-sectional study[44] and **three** economic evaluation studies of individual biologics (mepolizumab,[45] benralizumab,[46] and dupilumab[47]).

All studies included were published in English language between **2018 and 2024** and were conducted in the United States, United Kingdom, Canada, Japan, Turkey, Singapore, Spain etc.

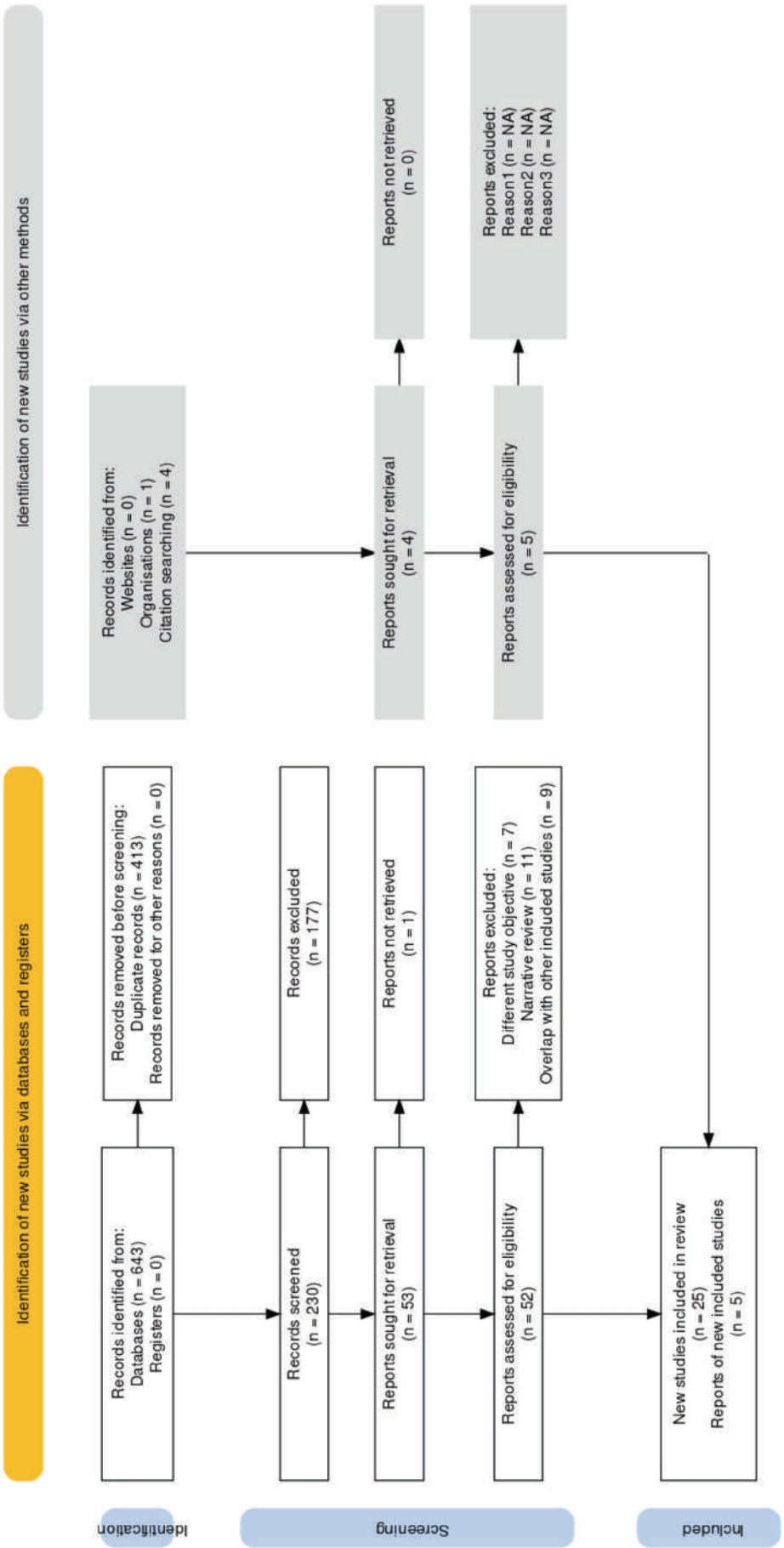


Figure 1: Flow chart of retrieval of articles used in the results.

5.2.2 Quality assessment / risk of bias

Risk of bias was assessed using Risk of Bias in Systematic Reviews (ROBIS) for systematic review[15], ROB2 for randomised control trial[16] and Critical Appraisal Skill Programme (CASP) checklist for non-RCTs and observational study[17]. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias.

Risk of bias assessment for included systematic review

Based on ROBIS assessment tools, most of the SRs either with MA / NMA or without quantitative analysis showed low risk of bias. Most of the included studies were consists of RCTs with a good profile of risk of bias assessment. However, there were two SRs required some concerns on domain 3, 4 and 5. An SR by Calzetta L. et. al. included observational studies of the real-world data where most of the data collected were retrospectively from registry. Meanwhile, an SR by Israel E. et. al. not only included RCTs but also conference posters as well as letter to editor in their assessment.

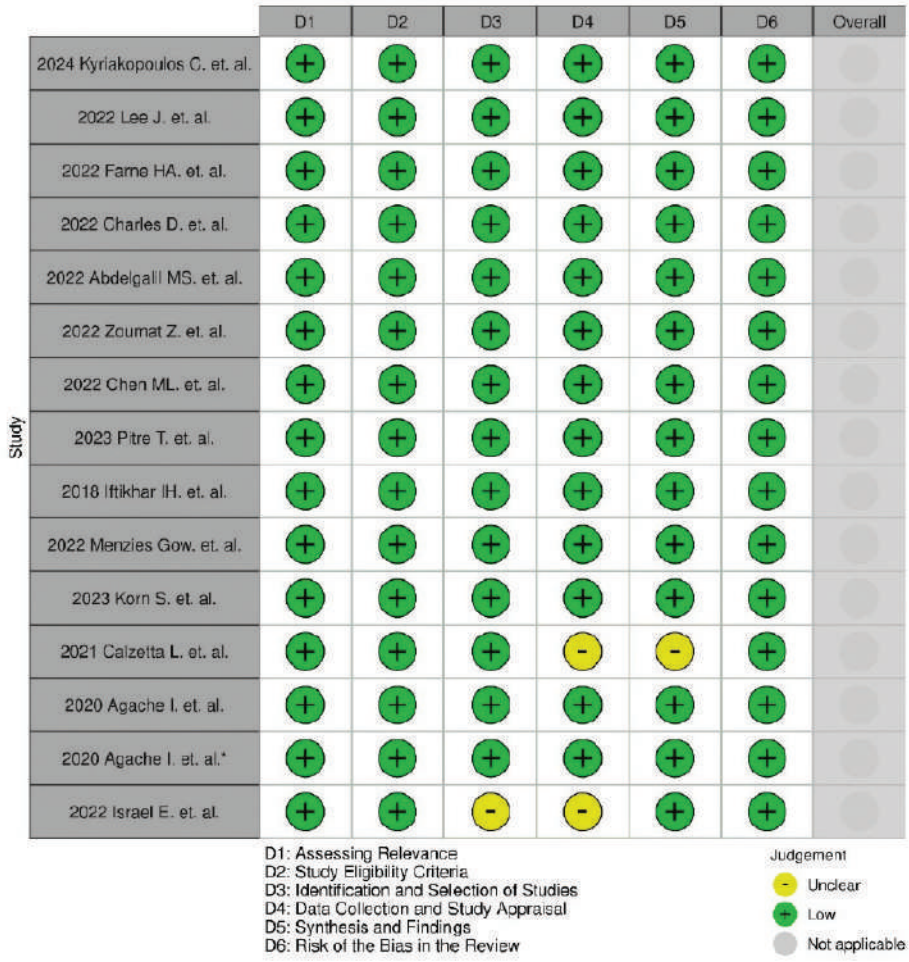


Figure 2: Summary of risk of bias assessment for systematic review using ROBIS

Risk of bias assessment for included RCT studies

Overall, the RCTs assessment showed moderate to low risk of bias. Based on the RoB2 assessment tools, three RCTs showed an issue in domain 1. The randomisation was not clearly defined the randomisation process as well as allocation concealment process. Randomisation is one of the important criteria which might affect the whole quality of the RCT.

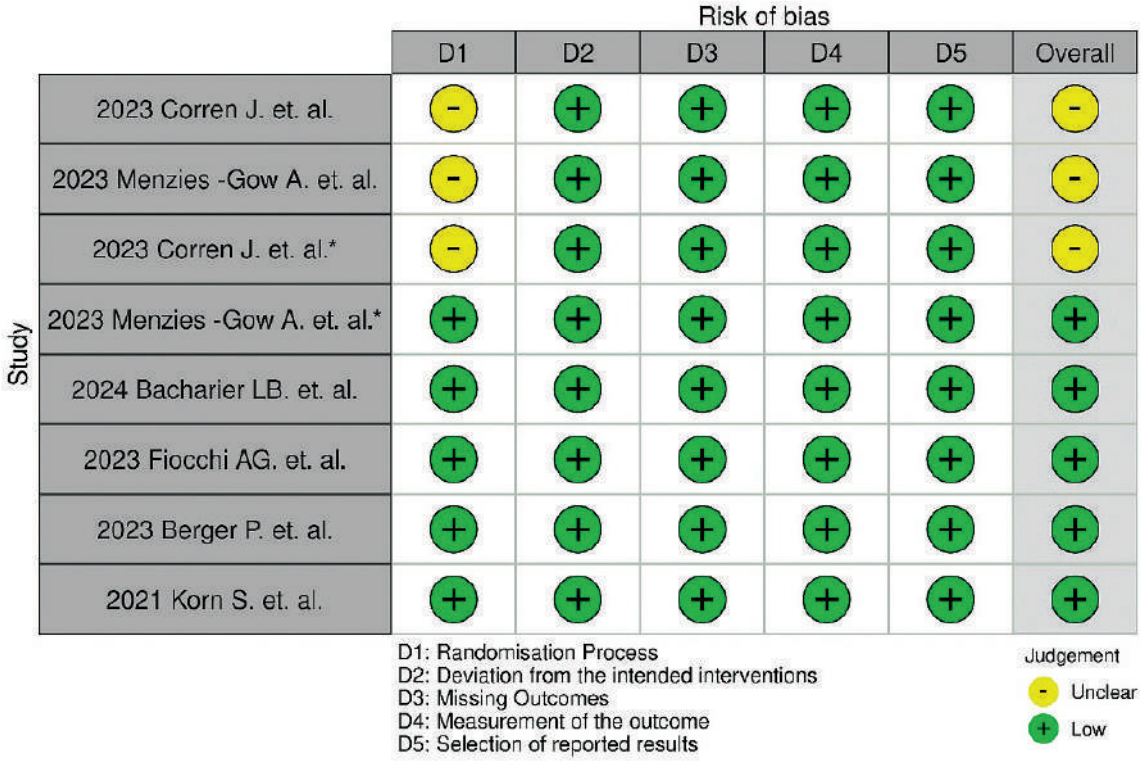


Figure 3: Summary of risk of bias assessment for RCT using ROB2

Risk of bias assessment for included non-RCT studies

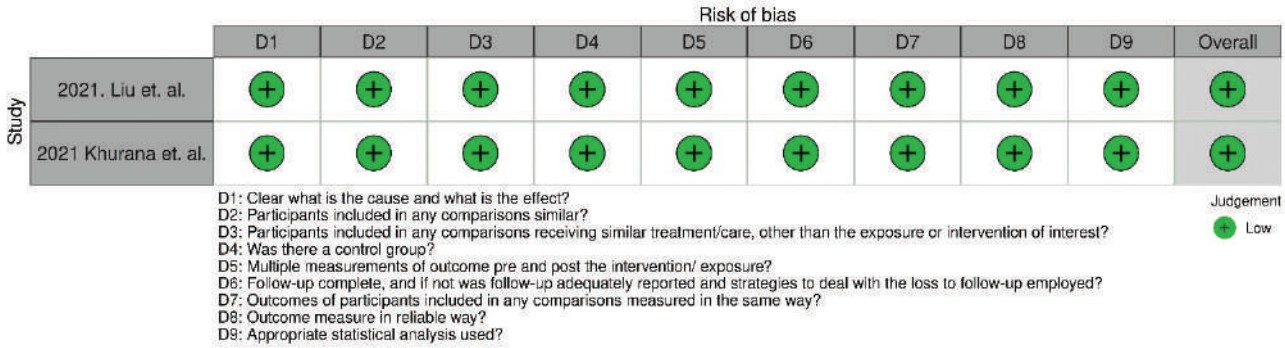


Figure 4: Summary risk of bias assessment for non-RCT

5.2.3 Characteristics of the included studies

Table 1 described a general characteristic of the included studies. Overall, all studies involved patient with severe uncontrolled asthma where most of them were at age of ≥12 years old. There were two studies observed an effect of biologic on children within age of 6 – 11 years old. Three SRs with NMA were also included in addition to seven SRs with MA to determine the pooled results of the reviewed biologics for various outcomes. An extended study of RCTs were also included where the main objective of those extended study was to assess the long-term benefits of the reviewed biologics especially on safety profile. The longest followed-up period of the extended study since parent study was more than five years and the least was two years.

Table 1: Characteristics of the included studies

Studies	Types of study	Objectives	Patients characteristics	Study treatments	Reported Outcomes
2024 Kyriakopoulos C. et. al.	SR & MA of RCTs 51 in qualitative and 48 in quantitative analysis	To assess the efficacy and safety of licensed biologics agents in patients with severe asthma	Patients ≥12 years old with moderate to severe uncontrolled/ inadequately controlled asthma	omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab and tezepelumab versus placebo	Exacerbations, asthma control, lung function, hospital admission, OCS used and AEs
2022 Lee J. et. al.	SR & MA 17 RCTs	To determine how well type 2 inflammation-specific agents targeting IL reduced the rate of asthma exacerbations in patients with severe asthma	Patients with severe asthma	benralizumab, dupilumab, mepolizumab, lebrikizumab, reslizumab and tralokinumab versus placebo	Annual asthma exacerbations
2022 Farne HA. et. al.	SR & MA 17 RCTs (16 in MA)	To compare the effects of therapies targeting IL-signalling (anti-IL5 or ILRα) with placebo	Adults and children with chronic asthma and specifically in those with eosinophilic asthma refractory to existing treatments	mepolizumab, Benralizumab and reslizumab	Exacerbations, health related QoL, and lung function
2022 Charles D. et. al.	SR & MA 22 studies	To evaluate the real-world efficacy of recently and nearly licensed biological therapies for severe asthma to assess the generalisability of the RCT data	Adult with severe asthma with mean age 52 and 60 years old	benralizumab, mepolizumab, dupilumab and reslizumab	Exacerbations, asthma control, OCS used, FEV1, FeNO and eosinophil count

Studies	Types of study	Objectives	Patients characteristics	Study treatments	Reported Outcomes
2022 Abdelgalil MS. et. al.	SR & MA 4 RCTs	To combine the existing data and assess the efficiency and safety of tezepelumab as a treatment for severe uncontrolled asthma	Adults with severe uncontrolled asthma	tezepelumab versus placebo	annual asthma exacerbation, lung function, asthma control, blood eosinophil count, FeNO, serum total IgE, treatment emergent adverse events
2022 Zoumat Z. et. al.	SR & MA 6 RCTs	To investigate the safety and efficacy of tezepelumab for patients with severe and uncontrolled asthma	patients with severe and uncontrolled asthma	tezepelumab	exacerbation, FeNO, QoL, total serum IgE levels, allergic status
2022 Chen ML. et. al.	SR & MA Qualitative: 46 studies Quantitative: 43 studies	To elucidate the incidence of ADA associated with the used of reviewed biologics and to evaluate the impact of ADA development on reported clinical outcomes and AEs	Adults and children with moderate to severe asthma with age ranged from 6 to 82 years (6 to 11 years for dupilumab, mepolizumab and omalizumab) with 15% of patients had a history of CRS-NP	benralizumab, dupilumab, mepolizumab, tezepelumab, omalizumab and reslizumab versus placebo	ADA prevalence and treatment emergent ADA
2023 Pitre T. et. al.	SR & NMA 64 studies and pooled analysis of 60 studies	To compare the relative efficacy of biologics in asthma	Adults and children with moderate to severe asthma on medium to high dose ICS and other controller medications	omalizumab, reslizumab, mepolizumab, tralokinumab, tezepelumab, dupilumab, benralizumab, fevipiprant, ostegolimab, itepekimab versus placebo	Exacerbations, asthma control, lung function, hospital admission, OCS used and AEs
2018 Iftikhar IH. et. al	SR & NMA 26 RCTs	To synthesis data on the relative efficacy of the reviewed biologics	Adults with severe eosinophilic asthma	benralizumab, dupilumab, mepolizumab, lebrikizumab, reslizumab, and tralokinumab versus placebo	Exacerbations, asthma control and lung function

Studies	Types of study	Objectives	Patients characteristics	Study treatments	Reported Outcomes
2022 Menzies-Gow A. et. al.	SR & NMA Qualitative: 39 studies Quantitative NMA: 16 studies	To compare the efficacy of tezepelumab with five other approved biologics in terms of reducing exacerbations in patients with severe, uncontrolled asthma	Patients aged ≥12 years with uncontrolled asthma according to GINA step 4 or 5 treatment	benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab versus placebo	Annual asthma exacerbation, and hospitalisation and ED visit
2023 Korn S. et. al.	SR 20 RCTs	To assess the effects of biologics on annualised asthma exacerbation rate	Patients with severe uncontrolled asthma	tezepelumab, dupilumab, benralizumab, mepolizumab, reslizumab, and omalizumab versus placebo	exacerbation, hospitalisation, asthma control and lung function
2021 Calzetta L. et. al.	SR 59 studies	To provide a synthesis of the current literature on the OCS-sparing effect of reviewed biologics in studies carried out in real-world populations of severe asthmatic patients and assessed whether the mAbs may really overcome the problem related to dependence on OCSs in severe asthma	Adults with severe asthma	benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab versus placebo	OCS-sparing effect
2020 Agache I et. al.	SR 28 RCTs	To assess the efficacy and safety of reviewed biologics in patients with uncontrolled severe allergic asthma and to assess economic impact of the biologics versus SoC	Adults and children (in omalizumab) diagnosed with moderate to severe allergic asthma symptoms due to exposure to perennial aeroallergen	benralizumab, dupilumab and omalizumab versus SoC	Exacerbation, asthma control, lung function, OCS dose, healthcare resource utilisation, safety, ICER and resource used
2020 Agache I. et. a.	SR 19 RCTs	To evaluate the efficacy and safety of reviewed biologics in patients with severe eosinophilic asthma	Adults and children (in omalizumab) diagnosed with severe allergic asthma	benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab versus SoC/placebo	Exacerbation, asthma control, lung function, OCS dose, healthcare resource utilisation, safety, ICER and resource used

Studies	Types of study	Objectives	Patients characteristics	Study treatments	Reported Outcomes
2022 Israel E. et. al.	SR 23 studies (observational studies – prospective and retrospective)	To assess the published evidence relating to a broad range of clinical outcomes, safety, and health-care resource utilisation among patients with severe asthma receiving add-on therapy with mepolizumab in real-world setting	dult patients with severe asthma with mean-age 49 to 67 years-old	Mepolizumab	Exacerbations, maintenance OCS used, lung function, blood eosinophils count, asthma control, safety and economic evaluation
2023 Corren J. et. al.	RCT (NAVIGATOR trial)	To comprehensively evaluated the effects of tezepelumab in NAVIGATOR trial	Patients with severe allergic asthma	tezepelumab versus placebo	Annual asthma exacerbation, lung function, asthma control, changes in biomarkers
2023 Menzies-Gow A. et. al.	RCT (NAVIGATOR trial – HCU)	To evaluate to what extent tezepelumab reduced patient's healthcare utilisation (HCU)	Patients with severe allergic asthma	tezepelumab versus placebo	Healthcare utilisation including asthma related, unscheduled HCU, and annualised rates all caused of HCU
2023 Corren J. et. al.	RCT (post-hoc analysis of NAVIGATOR & PATHWAY trial)	To examine the efficacy and safety of tezepelumab in additional clinically relevant subgroups using polled data from PATHWAY and NAVIGATOR trial	Patients with severe uncontrolled asthma	tezepelumab versus placebo	Annual asthma exacerbation, blood eosinophil count, FeNO level, Allergen status, corticosteroid used, nasal polyps and safety
2023 Menzies-Gow A. et. al.	RCT (DESTINATION-trial)	To evaluate the long-term safety and efficacy of tezepelumab in individuals with severe uncontrolled asthma	Patients with severe uncontrolled asthma	tezepelumab versus placebo	Exposure-adjusted incidence of adverse events, exacerbations, asthma control, lung function, QoL and type 2 biomarker changes over 104 weeks
Bacharier LB. et. al.	RCT (EXCURSION – extended VOYAGE trial)	To evaluate the long-term safety and efficacy of dupilumab in children with moderate-to-severe asthma who previously participated in VOYAGE study	Children aged 6 – 11-year-old with moderate to severe asthma	tezepelumab versus placebo	treatment emergent adverse events, serious adverse events, adverse events related to permanent treatment discontinuation, annual asthma exacerbation, biomarkers changes, ADA incidence

Studies	Types of study	Objectives	Patients characteristics	Study treatments	Reported Outcomes
2023 Fiocchi AG. et. al.	RCT (extended VOYAGE trial – HRQoL in children)	To assess more detail, the impact of dupilumab on asthma control and health-related quality of life (HRQoL) in children and their caregivers	Children aged 6 – 11-year-old with uncontrolled to severe T2 asthma	dupilumab versus placebo	Asthma control that effect ACQ, PAQLQ and PACQOLQ
2023 Berger P. et. al.	RCT (TRAVERSE – extended QUEST and VENTURE – trial)	To evaluate long-term dupilumab efficacy in patients enrolled from QUEST and VENTURE with and without self-reported coexisting CRS-NP	Severe asthma patients with and without self-reported coexisting CRS-NP	dupilumab versus placebo	Annual asthma exacerbation, lung function, asthma control, OCS dose and treatment-emergent adverse events
2021 Korn S. et. al.	RCT (MELTEMI – extended BORA, SIROCCO, CALIMA & ZONDA-trial)	To evaluate the long-term safety and tolerability of benralizumab among adults treated for up to 5 years	Adults ≥18 years-old with severe uncontrolled asthma	benralizumab versus placebo	safety and tolerability, annual asthma exacerbation, OCS used, hospitalisation and ED visit
2021 Liu MC. et. al.	Non-RCT (OSMO-trial change to mepolizumab to omalizumab)	To assess the proportion of patients achieving pre-defined improvements in up to 4 efficacy outcomes and the relationship between patient baseline characteristics and treatment response	Patients with uncontrolled severe eosinophilic asthma	mepolizumab for 32 weeks (switching from omalizumab) versus placebo	Asthma control, QoL, lung function and exacerbation, OCS used and comorbidity
2021 Gibson PF. et. al.	Post-Hoc analysis (DREAM, MENSA, SIRIUS, and MUSCA-trial)	To investigate the efficacy of mepolizumab in patients with severe eosinophilic asthma and comorbidities	Patients ≥12 years-old with severe eosinophilic asthma	mepolizumab with SoC versus placebo with SoC	annual asthma exacerbation, lung function, asthma control,
2021 Casale T. et. al.	Retrospective real-world data	To describe the real-world effectiveness of mepolizumab in patients with severe asthma stratified by common overlapping comorbidities	Patients ≥12 years-old with severe asthma	mepolizumab versus placebo	exacerbation, hospitalisation, OCS used, and healthcare utilisation,

Studies	Types of study	Objectives	Patients characteristics	Study treatments	Reported Outcomes
Khurana S. et. al.	Non-RCT (COSMEX – extended COSMOS of MENSA and SIRUS-trial)	To assess the long-term safety and efficacy of mepolizumab in patients with the most severe eosinophilic asthma	Patients with most severe eosinophilic asthma	mepolizumab versus placebo	adverse events and withdrawal due to adverse events, ADAs incidence, exacerbation, asthma control, lung function, and OCS used
Tan LE. et. al.	Economic evaluation based on 3 RCTs	To evaluate the cost-effectiveness of mepolizumab added to SoC compared to SoC along among patients with severe uncontrolled eosinophilic asthma in the Singapore setting	Patients aged ≥12 with severe asthma	Mepolizumab 100mg + SoC versus SoC alone	Exacerbations, ICER/QALY, ICER/LY
Padiala-Galo A. et. al.	Cross-sectional multicentre study with cost-utility analysis	To assess the cost-effectiveness of benralizumab therapy and its one-year effectiveness, based on the decrease in the number of exacerbations and OCS used and the improvement of asthma control and lung function in the real-world	Adults ≥18 years old with refractory eosinophilic asthma and received benralizumab for at least 12 months	benralizumab	Effectiveness: exacerbations, asthma control, OCS used, and ED visit Economic evaluation: ICUR, ICER and NMB
Tohda Y. et. al.	Cost-effectiveness analysis	To assess the cost-effectiveness of dupilumab compared with other biologics as an add-on treatment to background therapy	Patients aged ≥12 years with uncontrolled, persistent asthma in Japan	dupilumab versus benralizumab, mepolizumab and omalizumab	ICER/QALY

5.2.4 EFFECTIVENESS

The outcomes of interest were asthma exacerbation rate (AER) and annual asthma exacerbation rate (AAER), the asthma control through assessment score of Asthma Control Questionnaire (ACQ), Asthma Control Test (ACT) and etc, lung function by Forced Expiratory Volume (FEV1) level assessment, reduction in hospitalisation and Emergency Department (ED) visit due to exacerbation, reduction in used of corticosteroid especially in oral corticosteroid (OCS) and quality of life by assessment score of several quality tools such as AQLQ, SGRQ, PAQLQ or care giver assessment with PACQLQ.

The assessment not only reported on overall population but also in several subgroups included in patient with different level of blood eosinophil count (BEC), patients with any comorbidities, different level of FeNO etc.

5.2.4.1 Asthma Exacerbations

The asthma exacerbations rate (AER) and annual asthma exacerbations rate (AAER) were reported in several studies. A few of the included RCTs were extended trials of parent studies conducted to assess the efficacy/ effectiveness of the biologics in longer durations (>12 months).

5.2.4.1(a) Overall population

Four SRs with MA pooled results on exacerbations of the assessed biologics. [18,19,20,21] Current SR and MA by Kyriakopolous C. et. al. reported that all biologics assessed, included mepolizumab, benralizumab, dupilumab and tezepelumab reduced the annual exacerbations rates (AAER). The pooled analysis of the biologics studies showed the AAER reductions by 44% (rate ratio 0.56 [95% CI 0.52 to 0.62; I^2 = 58.4%). The authors also reported that greater improvement was observed in dupilumab and tezepelumab; rate ratio 0.44 (95% CI 0.32 to 0.61, I^2 = 49.4%) and rate ratio 0.45 (95% CI 0.30 to 0.66, I^2 = 70%), respectively.[18] An NMA by Menzies Gow A. et. al. that indirectly compared between tezepelumab, and other biologics included benralizumab, dupilumab and mepolizumab also reported that tezepelumab had the numerically lowest AAER compared to others and ranked first in the network with SUCRA value of 84%.[27]

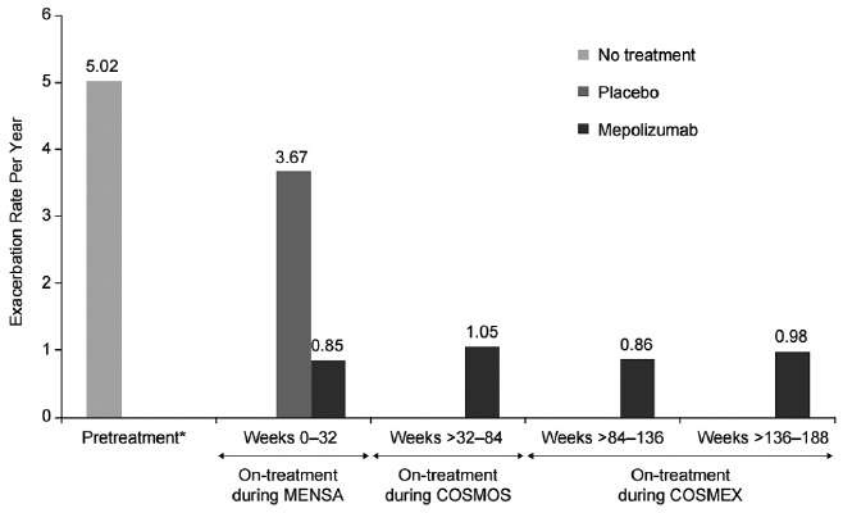
Pooled results from SR with MA by Lee K. et. al. on benralizumab, mepolizumab and dupilumab also reported favourable results towards the biologics compared to placebo with RR 0.58 [95% CI 0.51 to 0.66, I^2 = 72%, p<0.01 with the absolute risk reduction was 42%. The individual risk reduction was RR 0.58 (95% CI 0.44 to 0.77) in benralizumab, RR 0.46 (95% CI 0.37 to 0.56) in dupilumab and RR 0.51 (95% CI 0.45 to 0.58) in mepolizumab.[19] Another SR with MA by Charles D. et. al. evaluated the real-world efficacy of the benralizumab, mepolizumab and dupilumab in severe asthma. All individual biologics showed a significant reduction in AAER compared to placebo. However, the pooled results were only available for mepolizumab studies and benralizumab studies. The mean difference reductions were MD -3.17 (95% -3.74 to -2.59) in mepolizumab, MD -3.79 (95% CI -4.53 to -3.04) in benralizumab and MD -3.0 (95% CI -5.0 to -2.0) in dupilumab single study.[21]

On the other, Farne HA. et. al. reported significant improvement in asthma exacerbation rate (AER) with mepolizumab and benralizumab (rate ratio 0.45 [95% CI 0.36 to 0.55] and rate ratio 0.59 [95% CI 0.52 to 0.66, respectively) compared to placebo. Farne HA. et. al. also found that stopping subcutaneous mepolizumab likely resulted in shorter time to clinically significant exacerbations (hazard ratio, HR 1.61 [95% CI 1.17 to 2.22]).[20] The findings were also consistent with two SRs by Agache I. et. al where benralizumab, and mepolizumab significantly reduced the AER compared to standard of care and placebo (IRR 0.53-0.63 [95% CI 0.39-0.50 to 0.72-0.81], and IRR 0.49 [95% CI 0.38 to 0.66], respectively. The improvement also observed in dupilumab with an IRR 0.44-0.58 [95% CI 0.32-0.47 to 0.59-0.73].[30,31]

Two SR with MA by Abdelgalil MS. et. al.[22] and Zoumat Z. et. al.[23] reported that patients on tezepelumab had significantly reduced AAER with mean difference of 0.32 (95% CI -1.04 to -0.44), p < 0.00001, I^2 = 85% and 0.60 (95% CI 0.51 to 0.70), respectively. Zoumat Z. et. al. also assessed the effects of three difference doses of tezepelumab; 280mg, 210 mg and 70 mg administered four-weekly (Q4W). The observation showed that only patients on tezepelumab at 210mg and 280mg Q4W showed significant reduction in AER; 0.55 (95% CI 0.42 to 0.71) and 0.59 (95% CI 0.38 to 0.90), respectively.[23] In another pooled analysis study by Corren J. et. al., the authors pooled results from two tezepelumab trials which were PATHWAY and NAVIGATOR trial. The pooled results showed that patients on tezepelumab had a reduction of 60% AAER compared to patients on placebo (RR 0.40 [95% CI 0.34 to 0.48]).[35] In addition to that, one extended trial called DESTINATION was conducted by Menzies-Gow A. et. al. to evaluate the long-term efficacy of tezepelumab in severe asthma. The DESTINATION-trial was an extended study of two parent studies namely NAVIGATOR-trial and SOURCE-trial. Both trials assessed the subcutaneous 210 mg Q4W of tezepelumab compared to placebo. In DESTINATION study, patients who were randomised to receive tezepelumab in both NAVIGATOR- and SOURCE-trial continued to receive tezepelumab. Meanwhile those patients who were randomised for placebo in both parent studies, were randomised either to remain in placebo or to receive tezepelumab. The study period since parent study to extension study was 104 weeks (52-week in parent studies and another 52-weeks in DESTINATION-trial). At the end of the extension study period, both patients either on tezepelumab since parent studies or just received tezepelumab during the extension study showed significant improvement in reducing AAER (in NAVIGATOR-trial: 0.82 [95% CI 0.71 to 0.95] and 1.93 [95% CI 1.70 to 2.20], respectively, with overall rate ratio of 0.42 [95% CI 0.35 to 0.51]; in SOURCE-trial: 1.047 [95% CI 0.75 to 1.51] and 1.76 [95C% CI 1.27 to 2.45], respectively, with overall rate ratio 0.61 [95% CI 0.38 to 0.96]). The authors also reported that time to first asthma exacerbation was longer in patients initially randomised to tezepelumab group than in those who just started tezepelumab during the extension study (HR 0.64 [95% CI 0.54 to 0.75]).[36]

As for mepolizumab, on SR by Israel E. et. al. assessed the effectiveness of mepolizumab among patients with severe asthma in a real-world setting. The SR included studies involving study populations from various countries including Italy, Australia, Unite States, France, Japan, and Israel. At the end of the study period, they found that those who were treated with mepolizumab had significant reduction in AER ($p<0.001$) from baseline to 12-months followed-up ranging from 54% to 97% (at baseline; 2.10 – 4.16 events/year vs after 12- months followed-up; 0.85 – 0.07 events/year) compared to placebo. The SR also reported that 24% to 85% relative risk reductions from baseline to followed-up in the proportion of patients with ≥1 exacerbations before and after mepolizumab initiation.[32] One extended study also reported that mepolizumab sustained the reduction of the exacerbation rate. The extended study called COSMEX was conducted by Khurana S. et. al. to assess the long-term safety and efficacy of mepolizumab in the most severe eosinophilic asthma. The COSMEX was the extension of COSMOS study which was previously an extension study of two parent studies namely MENSA- and SIRIUS-trial. A total of 339 patients were included in the COSMEX study. Median duration of mepolizumab treatment in COSMEX study was 2.2 years (ranged 8-weeks – 3.3-years) which was equivalent to 718 patient-years of mepolizumab exposure. However, if counted from parent studies (SIRIUS and MENSA-trial), COSMOS, and COSMEX study, the maximum exposure durations in the 339 patients were 4.8 year (1,202 patient-years). Between COSMOS and the COSMEX study, there was a treatment gaps of varying length; treatment interval ≤12 weeks (continuous therapy group) and >12 weeks (interrupted therapy group). At the end of the COSMEX study, a total of 215 (63%) patients experienced 658 on-treatment exacerbation over the on-treatment period of 2.2 years. The annualised on-treatment exacerbation rate was 0.93 (95% CI 0.81 to 1.06) event/year. The authors reported that patients with continuous study participant since parent study (MENSA) had sustained reduction in exacerbation rate with prolonged mepolizumab treatment throughout multiple studies (MENSA, COSMOS and COSMEX) (**Figure 5**).[43]

One post-hoc analysis was conducted by Liu MC. et. al. on OSMO study to assess the pre-defined improvement of mepolizumab after switching from omalizumab. The included patients were those who were previously unresponsive with omalizumab. After 32-weeks of the OSMO study, the authors reported patients' response towards mepolizumab outcome of interest where 94% were identified as responder for at least one of four efficacy outcomes, 83% for at least two outcomes, 63% for at least three outcomes and 31% of responder for all four outcomes. In exacerbations rate outcome, the authors reported that the overall exacerbations in the year prior to mepolizumab switching were 50% of the patients experienced ≤2 exacerbations, 27% of the patients had three exacerbations and 23% had ≥4 exacerbations. After 32-weeks of OSMO trial, the rate ratio of AAER was significantly reduced compared to pre-treatment of mepolizumab. The AAER was reduced from 1.97 to 0.91 in patients with ≤2 exacerbations in prior year (RR 0.46 [95% CI 0.31 to 0.70]), 3.00 to 1.28 in patients with 3 exacerbations (RR 0.43 [95% CI 0.27 to 0.66]) and 6.42 to 1.61 in patients with ≥4 exacerbations in prior year (RR 0.25 [95% CI 0.16 to 0.38]).[41]



Exacerbation rate per year throughout the MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma), COSMOS (A Study to Determine Long-term Safety of Mepolizumab in Asthmatic Subjects), and COSMEX (COSMOS Extension) studies in patients with ≥188 weeks of continuous enrollment. In total, 95 patients with ≥188 weeks of continuous reporting across MENSA, COSMOS, and COSMEX with ≤12 weeks between the last dose in COSMOS and first dose in COSMEX are summarized (MENSA, placebo, n = 24; mepolizumab, n = 71). The mepolizumab group in MENSA contains patients on both 100 mg SC and 75 mg IV doses. Analyses include clinically significant exacerbations from MENSA and all exacerbations from COSMOS and COSMEX. *Pretreatment refers to the 12 months before enrollment in MENSA.

*Figure adopted from Khurana S. et. al.

Figure 5: Exacerbation rate per year across the studies

For benralizumab, Korn S. et. al. conducted MELTEMI-integrated study of BORA study which was an extension of three benralizumab trials; SIROCCO, CALIMA, and ZONDA. A total of 447 patients consisted of patients from each three parent studies were enrolled into the MELTEMI study. The study was to evaluate the long-term tolerability of adult patients after being treated with benralizumab for five years. Patients who were given benralizumab during the parent studies were continuously treated with benralizumab during the BORA and MELTEMI study and those in placebo during parent studies were randomised to receive benralizumab during the BORA and MELTEMI study. Benralizumab was initiated at two types of intervals, subcutaneous benralizumab 30 mg Q4W or every 8-weeks (Q8W). The authors reported that the severe asthma with 0.5 of exacerbation rate in parent studies was reduced to ≤0.5 in subsequent years of the integrated analysis period in patients who continuously received benralizumab since the parent studies. Meanwhile among patients on placebo who received benralizumab during BORA-extension studies, the AAER decreased 26.7% compared during in their parent studies with placebo (1.5 to 0.6). During an integrated period of MELTEMI, the rate was ≤0.6 in the subsequent years. The authors also observed that more patients who were treated with benralizumab had zero exacerbation either in parent studies or across BORA and MELTEMI study. Even patients in placebo group who started the benralizumab during BORA-extension study showed an improvement; 43% zero exacerbations during parent studies to 69% per year in BORA and later ≥63% had zero exacerbations per year for the remainder of MELTEMI study period.[40] In another one-year cross-sectional multicentre study by Padiala-Galo A. et. al. for data collection of benralizumab cost-analysis study reported that benralizumab significantly reduced the exacerbations up to 88% ($p < 0.001$).[46]

Meanwhile for dupilumab, one extension study involving children were included. The extension study was EXCURSION by Bacharier LB. et. al. to evaluate the long-term efficacy of dupilumab in children with moderate to severe asthma. The children were previously participated in VOYAGE-trial and 90% of the children were recruited in the EXCURSION study. The children who were previously treated with dupilumab in VOYAGE study was continuously treated with dupilumab and those in placebo group during VOYAGE study will be randomised, either to receive dupilumab or remain in the placebo group. The EXCURSION study had been followed up for another 52-weeks after the VOYAGE study completed. Overall, 96% of the children completed the EXCURSION study. At the end of the EXCURSION study, the authors found that the AAER was low and similar between children who were treated with dupilumab since VOYAGE study with children who just receive dupilumab during the EXCURSION study; 0.118 versus 0.124. Besides, most of the children (91%) remained exacerbation-free throughout the study period. Meanwhile, among children who had the exacerbations, 83% had single exacerbation event. Overall, dupilumab consistently reduced severe asthma exacerbations as well as further reduced the AAER.37 Focchi AQ. et. al. also reported on the extension study of VOYAGE-trial. The authors reported that all children showed high response towards treatment options and the response was higher in dupilumab group than placebo (79% versus 69% at week 24 and 86% versus 75% at week 52). Among the responders, higher proportion of dupilumab-treated patients were exacerbations-free during the treatment period compared to placebo (77.9% versus 67.1% at week 52).[38]

5.2.4.1(b) Subgroups Analyses

Several subgroup analyses were reported in assessment of asthma exacerbations after biologics treatment. Those subgroups were based on blood eosinophils count (BEC), FeNO level, allergen status and patients' comorbidities.

Subgroup: Baseline Eosinophil Count (BEC)

According to recent SR with MA by Kyriakopoulos C. et. al., greater reductions in AAER was observed among patients with high eosinophil count (BEC ≥300 cells/uL) compared to low eosinophil count (BEC <300 cell/UL) who were treated with biologics included mepolizumab, benralizumab, dupilumab and tezepelumab. The pooled rate ratio was 0.38 (95% CI 0.29 to 0.49) versus 0.67 (95% CI 0.55 to 0.83); $P_{subgroup\_heterogeneity}$ = 0.001. The authors also reported on the effectiveness of tezepelumab and dupilumab among patients with BEC ≥150 cells/uL and <150 cells/uL. The observation showed that tezepelumab and dupilumab was significantly effective in reducing the AAER in patients with BEC ≥150 cells/uL compared in those with BEC <150 cells/uL; rate ratio 0.40 (95% CI 0.34 to 0.46) and rate ratio 0.80 (95% CI 0.49 to 1.31), respectively; $P_{subgroup\_heterogeneity}$ = 0.007.[18] On the other hand, one SR by Korn S. et. al. assessed the AAER reductions in tezepelumab, dupilumab, benralizumab, and mepolizumab at various level of BEC subgroups; BEC ≥450 cells/uL, BEC ≥300 cells/uL, BEC 0 to < 300 cells/uL, BEC ≥150 cells/uL, BEC 150 to < 300 cells/uL and BEC 0 to < 150 cells/uL. At the end of the study, consistent AAER reductions in all biologics assessed were observed in high BEC subgroup (BEC ≥400 cells/uL, BEC ≥300 cells/uL and BEC ≥150 cells/uL). Meanwhile in tezepelumab and dupilumab, consistent AAER reductions were reported in all BEC subgroups except that tezepelumab also reduced the AAER at the lowest BEC subgroup (BEC 0 to <150 cells/uL). Other observation was reduction of AAER in BEC 150 to <300 cells/uL subgroup by dupilumab 300mg Q2W and in BEC 0 to <300 cells/uL by benralizumab.[28] Indirect pooled analyses by Menzies-Gow A. et. al. reported no significant differences between biologics (mepolizumab, benralizumab, dupilumab and tezepelumab) in reduction of AAER among patients with BEC ≥300 cells/uL and <300 cells/uL. On the other hand, tezepelumab was associated with a numerically lower AAER than almost all other biologics in both BEC subgroups. However, the authors reported that dupilumab 300mg had better RR compared to tezepelumab in AAER reductions in both BEC subgroups (RR 1.08 CrI [95% CI 0.54 to 2.27]).[27]

Another SR with NMA by Pitre T. et. al. reported that those with high eosinophilic asthma (≥300 cells/uL) benefited more with biologics compared to placebo group in reducing asthma exacerbations especially with tezepelumab (RR 0.30 [95% CI 0.22 to 0.43]) and dupilumab (RR 0.32 [95% CI 0.24 to 0.42]). Other biologics were benralizumab (RR 0.51 [95% CI 0.41 to 0.63]) and mepolizumab (RR 0.52 [95C% CI 0.43 to 0.64]). Meanwhile in low eosinophilic asthma (<300 cells/uL), nor moderate neither high certainty evidence retrieved on any biologics in reducing the exacerbations.[25] Consistent reductions in the risk of asthma exacerbation among BEC ≥300 cells/uL patients treated with benralizumab, dupilumab and mepolizumab were also observed in SR with MA by Lee J. et. al. with pooled RR of 0.41 (95% CI 0.32 to 0.53, I^2 = 68%, p < 0.01). Meanwhile, in patients with low-eosinophils subgroup (<300 cells/uL), the risk of asthma exacerbations was higher than those with BEC ≥300 cells/uL (RR 0.67 [95% CI 0.54 to 0.84, I^2 = 48%, p 0.05]).[19]

Various findings were also reported in individual study of benralizumab, mepolizumab and tezepelumab. For benralizumab, an SR by Farne HA. et. al. reported that although stronger effect of benralizumab in eosinophilic asthma compared to non-eosinophilic (rate ratio 0.55 [95% CI 0.48 to 0.63] versus 0.69 [95% CI 0.56 to 0.85]) toward asthma exacerbation, the difference was not significant (p = 0.08).[20] Meanwhile for mepolizumab, an SR by Israel E. et. al. reported that the AER was reduced with mepolizumab in BEC <300, 300<500, 500<700, and ≥700 cells/uL.32 Even Liu MC. et. al. reported that after switching from omalizumab, mepolizumab showed an improvement in all efficacy endpoints regardless the baseline BEC. The AAER reductions were 60%, 62%, 59% and 63% with BEC levels of ≥150 cells/uL, ≥300 cells/uL, ≥400 cells/uL and ≥500 cells/uL, respectively.[41] Significant reductions in AAER regardless the level of BEC also was reported in tezepelumab group compared to placebo. An SR with MA by Zoumat Z. et. al. reported that patients on tezepelumab had significantly reduced AAER in BEC <150 cells/uL, BEC 150 to <300 cells/uL, 300 to <450 cells/uL and ≥450 cells/uL; 0.61 (95% 0.42 to 0.88), 0.57 (95% CI 0.41 to 0.79), 0.41 (95% CI 0.27 to 0.64) and 0.23 (95% CI 0.15 to 0.34), respectively.[23] Pooled analyses of two tezepelumab trials (PATHWAY & NAVIGATOR) by Corren J. et. al. showed that tezepelumab, reduced the AAER in range of 65% - 72% (95% CI 44 – 55 to 79 – 83) in high-eosinophils subgroup (BEC ≥300 cells/uL). The AAER reductions were observed in BEC <300 cells/uL subgroup, ranges from 53% - 61% (95% CI 29 - 39 to 69 - 75).[35]

Subgroup: FeNO level

Another subgroup analysis was FeNO level; high level (FeNO ≥25 ppb) and low level (FeNO <25 ppb). Based on latest SR with MA by Kyriakopoulos C. et. al. dupilumab and tezepelumab showed greater AAER reduction in patients with higher FeNO levels compared to low FeNo levels; AAER rate ratio 0.33 (95% CI 0.28 to 0.40 versus 0.70 (95% CI 0.57 to 0.86), $P_{subgroup\_heterogeneity}$ < 0.001.18 Significant AAER reduction with tezepelumab among patients with high level FeNO was consistently reported in two studies. First study was an SR with MA by Zoumat Z. et. al. reported greater reduction in AAERs among patients with high FeNO level by 0.68 (95% CI 0.51 to 0.92) compared to low FeNO level (0.32 [95% CI 0.25 to 0.42].[23] The other study was a pooled analysis of two tezepelumab trials by Corren J. et. al. The authors reported that tezepelumab reduced the AAER in both level of FeNO with greater AAER reductions in patient with high FeNO level (within range 65% - 72% [95% CI 47 – 58 to 77 – 82]).[35]

Subgroup: Allergen status

Three studies reported that significant reductions of AAER with tezepelumab compared to placebo regardless the patients' allergen status. First SR with MA by Zoumat Z. et. al. reported that either with or without perennial allergen significant AAER reduction was observed; 0.42 (95% CI 0.33 to 0.53) and 0.49 (95% CI 0.36 to 0.67), respectively.[23] A trial by Corren J. et. al. also found that patients on tezepelumab had reduced AAER when compared to patients on placebo in three groups of allergen status. First group was patients with perennial aeroallergen sensitivity (AAER reductions by 58% [95% CI 47 to 67], second group was patients with both perennial and seasonal allergy (by 58% [95% CI 42 to 70] and in patients with perennial allergy only (by 59% [95% CI 41 to 71]).[33] Another Corren J. et. al. pooled analysis study reported that both patients with or without perennial aeroallergen sensitisation who were treated with patients on tezepelumab showed significant reduction in AAER over 52-weeks compared to placebo; 62% reduction in patients with perennial aeroallergen sensitisation (RR 0.38 [95% CI 0.30 to 0.47]) and 54% reduction in patients without (RR 0.46 [95% CI 0.34 to 0.62]).[35]

Subgroup: Comorbidity

Included studies on comorbidity subgroup were on dupilumab and mepolizumab. The dupilumab study was an open-label extension study (TRAVERSE) by Berger P. et. al. The study was the extension of two parent studies; QUEST and VENTURE which involved patients with and without self-reported coexisting chronic sinusitis-nasal polyps (CRS-NP). For TRAVERSE study, patients from two parent studies were randomised accordingly either continuously received dupilumab, change to dupilumab from placebo or remained with placebo treatment. At the end of 52-week treatment period of parent studies, dupilumab greatly reduced the AAER in both patients with and without self-reported CRS-NP subgroup compared to placebo. The reduction was 2.39 to 0.49 versus 2.36 to 1.48 in patient with self-reported CRS-NP subgroup and reduction of 2.00 to 0.51 versus 2.21 to 0.91 in without self-reported CRS-NP subgroup. Later, after 96-weeks treatment period of TRAVERSE study, progressive AAER reduction was recorded. The AAER reduction among patients with self-reported CRS-NP ranged within 0.41 - 0.45 in placebo patient who just started dupilumab treatment during extension study (placebo/dupilumab) and 0.32 – 0.35 in those who were continuously treated with dupilumab since parent studies (dupilumab/dupilumab). Meanwhile, among patients without self-reported CRS-NP, the AAER reduction ranged within 0.21 - 0.34 in placebo/dupilumab group and 0.33 – 0.41 in dupilumab/dupilumab group.[39]

Effects of mepolizumab towards several comorbidities were reported in three studies. First post-hoc analysis by Liu MC. et. al. reported the outcome after switching mepolizumab from omalizumab. At 32-week of study period, reductions in the AAER were approximately 50% or greater across nasal polyps, aspirin/NSAIDs intolerance, and GERD subgroups compared with the prior 12 months of study period.[41] Another post-hoc analysis by Gibson PG. et. al. was on four mepolizumab trial (DREAM, MENSA, SIRIUS and MUSCA trials) compared to placebo. The comorbidities assessed were upper airway comorbidity (nasal polyps, sinusitis, allergic rhinitis), psychopathologies, cardiovascular, GERD, diabetes mellitus, vocal cord dysfunction and OCS-dependent comorbidity categories (osteoporosis/bone fracture, bruising and weight gain). After further assessment, the analysis found that 49% reductions in AER with mepolizumab (rate ratio 0.51 [95% CI 0.45 to 0.59]) regardless the upper respiratory comorbidity status (68% and 45% reductions in patients with and without nasal polyps, 49% in patients both with and without sinusitis, and 50% in patients with and without allergic rhinitis, respectively). The AER reductions also observed in psychopathologies and diabetes mellitus ranging between 45% and 58%. Meanwhile the AER reductions cross OCS-dependent comorbidity categories ranged between 16% and

64%.[42] On the hand, one retrospective study that used real-world data was conducted by Casale T. et. al. to describe the real-world effectiveness of mepolizumab in patients with severe asthma stratified by common overlapping comorbidities. There were seven comorbidities of interest which were atopic disease (allergic rhinitis, conjunctivitis, atopic dermatitis, food allergies, anaphylaxis, eosinophilic esophagitis), nasal polyps, chronic sinusitis, obesity, respiratory infections including pneumonia, COPD and depression or anxiety. The most common patient comorbidities were atopic disease (73.2%), respiratory infections (55.6%) and chronic sinusitis (45.1%). A total of 639 patients with mean age of 50 years old involved with exception of 56-years old in COPD group. In all comorbidity subgroups, significant reductions ($p<0.001$) of 38% to 55% in the mean rate of exacerbations during follow-up (1.0 – 1.5 per year) versus baseline (2.2 – 2.6 per year) periods were observed. The greatest numerical improvements of AER were in the nasal polyp's subgroup and the lowest in depression or anxiety subgroup. Significant reduction ($p<0.001$) in proportions of patients with ≥1 exacerbation in all the subgroups also reported from 82% to 89% during the baseline period to 52% to 67% during the follow-up period.[44]

5.2.4.2 Asthma control

Asthma controls were reported in several number of studies involved Asthma Control Questionnaire (ACQ) score and Asthma Control Test (ACT) score of mepolizumab, benralizumab, dupilumab and tezepelumab.

5.2.4.2(a) Overall population

Asthma Control Questionnaire score

Kyriakopoulos C. et. al. reported that although all biologics included tezepelumab, mepolizumab, benralizumab and dupilumab improved asthma control by reducing the ACQ score by 0.34 points (95% CI -0.46 to -0.23, I^2 = 89.5%), the reduction did not reach the minimal clinically important difference (MCID) for the ACQ score (-0.50 points).[18] Indirect comparison of NMA conducted by Iftikhar IH. et. al. also reported improvement in ACQ score with biologics compared to placebo. The NMA reported that that mepolizumab ranked first in reducing the ACQ scores followed by dupilumab and benralizumab; -0.42 (95% CI -0.55 to -0.29), -0.31 (95% CI -0.50 to -0.21) and -0.28 (95% CI -0.38 to -0.18), respectively.[26] Other studies also reported an improvement in ACQ score among patients treated with dupilumab (MD -0.48 [95% CI -0.88 to -0.09]),[30] a significant improvement in ACQ-6 score with mepolizumab (-0.53 point [95% CI -0.76 to -0.30]), and with benralizumab treatment (0.78 [95% CI -1.02 to -0.54]).[21]

The ACQ-6 score was also reported in two tezepelumab individual studies. An SR with MA by Abdelgalil MS. et. al. showed a significant decreased in ACQ-6 score with tezepelumab compared to placebo. The mean difference was -0.32 (95% CI -0.43 to -0.21), p < 0.00001.22 Even in a long-term study by Menzies-Gow A. et. al., the improvement in ACQ-6 score was sustained throughout treatment period especially among patients who were initially received tezepelumab since parent study.[36] Meanwhile in individual mepolizumab studies, an SR by Farne HA. et. al. reported that subcutaneous mepolizumab had moderate effect on ACQ-score compared to placebo. However, the score did not meet MCID of 0.5 points in the ACQ score (MD -0.38 [95% CI -0.50 to -0.26]).[20] In contrast, SR of real-world data by Israel E. et. al. reported that the ACQ score was significantly improved with mean changes in the ACQ score from baseline to follow-up ranged from -0.5 to -1.9 points after mepolizumab initiated; p < 0.001.32 The post-hoc analysis of OSMO study by Liu MC. et. al. also reported that after 32-weeks of mepolizumab treatment, mean improvements in ACQ-5 scores exceeded the MCID point.[41] In Khurana S. et. al. COSMEX-extension study, there was interruption period between COSMEX study and initial trial where enrolled patients who supposedly received mepolizumab were not due to certain issue. During the interruption period, asthma condition getting worst. However, after restarting mepolizumab, the ACQ-5 score was continuously improved.[43]

Next individual study was dupilumab extension-study of VOYAGE-trial by Fiocchi AG. et. al. involving children with moderate to severe asthma. According to the study, a total of ACQ-7-1A score was improved in dupilumab compared to placebo. Since week-4, the LS mean difference versus placebo was -0.28 (95% CI -0.45 to -0.11; p = 0.0011) and was sustained through week-52 (LS mean difference -0.44 (95% CI -0.59 to -0.30; p < 0.0001). Further assessment on the asthma control was divided based on the ACQ-7-1A score which was well-controlled asthma (ACQ-7-1A score ≤0.75 points), adequately controlled asthma (ACQ-7-1A sore <1 point) and controlled asthma (ACQ-7-1A <1.5 points). The authors also found that the proportion of well-controlled asthma in patients treated with dupilumab was increased from 61% at week-24 to 70% at week-52 compared to placebo which only had small increased since week-24 to week-52 (43% to 46%). Similar trend of improvement also was reported in patients with adequately controlled asthma (ACQ-7-1A score <1 point) with dupilumab since week-24 to week-52 (65% to 76% with dupilumab vs 53% to 54% with placebo). Meanwhile in controlled asthma the increment from week-24 to week-52 was 79% to 85% with dupilumab and 70% to 73% with placebo.[38]

As for benralizumab, study by Padila-Galo. A. et. al. reported 100% of patients responded to benralizumab based on Spanish Severe Asthma Consensus. From the responses, 79.6% showed a very good response (52.3% controlled asthma and 27.3% complete response) and remaining 20.4% showed partial response.[46] Based on the ACQ and ACQ-6 score, benralizumab showed better improvement compared to placebo. The extension study by Korn S. et. al. reported that benralizumab increased patient percentages of well controlled asthma based on improvement in ACQ-6 score (57% to 64%).[40] Better improvements in ACQ score also reported in NMA by Iftikhar IH. et. al. (MD -0.26 [95% CI -034 to -0.17]; I^2 = 37%) in both eosinophilic and non-eosinophilic asthma.[26]

Asthma Control Test (ACT) score.

Charles D. et. al. found an improvement in ACT score with mepolizumab, benralizumab and dupilumab. The pooled results for mepolizumab and benralizumab were 6.15 point (95% CI 5.1 to 7.15) and 5.82 point (95% CI 3.39 to 8.25), respectively.[21] Israel E. et. al. also reported that mepolizumab significantly improved the score with mean changes from baseline to follow-up ranged from 5.00 to 8.53 points. The differences exceeded the established MCID of three points.[32] Meanwhile, the result for dupilumab single study was MD 9.0 (95% CI 5.0 to 12.0).[21] Agache I. et. al. in their SR reported that when compared to SoC, benralizumab and dupilumab improved asthma control; MD-0.17 (95% CI -0.34 to 0.00) and MD -0.27 (95% CI -0.40 to -0.14), respectively.[31]

5.2.4.2(b) Subgroups Analyses

Several subgroup analyses were reported in assessment of asthma control after biologics treatment. Those subgroups were based on blood eosinophils count (BEC), FeNO level, allergen status and patients' comorbidities.

Subgroup: Baseline eosinophils count (BEC)

Asthma Control Questionnaire (ACQ) Score

Several studies reported that the ACQ score was significantly improved with biologics among patients with high level of baseline eosinophil count (BEC ≥300 cells/uL) compared to placebo. Recent SR with MA by Kyriakopoulos C. et. al. reported a significant improvement in ACQ score after treatment with benralizumab, dupilumab and tezepelumab were observed in patients with BEC level ≥300 cells/uL (-0.39 [95% CI -0.50 to -0.28] points).[18] The NMA by Pitre T. et. al. reported patients on dupilumab had improved asthma control (MD -0.73 [95% CI -0.98 to -0.43]) compared to placebo in high eosinophilic asthma (≥300 cells/L).[25] Another NMA by Iftikhar IH. et. al. also reported that the magnitude of response with biologics was comparatively greater in the high level of BEC than low BEC level subgroup.[26] An SR by Korn S. et. al. also reported a greatest improvement in ACQ was demonstrated among patients with BEC ≥300 cells/uL who was treated with tezepelumab, dupilumab, benralizumab and mepolizumab. The improvement also observed in most trials reporting BEC ≥450 cells/uL subgroup involved tezepelumab, benralizumab and mepolizumab.[28]

Inconsistent findings in ACQ score were also reported among patients with BEC level ≥150 cells/uL and <150 cells/ uL. Kyriakopoulos C. et. al. reported that pooled analysis of tezepelumab showed significant improvement in BEC level ≥150 cells/uL; -0.42 (95% CI -0.56 to -0.28) but not in BEC <150 cells/uL (-0.07 [95% CI -0.30 to 0.19]).[18] Korn S. et. al. also reported that tezepelumab, benralizumab and mepolizumab improved the ACQ score in patients with BEC ≥150 cells/uL. Even in BEC 0 to <150 cells/uL, one benralizumab trial demonstrated efficacy in improving ACQ score. The ACQ improvement were also reported for tezepelumab and dupilumab 200mg dose in BEC 0 to <300 cells/uL subgroup.[28] However, Pitre T. et. al. reported that benralizumab, dupilumab and tezepelumab were probably did not improve asthma control in low BEC level compared to placebo (MD -0.23 [95% CI -0.41 to -0.06], MD -0.2 [95% CI -0.42 to 0.02], and MD -0.23 [95% CI -0.36 to -0.09], respectively).[25] Pooled analysis of two tezepelumab trials by Corren J. et. al. reported numerical improvements in ACQ-6 from baseline to week-52 in all BEC subgroups ranging from the highest BEC ≥450 cells/uL to the lowest BEC <150 cells/uL. The LS mean was ranging from -1.74 — -1.12 (121 – 130), with the LS mean difference between tezepelumab, and placebo ranging from -0.46 - -0.11 (-0.69 - -0.34 to -0.23 – 0.11).[35] For mepolizumab, Liu MC. et. al. reported that patients who were switched to mepolizumab from omalizumab showed an

improvement in ACQ-5 at week-32. The improvement increased from LS mean change (SE) of 1.46 (0.12) in patients with BEC ≥150cells/uL to LS mean change (SE) of 1.76 (0.15) in patients with BEC ≥500 cells/uL.[41] The extension study of benralizumab trial also reported that benralizumab reduced percentages of not well controlled asthma in placebo patients high BEC level (≥300 cells/uL) after they were treated with benralizumab during the extension period in two benralizumab intervals (Q4W and Q8W; 66.7% to 47.6% and 55.1% to 35.7%, respectively).[40]

Subgroup: FeNO level

Asthma Control Questionnaire (ACQ) score

Recent SR and MA by Kyriakopoulos C. et. al. showed that significant reduction in ACQ score was observed with tezepelumab in patients with high FeNO level (≥25 ppb) compared to those with low FeNO level (<25 ppb); -0.67 (95% CI -1.02 to -0.32) versus -0.10 (95% CI -0.39 to 0.190 points, $P_{subgroup\_heterogeneity}$ = 0.014.[18] Another pooled analysis of two tezepelumab trials by Corren J. et. al. also reported similar results of significant reduction of ACQ score in high FeNO level compared to low FeNO level (-0.36 [95% CI -0.84 to -0.41] versus -0.13 [95% CI -0.30 to 0.05]).[35]

Subgroup: Allergy Status

Asthma Control Questionnaire (ACQ) score

Two Corren J. et. al. studies on tezepelumab reported that ACQ-6 scores were improved in either with or without perennial allergens when compared to placebo.[33,35] The mean changes (standard error) in patients with perennial aeroallergen sensitisation in placebo and tezepelumab group were -1.25 (0.06) and -1.54 (0.06) (LS mean difference, -0.29 (95% CI -0.45 to -0.13). Meanwhile, in patients without perennial aeroallergen sensitisation in placebo and tezepelumab group were -1.10 (0.08) and -1.52 (0.08) (LS mean difference, -0.42 (95% CI -0.63 to -0.20).[33] Another study reported the pooled LS mean in patients with perennial allergen was -1.34 with LS (mean difference) in tezepelumab and -0.66 (95% CI -1.05 to -0.26) in placebo. The pooled LS mean in patients without perennial allergen was -1.49 with LS (mean difference) -0.30 (95% CI -0.42 to -0.18).[35]

Asthma Symptom Diary (ASD) score

One study reported on ASD score after treatment with tezepelumab. Corren J. et. al. found that tezepelumab improved ASD scores from baseline to week-52 in patients with or without perennial aeroallergen sensitisation compared to placebo. The mean changes (standard error) in patients with perennial aeroallergen sensitisation in placebo and tezepelumab group were -0.63 (0.03) and -0.70 (0.03) (LS mean difference, -0.07 (95% CI -0.16 to -0.03). Meanwhile, in patients without perennial aeroallergen sensitisation in placebo and tezepelumab group were -0.51 (0.05) and -0.72 (0.04) (LS mean difference, -0.20 (95% CI -0.33 to -0.08).[33]

Subgroup: Comorbidities

One of dupilumab extension study (TRAVERSE) by Berger P. et. al. showed that either during parent studies and across extended period, dupilumab consistently improved the ACQ- 5 scores regardless of whether the patients was with or without self-reported chronic-rhino sinusitis–nasal polyps (CRS-NP).[39]

Two mepolizumab studies also reported on effects of comorbidity on the biologic effectiveness. According to Liu MC. et. al. all comorbidities (nasal polyps, aspirin/NSAIDs intolerance, and GERD) showed no effects on improvements of ACQ-5 which exceeded the MCID threshold at week-32 after treated with mepolizumab. However, in patients with comorbid nasal polyps, the improvement was higher than without nasal polyps.[41] Another post-hoc analysis by Gibson PG. et. al. reported 0.32-point improvement in ACQ-5 score with mepolizumab versus placebo in either patient with and without nasal polyps, sinusitis, or allergic rhinitis. The smallest improvement was observed in no psychopathology's subgroup (-0.27 [95% CI -0.38 to -0.17]). Meanwhile a wide confidence interval (CI) was observed for patients with diabetes mellitus compared with other comorbidities.[42]

5.2.4.3 Lung function

5.2.4.3(a) Overall population

Pooled analysis by Kyriakopolous C. et. al. reported that all biologics included mepolizumab, benralizumab, dupilumab and tezepelumab improved FEV1 by 0.11L (95% CI 0.09 to 0.14); I^2 = 50.1%.[18] An NMA by Iftikhar IH. et. al. reported that no significant difference inter-treatment differences among dupilumab, benralizumab and mepolizumab in improving FEV1. They also observed that dupilumab had the greatest increased in FEV1 compared to placebo (0.16L [95% CI 0.08 to 0.24]) followed with benralizumab (0.12L [0.08 to 0.17]).[26] Two SR with MA also reported significant increase in FEV1 mepolizumab (0.17L [95% CI 0.11 to 0.24][20] and MD 0.09 [95% CI 0.05 to 0.14][21]) and benralizumab (0.21L ([95% CI 0.08 to 0.34][20] and MD 0.08 [95% CI 0.02 to 0.15][21]) compared to placebo where benralizumab showed superior effect in eosinophilic patients.

Tezepelumab significantly improved lung function compared to placebo in four pooled analysis[22,23,35] one extended trial of tezepelumab studies.[36] Based on duration of intervention, one SR with MA found consistent improvement in FEV1 levels from since 4-weeks 0.11L (95% CI: 0.07 to 0.16) up to 52-weeks (0.16L [95% CI 0.11 to 0.21]) after tezepelumab administration. However, at week-52 although the FEV1 remained improved, the trend started to decrease.[23] In the extension trial by Menzies-Gow A. et. al., an improvement in the FEV1 was sustained throughout the treatment period either in patients who were initially received tezepelumab since parent study or from placebo group who were randomised to receive tezepelumab during the extension study.[36]

One SR by SR by Israel E. et. al. reported on significant improvement in FEV1, FVC and FEV1/FVC ratio by mepolizumab. The changes ranged from -0.03L to +0.40 L ($p < 0.05$) for FEV1, mean change ranging from +0.15 L to +0.16 L ($p < 0.0001$) for FVC and 61% to 72% of FEV1/FVC ratio with mean change ranging from 2.1% to 6.0% following 6 to 12 months of mepolizumab treatment.[32] An extension study by Khurana S. et. al. reported mepolizumab re-improved the FEV1 during an 'interruption period' between transition period of an initial trial and extended trial. Within the transition period there was about one-year gap where the patients involved did not received mepolizumab and their asthma getting worst. The one-year gap was referred as 'interruption period'. However, after restarting mepolizumab, FEV1 was continuously improved.[43] There was also one post-hoc analysis by Liu MC. et. al. reported that, after changing from omalizumab to mepolizumab, consistent improvements from baseline in pre-BD FEV1 were observed. The LS mean change (SE) ranging from 15mL – 225mL (69.8mL – 86.4mL).[41]

Another extension trial by Bacharier LB. et. al. reported on sustained improvement in the FEV1 in children after more than one year of treatment with dupilumab. Bacharier LB. et. al. also reported that children who just started dupilumab during the extension trial showed rapid improvements in FEV1, mean (SD) change from baseline of 8.7% (15.7points) as early as week 2 of dupilumab treatment. By week-2 to week-52 number of children with FEV1 ≥80% were increased up to 70% - 78% in all groups treated with dupilumab. In addition to that, children who did not have normal lung function at week-52 of parent study, were reported having improvement of lung function ranging from 36% - 49% after 52 weeks of the extension study.[37]

5.2.4.3(b) Subgroup Analyses

Subgroup: Blood Eosinophil Count (BEC)

Kyriakopoulos C. et. al. in an SR with MA conducted subgroup analysis of different level of BEC count towards the effects of biologics on FEV1. Between BEC count of ≥300 cells/uL and <300 cells/UL, benralizumab, dupilumab and tezepelumab significantly improved the FEV1 in both BEC level. However, the improvement was greater in BEC ≥300 cells/uL compared to <300 cells/uL; 0.18L (95% CI 0.14 to 0.22) versus 0.07L (95% CI 0.04 to 0.10); $P_{subgroup\_heterogeneity}$ <0.001. Another evaluation was conducted among patients with BEC level ≥150 cells/ uL and <150 cells/UL who were treated with tezepelumab and dupilumab. Both biologics showed significant improvement in both BEC level as the greater FEV1 improvement was observed in BEC ≥150 cells/uL than BEC <150 cells/uL; 0.18L (95% CI 0.13 to 0.24) and 0.10L (95% CI 0.02 to 0.17), respectively.18 On the other hand, an NMA by Pitre T. et. al. reported that dupilumab was probably superior to benralizumab and mepolizumab in improving lung function (MD 0.11L [95% CI 0.05 to 0.16] and MD 0.15L [95% CI 0.08 to 0.22], respectively) in patients with high eosinophilic asthma (≥300 cells/uL). Meanwhile when compared to placebo, mepolizumab was superior in improving lung function; MD 0.10L (95% CI 0.04 to 0.15).[25] The findings also in line with another NMA by Iftikhar IH. et. al. where they also reported that dupilumab showed the greatest response on FEV1 followed with benralizumab.[26] Pitre T. et. al. analysis also reported that tezepelumab was probably superior to mepolizumab (MD 0.15L [95% CI 0.05 to 0.24]) in BEC ≥300 cells/uL. Further assessment between dupilumab and tezepelumab, showed that both biologics probably improved lung function equally well (MD 0.11L [95% CI -0.08 to 0.1]). On the other hand, among low eosinophilic asthma (<300 cells/uL), no moderate or high certainty evidence found that any biologics improved lung function.[25]

In contrast, pooled analysis of two tezepelumab trials by Corren J. et. al. reported an improvement in all BEC level subgroups (high to low BEC level) ranging from BEC ≥450 cells/uL - <150 cells/uL with LS mean ranging from 0.44 – 0.07 and the LC mean difference between tezepelumab and placebo ranging from 0.27 – 0.00 (95% CI 0.18 - -0.09 to 0.36 – 0.08).[35] An extension study by Bacharier LB. et. al. also reported that FEV1 was improved among patients at various level of BEC after treatment with dupilumab compared to placebo.[37]

Subgroup: FeNO level

Kyriakopolous C. et. al. found that dupilumab and tezepelumab significantly improved FEV1 among patients with FeNO level ≥25 ppb compared to FeNO level <25 ppb; 021L (95% CI 0.15 to 0.28) versus 0.08 (95% CI -0.02 to 0.17); $P_{subgroup\_\ heterogeneity}$ = 0.023.[18] Pooled analysis of two tezepelumab studies by Corren J. et. al. also reported that tezepelumab showed an improvement in FEV1 among patients with high FeNO level ranging from 25 ≥ 50 ppb compared to placebo (LS mean was ranging from 0.25 to 0.35 with LS mean difference ranging from 0.20 – 0.21 (95% CI 0.11 – 0.12 to 0.28 - 0.30).[35] An extension study by Bacharier LB. et. al. also reported that FEV1 was improved among patients at various level FeNO concentrations after treated with dupilumab compared to placebo.[37]

Subgroup: Allergy status

Tezepelumab significantly improved the FEV1 regardless the perennial aeroallergen status compared to placebo; positive perennial aeroallergen status (LS mean difference 0.07L [95% CI 0.01 to 0.14]) and negative perennial aeroallergen status (LS mean difference 0.23L [95% CI 0.14 to 0.31]). The improvements with tezepelumab were observed as early as week-2 of treatment and were sustained throughout week-52 in both allergen status subgroups.[35]

Subgroup: Comorbidities

An extension study by Berger P. et. al. reported that dupilumab improved lung function in both groups of patients either with chronic rhinosinusitis-nasal polyps (CRS-NP) or without. The improvements were recorded as early as the treatment started and kept increasing and maintained through-out week-96 (0.43L – 0.45L in patients with CRS-NP and 0.29L in patients without CRS-NP).[39] A few comorbidities (NP, aspirin/NSAIDs intolerance, and GERD) also shown no significant effects towards FEV1 improvement after 32-weeks treated with mepolizumab. However, the improvement was higher in patients with comorbid nasal polyps than without.[41] One post-hoc analysis study by Gibson PG. et. al. reported that after being treated with mepolizumab, patients with upper airway comorbidity (nasal polyps, sinusitis, allergic rhinitis, psychopathologies, cardiovascular (CVS), GERD, vocal cord dysfunction and OCS-dependent comorbidity categories [osteoporosis/bone fracture, bruising and weight gain] improved in FEV1 (71.8 mL improvement) except in diabetes mellitus subgroup. Greater improvements were observed in those with NP, with sinusitis, in GERD and in all OCS-dependent subgroup except in eye- related subgroup.[42]

5.2.4.4 Hospital admission and Emergency Department (ED) visit

5.2.4.4(a) Overall population

Recent SR and MA by Kyriakopoulos C. et. al. reported that mepolizumab, benralizumab, and tezepelumab reduced up to 60% of hospitalisation and ED visit due to AAER (rate ratio 0.40 [95% 0.27 to 0.60], I^2 = 32%).[18] The reduction of those three biologics were also reported in NMA by Pitre T. et. al. where the author found that tezepelumab was superior to benralizumab in reducing the hospitalisation (RR 0.22, [95% CI 0.13 to 0.37]).[25] Another NMA by Menzies-Gow A. et al. reported that all the biologics in the network (mepolizumab, reslizumab, benralizumab, omalizumab, dupilumab and tezepelumab) had no statistically significant difference in reducing hospitalisation or ED visit due to AAER as tezepelumab took the lead in SUCRA ranked at 95%.[27]

Meta-analysis by Farne HA. et. al. observed that patients who were having more than three episodes of exacerbations in previous year showed the greatest reduction in ED visit after treatment with benralizumab; rate ratio 0.68 (95% CI 0.47 to 0.98; I^2 = 43%).[20] In a cross-sectional study by Padiala-Galo A. et. al. after one-year of benralizumab treatment, there was 83% reduction in ED visit was reported.[46]

Isarael E. et. al. reported that mepolizumab significantly reduced the AAER requiring hospitalisation about 54% to 83%. The reduction rate ranged from 0.11 – 0.77 events/year at baseline to 0.03 – 0.35 events/year at followed-up period; $p < 0.05$.32 Meanwhile, Khurana S. et. al. reported in an extension study of mepolizumab, the long-term effect (>2 years) on annualised rate of on-treatment exacerbations required ED visit was 0.13 (95% CI 0.10 to 0.18) event/year and 0.07 (95% CI 0.05 to 0.10) event/year in those that requiring hospitalisation.[43]

One post-hoc analysis of by Menzies-Gow A. et. al. reported that tezepelumab reduced re-hospitalisation compared to placebo; 1 versus 19 patients. The annual rates of all-caused ED visits and hospitalisation also showed significant reductions with tezepelumab compared to placebo; 28% (95% CI 2 to 46) and 59% (95% CI 35 to 74) reductions over 52 weeks, respectively. The analysis also showed the time to first asthma exacerbation that required ED visits or hospitalisation was prolonged in tezepelumab group with a risk reduction of 65% (HR 0.35 [95% CI 0.22 to 0.56) compared to placebo. In addition to that, the AAERs that required ED visit without hospitalisation over 52 weeks of tezepelumab treatment also reduced by 61% (95% CI 23 to 80) compared to placebo.[34] In long-term extension study (2 years) by Menzies-Gow A. et. al., greater reductions in hospital admission due to exacerbations in tezepelumab was observed compared to placebo.[36]

5.2.4.4(b) Subgroups Analyses

Subgroup: Blood Eosinophil Count (BEC)

Korn S. et al. reported that tezepelumab, dupilumab, benralizumab and mepolizumab reduced the exacerbations requiring hospitalisation, or ED visit among patients with high BEC level (≥300 cells/uL). The authors also observed various level of BEC subgroups and found greatest reduction of hospitalisation, or ED visit with tezepelumab in two BEC level subgroups; 90% reductions in BEC ≥300 cells/uL subgroup and 86% reduction in BEC ≥150 cells/uL subgroup. In addition to that, the authors also reported that only tezepelumab reduced the hospitalisation and ED visit among patients in low BEC level (0 to <150 cells/uL) subgroup.[28] Even pooled analyses by Corren J. et. al. showed that tezepelumab reduced AAER associated with hospitalisation or and ED visit over 52-weeks compared with placebo in patients with BEC <150 cells/uL (RR 0.40 [95% CI 0.18 to 0.93).[35]

Subgroup: FeNO level

Corren J. et. al. reported patients with high FeNO levels (≥50 ppb) reduced the hospitalisation or ED visit due to AAER over 52-weeks of tezepelumab treatment compared with placebo; RR 0.09 (95% CI 0.03 to 0.25).[35]

Subgroups: Allergy status

When analysed based on allergen status subgroups, pooled analysis of two tezepelumab trials by Corren J. et. al. found that both subgroups either with or without perennial allergen sensitisation reduced hospitalisation or ED visit due to exacerbations after treatment with tezepelumab. The reductions were 80% (RR 0.20 [95% CI 0.10 to 0.39]) in patient with perennial allergen and 74% (RR 0.26 [95% CI 0.12 to 0.59]) in those without.[35]

Subgroup: Comorbidity

Pooled analysis of two trials by Corren J. et. al. found that tezepelumab significantly reduced hospital admission or ED visit due to AAER in patients with a history of NP (RR 0.06 [95% CI 0.01 to 0.52) compared to those without NP.[35]

In one mepolizumab retrospective analysis of real-world data by Casale T. et. al. patients who were treated with mepolizumab reduced the rate of exacerbations requiring hospitalisation in all comorbidities subgroups ($p < 0.05$) except in the nasal polyp subgroup ($p = 0.083$). The mean rate was reduced by 57% to 83% during the follow-up periods (0.01 – 0.07 per year) versus baseline (0.06 – 0.22 per year). In addition to that, the proportion of patients with ≥1 exacerbation requiring hospitalisation was 4% to 16% during the baseline period, reduced to 1% to 6% during the follow-up period.[44]

5.2.4.5 Oral corticosteroid (OCS) intake

5.2.4.5(a) Overall population

For the effect of biologics on OCS dose reduction, Kyriakopoulos C. et. al. found that in all the biologics that being reviewed, benralizumab, mepolizumab, dupilumab and tezepelumab also increased the probability of OCS reduction to <5mg/day by 74% (risk ratio 1.74 [95% CI 1.23 to 2.46]; I^2 = 44.1%). Meanwhile, the probability of the biologics to reduced OCS dose more than 50% was increased up to 68% (risk ratio 1.68 [95% CI 1.29 to 2.19]; I^2 = 27.2%. Even the probability of OCS discontinuation also increased with the benralizumab, dupilumab and tezepelumab (rate ratio 1.63 [95% CI 1.29 to 2.19], I^2 = 27.2%).[18] Two NMA studies also reported that benralizumab, dupilumab and mepolizumab probably reduced the used of OCS and mean daily steroid doses compared to placebo; rate ratio (RR) 1.77 (95% CI1.29 to 2.43), RR 1.49 (95% CI 1.22 to 1.83) and RR 1.61 (95% CI 1.07 to 2.41)25 or mean difference (MD) -8.35mg [95% CI -13.88 to -2.87], -13 (95% CI -20 to -5), and -5.30mg [95% CI -7.50 to -3.10].[19]

Calzetta L. et. al. specifically assessed the OCS-sparing effects of benralizumab, dupilumab and mepolizumab where the studies were carried-out in real-world populations. Rapid reduction in OCS consumption was observed after 3- , 4- and 6-months of treatment with benralizumab. The results were summarised in **Table 2**. Meanwhile for dupilumab, the assessment was reported after one year of treatment. After one year, the OCS dose was reduced from 20mg/day to 5.0mg/day and 24% of the included patients completely stopped the OCS consumption and 78% of the patients reduced the OCS consumption more than 50%. As for mepolizumab, the results were simplified in **Table 2** after 6-months and ≥ one-year of the mepolizumab initiation. The authors conducted Pearson's Correlation analysis and they found that the reduction in dose of OCS induced by the biologics was significantly correlated with level of OCS dose at baseline ($p < 0.001$) and the sample size included in the studies ($p < 0.05$).[29]

Table 2: OCS-sparing effect of benralizumab and mepolizumab

Biologics		After 4 weeks	After 3 months	After 6 months	After 1 year	After > 1 year
Benralizumab	OCS consumption (%)			stopped in 81.8% - 95% of patients		
	Dose reduction (mg/day)	completely stopped the use of OCS from 15.6 mg/day to 0 mg/day	OCS was reduced from 19.6 mg/day to 7.5 mg/day and further decreased up to 6 months of treatment: 5 mg/day	consistently reduced in another 5% to 18.2% patients from 18.7 mg/day to 0.25 mg/day		
Mepolizumab	OCS consumption (%)			patients requiring OCS was reduced to range of 32.2% - >50% and 68% of patients discontinued OCS	34% to 45% of patients discontinued OCS therapy. OCS burst reduced from 96% to 50%	used of OCS dropped from ranged of 76%-92.8% at baseline to 12%-34.7% 40% patients completely suspended OCS
	Dose reduction (mg/day)				reduced from 10 -18 mg/day to 2 - 9 mg/day (reduced between 20% to 50%)	28% - 62.1% patients reduced the dose from 9.2 – 24.11 mg/day to 1.3 – 4.0 mg/day

Isreal E. et. al. reported on used of maintenance OCS (mOCS) among patients who were treated with mepolizumab. The study showed that after few months on mepolizumab treatment, the mOCS was discontinued from 22% – 100% of patients at baseline to 26% – 79% at followed-up. The dose of mOCS also significantly reduced or totally stopped with mepolizumab treatment. The mean change during followed-up ranged from 0 mg/day to 22 mg/day; $p < 0.05$ with 14.8 to 100% reduction from baseline.[32] Sustained reductions in OCS usage with prolonged mepolizumab treatment also reported in Khurana S. et. al. extension study. The authors reported that, 45% patients who were continuously treated with mepolizumab for ≥128 weeks stopped the OCS intake between week-124 and week-128. Meanwhile, 58% of patients with data up to 232-weeks no longer required OCS between 228- and 232-weeks.[43] An SR by Agache I. et. al. also reported that mepolizumab showed a reduction in OCS dose to ≤5 mg/day (crude RR 1.71 [95% CI 1.11 to 2.55], $p = 0.01$).[30]

According to a cross-sectional study by Padiala-Galo A. et. al., after one-year of benralizumab treatment, number of patients requiring prednisolone was reduced up to 79.8%. Meanwhile number of corticosteroid-dependent patients was reduced to 55.6%. In addition to that, number of OCS courses also reduced about 82.8% with 47.7% of patient stopped the OCS as well as the maintenance therapy after one-year of benralizumab treatment.46 Meanwhile, the extension study of benralizumab trial by Korn S. et. al. showed sustained reduction in OCS used since parent study up to extension study period ranging from 15% to 24%.[40]

Another extension study by Bacharier LB. et. al. was also on systemic corticosteroid used among children. The authors reported that children treated with dupilumab required low systemic corticosteroid dose throughout the study period. The individualised annualised rate of systemic corticosteroid was within 0.18 – 0.19 courses per year.[37]

5.2.4.5(b) Subgroup Analyses

Subgroup: Blood Eosinophil Count (BEC)

Extension study by Korn S. et. al. reported that benralizumab further reduced the OCS consumption among patients with high BEC level (≥300 cells/uL) since baseline of the parent studies ranging from 35% - 43% to 17% - 29% across the extension study period. A total daily dose also consistently reduced since the parent study to the extension study period; median 10 - 15mg to median 5 – 10mg.[40]

Subgroup: Comorbidity

One dupilumab extension study by Berger P. et. al. reported that mean OCS dose was further reduced since parent studies and throughout extension study period (week-96) regardless of whether the patient in self-reported CRS-NP group or not. The improvement was observed in all patients who were treated with dupilumab either in group of patients who were continuously treated with dupilumab since parent study or in group of patients who just started dupilumab during the extension study. The mean OCS dose reduction ranged from 37.9% - 85.7% in patient with self-reported CRS-NP and from 50.5% - 89.6% in patients without self-reported CRS-NP throughout the study period. The study also reported that 46.2% - 85.0% of patients with self-reported CRS-NP and 60.0% - 91.7% of patient without self-reported CRS-NP reduced the OCS dose less than 5mg. In addition to that, the authors also reported that 38.5% - 71.4% patients with self-reported CRS-NP and 46.7% - 83.3% patients without self-reported CRS-NP were no longer required OCS.[39]

Based on real-world data, Casale T. et. al. reported that mepolizumab reduced about 67% to 79% mean daily OCS dose where 39% to 47% of them reduced ≥50% of the OCS dose. The greatest reduction in the OCS dose was observed in NP subgroup and the lowest reduction in obesity and respiratory infection subgroups. Meanwhile, patients with COPD had numerically highest OCS used during the baseline period compared with other subgroups. The authors also reported that the mean number of OCS bursts and proportion of patients requiring chronic OCS used was significantly ($p<0.001$) reduced by 33% to 48% and 32% to 41%, respectively, in all subgroups. The largest reductions were observed in the obesity and nasal polyp subgroups.[44]

5.2.4.6 Other outcomes

Reduction in blood Eosinophil (bEos)

An SR and MA by Charles D. et. al. reported that mepolizumab, and benralizumab was associated with reduction of blood eosinophils (bEos); -609.19 cell/uL (95% CI -793.20 to -425.68) and -518.68 cell/uL (95% CI -820.24 to -217.12), respectively.[21] An SR by Israel E. et. al. reported that all the included studies showed low mean bEos with mepolizumab ($p < 0.01$) where the post-treatment mean (SD) absolute bEos ranging from 77 – 177 cells/uL with percentage reductions from baseline to followed-up ranged from 69% to 92%.[32] Khurana S. et. al. reported that during mepolizumab extension study, there was about one-year period (interrupted period) where the patients involved did not received mepolizumab and their asthma symptom getting worst. However, after restarting mepolizumab, there was marked reduction in the bEos.[43] For benralizumab, Farne HA et. al. found that marked reduction in bEos count with benralizumab was reported in both eosinophilic and non-eosinophilic asthma (MD -104.74 [95% CI -116.12 to -93.35], $I^2 = 36\%$).[20]

Tezepelumab also showed significant reduction in bEos when compared to placebo which was reported in two SR and MA studies.[22,23] First study was by Abdelgalil MS. et. al. where the mean difference reported was MD -139.38 cells/mcL [95% CI -150.37 to -128.39], $p < 0.00001$.[22] Meanwhile, the second SR and MA by Zoumat Z. et. al. observed the bEos reduction at different followed-up periods (after 4-, 12-, 24- and 52-weeks); pooled analysis of significant reduction in bEos -151.05 cells/uL (95% CI -165.99 to -136.12), $I^2 = 12.11\%$.[23] Sustained reductions in bEos also observed in extension study by Menzies-Gow A. et. al. especially in patients continuously received tezepelumab since parent study.[36] The reduction in bEos with tezepelumab was observed as early as week-2 and was sustained throughout 52-weeks of treatment period either in patients with or without perennial aeroallergen sensitisation.[33]

An extension study by Bacharier LB. et. al. reported that all children who were treated with dupilumab were continuously reduced the bEos since parent study throughout the extension study.[37]

Reduction in FeNO level

According to SR and MA of real-world data by Charles D. et. al. mepolizumab significantly reduced FeNO level concentrations by -14.23 ppb (95% CI -19.71 to -8.75). However, benralizumab showed no significant change in FeNO level concentration (-14.18 ppb [95% CI -36.54 to 8.17]).[21]

Two SR with MA studies reported that tezepelumab significantly reduced FeNO level concentration compared to placebo; MD -10 ppb [95% CI -15.8 to - 4.18], $p < 0.00001$[22] and -12.41 ppb (95% CI -14.28 to -10.53.[23] The reduction of FeNO level concentration were seen as early as 2-week and was sustained up to 52- to 104-weeks.[33,36] The reduction in FeNO level concentrations also reported either in patients with or without perennial aeroallergen sensitisation subgroups.[33]

An extension study by Bacharier LB. et. al. reported that all children who were treated with dupilumab were continuously reduced the FeNO concentration since parent study throughout the extension study.[37]

Reduction in Serum IgE

Significant decrement in serum total IgE was observed in tezepelumab group compared to placebo. Two SR and MA studies by Abdel Galil MS. et. al.[22] and Zoumat Z. et. al.[23] MA reported that the mean difference was -123.51 UI/mL (95% CI -206.52 to -40.50); $p = 0.004$ and -122.90 IU/mL (95% CI -167.80 to -78.01); $p = 0.00$, respectively. An extension study by Menzies-Gow A. et. al. also reported that total serum IgE concentration was reduced progressively up to 104 weeks in tezepelumab groups.[36] Tezepelumab also reduced serum IgE concentration regardless of the allergen status either with or without perennial aeroallergen sensitisation. The gradual reductions were observed over 52 weeks of treatment period.[33]

The serum IgE also continuously decreased since parent study throughout the extension study in children treated with dupilumab. The decrement during parent study was 77.8% (IQR 67.2 to 84.1) and continued to decrease during the extension study up to 80% - 90%.[37]

Reduction in Sino-nasal Outcome Test-22 (SNOT-22) scores

Only one study retrieved reported on this outcome which was by Israel E. et. al. The study reported that mepolizumab significantly improved the SNOT-score from 16.9 points at baseline to 40.5 points after mepolizumab treatment.[32]

5.2.5 SAFETY

Fourteen studies reported on safety issue of biologics[18,20,22-25,30-32,35-37,39-40] and one SR and MA reported on antidrug antibodies (ADA) incidence related to the biologics24 were included in this HTA.

According to SR and MA by Kyriakopoulos C. et. al. reviewed biologics consisted of omalizumab, benralizumab, mepolizumab, reslizumab, dupilumab and tezepelumab were not associated with increased risk but 5% reduction in serious adverse events (risk ratio 0.95 [95% CI 0.92 to 0.99]; I^2 = 72.5%).[18]

5.2.5.1 Biologics-related adverse events (AEs)

i. Tezepelumab

Inconsistent studies reported on the tezepelumab-related AEs. Where one SR and MA by Abdelgalil H. et al. showed that patients on tezepelumab had significantly lower risk of any AEs when compared to placebo; RR 0.71 (95% CI 0.54 to 0.93), p = 0.01.[22] However, another SR and MA by Zoumat Z. et. al. found that the pooled estimated of the included studies showed no significant difference in the incidence of AEs in tezepelumab when compared to placebo; 0.79 (95% CI 0.55 to 1.12) with high heterogeneity (I^2 = 96.9%).[23] In addition to that, post hoc analysis of pooled data from two tezepelumab trial by Corren J. et. al. reported that slight difference between AEs in tezepelumab and placebo were observed; 75% and 77%, respectively. The most common AEs reported in both groups were nasopharyngitis, upper respiratory tract infection (URTI), headache and asthma. The causality assessment between the treatment and the AEs where 9% of patients in tezepelumab group and 8% in placebo group reported to experience AEs related to treatment.[35] Similar list of the most common AEs were also reported in the extension study by Menzies-Gow A. et. al. along with bacterial bronchitis which occurred in more than 10% of patients.[36]

ii. Dupilumab

Agache I. et. al. reported in their two SRs that dupilumab showed no difference with placebo; RR 1.00 (95% CI 0.88 to 1.13).[30-31] There were two extension studies of dupilumab trials reported that the incidence rate of adverse events was similar between parent studies and the extension studies. First extension study was conducted by Bacharier LB. et. al. among children with severe asthma. The authors reported that the most common reported treatment-emergent adverse events (TEAE) were nasopharyngitis, pharyngitis, URTI, and injection-site reactions. According to an investigator of the trial, 14% of the children experienced at least one TEAE of dupilumab related.[37] Another extended study by Berger P. et. al. reported that consistent incidence rate of adverse events was observed either in patient with or without self-reported coexisting CRS-NP. The rate ranged between 76.0% to 83.3% in patients with CRS-NP and between 72.1% to 80.0% in those without self-reported coexisting CRS-NP.[39]

iii. Benralizumab

Agache I. et. al. reported in their two SRs that benralizumab no difference in drug-related adverse events compared to placebo; RR 1.41 (95% CI 0.87 to 2.27).[30-31] In the extension study by Korn S. et. al. patients who were initiated with benralizumab since parent study showed similar AEs rate during the extended study (65 – 85 per 100 patient-years). On the other hand, those who just started the benralizumab during the extension study generally had higher rates of adverse events (46 – 88 per 100 patient-years) than those who were treated with benralizumab since parent study. Then at the end of the extension study period, the overall AEs rates across treatment group were similar or lower than the parent studies; 28.5 – 32.4 per 100 patient-years. Korn S. et. al. reported that the most common adverse events during the extension period were nasopharyngitis (11.1 – 12.1 per patient-years), worsening asthma (4.3 – 7.4 per 100 patients-years), bronchitis (3.2 – 6.8 per 100 patient-years), headache (3.9 – 6.3 per 100 patient-years), viral URTI (2.4 – 5.3 per 100 patient-years), sinusitis (2.5 – 4.3 per 100 patient-years) and URTI (1.0 – 3.6 per 100 patient-years).[40]

iv. Mepolizumab

Agache I. et. al. reported in their SR that mepolizumab increased drug-related adverse events compared to placebo; RR 1.35 (95% CI 1.01 to 1.80).[31] The most common reported adverse events were headache, nasopharyngitis and injections site-reactions.

5.2.5.2 Adverse events that lead to discontinuation of the biologics

An NMA by Pitre T. et al. reported that the risk of biologics leading to treatment discontinuation was RR 1.65 (95% CI 0.79 to 3.45) in benralizumab, RR 1.03 (95% CI 0.46 to 2.30) in dupilumab, RR 0.65 (95% CI 0.36 to 1.16) and RR 0.68 (95% CI 0.34 to 1.35) in tezepelumab, which were all not statistically significant. The reasons of the discontinuation were anaphylactic reaction, malignancy, liver function abnormality, asthma-related event requiring intubation, non-asthma related events and drug-related adverse events which were not specified in the included studies.[25]

i. Tezepelumab

Corren J. et. al. reported in their post-hoc analysis of two tezepelumab trials that the rate of treatment discontinuation due to AEs was quite similar in both tezepelumab and placebo groups; 2% versus 3% where the discontinuation due to serious AEs occurred in 1% of tezepelumab group and 2% in placebo group. One of tezepelumab discontinuation reported was arthralgia in one patient. No other reason was specified in the study.[35]

ii. Dupilumab

Bacharier LB. et. al. reported that treatment discontinuation due to TEAE was rare in dupilumab. The discontinuation only occurred in three children who were having allergic conjunctivitis, ascariasis, and pulmonary TB.[37]

iii. Benralizumab

According to an SR and MA by Farne HA. et. al. benralizumab had more clinically significant adverse events that lead to the discontinuation; risk ratio 2.04 (95% CI 1.03 to 4.03). The discontinuation was mostly due to urticarial as well as worsening asthma.[20] An extension study by Korn S. et. al. reported that two to three patients discontinued benralizumab treatment due to AEs (the study did not specify the AEs).[40]

iv. Mepolizumab

Meanwhile for mepolizumab the adverse events that lead to discontinuation showed no difference with placebo; risk ratio 0.72 (95% CI 0.18 to 2.92).[20] According to an SR by Israel E. et. al., the discontinuation rate due to mepolizumab adverse events ranged from 0% to 11% of patients (after 6 – 24 months followed-up). There were various reasons of the discontinuation, and the common reasons were no clinical improvement, severe headache, severe arthralgia, allergic rash, persistent eczematous on face, trunk, and upper limb, and pruritis.[32]

5.2.5.3 Serious adverse events (SAEs)

According to an SR and MA by Kyriakopoulos C. et. al. that also included benralizumab, mepolizumab, dupilumab and tezepelumab in their analysis, showed that biologics were associated with a significant reduction of SAEs (risk ratio 0.76 [95% CI 0.65 to 0.89], I^2 = 24.3%).[18] However, the results were inconsistent with other studies as reported below.

i. Tezepelumab

An SR and MA by Abdelgalil H. et. al. found that the SAEs incidence had no significant difference between tezepelumab and placebo; RR 0.92 (95% CI 0.6 to 1.38), p = 0.70.[22] A post-hoc analysis of two tezepelumab trials by Corren J. et. al. reported a slight difference in the overall SAEs incidence between tezepelumab and placebo; 9% and 13%, respectively. Further analysis reported that similar incidence of benign and malignant neoplasm, and severe infections was observed in both treatment groups. Cardiac disorders were also reported where 0.8% were observed in tezepelumab group and 0.3% in placebo group. No anaphylactic reaction was reported in both groups.[35] For long-term safety profile observation, an extension study by Menzies-Gow A. et. al. showed that fewer SAEs were reported among patients who were continuously treated with tezepelumab since parent study compared to those patients who just started tezepelumab during extension study. The cardiac disorders also reported as the pooled on-study incidence of cardiac disorders was 1.30 per 100 patient-years in all tezepelumab group. However, further assessment showed that no causality of cardiac disorders to tezepelumab.[36]

ii. Dupilumab

Agache I. et. al. found that dupilumab may increase the drug related SAE; RR 1.46 (95% CI 0.60 to 3.54), however the findings were not significant.[31] An extension study Bacharier LB. et. al. reported that seven SAEs occurred in children treated with dupilumab. However, only 1 case of pulmonary TB was found to be related to dupilumab and was discontinued. According to the authors, the patient was from a geographical area with endemic tuberculosis.[37] Another extension study by Berger P. et. al. reported that patients with self-reported coexisting CRS-NP had higher serious TEAEs compared to those without either in parent study or extended study. The incidence of serious TEAEs ranged from 13.5% to 16.0% in patient with self-reported coexisting CRS-NP and from 8.1% to 11.5% in those without.[39]

Bacharier LB. et. al. also reported on AEs which was specify as adverse events of special interest (AESI). They reported that the AESI was low among children treated with dupilumab compared to placebo. Those AESI were hypersensitivity reactions which was reported as non-serious (3%), two events of anaphylactic reactions which was later found to be unrelated to the dupilumab, parasitic infections (2%) included one ascariasis case that caused treatment discontinuation and non-serious eosinophilia events in 15 patients (4.1%).[37]

iii. Benralizumab

The SR and MA by Farne HA. et. al. reported that subcutaneous benralizumab showed significant reduction in SAEs incidence when compared to placebo (risk ratio 0.76, 95% CI 0.62 to 0.93) as the most common SAE reported was worsening asthma.20 However, an SR by Agache I. et. al. reported an inconclusive finding of benralizumab in reducing SAEs (RR 0.56 [95% CI 0.22 to 1.44].[30-31] According to Korn S. et. al. the overall rates of SAEs across treatment groups with benralizumab were similar during the extension studies and was either similar or lower than parent studies (6.3 – 8.4 per 100 patient-years). Similar or low rate of hypersensitivity in patients treated with benralizumab was also reported (4.8 – 5.8 per 100 patient-years).[40]

iv. Mepolizumab

On the other hand, Farne HA. et. al. found that no significant difference between subcutaneous mepolizumab with placebo.[20] In addition to that, Agache I. et. al. also reported inconclusive findings of mepolizumab in reducing SAEs compared to placebo; RR 0.98 [95% CI 0.06 to 15.63].[30-31]

5.2.5.4 Treatment-related deaths

According to SR and MA by Kyriakopoulos C. et. al. death during study period showed no difference between biologics (omalizumab, benralizumab, mepolizumab, reslizumab, dupilumab and tezepelumab) and control groups (risk ratio 0.91 [95% CI 0.39 to 2.09], I^2 = 0%).[18]

i. Tezepelumab

Menzies-Gow A. et. al. reported that pooled death incidence among patients treated with tezepelumab since parent study was 0.80 per 100 patient-years and 0.58 per 100 patient-years among patients who were treated with tezepelumab during extended study period. The difference between those patients was 0.22 (95% CI 0.61 to 0.94). When compared between tezepelumab and placebo, there was 11 deaths in tezepelumab and five in placebo group. Those death was not related to the study's treatments either in placebo or tezepelumab.[36]

ii. Dupilumab

One death also reported in dupilumab study by Berger P. et. al. and was considered as not related to dupilumab because the patient already had metastatic colon cancer with history of iron deficiency.[39]

iii. Benralizumab

Another death was also reported in benralizumab study by Korn S. et. al. The death was due to influenza which occurred outside on-treatment window (85 days after final dose of benralizumab).[40]

5.2.5.5 Antidrug antibodies (ADA)

Biologics therapies are more likely to be immunogenic than conventional small-molecule drugs, leading to the formation of antidrug antibodies (ADAs), which can impact biologic effectiveness and increase the incidence of adverse events.[24]

One SR and MA by Chen ML. et al. examined the incidence of ADAs associated with the use of the biologics among patients with moderate to severe asthma. The SR included 46 studies consists of different types of biologics; benralizumab, dupilumab, mepolizumab, tezepelumab, omalizumab and reslizumab. Forty-three studies were meta-analysed and the pooled prevalence of ADA at baseline across all the biologics was 1.59% (95% CI 0.80-2.61). At any point during followed-up, the pooled prevalence of ADAs was higher in the biologic's groups than placebo group; 4.66% (95% CI 3.24 to 6.29) versus 2.74% (95% CI 1.41 to 4.42). Based on types of biologics, ADAs prevalence was highest in benralizumab and lowest in omalizumab. The findings were simplified in table 3. For specific ADAs incidence related to specifics biologics, the authors examined the treatment emergent ADAs (TE-ADAs). The overall incidence of TE-ADAs in all the biologics groups was 2.91% (95% CI 1.60 to 4.55) versus 1.00% (95% CI 0.12 to 2.41) in the placebo groups. The incidence of TE-ADAs between biologics was significantly different ($p<0.001$) where the incidence was highest in benralizumab and lowest in omalizumab. The percentage of the incidence were presented in **Table 3**. Another observation was on neutralising antibodies (NAbs) incidence. Most of NAbs incidence was reported in benralizumab groups and almost none in other biologics. The overall pooled incidence of NAbs was 1.16% (95% CI 0.05 to 3.23) in biologics groups and 0.55% (95% CI 0.01 to 1.57) in placebo group. When comparing the risk of TE-ADAs and NAbs between benralizumab and placebo, benralizumab arms had approximately five-fold statistically significant increase in risk of TE-ADAs and four-fold increase in NAbs compared to placebo; RR 4.90 (95% CI 2.69 to 8.92) and RR 3.93 (95% CI 2.27 to 6.82), respectively. Although there was an incidence of ADAs related to biologics, none of the incidence affect the efficacy and safety outcomes of those biologics. Further observations found that the ADAs incidence was related to the biologics dose, administration route and dosing interval as lower dose, subcutaneous route and longer dosing intervals associated with higher ADA development.[24]

Table 3: Percentage of ADAs Prevalence, TE-ADAs Incidence, and NAbs Incidence

Biologics	% (95% CI)		
	ADAs Prevalence	TE-ADAs Incidence	NAbs Incidence
Benralizumab	12.03% (95% CI 9.97 to 14.25)	8.35% (95% CI 5.60 to 11.57)	7.12% (95% CI 4.05 to 10.94)
Dupilumab	5.70% (95% CI 2.53 to 10.00)	7.61% (95% CI 6.51 to 8.84)	NA
Mepolizumab	4.08% (95% CI 1.98 to 6.80)	3.63% (95% CI 0.39 to 9.15)	0.00 (95% CI 0.00 to 0.01)
Tezepelumab	3.71% (95% CI 2.68 to 4.88)	1.12% (95% CI 0.11 to 2.77)	0.00 (95% CI 0.00 to 0.25)
Omalizumab	0.00 (95% CI 0.00 to 0.12)	0.00% (95% CI 0.00 to 0.15)	NA
Reslizumab	6.92% (95% CI 4.22 to 10.19)	4.39% (95% CI 2.88 to 6.20)	0.00 (95% CI 0.00 to 0.52)

Korn S. et. al. detected 4.5% to 10.0% ADAs before benralizumab extension study period. During the extended study, 1.9% to 5.7% ADAs incidence was detected. Meanwhile, 5.3% to 10.4% NAbs were expressed per treatment group before and during the extended study period. The authors also reported that no ADAs status affected the incidence of adverse events or serious adverse events and no correlation between ADAs and hypersensitivity adverse events.[40]

Another extension study involved children with severe asthma by Bacharier LB. et. al. reported that ADAs incidence was low either among children who were continuously being treated with dupilumab since parent study or among children who were just having dupilumab during the extended study; 3% versus 8%.[37]

5.2.6 COST-EFFECTIVENESS

There were three SR[30-32] reported on economic evaluations of biologics and three individual studies on mepolizumab[45], benralizumab[46], and dupilumab[47] included in this HTA report. Overall, most of the included studies reported that the biologics had higher ICER/QALY gain than Willingness to Pay (WTP) threshold of corresponding countries. According to the Agache I. et. al., the potential saving was related to decrease rate of hospitalisation, Emergency Department (ED) care, primary care visits and the management of clinically significant exacerbations.[30-31] The correlations between number of severe exacerbations and cost of oral corticosteroid (OCS) as well as ED visit was very strong; R=0.839 (95% CI 0.709 to 0.913) and R=0.849 (95% CI 0.726 to 0.919), respectively.[46]

i. Mepolizumab

Agache I. et. al. reported the cost-utility ICER/QALY for mepolizumab was 385, 546$.[30-31] Another SR by Israel E. et. al. reported that two economic evaluation studies from Italy and United States of America (US) reported significant decrement in the mean number of hospitalisations in 12-months following mepolizumab initiation. Meanwhile, in the US study, there was significant reduction from baseline to followed-up period in mean exacerbation-related costs per patient (US$5,178 versus US$2,383; $p < 0.001$).[32]

Tan LE. et. al. conducted an economic evaluation study based on Singapore healthcare perspective. The study showed that mepolizumab with standard of care (SoC) accumulated more QALYs and incurred higher costs relative to SoC alone. The ICER/QALY was SGD335,486 (US$238,195) and the ICER per LY gained was SGD208,238 (US$147,846) with an average of five exacerbations avoided per patient over a lifetime. Based on the sensitivity analysis, the ICER was consistently above WTP threshold (SGD250,000) and the analysis showed that the ICER was highly sensitive to mepolizumab price as well as proportion of exacerbations that required intensive care unit (ICU) stay. On the other hand, by restricting the use of mepolizumab to the patients with higher baseline exacerbation rate (three per year) resulted in an ICER of SGD238,876 (US$169,602) per QALY gained. Then by ranging the hypothetical mepolizumab price reduction between 20% to 80%, the ICER was reduced between SGD190,995 (US$135,606) and SGD47,354 (US$33,621) per QALY gained.

Another scenario by using a utility weigh mapped from St George's Respiratory Questionnaire (SGRQ) results that gave a larger gain in utility with mepolizumab, the ICER/QALY gained ranged between SGD206,265 (US$146,448) and SGD211,328 (US$150,043).[45]

ii. Benralizumab

Agache I et al. reported that the benralizumab ICER varied from 39,135£/QALY to 412, 000$/QALY.[30-31] However, the original paper did not describe further the drivers and the parameters involved.

Padiala-Galo A et al. conducted a cross-sectional multicentre study in Spain to assess the cost-effectiveness of benralizumab therapy and its 1-year effectiveness based on decreasing of exacerbations and OCS used and the improvement of asthma control and lung function in real world. With benralizumab the number of exacerbations was decreased about 88%, the ED visit also reduced up to 83% and the steroid consumption was reduced up to 82.8%. The direct healthcare costs before benralizumab and after initiation of benralizumab showed that the increment in the cost was only due to the additional cost of the benralizumab meanwhile the cost reduction was observed in many areas included cost of complementary tests, ED care and admissions and the OCS or inhaled corticosteroid (ICS) used. The cost-effectiveness analysis (CEA) indicated that with benralizumab, the incremental cost of €602/year was required to avoid one severe exacerbation and €3,300/year to avoid any exacerbation in each patient. Meanwhile for each one-point increment in Asthma Control Test (ACT), the cost was estimated about €327.95 per year. The incremental utility at one-year of benralizumab treatment compared to baseline treatment period was 0.138 QALYs with incremental cost of €2,499. The cost-utility analysis initiated that the incremental cost utility ratio (ICUR) obtained was €18,177/QALY. With the WTP threshold €24,000, the likelihood of benralizumab providing a better cost-utility compared with the baseline treatment option was 80.9%. The Net Monetary Benefit (NMB) obtained with benralizumab was €813 (as it was higher than 0) which indicated that benralizumab was an efficient treatment option compared to the baseline option.[46]

iii. Dupilumab

Agache I. et. al. reported that dupilumab ICER was 401, 000$/QALY among patients with high BEC count (≥300 eosinophils cells/uL).[30]

Cost-effectiveness analysis conducted by Tohda Y. et al. in Japan was indirectly comparing dupilumab with benralizumab, mepolizumab and omalizumab. The dupilumab subgroup was generated from VENTURE/QUEST trial which best matched the patient phenotypes of the comparator biologics (benralizumab based on ZONDA trial, mepolizumab based on SIRIUS trial and omalizumab based on INNOVATE trial). The Japan-specific WTP was ¥5,000,000 per QALY gained. First comparison was between dupilumab and benralizumab where in base case analysis, the number of severe exacerbations per patient over lifetime were 43.55 for dupilumab with SoC and 44.83 for benralizumab with SoC. Thus, when compared with benralizumab, dupilumab was associated with 1.27 fewer severe exacerbations per patient over a lifetime than benralizumab. Besides that, dupilumab also associated with 0.13 more LYs and 0.17 more QALYs per patient compared to benralizumab. This improvement showed that dupilumab was a dominant strategy compared to benralizumab as an add-on therapy with a reduction of ¥2,316,832 total cost per patient. Next, when compared to mepolizumab, dupilumab was associated with 6.15 fewer severe exacerbations per patient over a lifetime. Dupilumab also associated with a 0.59 increase in LY and 0.61 increased in QALYs per patient. As an add-on treatment, dupilumab was found to be cost-effective compared to mepolizumab with an ICER of ¥1,010,921 (US$9,9190) per patient with an increment of ¥619,179 per patient in total cost. On the other, when compared to omalizumab, although patients on dupilumab had 4.95 fewer severe exacerbations, 0.49 increased in LYs and 0.44 increased in QALYs per patient, the total cost of omalizumab was much lower compared to dupilumab. Thus, with an ICER of ¥10,802,368 (US$98,203), dupilumab was found not to be cost-effective when compared to omalizumab. According to deterministic sensitivity analysis, the key drivers on the incremental costs were most influenced by the discontinuation rates and the price of each biologic per vial. In scenarios analysis, comparison between dupilumab and benralizumab was consistently associated with decreased costs, increased QALYs and fewer exacerbations which was consistently economically dominant. On the other hand, comparison between dupilumab and mepolizumab was associated with increased costs and QALYs and fewer severe exacerbations with an ICER that always lower than Japan WTP threshold. As for dupilumab versus omalizumab, it was associated with increased QALYs and fewer severe exacerbations but at higher cost.[47]

5.2.7 ORGANISATIONAL

Menzies-Gow A. et al. found reduction in healthcare utilisation (HCU) with tezepelumab across all outcomes measured compared to placebo. Patients with tezepelumab showed fewer asthma-related unscheduled specialist visits compared to placebo (285 versus 406 events), telephone calls with a healthcare provider (234 versus 599 events), ambulance transports (5 versus 22 events), and home visits from a healthcare provider (18 versus 22 events).[34]

A retrospective analysis of real-world data by Casale T. et. al. reported that mepolizumab also reduced the HCU compared to placebo. The study reported that the highest baseline period rates of inpatient admission and ED visits because of exacerbation was observed among obesity, respiratory infection, COPD, and depression/anxiety subgroups ([0.22 and 0.80], [0.15 and 0.60], [0.17 and 0.70], and [0.23 and 0.60], respectively). During the followed-up period, the mean number of exacerbation-related inpatient admissions and ED visit was significantly reduced ($p < 0.05$) by at least 50% compared to baseline in all the comorbidities subgroups. In addition to that, the mean number of exacerbation-related outpatient visits also significantly reduced ($p<0.05$) by 46% to 56% in all the comorbidities subgroups. The outpatient pharmacy claims per patients also reduced by 36% to 51% in the follow-up compared to baseline in all the comorbidities subgroups.[44]

5.2.8 SOCIAL

The included studies also assessed the quality of life (QoL) of severe asthma patients and the QoL of caregivers of the paediatric patients. Different tools were used for the assessment which were Asthma Quality of Life Questionnaire (AQLQ), St George's Respiratory Questionnaire (SGRQ), Paediatric Asthma Quality of Life Questionnaire (PAQLQ), and Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ-IA) global score.

5.2.8(a) Overall population

Asthma Quality of Life Questionnaire (AQLQ) score

Kyriakopoulos C. et. al. reported that all the biologics assessed namely benralizumab, mepolizumab, dupilumab and tezepelumab improved QoL by improving the AQLQ score by 0.38 points (95% CI 0.26 to 0.49); I^2 = 75.5% but the score did not reach up to minimal clinical important difference (MCID) 0.50 points.[18] The NMA by Iftikhar IH. et. al. showed that the greatest increased in AQLQ score was observed in dupilumab (0.27 [95% CI 0.09 to 0.45]) followed with mepolizumab (0.26 [95% CI 0.15 to 0.37]) and benralizumab (0.26 [95% CI 0.10 to 0.41]) compared to placebo.[26]

An SR with MA analysis by Farne HA. et. al. also reported that better improvement in AQLQ score with benralizumab compared to placebo; MD 0.23 (95% CI 0.11 to 0.35).[20] Tezepelumab also showed significant improvement in QoL and AQLQ+12 score reported in two SRs with MA compared to placebo; 0.15 (95% CI 0.00 to 0.29), I^2 = 60.03%, p = 0.02[23] and MD 0.32 (95% CI 0.20 to 0.44), p < 0.00001, I^2 = 0%, respectively.[22] Israel E. et. al. also reported that patients on mepolizumab had significantly improved AQLQ and mini-AQLQ score (p < 0.001). The changes were from 3.48 – 4.05 mean baseline to 0.86 – 1.24 points after treated with mepolizumab.[32]

On the other hand, one extension study by Fiochi AD. et. al. assessed the health related QoL (HRQoL) children who were treated with dupilumab as well as their care givers. Dupilumab significantly improved the HRQoL as demonstrated by the change from baseline in PAQLQ scores among children with BEC ≥150 cells/uL and BEC ≥300 cells/uL. The LS mean difference in dupilumab versus placebo was statistically significant from week-24 onwards and at week-52; 0.34 (95% CI 0.16 to 0.52); p = 0.0002. According to the checklist, the improvements was observed in individual domain scores of emotional functions, activity limitation and symptoms. For care giver assessment, the LS mean difference change from baseline in PACQLQ global score among the caregivers of the children treated with dupilumab was 0.25 (95% CI 0.00 to 0.50; p = 0.0531) at week -24 and 0.47 (95% CI 0.22 to 0.72; p = 0.0003) at week-52 compared to placebo. On the other hand, the improvement was seen since week-12 in caregivers of children with baseline blood eosinophils ≥300 cells/uL. Domains of activity limitation and emotional function showed significantly greater improvements by week-52 in all the caregivers.[38]

St. George's Respiratory Questionnaire (SGRQ)

An SR and MA by Farne HA. et. al. reported that mepolizumab reduced the SGRQ scores by a clinically meaningful improvement compared to placebo (MD -6.37 [95% CI -8.76 to -3.98]; I^2 = 36%).[20] In post-hoc analysis by Liu MC. et. al. reported an improvement in SGRQ score at a different baselines quartile before switching to mepolizumab from omalizumab; SGRQ-total scores <45 in 28% patients, SGRQ-total scores 45 - <55 in 21% patients, SGRQ-total scores 55- <70 in 28% patients and SGRQ-total scores ≥70 in 23% patients. After switching to mepolizumab (at week-32), the mean improvements regardless the baseline quartiles of the SGRQ-total scores exceeded the MCID points were observed. The LS mean change (SE) before and after mepolizumab treatment was -1.42 (0.23), -1.24 (0.21), -1.62 (0.176) and -1.49 (0.234) for each quartile, respectively. The improvement from baseline were generally numerically greater in patients with higher (worse) baseline of SGRQ-total scores.[41]

Farne HA. et. al. reported strong improvement in SGRQ score with benralizumab compared to placebo especially among eosinophilic patients (MD -11.16 [95% CI -15.10 to -7.22]).[20] An improvement in SGRQ score of the extension studies by Menzies-Gow A. et. al. was sustained throughout the treatment period especially among patients who received tezepelumab since parent study.[36]

5.2.8(b) Subgroup Analyses

Subgroup: Blood Eosinophil Count (BEC)

Asthma Quality of Life Questionnaire (AQLQ) score

In subgroups analysis by Kyriakopoulos C. et. al. all biologics that being assessed included benralizumab, dupilumab and tezepelumab showed significant improvement in AQLQ regardless the BEC level of either ≥300 cells/uL or <300 cells/uL with greater improvement in higher BEC level; 0.34 (95% CI 0.15 to 0.53) versus 0.21 (95% CI 0.08 to 0.33) points, $P_{subgroup\_heterogeneity}$ = 0.23).[18] The studies by Kyriakopoulos C. et. al.[18] and Korn S. et. al.40 also assessed the effects of tezepelumab between the BEC level ≥150 cells/uL and <150 cells/uL. Both studies reported that the AQLQ improvement only significant in BEC level ≥150 cells/uL; (0.41 [95% CI 0.26 to 0.57]).[18] In SR with NMA by Iftikhar IH. et. al., dupilumab showed greatest magnitude of effects when compared to benralizumab.[26]

Subgroup: FeNO level

Asthma Quality of Life Questionnaire (AQLQ) score

Kyriakopoulos C. et. al. reported that tezepelumab showed greater increased in AQLQ among patients with FeNO level ≥25 ppb than FeNO level <25 ppb (0.65 [95% CI 0.27 to 1.03] versus 0.02 [95% CI -0.30 to 0.33] points, $P_{subgroup\_heterogeneity}$ = 0.012).[18] Similar findings also reported in Corren J. et. al. where significant improvement in AQLQ with tezepelumab was observed in patients with the highest FeNO ≥50 ppb compared to low FeNO level (LS mean difference 0.65 [95% CI 0.41 to 0.89] versus 0.08 [95% CI -0.11 to 0.27]).[35]

Subgroup: Allergy status

Asthma Quality of Life Questionnaire (AQLQ) score

Two studies by Corren J. et. al.[33,35] found that when compared with placebo, tezepelumab improved AQLQ(S)+12 scores in both patients with and without perennial aeroallergen sensitisation (LS mean difference, 0.34 [95% CI 0.17 to 0.51] and LS mean difference, 0.36 [95% CI 0.13 to 0.59], respectively).[35]

St George's Respiratory Questionnaire (SGRQ) score

Corren J. et. al. also reported that when compared with placebo, tezepelumab improved SGRQ scores in both patients with and without perennial aeroallergen sensitisation (LS mean difference -5.65 [95% CI -8.96 to -2.35] and LS mean difference, -7.83 [[5% CI -12.49 to -3.17], respectively).[33]

Subgroup: Comorbidity

One of dupilumab extension study by Berger P. et. al. showed that either during parent studies and across the extension study period, dupilumab consistently improved the AQLQ scores regardless of whether the patients were with or without self-reported CRS-NP.[39]

According to Liu MC. et. al. all comorbidities (NP, aspirin/NSAIDs intolerance, and GERD) showed no effects on improvements of SGRQ which exceeded the MCID threshold at week-32 after switching from omalizumab to mepolizumab. In addition to that, patients with comorbid nasal polyps showed greater improvement than those without nasal polyps.[41] Another study by Gibson PG. et. al. also reported on SGRQ improvement with mepolizumab among patients with varies comorbidity compared to placebo. The improvements were seen among patients with upper respiratory comorbidities; 11.3-point improvement in with NP subgroup versus 6.0-point improvement in without NP subgroup, 8.6-point improvement in sinusitis subgroups compared to 6.3-point improvement in no sinusitis subgroup and 8.6-point improvement in allergic rhinitis versus 6.1-point in no allergic rhinitis. The SGRQ total score improvement with mepolizumab was consistent across all other comorbidities subgroups ranging from 5.0-point in obesity subgroup to 11.6-point improvement in psychopathologies subgroup.[42]

6.0

PART B: ECONOMIC IMPLICATION

6.0 PART B: ECONOMIC IMPLICATION

6.1 BACKGROUND

Severe asthma is a chronic respiratory condition that significantly impairs the quality of life for affected individuals, often leading to frequent exacerbations, increased healthcare resource utilisation and a substantial economic burden on healthcare systems globally. While standard asthma treatments have been effective for many patients, a subset continues to experience uncontrolled symptoms, necessitating the exploration and adoption of novel therapeutic options. Biologic therapies have emerged as a promising intervention for severe asthma, demonstrating efficacy in improving outcomes for patients who remain uncontrolled despite standard care. However, the economic implications and cost-effectiveness of integrating these biologics into the healthcare system specifically within the Malaysian context remain uncertain.

Therefore, this economic evaluation compared the addition of biologics in the Standard of Care (SoC) of severe uncontrolled Type 2 asthma (eosinophilic) phenotype patients in Malaysia with the SoC alone (without biologics). The SoC followed the Clinical Practice Guidelines (CPG) Management of Asthma 2017. For this review, the expert committees agreed further assessment on mepolizumab, dupilumab, benralizumab and tezepelumab only.

6.2 OBJECTIVE

The objectives of the economic evaluation were:

1. To estimate the cost-effectiveness of tezepelumab, benralizumab, mepolizumab and dupilumab for the treatment of severe asthma in comparison with SoC.

2. To calculate the incremental cost-effectiveness ratio (ICER) of the biologics with asthma's SoC.

6.3 METHODS

A literature-based state transition model (Markov cohort simulation) was developed using Microsoft Excel Workbook 2021 to estimate the lifetime costs and quality-adjusted life years (QALYs) of using biologics in reducing the asthmas' exacerbations. This type of model was chosen for its ability to extrapolate efficacy data from short-term clinical trials of the biologics to longer-term cost-effectiveness results.

6.3.1 Model Structure

The model structure was constructed with reference to other published studies and in consultation with expert committees consisting of multidisciplinary experts such as clinical oncologists, health economist, public health physicians and pharmacist. In this model, the Markov model (**Figure 6**) incorporated five health states. The following showed the five health states used in the model:

A. Day-to-day Symptoms
B. Oral Corticosteroid (OCS) Burst
C. Emergency Department (ED) Visit
D. Hospitalisation
E. Death due to Other Causes
F. Death due to Asthma

The simulated clinical pathways were as follows:

1. The simulation began with the initial presentation of severe asthma patients in state A. The cohort age started at 12 years old.
2. The patients had a chance to remain at State A, move either into State B, State C or State D.
3. Thereafter, the patients in the exacerbation states of B, C or D had a chance to return to State A or move to State E or State F.
4. All patients in State A, State B, State C and State D had a chance to move to State E.
5. However, only patients in State C and State D had a chance to move either to State E or State F.
6. The output for the model was the ICER.
7. The cycle length was 4 weeks.
8. The time horizon was lifetime (63 years).
9. The perspective was the Ministry of Health's perspective.

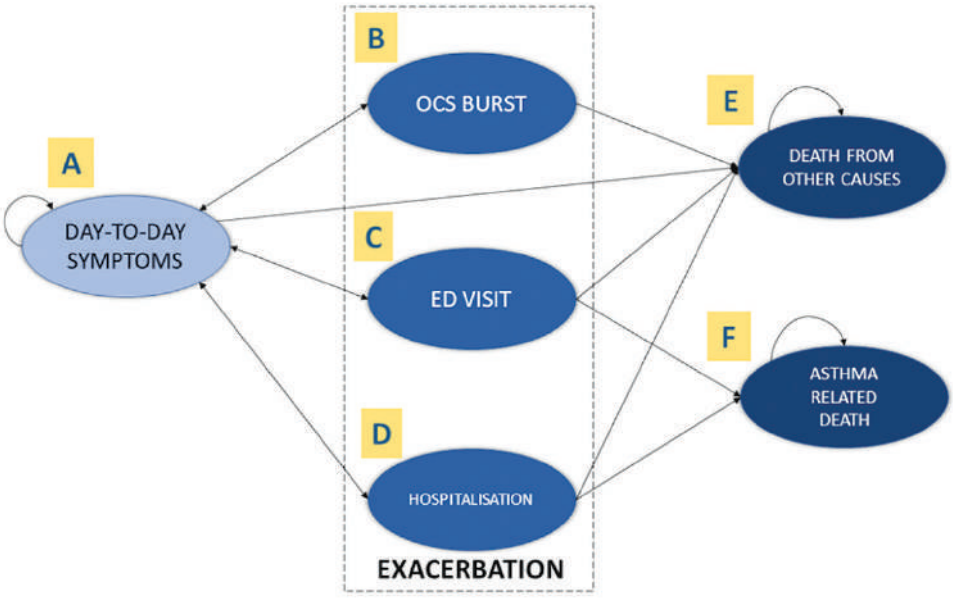


Figure 6: Markov Model of Asthma Biologics

6.3.2 Model Input

The epidemiological, disease-related data and healthcare utilisation costs were obtained from the local settings whenever available or literature review when local data was not available.

A. Treatment Dose

The recommended treatment dose (**Table 4**) for each biologic was obtained from the Ministry of Health Medicines Formulary except for tezepelumab as it was not registered in Malaysia. Hence, its recommended treatment dose was referenced from published literature. The recommended doses were important as the correct doses influence the cost of treatment per cycle.

Table 4: Recommended Dose for Asthma Biologics

Biologics	Recommended Dose	Reference
Tezepelumab	210mg every 4 weeks	Pitre et al. 2023[25]
Benralizumab (Fasenra)	30 mg every 4 weeks (first 3 doses) then every 8 weeks	Pharmaceutical Services Program MOH
Mepolizumab (Nucala)	100 mg every 4 weeks	
Dupilumab (Dupixent)	Initial dose 600mg, followed by 300 mg every 2 weeks	

B. Annual Asthma Exacerbation

The annual asthma exacerbation for SoC cohort (**Table 5**) was obtained from published literature and agreed upon by the expert committees. The annual exacerbation was converted into a 4-weekly transition probability to fit into the Markov model.

Table 5: Annual Asthma Exacerbation

Annual Asthma Exacerbation	Base Case Value	Reference
Standard of Care (SoC) Cohort	2.21	Tan L.E. et al. 2022[45]

C. Effectiveness Data

The effectiveness parameters in this model were obtained from published clinical trials as shown in **Table 6**. Specifically, Tan L.E. et. al. used four clinical trials (MENSA, MUSCA, DREAM and SIRIUS) as baseline characteristics of patients to be used in the study as they matched closely to the local population.[45] Moreover, the relative risk for each biologic was obtained from a systemic review and meta-analysis paper by Pitre et al.[25] The effectiveness was not obtained based specifically on the 12-year-old cohort, but rather on a network meta-analysis study that included both paediatric (12 years old and above) and adult (over 18 years old) cohorts in which the adult population comprises 80% of the cohort. Since the time horizon was lifetime, the majority of the cohort's lifetime were spent in adulthood. Therefore, the population was modelled in parallel with the reference study. In addition, the age-adjusted mortality rates from the Department of Statistics Malaysia (DOSM) were used in the model to match accurately with the local population.[52]

Table 6: Effectiveness Data

Proportion of Exacerbation	Base Case Value	Distribution	Reference
OCS Burst	52.78 %	Beta	Tan L.E. et al. 2022[45]
ED Visit	12.5 %		
Hospitalisation	34.72 %		
Relative Risk exacerbation compared to placebo			
Tezepelumab	0.3	Log-normal	Tan L.E. et al. 2023[25]
Benralizumab	0.51		
Mepolizumab	0.52		
Dupilumab	0.32		
Death			
Probability death due to ED Visit	0.000616	Beta	Tan L.E. et al. 2022[45]
Probability death due to hospitalization	0.01316		
Mortality rate of asthma death	1.1		DOSM 2023[52]
Mortality rate of other causes	*age-adjusted mortality		
Percentage difference of OCS sparing compared to SoC			
Tezepelumab	3.36 (0.03 - 0.04)	Beta	Pitre et al. 2023[25]
Benralizumab	43.12 (0.34 - 0.52)		
Mepolizumab	34.16 (0.27 - 0.41)		
Dupilumab	27.44 (0.22 - 0.33)		

D. Transitional Probabilities

The transitional probabilities (4 weekly) used in the Markov model were obtained from literature as shown in **Table 7** and agreed upon by the expert committees.

Table 7: Transitional Probabilities Data

From	To	Transition Probabilities	Distribution	Reference
Day-to-day symptoms	OCS burst	0.0825	Beta	Tan L.E. et al. 2022[45]
Day-to-day symptoms	ED Visit	0.0202		
Day-to-day symptoms	Hospitalisation	0.055		
Day-to-day symptoms	Death from other causes	*age-adjusted probability		DOSM 2023[52]
OCS burst	Day-to-day symptoms	0.0824		Anderson et al 2020[50]
ED Visit	Day-to-day symptoms	0.0193		
ED Visit	Death from asthma	0.000047		Tan L.E. et al. 2022[45]
Hospitalisation	Day-to-day symptoms	0.052		
Hospitalisation	Death from asthma	0.0113		
All states	Death from other causes	*age-adjusted probability		DOSM 2023[52]

E. Health Utilities

The health utility value (**Table 8**) for SoC cohort was obtained from Yee VY. and Shafie AA. as the study was conducted in a hospital setting in Malaysia. Specifically, the asthma SoC represents poor control and high adherence to asthma treatment of patients in Malaysia, which represented the model's population in this model.[51] Furthermore, health utilities in the exacerbation states were derived from Tan L.E. et. al.[45] while the long-term OCS use utility was derived from Norman et. al.

Table 8: Health Utility Parameters

Variables	Parameter	95% CI	Distribution	Reference
Asthma SoC	0.5316	0.38 - 0.68	Beta	Yee VY. and Shafie AA. (2018)[51]
OCS burst	0.4316	0.35 - 0.52		Tan L.E. et al. 2022[45]
ED visit	0.3816	0.31 - 0.46		
Hospitalisation	0.3316	0.27 - 0.40		
Long term OCS use	0.5086	0.47 - 0.51		Norman et al. 2013[53]

F. Resource and Cost Data

The costs used in the model (**Table 9**) were obtained from the Pharmaceutical Services Program MOH, DRG Casemix (2023) and published literature. The cost of treatment per patient in the SoC cohort was derived from Yee VY. and Shafie AA.[51] It included the cost of drugs, personnel attending the patients, consumable costs, cost of fixed assets and cost of maintenance of the building (clinic and emergency department building). For the cost of OCS-related comorbidities, it was derived from Canonica GW. et. al. which studied the cost of OCS-related comorbidities and treatments in patients with severe asthma.[54] All costs were converted into Ringgit Malaysia (MYR) from the reference articles and inflated for 2024 using CCEMG-EPPI Centre Cost Converter. Lastly, one time of gross domestic product (GDP) per capita in 2022 for Malaysia which is equivalent to MYR 54,863/QALY was used as the WTP threshold in this analysis.

Table 9: Cost Parameters

Variables	Base Case	95% CI	Distribution	Reference
Cost of SoC	RM 178.38	142.70 – 214.06	Gamma	Yee VY. and Shafie AA. (2018)[51]
Cost of OCS Burst	RM 65.19	52.15 – 78.23		
Cost of ED Visit	RM 583.86	467.09 – 700.63		Iqbal et al.[55] (2014)
Cost of hospitalisation	RM 4,215.27	3,372.22 – 5,058.32		DRG Casemix 2023
Cost of OCS-related Comorbidities	RM 358.94	287.15 – 430.73		Canonica GW. et. al. (2019)[54]
Cost of Tezepelumab	****	****		Pharmaceutical Services Program MOH
Cost of Benralizumab	****	****		
Cost of Mepolizumab	****	****		
Cost of Dupilumab	****	****		

6.3.3 Sensitivity Analysis

Two sensitivity analyses were applied in the study namely deterministic and probabilistic separately for each respective biologic. First, the deterministic sensitivity analysis was performed as a one-way sensitivity analysis to evaluate the impact of variations in key model inputs on the model results. The input parameters were varied over a specified range, standard deviation or using values of reported upper and lower limits of 95% confidence interval. The input parameters tested in the sensitivity analyses were:

- Individual drug (intervention) cost
- Drug relative risks in reducing exacerbation compared to placebo
- Health utility value for long-term OCS use
- Health utility value for OCS burst
- Health utility value for hospitalisation

Second, the cost-effectiveness of the interventions was estimated using probabilistic sensitivity analysis. Based on 1000 iterations of Monte Carlo simulations used to handle uncertainty, the probabilistic sensitivity analysis was more robust. Various parameters and assumptions were assigned as probability distributions rather than fixed values. They allowed for a more realistic representation of uncertainty in the model. The analysis generated a range of possible outcomes, providing a more comprehensive understanding of the cost-effectiveness of the interventions as it ran multiple iterations and sampling from these distributions.

6.3.4 Model Assumption:

The following key assumptions were used in this model:

1. Health utility values for OCS burst, ED visits and hospitalisations were assumed to be four weeks.
2. Baseline characteristics of patients included in this model (age, number of exacerbations in the past 12 months, oral corticosteroid doses) followed a sample population of Singaporeans by Tan et al. L.E.45 and achieved consensus with local experts.
3. The asthma exacerbation states were mutually exclusive into three different subcategories:

   - asthma-related event that required OCS burst without (ED) visit
   - asthma-related ED visit
   - asthma-related hospitalisation

4. The risk of patients in the exacerbation states to remain in the same state was negligible in the following cycle. They either recovered or died.
5. The asthma-related death could only be attributed to the exacerbation states that required ED visits and hospitalisation. Death from other causes could occur in all health states.
6. The risks of death given OCS burst would be the same risk as other causes of death.
7. The OCS sparring begins in 28th week and the percentage sparring followed the results from Pitre et al.[25]
8. The SoC cohort was on OCS maintenance throughout lifetime.

6.4 RESULTS

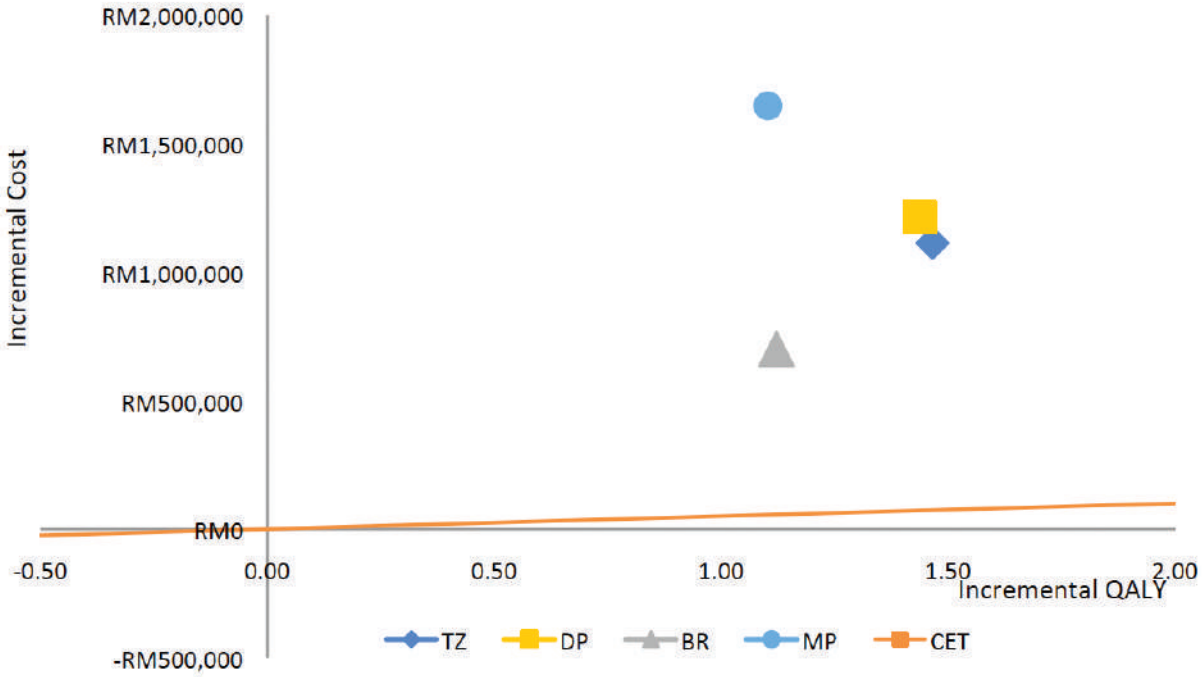
6.4.1 Base case analysis

The results of the model reflected the ICERs of using additional biologics in the SoC of severe asthma in comparison with the SoC without the biologics. The base case result is presented in **Table 10**.

Table 10: Incremental Cost-effectiveness Ratios (ICERs) for Base Case (Deterministic)

Strategies	Total Cost per Patient	Total QALY per Patient	Incremental Cost	Incremental QALY	ICER
SoC	RM187,117	10.43	-	-	-
Tezepelumab plus SoC	RM1,299,290	11.90	RM 1,112,173	1.47	RM 759,126
Benralizumab plus SoC	RM 886,671	11.55	RM 699,554	1.12	RM 623,901
Mepolizumab plus SoC	RM1,888,486	11.53	RM 1,701,369	1.10	RM 1,543,407
Dupilumab plus SoC	RM1,457,206	11.87	RM 1,270,090	1.44	RM 883,807

The base case results showed that the deterministic ICER for benralizumab was the lowest among the biologics which is RM623,901 per QALY gained. Over the lifetime of the patient cohort (63 years), there was a marginal cost increase of RM886,671 and a marginal benefit of 1.12 QALYs per patient when benralizumab was added to the SoC treatment compared with SoC alone. Besides that, the deterministic ICER for mepolizumab was the highest which was RM1,543,407 per QALY gained, followed by dupilumab (RM883,807 per QALY gained) and tezepelumab (RM759,126 per QALY gained). Nevertheless, all the ICERs were above the WTP threshold. **Figure 7** demonstrates the ICERs on the cost-effectiveness plane.



Notes: **TZ**: Tezepelumab, **DP**: Dupilumab, **BR**: Benralizumab, **MP**: Mepolizumab, **CET**: Cost-effectiveness Threshold (WTP). Each biologic represented an additional treatment in the SoC..

Figure 7: Cost-effectiveness Analysis Plane (Deterministic)

6.4.2 Sensitivity Analysis

6.4.2.1 One Way Analysis (OWA)

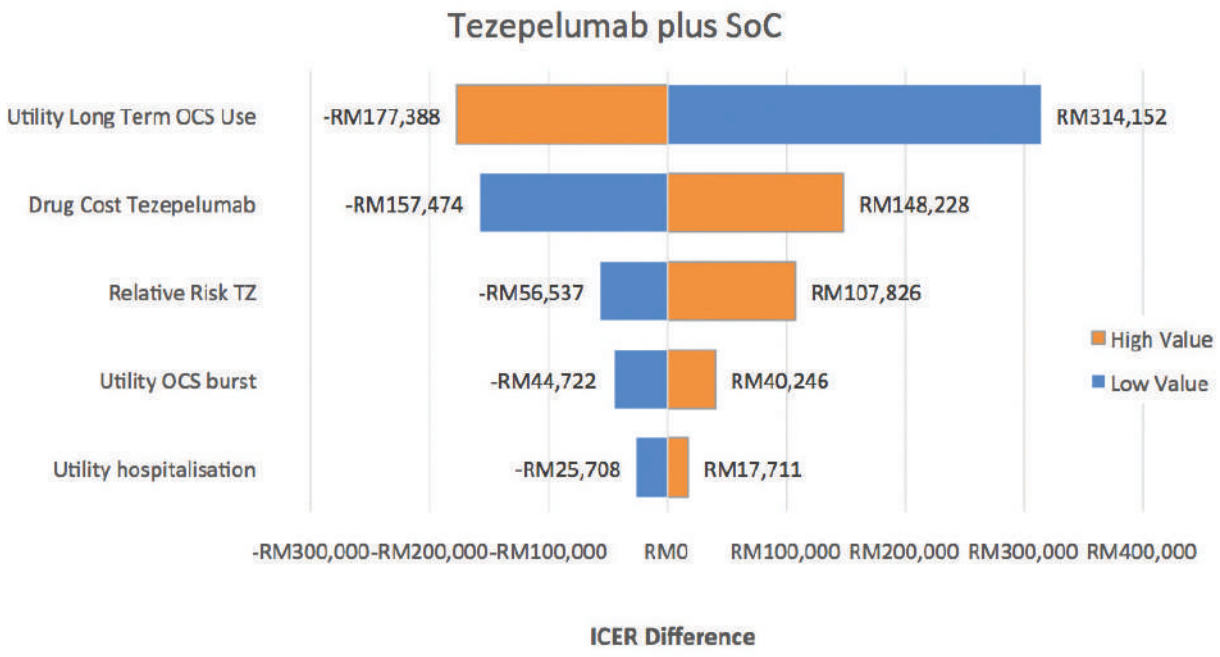
A one-way sensitivity analysis was performed for each biologic to determine the parameters that may affect the ICER by varying the value of the clinical parameters and costs. The findings from the analysis were presented in **Table 11** and plotted as tornado diagrams to demonstrate the ICER obtained from different scenarios in comparison to the deterministic ICER.

The sensitivity analysis for tezepelumab showed that by varying the input parameters, the estimated ICERs ranged from a lower bound of RM 581,610 per QALY gained to an upper bound of RM 1,073,150 when comparing tezepelumab plus SoC to SoC alone.

Furthermore, the most sensitive input parameter in the model was the health utility value for long-term OCS use followed by the drug cost and its relative risk. The health utility value for OCS burst had a moderate impact on the ICERs while the health utility value for hospitalisation had a lower impact on the ICERs. Nonetheless, all the ICERs generated were higher than the WTP threshold. Moreover, the most sensitive key parameters for tezepelumab were the same key parameters that were most sensitive to ICERs for benralizumab, mepolizumab and dupilumab as shown in **Figure 8, Figure 9, Figure 10** and **Figure 11**.

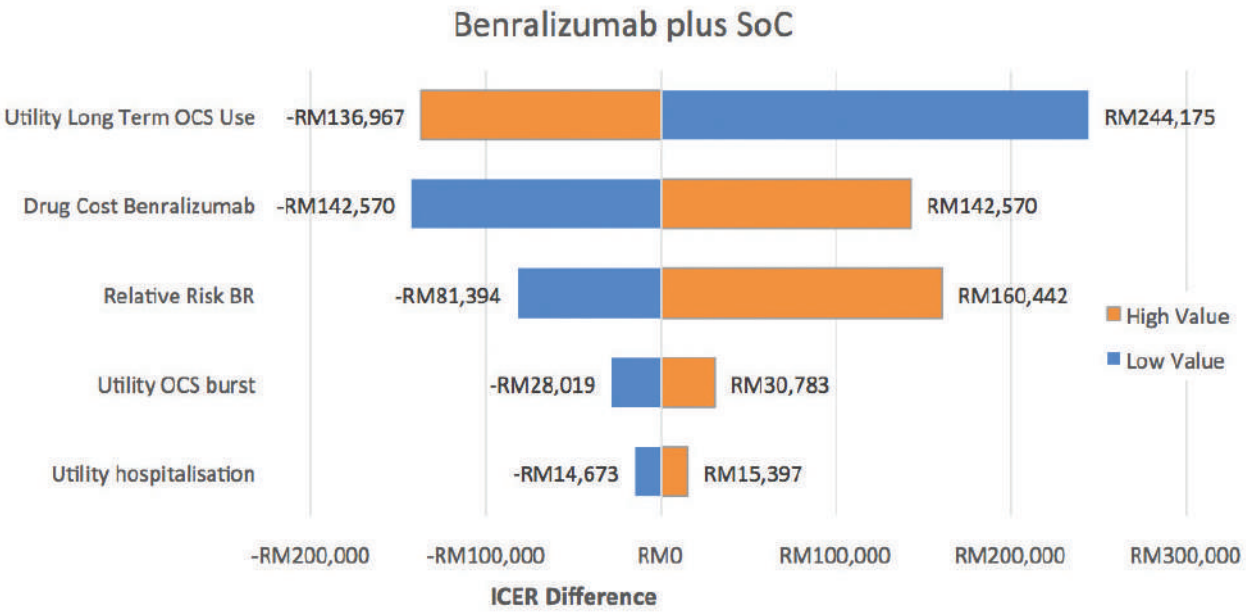
Table 11: Sensitivity Analysis of Key Parameters (Biologics plus SoC versus SoC)

Parameters	95% CI limit / Range / SD	ICER of lower value input	ICER of higher value input
Tezepelumab			
Drug Cost	± 20% from the actual costs	RM 601,524	RM 907,225
Relative Risk in reducing exacerbation compared to placebo	0.21 – 0.43	RM 702,461	RM 866,824
Health utility value for long-term OCS use	0.41 – 0.61	RM 1,073,150	RM 581,610
Health utility value for OCS burst	0.35 – 0.52	RM 714,276	RM 799,243
Health utility value for hospitalisation	0.27 – 0.40	RM 733,289	RM 776,708
Benralizumab			
Drug Cost	± 20% from the actual costs	RM481,331	RM766,472
Relative Risk in reducing exacerbation compared to placebo	0.41 – 0.63	RM542,508	RM784,344
Health utility value for long-term OCS use	0.41 – 0.61	RM868,077	RM486,935
Health utility value for OCS burst	0.35 – 0.52	RM595,883	RM654,685
Health utility value for hospitalisation	0.27 – 0.40	RM609,229	RM639,298
Mepolizumab			
Drug Cost	± 20% from the actual costs	RM 1,228,292	RM 1,858,522
Relative Risk in reducing exacerbation compared to placebo	0.43 – 0.64	RM 1,358,481	RM 1,946,852
Health utility value for long-term OCS use	0.41 – 0.61	RM 2,145,496	RM 1,205,194
Health utility value for OCS burst	0.35 – 0.52	RM 1,474,627	RM 1,618,916
Health utility value for hospitalisation	0.27 – 0.40	RM 1,458,979	RM 1,530,396
Dupilumab			
Drug Cost	± 20% from the actual costs	RM 702,161	RM 1,065,453
Relative Risk in reducing exacerbation compared to placebo	0.24 – 0.42	RM 826,551	RM 983,699
Health utility value for long-term OCS use	0.41 – 0.61	RM 1,254,258	RM 682,289
Health utility value for OCS burst	0.35 – 0.52	RM 837,604	RM 935,404
Health utility value for hospitalisation	0.27 – 0.40	RM 820,563	RM 868,279



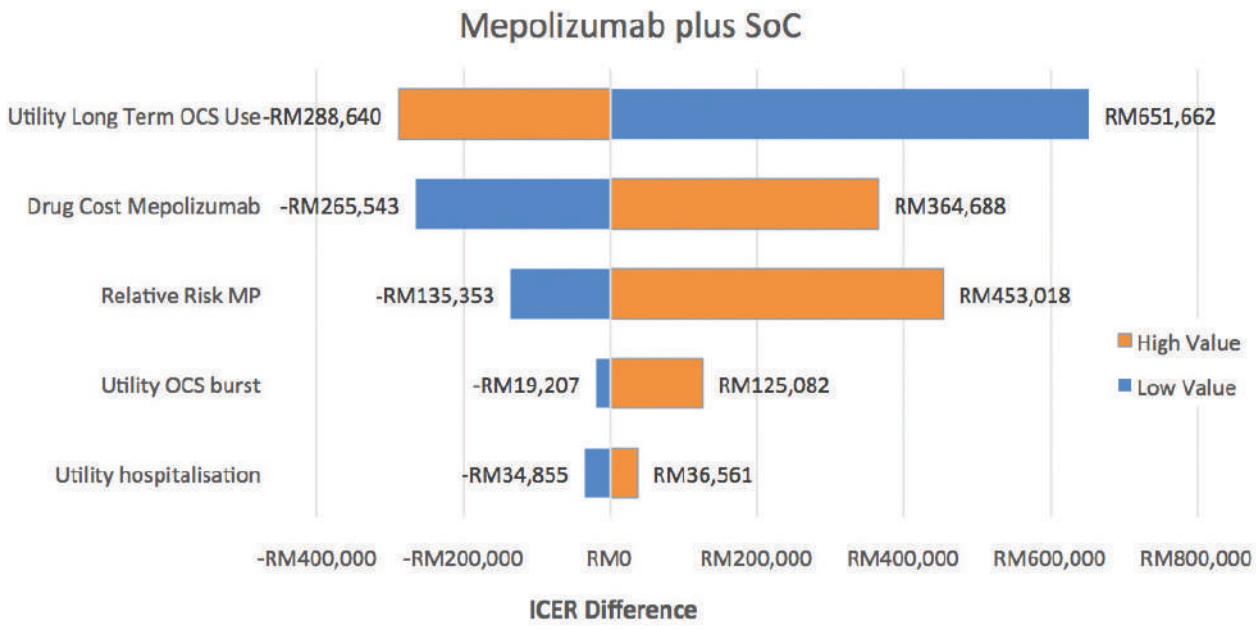
Notes: Base-case ICER = RM759,126

Figure 8: Tornado Diagram for Tezepelumab plus SoC



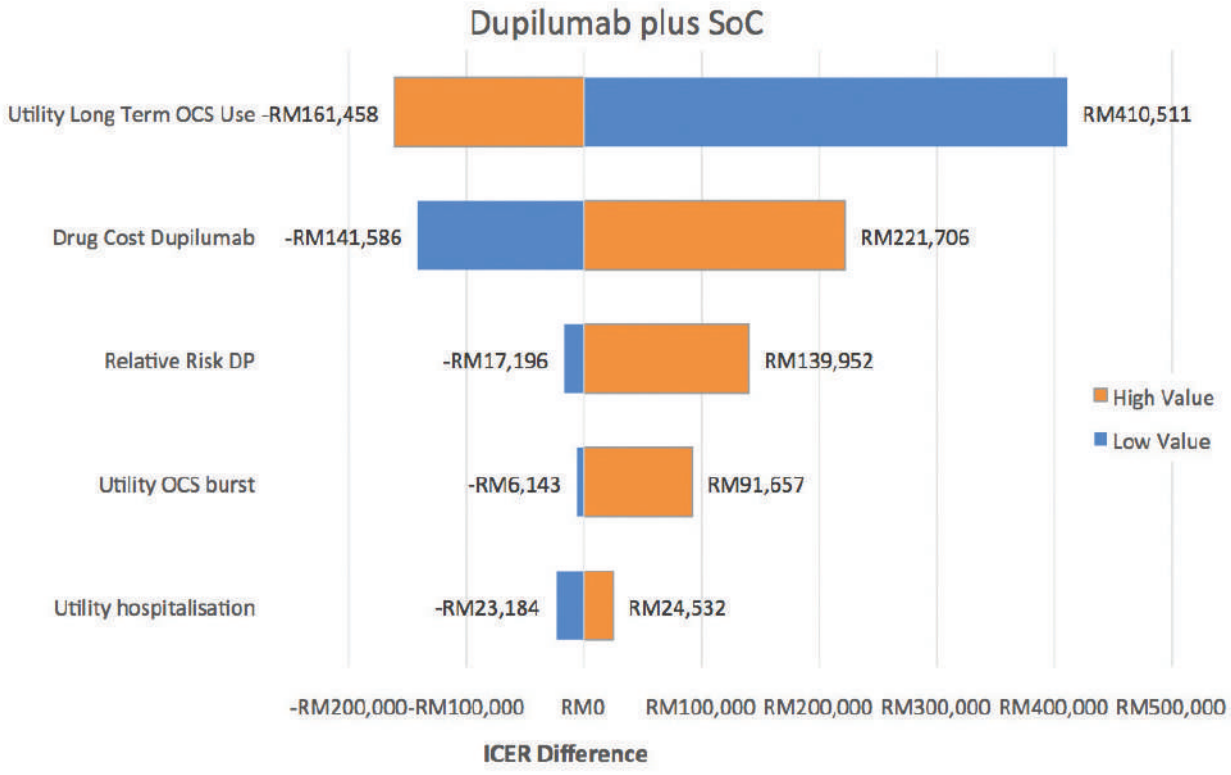
Notes: Base-case ICER = RM623,901

Figure 9: Tornado Diagram for Benralizumab plus SoC



Notes: Base-case ICER = RM1,543,407

Figure 10: Tornado Diagram for Mepolizumab plus SoC



Notes: Base-case ICER = RM 883,807

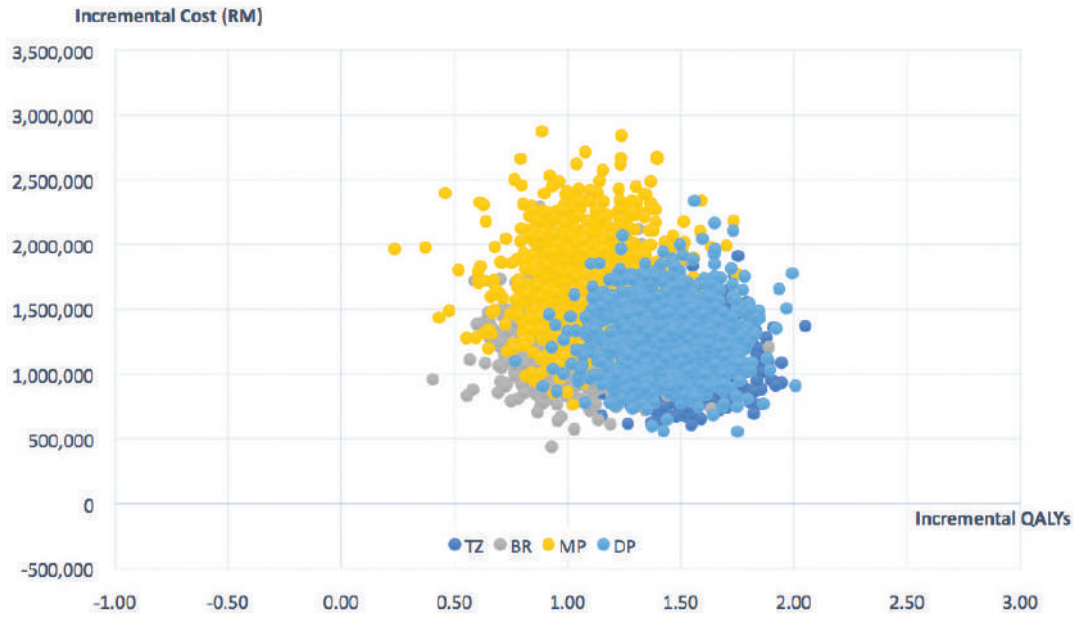
Figure 11: Tornado Diagram for Dupilumab plus SoC

6.4.2.2 Probabilistic Sensitivity Analysis (PSA)

For probabilistic sensitivity analysis, a Monte Carlo simulation of 1000 iterations (**Figure 12**) was conducted to randomly sample values from the key parameter distributions to produce a distribution of outcomes. **Table 12** shows that the model results were consistent and robust in comparison to the deterministic results. Similar to deterministic ICERs, all the probabilistic ICERs were above WTP threshold. **Figure 12** demonstrates the ICERs on the cost-effectiveness plane.

Table 12: Incremental Cost-effectiveness Ratios (ICERs) for PSA

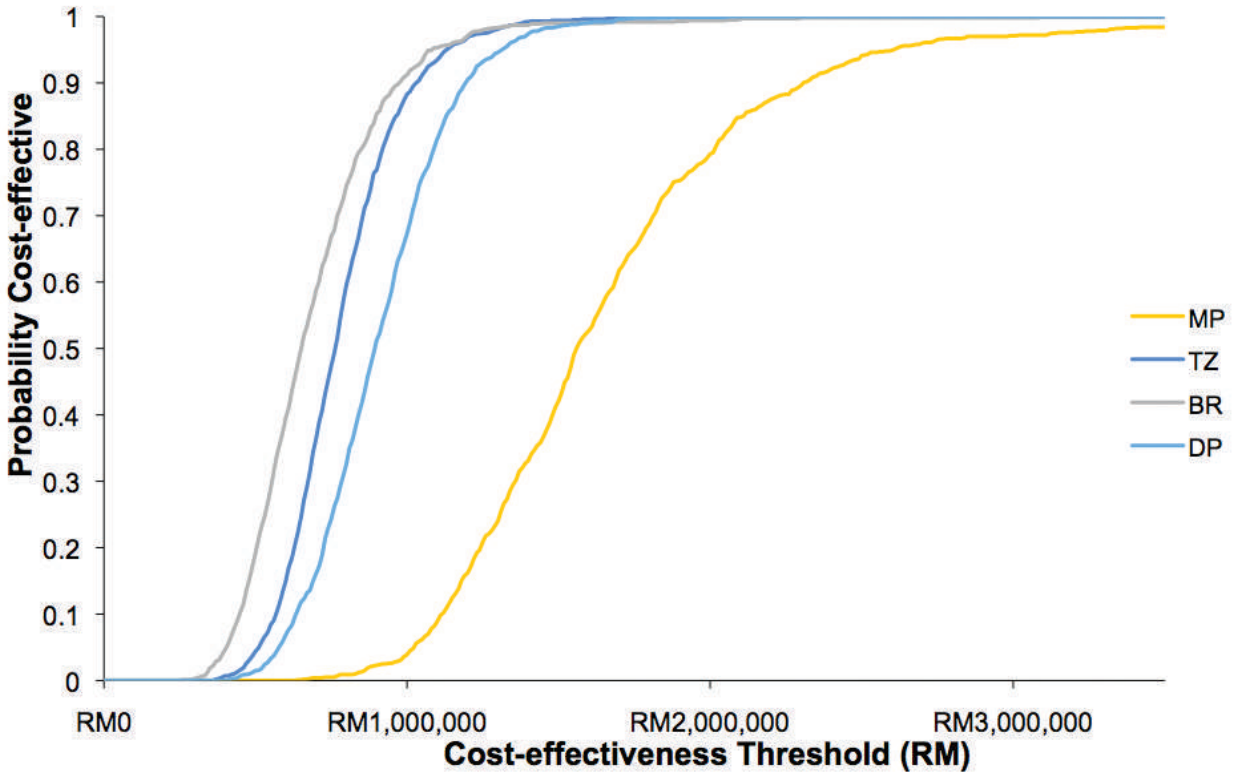
Strategies	Total Cost per Patient	Total QALY per Patient	Incremental Cost	Incremental QALY	ICER
SoC	RM 185,905	10.42	-	-	-
Tezepelumab plus SoC	RM 1,294,995	11.88	RM 1,109,090	1.46	RM 760,219
Benralizumab plus SoC	RM 908,876	11.54	RM 721,435	1.10	RM 658,837
Mepolizumab plus SoC	RM 1,891,377	11.51	RM 1,705,471	1.09	RM 1,559,840
Dupilumab plus SoC	RM 1,457,094	11.85	RM 1,271,189	1.43	RM 891,234



Notes: **TZ** : Tezepelumab, **BR** : Benralizumab, **MP** : Mepolizumab, **DP** : Dupilumab

Figure 12: Cost-effectiveness Analysis Plane (Monte Carlo simulation of 1000 iterations)

On top of that, a cost-effectiveness acceptability curve had been plotted as shown in **Figure 13**. It shows that the probability of the cost-effectiveness of biologics increased as the cost-effectiveness threshold increased. At the cost-effectiveness threshold of RM 1 million, the probability of cost-effectiveness was the highest for benralizumab (91.2%), followed by tezepelumab (88.3%), dupilumab (67.3%) and mepolizumab (3.9%). It demonstrated the probability of cost-effectiveness of biologics at the willingness of pay of the provider.



Notes: **TZ** : Tezepelumab, **BR** : Benralizumab, **MP** : Mepolizumab, **DP** : Dupilumab

Figure 13: Cost-effectiveness Acceptability Curve

6.4.3 Scenario Analyses

The scenario analyses illustrated three different scenarios when certain key parameters were adjusted. The ICERs from each scenario were compared with the base case results.

1. Duration of treatment

   In this scenario, the duration of treatment was shortened from 63 years to 20 years (261 cycles) and 30 years (391 cycles). When the duration was shortened to 20 years, the ICERs achieved cost savings of an average of 44%. In addition, when the duration was shortened to 30 years, the ICERs achieved cost savings of an average of 25%.

2. Dose Treatment Frequency

In this scenario, the dose treatment of tezepelumab, benralizumab and mepolizumab was extended from 4-weekly to 8-weekly, except for dupilumab which was extended from 2-weekly to 4-weekly. The ICERs achieved cost savings of an average of 50%, except for benralizumab, in which the ICER achieved cost savings of an average of 30%.

3. Drug Cost

A hypothetical and gradual reduction of biologic drug costs for respective biologics was used to determine the percent of drug cost reduction needed for the ICERs to be cost-effective in Malaysia. The outcomes demonstrated that all drugs except benralizumab need to achieve more than 90% cost reduction for ICERs to be cost-effective.

All the results from the scenario analyses are shown in **Table 13**.

Table 13: Scenario Analyses

Scenario	1	2		3	4
Parameter	Base case result	Duration of treatment		Dose Frequency	Drug Cost
Default Value(s)	-	12 – 75 years old (63 years)		Dose Frequency Reference	Drug Cost Reference
Alternative Value(s)	-	12 – 32 years old (20 years)	12 – 42 years old (30 years)	Extended by 4 weeks (except Dupilumab extended by 2 weeks)	Drug Cost Reduction
Tezepelumab plus Soc	RM760,219	RM419,599 (44.8%↓)*	RM565,553 (25.6%↓)**	RM387,394 (49.0%↓)***	93%†
Benralizumab plus SoC	RM623,901	RM360,798 (23.6%↓)*	RM476,495 (23.6%↓)**	RM442,565 (29.1%↓)***	81%†
Mepolizumab plus SoC	RM1,559,841	RM866,286 (44.5%↓)*	RM1,156,845 (25.8%↓)**	RM780,243 (50.0%↓)***	95%†
Dupilumab plus SoC	RM891,234	RM490,831 (44.9%↓)*	RM662,194 (25.7%↓)**	RM437,501 (50.9%↓)***	92%†

**Percentage reduction in ICER by limiting biologic treatment to 20 years compared to the base case result.*
*** Percentage reduction in ICER by limiting biologic treatment to 30 years compared to the base case result.*
**** Percentage reduction in ICER by extending biologic treatment frequency by 4 weeks (except Dupilumab by 2 weeks) compared to the base case result.*
† Percentage drug cost reduction required for the ICERs

7.0

DISCUSSION

7.0 DISCUSSION

According to GINA 2024, biologics are considered as an add-on therapy in patients with severe uncontrolled asthma.[3] Thus, this review was conducted to assess the clinical efficacy and health-related outcomes as well as economic implication of four biologics for severe asthma namely mepolizumab, benralizumab, dupilumab and tezepelumab. Thirty included studies consisted of seven systematic reviews with meta-analysis, and network meta-analysis of the biologics where the most recent was published in 2024. Other studies were five systematic reviews, and randomised controlled trials of the individual biologics. Five extended studies of the individual biologics were also included. The extended studies were to assess the long-term safety and benefits of the biologics in reducing exacerbations, improving asthma control and lung function, reducing the OCS used as well as any healthcare utilisation including hospitalisation and Emergency Department visit due to exacerbations. On the other hand, there were also studies included specifically reviewed on the usage of biologics among children. The remaining studies were cross sectional, post-hoc analysis of RCTs and economic evaluation.

The evidence synthesis had shown that all four biologics in addition to standard of care reduced asthma exacerbations rate including annual asthma exacerbation rate, reduce hospitalisation and Emergency Department visit, improved asthma controlled through Asthma Control Questionnaire score, improvement in lung function based on increment in Forced Expiratory Volume 1 among patients with high level of blood eosinophil count (BEC ≥300 cell/uL). An SR with network meta-analysis by Nopsopon T. et. al. also reported similar findings where tezepelumab was ranked first in SUCRA level for the exacerbation reduction, dupilumab for the improvement in lung function, and mepolizumab for improvement in ACQ score.[48] On the other hand, inconsistent findings were observed among patients with low level of BEC (<150 cells/uL) who were treated with tezepelumab. Another finding was reduction in corticosteroid consumption after treatment with the biologics as early as four-weeks of treatment. Most of the included studies reported the reduction in three conditions which were oral corticosteroid dose reduction lower than 5mg, reduction in more than 50% of oral corticosteroid dose and discontinuation of oral corticosteroid. Other outcomes observed in the included studies were reduction in blood eosinophils, reduction in FeNO level and reduction in IgE.

Instead of subgroup analysis of BEC level, other subgroups analysis reported were FeNO level, allergen status, and comorbidity. However, the results were uncertain and differ from each biologic. In terms of healthcare utilisation, there were studies that described biologic increased potential of reducing healthcare utilisation. From the included studies, tezepelumab and mepolizumab described a reduction in home visits from a healthcare provider, outpatient visit related to exacerbation and even reduction in outpatient pharmacy claim per patients. Consistent improvement was also reported by Hardtstock F. et. al. where benralizumab and mepolizumab reduced the sick leave days among severe asthma patients.[49]

Quality of life among patients with severe asthma improved with all reviewed biologics. Different tools of assessments being used included Asthma Quality of Life Questionnaire score, and St. George's Respiratory Questionnaire score in the overall population. On the other hand, for paediatric patient the tools used was Paediatric Asthma Quality of Life Questionnaire and Paediatric Asthma Caregiver's Quality of Life Questionnaire for their caregivers. Among the caregivers, domains of activity limitation and emotional function improved greatly by 52-weeks of biologics treatment.

For safety, inconsistent findings were observed in biologics-related adverse events among mepolizumab, benralizumab, dupilumab and tezepelumab compared to placebo. Non-outstanding adverse events were reported except that small rate of adverse events that lead to the discontinuation of the biologics. Those adverse events were anaphylactic reaction, malignancy, liver function abnormality, asthma-related event requiring intubation, pneumonia etc. The most common adverse events reported were nasopharyngitis, headache, sinusitis, and bronchitis. Death incidence also reported but was not related to the biologic's treatment. Anti-drug antibodies development was another risk that might happened with biologics with possibility of affecting the effectiveness of the biologics. However, based on retrieved studies, anti-drug antibodies did not show any risk of affecting the biologics efficacy as well as safety.

In spite of undeniable effectiveness and acceptable safety profile, the price of the biologics plays an important role in determining the cost-effectiveness of the biologics in most of the countries. The economic evaluation studies reported that most of ICER were above Willingness-to-Pay thresholds. On the other hand, other potential saving might relate to the decrease in health-care utilisation such as primary care visit, and hospitalisation and emergency department visit.

As for economic implication, economic evaluation of biologics in severe asthma patients has yielded valuable insights into the cost-effectiveness of the biologics compared to SoC. The findings indicated a range of QALY gained from 1.10 to 1.47, with corresponding ICERs ranging from RM623,901 to RM1,543,307. Remarkably, these results aligned closely with similar studies conducted in diverse healthcare settings worldwide.

For instance, Habash et al. from Canada reported an ICER of $192,537 (2022 Canadian Dollar) for tezepelumab with a QALY gained of 1.077.[56] Meanwhile, Tan LE. et al. from Singapore estimated an ICER of $335,486 for mepolizumab with a QALY gained of 0.459.[45] Similarly, Rind DM. et. al. through Institute for Clinical Economic Review (ICER) report from the United States revealed ICERs of $371,000 and $351,000 for benralizumab and dupilumab, respectively, with QALYs gained of 1.41 and 1.63.[57] This study's result alignment with international findings highlights the robustness and generalisability of the economic analysis. It also strengthened the validity of conclusions regarding the cost-effectiveness of biologics in severe asthma.

Limitations

The authors acknowledge some limitations in the review, and these should be considered when interpreting the results. Although there was no restriction in language during the search, only the full text articles in English published in peer-reviewed journals were included in the report, which may have excluded some relevant articles and further limited our study numbers. One of the important limitations was the methodological quality of the included studies, particularly in terms of heterogeneity. This could be due to the differences in the baseline characteristics of the study participants, differences in the inclusion and exclusion criteria of each study, assessment of outcomes, and the differences among the biologics itself. On the hand, most of the included studies especially the RCTs were funded by the industries where the reliability of the results reported were out of control. However, the main strength of this review is the degree of rigour in the conduct of the review. The methods were in accordance with those proposed by the Cochrane Collaboration for conducting systematic reviews of interventions and PRISMA statement. Additionally, two different reviewers assessed the quality of the included studies. For the economic evaluation part, the Markov model utilised in this study had several limitations that warrant consideration. Firstly, it relied on trial-based clinical parameters sourced from a literature review, as there was a dearth of real-world local data. While this approach allowed for the construction of the model, it introduced the risk of underestimating or overestimating the outcomes due to potential discrepancies between trial conditions and real-world scenarios. Secondly, the model operated under the assumption that transition probabilities between health states remain fixed over time. However, in practical contexts, these probabilities may fluctuate due to various external factors or evolving dynamics within the system. Consequently, the model's predictive accuracy may be compromised as it failed to adapt to changing circumstances. Thirdly, the model lacks the capability to accommodate heterogeneity in patient characteristics, such as variations in asthma symptoms, disease progression trajectories, and individual comorbidities. The cohort population used in the model may overlook crucial nuances that could influence individual outcomes, thereby limiting its generalisability and applicability in diverse clinical settings.

8.0

CONCLUSION

8.0 CONCLUSION

Based on the above review, mepolizumab, benralizumab dupilumab and tezepelumab significantly reduced the exacerbations and hospitalisation/ED visit, improved lung function, asthma control, quality of life and reduced the used of oral corticosteroid especially among patients with high level of BEC (≥300 cells/uL) and unresponsive to the optimal therapy with acceptable safety profile.

In terms of economic implications, those biologics were effective but at higher cost as the ICER/QALY were higher than the Willingness to Pay (WTP) threshold.

9.0

RECOMMENDATION

9.0 RECOMMENDATION

Biologics (mepolizumab, benralizumab, dupilumab or tezepelumab) may be used as an **add-on therapy** for severe asthma in patients with; high BEC level (≥300 cells/uL) and unresponsive to the optimal therapy. Taken into consideration the economic implication, effective price negotiations may improve cost-effectiveness of these treatment.

10.0

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11.0

APPENDICES

APPENDIX 1: HEALTH TECHNOLOGY ASSESSMENT PROTOCOL

BIOLOGICS IN SEVERE ASTHMA

1.0 BACKGROUND INFORMATION

Asthma affects more than 300 million people worldwide.[3] In Malaysia, the prevalence is estimated between 8.9 and 13.0% in children and 6.3% in adults.[12] According to National Health and Morbidity Survey 2011, age group above 75 years had the highest prevalence of asthma (10.7%; 95% CI, 7.5 to 15.2), followed by age group 5 to 9 years (8.5%; 95% CI, 7.3 to 9.8) and age group 15 to 19 years (8.1%; 95% CI, 6.6 to 10.0).[6,22] According to World Health Organization (WHO), up to 10% of adults and 2.5% of children with asthma have severe asthma, with a reduced quality of life and an increased risk.[3]

Severe asthma generally refers to a clinical situation where a prior diagnosis of asthma exists, and asthma-like symptoms and asthma attacks persist despite prescription of high-dose asthma therapy.1 Meanwhile, severe childhood asthma (SCA) is defined as asthma that remains uncontrolled even after adherence to optimise combination of high-dose inhaled corticosteroid and long-acting beta-agonist (ICS-LABA) and despite management of contributory factors and comorbidities, or asthma that worsens when high dose treatment is decreased.[10]

Generally, there are two main types of severe asthma which are categorised based on the individual's response to treatment: Type 2 inflammation and Non-Type 2 inflammation. Type 2 inflammation includes allergic asthma and eosinophilic asthma. Non-Type 2 inflammation includes non-eosinophilic asthma which does not respond well to inhaled corticosteroids.[19]

Despite evidence-based asthma management recommendations and treatments, asthma control is still suboptimal.[12] A local study on asthma control reported that 37% patients had well-controlled asthma, 36% were partly controlled and 27% uncontrolled.[12] Patients with severe, uncontrolled asthma are at risk of recurrent asthma exacerbations and hospitalisations even with standard treatment and consequently experience poor health-related quality of life. Additional treatment options for these patients include biologic therapies.[6,7]

Current approved biologic therapies for severe asthma target key mediators of type 2 (T2) inflammation in eosinophilic or allergic asthma, including interleukin (IL)-5, IL-4, IL-13 and immunoglobulin E (IgE), and are prescribed based on indicators of these phenotypes, including dependence on oral corticosteroids (OCS) for disease control. The biologics reduce asthma exacerbations, improve lung function, reduce oral corticosteroid use and improve quality of life in appropriately selected patients.[20] At the moment, there are five approved biologics (monoclonal antibody) available for severe asthma **omalizumab, mepolizumab, reslizumab, benralizumab** and **dupilumab**.[6,7] Another biologic is tezepelumab, the anti-thymic stromal lymphopoietin.[13]

1.1 Types of Biologic Treatment for Asthma

i. Omalizumab – anti-IgE
First humanised anti-IgE monoclonal antibody, was approved for used in patients over 12 years old by the USFDA in 2003 and by the EMA in 2005. In 2009, the indication was extended to the children over 6 years old by EMA. [13]

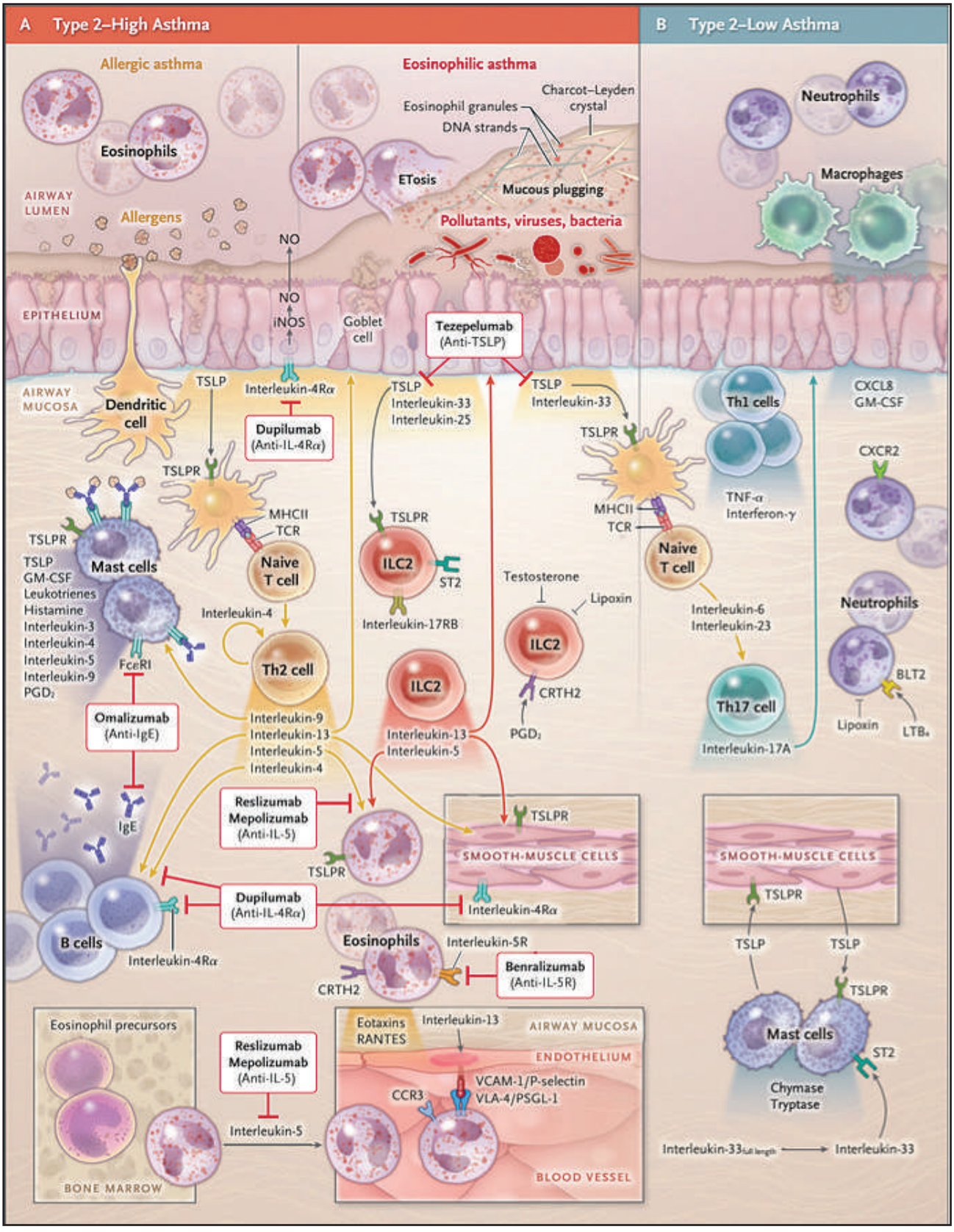
ii. Mepolizumab – anti-IL5
Has a marketing authorisation in UK as an add-on treatment for severe eosinophilic asthma in adults, adolescent and children aged 6 years and older.[14]

iii. Reslizumab – anti-IL5
As an add-on therapy for the treatment of severe eosinophilic asthma that is inadequately controlled in adults (≥18-years old).[15]

iv. Benralizumab – anti-IL5 receptor α
As add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists. Benralizumab is approved for patients as young as 12-years old.[16]
The recommended dosage is 30 mg every 4 weeks for the first 3 doses then every 8 weeks, given by subcutaneous injection using a pre-filled syringe.[16]

v. Dupilumab – anti-IL4 receptor α
As an add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO [fractional exhaled nitric oxide] who are inadequately controlled with high dose ICS [inhaled corticosteroid] plus another medicinal product for maintenance treatment.
Dupilumab is approved for patients ≥12-years old.[17]

vi. Tezepelumab - anti-thymic stromal lymphopoietin
First approved biologics that targets thymic stromal lymphopoietin (TSLP). It received regulatory approval from USFDA in 2021 for treatment of severe asthma in patients over 12 years of age.[11,13] Unlike other biologic therapies, it is not restricted to patients with allergic or eosinophilic asthma.[11]



*adopted from Brussels GG et al.[3]

Figure 1: Biologics treatment for asthma

1.2 Reasons for request

i. Severe asthma despite globally showing 3-14% of all asthma but recent local studies have shown that prevalence of uncontrolled asthma including severe asthma is about 20%.

ii. In spite of low percentage but they consume many health care facilities once they are admitted and seen in hospital facilities.

iii. The hope that the biologics can be reviewed and assessed cost effectiveness as they have been proven to have good response from patients and able to reduce the morbidity and hospitalisation of this group of patients.

2.0 POLICY QUESTION

2.1 Should biologics be used to treat severe asthma?

2.2 Which biologics should be used to treat different severe asthma phenotypes?

3.0 OBJECTIVES

3.1 To assess the effectiveness and safety of biologics in treatment of severe with regards to patient outcomes such as asthma control (exacerbation, spirometry, symptoms, quality of life [QoL], oral corticosteroid [OCS] sparing effects, hospital admission, Emergency Department ([ED] visit etc), mortality and adverse events or complications.

3.2 To assess the economic implication, social, ethical, and organisational aspects related to the biologics in treatment of severe asthma.

3.3 To identify which types of biologics are better in treating severe asthma.

The following **research questions** will be addressed:

3.1.1 What is the best option for severe asthma?

3.1.2 Does different types of biologics affect different types of severe?

3.1.3 Is biologics in treatment of severe asthma cost-effective?

3.1.4 Which is the best type of biologics for treatment of severe in term of efficacy and cost-effective?

3.1.5 What is the social, ethical, and organisational implication/ impact related to the use of biologics in treatment of severe?

4.0 METHODS

4.1 Search Strategy

Electronic database will be searched for published literatures pertaining to molecular profiling for early breast cancer detection.

4.1.1 Databases as follows: MEDLINE, EMBASE, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), INAHTA Database, HTA database and FDA database.

4.1.2 Additional literatures will be identified from the references of the retrieved articles.

4.1.3 General search engine will be used to get additional web-based information if there is no retrievable evidence from the scientific databases.

4.1.4 There will be no limitation applied in the search such as year and language.

4.1.5 The search strategy will be included in the appendix.

4.2 Inclusion and Exclusion Criteria

4.2.1 Inclusion criteria

a. Population : Patient with severe asthma

b. Intervention : Biologics (mepolizumab, benralizumab, dupilumab and tezepelumab)

c. Comparators :
   i. Standard treatment
   ii. Between biologics
   iii. No comparator

d. Outcome :
   a. Effectiveness: Exacerbation rate, asthma control (exacerbation, spirometry, symptoms, quality of life (QoL), OCS sparing effects, hospital admission, ED visit etc), mortality, FEV1, FeNO and eosinophil count.
   b. Safety: adverse events, complications (OCS burst)
   c. Economic implications: cost-effectiveness, cost-utility, cost-benefit analysis
   d. Potential psychological and behavioural harms and benefits of the biologics
   e. Training requirements or learning curve

e. Study design : HTA reports, systematic reviews (SRs) with/out meta-analysis (MA) / network MA, randomised controlled trials (RCTs), cohort studies, and economic evaluation

f. English full text articles

4.2.2 Exclusion criteria

a. Study design : Animal study, laboratory study, case-control, case report, case series, narrative review

b. Non-English full text articles

Based on the above inclusion and exclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

4.3 Critical Appraisal of Literature

The risk of bias of all retrieved literatures will be assessed using the relevant checklist of Critical Appraisal Skill Programme (CASP, ROBIs for systematic review and Cochrane risk of bias tool for randomised trials (RoB 2).

4.4 Analysis and Synthesis of Evidence

4.4.1 Data extraction strategy

The following data will be extracted:

a. Details of methods and study population characteristics

b. Detail of intervention and comparators

c. Details of individual outcomes specified.

Data will be extracted from selected studies by a reviewer using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion.

4.4.2 Methods of data synthesis

Data on the accuracy, safety and cost-effectiveness associated with molecular profiling in breast cancer will be presented in tabulated format with narrative summaries. Meta-analysis may be conducted for this HTA.

5.0 REPORT WRITING

6.0 REFERENCES

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APPENDIX 2: SEARCH STRATEGY

Database: Ovid MEDLINE(R) ALL <1946 to January 17, 2024>
Search Strategy:

----------*the list was simplified for reporting purposes ----------

1. Asthma/
2. asthma*.tw.
3. (bronchial adj1 asthma).tw.
4. ((severe or Life threatening or Difficult-to-treat or uncontrolled) adj1 asthma).tw.
5. severe asthma.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
6. severe asthma.tw.
7. type 2 asthma.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
8. type 2 asthma.tw.
9. Antibodies, Monoclonal/
10. (monoclonal adj1 antibod*).tw.
11. Omalizumab/
12. 242138-07-4.tw.
13. 2p471x1z11.tw.
14. Omalizumab.tw.
15. mepolizumab.mp.
16. Mepolizumab.tw.
17. Nucala.tw.
18. reslizumab.mp.
19. Reslizumab.tw.
20. Cinqair.tw.
21. benralizumab.mp.
22. Benralizumab.tw.
23. Fasenra.tw.
24. dupilumab.mp.
25. Dupilumab.tw.
26. Dupixent.tw.
27. tezepelumab.mp.
28. tezepelumab.tw.
29. tezepelumab-ekko.tw.
30. Tezspire.tw.
31. limit to (humans and yr="2018 -Current" and (clinical trial, all or meta-analysis or randomized controlled trial or "systematic review"))

APPENDIX 3: EVIDENCE TABLE

<Available upon request>

APPENDIX 4: LIST OF EXCLUDED STUDIES

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