11 December 2025
EMADOC-1829012207-16378
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Exdensur

International non-proprietary name: depemokimab

Procedure No. EMEA/H/C/006446/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# Table of contents

# List of abbreviations

| | |
|---|---|
| AA | Amino Acid |
| ACQ-5 | Asthma Control Questionnaire-5 |
| ADA | Anti-Drug Antibodies |
| ADC | Antibody–Drug Conjugate |
| ADCC | Antibody-Dependent Cellular Cytotoxicity |
| ADCP | Antibody-Dependent Cellular Phagocytosis |
| ADR | Adverse Drug Reaction |
| ADSD | Asthma Daily Symptom Diary |
| AE | Adverse Event |
| AER | Annualised Exacerbation Rate |
| AERD | Asthma-Exacerbated Respiratory Disease |
| AESI | Adverse Event of Special Interest |
| AI | Autoinjector |
| AIL-5 | Anti–Interleukin-5 |
| AIL-5/R | Anti–Interleukin-5 Receptor |
| ALT | Alanine Aminotransferase |
| ANCOVA | Analysis Of Covariance |
| ANOVA | Analysis Of Variance |
| ANSD | Asthma Nightly Symptom Diary |
| AS | Active Substance |
| ASMF | Active Substance Master File |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical Classification |
| AU | Absorption Units |
| AUC | Area Under the Concentration-Time Curve |
| AUCtau, Ss | Area Under the Concentration-Time Curve During a Dosing Interval at Steady State |
| $AUC_{0-\infty}$ | Area Under the Concentration-Time zero to infinity |
| $AUC_{0-t}$ | Area Under the Concentration-Time zero to given timepoint |
| B/R | Benefit/Risk |
| BDBA | Bayesian Dynamic Borrowing Analysis |
| BDP | Bulk Drug Product |
| BDS | Bulk Drug Substance |
| BEC | Blood Eosinophil Count |
| BECpredicted, Week 52 | Predicted Blood Eosinophil Count at Week 52 |
| BLI | Biolayer Interferometry |

| | |
|---|---|
| BLQ | Below Limit of Quantification |
| BMI | Body Mass Index |
| BP | British Pharmacopoeia |
| BW | Body Weight |
| CAT | Committee For Advanced Therapies |
| CCI | Commercially Confidential Information |
| CDC | Complement Dependent Cytotoxicity |
| CDR | Complementarity-Determining Region |
| CFU | Colony Forming Unit |
| CGE | Capillary Gel Electrophoresis |
| CHMP | Committee For Medicinal Products for Human Use |
| ChP | Chinese Pharmacopoeia |
| CI | Confidence Interval |
| CIC | Circulating Immune Complexes |
| cIEF | Capillary Isoelectric Focusing |
| CL | Clearance |
| CL/F | Apparent Clearance Following Extravascular Administration |
| CMAX | Maximum Concentration |
| CMH | Cochran–Mantel–Haenszel |
| COMP | Committee for Orphan Medicinal Products |
| COMSA | Core Outcome Measures Sets for Severe Asthma |
| COVID-19 | CoronaVirus Disease 2019 |
| CPP | Critical Process Parameter |
| CP | Control Point (Process Controls) |
| CQA | Critical Quality Attribute |
| CRO | Clinical Research Organisation |
| CRS | Chronic Rhinosinusitis |
| CRSwNP | Chronic Rhinosinusitis with Nasal Polyps |
| CSR | Clinical Study Report |
| CT | Computed Tomography |
| CTD | Common Technical Document |
| Cthrough | Concentration at through |
| CUB | Crude Unprocessed Bulk |
| CV | Coefficient Of Variation |
| DART | Developmental And Reproductive Toxicity |
| DNA | Deoxyribonucleic Acid |
| DP | Drug Product |

| | |
|---|---|
| DS | Drug Substance |
| EC50 | Concentration At Half-Maximal Effect |
| EC90 | Concentration At 90% Of Maximal Effect |
| ECG | Electrocardiogram |
| ECLIA | Electrochemiluminescence Immunoassay |
| ED | Emergency Department |
| ED50 | Dose At Half-Maximal Effect |
| EDTA | Disodium Edetate Dihydrate |
| EGFR | Estimated Glomerular Filtration Rate |
| ELISA | Enzyme-Linked Immunosorbent Assay |
| EMA | European Medicines Agency |
| EMAX | Maximum Effect |
| ENPS | Endoscopic Nasal Polyp Score |
| EPAR | European Public Assessment Report |
| EPCB | End-of-Production Cell Bank |
| ePPND | enhanced Pre- and Post-Natal Development study |
| EPR | Essential Performance Requirements |
| ercAEs | eosinophil-related cutaneous Adverse Events |
| ERS | European Respiratory Society |
| ESS | Endoscopic Sinus Surgery |
| EU | European Union |
| EU/mL | Endotoxin Units/Milliliter |
| EUBD | European Union Birth Date |
| EUFOREA | European Forum for Research and Education in Allergy and Airway Diseases |
| EURD | European Union Reference Dates |
| EVA | Ethyl Vinyl Acetate copolymer |
| FAS | Full Analysis Set |
| Fc | Fragment Crystallisable |
| FcRn | Neonatal Fc Receptor |
| FcγR | Fc Gamma Receptors |
| FEV1 | Forced Expiratory Volume In 1 Second |
| FDA | Food And Drug Administration |
| FP | Fluticasone Propionate |
| FP | Finished Product |
| Frel | Relative Bioavailability |
| FVC | Forced Vital Capacity |
| FSC-A | Forward Scatter Area |

| | |
|---|---|
| FP HFA | Fluticasone Propionate Hydrofluoroalkane |
| FTIH | First Time in Human |
| GCP | Good Clinical Practice |
| GINA | Global Initiative for Asthma |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| GM-CSF | Granulocyte-Macrophage Colony-Stimulating Factor |
| GSK | GlaxoSmithKline |
| HC | Heavy Chain |
| HCl | Hydrogen chloride |
| HCP | Host Cell Protein |
| HF | Human Factors |
| HLonset | Half-Life for drug on-/offset |
| HMW | High Molecular Weight |
| HR | Hazard Ratio |
| HRQoL | Health-Related Quality of Life |
| HV | Healthy Volunteers |
| IA | Interim Analysis |
| IBD | International Birth Date |
| IC50 | Half maximal Inhibitory Concentration (potency measure) |
| ICH | International Council for Harmonisation |
| ICE | Intercurrent Event(s) |
| ICS | Inhaled Corticosteroids |
| ID | Identification Number |
| IHC | Immunohistochemistry |
| IgE | Immunoglobulin E |
| IgG | Immunoglobulin G |
| IL | Interleukin |
| INCS | Intranasal Corticosteroids |
| INN | International Nonproprietary Name |
| IPC | In-Process Control |
| IRT | Interactive Response Technology |
| ISE | Integrated Summary Of Efficacy |
| ISO | International Organization for Standardization |
| ISR | Incurred Sample Reanalysis |
| IV | Intravenous |
| JP | Japanese Pharmacopoeia |

| | |
|---|---|
| KD | Dissociation Constant |
| kDA | Kilo Dalton |
| Kin | Zero-order Production Rate Constant |
| KinExA | Kinetic Exclusion Assay |
| KG | Kilogram |
| KPI | Key Performance Indicator |
| L | Liter |
| LABA | Long-Acting Beta Agonists |
| LAMA | Long-Acting Muscarinic Antagonists |
| LC | Light Chain |
| LIVCA | Limit Of In Vitro Cell Age |
| LMK CT | Lund–Mackay Computed Tomography |
| LLOQ | Lower Limit of Quantitation |
| LMW | Low Molecular Weight |
| LS | Least Squares |
| LT | Leukotriene |
| SD | Standard Deviation |
| mAb | Monoclonal Antibody |
| MAA | Marketing Authorisation Application |
| MAR | Missing At Random |
| MCB | Master Cell Bank |
| MDR | Medical Device Regulation |
| MG | Milligram |
| MIDD | Model-Informed Drug Development |
| ITT | Intent- To-Treat |
| ML | Milliliter |
| MMRM | Mixed Model Repeated Measures |
| MS | Milliseconds |
| MSX | L-Methionine Sulfoximine |
| N | Number |
| NA | Not applicable |
| NAb(s) | Neutralizing Antibodies |
| NAS | New Active Substance |
| NBOps | Notified Body Opinions |
| ng | Nanogram |
| NOAEL | No Observed Adverse Effect Level |
| nM | Nanomolar |

| | |
|---|---|
| NP | Nasal Polyp |
| NPS | Nasal Polyp Score |
| NTU | Nephlometric Turbidity Unit |
| OCS | Oral Corticosteroids |
| OLE | Open-Label Extension |
| OR | Odds Ratio |
| PACMP | Post-Approval Change Management Protocol |
| PAES | Post-Authorisation Efficacy Study |
| PAM-REC | Post Authorisation Measure Recommendation |
| PASS | Post-Authorisation Safety Study |
| PAR | Proven Acceptable Range |
| PBPK | Physiologically Based Pharmacokinetics |
| PBRER | Periodic Benefit Risk Evaluation Report |
| PC20 | Provocative Concentration producing 20% fall in FEV1 |
| PD20 | Provocative Dose producing 20% fall in FEV1 |
| PD | Pharmacodynamics |
| PDs | Protocol Deviations |
| PDCO | Paediatric Committee |
| PDE | Permitted Daily Exposure |
| PEF | Peak Expiratory Flow |
| PFS | Pre-Filled Syringe |
| pg | Picogram |
| Ph. Eur. | European Pharmacopoeia |
| PI | Product Information |
| PK | Pharmacokinetics |
| PKPD | Pharmacokinetics- Pharmacodynamics |
| PL | Package Leaflet |
| pM | Picomolar |
| PopPK | Population Pharmacokinetics |
| PP | Process Parameter |
| PPD | Protected Personal Data |
| PPQ | Process Performance Qualification |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PRIME | PRIority MEdicine |
| PRS | Primary Reference Standard |
| PS80 | Polysorbate 80 |
| Pslp | Slope for Placebo Effect |

| | |
|---|---|
| PSUR | Periodic Safety Update Report |
| PT | Preferred Term |
| Q26W | Administration every 26 weeks |
| Q4M | Administration every 4 months |
| Q5M | Administration every 5 months |
| Q6M | Administration every 6 months |
| QWP | Quality Working Party |
| QC | Quality Control |
| qPCR | Quantitative Polymerase Chain Reaction |
| QTcF | QT Interval Corrected by Fridericia's Formula |
| QS | Quantum sufficit (the amount which is needed) |
| R-CGE | Reduced Capillary Gel Electrophoresis |
| RCT | Randomised Controlled Trial |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| RS | Reference Standard |
| RSD | Relative Standard Deviation |
| RR | Rate Ratio |
| RT | Room Temperature |
| SABA | Short-Acting Beta Agonists |
| SAMA | Short-Acting Muscarinic Antagonists |
| SAE | Serious Adverse Event |
| SAG | Scientific Advisory Group |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SCF | Stem Cell Factor |
| SCS | Systemic Corticosteroids |
| SD | Standard Deviation |
| SEC | Size Exclusion Chromatography |
| SGRQ | St. George's Respiratory Questionnaire |
| SmPC | Summary Of Product Characteristics |
| SNOT-22 | Sino-Nasal Outcome Test (22 Items) |
| SOC | System Organ Class |
| SoC | Standard of Care |
| SoE | Strength of Evidence |
| SPR | Surface Plasmon Resonance |
| SSD | Safety Syringe Device |

| | |
|---|---|
| T1/2 | Half-Life |
| TAMC | Total Aerobic Microbial Count |
| Th2 or T2 | Type 2 |
| Tmax | Time to Maximum concentration |
| TOCS | Time Out of Cold Storage |
| TPA | Tipping Point Analysis |
| TSE | Transmissible Spongiform Encephalopathy |
| TSLP | Thymic Stromal Lymphopoietin |
| TYMC | Total Yeast and Molds Count |
| µL | Microliter |
| µM | Micromolar |
| UF/DF | Ultrafiltration/Diafiltration |
| ULN | Upper Normal Limits |
| ULOQ | Upper Limits Of Quantification |
| UNC | Uncertainties |
| UPB | Unprocessed Bulk |
| US | United States |
| USP | United States Pharmacopoeia |
| USP-NF | United States National Formulary |
| UV/VIS | Ultraviolet/Visible |
| V | Volume |
| VCC | Viable Cell Concentration |
| VCV | Viral Clearance Validation |
| VLP | Virus-Like Particle |
| VPC | Visual Predictive Check |
| VRS | Verbal Response Scale |
| Vz/F | Apparent Volume of Distribution |
| WCB | Working Cell Bank |
| WFI | Water for Injection |
| WoE | Weight of Evidence |
| WRS | Working Reference Standard |
| XMuLV | Xenotropic Murine Leukaemia Virus |
| YTE | Fc region Modification Extending Half-Life |

# 1. Executive Summary

On 11 December 2025, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the granting of a marketing authorisation for the medicinal product Exdensur (depemokimab) intended for severe asthma with type 2 inflammation characterised by blood eosinophil count and for severe chronic rhinosinusitis with nasal polyps (CRSwNP).

Exdensur will be available as a 100mg solution for injection in pre-filled pen and in syringe, for subcutaneous administration.

Exdensur targets human IL-5 with a high binding affinity of 10.5 pM, thereby blocking the binding to the IL-5 receptor alpha expressed on the cell surface with picomolar potency (IC50 4 pM) in vitro. Depemokimab contains a triple amino acid substitution (YTE) in the fragment crystallisable (Fc) region which increases binding to the neonatal Fc receptor and thereby extends the half-life when compared to the IgG1 wildtype.

In severe asthma, inhibition of IL-5 has demonstrated an improvement in epithelial integrity, mucus plugging and reduction in tissue remodelling. However, the mechanism of action has not been definitively established.

The full indications for Exdensur are:

Asthma

Exdensur is indicated as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by blood eosinophil count in adults and adolescents 12 years and older who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another asthma controller (see section 5.1).

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Exdensur is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

Exdensur should be prescribed by a physicians experienced in the in the diagnosis and treatment of asthma or CRSwNP.

Asthma

The main evidence of efficacy of Exdensur in severe asthma is based on two replicate Phase III clinical studies (SWIFT-1 and SWIFT-2). The studies were conducted in patients aged 12 years and older with uncontrolled severe asthma with an eosinophilic phenotype (defined by elevated blood eosinophil count) despite treatment with inhaled corticosteroids and an additional controller medication. The two studies met their primary endpoint by showing superiority of 100 mg depemokimab over placebo (both in addition to standard of care) in the annualised rate of clinically significant exacerbations.

CRSwNP

The main evidence of efficacy of Exdensur in CRSwNP is based on two replicate Phase III studies (ANCHOR-1 and ANCHOR-2). The studies were conducted in patients with symptomatic and severe CRSwNP whose disease was not controlled despite the use of intra-nasal corticosteroids and who had prior treatment with systemic corticosteroid within the past 2 years, and/or had a documented history of prior surgery for CRSwNP or had contra-indications for these treatments. The two studies met their co-primary endpoints by showing superiority of 100 mg depemokimab over placebo (both in addition to standard of care) in the

endoscopic nasal polyps score and nasal obstruction verbal rating score. The pooled analyses showed a numerical delay in the time to first nasal surgery (actual or on waiting list) and need for initiation of other maintenance treatments impacting type 2 inflammation.

The pooled analyses showed a numerical delay in the time to the first nasal surgery (actual or on waiting list) and need for initiation of other maintenances treatment impacting type 2 inflammation (including biologicals indicted for CRSwNP) with a hazard ratio (HR) of 0.735 (95% CI 0.495, 1.092).

The most relevant safety concern was use in pregnant patients (information is missing) and the most commonly reported adverse reaction was local injection site reactions (2%).

Detailed recommendations for the use of this product are described in the summary of product characteristics (SmPC), which will be published on the EMA website in all official European Union languages after the marketing authorisation has been granted by the European Commission.

This report summarises the scientific review leading to the opinion adopted by the CHMP.

# 2. Administrative/regulatory information and recommendations on the procedure

## *2.1. Information on the product*

| ***Product data*** | |
|---|---|
| Product name | Exdensur |
| Active substance | Depemokimab |
| INN or common name | Depemokimab |
| Applicant | Glaxosmithkline Trading Services Limited<br>12 Riverwalk<br>Citywest Business Campus<br>Dublin 24<br>D24 YK11<br>IRELAND |
| EMA Product Number | EMEA/H/C/006446 |
| ATC code and Pharmacotherapeutic group | R03DX12 |
| Pharmaceutical form(s) and strength (s) | Solution for injection<br>100 mg |
| Packaging | pre-filled syringe (glass) and pre-filled syringe (glass) in pre-filled pen |
| Package size(s) | 1 pre-filled pen and 1 pre-filled syringe |
| Route of administration | Subcutaneous use |
| Device or diagnostic | Integral device, Class IIa |

| Product data | |
|---|---|
| Orphan designation | N |
| Orphan indication status confirmed | Not applicable |
| PRIME scheme | Not applied for |
| Type of marketing authorisation granted at opinion | Standard |
| Legal basis | Article 8.3 of Directive 2001/83/EC |
| Final indication | Asthma<br><br>Exdensur is indicated as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by blood eosinophil count in adults and adolescents 12 years and older who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another asthma controller (see section 5.1).<br><br>Chronic rhinosinusitis with nasal polyps (CRSwNP)<br><br>Exdensur is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. |
| New active substance status | Granted |

## 2.2. Scientific advice

**Table 1: Scientific advice and protocol assistance**

| Date | Topic (quality/ non-clinical/ clinical) | Reference number |
|---|---|---|
| 26 March 2020 | Quality<br>Non-clinical<br>Clinical | EMEA/H/SA/4383/1/2019/III |
| 24 June 2021 | Non-clinical<br>Clinical | EMA/SA/0000059022 |
| 11 November 2021 | Quality | EMA/SA/0000069405 |
| 14 September 2023 | Quality | EMA/SA/0000141798 |
| 22 February 2024 | Clinical | EMA/SA/0000158669 |

The applicant received Scientific Advice on the development of depemokimab (GSK3511294) as add-on treatment for severe asthmatics with an eosinophilic phenotype from the CHMP on 26 March 2020 (EMEA/H/SA/4383/1/2019/III). The Scientific Advice pertained to the following quality, non-clinical, and

clinical aspects:

- Acceptability of the overall non-clinical development plan, including not performing a monkey juvenile toxicity study for dosing of adolescent participants in clinical trials and that an enhanced pre- and postnatal development study is not warranted.
- Design of a single, 52-week, randomised, double-blind, placebo-controlled, study of the efficacy (reduction in exacerbations and additional markers of asthma control) and safety of GSK3511294 100 mg SC adjunctive therapy administered every 26 weeks in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype (n=525, p-value <0.01), including acceptability to progress from a single ascending dose first time in human study in eosinophilic mild-to-moderate asthmatics to the proposed Phase 3 clinical programme, dose regimen and statistical analyses. During the procedure the clinical development plan was revised to include two replicate 52-week studies as described above (each study to include approximately n= 375 [2:1 randomised GSK3511294:placebo] and p-value <0.05).
- Design of a 52-week non-inferiority switch study assessing exacerbation rate, additional markers of asthma control and safety in adult and adolescent participants switched to GSK3511294 100 mg SC given at 26-week intervals compared with continuation of mepolizumab 100 mg SC every 4 weeks or benralizumab 30 mg SC every 8 weeks, including non-inferiority margins and statistical analyses.
- Acceptability of proposed anti-drug antibody and neutralising antibody assay development approach, proposed data to support the device strategy, and plan to apply for a partial waiver for GSK3511294 in paediatrics below 12 years.

The applicant received Scientific Advice on the development of depemokimab for the treatment of chronic rhinosinusitis with nasal polyps from the CHMP on 24 June 2021 (EMA/SA/0000059022). The Scientific Advice pertained to the following non-clinical and clinical aspects:

a. Adequacy of the non-clinical safety programme for the proposed clinical development programme.
b. Progression from the first time in human study to the proposed Phase 3 clinical programme.
c. Rationale for Phase 3 study dose selection; Phase 3 study design including target population, duration of treatment, use of placebo, and estimand strategy for primary and secondary endpoints; size of safety database; adequacy of a single pivotal study to support a marketing authorization in the proposed indication.

The applicant received Scientific Advice on the development of depemokimab for the treatment of severe eosinophilic asthma from the CHMP on 11/11/2021 (EMA/SA/0000069405). The Scientific Advice pertained to the following quality aspects:

- The strategy for developing the commercial specifications for depemokimab drug substance and drug product; approach to use prior knowledge and platform validation in support of analytical methods for a marketing authorization application; introduction of a new like-for-like syringe with improved manufacturing controls in both the safety syringe device and autoinjector and the need for a further clinical study to support registration; approach to file for a changed process for drug substance manufacturing in the marketing authorization application submission, which may be prior to obtaining clinical data from that material use.

The applicant received Scientific Advice on the development of depemokimab for the treatment of eosinophilic asthma from the CHMP on 14/09/2023 (EMA/SA/0000141798). The Scientific Advice pertained

to the following quality aspects:

- Finished product release and stability specifications; risk-based approach for identifying essential performance requirements (EPRs) and list of identified EPRs for the depemokimab safety syringe device and autoinjector; container closure integrity and device functionality tests for depemokimab safety syringe device and autoinjector; comparability strategy to assess the impact of the changes in the drug substance and drug product manufacturing processes on product quality and process robustness.

The applicant received Scientific Advice on the development of depemokimab for the treatment of asthma with an eosinophilic phenotype and chronic rhinosinusitis with nasal polyps from the CHMP on 22/02/2024 (EMA/SA/0000158669). The Scientific Advice pertained to the following clinical aspects:

- Sufficiency of the clinical pharmacology development package, including information generated to support selection of dose level/regimen, need for dose adjustments and exposure/QTc analysis strategy to mitigate arrhythmogenic liability; acceptability of the safety interim analysis (including associated blinding strategy to support study integrity) for Phase 3 and overall size of the clinical safety database (and associated analysis) for a marketing authorization application in the intended indications; adequacy of the integrated efficacy analysis strategy for Phase 3, including choice of efficacy endpoints, their applicability to study subgroups and associated statistical analyses; acceptability of the clinical development package, including partial extrapolation, to assess benefit-risk in the intended indications.

## *2.3. Eligibility to the centralised procedure*

The applicant Glaxosmithkline Trading Services Limited submitted on 18 December 2024 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Exdensur (depemokimab), through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 October 2023.

The applicant applied for the following indications:

Asthma

*Exdensur is indicated as an add-on maintenance treatment of asthma in adult and adolescent patients aged 12 years and older with type 2 inflammation characterised by an eosinophilic phenotype who are inadequately controlled on medium- to high-dose inhaled corticosteroids (ICS) plus another asthma controller.*

Chronic rhinosinusitis with nasal polyps (CRSwNP)

*Exdensur is indicated as an add-on treatment of adult patients with inadequately controlled CRSwNP.*

## *2.4. Legal basis and dossier content*

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and

clinical data based on applicants' own tests and studies.

## 2.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decisions on the granting of product-specific waivers, P/0396/2020 for treatment of asthma and P/0417/2021 for treatment of nasal polyposis.

## 2.6. Information on orphan market exclusivity

### 2.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## 2.7. Applicant's request(s) for consideration

### 2.7.1. New active substance status

The applicant requested the active substance depemokimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

### 2.7.2. CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CHMP considers that depemokimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

## 2.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

| | |
|---|---|
| ***Rapporteur:*** | Peter Mol |
| ***Co-Rapporteur:*** | Petr Vrbata |

The Rapporteur and Co-Rapporteur appointed by the PRAC were:

| | |
|---|---|
| ***PRAC Rapporteur:*** | Gabriele Maurer |
| ***PRAC Co-Rapporteur:*** | Bianca Mulder |

| | |
|---|---|
| The application was received by the EMA on | 18 December 2024 |

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|---|---|
| The procedure started on | 23 January 2025 |
| The CHMP Rapporteur's first Assessment Report was received on | 14 April 2025 |
| The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on | 16 April 2025 |
| The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on | 28 April 2025 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 22 May 2025 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 13 August 2025 |
| The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on | 22 September 2025 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 02 October 2025 |
| A GCP inspection at one clinical site in Japan, one clinical site in Romania and one at the Sponsor site in UK, between 11 June and 05 Sep 2025. The outcome of the inspection carried out was issued on 06 Oct 2025. | 06 October 2025 |
| The CHMP agreed on a list of outstanding issues to be sent to the applicant on | 16 October 2025 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 10 November 2025 |
| The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on | 26 November 2025 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Exdensur on | 11 December 2025 |
| Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS) | 11 December 2025 |

## *2.9. Final CHMP outcome*

### 2.9.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 2.5 of this report.

### 2.9.2. Final opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Exdensur is favourable in the following indications:

Asthma

Exdensur is indicated as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by blood eosinophil count in adults and adolescents 12 years and older who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another asthma controller (see section 5.1).

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Exdensur is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

## 2.9.3. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

## 2.9.4. Other conditions and requirements of the marketing authorisation

### *2.9.4.1. Periodic safety update reports*

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European Medicines Agency web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

## 2.9.5. Conditions or restrictions with regard to the safe and effective use of the medicinal product

### *2.9.5.1. Risk management plan (RMP)*

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

### 2.9.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

### 2.9.7. Proposed list of recommendations

**Table 2: Proposed list of recommendations**

| *Description of Recommendations* |
|---|
| • The applicant should provide results of leachable study at the end of the shelf-life to support the final conclusion on leachable characterization. The results of leachable studies will be submitted before the end of 2026. |
| • The applicant should systematically trend potency results of routine batches to evaluate whether batches test systematically at 100%, or well below this value, due to the assigned value of the current primary reference standard. The results of this trending (at least the first 30 batches) should be provided. The collected trending data will be submitted after the release of the last batch tested with the current primary reference standard or after 30 batches have been tested, whichever comes sooner. |
| • Final safety results of the active controlled study NIMBLE in asthma will be presented in the full CSR. The full CSR shall be submitted by end of April 2026. |

# 3. Introduction

## *3.1. Therapeutic Context*

### *Asthma*

Asthma is a chronic heterogeneous lung disease characterised by inflammation, airway hyperresponsiveness and variable airflow obstruction. Symptoms vary over time and in intensity and can include wheezing, shortness of breath, chest tightness, and cough. Despite optimal guideline-directed treatment, patients with asthma can experience exacerbations caused by an accentuation of existing inflammatory processes and a loss of disease control. Repeat exacerbations have been associated with lung function decline and can lead to hospitalisation and potentially death.

Many patients with asthma can be adequately controlled with standard medical care, including inhaled corticosteroids (ICS), short-acting and long-acting beta agonists (SABA, LABA), short-acting and long-acting muscarinic antagonists (SAMA, LAMA), and leukotriene antagonists. Exacerbations usually necessitate short-term treatment with systemic corticosteroids (CS), for which repeated use has been associated with increased risk of infections, hyperglycaemia, metabolic syndrome, osteoporosis, and ocular abnormalities.

Type 2 inflammation is the underlying pathology for more than 80% of people with severe asthma and is driven by Th2 and ILC2 cells, which both produce IL-5. Uncontrolled eosinophilic inflammation, reflective of

IL-5 driven disease, is a recognised risk factor for severe disease exacerbations, airway remodelling and lung function decline in asthma.

Asthma guidelines recommend add-on targeted therapy with biologics for asthmatic patients who have evidence of type 2 inflammation and frequent exacerbations and/or poor symptom control, despite treatment with optimised ICS-LABA. Three biologicals targeting IL-5 or its receptor (mepolizumab, reslizumab, and benralizumab) have been shown to reduce exacerbations in asthma patients with type 2 inflammation characterised by increased eosinophils and are approved globally for the treatment of severe asthma with an eosinophilic phenotype, administered as an add-on treatment once every 4 to 8 weeks.

While these therapies, and those targeting other pathways (such as dupilumab and tezepelumab), have been shown to decrease exacerbations, reduce the requirement for systemic CS, and enhance patient outcomes, a lack of adherence to the indicated dosing schedules (SC or IV administration every 2 to 8 weeks) can impact these endpoints. In general, biologics with shorter dosing intervals have worse adherence and there is a need for treatments that have a favourable benefit-risk profile with a prolonged dosing interval in this patient population.

### *CRSwNP*

CRSwNP is a chronic inflammatory disease of the nasal passage linings and/or sinuses leading to soft tissue growth in the upper nasal cavity. The resultant swellings, which can grow in both nostrils (bilateral), greatly impact a patient's health-related quality of life (HRQoL) due to nasal obstruction, loss of smell and/or taste, rhinorrhoea (runny nose) and/or postnasal drip. The symptoms can be of varying severity.

Many patients with CRSwNP can be adequately controlled with standard medical care (intranasal corticosteroids (INCS), occasional nasal douching, and antibiotic courses). For severe symptoms, intermittent courses of oral corticosteroids can be supplied when short term relief is required.

Although systemic CS reduce the inflammatory response and might temporarily reduce NP size and improve symptoms, their use is associated with adverse effects. Surgery to remove the NP tissue may also be indicated for severe cases of CRSwNP, i.e., ''bilateral CRSwNP with a nasal polyp score (NPS) of at least 4 of 8 points and persistent symptoms, including loss of smell and/or taste, nasal obstruction, secretion and/or postnasal drip, and facial pain or pressure, with the need for add-on treatment to supplement intranasal corticosteroids''.[1]

Surgery involves the removal of the NP tissue and diseased nasal mucosa, restoring aeration of the nasal passage and sinuses. Surgery is associated with high recurrence rates, and scarring or mucosal damage, or both.

Type 2 inflammation has been reported as the underlying pathology in more than 80% of people with inadequately controlled CRSwNP. Patients with CRSwNP associated with tissue eosinophilia constitute the majority of those who have a recurrence after surgery. Hence alternative treatment options are needed for this patient group that can reduce NP size and nasal obstruction, reduce the need for nasal surgery and systemic CS use, and improve sino-nasal symptoms and HRQoL.

Three mAbs, i.e. biologicals, are approved globally for the treatment of adult patients with CRSwNP in

[1] Bachert C, Han JK, Wagenmann M et al. EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: Definitions and management. Allergy Clin Immunol 2021;147:29-36. https://doi.org/10.1016/j.jaci.2020.11.013

addition to SoC when administered once every 2 to 4 weeks: mepolizumab (an IL-5 inhibitor), dupilumab (an IL-4/IL-13 inhibitor), and omalizumab (an IgE inhibitor). These products have been approved as add on treatment with intra-nasal corticosteroids for adults with severe, uncontrolled CRSwNP, usually after failure of oral corticosteroids or surgery.

While these biologics reduce the need for systemic CS and surgery, and improve patient outcomes, difficulties in adhering to the dosing schedule or maintaining long-term treatment persistence could potentially negatively impact these benefits.
Products with a prolonged dosing interval may improve patient's conveniences and might theoretically be associated with improved adherence.

## *3.2. Aspects of development*

As an anti-IL-5 therapy and long-acting subcutaneous (SC) injectable, depemokimab has been designed to deliver an efficacy and safety profile similar to current anti-IL-5/IL-5R mAbs but with a reduced dosing frequency (once every 6 months as compared with existing therapies administered every 4 or 8 weeks) due to its longer half-life and high potency. An anti-IL5 antibody targeting the same epitope as mepolizumab (Nucala) but with an extended duration of action, 7 amino acid (aa) changes to mepolizumab but with safety and efficacy expected to be similar.

Depemokimab has been evaluated in a program of clinical studies for the treatment of asthma and CRSwNP, both chronic airway diseases driven by type 2 inflammation. The clinical development program for asthma and CRSwNP comprises 9 clinical studies (3 Phase 1 studies and 6 Phase 3 studies):

- Phase 1 studies conducted in adult participants with mild to moderate asthma and blood eosinophil count ≥200 cells/µL (First Time in Human (FTIH) study; 205722), healthy adult participants (214099), or healthy Chinese adult participants (208021).

By applying MIDD for dose regimen selection from the FTIH study data and building on precedented safety of anti-IL-5/R therapies, it was decided to transition depemokimab directly from Phase 1 to confirmatory Phase 3 studies.

- Phase 3 asthma studies:
    - Two completed replicate 52-week placebo-controlled pivotal Phase 3 studies evaluating the efficacy and safety of depemokimab 100 mg SC once every 26 weeks in adult and adolescent participants with asthma with type 2 inflammation characterised by an eosinophilic phenotype (SWIFT-1 [206713] and SWIFT-2 [213744]).
    - A completed open-label long-term Phase 3 study that enabled participants who completed SWIFT-1 and SWIFT-2 to receive depemokimab 100 mg SC once every 26 weeks for a further 52 weeks (AGILE [212895]).
    - An on-going non-inferiority Phase 3 study evaluating the efficacy and safety depemokimab 100 mg SC once every 26 weeks in adult and adolescent severe asthmatic participants with an eosinophilic phenotype compared with continuing treatment with mepolizumab or benralizumab (NIMBLE [206785]). Note a summary of key results is included in this submission.

- Phase 3 CRSwNP studies:
    - Two completed replicate 52-week placebo-controlled pivotal Phase 3 studies evaluating the efficacy and safety of depemokimab 100 mg SC once every 26 weeks in adults with inadequately controlled CRSwNP (ANCHOR-1 [217095] and ANCHOR-2 [218079]).

## *3.3. Description of the product*

Depemokimab is a new biological entity that targets human IL-5, thereby blocking the binding to the IL-5 receptor alpha expressed on the cell surface with picomolar potency (IC50 4 pM) *in vitro*. Depemokimab contains a triple amino acid substitution (YTE) in the fragment crystallisable (Fc) region which increases binding to the neonatal Fc receptor and thereby extends the half-life.

The originally proposed indications were:

*Asthma*

*Exdensur is indicated as an add-on maintenance treatment of asthma in adult and adolescent patients aged 12 years and older with type 2 inflammation characterised by an eosinophilic phenotype who are inadequately controlled on medium- to high-dose inhaled corticosteroids (ICS) plus another asthma controller.*

*Chronic rhinosinusitis with nasal polyps (CRSwNP)*

*Exdensur is indicated as an add-on treatment of adult patients with inadequately controlled CRSwNP.*

*The proposed posology (both indications) was:*

*The recommended dose of depemokimab is 100 mg administered subcutaneously once every 6 months for adults (both indications) and adolescents (only asthma indication).*

The final approved indications are:

*Asthma*

*Exdensur is indicated as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by blood eosinophil count in adults and adolescents 12 years and older who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another asthma controller (see section 5.1).*

The final posology for adults and adolescents aged 12 years and over is:

*The recommended dose of depemokimab is 100 mg administered subcutaneously once every 6 months.*

*Chronic rhinosinusitis with nasal polyps (CRSwNP)*

*Exdensur is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.*

The final posologyis:

*The recommended dose of depemokimab is 100 mg administered subcutaneously once every 6 months.*

## *3.4. Inspection issues*

### 3.4.1. GMP inspection(s)

No inspection was required. Sufficient information on EU-GMP compliance has been provided for all sites.

### 3.4.2. GLP inspection(s)

No inspection was required.

### 3.4.3. GCP inspection(s)

A routine GCP inspection was conducted for two clinical sites, and a sponsor inspection was completed for study 218079 (ANCHOR-2).

No critical findings were detected during the investigator and sponsor inspections.

Investigators site findings were site specific and did not impact the validity of the data.
Regarding the sponsor inspection, major findings have been identified on the data quality, sponsor management of the trial, protocol deviation process, safety reporting and clinical study report. The corrective and/or preventive action performed were considered adequate. The inspection team concluded that the data may be used to support the Marketing Authorisation Application submitted to the EMA for Exdensur and this was supported by CHMP.

# 4. Quality aspects

## *4.1. Introduction*

The finished product (FP) is presented as a solution for injection containing 100 mg of depemokimab as active substance (AS) in 1 mL solution.

Other ingredients are histidine, histidine monohydrochloride, trehalose dihydrate, arginine hydrochloride, disodium edetate, polysorbate 80 (E 433), and water for injections.

The product is available in a pre-filled Type I glass syringe with a fixed needle (stainless steel) and passive safety needle guard (safety syringe device, SSD), or pre-filled Type I glass syringe with a fixed (stainless steel) in a prefilled pen (auto-injector, AI).

## *4.2. Active substance*

### 4.2.1. General information

Depemokimab is a recombinant glycosylated humanised IgG1κ monoclonal antibody specific for human interleukin-5 (IL-5). The predicted amino acid sequences of the mature heavy and light chains are provided.

The antibody consists of two kappa light chains (LC) and two IgG1 heavy chains (HC) with a total of 1338 amino acids. The heavy chains are connected to each other by two interchain disulfide bonds, and a light chain is attached to a heavy chain by a single interchain disulfide bond. Each light chain has two intrachain disulfide bonds, and each heavy chain has four intrachain disulfide bonds. The antibody is N linked glycosylated on each heavy chain at asparagine (N299) with fucosylated bi-antennary structures with varying amounts of terminal galactose and low levels of high mannose, afucosylated, and sialic acid species. The total estimated molecular mass of 149 kDa for depemokimab.

Depemokimab binds to circulating human IL5 with high affinity and specificity thus blocking the interaction between IL5 and the alpha chain of the IL5 receptor complex that is highly expressed on the eosinophil cell surface.

In addition, three amino acids substitutions, M252Y/S254T/T256E (termed 'YTE'), were introduced into the constant region to increase affinity for the neonatal Fc receptor (FcRn), which is responsible for antibody recycling to the interstitial fluid following cellular internalization, resulting in extended *in vivo* half-life.

### 4.2.2. Manufacture, characterisation, and process controls

The following facilities are responsible for the manufacture, testing and release of depemokimab. Sufficient information on EU-GMP compliance has been provided for all sites involved in the manufacturing and testing of depemokimab active substance.

Description of manufacturing process and process controls

The depemokimab active substance manufacturing process has been adequately described. The manufacturing process is straightforward and common for a recombinant DNA technology based monoclonal antibody production system. Main steps are cell culture, expression of antibody, harvesting, antibody capture, virus inactivation, purification, and AS filling in storage containers. The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step.

Overviews of the control strategy for the manufacturing process, including process parameters and in-process controls (IPCs), are provided for the upstream and downstream processes.

The manufacturing process starts from a WCB vial followed by serial cell culture expansion in shake flasks, rocking motion bags and seed bioreactors. Seed bioreactor cultures are used to inoculate the production bioreactor. The total culture duration from MCB thaw to the end of the production bioreactor culture is monitored to ensure that the validated limit of in vitro cell age (LIVCA) is not exceeded. The material from the production bioreactor is harvested in a continuous manner and cells and cell debris are removed.

The purification process involves seven steps, including protein A chromatography, low pH virus inactivation (pH: 3.30-3.60), anion exchange chromatography, virus filtration, ultrafiltration/diafiltration and final filtration, followed by freezing, storage and shipping.

Reprocessing for either Virus Filtration or Final Filtration steps can be executed in the event of a filter integrity test failure or other operational deviations not associated with excursions from microbial control action limits. Protocols are in place defining the acceptance criteria for reprocessing operations during commercial manufacturing. Reprocessing through either unit operation can only occur one time for each AS batch.

Hold times for process intermediates applied in the AS manufacturing process are provided and are based on biochemical and microbiological stability validation data (shortest hold time is used for the maximum in-process hold time).

Overall, the manufacturing process for AS has been clearly defined and the purpose of each manufacturing process step has been discussed in sufficient detail. The overall manufacturing process has been outlined in high-level flow-diagrams and tables with process parameters and applied in-process controls are provided for each manufacturing step. Sufficient justification about seed maintenance steps, process parameters, media/buffer composition, non-sterilising filters and batch size is provided.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

Media and feed solutions are prepared according to specific standard operating procedures and are released for use according to the specifications. Sufficient information on the quality oversight of the media is provided.

Sufficiently detailed information is provided on the starting materials. Depemokimab is similar to mepolizumab, another IL-5-binding monoclonal antibody developed by GSK. In order to enhance the serum half-life of the antibody, the "YTE" substitutions (M254Y/S256T/T258E) were introduced into the heavy chain constant region for improved neonatal Fc receptor (FcRn) binding. Finally, the entire light chain expression cassette and the entire heavy chain expression cassette were subcloned into the expression vector. The functions and locations of all genetic components of the depemokimab expression vector are provided. The expression vector was sequenced and confirmed. The nucleotide and corresponding amino acid sequences of HC and LC coding regions are provided.

The production cell line is of CHO origin. The generation of the expression vector and the initial cell clone, from which the cell banks used for AS manufacturing are derived are described in sufficient detail. The cells were adapted to culture in a defined medium. Clonality of the initial cell clone is ensured.

The cell bank system is two-tiered, consisting of a MCB and WCB. The manufacturing and characterization of the cell banks are sufficiently described. The media used in the manufacture of the MCB and WCB are chemically defined, protein free and all materials are animal origin free. Cell banks were characterised in line with ICH Q5A, ICH Q5B and ICH Q5D guidelines. These include examination of identity, purity, safety, and genetic characterization. The cell bank was manufactured in accordance with current Good Manufacturing Practices (cGMP). Current stock/number of MCB/WCB vials and storage location are indicated. The MCB and WCB are considered suitable for use in the manufacture of AS.

Sufficient information related to future WCBs (preparation and testing) is provided. The qualification protocol is provided, outlining the data and analysis required to assess replacement WCB performance at scale including cell growth performance from vial thaw through production bioreactor, AS release testing and AS stability testing.

Genetic stability of the cells was determined for end of production cell bank (EPCB) at limit of in vitro cell age (LIVCA). The total cultivation duration from MCB to harvest is considered sufficiently justified.

Taken together, it is considered that the cell banks have been sufficiently characterised and free of microbial and viral contaminants, and the stability of the cell line has been confirmed for EPCB at LIVCA in line with current guidance. Sufficient information related to the oversight/control of fermentation medium composition and the adequacy of stability monitoring of future WCBs is provided.

Control of critical steps

An overview of critical in-process controls and critical in-process tests performed throughout the AS manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the AS manufacturing process with regard to critical, as well as non-critical parameters and in-process tests. The overall strategy for actions taken when PPs (process parameter), CPPs (critical process parameter) or critical IPCs (in-process control) limits are exceeded is adequately defined in the dossier.

Information is provided on tests and acceptance criteria performed at critical steps. CPPs and PPS are in line with process evaluation and virus validation studies. In general, the presented process controls for AS manufacturing are appropriate. Sufficient justification regarding UF/DF, specifically the impact of the Gibbs-Donnan effect is provided. See additional comments below on control strategy.

An overview of the microbial control strategy, including in-process bioburden and endotoxin testing, is also provided. In-process bioburden and endotoxin testing are conducted in parallel to manufacturing. The in-process bioburden and endotoxin test results are required for batch release. However, results are not required to progress to the next stage within the AS manufacturing process. This is considered acceptable.

Process validation and/or validation

The AS manufacturing process has been validated adequately. Consistency in production has been shown on three full-scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces AS of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Extensive information has been provided about the process validation and evaluation, which has followed a three-stage approach comprising process design including comprehensive process characterisation, process performance qualification and continued process verification.

The level of detail provided for the process design and process characterizations studies is comparable to the level of detail provided for similar products/manufacturing processes (i.e., a recombinant DNA technology based monoclonal antibody production system).

Critical Quality Attributes (CQAs) for depemokimab were defined based on relationships of product attributes and characteristics with drug safety and efficacy, on structure-function studies, and on knowledge gained from clinical and pre-clinical studies. A series of process risk assessments were performed that considered the CQAs and available process development and clinical manufacturing data, and used the information to identify the parameters and attributes that should be investigated during process characterization studies.

A tiered evaluation approach for the process characterisation studies was followed in which the impact of varying parameters within the studied ranges on quality manufacturing attributes was evaluated.

Small-scale models were developed and qualified where appropriate and were used to execute the process characterization studies. Justification is provided related to the qualification of the small-scale models of the seeding bioreactors. In addition, small scale studies have been used for virus clearance studies related to viral inactivation/clearance steps. The cumulative process knowledge gained from process development and process characterization studies, were leveraged to determine acceptance criteria prior to executing the PPQ (process performance qualification). Although the applicant mentions design space and has performed univariate and multivariate interactions studies to support process parameter ranges, no design space is claimed. Taken together, the process design and process characterisation studies are considered sufficiently addressed.

The AS process performance qualification was performed at the commercial scale using three consecutive batches. Acceptance criteria defined in the PPQ protocol were based on the cumulative process knowledge gained during development, commercial-scale production experience, proven acceptable ranges (PARs) established during process characterization, and the AS release specifications.. Consistent results were achieved during the culture and harvest stages. All PPQ acceptance criteria were met. Minor deviations were investigated and did not impact the product quality attributes or PPQ acceptance criteria. Taken together, the PPQ studies demonstrate that the manufacturing process is able to consistently manufacture AS that meets specifications.

The purification process was evaluated to determine its ability to reduce the level of process-related impurities using eight representative batches. The results for all process-related impurities were consistently below the safe limits, and the clearance of the tested impurities is considered controlled throughout the purification process.

Small-scale models were qualified for resin lifetime evaluation. In addition, at-scale verification over one full lifecycle of each chromatography resin is currently progressing under a validation protocol, with interim results being reported. Validation of the lifetime for the UFDF membrane is planned for concurrent execution under a validation protocol. The protocol for the at scale validation of membrane lifetime is provided.

Seven in-process pool holds have been identified in the manufacturing process of AS. Biochemical and microbial hold studies were performed to determine the maximum acceptable hold time. The maximum allowed hold times during manufacturing were set based on the shortest established maximum hold time of either the biochemical stability or microbial control study for each in process pool.

Reprocessing is allowed once in AS manufacturing process for either Virus Filtration, or Final Filtration in the event of a filter integrity test failure. Small-scale process validation studies were performed, and the results indicated no impact on product quality. All data met the protocol acceptance criteria. It is indicated that the results of the small-scale reprocessing validation will be validated at commercial scale at the first occurrence of each type of reprocessing.

The shipping validation studies for AS have been completed and are presented in sufficient detail. The insulated temperature-controlled shipping container is validated to of maintain the temperature for the anticipated shipment duration.

As part of continued process verification approach, process parameters and product quality attributes will be monitored, evaluated for trending, and reviewed for potential process improvement. A risk management

approach will be applied throughout the product lifecycle to maintain process control and to meet product quality requirements.

Taken together, the presented process validation studies are considered to be appropriately addressed and in line with current guidance. Confirmation that any changes to the process hold time after approval of the MAA will be submitted as part of a variation submission is provided.

Manufacturing process development

A science- and risk-based approach aligned with ICH Q8, Q9, Q10 and Q11 has been applied to depemokimab manufacturing process development.

Depemokimab AS was initially manufactured using Non-Clinical Process 1 (production bioreactor scale). To accommodate clinical demand, the manufacturing process was subsequently scaled up, with changes to facilitate an increase in scale and facility fit. This initial clinical AS manufacturing process is referred to as Process 1. To improve robustness and support process intensification of the AS manufacturing process, modifications were made based on process development work. This modified AS manufacturing process is referred to as Process 2. Process 2 was manufactured in the same facility and executed at the same manufacturing scale as Process 1. To support further cellular growth and process intensification, additional changes were made to the seed expansion and perfusion media. A further modified AS manufacturing process is referred to as Process 3a Development. The development process was then scaled up. This process is referred to as Process 3a. In anticipation of commercialization, Process 3a was transferred to the proposed commercial manufacturing site. This process is referred to as Process 3b and is the intended process for commercial registration.

Several changes have been introduced during the development of the manufacturing process to improve process robustness and performance. The modifications introduced to the manufacturing processes during the development have been adequately described and sufficient details and rationale for each step has been provided. The changes include introduction of the master and working cell banks, change in expansion and perfusion media, changes in feeding strategy, increase in manufacturing scale, changes in culture duration and culturing temperature, change in virus removal filter, formulation adaptation, and change in container closure system. In addition, in anticipation of commercialization, the manufacturing process was transferred from the clinical manufacturing site to the proposed commercial manufacturing site The development data supports the manufacturing process description.

For each change, the applicant performed extensive comparability assessments to evaluate the comparability of AS manufactured using the different manufacturing processes used during the developmental phases, It is considered demonstrated that AS manufactured using the different processes can be considered comparable and there are no concerns regarding comparability of the different processes and ASs produced accordingly.

A comprehensive description of the systematic approach taken to develop the control strategy for AS has been provided, which is based on the outcome of the characterization and validation studies as well as a risk-based approach and available prior knowledge. Overall, the rationale for control strategy is clearly presented.

A limited set of CPPs is proposed as part of the control strategy. According to the applicant, the implicit controls in the process and the robustness of the depemokimab molecule decreases the need for critical parameter controls. Whilst this position is in general not fully endorsed, the presented control strategy is considered sufficiently justified in view of the presented information on the systematic approach, process characterization and validation.

Characterisation

The AS has been sufficiently characterised by biochemical, biophysical and biological state-of-the-art assays revealing that the AS has the expected structure of a fucosylated humanised IgG1κ monoclonal antibody. The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the AS was adequately characterised by analysing charge and size variants and glycosylation. Biological characterisation of the AS indicates that this antibody has the ability to bind soluble IL-5 with high affinity, thereby preventing binding of IL-5 to the IL-5 receptor complex. Since the depemokimab –human IL5 complex prevents binding to the IL-5 receptor complex, Fc effector functionality; CDC or ADCC, is unlikely to occur, and therefore not relevant to the mode of action of depemokimab. Furthermore, specific binding of AS to FcRn is confirmed, which is responsible for antibody recycling. In summary, the characterization is considered appropriate for this type of molecule.

The impurity profile of depemokimab AS was determined through detailed biochemical, biophysical, and biological characterization studies in combination with process validation studies. The impurity profile includes process-related impurities and product-related impurities as defined in ICH Q6B.

A process-related impurities risk assessment was performed to evaluate the raw materials used in the upstream and downstream processes. The risk assessment identified several compounds as process-related impurities with potential safety risks to patients. The levels of these process-related impurities were evaluated using a variety of analytical methods. An N-nitrosamine risk assessment process assessed the potential for nitrosamine formation, dilution, and clearance capability during the depemokimab AS manufacturing process. Any levels of amines of concern or nitrosating agents are at a significantly low level which mitigates the risk of formation of N-nitrosamines. Effective clearance steps are included in the manufacturing process. There is no risk identified for the presence of N-nitrosamines in the depemokimab AS. In general, the results indicate that the depemokimab purification process is robust and provides consistent clearance of process-related impurities.

As product-related impurities, the applicant has considered charge variants, aggregates, and fragments. Purity profiles were generated using cIEF for charge variants, SEC and CGE for fragments, and SEC for aggregates. Individual peaks of interest from these profiles were further characterised by biochemical and biophysical methods. The AS exists primarily as a monomer. Analysis by SPR of the purified fractions shows lower binding activity of the HMW-rich fractions to both antigen and FcRn. Overall, product-related impurities are appropriately addressed. All product-related impurities are routinely controlled by release and shelf-life testing to assure consistency of AS manufacturing, refer to specification below.

### 4.2.3. Specification

Each batch of depemokimab active substance will comply with the specification presented. The depemokimab active substance specifications include appearance and description (colour, clarity), physicochemical characteristics (pH), identity, potency, quantity, purity (aggregation, fragments, isoforms), process related impurities (HCP) and Microbial Attributes (Bacterial Endotoxin and Bioburden).

Analytical procedures

Overall, the analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Depemokimab is tested using a combination of compendial (colour, clarity and degree of opalescence, pH, bacterial endotoxins and bioburden) and non-compendial methods (antigen binding, protein concentration, detection of charge variants, fragments and aggregates and host cell protein).

For compendial methods reference is made to the Ph. Eur. The compendial methods used for the release and stability analysis of AS have been verified to be suitable for their intended purpose in accordance with ICH guidelines and the results are provided for bioburden and bacterial endotoxin. The results meet the requirements set in the Ph. Eur. Related to bacterial endotoxin test, the applicant is encouraged to consider the feasibility of transitioning to Ph. Eur. 2.6.32 Test for bacterial endotoxins using recombinant factor C, eliminating the need for horseshoe crab-derived material and the applicant confirmed that a transition is planned.

Adequate method descriptions of the non-compendial analytical procedures that include method principle, critical assay conditions, sample preparation and system suitability criteria as well as data reporting details, have been provided for all methods.

Validation of the non-compendial analytical procedures is performed in line with ICHQ2 (R2). Pre-defined validation acceptance criteria were met, and all methods were considered validated for their intended use. Sufficient validation data is provided, including additional information on method transfers. Furthermore, where the analytical procedures will be used for both AS and FP analysis, the ranges are considered validated for both AS and FP.

Batch analyses

Batch analysis of the AS have been provided for 11 batches (including 3 PPQ batches). The results are presented against the proposed commercial specifications. The data provided are generally more consistent from batch to batch as of process 3a and 3b, and do not give raise to specific comments or concerns.

Specification and justification of specification

The proposed AS specification includes physico-chemical tests (appearance and pH), identity and potency tests (antigen binding), and protein concentration, (im)purity and product variants tests, and microbial tests (bacterial endotoxin and bioburden). In general, the specifications and test panel includes the test items in line with ICH Q6B and the general monograph for monoclonal antibodies for human use (Ph. Eur. 2031), and hence, are considered appropriate to ensure the quality of each batch of AS.

Justification is provided for the proposed acceptance criteria for each analytical test. In general, the approach used to set release and shelf-life acceptance criteria (statistical analysis (mean±3*SD), together with clinical experience and structure-function relationship data) is considered appropriate. However, the initially proposed acceptance criteria were not fully, as the proposed acceptance criteria were considered too wide compared to the limits proposed by the statistical analysis, and these have been tightened.

Appropriate justification is provided for excluding quality attributes / analytical methods that were included in the clinical release and stability specification but were removed from the commercial specification.

Reference standards

Currently, only a primary reference standard (PRS) is in place and used in routine analytical testing to control the quality of AS. A two-tiered reference material system (i.e. PRS and working reference standard (WRS)) will be established in the future and implemented for the manufacture of commercial AS, after which the

WRS batch will be used in routine analytical testing. Relevant information on the two historical reference standards has been provided, including release and characterization results.

The first RS batch was derived from a Process 1 AS batch. The second RS batch was derived from a Process 3b AS batch, representing material used in pivotal clinical studies. RS materials are filled in, protected from light. The current PRS is considered acceptable for its use. However, in order to ensure that there is no bias in the assigned potency between different reference standards, the applicant should commit to systematically trend potency results of batches tested against the current PRS and provide the results of this trending (at least the first 30 routine batches) (**REC 1**).

All reference standard batches manufactured to date have been subjected to stability studies based on acceptance criteria and methods that were current at the time of testing. The stability indicating parameters and the stability monitoring interval of the current PRS are provided. Prior to the expiration of the PRS or WRS, a new PRS or WRS will be generated using a commercial depemokimab AS batch.

Protocol and acceptance criteria for the qualification and stability testing of future PRS and future WRS has been provided and are considered adequate. Stability of the future PRS and WRS will be monitored.

Container closure

Depemokimab AS is stored in, sterilized, single-use, flexible bags. The components of the container closure system are sourced from qualified suppliers. Schematic diagram of the AS container as well as specifications are provided. Sterilisation of the bags is performed by irradiation according to ISO11137. The container closure systems are accepted based on supplier certificate check, material inspection check and sterilization check. The suitability of the container closure system for depemokimab AS is further supported by the stability studies.

A risk assessment was performed regarding leachables of the container closure system. The calculated highest patients exposure is considered a negligible risk to patients. In addition, the leachable risk is considered low due to the storage of active substance frozen at a low temperature.

Compatibility has been demonstrated in long-term and accelerated stability studies. The sample bags used for storage of the AS stability samples are of the same composition and manufactured by the same company as the container/closure system used for bulk drug ssubstances buts caled down.

Taken together, information provided is in line with the requirements provided in the EMA guideline on plastic immediate packaging materials (CPMP/QWP/4359/03) and is considered sufficient to conclude that the container closure system is considered suitable for long-term storage of AS at the proposed storage condition and provides adequate protection from microbial contamination.

### 4.2.4. Stability

The stability data provided includes data of three clinical batches and three PPQ batches of depemokimab AS to support this claim. Stability studies include storage at the recommended, accelerated (-20°C and +5°C up to 6 months), and stressed storage conditions (+30°C and +40°C up to 3 months, freeze-thaw and photostability).

Based on the comparability studies the clinical batches can be considered representative of the PPQ batches and can be used as primary stability batches to support the shelf life. The stability studies have been carried out in representative AS primary container closure bags compared to commercial primary packaging material

as regards product contact materials and closure, but of a smaller volume.

The parameters tested are the same as for release. The parameters used in the stability studies are considered stability indicating, as confirmed by forced degradation studies and validation of analytical procedures. The stability sampling strategy and stability testing panel are in line with ICH Q1A (R2) and ICH Q5C and are considered appropriate. A confirmation is provided that any changes to the stability protocol after approval of the MAA will be submitted as part of a variation submission.

Stability data at the recommended storage condition is provided to support the proposed shelf life. For all batches the stability data met the proposed commercial acceptance criteria at the recommended storage condition.

Stability studies at alternate recommended storage condition were performed to support potential temperature excursions below and/or alternative long term storage conditions. Results provided include 1 clinical batch and 1 month of storage for the remaining 2 clinical batches and support equivalent storage at.

At the accelerated conditions of -20°C and 5°C the results for all batches met specification criteria up to 6 months of storage. At the stressed conditions of 30°C and 40°C up to 3 months degradation was observed for the purity CQAs. These results are expected under stressed storage conditions and although no trend was observed during long-term storage for these parameters, small decrease was also observed at the accelerated storage conditions of 5°C (but still within acceptance criteria).

Both the freeze-thaw and the photostability testing were performed on 1 clinical batch and 1 PPQ batch. The freeze-thaw study demonstrates that AS is considered stable up to 5 freeze-thaw cycles. In addition, light sensitivity of AS was studied in line with ICH Q1B and significant degradation was observed. Therefore, the AS is considered sensitive to light.

The applicant commits to complete the ongoing stability studies on three clinical (primary) stability batches and three (supportive) PPQ batches. In addition, the applicant commits to add at least one commercial batch of AS annually to the ongoing stability program, provided manufacture occurred during the calendar year, and analyse it according to the specification.

## *4.3. Finished medicinal product*

### 4.3.1. Description of the product and pharmaceutical development

Two different FP presentations are included in this application: a safety syringe device (SSD) and an auto-injector (AI), both delivering a 100 mg dose as single dose. For both devices, the primary container is a pre-filled syringe (PFS) containing 1.0 mL of FP depemokimab.

Depemokimab Injection, 100 mg/mL is an aqueous solution containing the following target quantities of excipients: - histidine/ L-histidine HCl monohydrate, -arginine HCl, trehalose dihydrate, disodium edetate dihydrate (EDTA), and polysorbate 80 (PS80) at pH 6.0. A target fill volume of 1.06 mL is provided in the PFS to ensure the required 1.0 mL volume is delivered.

The primary container, the PFS, is composed of clear glass siliconised barrel with 29G stainless steel needle with a needle shield covered by a rigid needle shield, sealed on the flange end with a plunger stopper. The safety syringe device consists of three components (needle guard, plunger rod, and a finger flange) which are assembled together with the PFS. The autoinjector consists of two subassembly components (syringe unit and drive unit) that are assembled together with the PFS. The finished product contacts only the prefilled

syringe components and is not in direct contact with the SSD or AI subassembly components. General suitability of the commercially proposed container closure systems PFS, SSD and AI is sufficiently justified and supported by NBOps (for SSD and for AI), concluding that the medical device part fulfils the applicable General Safety and Performance Requirements of the MDR. Container closure integrity has been tested with dye ingress method during stability. Information on the sterilization of the primary packaging is registered in the dossier.

In-use stability was evaluated based on exposure to light and room temperature conditions. The-in use stability claim of 8 hours is sufficiently justified based on these studies. The finished product is sensitive to light but measures are in place to prevent product deterioration during manufacturing as well as during storage and in-use.

### 4.3.2. Manufacture of the product and process controls

Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

The FP manufacturing process consists of the thawing of BDS (bulk drug substance), manufacture of a diluent solution, followed by compounding of the BDS to create bulk drug product (BDP). The BDP is first filtered to reduce bioburden and then sterile filtered and aseptically filled into prefilled syringes (PFS), which are stoppered to achieve the DFP. Prefilled syringes are 100% visually inspected, assembled in SSD or AI, labelled, and stored at 2-8°C protected from light. Reprocessing of the BDP during bioburden reduction filtration may occur in the event of filter integrity failure or an event requiring reattachment of the holding bag to a new filling assembly.

The manufacturing process is a standard process. Process parameters and their acceptable ranges are provided and supported with process characterization studies. In Process Controls are considered appropriate. Information provided on the analytical methods for the In Process Controls is considered sufficient.

In general, the control strategy and the acceptance criteria are supported. The omission of certain process parameters in the description of the commercial manufacturing has been adequately justified and sufficient rationale has been provided for those parameters for which no PAR has been defined. It has been defined in the dossier which IPCs are controlled with action limits and which are controlled with acceptance criteria. and it is defined in the dossier what action is taken in case an IPC acceptance criterion is not met.. All hold times for intermediates are supported with appropriate data.

Process performance qualification was performed for three consecutive batches of depemokimab 100mg/mL PFS at the proposed manufacturing site and at the commercial scale. A bracketing approach was applied for the different batch sizes. The Process Validation activities covered the whole set of manufacturing stages from thawing of active substance  to PFS assembly into SSD or AI (syringes). The results of the PPQ studies demonstrate that the manufacturing process is able to consistently manufacture FDP that meets its specifications. IPC and release testing and data on the process parameters for the PPQ runs have been provided. Batch homogeneity has been investigated and the results are within the acceptance criteria. Manufacturing instructions throughout the process also include controls such as protection from light, including the use of shrouding where applicable at the finished product manufacturing site..

Reprocessing has been validated at small-scale and it was confirmed at full-scale with a clinical batch that there is no impact on product quality. Supportive validation studies entailed filter validation, aseptic process

validation, shipping validation as well as media fills and shipping under stress conditions. A hold-time has been validated for the filtered solution in the holding bag via nutrient media trials. The cumulative maximum Time Out of Cold Storage (TOCS) is supported by stability studies at 25°C for several days when protected from light. An extractable and leachables assessment is also provided and indicates that the risk of patient exposure to leachables in depemokimab DP is negligible. Results of the leachables study after 12 months are included in the dossier. However, results of leachable study at the end of the shelf-life are expected (**REC 2**). Validation of sterilization by filtration includes alsosolution compatibility data.

The information provided regarding the changes in the manufacturing process during development is in general considered sufficient. The only major change in the FDP manufacturing reported is a facility change and concurrent change from a vial presentation (using DS from process 1) to a PFS presentation (using DS from process 2). A detailed assessment of impact of these changes on product quality has not been provided. However, as product manufactured with Process 1 has been used for the first in human study only and that manufacturing process used for the pivotal clinical trial and for the proposed commercial process are identical, the issue is not further pursued. Furthermore, the introduction of a new DS manufacturing process (change form process 2 to process 3) has triggered also a comparability assessment at DP level. The provided comparability data indicate no major changes in DP quality following changes in the manufacturing process, although minor differences are observed for cIEF results between DS from process 1 and process 2/3. A clarification on the different FDP PFS configurations used during the clinical trials of phase III (PFS1, PFS2a and PFS2b) has been provided. It is clarified that PFS2b is the validated configuration and proposed for the commercial process.

All aspects of the development of paediatric presentation have been addressed in the responses.

## 4.3.3. Product specification

Depemokimab FP is tested using a combination of compendial (colour, clarity, visible particles, pH, osmolality, bacterial endotoxin, sterility, volume of injection in container, and sub-visible particles) and non-compendial methods (potency, identity, protein concentration, detection of impurities including aggregation, fragmentation and charge variants, container closure integrity, polysorbate 80, device functionality).

Depemokimab finished product specifications largely overlap with active substance specifications. As the PFS's containing the FP are assembled into SSD and AI integral medical devices, a set of dedicated specifications has been instated for SSD and AI functionality. The applicant has justified the choice of the critical functionality parameters based on usability studies and a risk-based approach. The whole set of quality attributes tested in the specifications is considered adequate and no concerns are raised.

***Analytical methods***

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Overall, adequate descriptions of the non-compendial analytical procedures used in routine control of DP have been provided, including the principle of the methods, standard/control/sample preparation, procedure, critical assay conditions, system suitability criteria, calculation methods, representative chromatograms and the way of reporting results.

Compendial methods have been verified to be suitable for their intended purpose according to compendial requirements and the results are presented for bacterial endotoxin and sterility. Non-compendial methods

have been adequately validated according ICHQ2(R2) and adequate method validation reports have been provided.

***Batch analysis***

Batch analysis data are provided for ten finished product PFS batches and subsequent integral devices batches. The batches include clinical batches and batches used for primary stability studies as well as the three PPQ batches manufactured at commercial scale in the commercial manufacturing site. Also batch data for the two early clinical batches and one development batch were included in the dossier.

In general, the batch data are compliant with the proposed specifications, consistent and do not give rise to concerns.

Justification of specifications is provided for the proposed acceptance criteria for each analytical test of the DP specifications. In general, the approach to set the acceptance criteria (i.e. statistical analysis (mean±3*SD), together with clinical experience and structure-function relationship data) is supported.

Acceptance criteria have been adequately justified or tightened.

A summary of the risk- assessment for elemental impurities in accordance with ICH Q3D has been included in the dossier. Three depemokimab FP batches have been tested for elemental impurities and the detected elemental impurity levels are below the 30% PDE threshold, therefore depemokimab is considered low risk with respect to elemental impurities. A nitrosamine evaluation and risk assessment has been provided inmodule 1.2 and a short summary is provided in CTD section 3.2.P.5.5 (and 3.2.S.3.2). No risk for the presence of N-nitrosamine in FP has been identified.

***Reference materials***

The same product-specific reference standard is used for release and stability testing of depemokimab active substance and depemokimab finished product.

## 4.3.4. Stability of the product

The proposed shelf-life and storage conditions for depemokimab finished product is 24 months at 2-8°C protected from light including an in-use period of 7 days at room temperature (up to 30°C), when protected from light and 8 hours once the pack is opened.

The long-term stability data provided includes real time data of three depemokimab DP clinical batches until 24 months (primary stability batches) and three depemokimab DP process performance qualification (PPQ) batches until 12 months at the recommended storage conditions. Stability studies include also accelerated storage temperature of 30°C, stressed storage temperatures of 40°C and -20°C, freeze-thaw stability, photostability, long-term storage with allowance for room temperature storage (2-8°C for 12 months followed by 1 or 2 weeks at 30°C/35% RH or 25°C/60% RH). The container closure used in the stability studies is the same as the proposed commercial container closure.

In general, the stability protocol proposed is in line with the requirements of ICH Q5C and ICH Q1A. The parameters tested and the methods are the same as for release. The parameters tested in the stability studies are considered stability indicating. Stability of the finished product has been tested in the PFS and data are provided in P.8. Functionality of the assembled SSD and AI has been studied in the Design Verification studies (P.2.4) and data are provided until 24 months at the proposed storage conditions. It is confirmed that any changes to the stability protocol after approval of the MAA will be submitted as part of a

variation submission.

Sufficient and adequate stability data have been provided to support the claimed shelf life for DP. The stability data also indicate that long-term storage at 2-8°C for 12 months followed by up to 2 weeks at 30°C / 35% RH or 25°C/60% RH do not impact the quality profile. The only observed differences, fall within the specifications. These findings support that the DP can be stored up to 1 week at room temperature if protected from light, as prescribed in the SmPC. Results of the ongoing stability evaluation at long-term storage for 24 months with room temperature storage allowance have been providedto support the special precaution for storage in the SmPC.

Photostability has been evaluated according to ICH Q1B. There is evidence that the product must be protected from light in the long-term storage condition (in the carto packaging). This is adequately reflected in the SmPC. In-use photostability conditions have been verified and it is shown that there is no impact on DP quality when the product is exposed to light up to 16 h at room temperature. Therefore, the prescription to use the DP within 8 hours if the exposed to light, as stated in the SmPC, is supported.

The applicant commits to complete the ongoing stability studies on three clinical (primary) stability batches and three (supportive) PPQ batches. In addition, the applicant commits to add at least one commercial batch of DP annually to the ongoing stability program, provided manufacture occurred during the calendar year, and analyse it according to the specifications.

### 4.3.5. Post approval change management protocols

The post-approval change management protocol (PACMP) previously submitted has been withdrawn. No post-approval change management protocol (PACMP) is currently included in the application.

### 4.3.6. Adventitious agents

The risk of potential contamination from non-viral and viral adventitious agents associated with the manufacture of depemokimab cell banks, active substance (AS), and depemokimab finished product (FP) was examined and was assessed through extensive testing and appropriate raw material sourcing and risk assessment. Depemokimab is manufactured in accordance with current GMP and adventitious agents are controlled in accordance with the guidelines by the International Conference on Harmonization (ICH) Q5A(R1), Q5D, and Q7A.

No material of human or animal origin is used during the manufacturing of AS. Plant sourced trehalose is used in the formulation of FP. The trehalose manufacturing process uses enzymes produced by a microbial production process which uses bovine milk derived materials. According to the applicant, the animal derived materials are removed through the purification process (filtration, decolorization and deionization) of trehalose. It is agreed that the TSE risk through the use of trehalose is low if not negligible.

The applicant has addressed both non-viral and viral contaminants. In-process testing is in place to ensure bioburden and mycoplasma control during the manufacturing, and cell banks have been tested to be free from non-viral (sterility and mycoplasma) and viral adventitious agents. Furthermore, release of depemokimab production batches requires testing of unprocessed bulk for the presence of adventitious viruses to detect possible introduction of adventitious viral agents during the cell culture process.

Viral clearance validation (VCV) studies were performed in line with the requirements in ICH Q5A(R2) to demonstrate the capability of the AS manufacturing process to remove and/or inactivate viruses. The manufacturing process of AS includes 3 steps to inactivate or remove viruses. The small-scale models for

adequately represent the commercial process. The choice of model viruses is considered appropriate to capture the relevant risks of viral contamination.

The concentration of retrovirus-like particles (VLPs) are typically found in CHO cells used to prepare a broad range of recombinant biopharmaceuticals. While these particles are inert, the concentration of these particles at harvest is assessed against the virus clearance capacity of the purification process to confirm that depemokimab provides an adequate assurance of virus safety. The results of the VCV studies demonstrate that commercial depemokimab manufacturing process can clear the specific model virus XMuLV by >15.51 log10.

The cumulative inactivation/removal of different types of viruses during the manufacturing process is considered to be sufficiently demonstrated.

## *4.4. Discussion on chemical, pharmaceutical and biological aspects*

In general, information on development, manufacture and control of the active substance (AS) and finished product (FP) have been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The AS, depemokimab, is a recombinant fucosylated humanised IgG1κ monoclonal antibody specific for human interleukin-5 (IL-5). The manufacturing process of AS is straightforward and common for a recombinant DNA technology based monoclonal antibody production system. Overall, the process has been adequately validated and consistency in production has been shown. The level of detail provided for the manufacturing development, process design and process characterizations studies is comparable to the level of detail provided for similar products/manufacturing processes. Although a limited set of critical process parameters (CPPs) is proposed as part of the control strategy, the presented control strategy is considered overall sufficiently justified in view of the presented information on the systematic approach, process characterization and validation.

The general approach used to set release and shelf-life acceptance criteria of the AS, i.e. statistical analysis (mean±3*SD), together with clinical experience and structure-function relationship data, is considered appropriate. Overall, the analytical methods used have been adequately described and (non-compendial) methods appropriately validated in accordance with ICH guidelines. The claimed shelf life for AS is sufficiently supported.

Depemokimab FP is provided as solution for injection. The primary container of the sterile liquid FP is a pre-filled syringe (PFS) containing 1.0 mL of FP. The PFS is further assembled in safety syringe device (SSD) or an auto-injector (AI). Both presentations deliver a single dose of 100 mg Depemokimab.

Sufficient and adequate stability data have been provided to support the claimed shelf life of the FP. The batches used in clinical trials are representative with regard to the commercial product. All aspects of the development of paediatric presentation have been addressed.

No major objections are raised. Two recommendations as post-authorisation measure have been included.

The recommendations are related to leachable studies and the potency assignment of the current PRS. The results of the leachable study at the end of shelf life should be provided, when available. In view of the total control strategy in place to assure quality of Exdensur, together with the mode of action of Exdensur, the risk

for patient safety is ultimately considered low. These requests are intended to further ensure product quality and control, and to align with the current quality standards, but do not have impact on the B/R or SmPC.

### *4.5. Conclusions on the chemical, pharmaceutical and biological aspects*

In general, the provided documentation is of good quality and relevant areas have, for most part, been satisfactorily covered. The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are, for most part, controlled satisfactorily. Data has been presented to give reassurance on viral/TSE safety.

No major objections were raised, but two recommendations as post-authorisation measure have been included.

### *4.6. Recommendations for future quality development*

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1) The applicant should provide results of leachable study at the end of the shelf-life to support the final conclusion on leachable characterization. The results of leachable studies will be submitted before the end of 2026.

2) The applicant should systematically trend potency results of routine batches to evaluate whether batches test systematically at 100%, or well below this value, due to the assigned value of the current primary reference standard. The results of this trending (at least the first 30 batches) should be provided. The collected trending data will be submitted after the release of the last batch tested with the current primary reference standard or after 30 batches have been tested, whichever comes sooner.

## 5. Non-clinical aspects

### *5.1. Introduction*

Depemokimab is an antibody specific for human Interleukin-5 (IL-5) and was generated by engineering, through affinity maturation and bioinformatical analysis to improve binding to human IL-5 and to the neonatal Fc receptor (FcRn) compared to mepolizumab. The increased affinity allows for extending the dosing interval from every four weeks to once every three to six months. A TF-1 cell-based assay was used for the (de)selection of antibodies. The TF-1 cells proliferate in response to stimulation with human IL-5 and affinity improved IL-5 binding cloneswere tested to inhibit IL-5 induced proliferation of the TF-1 cells. GSK3511294/ depemokimab was selected as the lead molecule that demonstrated the best inhibition of IL-5 induced proliferation of TF-1 cells. One single dose 4-week toxicity study and a pivotal 26-weeks repeated dose toxicity study 2017N319933 were conducted in compliance with GLP.

### *5.2. Analytical methods*

An ECLIA method based on a sequential flow-through sandwich antigen capture immunoassay with fluorescence detected on the Gyrolab platform was used for the determination of depemokimab in monkey plasma. The lower and upper limits of quantitation (LLOQ and ULOQ) were 300 and 200.000 ng/ml. ISR was performed in Covance Study 8342-663.

Determination of total IL-5 was used for pharmacodynamic evaluation, and a method was developed. The non-GLP method demonstrated a tolerance to depemokimab of 5000 µg/ml and an assay range of 0.1 to 50 ng/ml, LLOQ and ULOQ, respectively. The method was evaluated for accuracy, precision, selectivity, stability (18h at RT, 27 hr at 4°C and 368 days at 180°C), dilution linearity (2x, 5x and 10x dilution of native analyte, 25X and 3333X dilution using spiked recombinant analyte), freeze thaw stability (5 cycles from -80°C to ambient temperature). The method met the acceptance criteria.

For the detection of antibodies against depemokimab, an ECLIA method was developed for monkey serum. The initial method was potentially impacted by high levels of depemokimab and low levels of drug tolerance (sensitivity 5 ng/mL; drug tolerance 0.39 µg/mL) A second bridging ECLIA utilising acid dissociation, was validated with 2.4 ng/mL sensitivity and 25 µg/mL drug tolerance.

In addition, a method for the detection of depemokimab specific circulating immune complexes (CIC) in monkey serum was developed, with an assay sensitivity of 0.1 µg/mL and 1.7 mg/mL drug tolerance.

## *5.3. Pharmacology*

## 5.3.1. Pharmacodynamics

### *5.3.1.1. Primary pharmacodynamics*

*In vitro* pharmacology

Depemokimab is an antibody specific for human IL-5 and was generated by engineering, through affinity maturation to improve binding to human IL-5 compared to mepolizumab.

The TF-1 cells proliferate in response to stimulation with the cytokine, human Interleukin-5 (IL-5) and the TF-1 cell assay was used to measure the ability of the affinity improved IL-5 binding clonesto inhibit IL-5 induced proliferation of the TF-1 cells. . The studies resulted in the identification of GSK3511294 (depemokimab), as the lead molecule.

The applicant has described the selection process and used an IL-5 responsive TF-1 erythroblast cell line for investigating inhibition of the IL-5-induced proliferation TF-1 cells by depemokimab.

To calculate an accurate affinity for depemokimab binding to human IL-5 at 25ºC KinExA analysis was used. This analysis allows the combination of a concentration driven interaction and an affinity driven interaction to determine an accurate affinity. The affinity to human IL-5 at 25ºC by KinExA was 10.5pM (range 0.88-31.97pM) for depemokimab and 122.8pM for mepolizumab. The affinity of depemokimab for human IL-5 was greater than 10-fold higher than that of mepolizumab.

To demonstrate that depemokimab binds to the same epitope on human IL-5 as mepolizumab, a competition assay was used Data were analysed by determining whether binding curves were visible for the second analyte in each combination. Where no binding curve is visible, it is very likely that that the first analyte did prevent binding of the second analyte. It is suggested that the two analytes compete for the same or an overlapping epitope. No second binding event was observed in either of the combinations tested and therefore depemokimab competes with mepolizumab for binding to human IL-5 and is therefore likely to bind to the same or a similar epitope. The binding affinity and kinetics of depemokimab to cynomolgus and human IL-5 was determined at 37ºC. The difference in the affinity of depemokimab for human IL-5 (KD 39.1pM) and cynomolgus IL-5 (KD 23.9pM) was around two-fold less compared to mepolizumab that has equivalent affinities for human and cynomolgus IL-5 of 54.2 and 55.4pM respectively.

The applicant has conducted binding studies under different conditions and experimental set-ups to evaluate the affinity of depemokimab for IL-5 and to compare it with mepolizumab

The binding of depemokimab to mouse, rat, rabbit and dog recombinant IL-5 was assessed. Depemokimab bound to human IL-5, but did not bind to mouse, rat, rabbit or dog IL-5. There was no binding signal detected above the level of the non-specific binding for any of these proteins even though they were used at a 10-fold higher concentration than the human IL-5 (1µM vs 100nM).

Depemokimab is a fully human anti-IL-5 IgG1 antibody. In a heavy chain constant region, three amino acid substitutions (M252Y/S254T/T256E Eu numbering, or YTE) were incorporated, which have previously been shown to improve the binding to human IgG to FCRn at pH 6. These modifications can affect the binding characteristics to other FC receptors. The binding of depemokimab to recombinant soluble human FC gamma receptors (FCɣRs) was assessed. Antibodies were analysed against a positive control antibody containing a wild type human IgG1 FC region and a negative control antibody containing two-point mutations in the FC region which reduce the interaction with FC gamma receptors (L235A/G237A). Binding affinities (KD) of depemokimab for the different FC gamma receptors are (between brackets fold reduction compared to the human IgG1 wildtype control): CD64/FCɣRI 39.8 nM (1.2x), CD32a/FCɣRIIa (H131) 907 nM (1.8x), CD32a/FCRIIa (R131) 948 nM (1.6x), CD32b/FCɣRIIb 776 nM (0.7x), CD16a/FCɣRIIIa (V158) 261 nM (1.5x) and CD16a/FCɣRIIIa (F158) 843 nM (1.4x). In general, depemokimab showed an approximately 1.5-fold reduced affinity for FC receptors compared to human IgG1 wildtype control, except for CD32b/FCɣRIIb, where the affinity was 1.4-fold increased.

For complement component C1q binding the affinity of depemokimab was 1.6-fold reduced compared to the human IgG1 wildtype control for (KD values of 750 nM and 465 nM, respectively).

As IL-5 is a soluble target, antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC) do not play a major role in the activity of depemokimab.

Depemokimab binds to FCRn at pH 7.4 with an affinity of 2650nM and at pH 6.0 with an affinity of 130nM. The binding affinity of depemokimab for human FcRn at pH 7.4 was approximately 20-fold lower compared to pH 6.0. The binding at pH 6.0 was a 2.8-fold increase compared to the human IgG1 wildtype control.

The binding affinity of depemokimab for human FcRn at 37°C was determined and compared with that for mepolizumab (an anti-human IL-5 IgG1 wild-type antibody). Binding affinities were determined using a steady state affinity fit method. At pH 6.0 depemokimab had a 13-fold higher affinity for human FCRn compared to mepolizumab (~ 157nM and ~ 2082nM, respectively).

Interleukin-5 mediates the growth and differentiation of eosinophils in the bone marrow and also mediates their recruitment and activation within tissues. The functional activity of depemokimab was studied *in vitro* by evaluating the binding of depemokimab, to native IL-5 and its ability to inhibit TF-1 cell proliferation and by evaluation of inhibition of cytokine (IL-5)-mediated eosinophil shape change.

The TF-1 cells proliferate in response to stimulation with the cytokine, human Interleukin-5 (IL-5) and the TF-1 cell assay was used to measure the ability of the affinity matured IL-5 binding clones to inhibit IL-5 induced proliferation of the TF-1 cells. The test antibodies were pre-incubated with the human IL-5 before being added to the TF-1 cells. The antibody, cytokine and cells were incubated for 3 days and the number of viable cells per well was determined. Depemokimab and mepolizumab, when tested in the 1nM – 0.042pM concentration range, caused a dose dependent inhibition of TF-1 cell proliferation induced by 3pM of human

and cynomolgus IL-5. Depemokimab was a potent inhibitor of the human and cyno IL-5 mediated proliferation of TF-1 cells (IC50 ~4 pM), whereas mepolizumab was approximately 30-fold leas potent with an IC50 ~114 pM for human IL-5 and ~142 pM for cyno IL-5.

An eosinophil shape change assay was used to measure the inhibition of recombinant IL-5-mediated eosinophil shape change in human whole blood by depemokimab or mepolizumab. This assay is based on an IL-5-induced shape change of eosinophils that can be detected by measuring a shift in FSC-A as assessed by flow cytometry. Depemokimab and mepolizumab (both 10µg/ml equals ~67 nM) inhibited recombinant IL-5-mediated eosinophil shape change, in whole blood, from six different healthy donors.

The stability of depemokimab was assessed in a 6-week *in vitro* serum stability study at 37°C, using pooled control human and cynomolgus monkey serum. Samples derived from the study were tested in an immunoassay, where remaining active depemokimab was captured using immobilised biotinylated IL-5 and detected using a directly labelled anti-human Fc monoclonal reagent. In both human and cynomolgus monkey serum the recovery of active depemokimab showed a gradual drop over time, reaching 73.1% and 77.1% of the $T_0$ concentration respectively after 6 weeks. For mepolizumab recovery of active depemokimab showed a slightly stronger gradual drop over time, reaching 51.0% (human) and 64.2% (cyno) of the $T_0$ concentration, showing that the recovery loss over time for depemokimab was less compared to mepolizumab. The reason for the difference in serum stability between depemokimab and mepolizumab is unknown. However, the consequence of this instability was further investigated *in vivo* in a long-term pharmacokinetic (PK)/ pharmacodynamic (PD) study in cynomolgous monkey.

*In vivo* pharmacology

A 39-week PK/PD study (2017N311376) was conducted with depemokimab in cynomolgus monkeys in which (D and PK parameters were evaluated. The results of the study were evaluated in several reports: PD total IL-5 and the method were reported in 2015N263501, the eosinophil count suppression in 2017N312779_00, PK data in 2017N311897 and ADA results were reported in 2017N324118.

In the study male and female cynomolgus monkeys (n=2/sex/group) were treated with: vehicle control, a single IV dose of depemokimab (0.05 mg/kg or 1 mg/kg), or mepolizumab (1 mg/kg). In a second part of the study the IV control group (Group1) received a subcutaneous (SC) administration of depemokimab at a target dose of 1 mg/kg, what might explain the increase of total IL-5 in this group at the end of the study. Combined PK data indicate a dose proportional increase of exposure of depemokimab and a comparable exposure between IV and SC administration. A clearly longer and higher exposure was demonstrated for depemokimab compared to mepolizumab. PK data from study 2017N311376 reported in study 2017N311897, and ADA results reported in study 2017N324118 are presented and assessed in in section 5.3.2. Pharmacokinetics.

A method for the determination of total IL-5 in cynomolgus (cyno) monkey serum has been validated. The assay uses the "all-in-one" homogenous format. This involves both the capture and detection antibody being pre-mixed with the sample prior to being transferred to a streptavidin coated plate. Commercially available biotinylated antibody is used as the capture antibody and MSD sulfo-tagged antibodies used as the detection antibody. The method is selective for total IL-5 and covers a range from 5 (LLOQ) to 10.000 (ULOQ) pg/mL. The method was evaluated for accuracy, precision, selectivity, parallelism, dilution linearity, cyno serum matrix. The method met the acceptance criteria.

After a single dose depemokimab or mepolizumab (IV), low total IL-5 concentrations at the pre-dose stage gradually increased over time at different rates depending on the treatment and dose. The vehicle group remained consistently low and below LLOQ, due to the IL-5 being rapidly cleared as there is no drug present. All depemokimab and mepolizumab treated groups showed increasing IL-5 levels over time. IL-5 concentrations reach a Cmax of ~ 800 pg/mL for mepolizumab and between 2000-3000 pg/mL for both doses depemokimab, all treatments showed a Tmax of around 4 weeks. Total IL-5 concentrations declined rapidly in the mepolizumab treated group up to below LLOQ (10 pg/mL) around day 100. Total IL-5 concentrations in the depemokimab 0.05 mg/kg group remained elevated around peak level (2000-3000 pg/mL) up to day 150 followed by a decline to ~ 100 pg/mL at day 250. In the depemokimab 1 mg/kg group total IL-5 remained elevated around peak level (2000-3000 pg/mL) up to day 225 followed by a decline to ~ 700 pg/mL at day 250.

The effect of treatment on eosinophil count has been described in study 2017N312779. This report presents statistical summary graphs of blood eosinophil levels determined from the cynomolgus *in vivo* PKPD study comparing the effect of depemokimab and mepolizumab. Data were normalised relative to the baseline response. As a result in the vehicle group treated animals, the normalised ratio EO's was ~ 1 during the whole study, with an exception on days 43 and 50 that showed a 50% drop. The range of the normalised EO ratio is between 0.5-2; 50% change of baseline. For mepolizumab (1 mg/kg) a comparable range of the normalised EO ratio is seen with the exception between days 2 to 29 where the normalised EO ratio is below 0.5, showing inhibition of the eosinophil count. Following treatment of depemokimab (0.05 mg/kg) the normalised EO ratio is below 0.5 from day 8 to 64, whereas the clearest effect was demonstrated following depemokimab 1 mg/kg treatment with a normalised EO ratio below 0.5 from day 2 to 155, showing a prolonged inhibition of eosinophil count.

The PK characteristics of depemokimab in monkeys are after a 1 mg/kg SC dose comparable to the recommended human dose of 100 mg (SC, once every 6 months), with a Tmax of 7 and 14 days, respectively and Cmax around 12 µg/mL, whereas the estimated terminal phase half-life in human is 38-53 days, which is approximately 2 times the half-life observed in monkeys.

#### *5.3.1.2. Secondary pharmacodynamics*

No secondary pharmacology studies have been conducted. See discussion section 5.5.1.

#### *5.3.1.3. Safety pharmacology*

Considering the nature of the product and in accordance with ICH S6 no *in vitro* and dedicated *in vivo* safety pharmacology studies were conducted. The applicant mentions that depemokimab demonstrated high specificity for its target, and functional effects on the major physiological organ systems (e.g., cardiovascular, respiratory and central nervous systems) were not expected following treatment. Cardiovascular parameters are specifically evaluated in toxicity study 2017N319933. In this study, an increase in QTc (approximately 7%) was observed in 4/6 animals at 100 mg/kg during Week 14 at an exposure that was >70-fold higher than clinical exposure. In animals in the low dose group with sufficiently high depemokimab exposure (~10-fold clinic al exposure), prolonged QTc was not observed. In addition, QTc prolongation was evaluated from the ECGs that were included as clinical monitoring endpoints in the clinical studies. To date, no signals regarding prolonged QTc in the clinical settings were reported. See section 6.4. clincil safety for further information.

#### *5.3.1.4. Pharmacodynamic drug interactions*

No pharmacological interaction studies were conducted. See discussion section 5.5.1.

## 5.3.2. Pharmacokinetics

#### *5.3.2.1. Absorption*

A single dose PK study was performed in Cynomolgus monkeys, with IV doses of 0.05 or 1 mg/kg bw, or an SC dose of 1 mg/kg. Depemokimab showed a biphasic decline, with an initial distribution phase, followed by a slow elimination phase. The steady state volume of distribution was low (77.8-79.7 ml/kg). Plasma clearance was low (0.0942 - 0.105 mL/hr/kg). Systemic exposure of depemokimab increased in a dose-proportional manner over the dose range of 0.05-1 mg/kg. Terminal elimination half-life (T1/2) was approximately 24 days in monkeys. After SC administration, T1/2 was approximately 22 days. Bioavailability after SC administration was complete (111%).

In another study, the SC toxicokinetics of depemokimab were determined in a single dose toxicity study in cynomolgus monkeys dosed with 10 and 100 mg/kg (3/sex/group). Tmax ranged from 48 to 120 hours post dose. Systemic exposure of depemokimab increased in a dose proportional manner. No apparent gender differences were observed. Serum samples were analysed for anti-depemokimab antibodies and circulating immune complexes (CIC). Only a control animal tested positive with the acid dissociation ADA. Three animals however tested positive with the CIC detection method (1 from the low dose group and 2 from the high dose group).

Multiple dose toxicokinetics were determined in a 6 month repeat dose SC toxicity study in cynomolgus monkeys (3/sex/group) who received 2 doses of depemokimab (10 and 100 mg/kg bw) on Day 1 and during Week 14. Tmax ranged from 48 to 192 hours. Systemic exposure increased approximately proportionally with increasing dose. No accumulation was observed after the second dose. Depemokimab was quantifiable for at least 2016 hours post the Week 14 dose, except in 1 animal. No apparent gender differences were observed.

Serum samples were analysed for anti-depemokimab antibodies using the analytical method utilizing acid dissociation. During the dosing phase, 3 males and 2 females from the low dose group tested positive for ADA's, although both females were positive for ADA's prior to depemokimab administration. In the high dose group, 1 male and 2 females tested positive for ADA's. Four of the low dose animals were also tested for ADA's in the 30 weeks off dose period; 3 of them tested positive for at least a part of this period (the 4th was sacrificed on Day 25 of the off-dose period), versus none of the control animals that were tested in the off-dose period. ADAs were associated with marked decreases in depemokimab plasma concentrations in only one male with a high ADA titer, suggesting an effect of ADA on exposure. However, reduced depemokimab exposure was not observed in the remaining animals who developed ADAs.

#### *5.3.2.2. Distribution*

The large molecular weight of depemokimab and its composition of naturally occurring amino acids precludes the requirement to perform standard distribution studies in nonclinical species [ICH S6(R1), 2011]. Consistent with the known biodistribution of monoclonal antibodies, depemokimab has a low volume of distribution (77.8-79.7 ml/kg), suggesting a distribution to plasma and extravascular fluid.

An *in silico* placental transfer was used to simulate an ePPND study with depemokimab at 10 and 100 mg/kg/dose given on gestation day 20, 85, and 150 and compare this with the results of the ePPND study

with mepolizumab. The model predicted only minor increases (up to 2-fold) in PK parameters in the fetus with depemokimab as well as foetal-to-maternal ratios compared with those with mepolizumab.

#### *5.3.2.3. Metabolism*

No metabolism studies with depemokimab were conducted in animals. The absence of metabolism studies is in accordance with ICH S6(R1).

#### *5.3.2.4. Excretion*

As depemokimab is a monoclonal antibody, no renal excretion is anticipated due to its molecular size Therefore, no specific studies to measure excretion of depemokimab were conducted. The absence of excretion studies is in accordance with ICH S6(R1).

#### *5.3.2.5. Pharmacokinetic drug interactions*

Drug-drug interaction at the PK level is highly unlikely for this type of product since biotechnology-derived substances do not metabolize via CYP P450 enzymes. In addition, neutralisation of IL-5 is not expected to alter gene expression of CYP and transporters, which could alter drug metabolism.

## *5.4. Toxicology*

### 5.4.1. Single-dose toxicity

A GLP-compliant 4-week single dose toxicity study testing with depemokimab at 10 and 100 mg/kg in cynomolgus monkey was conducted. Based on the exposure data of a previous PK study, this single administration of depemokimab is expected to provide a continuous exposure for at least 4 weeks. At 10 mg/kg, adverse vascular inflammation in kidney, heart, pancreas, spleen, and liver was observed in one female. Immune complex deposition of monkey IgG, IgM and/or C3 were found in the tunica intima and/or tunica media of blood vessels from these tissues (except for spleen). The severity and distribution of the vascular inflammation was much greater than the numbers of associated granular deposits. No depemokimab was detected in the affected tissues. One female receiving 100 mg/kg demonstrated minimal and focal inflammation of a bronchial artery. Anti-drug antibodies (ADAs) and depemokimab-specific circulating immune complexes (CICs) were not detected in the affected monkeys. Low ADA levels were detected in one control animal. Depemokimab-specific CICs were detected in 1 low dose and 2 high dose animals with no vasculitis. The NOAEL could not be determined due to the adverse vasculitis observed in the low dose group.

### 5.4.2. Repeat-dose toxicity

A GLP-compliant repeat dose toxicity study in cynomolgus monkeys receiving depemokimab 10mg/kg and 100 mg/kg once every 3 months for 26 weeks has been performed. The control group and main dose groups contained 3 males and 3 females, but 2 males and 2 females were added to the control group and the group dosed with 10 mg/kg, respectively, for observation during a 30-week off-dosing period. Decrease in eosinophil counts was observed in 4/5 males and 2/5 females receiving 10 mg/kg (down to 0.16-fold compared to baseline values) and in 3/3 males and 2/3 females receiving 100 mg/kg (down to 0.12-fold compared to baseline values) and was seen throughout the dosing period. In one male at 10 mg/kg, the eosinophil counts returned to baseline levels by Week 21 and remained above or near pretest values during the off-dosing period. This male was ADA positive beginning Week 13, and the ADA titre was relatively very high in this animal. In the other recovery male, the decreased eosinophil count persisted during the off-dosing period, indicating this effect is not completely reversible after 30 weeks. One female in the recovery

group died after 25 days off dosing, probably caused by an infection, while the other female did not have decreased eosinophils by dosing. ADAs with mostly relatively low titre were detected in 3/5 males in the 10 mg/kg and in 1/3 males and 2/3 females receiving 100 mg/kg. Apart from one male with the only high titre of ADAs, ADA mediated reduced depemokimab exposure was not observed in the remaining animals who developed ADAs. An increase in total IL-5 from Week 2 was noted in monkeys of both dose groups, indicating target engagement. However, this effect was also non-dose proportional, possibly due to a high variability in total IL-5 concentrations. Increase in QTc (approximately 7%) were seen in 4/6 animals at 100 mg/kg with exposure multiples of > 70-fold during Week 14.

## 5.4.3. Genotoxicity

No genotoxicity studies were conducted as monoclonal antibodies do not directly interact with DNA or other chromosomal material, which is in line with ICH S6(R1) guideline.

## 5.4.4. Carcinogenicity

No carcinogenicity studies were conducted. The applicant conducted a weight-of-evidence (WoE) assessment to evaluate the potential of depemokimab to cause carcinogenicity.

The WoE assessment on the potential of depemokimab to cause carcinogenicity conducted by the applicant generally followed the WoE approach recommended in the ICH S1B(R1) guideline. Based on literature, whether there is a role for IL-5 and eosinophils in tumour immune surveillance is poorly characterised (Lowe, 1981; Samoszuk,1997; Cormier, 2006; Simon, 2020; Grisaru-Tal, 2020). *In vitro* studies with depemokimab did not show off-targeting bindings, and *in vivo* studies demonstrated no effects suggesting secondary pharmacology, hormonal alterations, and immune modulation. No neoplastic changes were noted in the 26-week study in cynomolgus monkeys. With respect to data from other mAbs in class, increased tumour incidence was not reported in the clinical trials with reslizumab (Kips, 2003; Klion, 2004; Walsh, 2013). Nevertheless, in placebo-controlled clinical studies, the incidence of malignant neoplasm in the treatment groups (6/1028, 0.6%) was reported to be higher than patients in the placebo group (2/730, 0.3%). The observed malignant neoplasms in reslizumab-treated patients, with the majority of malignancies being diagnosed within less than 6-month reslizumab exposure, were diverse in nature without clustering of any specific tissue type (Cinqair US PI, 2020). In addition, there was no data on 2-year rat carcinogenicity study with reslizumab or mepolizumab. On request, the applicant updated the WoE assessment on the carcinogenic potential of depemokimab. See discussion section 5.5.1.

## 5.4.5. Developmental and reproductive toxicity

No developmental and reproductive toxicity (DART) studies were conducted. The DART risk with depemokimab was assessed using a weight-of-evidence (WoE) approach.

No reproductive, developmental, and/or juvenile toxicities were reported in genetically modified animals (e.g. IL-5 deficient mice), studies with mouse anti-rat IL-5 mAb, and other in-class mAbs including mepolizumab, benralizumab and reslizumab (Kopf, 1996; Gouon-Evans, 2002; Sferruzzi-Perri, 2003). However, no terminal necropsy of the infants was performed in the ePPND study with mepolizumab. Because of this, there were no teratogenic data with mepolizumab. Nevertheless, teratogenic effects were not reported with other in-class mAbs including reslizumab (anti-IL-5 mAb) and benralizumab (anti-IL-5R mAb). Furthermore, no effects on reproductive organs were identified in the general toxicity studies with depemokimab and other mAbs in class. The modification of the Fc region of depemokimab resulted in a 13-fold increase in binding affinity to neonatal Fc receptor (FcRn) compared to mepolizumab. This further leads to reduced systemic clearance and

a longer serum half-life. Because of the longer half-life and the active transport of depemokimab across placenta via FcRn binding, foetal exposure to depemokimab might be increased during later stage of gestation. To address the potential increased foetal exposure, the applicant used an *in silico* model to simulate an ePPND study with depemokimab at 10 and 100 mg/kg/dose given on gestation day 20, 85, and 150. The submitted model is not a classical PBPK model. The applicant developed a three-compartment model derived from the PBPK model by Sepp et al. (2015; 2019; 2020). The simplified model essentially simulated antibody transfer through three compartments (mother, foetus, and placental endosomal space) using the PBPK model, along with PK data from the ePPND study performed with mepolizumab and the PKPD study performed with depemokimab and mepolizumab.

In the model, non-selective pinocytosis leads to the creation of endosomes where antibody interaction with the FcRn receptor occurs. The bound antibody complex can subsequently be released into the maternal or foetal compartments, while unbound antibodies are metabolised. Transfer to the placental endosome occurs by non-specific pinocytosis from both the maternal and foetal compartments. The rate of pinocytosis from the foetal compartment was assumed to be equal to the rate from the maternal compartment. Endosomal recycling transfers mAbs from the placental endosome to either the maternal or foetal compartments. The model includes a parameter (Frec, M) that controls the fraction of endocytic recycling that returns Abs to the mother. This parameter was determined by fitting to literature data.

During the comparison between simulated ePPND studies using depemokimab and mepolizumab at 10 and 100 mg/kg, the simulations showed that there was a slight increase (less than 2-fold) in depemokimap foetal exposure as well as the foetal-to-maternal ratios compared to mepolizumab. This indicated that the extended half-life of depemokimab did not lead to considerable accumulation of foetal mAb concentrations versus maternal levels. Depemokimab is intended for patients of 12 years of age or older, and this mAb is also used as an add-on treatment of adult patients with inadequately controlled CRSwNP. According to the applicant, the monkeys used in the 4-week single dose and 26-week repeat dose toxicity study with mepolizumab were 2 to 4 years of age at the study start, corresponding to the beginning of adolescence in humans. In these general toxicity studies, no effects on late developing organs systems (i.e. bone and reproductive systems) were identified. Furthermore, the ePPND study with mepolizumab did not show drug-related adverse effects including no effects on immune system development through 9 months postpartum in offspring exposed to mepolizumab for 3 to 6 months postpartum. There is high variability in eosinophil counts in offspring with the number of eosinophils present at very low levels across vehicle and mepolizumab-dosed groups at the 6 month postpartum follow-up. Decreased eosinophil counts were noted in adult monkeys and humans treated with depemokimab that were reversible following clearance of depemokimab.

## 5.4.6. Toxicokinetics and exposure margins

Toxicokinetics of depemokimab was studied in the 4-week single dose and the 26-week repeat-dose studies in Cynomolgus monkeys. Exposure of depemokimab increased dose-proportionally in both studies, with no relevant differences between males and females. Relevant accumulation was not observed after the second dose in the repeated dose study.

Serum samples in the single dose study were analysed for anti-depemokimab antibodies and circulating immune complexes (CIC). Only one animal tested positive with the acid dissociation ADA, which was a control animal. Three animals however tested positive with the CIC detection method (one from the low dose group and 2 from the high dose group).

Serum samples in the repeated dose study were analysed for anti-depemokimab antibodies using the

analytical method utilising acid dissociation. During the dosing phase, 3 males and 2 females from the low dose group tested positive for ADA's, although the females did so prior to depemokimab administration. In the high dose group, 1 male and 2 females tested positive for ADA's. 4 of the low dose animals were also tested for ADA's in the 30 week off dose period; 3 of them tested positive for at least a part of this period (the 4th was sacrificed on Day 25 of the off-dose period), versus none of the control animals that were tested in the off-dose period. ADAs were associated with marked decreases in depemokimab plasma concentrations in one male with a high ADA titer, however, reduced depemokimab exposure was not observed in the remaining animals who developed ADAs.

The PK profile of the cynomolgus monkey is similar to that in humans, supporting the use of the cynomolgus monkey in the toxicity studies. Depemokimab is highly bioavailable following 1 mg/kg SC administration, and the apparent terminal half-life is similar to the IV half-life (22-24 days). In humans, the geometric mean terminal half-life ranged from 38 to 53 days. Serum clearance (0.0974-0.105 mL/h/kg in monkeys; 0.056-0.11 mL/h/kg in humans) and volume of distribution (0.078-0.080L/kg in monkeys; 0.10-0.15 L/kg in humans) were low. After repeated dosing of 10 and 100 mg/kg in monkeys, Tmax ranged from 48 to 192 hours, which is slightly faster than in humans (8-14 days). Systemic exposure increased proportionally with increasing dose in both monkeys and humans, and no sex difference were observed.

## 5.4.7. Exposure margins

Exposure multiples were calculated for human Patients with Asthma and CRSwNP Local tolerance

No standalone studies on local tolerance of depemokimab were conducted since there were no injection site reactions identified during the clinical and histopathological analysis of the injections in the single and repeated dose toxicity studies in monkeys.

## 5.4.8. Other toxicity studies

Immunogenicity

For immunogenicity, no specific animal studies were conducted. Immunogenicity was addressed using data derived from the 4-week single dose toxicity study and 26-week repeat dose toxicity study in cynomolgus monkeys. In the 4-week single dose toxicity study, none of the animals developed ADAs, except for low levels in one control animal. In addition, depemokimab-specific CICs were detected in 1 low dose and 2 high dose animals. While ADAs were detected in 6 animals in the 26-week repeat dose toxicity study, there was only one male at 10 mg/kg with a high ADA titre in which the depemokimab exposure was reduced. Vasculitis in multiple organs caused by immune complex formation was observed in one female at 10 mg/kg in the 4-week single dose toxicity study. Nevertheless, events consistent with type III hypersensitivity/immune complex disease have not been observed in patients receiving depemokimab to date in the clinical studies. Therefore, the observed vasculitis in one monkey is more likely due to spontaneous immune complex formation in response to unknown antigen.

Although effect of ADA on PK and pharmacology or immune complex disease was observed in cynomolgus monkeys, none of these effects were observed in clinical studies.

Tissue bindings

Depemokimab is an anti-IL-5 mAb derived from mepolizumab with 7 amino acid differences in the antibody's heavy chain. Of these 7 amino acid exchanges, 4 amino acid substitutions are located in the CDRs of the variable binding domain, and this results in a higher affinity to the target antigen IL-5. While mAbs generally

have high specificity for their target, off-target binding has been observed with mAbs. The modification of the mepolizumab antigen binding site theoretically may have introduced a different off-target profile for depemokimab. Furthermore, findings such as increased QTc and vasculitis that cannot be attributed to pharmacology were observed in general toxicity studies with depemokimab. These findings were not detected with mepolizumab. To address the concern of off-target bindings as well as rely on the safety profile of mepolizumab to assess developmental and reproductive toxicity risk, the applicant investigated tissue cross-reactivity of depemokimap using tissues of cynomolgus monkeys and humans. To investigate potential off-target bindings, studies on tissue cross reactivity of depemokimab using cynomolgus monkey and human tissues were conducted. The potential human tissue bindings were assessed in one preliminary non-GLP-compliant immunohistochemistry (IHC) study with biotinylated depemokimab at concentrations of 0.6 and 2.5 µg/mL testing limited number of human tissues, and one definitive GLP-compliant IHC study with depemokimab at 0.63, 2.5, or 5 µg/mL examining a selected panel of 40 human tissues (3 donors per tissue). One non-GLP-compliant preliminary IHC study with biotinylated depemokimab at concentrations of 2.5 or 5 µg/mL using cynomolgus monkey tissues from 3 donors per tissue was conducted. Staining was noted in several tissues tested, but these were either very minimal staining possibly due to hydrophobic interactions or staining of collagen, plasma, or content in the lumen of renal tubules. Minimal staining was also observed in the negative control, suggesting that there is also some unspecific background staining. All of the staining was considered non-specific. Specific staining was not observed in any of the tissues examined, including kidney, liver, spleen, pancreas, heart, and lung. In the definitive GLP-compliant study, staining was noted with biotinylated depemokimab in 34 out of the 40 tissues examined, with comparable staining present in only 6 tissues in one or both the negative control groups. Nevertheless, the staining was present within plasma, extra-cellular matrices, red blood cells, or bone marrow precursor cells. Furthermore, the staining was ill-defined and not localised to a specific cellular component. Therefore, the staining observed was considered non-specific. The applicant concluded that no specific positive staining was observed in any human tissues examined.

The results of cynomolgus monkey and human tissue binding studies support the arguments that the increased QTc in the 26-week repeated dose toxicity study with depemokimab was unlikely attributed to a direct off-target binding effect of depemokimab to cardiac tissues, and that off-target effects impacting developmental and reproductive toxicity risk assessment are not expected.

Immunotoxicity

No dedicated immunotoxicity studies were conducted. The applicant discussed the potential for depemokimab to cause immunotoxicity by reviewing the pharmacology, data from genetically modified animals as well as available non-clinical and clinical data of depemokimab.

Depemokimab reduces the number of eosinophils by blocking IL-5. According to literature, eosinophils were suggested to be involved in innate immunity against certain helminths. It was suggested that IL-5 may alter the kinetics of clearance for helminth infection but does not prevent clearance or increase the chances of initial infection (Kopf, 1996; Tanaka, 2000). Furthermore, IL-5 deficient mice, who had no eosinophilia as that observed in normal mice upon Mesocestoides corti infection, did not show increased worm burden. Reduced eosinophil counts were observed in the non-clinical and clinical studies with depemokimab. Helminth infections were not noted in the non-clinical studies. However, less helminth infections are expected in animals in laboratory settings that live in a controlled environment. Nevertheless, no findings indicating increased parasite infections or other immunotoxicity were reported in the clinical settings.

Dependence

No studies were conducted to evaluate the dependence potential of depemokimab. See discussion section 5.5.1.

Comparability and impurities

Depemokimab was initially manufactured using Non-Clinical Process 1. Depemokimab produced in this manufacturing process were used in toxicology studies, including tissue cross-reactivity studies. However, to accommodate clinical demand, the manufacturing process was later scaled up from a , with changes in manufacturing processes to facilitate an increase in scale and facility fit. The subsequent manufacturing processes included Process 1, Process 2, Process 3a, and Process 3b. All these processes were of , and drug substance manufactured using these processes were tested in clinical studies, of which depemokimab manufactured in Process 3b were intended for commercial use. Changes in manufacturing processes for protein therapeutics may affect the pharmacological activity, PK, or safety profile of the drug. To evaluate the effects of these changes, a comparability assessment was performed. No non-clinical toxicology studies were conducted as part of the assessment due to the benign safety profile of depemokimab (only reduced eosinophils observed as the pharmacological effect) and low immunogenicity in cynomolgus monkeys. The comparability assessment focused on bioanalytical analysis and bioactivity assays. During the comparability assessment, no meaningful differences in the materials produced in different processes were found. All the measured parameters such as potency, process-related impurities were within acceptance criteria.

Phototoxicity

No non-clinical phototoxicity studies were conducted provided that proteins such as mAbs are not photoreactive, and there is no concern with respect to phototoxicity in patients.

Extractables and leachables

No toxicology studies were conducted for extractables and leachables as the results of extractable studies demonstrated low potential for leachables.

### 5.4.9. Ecotoxicity/environmental risk assessment

The active substance depemokimab is a protein and a naturally occurring substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, depemokimab is not expected to pose a risk to the environment.

## *5.5. Overall discussion and conclusions on non-clinical aspects*

### 5.5.1. Discussion

*Analytical methods*

None of the methods were validated in compliance with GLP (i.e. no signed GLP statements were present). Although validation of the methods used for the analysis of toxicokinetics in the pivotal studies should be performed in compliance with GLP, no consequences for the conclusions of these studies are expected as they are considered to be fit for purpose.

*Pharmacology*

The applicant has adequately described the selection process and used an IL-5 responsive TF-1 erythroblast cell line for investigating inhibition of the IL-5-induced proliferation of TF-1 cells by depemokimab.

*In vitro antibody characterisation*

The applicant has demonstrated that the affinity of depemokimab for human IL-5 was around 2-10 fold higher than that of mepolizumab and that both antibodies share or have overlapping epitopes. No in vivo efficacy studies were conducted, what is agreed given the lack of cross reactivity with mouse, rat, rabbit and dog IL-5. The applicant has adequately characterised the FC receptor interaction of depemokimab and the small changes in affinity for FC gamma and complement receptor are not expected to have a relevant biological effect. At pH 6.0 depemokimab had a 13-fold higher affinity for human FCRn compared to mepolizumab (~ 157nM and ~ 2082nM, respectively), what is anticipated to have a positive effect of recycling of depemokimab and extended half-life in vivo.

*Mechanism of action inhibition of IL-5-induced proliferation of TF-1 cells*

The applicant has demonstrated IL-5 inhibition by depemokimab in two functional assays: IL-5-induced TF-1 cell proliferation assay and an IL-5-induced eosinophil shape change assay. The high concentration depemokimab used in the eosinophil shape change assay assay probably results in saturation of IL-5 and without a dose range curve, the result of this assay is of limited value for the interpretation of the functional activity of depemokimab related to eosinophils.

*Mechanism of action IL-5 inhibition for treatment of asthma characterised by an eosinophilic phenotype*

Preclinical models have been successful in the evaluation of new therapeutic approaches and for asthma animal studies in e.g. mice, rats, guinea pigs, sheep, dogs have been described (Woodrow et al, 2023, Cells, 12, 1091). The lack of binding of depemokimab to mouse, rat, rabbit or dog IL-5 precluded the use of these models. Instead, in vitro, IL-5 inhibition and IL-5-induced modulation of eosinophils was studied to demonstrate involvement of critical molecules in the disease process of eosinophilic asthma; IL-5 and eosinophils.

As eosinophils are a main player in the inflammatory process of chronic rhinosinusitis with nasal polyps (CRSwNP), the no preclinical data also supports the treatment of CRSwNP.

*In vivo pharmacokinetics and pharmacodynamics (PK/PD)*

The applicant has conducted a long-term PK/PD study in cynomolgus and described the plasma exposure of the parent compound and as PD parameters the total IL-5 concentrations and eosinophil count in plasma. Upon CHMP's request, a discussion about the PK/PD relationship in relation to the intended treatment was provided and adequately clarified the proposed mode of action. After a single dose depemokimab or mepolizumab (IV), low total IL-5 concentrations at the pre-dose stage gradually increased over time at different rates depending on the treatment and dose. This is a consequence of the drug complexing with the IL-5 that is present, resulting in an extended half-life of the IL-5. It is likely that binding of depemokimab to IL-5 results in an inactive complex, though as a result of technical limitations this was not supported by data. The dynamic reduction and prolonged suppression of eosinophil numbers in the circulation is explained by differences in half-life between peripheral eosinophils (half-life 2 days in cynomolgus monkeys, Zia-Amirhosseini, 1999) and tissue eosinophils (half-life ~ 6 days, Kanda, 2021). Depemokimab does not fully eliminate circulating eosinophils as IL-3 and GM-CSF are unaffected and cells in the bone marrow continue eosinophil cell production (Kopf, 1996), what is in contrast to benralizumab an antibody that is supposed to

actively kills eosinophils via ADCC (Dagher, 2022). As a result, following depemokimab administration eosinophils may keep entering the circulation and take much longer to be exhausted than anticipated by the half-life of circulating eosinophils. Based on the PK/PD relationship observed in monkeys, it is expected that there would be a substantial drop of blood eosinophil counts in the first week; however, tissue eosinophils in the lungs and nose in the monkeys might take weeks to get exhausted following the initial dose of depemokimab. Overall, the data from the 39-week PK/PD study indicate that the dose and dosing frequency of depemokimab in monkeys produced a pharmacological effect, i.e., sustained suppression of eosinophils at a high-level contributing to a reduction of an eosinophil-driven inflammatory response in affected tissues. Furthermore, the longer exposure to depemokimab, possibly caused by the increased FCRn affinity, combined with the higher potency of depemokimab resulted in a prolonged circulation of total IL-5 complex compared to mepolizumab.

*Pharmacokinetics*

The PK summary mentions an assay for the detection of depemokimab in monkey serum, with an LLOQ of 30 ng/ml. This method is used in study 2017N311897. Upon CHMP's request, a bioanalytical report for the qualified method was provided which showed that the method was fit for purpose.

*Toxicology*

Single-dose toxicity

For the observed vasculitis, the absence of ADAs and no depemokimab detected in the immune complex deposits implies that an effect of depemokimab as the circulating antigen to induce immune complex formation and the subsequent vascular inflammation is unlikely. However, other effects of depemokimab (e.g. immunomodulation) to cause vasculitis cannot be excluded. Nevertheless, the relationship between treatment with depemokimab and vasculitis is unclear as such effect on blood vessels was not observed in the 26-week repeated dose toxicity study in cynomolgus monkeys. According to the applicant, the arterial changes in multiple organs in the current study were morphologically similar to spontaneous arteritis reported in monkeys (Sato et al., 2012; Porter et al., 2003). Furthermore, monkeys have been reported to have spontaneous immune complex-related granular deposits in response to unknown antigens and high circulating levels of spontaneous immune complex formation compared to humans (Alexander et al., 1985; Hebert et al., 1991; Rojko et al., 2014). In view of the demonstration of immune complexes containing no depemokimab in the affected animals, these effects not observed in the 26-week repeat dose toxicity study, and the high circulating levels of spontaneous immune complex formation in monkeys reported in literature, it is agreed that the observed adverse vasculitis is likely a background finding in cynomolgus monkey, and that the clinical relevance is considered limited.

*Repeat dose toxicity*

In the 26-week repeat dose toxicity study, prolonged QTc was observed in 4 out of 6 animals at 100 mg/kg. Depemokimab was produced by modification of mepolizumab including modification of the antigen binding site. Such modifications might lead to a change of the off-target binding profile, resulting in an off-target effect manifested as prolonged QTc. The applicant was asked to compare the off-target binding profiles between mepolizumab and depemokimab during a Scientific Advice procedure ((EMA/SA/0000059022, 2021)). Nevertheless, the applicant pointed out that the findings observed were minor and inconsistent with a clear off-target effect. Tissue cross reactivity studies indicated no binding to cynomolgus monkey or human cardiac tissue. Furthermore, these effects were observed in animals with exposure that was >70-fold higher than clinical exposure. In animals in the low dose group with sufficiently high depemokimab exposure (~10-

fold clinical exposure), prolonged QTc was not observed. In addition, QTc is clinically monitorable, and ECGs were included as clinical monitoring endpoints in the clinical studies. To date, no strong signals regarding prolonged QTc in the clinical settings were reported. Therefore, it is agreed that the clinical relevance of increased QTc is limited, and further investigations (e.g. protein arrays) for the off-target bindings are not required. On request, the applicant provided detailed discussions demonstrating that the observed QTc was not treatment related, and the NOAEL was determined at 100 mg/kg with an exposure margin of >70-fold clinical exposure. . The NOAEL in the 26week repeat dose toxicity was considered by the Rapporteur to be 10 mg/kg instead of 100 mg/kg due to the increase in QTc at 100 mg/kg in 4/6 animals at 100 mg/kg, which is considered to be an adverse effect. The exposure margin is 8.48 or 9.65 when based on AUC and 10.9 or 12.0 when based on Cmax (for patients with asthma or CRSwNP, respectively).

In most treated animals in both single dose and repeat dose toxicity study there was a substantial reduction in eosinophil counts in the treatment groups, which was consistent with the expected pharmacology. However, the eosinophil counts reduced in a non-dose proportional manner in terms of severity. Furthermore, there was a large variation in individual eosinophil counts in animals during the pretreatment period of the depemokimab group and in the control group. Therefore, reduction in eosinophil counts is considered non-adverse pharmacological response.

Carcinogenicity

On request, the applicant provided additional literature data to update the weight-of-evidence assessment on the carcinogenic potential of depemokimab. While the EPAR summary for benralizumab commented on the uncertain role of eosinophils in tumour surveillance, a similar comment was not expressed for the anti-IL-5 mAb reslizumab EPAR approved prior to benralizumab approval; no comment on the role of eosinophils in cancer was made in the mepolizumab EPAR. The USPIs for the anti-IL-5 and anti-IL-5Ra mAbs all contain a common statement regarding the unclear role of eosinophils in malignancies.

Most of the observations regarding the role of eosinophils in cancer come from murine models which can provide mechanistic insights into tumour biology and treatment, but are experimental models and the context of the murine model (e.g., immunogenic or nonimmunogenic tumour, and mouse strain and type 1 or type 2 immunity balance) is often not fully considered leading to the apparent conflicting conclusions about eosinophil function in tumours in publications (Ghaffari, 2023).

A recent publication suggested that eosinophils may play a role in tumour microenvironment and affect carcinogenesis. Blomberg (2023) demonstrated that eosinophils were required for intratumoural activation of CD8+ T cells induced by the combination treatment of cisplatin and nivolumab, an anti-PD-1 mAb. However, this observation on eosinophils had a specific context. First, nivolumab was administered and it directly acted on CD4+ T cells resulting in upregulation of IL-5 production, which further promoted eosinophil proliferation in the bone marrow. Second, eosinophils infiltrated tumours in an IL-33-dependent manner. And third, intratumoural CD8+ T cells were somehow activated (not recruited) by eosinophils. Therefore, all the components are needed together: presence of nivolumab, intratumoural expression of IL-33, and intratumoural recruitment of CD8+ T cells, for eosinophils to have an effect in cancer treatment, for certain types of tumours. In fact, the authors of the study indicated that not all tumours would provide the right conditions for eosinophils to have an effect, even in the presence of immune checkpoint blockade. Furthermore, the study provided evidence that eosinophils did not affect tumour growth in the absence of nivolumab. Therefore, the current evidence suggests that eosinophils may limit tumourigenesis, only under specific circumstances.

In contrast to the findings discussed above, in a meticulously conducted mechanistic study in mice for the role of IL-5 in carcinogenesis, genetic IL-5 deficiency protected the lungs from metastasis of different types of tumour cells (lung carcinoma, melanoma, and colon adenocarcinoma) whereas IL-5 reconstitution or adoptive transfer of normal eosinophils into IL-5-deficient mice exerted pro-metastatic effects. The potential mechanism for IL-5-dependent metastasis was that eosinophil-secreted CCL22 facilitated metastasis through local recruitment of regulatory T cells (Tregs), with no local increases in CD8+ T cells and B cells in the lungs. The same study also demonstrated that IL-5 deficiency did not affect the growth of primary tumours or the size of metastatic lesions (Zaynagetdinov, 2015).

Interestingly, in an abstract presented in the American Association for Cancer Research Annual Meeting 2024 (Lacouture, 2024), benralizumab was tested in a Phase 2 trial (NCT04552288) in cancer patients with Grade 2/3 eosinophil-related cutaneous adverse events (ercAEs) from PI3K inhibitors, anti-drug conjugates (ADC), checkpoint inhibitors (CPI), or targeted therapies. Benralizumab demonstrated favourable safety and efficacy for Grade 2/3 ercAEs from cancer therapies, without showing association with any cancer related endpoints. It should be noted that the poster did not indicate how soon benralizumab was administered after cancer treatments.

The strongest evidence that eosinophils are not critical cells in human cancers comes from the PASS (Post Authorization Safety Study; EMA 2018) for benralizumab (NCT04991805) that recently posted study results (EMA, 2025). In this study the primary endpoint was to assess the incidence of malignancies in severe asthma patients receiving benralizumab (2531 patients) compared with those receiving non-benralizumab biologics (5824 patients), and those not receiving biologics (4927 patients). While it is not clearly stated in publicly available documents, the 'non-benralizumab biologics' used in the severe eosinophilic asthma population would likely include mepolizumab and reslizumab. The conclusion of this observational study was that there was no observed increase in risk of malignancies associated in the 3 groups that were evaluated. These real world clinical results for an antibody that eliminates eosinophils when combined with studies that reviewed clinical cancer rates in patients using anti-IL-5 mAbs, which only reduce the number of circulating eosinophils (Mota, 2023), provide accumulating clinical evidence that the totality of nonclinical and clinical data with anti-IL-5 and anti-IL-5Ra treatments supports a low risk for these treatments, including depemokimab, as discussed in the weight-of-evidence assessment of carcinogenic potential.

In summary, the malignancy risk in humans from an antibody targeting IL-5 neutralization, such as depemokimab, is considered low based on currently available nonclinical data and more importantly on the evolving clinical safety data with agents targeting IL-5 and eosinophils. See clinical safety section 6.4. for further details.

While the role of IL-5 and eosinophils in tumour surveillance is poorly characterised, this cannot be resolved by the experimental data generated in rodent given the complexity of species-specific differences in immune system and the effects of experimental conditions on the Th1/Th2 balance. Considering the totality of evidence, particularly that 1) the results of the 6-month carcinogenicity in transgenic mice with reslizumab were negative although there exists species differences in immune system, 2) there were no clear clinical evidence with other products in class indicating an increased carcinogenic potential, and that 3) eosinophils are not completely depleted upon depemokimab treatment as the differentiation of eosinophils is also controlled by IL-3, GM-CSF, and SCF, it is concluded that there is insufficient evidence that depemokimap poses a risk of cancer. The applicant's updated weight of evidence is agreed.

<u>Developmental and reproductive toxicity</u>

The *in silico* simulation of an ePPND study with depemokimab at 10 and 100 mg/kg/dose given on gestation day 20, 85, and 150 indicated that the extended half-life of depemokimab did not lead to considerable accumulation of foetal mAb concentrations versus maternal levels. A possible explanation for the lack of considerable accumulation is the fact that FcRn-mediated placental transfer is bidirectional.

The presented *in silico* model is intended to replace an in vivo study, it is therefore essential that all underlying assumptions are transparently described, thoroughly justified, and any potential concerns adequately addressed.

The model was calibrated using an enhanced pre- and postnatal development (ePPND) study conducted with mepolizumab, a compound expected to exhibit similar/same pharmacological properties. This study revealed no developmental toxicity associated with mepolizumab administration. Intravenous administration of mepolizumab to pregnant monkeys did not result in maternal toxicity, nor did it affect pregnancy outcomes or natural delivery. Offspring were passively exposed to mepolizumab *in utero*, with detectable plasma concentrations persisting up to six months postpartum. No adverse effects were observed on the physical, hematologic, or immunologic development of the offsprings. The No Observed Adverse Effect Level (NOAEL) corresponded to the highest administered dose (100 mg/kg). The exposure corresponded to 30 times clinical exposure. Concentrations of the active substance were collected from postpartum day 14 and offsprings were clinically monitored for nine months. It should be noted that no terminal necropsy was performed on the offspring at the end of the study.

The model satisfactorily predicts the measured postpartum concentrations (within a 2–3-fold range). Given that exposure occurred only during gestation and that foetal elimination of the active substance was estimated to be slightly slower than maternal elimination (approximately 15% lower), significant accumulation in the foetus is unlikely. This is consistent with the molecular structure of mepolizumab, a humanised IgG1 antibody. The same model was applied to predict concentrations of depemokimab, which has enhanced affinity for the neonatal Fc receptor (FcRn).

Several assumptions underlying the presented data were not adequately justified, particularly those concerning the equivalence of non-specific pinocytosis rates between the maternal and foetal compartments, as well as the rate of antibody recycling to the maternal compartment. The model assumes that 10% of antibodies are recycled to the maternal compartment. However, in vivo the extent of the recycling process remains insufficiently characterised and is generally considered a minor pathway. Its modulation may depend on factors such as transcytosis saturation or cellular preference for recycling over transcytosis.

It is acknowledged, in agreement with the applicant, that enhanced FcRn alone is unlikely to significantly influence the frequency of the recycling process (beyond the part of antibodies protected by enhanced affinity to the FcRn receptor). Regardless of the recycling extent, this process would primary slow the transfer of antibodies to the foetus, rather than reduce concentrations already present in the foetal circulation. From a physiological perspective, it is unlikely that antibodies that have crossed the placenta and entered the foetal stroma would return to the placenta and re-entered maternal circulation.

Nonetheless, the applicant has presented simulation, where the unidirectional placental transfer is considered. In this simulation, the fetal-to-maternal AUC ratio (during gestation) increased to 0.55 from 0.44 for and the fetal-to-maternal Cmax ratio increased to 1.53 from 1.18.

Furthermore, the crucial parameter of the model is the affinity of depemokimab to FcRn. This value was experimentally evaluated for human receptor; however, initially, data for monkey receptor was not obtained

due to "technical difficulties". The value for human receptor is approximately 13-fold higher compared to mepolizumab. On request, the in *vitro* FcRn binding affinities of depemokimab and mepolizumab were re-evaluated at 25 °C. The results indicate that depemokimab has approximately 4-fold greater affinity for FcRn at pH 6.0 compared to mepolizumab, which is consistent with the values applied in the *in silico* model.

The initial rate of antibody transfer is low but gradually increases during pregnancy. According to the model assumption, the ratio of foetal-to-maternal antibodies is low in the second trimester but slowly increases until the ratio is approximately 1 just prior to birth. To model this phenomena, FcRn creation and degradation reactions as a function of time were added to the compartmental model. Nonetheless, in physiological conditions, the level of classical IgG surpasses the maternal level around the expected date of delivery. This is consistent with the observed experimental data with mepolizumab, where levels of mepolizumab were measurable in infants at about 2.4-fold the maternal plasma concentration just after birth. In addition, molecules with high affinity for the FcRn receptor exhibit an increase (approximately twice) in placental transfer.

Although molecules with increased affinity for the neonatal Fc receptor are expected to cross the placental barrier more efficiently, this is not anticipated to significantly impact the overall DART risk. This conclusion is also supported by the ePPND study conducted with mepolizumab, where administration of doses up to 30-fold higher than the expected clinical exposure did not reveal safety concerns. The results of the placental transfer model suggest that the enhanced FcRn affinity of depemokimab does not result in clinically relevant increases in fetal exposure, as the fetal exposure was very low in mepolizumab already. Even if foetal concentrations were to exceed maternal maximal levels by up to twofold, the margins of safety are considered adequate. Furthermore, no reproductive, developmental, or juvenile toxicities have been reported in genetically modified animals (e.g., IL-5 deficient mice), in studies using mouse anti-rat IL-5 mAbs, or with other in-class mAbs. Overall, a potential slight increase in foetal exposure to depemokimab is not considered to significantly affect the DART risk.

The available literature and non-clinical data indicates that the target biology does not play a role in embryo-foetal development and reproduction.

Considering 1) the youngest intended patient age (≥12 years of age), 2) no target organs identified (neither in the general toxicity studies using adolescent monkeys nor the ePPND study with mepolizumab), 3) available adult clinical data suggesting no safety concerns, and 4) high target selectivity it is agreed that the toxicity risk for adolescent patients treated with depemokimab is low, and a dedicated juvenile animal study is not considered needed.

Based on data presented on other toxicity studies it is agreed that immunogenicity of depemokimab is not considered of clinical concern based on the data available to date.

Compared to mepolizumab, changes in the variable and Fc binding regions of depemokimab could potentially lead to different off-target interactions, affecting the safety profiles of the molecules. The applicant has not discussed secondary pharmacodynamics. No studies investigating secondary pharmacodynamic endpoints were conducted. However, toxicology studies evaluating cross-tissue reactivity did not reveal any interactions with a panel of selective human tissues (39 human tissues, three donors per tissue) at concentrations of 0.63, 2.5 or 5 µg/mL. This suggests that depemokimab does not exhibit significant off-target effects at these concentrations. Additionally, the affinity to FcγRI is comparable to wild-type IgG. The reduced affinity to FcγRIIa and FcγRIIIa, along with a slight increase in affinity to FcγRIIb (1.4 fold) does not indicate an increased risk of ADCP activity. Low affinity to C1q also reduces the potential for CDC activity. No other

signals from toxicology or clinical studies require a specific secondary pharmacology study. The presented data does not indicate significant off-target effects in humans. It can therefore be agreed that no secondary pharmacology studies have been conducted.

No findings indicating increased parasite infections or other immunotoxicity were reported in the clinical settings. Clinical data is considered more relevant, and data on parasite infections will be collected post approval. Therefore, it is agreed that for depemokimab concern for immunotoxicity is low.

No studies were conducted to evaluate the dependence potential of depemokimab.

It is agreed that the dependence potential of depemokimab is considered low as 1) depemokimab due to its large molecule size is not expected to cross the blood-brain-barrier, 2) the PK/PD characteristics of depemokimab are very different from drugs with high dependence potential (usually characterised as rapid onset/short acting acive substances), and 3) absence of abnormal behaviour or withdrawal symptoms upon cessation of dosing in the recovery periods in the repeat dose toxicity study.

Based on the comparability assessment, it is agreed that the toxicological data derived from products generated in Non-Clinical Process 1 can be used to support the safety of the depemokimab intended for commercial use.

Non-clinical data supports sections 4.6. and 5.3 of the SmPC.

## 5.5.2. Conclusions

*Pharmacodynamics*

Depemokimab is an antibody specific for human Interleukin-5 (IL-5) and was adequately characterised by binding studies to IL-5, FCRn receptor, FCγ receptors and complement receptor, and inhibition of IL-5 induced proliferation was demonstrated in vitro. In monkeys, depemokimab sustained suppression of eosinophils that can result in a reduction of an eosinophil-driven inflammatory response in affected tissues.

QTc prolongation was observed in cynomolgus monkey dosed 100 mg/kg resulting in exposure level >70-fold clinical exposure and is considered of low risk for patients.

*Pharmacokinetics*

The pharmacokinetics of depemokimab have been assessed in the Cynomolgus monkey, which is the only species relevant for the toxicity studies. The pharmacokinetic profile of depemokimab in cynomolgus monkeys was as expected for an antibody and adequately described and supports the rationale for the route of administration and the dosing interval.

*Toxicology*

The single dose toxicity, repeat dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, juvenile toxicity, immunogenicity, immunotoxicity, off-target bindings, dependence, comparability and impurities, phototoxicity, extractables and leachables have been adequately addressed via in vivo, ex vivo studies or WoE assessment. From a non-clinical point of view, no serious safety concerns are expected, and the applicant's discussions on the provided data are considered sufficient.

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# 6. Clinical aspects

## *6.1. Introduction*

### 6.1.1. GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

### 6.1.2. Tabular overview of clinical trials

**Table 3: Tabular overview of main clinical studies**

| Study ID | Enrolment status<br>Start date<br>Total enrolment/ enrolment goal | Design<br>Control type | Study & control drugs<br>Dose, route of administration and duration<br>Regimen | Population<br>Main inclusion/ exclusion criteria |
|---|---|---|---|---|
| **Phase 1** | | | | |
| 205722 (FTIH) | Completed<br><br>17 October 2017<br><br>48/48 | Randomised, double-blind, placebo-controlled, single ascending dose | Depemokimab single doses of 2, 10, 30, 100 and 300 mg SC injection<br><br>Placebo SC injection, once | Mild-to-moderate asthma patients, 18-65 years, blood eosinophils ≥200 cells/µL |
| 214099 | Completed<br><br>06 December 2022<br><br>140/140 | Randomised, single-dose | Depemokimab 100 mg SC injection via SSD, once<br><br>Depemokimab 100 mg SC injection via AI, once<br><br>Randomised 1:1 | Healthy participants 18-50 years |
| 208021 | Completed<br><br>10 December 2021<br><br>20/20 | Single-dose, open-label | Depemokimab 100 mg SC injection, once<br><br>Depemokimab 300 mg SC injection, once | Chinese healthy participants 18-45 years |

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| **Phase 3** | | | | |
| SWIFT-1 (206713) | Completed<br><br>17 March 2021<br><br>395/375 | Randomised, double-blind, placebo-controlled, parallel-group | Depemokimab 100 mg SC injection, once every 26 weeks<br><br>Placebo SC injection, once every 26 weeks<br><br>Randomised 2:1 | Inclusion:<br>Adult and adolescent participants ≥12 years with uncontrolled severe asthma with an eosinophilic phenotype, reduced lung function, medium-to-high dose ICS maintenance treatment<br><br>Exclusion:<br>Known immunodeficiency, eosinophilic disease, smoking, prior treatment with mepolizumab, reslizumab, benralizumab (<12 months), omalizumab, dubilumab (<130 days) |
| SWIFT-2 (213744) | Completed<br><br>04 February 2021<br><br>397/375 | | | |
| AGILE (212895) | Ongoing<br><br>01 March 2022<br><br>640/750 | Open-label extension | Depemokimab 100 mg SC injection, once every 26 weeks | Inclusion:<br>Participants who completed study intervention treatment during SWIFT-1 or SWIFT-2<br><br>Exclusion:<br>Clinically significant change in health status |
| NIMBLE (206785) | Ongoing<br><br>26 January 2021<br><br>1090/1700 | Randomised, double-blind, double-dummy, parallel-group, noninferiority | *Test*<br>Depemokimab 100 mg SC injection, once every 26 weeks<br><br>Placebo SC injection, once every 26 weeks<br><br>*Comparator*<br>Mepolizumab 100 mg SC injection, once every 4 weeks<br><br>Placebo SC injection, once every 4 weeks<br>*OR*<br>Benralizumab 30 mg SC injection, once every 8 weeks<br><br>Placebo SC injection, once every 8 weeks<br>Test vs. comparator randomised 1:1 | Adult and adolescent participants ≥12 years with severe asthma with an eosinophilic phenotype who have benefitted from mepolizumab or benralizumab on annualised rate of clinically significant exacerbations, medium-to-high dose ICS maintenance treatment<br><br>Exclusion:<br>Treatment with omalizumab, dubilumab, reslizumab (<130 days) |

| | | | | |
|---|---|---|---|---|
| ANCHOR-1 (217095) | Completed<br><br>22 April 2022<br><br>276/250 | Randomised, double-blind, placebo-controlled, parallel-group | Depemokimab 100 mg SC injection, once every 26 weeks<br><br>Placebo SC injection, once every 26 weeks<br>Randomised 1:1 | Inclusion:<br>Adult participants ≥18 years with CRSwNP, with prior treatment with systemic CS <2 years, and/or contraindication/ intolerance to systemic CS, and/or documented history of prior surgery for NP<br><br>Exclusion:<br>Known immunodeficiency, eosinophilic disease, prior treatment with mepolizumab, reslizumab, benralizumab (<12 months), omalizumab, dupilumab (<130 days) |
| ANCHOR-2 (218079) | Completed<br><br>18 April 2022<br><br>264/250 | | | |

AI = autoinjector; CS = corticosteroids; CRSwNP = chronic rhinosinusitis with nasal polyps; NP = nasal polyps; SC = subcutaneous; SSD = safety syringe device

## *6.2. Clinical pharmacology*

Depemokimab (GSK3511294) is a humanised, affinity matured mAb that prevents human IL-5 from binding to its receptor. Depemokimab is engineered to have an extended half-life and improved IL-5 potency, allowing less-frequent dosing compared with currently approved anti-IL-5 therapies. As a long-acting anti-IL-5 therapy, depemokimab is anticipated to deliver similar efficacy and safety as currently approved therapies in its class but with a single administration every 26 weeks, as opposed to the current regimen of every 4 weeks for mepolizumab and reslizumab or every 8 weeks for benralizumab (every 4 weeks for the first 3 doses). The clinical pharmacology studies in healthy volunteers and patients are summarised in Table 4, focussing on PK aspects.

**Table 4: Studies relevant for the PK/PD evaluation**

| Studies | Phase | Population | Treatments | Route | Device | Assessment design |
|---|---|---|---|---|---|---|
| 205722[1] | 1 | Adult asthma patients with BEC ≥ 200 cells/μL at screening | Depemokimab 2, 10, 30, 100, 300 mg or placebo as a single dose | SC | syringe + vial | **PK:** 2 and 8h, and 1, 2, 4, 7, 14, 28, 56, 84, 126, 168, 182, 224, 252 and 280 days post-dose[a] |
| 208021[2] | 1 | Chinese HVs | Depemokimab 100 or 300 mg as a single dose | SC | SSD | **PK:** 2 and 8h, and 1, 2, 4, 7, 14, 28, 56, 84, 126, 168, 182 and 210 days post-dose |
| 214099[3] | 1 | HVs | Depemokimab 100 mg as a single dose | SC | SSD or autoinjector | **PK:** 2 and 8h, and 1, 2, 4, 7, 14, 28, 56, 84, 126, 168 and 182 days post-dose |
| 206713[4] | 3 | Adult and adolescent (≥ 12 years) asthma patients with BEC ≥ 300 cells/μL in the past 12 months prior to Visit 1 or ≥ 150 cells/μL at Screening Visit 1 | Depemokimab 100 mg or placebo at Week 0 and Week 26 | SC | SSD | **PK:** 14, 28, 56, 84, 140, 182, 196, 224, 280 and 364 days post-first dose |
| 213744[5] | 3 | Adult and adolescent (≥ 12 years) asthma patients with BEC ≥ 300 cells/μL in the past 12 months prior to Visit 1 or ≥ 150 cells/μL at Screening Visit 1 | Depemokimab 100 mg or placebo at Week 0 and Week 26 | SC | SSD | **PK:** 14, 28, 56, 84, 140, 182, 196, 224, 280 and 364 days post-first dose |
| 217095[6] | 3 | Adult (≥ 18 years) CRSwNP patients with no specific BEC inclusion criteria | Depemokimab 100 mg or placebo at Week 0 and Week 26 | SC | SSD | **PK:** 28, 56, 84, 140, 182, 196, 224, 280 and 364 days post-first dose |
| 218079[7] | 3 | Adult (≥ 18 years) CRSwNP patients with no specific BEC inclusion criteria | Depemokimab 100 mg or placebo at Week 0 and Week 26 | SC | SSD | **PK:** 28, 56, 84, 140, 182, 196, 224, 280 and 364 days post-first dose |

[a] After Week 26, PK sampling depended on the treatment group as follows: no more samples for the 10 mg treatment group; PK sample on day 252 after dose for the 30 and 100 mg treatment groups; PK samples on days 224 and 280 after dose for the 300 mg treatment group.
See **Glossary** for clarification of abbreviations.

## 6.2.1. Methods

### *6.2.1.1. Bioanalytical methods*

Depemokimab concentrations in human plasma for the FTIH study were quantitated by a validated ElectroChemiLuminescence (ECL) immunoassay. The assay was validated according to current standards. Subsequent studies were outsourced and using validated ECL immunoassays with a calibration range of 100 to 5000 ng/mL.

Validation experiments investigated verification of assay range, inter- and intra-assay accuracy and precision, selectivity (matrix effect), specificity, stability, dilutional linearity, parallelism, incurred sample re-analysis and robustness (e.g. incubation time, equipment and analyst) for all labs and showed adequate performance and met the criteria of the relevant guidance.

Accuracy and precision data for the bioanalytical assays that supported serum depemokimab concentration determinations in clinical study samples showed that for the QC samples accuracy (%bias) was within the ranges of −7.3% to 11.7% and precision (%CV) was ≤11.1% for all clinical studies (all < 20%).

Several non-zero concentrations were reported for the Week 0 D1 pre-dose sampling time-point in Phase I and Phase III studies. The applicant confirmed that the participants of the studies were treatment naïve. The applicant discussed the possibility of sample contamination, interference with another anti-IL-5 drug, and the selectivity of the bioanalytical methods used. The overall incidence of detectable depemokimab levels in baseline pre-dose samples across all studies was less than 3.4 %. It was concluded that the impact of unexpected baseline non-zero concentrations on pharmacokinetic results was negligible.

In general, storage periods of PK samples at the clinical sites and bioanalytical labs seemed to be covered by the sufficiently long, validated, long-term stability data showing stability at −20°C for 712 days and at −70°C for 907 days.

Incurred Sample Reanalysis results were sufficient with ≤30% deviation for ≥67% of reanalysed samples in all studies.

The GSK assay and Frontage US assay were cross validated using spiked QC samples and the 2 Frontage assays were then cross validated using QC samples and incurred samples to ensure the data interchangeability.

#### *6.2.1.2. PD biomarkers*

The assay for total IL-5 measurement was validated. Total IL-5 was quantitated in human serum for FTIH study at Resolian in Malvern (US). The applicant claims the analytical method is selective, sensitive, precise, and accurate for the determination of total IL-5 in human serum over an analytical range of 16 to 10000 pg/mL. No significant interference effect of depemokimab on the quantification of IL-5 was observed in the test with high concentrations (1 and 100 µg/mL) of depemokimab.

#### *6.2.1.3. Immunogenicity*

An analysis strategy to investigate immunogenicity for depemokimab was provided. The Anti-Drug Antibodies (ADA) assays utilised a homogenous bridging format of ECL assays. The Neutralizing Antibodies (Nab) assays were competitive Ligand Binding Assays. The ADA positive control was a rabbit polyclonal antibody. The NAb positive control was anti-depemokimab mouse monoclonal Ab (mAb027).

The first-generation ADA assay, used in the 205722 (FTIH) Phase 1 study, used acid dissociation to enhance drug tolerance, achieving a drug tolerance of 50 µg/mL at 250 ng/mL ADA and 1.6 µg/mL in the confirmatory assay. The assay sensitivity was 19.53 ng/mL, and specificity to IL-5 was limited, tolerating only up to 313 pg/mL in screening and 1.25 ng/mL in confirmatory assays. The screening cut point produced a 6.0% false positive rate, within the accepted 2–11% range. The confirmatory cut point for a 1% false positive rate was 25.17%.

The other clinical studies used second-generation assays developed at US and China Frontage laboratories, which showed improved performance. The US assay had a sensitivity of 8.7 ng/mL, with a drug tolerance of 50 µg/mL at 250 ng/mL ADA. The normal and diseased serum confirmatory cut points targeting 1% false positive rate were calculated to be 18.41% and 18.25%, respectively. The China assay had a sensitivity of 3.52 ng/mL. The normal and diseased serum confirmatory cut points targeting 1% false positive rate were calculated to be 11.08% and 9.74%, respectively. The China assay tolerated less IL-5 interference. Even though the China-CRO had a 2-fold better sensitivity, a 2-fold lower confirmation cut point due to lower sample analysis variability, but also 6-fold lower target interference, cross-validation confirmed assay comparability.

Neutralizing antibody (NAb) assays, including methods from GSK, US Frontage, and China Frontage, showed comparable sensitivities (GSK: 95.3 ng/mL; US: 94.14 ng/mL; China: 107 ng/mL) and drug tolerance (GSK: up to 30 µg/mL; US: 20.9 µg/mL; China: 5 µg/mL at 500 ng/mL Positive Control levels). Confirmatory IL-5 tolerance was up to 100 ng/mL. Assay cut points targeted a 1% false positive rate.

ADA and NAb assays were validated in accordance with the guidelines. The employed two-tiered strategy including a screening, confirmatory and neutralization assay is in agreement with the Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010). The method was adequately validated and cross-validated for the use at different laboratories.

#### *6.2.1.4. Statistical analysis*

The PK parameters in the intense PK sampling studies were analysed using ANOVA models where PK parameters were logarithmically transformed and relevant contrasts with corresponding 90% confidence intervals (CIs) were calculated. For study 205722 a power model was used to check for dose proportionality.

### 6.2.2. Pharmacokinetics

#### *6.2.2.1. Introduction*

Pharmacokinetics of depemokimab were investigated in healthy and mild-to-moderate asthmatic participants, target patient Asthma and CRSwNP populations, and special populations.

Conventional non-compartmental data analysis was used for all pharmacokinetic studies with intense sampling (FTIH: 205722, China PK: 208021, and PK comparability 214099). Population PK was used to determine the PK in patients where sparse sampling was employed (Section 6.2.2.2. Evaluation and qualification of models).

#### *6.2.2.2. Evaluation and qualification of Population PK model*

A population PK meta-analysis of PK data from the four Phase 3 studies in the asthma and CRSwNP target patient populations and the three Phase 1 studies in healthy and mild-to-moderate asthmatic participants was performed. The analysis was done specifically to characterize the depemokimab pharmacokinetics in these populations and to evaluate the impact of intrinsic and extrinsic factors (covariates).

The depemokimab PK data were well described by a 1-compartment PK model with first-order absorption and elimination, parameterised in terms of first-order absorption ka, Frel, CL, and V. Variability between participants in PK parameters were characterised in ka, Frel and CL (Table 5).

**Table 5: Parameter estimates of the final depemokimab PK model**

| | Unit | Value | RSE (%) | SHR (%) |
|---|---|---|---|---|
| CL/F | (L/day) | 0.0920 | 0.860 | |
| V/F | (L) | 6.29 | 0.997 | |
| WT on CL | (allo. exponent) | 0.841 | 3.78 | |
| WT on V | (allo. exponent) | 0.887 | 3.64 | |
| $F_{rel}$ | | 1.00 | (FIX) | |
| $k_a$ | (/day) | 0.212 | 4.05 | |
| TAD < 3h on RUV | † | 5.18 | 7.58 | |
| CRSwNP participant population on CL | (frac. change) | 0.0625 | 16.3 | |
| Albumin on CL | (frac. change per g/L) | -0.00684 | 23.2 | |
| Estimated glomerular filtration rate on CL | (frac. change per mL/min/1.73 $m^2$) | 0.00134 | 17.1 | |
| Asian race on V | (frac. change) | 0.0788 | 17.5 | |
| CRSwNP participant population on $F_{rel}$ | (frac. change) | -0.0509 | 29.3 | |
| Age on $k_a$ | (frac. change per year of age) | -0.00735 | 31.3 | |
| Abdomen injection site on $k_a$ | (frac. change) | 0.520 | 23.9 | |
| Study population FTIH Asthma on CL | (frac. change) | 0.155 | 12.9 | |
| Study population China PK HV on CL | (frac. change) | -0.219 | 8.79 | |
| 2 mg dose on CL | (frac. change) | -0.349 | 71.1 | |
| Participant population HV on V | (frac. change) | -0.0513 | 24.9 | |
| Study population FTIH Asthma on $F_{rel}$ | (frac. change) | -0.173 | 17.2 | |
| Participant population HV on $k_a$ | (frac. change) | 0.588 | 21.0 | |
| Study population FTIH Asthma on $k_a$ | (frac. change) | 0.627 | 23.6 | |
| Study population China PK HV on $k_a$ | (frac. change) | 0.405 | 27.9 | |
| | | | | |
| IIV CL | (CV) | 0.101 | 6.06 | 10.2 |
| IIV $F_{rel}$ | (CV) | 0.167 | 3.52 | 8.49 |
| IIV $k_a$ | (CV) | 0.351 | 6.37 | 24.7 |
| Correlation IIV $F_{rel}$ - IIV $k_a$ | (Cor) | 0.638 | 6.74 | |
| IIV RUV | (CV) | 0.488 | 4.20 | 0.361 |
| | | | | |
| RUV | (CV) | 0.178 | 1.95 | 2.04 |

The IIV and RUV parameters are reported on the SD scale, which for exponential IIV and additive RUV on the log-scale corresponds to the approximate CV scale. The RSE for IIV and RUV parameters are reported on the approximate SD scale. The RSE for the correlation is reported for the square-root of the eta covariance. The continuous covariate effects are defined as the fractional change in parameter per one unit change in covariate. Allometric exponents are unitless as defined with power models.

† Defined as the fractional change in RUV magnitude.

The estimated typical parameters are the values for a 75 kg, 50 years old, non-Asian SWIFT Asthma patient, with baseline albumin of 45 g/L and baseline eGFR of 93.53 mL/min/1.73$m^2$, receiving a dose of depemokimab, into the upper arm or thigh.

The differences that were observed for HVs and/or phase 1 studies were mainly explained by study effects, which may represent the differences between study phases, assays and/or protocols. These study effects were needed in order to describe the typical depemokimab plasma concentration-versus-time profiles in the different studies. It should be noted that this makes the PopPK model less useful for predicting scenarios outside the range of studies and data.

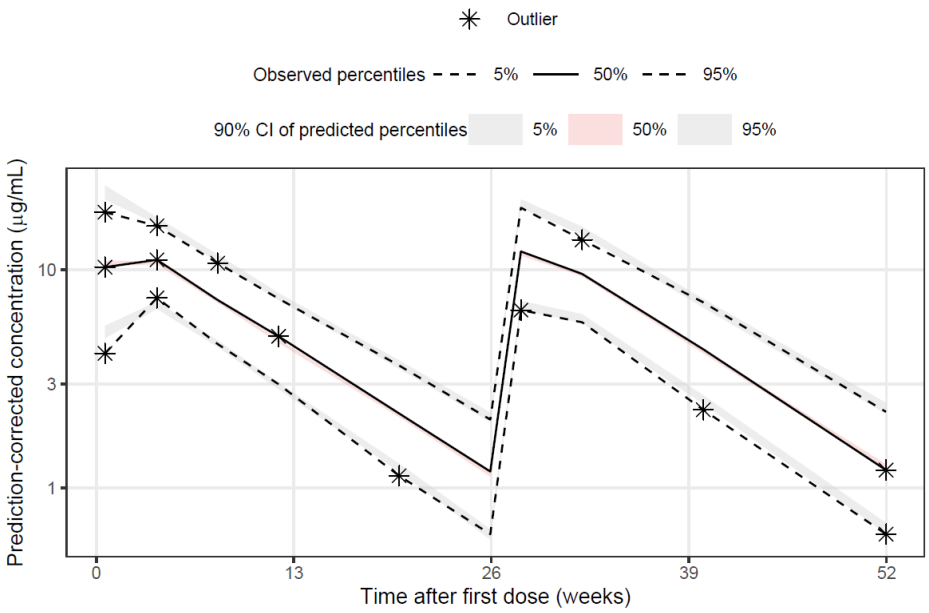
The effect of covariates on depemokimab $AUC_{tau,ss}$ were illustrated in forest plots (see Section 6.2.2.13. ). No differences were observed based on the parameters age, race, or injection site. An effect on depemokimab $AUC_{tau,ss}$ was observed for parameters body weight, albumin, eGFR, and target population.

Furthermore, for the studies (FTIH: 205722, China PK: 208021, PK comparability 214099, SWIFT-1: 206713, SWIFT-2: 213744, ANCHOR-1: 217095, and ANCHOR-2: 218079) parameter estimates from the population PK analysis (one-compartment model with first-order absorption and first-order elimination) were consistent with the results from the non-compartmental analysis (FTIH: 205722, and China PK: 208021).

The individual PK exposure metrics were subsequently used as input in exposure-response analyses. Visual predictive checks of the final depemokimab PK model were provided to compare the predictive performance to real world data of the China PK, device PK, FTIH, SWIFT, and ANCHOR studies. A sufficient predictive performance of the model based on the real-world concentration data measured in the different studies was observed with confidence intervals similar to observed data.

In general, the popPK model for depemokimab can be considered fit-for-purpose as demonstrated by parameters estimated with acceptable precision and shrinkage (<30%) (Table 5) and VPCs which show no major deficiencies (Figure 1). However, as various study effects were needed in order to describe the typical depemokimab plasma concentration-versus-time profiles in the different studies, the PopPK model is considered less useful for predicting scenarios outside the range of studies and data.

**Figure 1 Prediction-corrected visual predictive check of depemokimab plasma concentrations versus time after first dose, for the depemokimab PK analysis data set, using the final depemokimab PK model.**




### *6.2.2.3. Absorption*

The absorption of depemokimab has been characterised by 2 PK studies; A FTIH study (214099) and a China PK study (208021):

FTIH study conclusions:

Following a FTIH study where several ascending single SC doses of depemokimab in participants with mild-to-moderate asthma were investigated, the pharmacokinetics of depemokimab were found to be dose proportional over the SC dose range 10 – 300 mg. There was a less than dose proportional increase from

2 mg to 10 mg, based on $AUC_{0-\infty}$ and $C_{max.}$ The geometric mean terminal phase half-life (38 to 53 days) was increased approximately two-times compared with conventional IgG1 monoclonal antibodies targeting soluble ligands, due to the YTE mutation incorporated into the Fc domain of the molecule. Preliminary population PK analysis was conducted, and results were consistent with the non-compartmental analysis.

For further results, see Section 6.2.2.10.

China PK study conclusions:

PK of depemokimab was dose-proportional following a single SC dose of 100 mg or 300 mg depemokimab in Chinese healthy participants. The geometric mean CL/F, Vz/F and $t_{1/2}$ of depemokimab were estimated to be approximately 0.058 L/day, 5 L, and 59 days, respectively, following single SC dose of 100 mg or 300 mg depemokimab in Chinese healthy participants. No dose-dependency in these PK parameters was observed. CL in Chinese at 100 mg and 300 mg depemokimab is lower at 0.059-0.0.057 L/day compared to the FTIH study where CL values ranged from 0.118 to 0.160 L/day. In Chinese a longer $t_{1/2}$ of about 59 days compared to the FTIH study $t_{1/2}$ of 39-40 days was also observed. In conclusion, CL in Chinese is about 50% lower and $t_{1/2}$ about 45% longer when compared to the FTIH study. This effect could partially be explained by the lower body weight of Chinese. However, the forest plot in Section 6.2.2.13. indicates lower bodyweight can result in approximately 33% higher $AUC_{tau,ss}$ and not 50%. Please refer to discussion and conclusions on clinical pharmacology section 6.2.6.

Overall, following a single subcutaneous administration (doses ranging from 2 to 300 mg), maximum observed plasma concentrations (Cmax) were achieved at a median time ranging from 8 to 14 days. After a single subcutaneous administration of 100 mg depemokimab, the average Cmax (%CV) was 12.2 mcg/mL (16%).

#### *6.2.2.4. Bioavailability*

No biopharmaceutic study was conducted to estimate the absolute bioavailability of depemokimab following SC administration. Depemokimab has not been administered using an IV formulation in humans.

A relative bioavailability study was conducted in order to compare SC administration of SSD and AI injection devices at various body sites. Following a single 100 mg SC dose administered to healthy participants the depemokimab $C_{max}$, $AUC_{0-\infty}$ and $AUC_{0-t}$ were comparable between the AI and the SSD injection devices, with the 90% CIs within the conventional bioequivalence acceptance range of 80-125%.

Depemokimab $C_{max}$ and other PK parameters across the 3 sites of injection (arm, abdomen, and thigh) overlapped and did not markedly differ, irrespective of the treatment groups (SSD and AI injection devices).

#### *6.2.2.5. Formulation development*

Four drug substance (DS) manufacturing processes (Process 1 [non-clinical and clinical], Process 2, Process 3a and the proposed DS manufacturing process [], Process 3b) and their associated drug product (DP) configurations were used to support non-clinical and clinical studies of the marketing application. The DS and DP have the same formulation with the exception of the depemokimab concentration. For further assessment of the different formulations, reference is made to Quality Section 4.3.

The various AS and FP formulations are not expected to have impacted the assessment of the pharmacokinetic properties of depemokimab.

#### *6.2.2.6. Influence of food*

Food can affect the pharmacokinetics and bioavailability of orally administered drugs. This application concerns a SC injection of depemokimab, and therefore studies to assess the effect of food on depemokimab absorption are not relevant.

#### *6.2.2.7. Distribution*

In healthy and mild-to-moderate asthmatic participants, depemokimab distributes into a central volume and declines in a mono-exponential manner after SC administration. Point estimates of geometric mean values or apparent volume of distribution (Vz/F) ranged from 6 to 9 L. This is consistent with the general biodistribution of monoclonal antibodies that have limited ability to cross cellular membranes due to their size (~150 kDa) and are primarily confined to the vascular and interstitial spaces. For depemokimab Vz/F was consistent and independent of dose across all studies, indicating dose linear pharmacokinetics.

The mean popPK value for Vz/F was 6.3 L (see Table 5 above).

#### *6.2.2.8. Metabolism*

Depemokimab is a humanised IgG1 monoclonal antibody that is catabolised by ubiquitous proteolytic enzymes, not restricted to hepatic tissue. Since the target for depemokimab is a soluble cytokine (not a membrane-bound receptor), it does not undergo target-mediated degradation. The normal catabolic degradation of depemokimab to small peptides and individual amino acids is not expected to be impacted by hepatic impairment.

#### *6.2.2.9. Elimination*

Overall, $t_{1/2}$ was consistent across studies and independent of dose. After SC administration, geometric mean $t_{1/2}$ ranged from 38-53 days.

#### *6.2.2.10. Dose proportionality and time dependency*

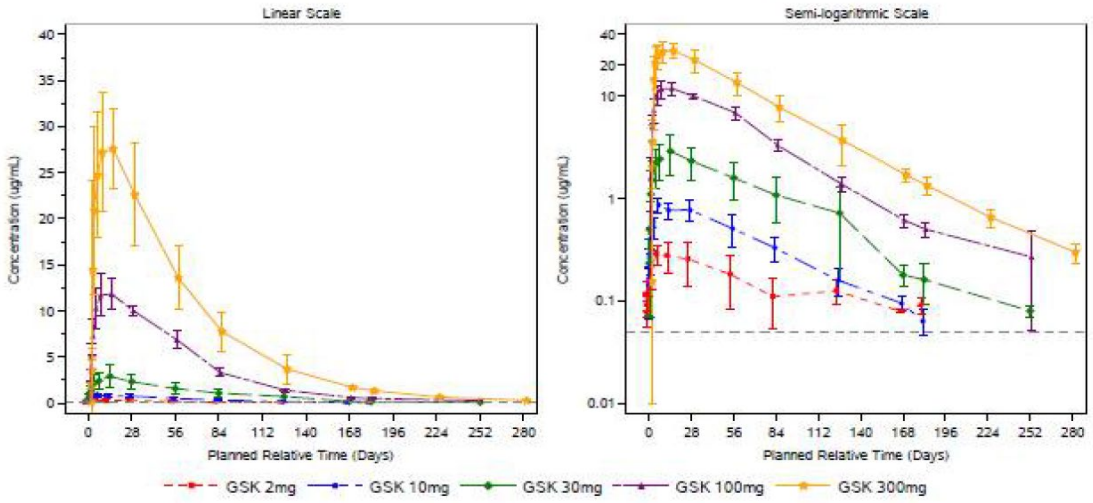
##### 6.2.2.10.1. Dose proportionality

Results of the FTIH study indicate that the pharmacokinetics of depemokimab are linear and dose-proportional over the SC dose range 10 – 300 mg (Table 6 and Figure 2).

**Table 6: Summary of Depemokimab Plasma PK Parameters Following Single SC Administration of Different Doses of Depemokimab in Caucasian Participants with Mild-to-Moderate Asthma**

| Parameter (units) | Depemokimab SC Administration | | | | |
|---|---|---|---|---|---|
| | 2 mg (N=6) | 10 mg (N=6) | 30 mg (N=9) | 100 mg (N=9) | 300 mg (N=6) |
| n | 6 | 6 | 9 | 9 | 6 |
| $AUC_{0-\infty}$ | 24.8 | 68.9 | 208.3 | 846.7 | 1873.7 |
| (day*µg/mL)[1] | 51.6 | 23.6 | 39.6 | 7.3 | 25.5 |
| $AUC_{0\text{-}Week26}$ | 21.8 | 64.5 | 199.9 | 805.4 | 1789.5 |
| (day*µg/mL)[1] | 42.7 | 24.3 | 39.9 | 7.7 | 26.3 |
| $C_{max}$ | 0.3 | 0.9 | 2.8 | 12.2 | 28.6 |
| (µg/mL)[1] | 25.3 | 18.3 | 41.1 | 15.9 | 23.3 |
| $T_{max}$ | 11.0 | 8.0 | 13.9 | 14.0 | 13.9 |
| (day)[2] | (7.0, 28.0) | (7.0, 28.9) | (4.0, 28.0) | (4.0, 16.0) | (2.0, 15.0) |
| CL/F | 0.1 | 0.1 | 0.1 | 0.1 | 0.2 |
| (L/day)[1] | 51.6 | 23.6 | 39.6 | 7.3 | 25.5 |
| Vz/F | 6.1 | 9.2 | 7.8 | 6.6 | 9.3 |
| (L)[1] | 37.6 | 34.7 | 40.4 | 12.1 | 30.6 |
| $t_{1/2}$ | 52.5 | 43.9 | 37.6 | 38.9 | 40.4 |
| (day) [1] | 37.3 | 16.2 | 10.7 | 11.7 | 6.3 |

**Figure 2: Mean (±SD) Depemokimab Plasma Concentration-Time Plot Following Single Subcutaneous Administration of Depemokimab at 2, 10, 30, 100 or 300 mg in Participants with Mild-to-Moderate Asthma (Linear and Semi-Log)**




Drug name is referred as "GSK" in the figure, however, it denotes depemokimab.
Dashed line represents LLOQ.

#### 6.2.2.10.2. Accumulation

The applicant states that no accumulation was observed for depemokimab after two consecutive doses only. This statement is made based on clinical studies in which subjects received a dose in week 0 and in week 26. Furthermore, significant accumulation was also not present in simulations of the popPK model.

An accumulation index of approximately 1.10 is calculated from the worst-case scenario of a $t_{1/2}$ of 53 days with an interval of 182 days. In addition, no accumulation was observed in the target population based on two administrations. Based on these results alone it is likely that no relevant accumulation may be expected for depemokimab with a dosing interval once every 6 months.

The geometric mean half-life of 48 days in the SWIFT and ANCHOR study participants suggests that steady-state conditions are expected around 240 days. The dosing interval of 182 days is relatively long for the half-life of 48 days. Therefore, despite the long half-life, depemokimab accumulation is negligible following repeat dosing (>1 dose). The final depemokimab PK model was used to simulate four doses of depemokimab over a two-year period, assuming linear PK over time. In the 2-year simulations, the PK parameters remained relatively stable, with accumulation ratios below 10%, which is not considered clinically relevant.

#### 6.2.2.10.3. Time dependency

Depemokimab pharmacokinetics are expected to remain stable over time. This is supported by the results from the popPK analysis that do not suggest any changes to primary PK parameters over time, as no time-dependent adjustments were needed to fit the data. However, the popPK data consists of only 2 consecutive doses and therefore this is not considered sufficient proof of no changes in PK over time. The wide range of baseline BEC (reflecting variation in levels of type 2 inflammation) in the popPK analysis dataset was not found to impact the depemokimab CL. This suggests that within-patient changes in asthma or CRSwNP disease status over time are not very likely to result in relevant changes in depemokimab CL.

Data from the long-term extension study AGILE show that there was sustained and consistent blood eosinophil count suppression over a total treatment duration of up to two years. Even though PK was not measured, this suggests there were no significant changes in depemokimab CL over time. Furthermore, there have also been no observations of significant changes in mepolizumab CL over time, and review of literature evidence does not suggest time-dependent CL of therapeutic proteins used in type 2 inflammatory conditions.

### *6.2.2.11. Intra- and inter-individual variability*

Inter-individual variability of depemokimab was investigated in the FTIH study (study 205722) and China PK study (study 208021).

For the non-compartmental analysis of the FTIH study between-subject CV for AUC is 7-8% and for $C_{max}$ 16% for the 100 mg dose. For the non-compartmental analysis of the China PK study between-subject CV for AUC is 12-13% and for $C_{max}$ 18% for the 100 mg dose.

Within-subject variability was not provided nor calculated in any of the PK studies.

From the Empirical Bayes estimates and predicted secondary PK parameters from the popPK analysis all between-subject CV values were estimated to be below 30%.

Overall, the intra- and inter-individual variability was low to moderate, below 30% both for $C_{max}$ and AUC and below 40% for $C_{trough}$.

### *6.2.2.12. Pharmacokinetics in the target population*

Pharmacokinetics was further evaluated as other objective in four Phase 3 studies assessing efficacy and safety of depemokimab on patients with severe uncontrolled asthma of eosinophilic type (studies 206713 Swift 1 and 213744 Swift 2) and patients with chronic rhinosinusitis with nasal polyps (studies 217095 Anchor 1 and 218079 Anchor 2). Within these studies, the concentration-time profile of 100 mg depemokimab administered subcutaneously at week 0 and week 26 was monitored.

For the Asthma studies maximum depemokimab plasma concentrations were observed 2 weeks after depemokimab 100 mg SC dosing on Day 1 and Week 26, followed by a gradual, monophasic decline in concentrations over the remainder of the dosing interval.

In the Swift 1 study, 250 of the 259 randomised participants were included in the PK population. Concerns regarding data integrity and GCP deviations resulted in the closure of site no. 250190 and the exclusion of 7 subjects from PK analysis. The reason for exclusion of the remaining 2 subjects was given as not having received treatment after randomization. Swift 1 study also included 8 adolescent participants within age group of 12 – 17 years (3 [1%] in depemokimab group and 5 [4%] in placebo group).

In the Swift 2 study, no detectable depemokimab concentrations were reported for 7 participants assigned to depemokimab group at Site 251152 at all sampling timepoints with the exception of Week 20 visit. The samples that were BLQ were re-analysed confirming the BLQ results. These pharmacokinetic results were unexpected for participants receiving a complete dose of depemokimab at Day 1 and Week 26 and a full investigation has been performed by the applicant. Although the reason for undetectable plasma concentrations of depemokimab in these participants was not identified, this issue raised a GCP concern. Since these subjects were included in the PK dataset, this incident is not considered to have an impact on the study reliability.

For the CRSwNP studies maximum depemokimab plasma concentrations were observed 4 and 2 weeks after depemokimab 100 mg SC dosing on Day 1 and Week 26, respectively (the first sampling timepoint post dosing). Maximum concentrations were followed by a gradual, monophasic decline in concentrations over the remainder of the dosing interval. However, here the restricted sampling time points should be taken into account. In the Phase I PK studies with more dense sampling median time to peak concentration ranged from 8 to 14 days.

Exposure in Asthma patients was on average 14% higher as compared to the CRSwNP patients, which was not considered clinically relevant.

A summary of the popPK results in the Asthma and CRSwNP target patient populations was provided (Table 7). A low variability in primary and secondary PK parameters was observed.

**Table 7: Derived secondary PK parameters for participants receiving depemokimab 100 mg SC Q26W, stratified by target patient population**

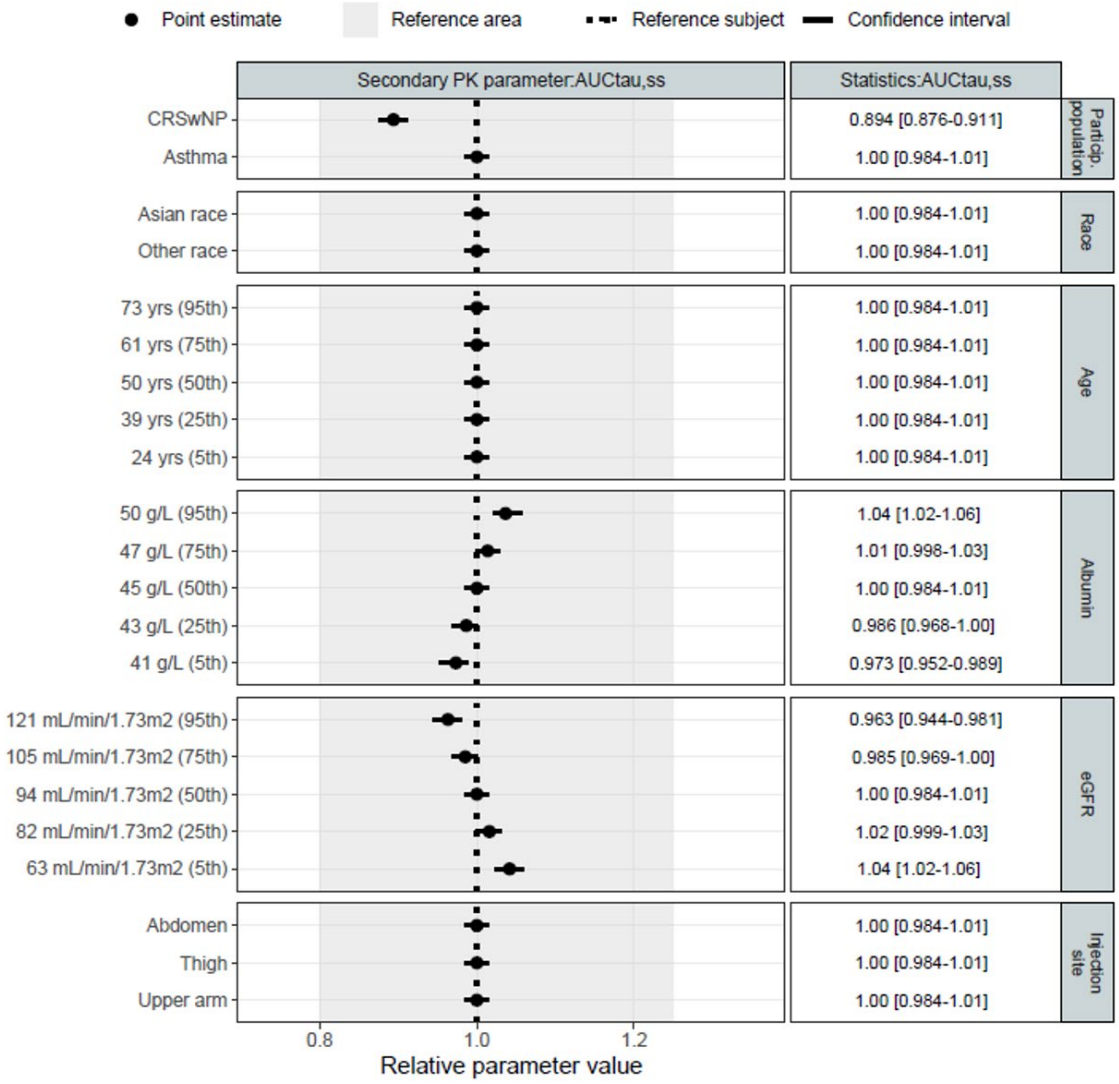
| Parameters: geometric mean (%CV) | Asthma | CRSwNP | Overall |
|---|---|---|---|
| | N=494 | N=272 | N=766 |
| $AUC_{tau,ss}$ (µg*day/mL) | 1081 (27.75) | 950.3 (26.57) | 1033 (28.06) |
| $C_{av,ss}$ (µg /mL) | 5.939 (27.75) | 5.221 (26.57) | 5.674 (28.06) |
| $C_{max,26-52}$ (µg/mL) | 13.63 (27.69) | 12.46 (27.32) | 13.20 (27.90) |
| $C_{trough,week26}$ (µg/mL) | 1.227 (37.00) | 0.9817 (35.74) | 1.134 (38.27) |
| $C_{trough,week52}$ (µg/mL) | 1.315 (38.37) | 1.041 (37.03) | 1.211 (39.73) |
| $t_{1/2}$ (day) | 48.55 (9.645) | 45.75 (9.529) | 47.54 (10.01) |
| $T_{max\ 0-26}$ (day) | 14.21 (2.673) | 13.99 (2.650) | 13.17 (3.432) |
| $T_{max\ 26-52}$ (day) | 13.81 (2.530) | 13.64 (2.529) | 12.83 (3.278) |

In summary, across all four Phase 3 studies, very similar mean plasma concentration profiles of depemokimab were observed. Maximum concentrations were mostly detected two weeks after dosing and were followed by a gradual decline in concentration over the remainder of the dosing interval. Similar pre-dose concentrations at week 26 and week 52 indicate no depemokimab accumulation.

#### *6.2.2.13. Special populations*

Assessment of covariates was done in a phased approach, testing structural covariates (such as albumin) and exploratory covariates (such as race), sequentially. The final model included the following covariate-parameter relationships applicable to the target population, in addition to body weight: albumin, eGFR and participant population CRSwNP on CL; Asian race on V; abdomen injection site and age on ka; and participant population CRSwNP on $F_{rel}$. Figure 3 demonstrated the impact of these factors on $AUC_{tau,ss}$. For the effect of body weight on $AUC_{26weeks,ss}$, see Section 6.2.2.13.6.

**Figure 3 Forest plots illustrating the effects of covariates on depemokimab $AUC_{tau,ss}$**



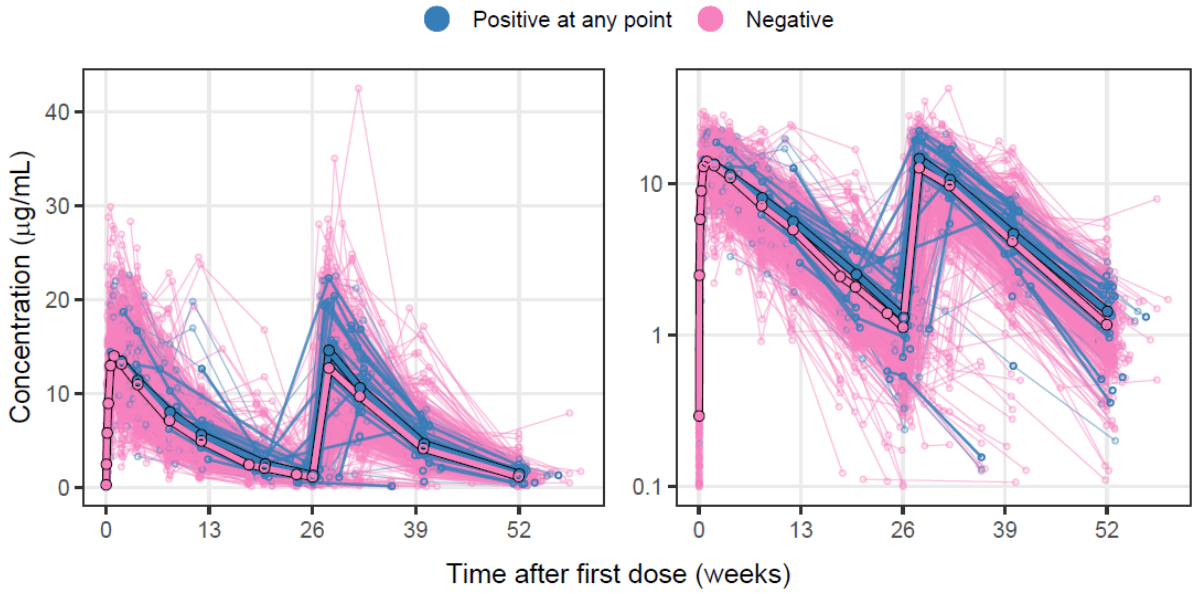

Reference: 76 kg, 50 years, non-Asian asthma patient, with baseline albumin of 45 g/L and baseline eGFR of 94 mL/min/1.73m², receiving a dose of depemokimab 100 mg, into the upper arm

#### 6.2.2.13.1. Immunogenicity

Anti-depemokimab antibodies did not impact the pharmacokinetics of depemokimab and there was no evidence of a correlation between antibody titres and changes in eosinophil level. The overall incidence of ADA positive status in any time point was 8.1%. No major differences in depemokimab concentrations were observed between ADA positive and ADA negative subjects. There was no identified clinically significant effect of ADA on the pharmacokinetics of depemokimab.

The population PK analyses further indicated that ADA status was not found to be a significant covariate describing the PK of depemokimab. In Figure 4 the individual depemokimab plasma concentrations over time colored by the ADA status are displayed. The plot confirms that anti-depemokimab antibodies do not seem to impact the concentration-versus-time profiles of depemokimab.

**Figure 4: Individual observed depemokimab plasma concentrations versus time after first dose for the subjects receiving the dose of 100 mg in the depemokimab PK analysis data set, colored by (time-invariant) ADA status.**




#### 6.2.2.13.2. Impaired renal function

Depemokimab is a humanised IgG1 monoclonal antibody with a large molecular weight of around 150 kDa. It is eliminated by glomerular filtration and therefore changes in renal function should not affect the elimination. The applicant did not perform a renal impairment study.

eGFR was found to be positively correlated with CL/F in the popPK model. This relationship was of small magnitude and is not believed to be due to direct elimination via the kidneys, but has been observed for other mAbs used in inflammatory diseases.

In total 32 subjects were included with eGFR values <60 mL/min/1.73m$^2$, of which 2 subjects had eGFR values <30 mL/min/1.73m$^2$. Although very little data is present for patients with severe loss of renal function, the CL/F measured in these subjects was 0.064 and 0.096 L/day, on average 18% lower. These values are within the observed range for subjects with normal renal function. Therefore, this effect does not appear to be clinically relevant, and subjects can be treated with the same dose. The summary statistics of the final PK model stratified by renal impairment are provided in Table 8.

**Table 8: Summary statistics of the primary PK parameters based on the final depemokimab PK model, for the patients in the SWIFT Asthma and ANCHOR CRSwNP study populations, stratified by renal impairment.**

| | Normal N=398 | Mild loss N=336 | Mild to moderate loss N=30 | Severe loss N=2 | Overall N=766 |
|---|---|---|---|---|---|
| **CL/F (L/day)** | | | | | |
| Mean (SD) | 0.0976 (0.0229) | 0.0975 (0.0196) | 0.104 (0.0184) | 0.0796 (0.0226) | 0.0977 (0.0214) |
| Geometric mean (%CV) | 0.0951 (23.1) | 0.0956 (20.1) | 0.102 (17.6) | 0.0779 (29.5) | 0.0955 (21.7) |
| Median (min, max) | 0.0946 (0.0411, 0.198) | 0.0967 (0.0514, 0.182) | 0.102 (0.0747, 0.144) | 0.0796 (0.0636, 0.0956) | 0.0957 (0.0411, 0.198) |
| **V/F (L)** | | | | | |
| Mean (SD) | 6.58 (1.39) | 6.72 (1.20) | 7.44 (1.24) | 6.21 (2.02) | 6.68 (1.32) |
| Geometric mean (%CV) | 6.44 (20.7) | 6.61 (18.0) | 7.34 (16.7) | 6.04 (34.0) | 6.55 (19.6) |
| Median (min, max) | 6.35 (3.42, 12.4) | 6.59 (3.69, 11.8) | 7.33 (4.93, 10.4) | 6.21 (4.78, 7.63) | 6.54 (3.42, 12.4) |
| **$k_a$ (/day)** | | | | | |
| Mean (SD) | 0.222 (0.0531) | 0.199 (0.0461) | 0.185 (0.0523) | 0.194 (0.00333) | 0.210 (0.0515) |
| Geometric mean (%CV) | 0.215 (25.5) | 0.194 (24.3) | 0.178 (28.8) | 0.194 (1.72) | 0.204 (25.8) |
| Median (min, max) | 0.217 (0.0981, 0.387) | 0.198 (0.0949, 0.347) | 0.170 (0.102, 0.308) | 0.194 (0.191, 0.196) | 0.208 (0.0949, 0.387) |
| **$F_{rel}$** | | | | | |
| Mean (SD) | 0.998 (0.151) | 0.994 (0.145) | 1.03 (0.166) | 1.08 (0.0445) | 0.998 (0.149) |
| Geometric mean (%CV) | 0.987 (15.6) | 0.983 (15.1) | 1.02 (16.1) | 1.08 (4.14) | 0.986 (15.4) |
| Median (min, max) | 0.991 (0.574, 1.51) | 0.998 (0.588, 1.38) | 1.02 (0.776, 1.42) | 1.08 (1.05, 1.11) | 0.997 (0.574, 1.51) |

#### 6.2.2.13.3. Impaired hepatic function

Hepatic function does not impact the elimination of depemokimab and therefore a hepatic impairment study was not conducted. Based on pooled population PK analysis, there was no evidence of an association between depemokimab CL and common markers of liver function or damage, such as total bilirubin, alanine aminotransferase, and aspartate aminotransferase, in asthma and CRSwNP patients.

#### 6.2.2.13.4. Gender

Population pharmacokinetic analyses indicated there was no clinically relevant effect of gender on depemokimab pharmacokinetics.

#### 6.2.2.13.5. Ethnic factors

Table 9 shows that exposure to depemokimab was approximately 18% higher in Asians as compared to the White population, which is not considered clinically relevant. Therefore, no clinically meaningful impact of race on the depemokimab PK was found in asthma and CRSwNP patients, and no dose adjustment is required based on race or ethnicity.

However, in the comparison of the FTIH study and Chinese PK study (Section 6.2.2.3. ) CL in Chinese was about 50% lower (and thus exposure two times higher) and $t_{1/2}$ about 45% longer when compared to the FTIH study (White-White/Caucasian/European heritage).

There are more differences between the FTIH study and Chinese PK study besides the ethnicity/race. Differences in bodyweight, age, albumin, healthy versus disease, and bioanalytical assay also affect the PK variability. In addition to this, pooling data from multiple studies allows for adjusting for confounding factors and more power to accurately identify covariate effects than when analyzing studies independently. Although some variation between the China PK and FTIH study was explained by the identified covariates in the population PK analysis, some variation in the PK was left unexplained and was handled with the implementation of study effects in the population PK analysis. The study effects were implemented to reflect differences between the studies that were not explicitly tested or measured, including differences in bioanalytical assay or study conduct (Table 9). It can be observed that study effects for FTIH study and China

PK study had to be implemented on CL, $F_{rel}$ and $k_a$, as FTIH Asthma and China PK HV study populations appear to have slightly faster and slower elimination, respectively, compared to the other study populations.

The conclusions from the popPK analysis on the absence of ethnic sensitivities were supported by the derived individual PK parameters from Asian ANCHOR and SWIFT study participants (N=154), demonstrating consistency with the overall patient population. Results of the subgroup analyses were generally consistent with the results from the primary analyses as discussed in the clinical efficacy section.

**Table 9: Derived secondary PK parameters from SWIFT-1 and 2 and ANCHOR-1 and 2 studies, stratified by race, Japan and China**

| PK parameters<br><br>Geometric mean (%CV) | Asian<br><br>N=154 | Black or African American<br><br>N=26 | White<br><br>N=578 | Asian - China<br><br>N=72 | Asian - Japan<br><br>N=70 | Overall<br><br>N=766 |
|---|---|---|---|---|---|---|
| $AUC_{tau,ss}$ (µg*day/mL) | 1181 (27.64) | 952.0 (31.72) | 1001 (26.71) | 1085 (25.15) | 1280 (28.70) | 1033 (28.06) |
| $C_{max,W26-52}$ (µg/mL) | 14.65 (27.79) | 12.08 (31.37) | 12.91 (26.99) | 12.99 (24.18) | 16.43 (27.19) | 13.20 (27.90) |
| $C_{av,ss}$ (mg /mL) | 6.489 (27.64) | 5.231 (31.72) | 5.502 (26.71) | 5.959 (25.15) | 7.033 (28.70) | 5.674 (28.06) |
| $C_{trough,W52}$ (µg/mL) | 1.497 (38.49) | 1.138 (44.77) | 1.150 (37.34) | 1.452 (38.20) | 1.540 (40.14) | 1.211 (39.73) |
| $t_{1/2}$ (day) | 49.80 (10.17) | 48.02 (10.33) | 46.96 (9.569) | 51.26 (10.55) | 48.49 (9.230) | 47.54 (10.01) |

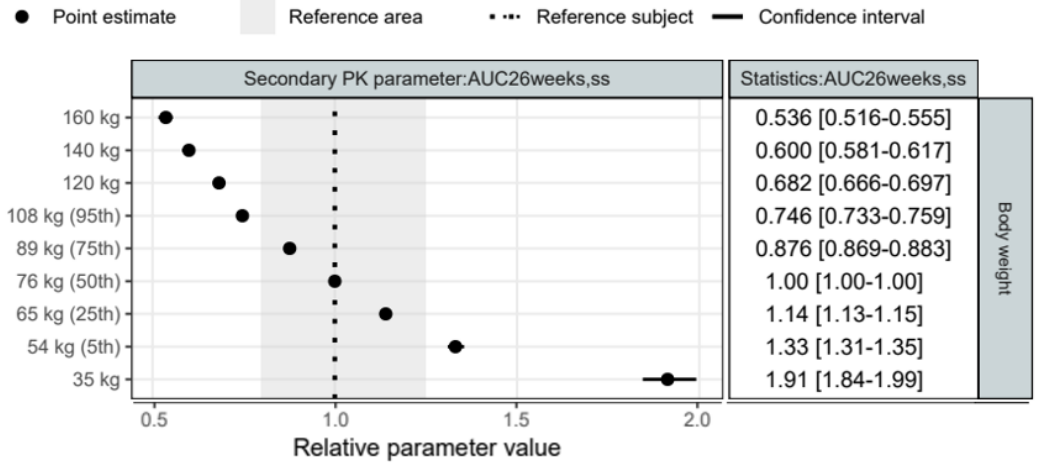
Note: Asian race category also includes Asian-China and Asian-Japan. Also, race categories with small N (<10) are not presented (i.e. American Indian or Alaska Native and Other). The Overall population is therefore not a sum of the categories presented.
Note: ANCHOR-1 and 2 and SWIFT-1 and 2 participants all received 100 mg SC Q26W.

#### 6.2.2.13.6. Weight

Weight was the major determinant of depemokimab exposure and satisfied conventional allometry with coefficients of 0.841 for CL/F and 0.887 for V/F, typical for a mAb such as depemokimab. Over the body weight range of 54 to 108 kg (corresponding to the 5$^{th}$ to 95$^{th}$ percentiles), the difference in all exposure metrics was less than 1.3-fold. This magnitude of effect of a typical body weight on depemokimab exposure is not considered clinically relevant.

Forest plots show the impact of body weight on depemokimab PK over the broader range of 35–160 kg (see Figure 5). For obese subjects weighing 140-160 kg exposure to depemokimab may be decreased 2-fold.

**Figure 5: Forest plot illustrating the effect of body weight on depemokimab $AUC_{26weeks,ss}$**




Reference: 76 kg, 50 years, non-Asian asthma patient, with baseline albumin of 45 g/L and baseline eGFR of 94 mL/min/1.73m², receiving a dose of depemokimab 100 mg, into the upper arm

#### 6.2.2.13.7. Elderly

No dose adjustment is recommended for elderly patients based on the similar PK between patients aged 18-64 years old and patients of 65 years and older observed in the SWIFT and ANCHOR studies. In total 176 subjects were ≥ 65 years old. An overview of the elderly study participants with PK data was provided in Table 10. In the SWIFT and ANCHOR studies, out of the 765 patients, there were 176 elderly, 144 participants with PK data aged 65 years to 74 years, 31 participants were aged 75 years to 84 years, and one participant was older than 85 years (93 years).

**Table 10: Age ranges studied in the elderly PK population**

| PK trials | Age 65-74 (Older subjects number /total number) | Age 75-84 (Older subjects number /total number) | Age 85+ (Older subjects number /total number) |
|---|---|---|---|
| SWIFT-1 | 50/250 | 12/250 | |
| SWIFT-2 | 56/243 | 9/243 | |
| ANCHOR-1 | 24/143 | 5/143 | 1/143 |
| ANCHOR-2 | 14/129 | 5/129 | |

#### 6.2.2.13.8. Paediatric population

The depemokimab plasma concentrations and derived PK exposure parameters in asthma adolescents were similar to those from asthma adults (Table 11). Therefore, no dose adjustment is provided for adolescent asthma patients (12 – 17 years old). This is based on results of 15 adolescents of which 4 were 12y, 2 were 13y, 2 were 14y, 1 was 15y, 3 were 16y, and 3 were 17y. The adolescent group was well represented across the age range 12-17 years. Median body weight was 72 kg, and body weight ranged from 40 to 141 kg.

**Table 11: Derived secondary PK parameters for SWIFT-1 and 2 participants receiving 100 mg SC Q26W, by age group**

| Parameter - geometric mean (%CV) | 12-17 years old N=15 | 18-64 years old N=352 | >= 65 years old N=127 | Overall N=494 |
|---|---|---|---|---|
| $AUC_{tau,ss}$ (µg*day/mL) | 1051 (31.18) | 1068 (28.34) | 1121 (25.46) | 1081 (27.75) |
| $C_{av,ss}$ (µg /mL) | 5.773 (31.18) | 5.868 (28.34) | 6.161 (25.46) | 5.939 (27.75) |
| $C_{max,26-52}$ (µg/mL) | 14.58 (30.44) | 13.60 (28.49) | 13.59 (25.14) | 13.63 (27.69) |
| $T_{max,\ 26-52}$ (day) | 10.83 (8.750) | 13.17 (16.47)) | 15.22 (15.83) | 13.59 (17.80) |
| $C_{trough,week52}$ (µg/mL) | 1.081 (39.32) | 1.280 (39.02) | 1.451 (34.12) | 1.315 (38.37) |
| $t_{1/2}$ (day) | 44.73 (8.578) | 48.23 (9.802) | 49.91 (8.432) | 48.55 (9.645) |

No adolescents were included in the CRSwNP pivotal studies. Studies in children below 12 years of age have not been conducted.

#### *6.2.2.14. Pharmacokinetic interaction studies*

No drug interaction studies have been conducted for depemokimab. The potential for drug-drug interactions is considered to be low as depemokimab is catabolizsed by ubiquitous proteolytic enzymes, not restricted to hepatic tissue. The risk of drug -disease interaction due to an indirect effect on gene expression of cytochrome P450 (CYP450) or transporters is also considered to be low since the specific target for depemokimab is the cytokine interleukin-5 (IL-5).

In literature multiple sources confirm that the formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g. IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. This does not mention IL-5. There are no reports of IL-5 receptor γ (IL-5Rγ) being expressed on hepatocytes and elevation of systemic pro-inflammatory markers in severe asthma is minimal, so neutralization of IL-5 is not expected to alter gene expression of CYP450 or transporters.

### 6.2.3. Pharmacodynamics

#### *6.2.3.1. Mechanism of action*

Depemokimab targets human IL-5 with binding affinity (Kd 10.5 pM) and specificity, thereby blocking the binding to the IL-5 receptor alpha expressed on the cell surface with picomolar potency (IC50 4 pM) *in vitro*. Depemokimab contains a triple amino acid substitution (YTE) in the fragment crystallisable (Fc) region which increases binding to the neonatal Fc receptor and thereby extends the half-life. These modifications allow for dosing every 6 months.

IL-5 is a cytokine involved in Type 2 inflammation along with IL-4 and IL-13. Type 2 inflammation is an important component in the pathogenesis of asthma and CRSwNP. IL-5 is the key cytokine responsible for regulation of blood and tissue eosinophils; it is the most potent and specific cytokine for the eosinophil lineage and is responsible for cellular expansion, release from the bone marrow into the peripheral blood, and survival following a variety of triggers, typically TH2 stimuli.

Additional cell types that express IL-5R alpha including mast cells, plasma cells, epithelial cells, and fibroblasts, are also involved in inflammation. Depemokimab-mediated blocking of IL-5 engagement with the receptor on these cell types reduces their contribution to unwanted inflammatory responses.

In severe asthma, inhibition of IL-5 has demonstrated an improvement in epithelial integrity, mucus plugging

and reduction in tissue remodelling. However, the mechanism of action has not been definitively established.

#### *6.2.3.2. Primary and secondary pharmacology*

**FTIH study (205722)**

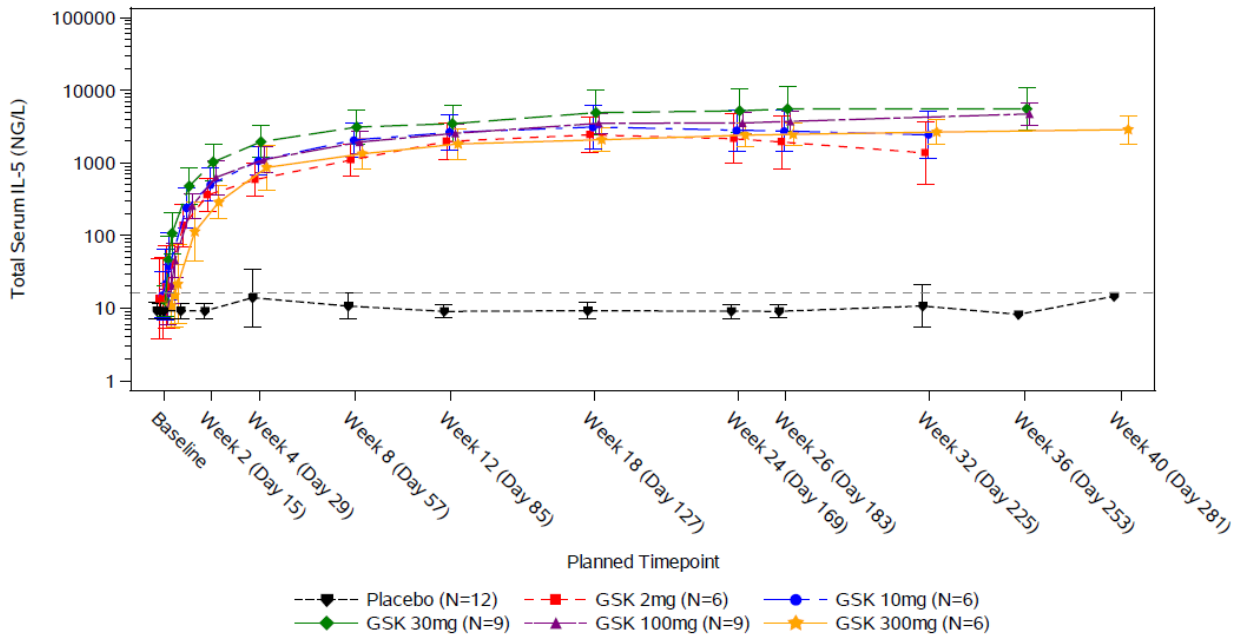
The effects of depemokimab on eosinophils were studied in blood of patients with asthma. Serum total IL-5 was also measured to supplement the pharmacology of depemokimab.

Study 205722 was a multi-centre, randomised, double-blind, placebo-controlled, parallel-group, single ascending dose study that evaluated safety, tolerability, immunogenicity, pharmacokinetics and pharmacodynamics of subcutaneously administered depemokimab (2, 10, 30, 100 and 300 mg) in 48 participants with mild-to-moderate asthma and blood eosinophils ≥200 cells/µL at screening. The main PD biomarkers were serum total IL-5 levels as a marker of target engagement and blood eosinophil levels as a marker of pharmacological response.

Serum total IL-5

The geometric mean serum total IL-5 (i.e., free IL-5 plus IL-5 bound to depemokimab) value at baseline for the placebo group (9.2 ng/L) was slightly lower than that of the depemokimab groups (10.4 to 15.1 ng/L), where most participants had baseline values below the limit of quantification of the assay (16.38 ng/L) in each dose group. From Week 1 onwards all participants in the depemokimab groups had measurable concentrations of serum total IL-5. An increase in serum total IL-5 from baseline was noted for all depemokimab groups for all study visits but no clear dose response was observed. The geometric mean serum total IL-5 values of the placebo group remained similar to baseline during the study (Figure 6).

**Figure 6: Geometric means (and 95% CIs) of total serum IL-5 data (ng/L)**



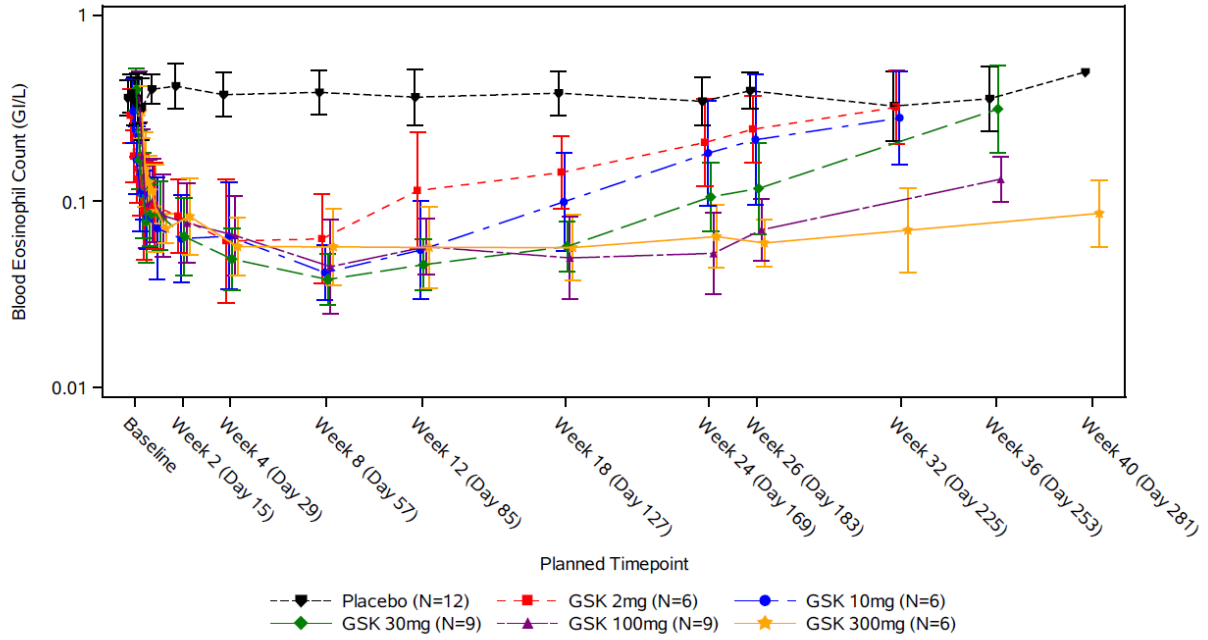

Note: Values below the lower limit of quantification (LLQ=16.38 NG/L) were imputed to LLQ/2. LLQ shown by horizontal reference line.
Note: 95% CI is only displayed when at least 3 participants contribute to the statistics and at least one value is not below the lower limit of quantification.
jm734075: /arenv/arprod/gsk3511294/mid205722/final_01/drivers/f_pd_il5.sas 11NOV2019 09:34

Blood eosinophil count

At baseline, geometric mean blood eosinophil counts were similar between the placebo (0.359 GI/L) and depemokimab groups (ranged from 0.288 GI/L to 0.398 GI/L). Blood eosinophil count reduction was observed from the first post-dose assessment (Day 2; 24 h) in all depemokimab groups compared to little change in the placebo group. Blood eosinophils were reduced by 54% compared to placebo 24 hours after dosing, which was the first post-dose assessment. The highest reduction was observed at Week 8 for most depemokimab groups. Up to Week 8 there was no difference between depemokimab groups in the magnitude of the blood eosinophil count reduction. A dose-related difference was observed in the duration of the response, with suppression of blood eosinophils being maintained for longer with increasing dose (Figure 7).

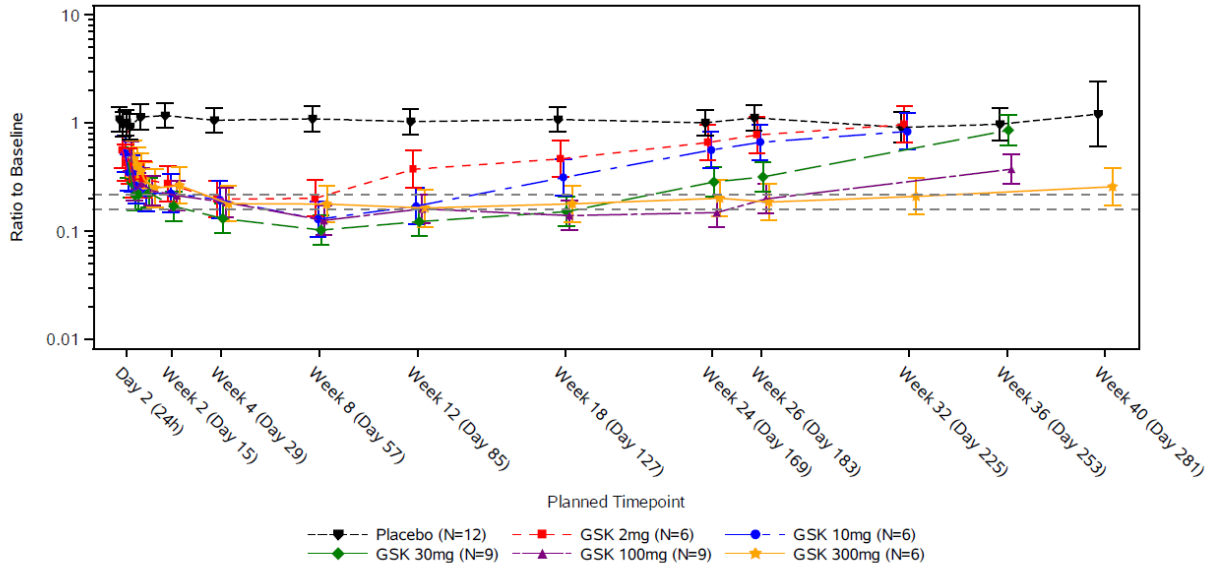
The results of the Mixed Model Repeated Measures (MMRM) analysis of the ratio to baseline for blood eosinophil data adjusted for differences in baseline blood eosinophil counts are presented in Figure 8.

**Figure 7: Geometric means (and 95% CIs) of blood eosinophil count data (GI/L)**




Note: 95% CI is only displayed when at least 3 participants contribute to the statistics.
jm734075: /arenv/arprod/gsk3511294/mid205722/final_01/drivers/f_pd_eos_abs.sas 07NOV2019 08:43

**Figure 8: Adjusted Geometric means (and 95% CIs) of ratio to baseline blood eosinophil data**




Note: Analysis was performed using an MMRM model on log-transformed data, with fixed categorical effects of treatment, planned timepoint and treatment-by-planned timepoint interaction and fixed continuous covariates of log Baseline blood eosinophil count and log Baseline blood eosinophil count-by-planned timepoint interaction. A Toeplitz covariance structure was used.
Note: Reference line at ratio=0.22 indicates a 78% reduction from Baseline, as observed in the Phase 3b mepolizumab MUSCA trial.
Note: Reference line at ratio=0.16 indicates an 84% reduction from Baseline, as observed in the mepolizumab MENSA pivotal Phase 3 trial.
jm734075: /arenv/arprod/gsk3511294/mid205722/final_01/drivers/f_pd_adjmean_eos.sas 07NOV2019 16:53

At Week 26, blood eosinophil counts were reduced by >80% from baseline in depemokimab 100 mg and 300 mg groups with adjusted geometric mean ratios to baseline blood eosinophils of 0.199 and 0.186, respectively (Table 12). The ratios of adjusted geometric means for these groups in comparison to placebo were 0.178 and 0.166, respectively (i.e., a reduction of 82% and 83%). The probability that the placebo-adjusted ratio to baseline in blood eosinophil count is <0.25 (i.e., >75% reduction in blood eosinophil count) at the 26-week timepoint was 95% for the depemokimab 100 mg group and 96% for the depemokimab 300 mg group (Table 12).

**Table 12: Statistical analysis of ratio to baseline blood eosinophil data at Week 26**

| | Placebo (N=12) | DEP 2 mg (N=6) | DEP 10 mg (N=6) | DEP 30 mg (N=9) | DEP 100 mg (N=9) | DEP 300 mg (N=6) |
|---|---|---|---|---|---|---|
| n | 12 | 6 | 6 | 9 | 9 | 6 |
| LS Geometric mean ratio to baseline | 1.119 | 0.776 | 0.663 | 0.317 | 0.199 | 0.186 |
| SE logs | 0.1359 | 0.1950 | 0.1932 | 0.1596 | 0.1571 | 0.1935 |
| 95% CI | (0.855, 1.464) | (0.527, 1.141) | (0.452, 0.972) | (0.231, 0.435) | (0.146, 0.271) | (0.127, 0.273) |
| Ratio to placebo | | 0.693 | 0.593 | 0.284 | 0.178 | 0.166 |
| SE logs | | 0.2391 | 0.2373 | 0.2082 | 0.2071 | 0.2375 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 95% CI | | (0.432, 1.113) | (0.371, 0.948) | (0.188, 0.428) | (0.118, 0.268) | (0.104, 0.266) |
| Prob(ratio to placebo<0.16) | | <0.01 | <0.01 | <0.01 | 0.31 | 0.44 |
| Prob(ratio to placebo<0.25) | | <0.01 | <0.01 | 0.27 | 0.95 | 0.96 |
| Prob(ratio to placebo<0.5) | | 0.09 | 0.24 | >0.99 | >0.99 | >0.99 |

Note: Analysis was performed using an MMRM model on log-transformed data, with fixed categorical effects of treatment, planned timepoint and treatment-by-planned timepoint interaction and fixed continuous covariates of log Baseline blood eosinophil count and log Baseline blood eosinophil count-by-planned timepoint interaction. A Toeplitz covariance structure was used. Assessor's note: the probabilities were derived from a Bayesian model as supportive analysis.
Note: n is the number of participants with non-missing data at the relevant planned timepoint.

Since the magnitude of reduction in blood eosinophils was comparable for all depemokimab groups at the early timepoints, it was not appropriate to fit the 4-parameter dose-response Emax Bayesian model at every time point. The analysis of the dose-response relationship was only conducted with the Bayesian model at the Week 26 timepoint, which had measurements in all cohorts and was considered the primary timepoint of interest. The result of this analysis is presented inTable 13.

**Table 13: Statistical analysis of ratio to baseline blood eosinophil data at Week 26 (Bayesian Emax sensitivity analysis)**

| | Placebo (N=12) | DEP 2 mg (N=6) | DEP 10 mg (N=6) | DEP 30 mg (N=9) | DEP 100 mg (N=9) | DEP 300 mg (N=6) |
|---|---|---|---|---|---|---|
| n | 12 | 6 | 6 | 9 | 9 | 6 |
| Posterior mean ratio to baseline | 1.024 | 0.886 | 0.623 | 0.338 | 0.211 | 0.171 |
| 95% CI | (0.786, 1.352) | (0.678, 1.124) | (0.453, 0.887) | (0.247, 0.451) | (0.168, 0.270) | (0.121, 0.243) |
| Ratio to placebo | | 0.865 | 0.609 | 0.331 | 0.206 | 0.167 |
| 95% CI | | (0.663, 1.000) | (0.412, 0.993) | (0.226, 0.497) | (0.148, 0.289) | (0.107, 0.278) |
| Prob(ratio to placebo<0.16) | | <0.01 | <0.01 | <0.01 | 0.07 | 0.43 |
| Prob(ratio to placebo<0.25) | | <0.01 | <0.01 | 0.08 | 0.87 | 0.96 |
| Prob(ratio to placebo<0.5) | | <0.01 | 0.23 | 0.98 | >0.99 | >0.99 |

Note: Analysis was performed using a 4-parameter Emax Bayesian dose response model fitted on log-transformed data

with log Baseline blood eosinophil count included as a covariate. Non-informative priors were used on all parameters in the model.

The Bayesian analysis was supportive of the MMRM analysis, with blood eosinophil reductions from baseline of 79% and 83% being noted in the depemokimab 100 mg and 300 mg groups, respectively (). The ratios of adjusted geometric means for these groups in comparison to placebo were 0.206 and 0.167, respectively. The probability that the placebo-adjusted ratio to baseline in blood eosinophil count is <0.25 (i.e., >75% reduction in blood eosinophil count) at the 26-week timepoint was 87% and 96% for the depemokimab 100 mg and 300 mg groups, respectively (Table 13).

A second sensitivity analysis was performed after the application of windowing to ensure that assessments were taken within an acceptable timeframe of the planned visit dates and times. At Week 26, all of the treatment groups had 1 participant excluded due to time deviations. Nevertheless, results were similar to the main analysis, with probabilities of 90% and 97% that the placebo-adjusted ratios to baseline in blood eosinophil count is <0.25 at the 26-week timepoint for the depemokimab 100 mg and 300 mg groups, respectively.

Since the Safety population was identical to the PD population and since no participants used oral corticosteroids or changed ICS asthma medication during the course of the study, no further sensitivity analyses were conducted.

QTc prolongation

The FTIH study 205722 also investigated the effect of depemokimab of the change from baseline QT corrected by Fridericia's formula (QTcF) in participants with mild to moderate asthma following a single subcutaneous (SC) administration ranging from 2 mg to 300 mg. The study is described under Section 6.2.2.

In the FTIH study 205722, 48 participants received active treatment or placebo (36 active; 12 placebo) Therefore the sample size for each cohort was relatively small (6/2 or 9/3), and modest overall (36/12). QTcF data was collected in triplicate at multiple timepoints during the study over a 150-fold dose range (2 mg to 300 mg SC).

*Results*

Individual QTcF change from baseline data over time were analysed using a repeated measures linear mixed-effect model adjusting for baseline QTcF. The results of this analysis by visit are plotted in Figure 9. A clinical range of interest of ±10 msec is indicated for reference.

The results of the analysis for change from QTcF data versus depemokimab plasma concentration are presented in Figure 10. The predicted increase in mean QTcF change from baseline with depemokimab plasma concentrations point estimates remained below 10 msec up to concentrations of 100 µg/mL, with a 95% lower CI consistent with zero change from baseline. However, the upper bound crossed the 10 msec line.

**Figure 9: Adjusted Mean QTcF Change from Baseline (95% CI) versus Placebo by Planned Time FTIH study 205722**

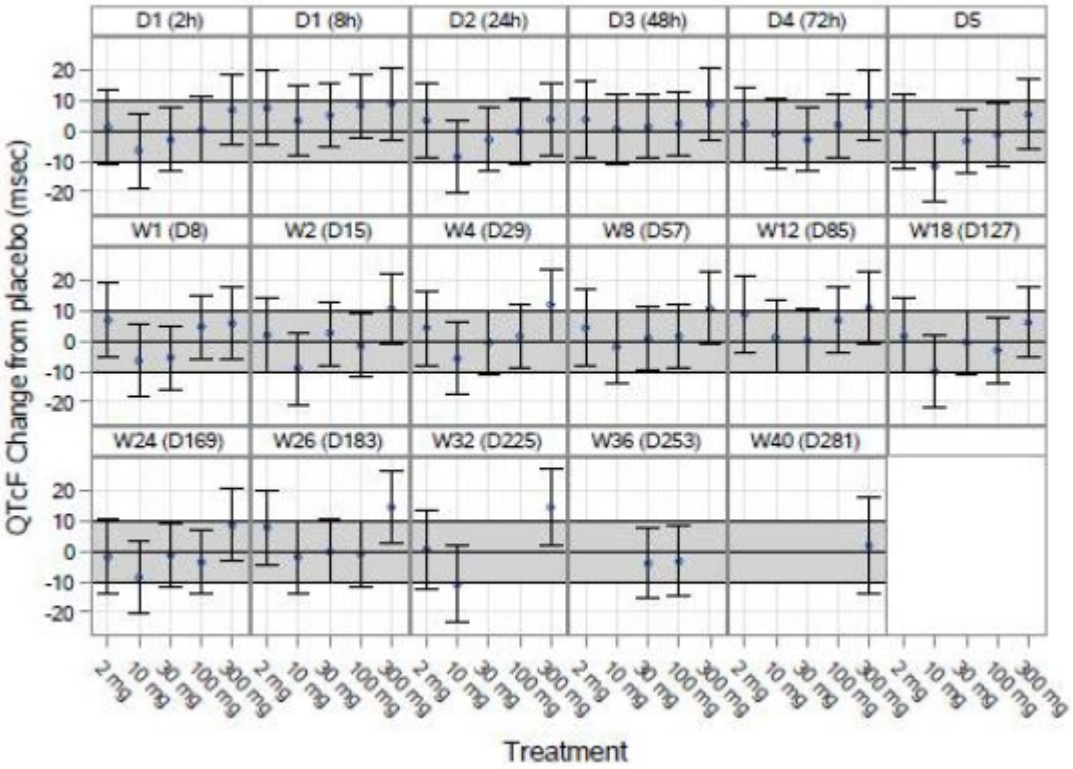
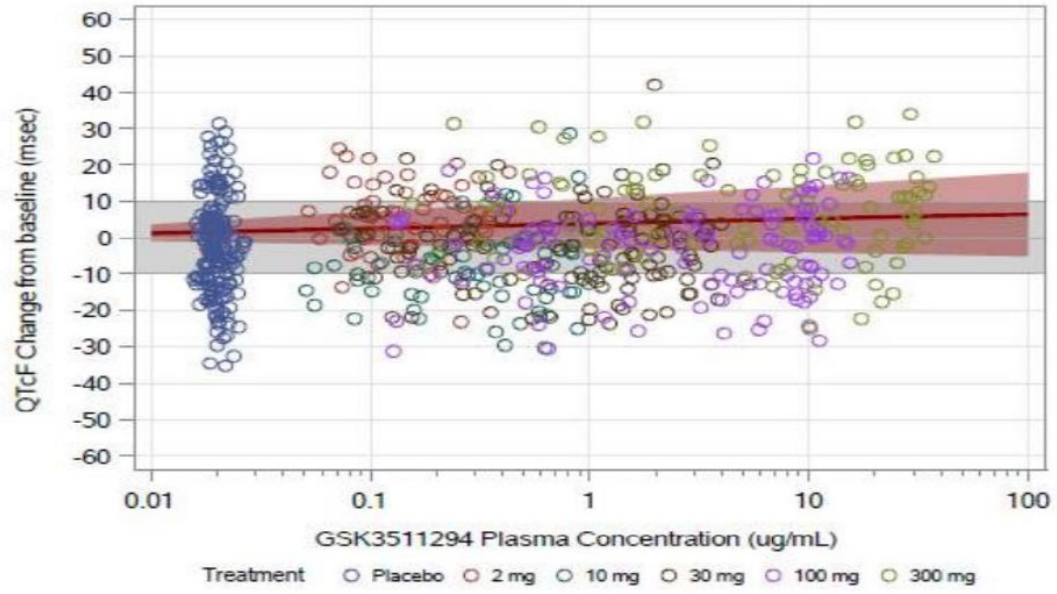



Figure 10: Adjusted Mean QTcF Change from Baseline (95% CI) versus Depemokimab Plasma Concentrations FTIH study 205722

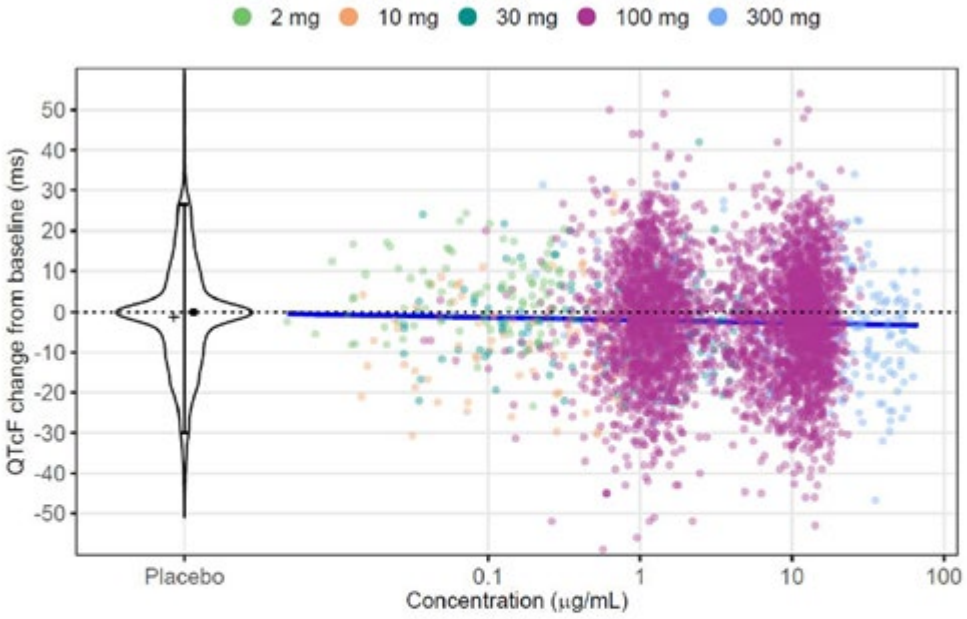



Drug name is referred as "GSK531194" in the figure, however, it denotes depemokimab.
Red line and red shaded region represents adjusted Mean QTcF Change from Baseline (95% CI).
Note: mean $C_{max}$ at 100 mg is approx. 15 µg/mL.

In depemokimab clinical studies ECG safety monitoring was implemented, including at Tmax. To further support the assessment of depemokimab cardiac safety, graphical assessment of the QTcF data with respect to depemokimab concentration was conducted based on all studies with PK sampling (i.e. studies [Phase 1 – FTIH study, China PK study, PK comparability study], SWIFT-1 and 2, ANCHOR-1 and 2).

The individual observed QTcF change from baseline versus (time-matched) individual predicted depemokimab concentration did not provide any indication of a positive relationship between QTcF and depemokimab concentrations (Figure 11).

**Figure 11: QTcF change from baseline versus time-matched predicted depemokimab concentration over all clinical studies**




Individual observed QTcF change from baseline versus (time-matched) individual predicted depemokimab concentration for the subjects in the QTcF analysis data set, colored by dose level. Data are presented on a semi-logarithmic scale. The blue line is the linear smooth of the data, using method = "glm". The black cross, square and error bar represent the mean, the median, 2.5th and 97.5th percentiles respectively, of the individual observed QTcF change from baseline for the placebo subjects, while the black violin plot displays the distribution of the individual observed QTcF change from baseline for the placebo subjects. The minimum and maximum predicted concentrations in the 100 mg dose arm (Asthma and CRSwNP participant populations pooled) were respectively 0.04 and 28.6 mg/mL. The maximum was 68 mg/mL over all the active treatment arms.

#### *6.2.3.3. Pharmacodynamic interactions with other medicinal products or substances*

No formal studies have been conducted.

#### *6.2.3.4. Genetic differences in PD response*

Not applicable.

#### *6.2.3.5. Immunological events*

**FTIH Study (205722)**

Nine participants out of 36 (25%) who received depemokimab had confirmed positive results for ADA at any-

time post-baseline. None of the participants in the placebo group tested positive. Out of the 9 ADA confirmed positive participants, 5 were in the depemokimab 30 mg dose group, which was also the dose group that had the highest median serum total IL-5 concentrations. The titre values were generally low (titre range 80-320) and were within 4 serial dilutions of being negative.

There were no major differences observed in the depemokimab plasma concentration and blood eosinophil count-time profiles between ADA positive and ADA negative participants.

**Chinese PK study (208021)**

No participants were positive for ADA at any visit in the depemokimab 100 mg (n=10) or 300 mg arm (n=10), respectively.

**PK study (214099)**

The immunogenicity incidence within the SSD treatment group was 1% (1/70). One participant confirmed positive for ADA only at Week 26 (Titre value of 80) and was negative for neutralizing antibodies. The immunogenicity incidence within the AI treatment group was 1% (1/70). One participant confirmed positive for ADA only at Week 26 (Titre value of 640) and was positive for neutralizing antibodies.

There was no observable impact of ADA on PK, PD or safety. There was no accelerated clearance of depemokimab in either the SSD or AI ADA positive study participants, and no increasing eosinophil counts in the AI positive participant. The ADA positive participants had similar safety profiles, as each reported 1 AE (SSD: injection site bruising; AI injection site erythema), which were similar to the AEs observed in ADA negative participants. Two SAE were reported for ADA negative participants, but none for ADA positive participants.

**Pivotal Phase 3 52-week trials in asthma and CRSwNP**

In patients who received at least one 100 mg dose of depemokimab administered SC every 6 months, 9% (44/499) of patients with asthma (SWIFT-1 and SWIFT-2) and 8% (21/272) of patients with CRSwNP (ANCHOR-1 and ANCHOR-2) were positive for anti-depemokimab antibodies (ADA) during the 52-week studies.

Across the placebo-controlled studies for asthma and CRSwNP indications, as well as the interim analysis for AGILE, a single arm open-label extension study, <1% of the patients were positive for neutralizing antibodies (5/963).

Anti-depemokimab antibodies did not discernibly impact the pharmacokinetics of depemokimab and there was no evidence of a correlation between antibody titres and changes in eosinophil level. Patients that were ADA positive had a generally similar profile of adverse reactions as those who were ADA negative. There was no identified clinically significant effect of ADA on pharmacokinetics, pharmacodynamics, or safety of depemokimab.

**Phase 3 supportive studies in asthma**

The percentage of patients who were positive for ADA was 7% (43/588) in an ongoing 52-week open-label extension asthma study (AGILE; n = 214 with data collected for 104 weeks) and 3% (17/531) in an ongoing 52-week study of asthma patients who were previously treated with either mepolizumab or benralizumab (NIMBLE).

A total of 3 participants (<1%) and no participants (0%) were positive for neutralizing antibodies in AGILE and NIMBLE, respectively.

There was no observable impact of immunogenicity on safety in either study.

**Chinese subpopulation**

Study participants from China reported a higher incidence of ADA in both asthma (19/38 in SWIFT-1, SWIFT-2 did not enroll study participants from China) and CRSwNP (10/34 in ANCHOR 1+2). Phase 1 study 208021 with healthy Chinese study participants (n=20) did not have any ADA positive study participants with the 100 mg or 300 mg dose.

For all studies, the titre values were low (80 or 160), with no increasing titre values observed. One participant had a transient positive NAb response. There was no apparent impact of ADA on safety, PK or PD findings.

## 6.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

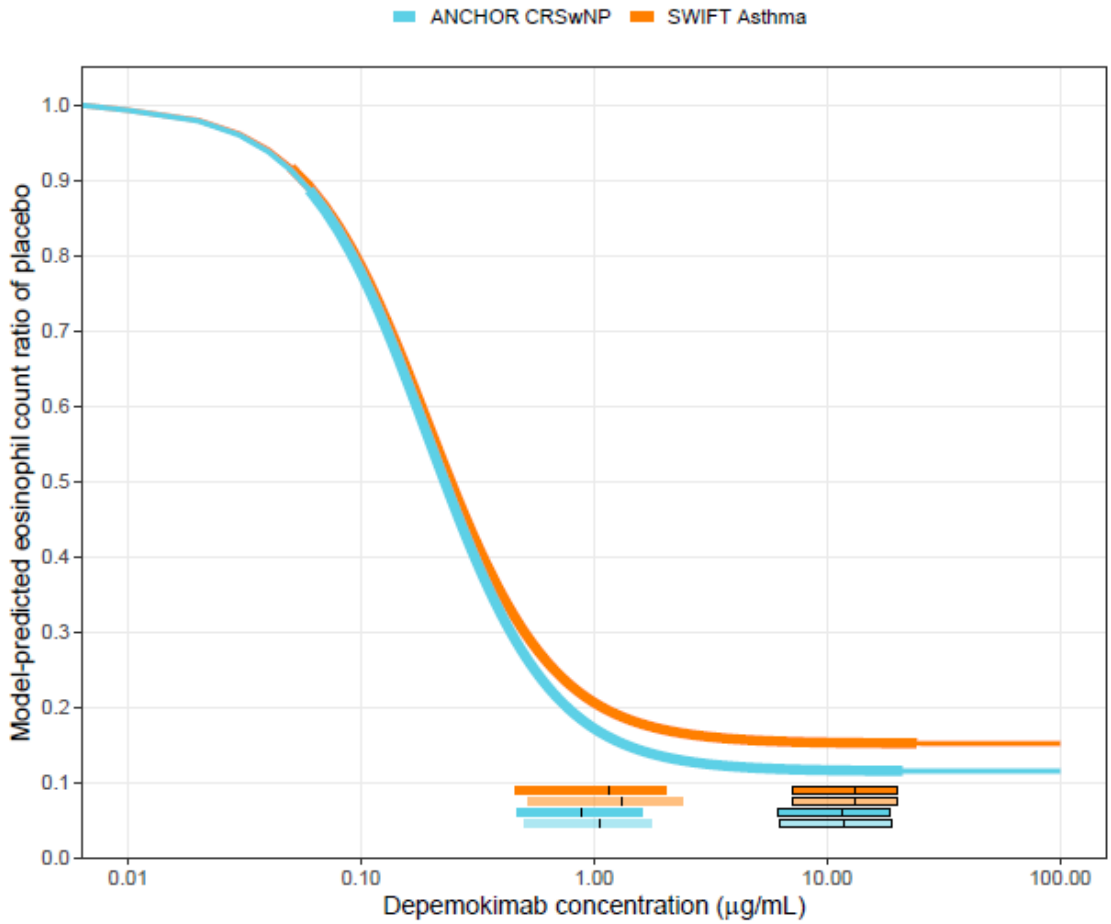
The overall aim of this analysis was to characterize the PK/PD relationship between depemokimab plasma concentrations and blood eosinophil count to support the depemokimab clinical development program in patients with asthma and CRSwNP. The data for the blood eosinophil count analysis originate from one phase 1 study (205722) and four phase 3 studies (206713, 213744, 217095, 218079).

The final model describing the time course of blood eosinophil count was an indirect-response model including a placebo linear model with baseline and slope for placebo effect ($P_{slp}$) representing the proportional change over a year, plus a numerical solution (differential equation) describing the depemokimab effect, parameterised in terms of half-life for drug on-/offset ($HL_{onset}$), concentration at half maximum effect ($EC_{50}$), maximum effect ($E_{max}$) and Hill coefficient, with predicted depemokimab concentrations inhibiting the zero-order production rate constant ($k_{in}$). The model includes the following covariate-parameter relationships relevant to the intended target populations: age, weight, Asian race in asthma participant population, Asian race in CRSwNP participant population, CRSwNP participant population and predicted baseline blood eosinophil count on $E_{max}$.

The (Pop) PK/PD model describing the relationship between depemokimab plasma concentrations and blood eosinophil count has been sufficiently described and appears fit-for purpose, based on parameter estimates and VPCs. Using this PK/PD model an $EC_{50}$ of 0.19 µg/mL and an $EC_{90}$ of 0.75 µg/mL for depemokimab were estimated.

In the SWIFT and ANCHOR study participants, the average predicted depemokimab $C_{trough}$ concentrations at Weeks 26 and 52 were 1.13 µg/mL and 1.21 µg/mL respectively, consistently above the clinical $EC_{50}$ and $EC_{90}$ for suppression of blood eosinophils. At a population level, all participants had Week 52 $C_{trough}$ above the estimated $EC_{50}$ and 90% of participants had Week 52 $C_{trough}$ at or above the estimated $EC_{90}$. This demonstrates that the range of the depemokimab plasma concentrations achieved to the end of the 26-week dosing interval are at the top of the PK/PD relationship and well-above $EC_{50}$, resulting in near maximal PD response to trough (Figure 12).

**Figure 12: Estimated depemokimab PK/PD relationship**




Note: The span of the thicker line represents the range of model-predicted depemokimab concentrations achieved. The coloured bands at the bottom represent the Ctrough and Cmax concentrations achieved, respectively (median and 2.5$^{th}$ to 97.5$^{th}$ percentiles) following 100 mg SC q26w dosing. Darker and lighter colours represent first and second dosing interval, respectively.

*PK/efficacy and PD/efficacy*

The depemokimab dose for late-phase development was identified using model-informed drug development (MIDD) principles using dose ranging data from FTIH study in asthma patients. No separate dose-ranging studies were conducted for depemokimab. Data from SWIFT-1 and 2 and ANCHOR-1 and 2 studies with a single-dose level were used to characterize the relationship between depemokimab exposure/PD and clinical efficacy (primary endpoints). It should be noted that the inter-subject variability in exposure metrics like AUC, and $C_{trough}$ was low to moderate, and eosinophils were near maximally suppressed for most individuals throughout the study.

Using negative binomial regression based on the SWIFT-1 and 2 data, there was no clear evidence of a relationship between depemokimab exposure quintiles and annualised exacerbation rate within the exposure range achieved in the studies. Looking at the PD-response on-treatment using negative binomial regression, there was no clear evidence of a relationship between blood eosinophil count reductions at Week 52 and annualised exacerbation rate in SWIFT-1 and 2.

Similarly, using linear regression based on the ANCHOR-1 and 2 data, treatment differences in ENPS were favourable for depemokimab compared to placebo across the tertiles of PK and PD metrics. The treatment differences across tertiles of PK and PD was consistent with the treatment effect in the overall population, although the tertiles with highest exposure or BEC suppression showed slightly larger treatment effects. Similar results were found for the co-primary endpoint mean nasal obstruction score (VRS) during weeks 49-52.

### 6.2.5. Dose selection and therapeutic window

Depemokimab targets the same IL-5 epitope as mepolizumab, establishing the same reduction in blood eosinophils as mepolizumab via the same IL-5 neutralization was expected to generate a comparable clinical efficacy and safety profile. Based on the FTIH study in mild-to-moderate asthma patients with a blood eosinophil count ≥200 cells/µL, it was estimated that a dose of 100 mg SC would produce a PD-response over 26 weeks (i.e. blood eosinophil count suppression) that is comparable to mepolizumab in asthma at the approved SC dose of 100 mg q4w. Therefore, a dosing regimen of 100 mg SC Q26W was selected for phase 3 studies in asthma and CRSwNP.

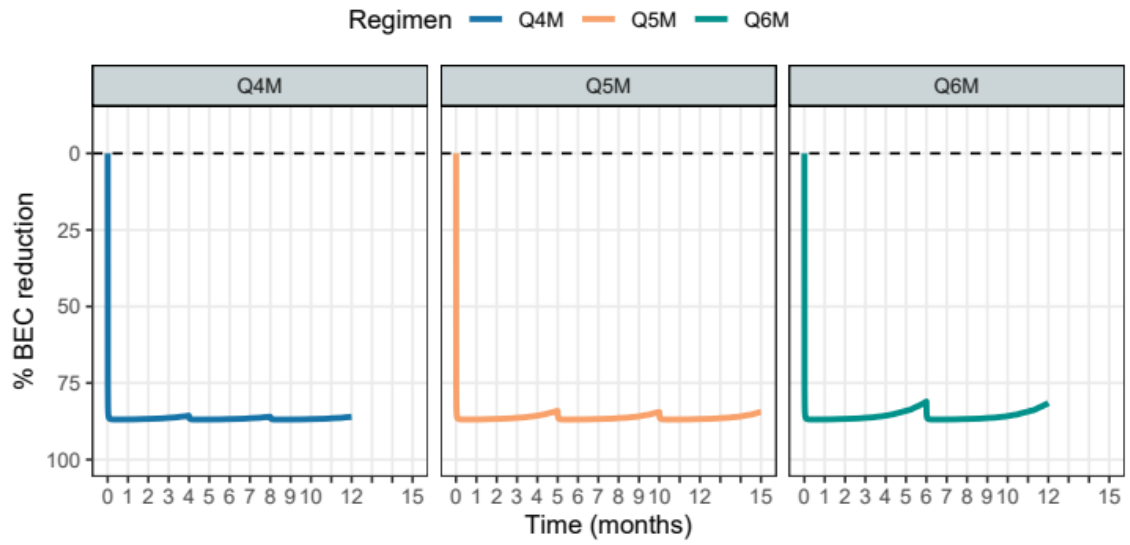
- The results from the SWIFT-1 and 2 and ANCHOR-1 and 2 studies provided confirmatory evidence for the recommended dosing regimen in asthma and CRSwNP. The recommended therapeutic depemokimab dose of 100 mg SC Q26W provided a clinically meaningful and statistically significant benefit compared to placebo for the primary and co-primary endpoints in the pivotal SWIFT-1 and 2 and ANCHOR-1 and 2 studies.
- In the FTIH study, a single-dose of 100 mg SC produced a rapid reduction in blood eosinophil count of 54% from baseline at 24 hours (first assessment). This was consistent with a rapid reduction in blood eosinophil counts in the SWIFT-1 and 2 and ANCHOR-1 and 2 studies, which was also sustained over the duration of the 26-week dosing interval and 52-week treatment duration. The reduction in blood eosinophil count compared to placebo at Week 52 was 79% and 85% in the Integrated SWIFT-1+2 and ANCHOR-1 and 2 analysis, respectively. This was reflected in a rapid onset of clinical efficacy which was sustained over the duration of the SWIFT-1 and 2 and ANCHOR-1 and 2 studies. Altogether, this supports the selected dose and dosing interval, and aligns with the MIDD predictions based on the asthma FTIH study, according to the applicant.
- The range of the depemokimab plasma concentrations achieved at the end of the 26 weeks dosing interval lie at the top of the concentration-PD relationship. This is consistent with the sustained reductions in blood eosinophil counts over the duration of the dosing interval, as observed in the SWIFT-1 and 2 and ANCHOR-1 and 2 studies.
- No clear relationship between PK or PD parameters and the primary efficacy endpoints in the SWIFT-1 and 2 and ANCHOR-1 and 2 studies was observed. This supports that treatment benefits are achieved across the PK/PD range observed in these study populations.
- The depemokimab pharmacokinetics were consistent between asthma and CRSwNP patients with an overall geometric mean half-life of 48 days, which is consistent with the YTE-modification and approximately double the half-life of a typical IgG monoclonal antibody.

In general, the presented PK, PD, and exposure-response results support the dose recommendation of 100 mg SC Q26W for depemokimab treatment in the asthma and CRSwNP target population.

However, whether this dose is optimal has not completely been characterised as only one dosing regimen has been tested in the Phase 3 studies. A single dose was supported as part of the clinical development programme during the CHMP SA EMA/SA/000015866)

Since it cannot be completely ruled out that there is some relationship between blood eosinophil counts and efficacy outcome, the applicant simulated and discussed the effects of Q4M and Q5M SC dosing on blood eosinophil counts, as requested. The final depemokimab PK/PD model was used to simulate the PD response and the results are presented graphically in Figure 13.

**Figure 13: Simulated PD response for depemokimab 100 mg SC Q4M, Q5M and Q6M regimens**




Simulated placebo-adjusted % BEC reduction versus time following administration of 100 mg depemokimab Q4M, Q5M or Q6M. The solid lines represents the median of the simulated data.

The PD response achieved in terms of nadir is similar across the regimens (~87% reduction) and near maximal over the entire dosing interval. This is also seen for other monoclonal antibodies that target IL-5 and reflects a redundancy in IL-5 signalling with GM-CSF and IL-3 through a common β sub-unit that results in low levels of circulating eosinophils despite maximal anti-IL5 pharmacology [Asquith, 2008].

Some variation between the dosing regimens becomes apparent towards the end of the dosing intervals, with a predicted PD response of 86%, 85%, and 82% for Q4M, Q5M, and Q6M, respectively.

## 6.2.6. Overall discussion and conclusions on clinical pharmacology

Bioanalysis

All assays can be considered suitable for their intended use. From the PK assessment one issue arose that concerns PK methods, i.e. the occurrence of (sometimes relatively high) pre-dose concentrations in phase 1 (FTIH) and phase 3 studies (e.g. SWIFT-2). The applicant confirmed that the participants of the studies were treatment naïve. Further discussion was provided on possible reasons for detectable pre-dose depemokimab concentrations, such as sample contamination or interference with another anti-IL-5 drug. The GSK assay, which supported Study 205722 (FTIH), was not validated for selectivity in disease state plasma. However,

the selectivity of the US and Chinese Frontage assays (based on the GSK assay), which have been used in other studies (including SWIFT-2), has been validated in disease state matrix. 100 % of blank disease state matrices were BLQ in all tests. Despite this result it is possible in ligand binding assays that some compounds or matrix components may cause a signal after binding to IL-5 or after non-specific binding especially in the case of a method with only a primary detecting antibody. The overall incidence of non-zero pre-dose depemokimab concentrations was, however, low across the studies. This issue was not further pursued.

*Pharmacokinetics*

Pharmacokinetic data provided supports the claims on ADME stated in section 5.2. of the SmPC, on special populations (hepatic/renal impairment, age, race and gender) in sections 4.2. and 5.2. and on drug-drug interactions in section 4.5. of the SmPC.

As presented, in section 6.2.2.14 pharmacokinetc interaction studies section, it is acceptable that no pharmacokinetic interaction studies have been conducted for depemokimab.

Pharmacodynamics

*Primary PD*

As primary pharmacodynamic parameters, total IL-5 concentration and eosinophil count in plasma were included. Total IL-5 levels were primarily assessed to confirm depemokimab target binding in early phase development. Following depemokimab dosing, total IL-5 accumulates because the depemokimab:IL-5 complex (biologically inactive) has a slower elimination rate than free IL-5. All depemokimab doses resulted in a fast and lasting increase in serum total IL-5 from baseline, but no dose-response relationship was observed.

Blood eosinophil levels were assessed as a marker of pharmacological response. The 100 and 300 mg doses were shown to have similar reductions in blood eosinophil count. At Week 26, the adjusted reduction compared to placebo was 82% and 83% in the depemokimab 100 mg, and depemokimab 300 mg groups, respectively. Both doses exceeded the pre-defined success criterion for placebo-adjusted ratio to baseline blood eosinophil count at Week 26, which was set to 80% reduction of blood eosinophil count based on data from Phase 3 studies with mepolizumab (another monoclonal antibody targeting the same epitope IL-5 receptor).

High blood eosinophil count has been associated with disease exacerbation in asthma and NP recurrence in CRSwNP. While in CRSwNP the tertile with highest BEC suppression showed slightly larger treatment effects of depemokimab, no relationship between PD effects and clinical effects (on exacerbation rate) of depemokimab was found in the exposure-response analyses in asthma. This finding supports that the exposures and the PD-responses achieved are at the top of the exposure/PD-response curve. Based on BEC suppression, a therapeutic window was defined as $C_{trough}$ levels of depemokimab above the $EC_{90}$ of 0.75 µg/mL, when the plateau is reached of the PK/PD curve, while $C_{max}$ should stay below 55 µg/mL as higher concentrations have not been studied/observed in clinical studies. However, based on the available data it cannot be confirmed whether these values correspond to the therapeutic window for optimal efficacy, considering that BEC suppression is not directly predictive of a therapeutic effect.

*Secondary PD - QTc interval prolongation*

Changes in QTc are not expected due to the high specificity of target interaction to reduce circulating eosinophils by targeting the IL-5 pathway and depemokimab's limited distribution or access to intracellular

targets, due to its physical size (~149 kDa). IHC studies with depemokimab did not show specific bindings to cardiac tissues.

In the preclinical programme, 4 out of 6 monkeys showed QTc prolongation of ~18 msec up to 72 h after the second dose of 100 mg/kg. The monkeys were exposed to a higher dose (100 mg/kg) administered with shortened dosing interval (12 weeks) compared with the proposed posology in humans. In humans, the selected dose for phase 3 program is 100 mg SC every 6 months, resulting in much lower exposure. The exposure for a 40-100 kg patient is 1.0-2.5 mg/kg every 6 months. From a toxicology point of view, the clinical relevance of prolonged QTc is therefore considered limited.

The provided FTIH study investigated doses from 2 mg to 300 mg in patient groups of 6-9 participants. A U-form dose-response curve was obtained from 2h post dose to about day 57 for the doses of 2 mg vs. 10-300 mg. Data obtained in these participants with mild-moderate asthma show a slightly positive direction coefficient in a ΔQTc-vs-Conc analysis, i.e. slight prolongation of QTc with higher depemokimab concentrations.
The $C_{max}$ of the 100 mg SC dose is approx. 15 µg/mL. At this dosage, the upper 90% confidence limit of the mean QTc change is about 18 msec, thus above 10 msec. At about a concentration of 1 µg/mL, the upper 90% confidence limit of the mean QTc change is about 10 msec.

These findings change when the Phase III clinical data are added, mostly obtained 14 days after dosing, which graph then showed a negative direction coefficient for the slope, i.e. slight shortening of QTc with higher concentrations. Overall, considering all information, a prolonged QTc effect is considered unlikely.

*Immunological events*

Assessment of immunogenicity was generally in line with EMA guidance on immunogenicity assessment (EMEA/CHMP/BMWP/14327/2006) and (EMA/CHMP/BMWP/86289/2010), however, according to (EMA/CHMP/BMWP/86289/2010), it is normally expected that the neutralising capacity of any antibodies induced will be measured and any deviation from this should be justified. Summary of neutralising antibodies (NAbs) has not been provided for immunogenicity assessment in study 205722 (FTIH). The applicant notes that the EMA guidance cited, EMA/CHMP/BMWP/86289/2010, specifically states in Section 2 (Scope) that "This guideline is aimed at products at final development stage (e.g., marketing authorization application stage)," leaving some flexibility regarding methodology applied in early development phases. Although in this guideline it is also clearly stated that many of the principles are relevant also to earlier phases of development, the applicant's position can be accepted. According to available data depemokimab was considered as a low-risk drug in regard to immunogenicity which was confirmed in larger studies than study 205722 (FTIH). From these studies data regarding NAb positive patients were provided in details: the NAb incidence was low and no effect of ADA (including NAb) positivity on efficacy, safety, PK and PD was observed. Non-evaluation of NAb incidence in study 205722 is therefore considered adequately justified.

A higher incidence of ADA was reported in Chinese participants in both asthma and CRSwNP studies, while a Phase 1 study with healthy Chinese participants (n=20) did not have any ADA with the 100 mg or 300 mg dose. In all cases, titre values were low and near the sensitivity limit of the method, with no increasing titre values observed. It is considered that this elevated incidence observed in the China subpopulation may be due to slightly lower cut points determined for the ADA method performed at the China CRO. Considering that there was no apparent impact of ADA on safety, PK or PD, this finding is not considered clinically relevant.

Overall, the incidence of immunogenicity was relatively low across the studies. There was no evidence of an increased risk for positive ADAs with longer depemokimab treatment and no identified clinically significant effect of ADA on PK, PD, or safety of depemokimab.

*PK/PD*

In general, the presented PK, PD, and exposure-response results support the dose recommendation of 100 mg SC Q26W for depemokimab treatment in the asthma and CRSwNP target population.

However, whether this dose is optimal has not completely been characterised as only one dosing regimen has been tested in the Phase 3 studies.

Therefore, simulations were performed of the effects of Q4M and Q5M SC dosing on blood eosinophil counts, specifically at the end of the dosing intervals, as it cannot be completely ruled out that there is some relationship between blood eosinophil counts and efficacy outcomes. Some variation between the dosing regimens becomes apparent towards the end of the dosing intervals, with a predicted PD response of 86%, 85%, and 82% for Q4M, Q5M, and Q6M, respectively. Considering that further reductions in blood eosinophil count have not resulted in better clinical outcomes for other anti-IL-5(R) biologicals, while a reduction of 50% or less has been associated with poor clinical outcomes in asthma, these results suggest that the proposed depemokimab 100 mg Q6M regimen cannot be further optimised based on PD response.

*Dose selection*

Phase 3 dose selection of depemokimab was based on pharmacology matching. The applicant justified using blood eosinophils as a predictor of efficacy in asthma based on the two mepolizumab Phase 3 studies, MENSA and MUSCA, where mepolizumab reduced annualised exacerbation rate ratio by approximately 50%, with reductions in blood eosinophils of 84% in MENSA and 78% in MUSCA. Based on these findings, the PD target was set at 80% BEC reduction for depemokimab.

While BEC as marker of the primary PD response of depemokimab is not disputed, the fact remains that no clear relationship has been established between BEC and clinical outcomes. However, considering that mepolizumab and depemokimab are comparable drug substances with a similar mode of action, it can be accepted that the PD target of 80% BEC reduction was used to predict 50% reduction in annualised exacerbation rate in patients with severe eosinophilic asthma (i.e. the primary endpoint), which was subsequently confirmed in the clinical phase 3 studies.

The applicant further notes that clinical trial simulations were conducted to evaluate various designs analysing the annualised exacerbation rate reduction using dose response models. Results demonstrated that across the various evaluated designs, a conventional dose-ranging approach was unlikely (<5% probability) to provide a more robust and precise estimate of the Phase 3 dosing regimen due to the high variability associated with the nature of clinical endpoint coupled with the inherent uncertainty in the underlying location of the exacerbation dose response ($ED_{50}$). It is therefore considered unlikely that inclusion of an alternative dosing regimen would have provided a better picture of the optimal clinical response to depemokimab. This reasoning is accepted.

*Obese subjects*

Population PK analyses indicated that exposure to depemokimab decreases with increasing body weight and weight was the major determinant of depemokimab exposure. Over the body weight range of 54 to 108 kg (corresponding to the 5th to 95th percentiles), the difference in all exposure metrics was less than 1.3-fold.

Forest plots showed the impact of body weight on depemokimab PK over the broader range of 35–160 kg. For obese subjects weighing 140-160 kg exposure to depemokimab may be decreased 2-fold. For a 160-kg patient, the predicted $C_{trough}$ (0.67 µg/mL) remained above the estimated $EC_{50}$ of 0.19 µg/mL, indicating that depemokimab exposure may be sufficient at the end of the 26-week dosing interval.

Forest plots illustrating the impact of body weight on PD response showed that the percentage reduction in blood eosinophil count (BEC) from placebo at Week 52 for a 160 kg patient is 71%. The applicant states that the magnitude of the body weight effect, even for extremely heavy patients, is minor and not of clinical importance, and dose adjustment based on body weight is not considered necessary. The 80% reduction in BEC was defined as a PD target for the mean population, not as a minimum requirement for each individual patient. Exposure-response analyses demonstrated that subgroups with the lowest BEC reductions in both asthma and CRSwNP were consistent with the estimated treatment differences observed in the overall population. Therefore, the predicted 71% BEC reduction in patients weighing up to 160 kg falls within the range of reductions associated with clinically meaningful efficacy in both indications, but reduced efficacy cannot be excluded. See Smpc section 5.2.for special populations

***Conclusions***

Pharmacokinetic and pharmacodynamic data provided support the claims as stated in Section 4.2, 4.5, 5.1 and 5.2 of the SmPC.

## *6.3. Clinical efficacy*

## 6.3.1. Dose response study

No Phase 2 dose-response study was performed. Based on a single ascending dose FTIH study in mild to moderate asthma participants with a blood eosinophil count ≥200 cells/µL, using MIDD principles, the applicant identified 100 mg SC once every 26 weeks as the dose and dosing frequency of depemokimab that matches Phase 3 mepolizumab-like PD response (blood eosinophil count suppression).

## Asthma

## 6.3.2. Main studies

### *6.3.2.1. SWIFT-1 and SWIFT-2*

#### 6.3.2.1.1. Study title (replicate studies)

A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype.

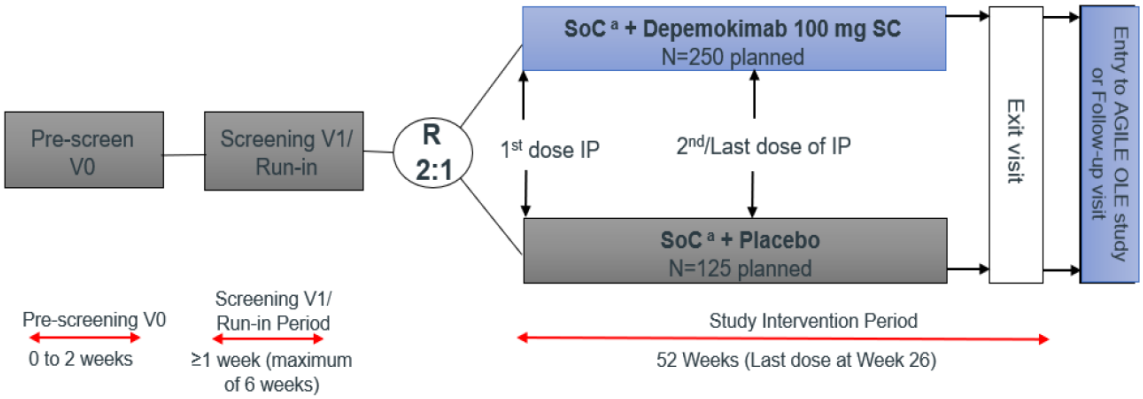
#### 6.3.2.1.2. Study design

SWIFT-1 and SWIFT-2 were replicate pivotal Phase 3 studies assessing efficacy and safety to support the asthma indication. Following screening and a run-in period of 1 to 6 weeks, these two 52-week multi-centres,

randomised, placebo-controlled, double-blind, parallel-group studies enrolled patients aged ≥12 years with severe uncontrolled eosinophilic asthma despite standard of care (SoC) treatment.

Participants who received both doses of study intervention and completed the Week 52 Exit Visit in SWIFT were eligible to participate in the open-label extension (OLE) study AGILE (212895). Participants who did not enter the OLE study were to be followed-up to Week 56.

**Figure 14: Study schema SWIFT-1 and SWIFT-2 (replicate studies)**




Abbreviations: IP = investigational Product; SC = subcutaneous; SoC = standard of care; OLE = open-label extension; R = randomization; V = Visit.

a. SoC = medium- to high-dose ICS plus additional controller; excludes biologics. Participants remained on their SoC asthma therapy throughout the Study Intervention Period.

**Treatment**

The study intervention was as follows:

- Depemokimab subcutaneous (SC) injection, 100 mg/mL; 1 mL SC injection PFS once every 26 weeks (Week 0 and Week 26), or
- Sterile 0.9% (w/v) sodium chloride solution; 1 mL SC injection of placebo PFS once every 26 weeks (Week 0 and Week 26).

Throughout the study, participants were to be maintained on their baseline maintenance asthma treatment consisting of medium- to high-dose ICS plus at least one other controller, e.g. LABA, LAMA, with or without maintenance OCS. Use of SABAs was also allowed throughout the study period.

**Randomisation**

Eligible participants were centrally randomised using an IRT system. Separate randomisation schedules were created for each country using validated randomisation software. Randomisation was stratified according to the participant's baseline ICS dose (medium or high dose) with the aim of randomising up to approximately 50% of participants on a medium ICS dose. Participants were randomised in a 2:1 ratio to receive depemokimab 100 mg SC or placebo SC.

**Blinding**

Investigators remained blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, depemokimab and placebo were administered as clear, low viscosity solutions

from PFS that were identical in appearance. Only haematology differential data (absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes) from post-randomisation samples were reported to the site or the central study team.

**Patient population**

SWIFT-1 and SWIFT-2 included male and female adults and adolescents ≥12 years of age with a documented physician's diagnosis of asthma for ≥2 years and a previously confirmed history of ≥2 asthma exacerbations requiring treatment with systemic CS (IM, IV, or oral) in the 12 months prior to Visit 1 despite the use of medium- to high-dose ICS (≥440 mcg fluticasone propionate HFA or equivalent).

Other **inclusion criteria** included:

- Eosinophilic asthma as documented by an elevated peripheral blood eosinophil count of ≥300 cells/µL demonstrated in the past 12 months prior to Visit 1 or an elevated peripheral blood eosinophil count of ≥150 cells/µL at Screening Visit 1.
- Persistent airflow obstruction as indicated by a pre-bronchodilator FEV1 <80% predicted at Visit 1 for participants ≥18 years of age; or a pre-bronchodilator FEV1 <90% predicted, or an FEV1:FVC ratio <0.8 at Visit 1 for participants 12-17 years of age.
- Evidence of airway reversibility or hyperresponsiveness defined by airway reversibility (FEV1 ≥12% and 200 mL) demonstrated at Visit 1 or Visit 2 using the maximum post bronchodilator procedure **OR** airway hyperresponsiveness (methacholine: PC20 <8 mg/mL, histamine: PD20 <7.8 micromol, mannitol: decrease in FEV1 as per the labelled product instructions) documented in the 24 months prior to Visit 2 (randomisation visit).
- A well-documented requirement for regular treatment with medium- to high-dose ICS in the 12 months prior to Visit 1 [with or without maintenance OCS] and current treatment with at least 1 additional controller medication besides ICS, for at least 3 months.
  The maintenance ICS dose must be ≥440 mcg FP HFA daily, or clinically comparable. Participants who were treated with medium-dose ICS also had to be treated with LABA to qualify for inclusion.

**Exclusion criteria** included:

- Presence of a known pre-existing, clinically important lung condition other than asthma, pre-existing parasitic infestation within 6 months prior to Visit 1, a known immunodeficiency other than that explained by the use of CSs taken as therapy for asthma, or presence of other conditions that could lead to elevated eosinophils such as hypereosinophilic syndromes.
- Current smoking or former smoking with a smoking history of ≥10 pack years
- Current diagnosis of vasculitis or active COVID-19 infection.
- Treatment with mepolizumab, reslizumab, or benralizumab within 12 months prior to Visit 1 or omalizumab or dupilumab within 130 days prior to Visit 1, or any mAb within 5 half-lives of Visit 1.
- Previous documented failure with anti-IL-5/5R therapy.
- QT interval corrected by Fridericia's method QTc(F) ≥450 msec or QTc(F) ≥480 msec (for participants with Bundle Branch Block). A 12-lead ECG central over-read was used at screening Visit 1 and 12-lead ECG machine read at randomisation Visit 2.

#### 6.3.2.1.3. Objectives and estimands

**Primary objective**

The primary objective was to show superiority of depemokimab 100 mg SC every 26 weeks versus placebo as assessed by the annualised rate of clinically significant exacerbations measured over the study intervention period of 52 weeks.

The null hypothesis was there is no difference in annualised exacerbation rate between depemokimab and placebo, which was tested at a 5% two-sided significance level.

**Estimand for the primary objective**

**Table 14: Estimand for primary objective**

| | |
|---|---|
| Population | Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype |
| Treatment conditions | Assignment to Depemokimab +SoC, regardless of discontinuation, compared to assignment to Placebo +SoC, regardless of discontinuation, over 52 weeks |
| Endpoint (variable) | Annualised rate of clinically significant exacerbations over 52 weeks |
| Population-level summary | Ratio of the annualised rates of clinically significant exacerbations between depemokimab + SoC and placebo + SoC |
| Intercurrent events and strategy to handle them | |
| Discontinuation due to reasons unrelated to COVID-19 | Treatment policy strategy, i.e. regardless of the intercurrent event occurring |
| Discontinuation due to COVID-19 | Hypothetical strategy, i.e. had the intercurrent event not occurred |
| Change in maintenance therapy (not important PDs) | Treatment policy strategy, i.e. regardless of the intercurrent event occurring |
| Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications) | Treatment policy strategy, i.e. regardless of the intercurrent event occurring |

The primary effect of interest is the ratio of the annualised rates of clinically significant exacerbations between the depemokimab and placebo groups, regardless of whether participants discontinued due to reasons unrelated to COVID-19, had a change in their maintenance therapy (important or not important PDs), or used prohibited medications (i.e. treatment policy strategy).

Discontinuations due to COVID-19 were handled as if the intercurrent event had not occurred (i.e. hypothetical strategy). Observed data for the period following this intercurrent event were to be excluded from the analysis. Data for this period was to be assumed "missing at random" (MAR) (based on all data included in the analysis under the current estimand strategy).

**Statistical methods for estimation and sensitivity analysis on primary estimand**

The primary population for the primary endpoint analysis was the FAS, which consisted of all randomised participants who received at least 1 dose of study intervention in the SWIFT studies, except for participants

excluded due to GCP deviations/data integrity issues.

Primary endpoint analyses were conducted at the individual study level (for each of SWIFT-1 and SWIFT-2) and in an integrated analysis of data from both studies.

The primary endpoint was assessed with a generalised linear model assuming a negative binomial distribution, with covariates for treatment, baseline ICS dose, exacerbation history, geographical region, and baseline pre-bronchodilator percent predicted FEV1.

Missing data or data excluded due to intercurrent events were handled as follows:

a. For participants who discontinued study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event were excluded from analysis. Data for this period were to be assumed "missing at random" (MAR) (based on all data included in the analysis under the current estimand strategy).

b. For participants who withdrew from the study, preventing assessment of the primary endpoint, the data for the period following withdrawal were to be assumed MAR (based on all data included in the analysis under the current estimand strategy).

Sensitivity analyses were to be conducted to investigate the conclusions from deviations from these assumptions regarding missing data for (b) above. Missing data for participants were to be based on data from participants who discontinued study intervention (off-treatment) but remained in the study. A tipping point analysis was to be conducted to impute missing data based on a plausible range of values for the rate of exacerbations per year. The imputed exacerbation rates were to be varied independently for treatment arms.

**Secondary objective**

The secondary objective was to evaluate depemokimab 100 mg (SC) every 26 weeks versus placebo on HRQoL and additional efficacy assessments on top of existing asthma therapy.

If the primary endpoint showed statistical significance the following secondary endpoints were tested according to the prespecified statistical hierarchy to control for multiplicity. The hypothesis was that depemokimab showed superiority over placebo for:

1) The difference in mean change from baseline in SGRQ at Week 52 between depemokimab and placebo +SoC

2) The difference in mean change from baseline in ACQ-5 at Week 52 between depemokimab and placebo +SoC

3) The difference in mean change from baseline in pre-bronchodilator ppFEV1 at Week 52 between depemokimab and placebo +SoC

4) The difference in mean change from baseline in ANSD at Week 52 between depemokimab and placebo +SoC

5) The difference in mean change from baseline in ADSD at Week 52 between depemokimab and placebo +SoC

6) Ratio of the rates of clinically significant exacerbations requiring hospitalisation and/or ED visit

between depemokimab and placebo +SoC

A number of other efficacy endpoints were prespecified in the study protocol, without control for multiplicity. These included time to event analyses (for clinically significant exacerbations, and clinically significant exacerbations requiring hospitalisation and/or ED visit), change from baseline analyses at additional discrete timepoints (for SGRQ, ACQ-5, ADSD, ANSD, and FEV1), responder analyses (for SGRQ and ACQ-5), and change from baseline in morning PEF.

In addition, blood samples were collected and the ratio to baseline and absolute blood eosinophil count over time were assessed at discrete timepoints during the 52-week period.

**Estimands for the secondary objective**

The treatment effect intended to be measured was the difference in change from baseline in HRQoL (SGRQ, ACQ-5, ANSD, ADSD) and lung function (FEV1) assessments at Week 52 between depemokimab and placebo treatment groups. Handling of ICE was defined similar to the primary estimand.

Additionally, the treatment effect intended to be measured was the ratio of the annualised rates of exacerbations requiring hospitalisation and/or ED visit over 52 weeks between depemokimab and placebo treatment groups. Handling of ICE was defined similar to the primary estimand.

**Statistical methods for estimation and sensitivity analysis on the secondary estimands**

Change from baseline in SGRQ total score, ACQ-5 score, pre-bronchodilator FEV1, ANSD, and ADSD at Week 52 were analysed using an MMRM model, with covariates of treatment, baseline ICS dose, exacerbation history, geographical region, baseline, visit, visit by baseline, and visit by treatment (plus pre-bronchodilator percent predicted FEV1 as a covariate for the non-FEV1 endpoints).

The annualised rate of clinically significant exacerbations requiring hospitalisation and/or ED visit over 52 weeks was analysed in the same manner and with the same covariates as the primary endpoint.

A fixed sequence hierarchical testing procedure was used to control Type I error for multiplicity arising from the primary and multiple secondary endpoints. This was carried out using a stepdown closed testing procedure where inference for an endpoint in the predefined hierarchy was dependent on statistical significance achieved for the previous endpoints in the hierarchy. The next endpoint in the hierarchy was to be tested only if the test for the previous endpoint was significant at the two-sided 5% level. The hierarchy of the secondary endpoints (1 to 6) is shown under Secondary objective.

#### 6.3.2.1.4. Results

**Participant flow and numbers analysed**

The SWIFT-1 and SWIFT-2 studies ran in parallel and commenced around the same time, i.e. 17 March 2021 and 04 February 2021 respectively. SWIFT-1 was completed (last observation last participant) on 21 November 2023 and SWIFT-2 on 11 April 2024.

<u>SWIFT-1</u>

A total of 622 participants were screened of whom 158 failed screening. A total of 69 (69/464 participants) participants did not meet the randomisation criteria at the end of the run-in period. Therefore, a total of 395 were 2:1 randomised.

Of these 395 randomised participants, 382 participants were included in the FAS population. A total of 13 participants were excluded due to GCP deviations (n=11) and n=2 participants were randomised in error but did not receive any study intervention.

Most participants completed study treatment, i.e., 236/250 (94%) in the depemokimab group and 126/132 (95%) in the placebo group. The main reasons for premature treatment discontinuation were lack of efficacy (n=4 [2%] for depemokimab vs. n=2 [2%] for placebo) and adverse events (n=3 [1%] vs. n=2 [2%]).

Most participants completed the study, i.e., 237/250 (92%) in the depemokimab group and 122/132 (92%) in the placebo group. The main reason for study withdrawal was withdrawal by participant (n=5 [2%] for depemokimab vs. n=5 [4%] for placebo).

A total of 34 intercurrent events occurred. The treatment policy strategy was applied for 20 (8%) and 13 (10%) subjects in the depemokimab and placebo group, respectively. For 1 subject (<1%), the hypothetical strategy was applied (treatment discontinuation due to COVID-19). Observed data for the period following this intercurrent event were excluded from the analysis and assumed to be missing at random.

SWIFT-2

A total of 663 participants were screened of whom 207 failed screening. A total of 59 (59/456 participants) participants did not meet the randomisation criteria at the end of the run-in period. Therefore, a total of 397 were 2:1 randomised.

Of these 397 randomised participants, 380 participants were included in the FAS population. A total of 17 participants were excluded due to GCP deviations (n=12) and n=5 participants were randomised in error but did not receive any study intervention.

Most participants completed study treatment, i.e., 239/252 (95%) in the depemokimab group and 125/128 (95%) in the placebo group. The main reasons for premature treatment discontinuation were subject withdrawal (n=8 [3%] for depemokimab vs. n=1 [<1%] for placebo) and lack of efficacy (n=3 [1%] vs. n=0).

Most participants completed the study, i.e., 233/252 (92%) in the depemokimab group and 117/128 (91%) in the placebo group. The main reason for study withdrawal was withdrawal by participant (n=10 [4%] for depemokimab vs. n=6 [5%] for placebo).

A total of 47 intercurrent events occurred. The treatment policy strategy was applied for 33 (13%) and 14 (11%) subjects in the depemokimab and placebo group, respectively. The hypothetical strategy was not applied for any subjects.

**Figure 15: Participant flow SWIFT-1**

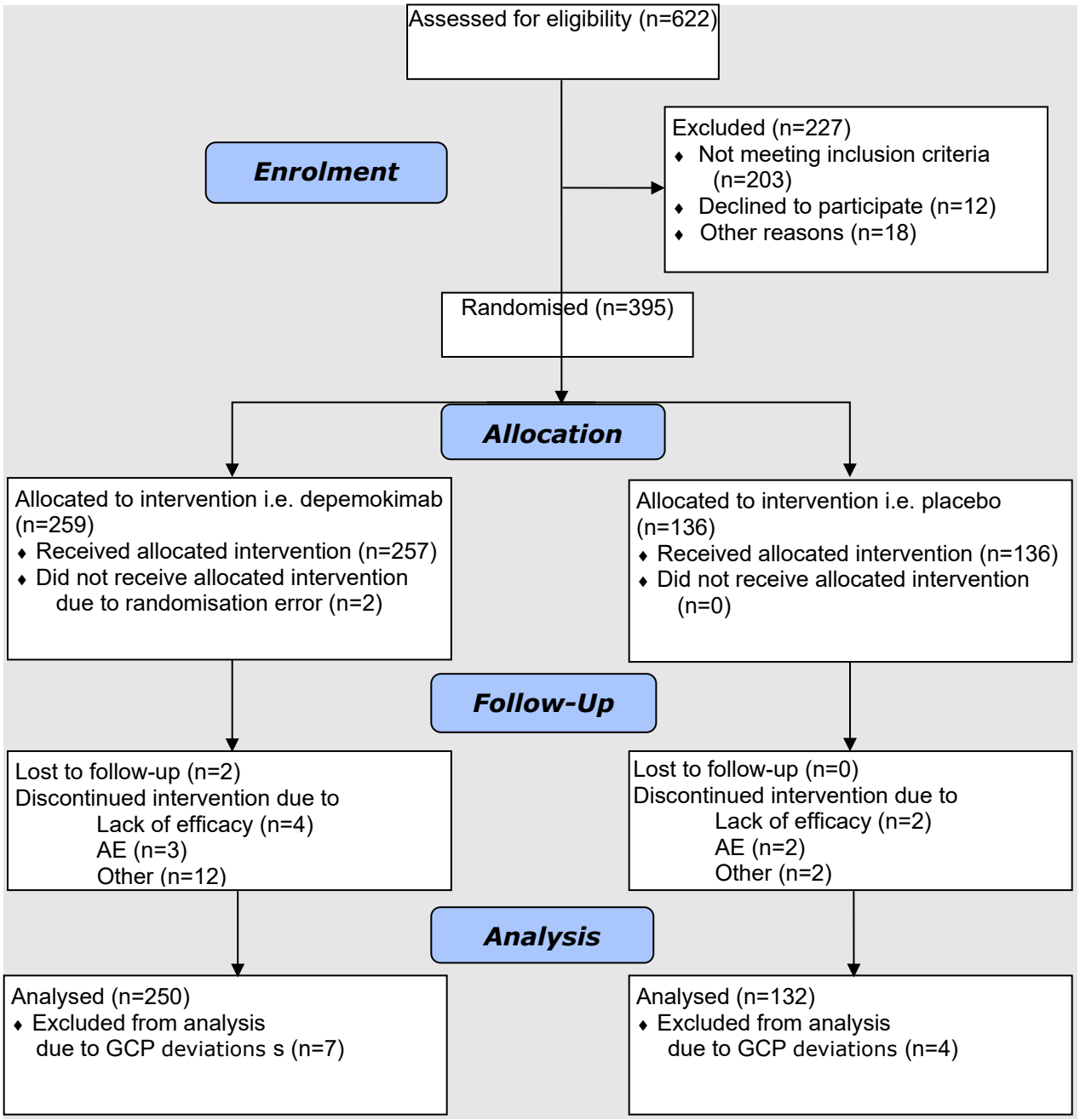
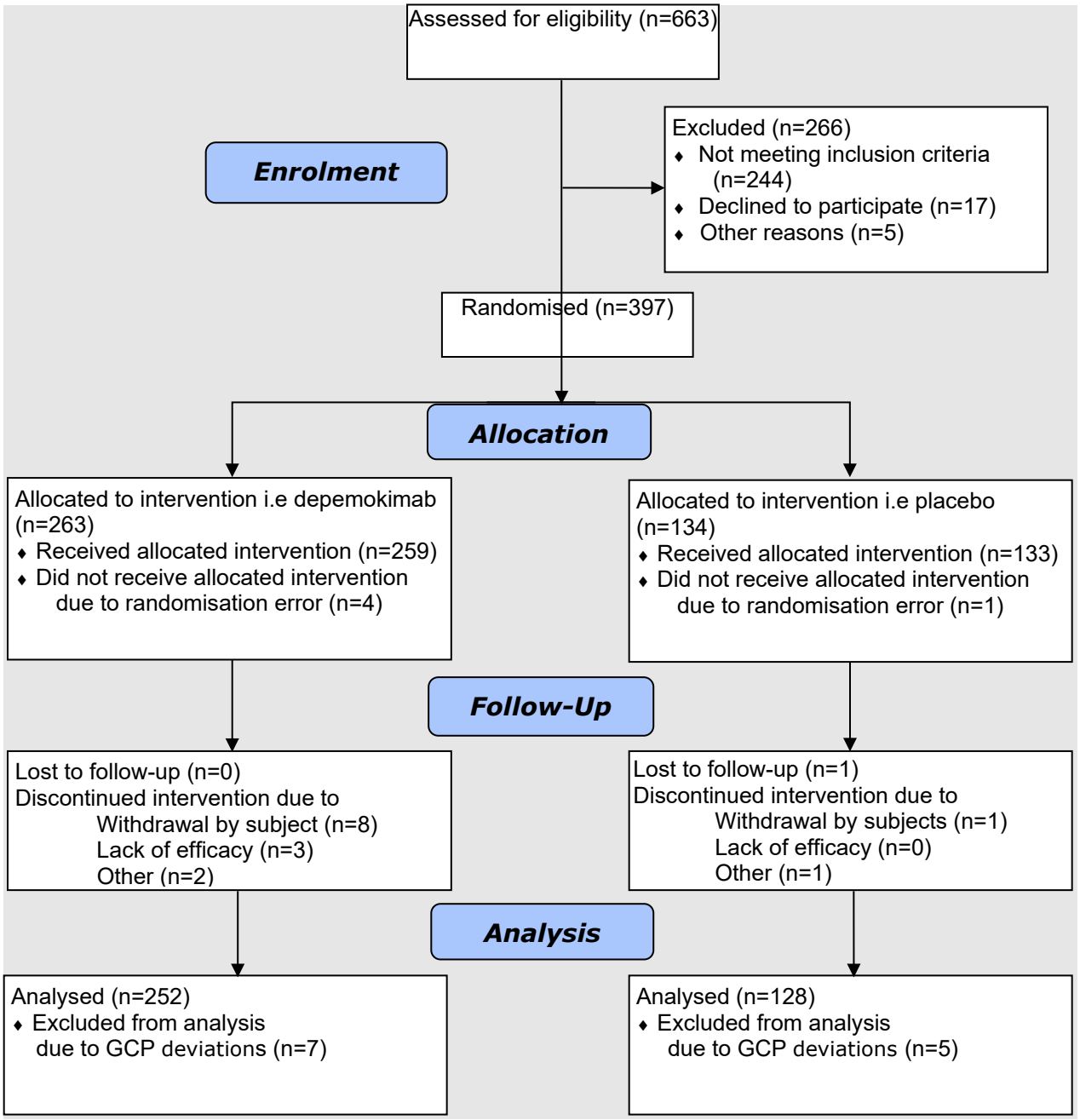


**Figure 16: Participant flow SWIFT-2**




**Deviations from study plan**

Both studies had two amendments.

***Rationale amendment 1***

Amendment 01 (SWIFT-1: 17 AUG 2021; SWIFT-2: 17 AUG 2021) was a global amendment to include modifications based on regulatory suggestion and additional changes were incorporated which aligned with program revisions and/or updates.

***Rationale amendment 2***

Amendment 02 (SWIFT-1: 08 APR 2022; SWIFT-2: 05 APR 2022) was a global amendment to include details about controlled early access to unblinded pharmacokinetics (PK) and pharmacokinetics pharmacodynamics (PKPD) data, a futility analysis and the use of blinded interim data to complete a psychometric analysis of the Asthma Daily/Nightly Symptom Diary (ADSD/ANSD) and PROMIS fatigue items.

Additional changes included repeated spirometry assessment and/or additional lab test if randomisation criteria were not to be met during screening, change in the ratio of medium/high ICS dose, allowance/permittance of authorised COVID-19 treatments, Global Initiative for Asthma (GINA) inhaled corticosteroid (ICS) doses update, and QT prolongation clarifications.

***Changes in planned analyses prior to unblinding or database lock***

Validation work was conducted on the ADSD/ANSD measures since the original protocol and SAP were finalised. Following additional regulatory agency feedback, ADSD/ANSD change from baseline at week 52 endpoints were added as secondary endpoints and into the hierarchy.

***Changes following study unblinding/database lock and post-hoc analyses***

For both SWIFT-1 and SWIFT-2 studies, data from several sites were excluded prior to unblinding from the primary analysis due to concerns about data integrity and GCP deviations. Supplementary analyses that include data from the sites have been produced for key efficacy and safety endpoints and are presented in the individual CSRs. However, the proposed prescribing information contains results from the analyses that exclude data from these sites.

An issue was also identified with a site in SWIFT-2 following completion of the statistical analyses; depemokimab concentrations could not be detected in 7 participants randomised to depemokimab and there was no evidence of PD effect (reduction of blood eosinophil count) in these participants. As this review was conducted after unblinding, the applicant decided to include all the participants in the FAS and safety population based on the intent-to-treat principle. A sensitivity analysis of the primary endpoint was carried out post-hoc excluding the participants from the site concerned to explore the impact of potentially anomalous data.

For SWIFT-1, updates to the planned statistical analysis occurred after study database lock (10 December 2023), while for SWIFT-2, these changes were implemented in SAP Amendment 03 (03 April 2024) before study database lock (07 May 2024). This concerned the following changes:

- The definition of screened population was updated to exclude the participants who failed at pre-screening.
- A typographical error in SAP (Section 4.3.2) was corrected, i.e. the covariate of 'baseline pre-bronchodilator % predicted FEV1' was updated to 'baseline pre-bronchodilator FEV1'.
- Analysis of annualised rate of clinically significant exacerbations by baseline ICS dose was performed with the approach of fitting interaction term to obtain treatment by subgroup interaction p-value for the forest plot.
- Analysis was performed with additional subgroups, i.e., baseline ICS dose (medium, high), baseline eosinophil subgroup 1 (<150, ≥150 cells/μL), baseline eosinophil subgroup 2 (<300, ≥300 cells/μL), and baseline ACQ-5 (<1.5, ≥1.5) for the primary and selected secondary endpoints

(SGRQ, ACQ-5, and FEV1), and the PD endpoint of change from baseline in blood eosinophil count at Week 52.

**Baseline data**

***Demographic characteristics***

SWIFT-1

**Table 15: Summary of demographic characteristics (SWIFT-1, SWIFT-2, and SWIFT-1+2 integrated)**

| | SWIFT-1 | | | SWIFT-2 | | | SWIFT-1+2 integrated | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Depem N=250** | **Placebo N=132** | **Total N=382** | **Depem N=252** | **Placebo N=128** | **Total N=380** | **Depem N=502** | **Placebo N=260** | **Total N=762** |
| **Gender, n (%)** | | | | | | | | | |
| Female | 144 (58) | 79 (60) | **223 (58)** | 160 (63) | 81 (63) | **241 (63)** | 304 (61) | 160 (62) | **464 (61)** |
| Male | 106 (42) | 53 (40) | **159 (42)** | 92 (37) | 47 (37) | **139 (37)** | 198 (39) | 100 (38) | **298 (39)** |
| **Age, years** | | | | | | | | | |
| Mean | 54.1 | 53.6 | **53.9** | 53.6 | 51.2 | **52.8** | **53.8** | **52.4** | **53.3** |
| SD | 13.8 | 14.9 | **14.2** | 16.0 | 16.6 | **16.2** | **14.9** | **15.8** | **15.2** |
| Median | 55.5 | 56.0 | **56.0** | 57.0 | 53.0 | **55.5** | **56.0** | **55.0** | **56.0** |
| Min. | 14 | 15 | **14** | 12 | 12 | **12** | **12** | **12** | **12** |
| Max. | 78 | 78 | **78** | 82 | 81 | **82** | **82** | **81** | **82** |
| **Age group, years** | | | | | | | | | |
| 12-17 | 3 (1) | 5 (4) | **8 (2)** | 12 (5) | 10 (8) | **22 (6)** | 15 (3) | 15 (6) | **30 (4)** |
| 18-64 | 185 (74) | 91 (69) | **276 (72)** | 169 (67) | 93 (73) | **262 (69)** | 354 (71) | 184 (71) | **538 (71)** |
| ≥65 | 62 (25) | 36 (27) | **98 (26)** | 71 (28) | 25 (19) | **96 (25)** | 133 (26) | 61 (23) | **194 (25)** |
| **Race, n (%)** | | | | | | | | | |
| Asian | 38 (15) | 20 (15) | **58 (15)** | 52 (21) | 23 (18) | **75 (20)** | 90 (18) | 43 (17) | **133 (17)** |
| Black or African American | 5 (2) | 3 (2) | **8 (2)** | 17 (7) | 11 (9) | **28 (7)** | 22 (4) | 14 (5) | **36 (5)** |
| White | 207 (83) | 109 (83) | **316 (83)** | 181 (72) | 91 (71) | **272 (72)** | 388 (77) | 200 (77) | **588 (77)** |
| **Region, n (%)** | | | | | | | | | |
| Europe | 158 (63) | 85 (64) | **243 (64)** | 108 (43) | 57 (45) | **165 (43)** | 266 (53) | 141 (55) | **408 (54)** |
| US | 33 (13) | 18 (14) | **51 (13)** | 90 (36) | 46 (36) | **136 (36)** | **123 (25)** | **64 (25)** | **408 (54)** |
| Rest of world | 59 (24) | 29 (22) | **88 (23)** | 54 (21) | 25 (20) | **79 (21)** | **113 (23)** | **54 (21)** | **167 (22)** |
| **Height, cm** | | | | | | | | | |
| Mean | 168 | 168 | **168** | 166 | 166 | **166** | 167 | 167 | **167** |
| SD | 9.8 | 9.3 | **9.6** | 10.1 | 9.5 | **9.9** | 10.0 | 9.4 | **9.8** |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Median | 168 | 168 | **168** | 165 | 165 | **165** | 167 | 166 | **167** |
| Min | 144 | 142 | **142** | 144 | 143 | **143** | 144 | 142 | **142** |
| Max | 196 | 188 | **196** | 191 | 191 | **191** | 196 | 191 | **196** |
| **Weight, kg** | | | | | | | | | |
| Mean | 78.7 | 80.5 | **79.3** | 79.8 | 79.1 | **79.6** | 79.3 | 79.8 | **79.4** |
| SD | 18.0 | 19.9 | **18.6** | 21.1 | 19.5 | **20.6** | 19.6 | 19.7 | **19.6** |
| Median | 77.4 | 77.0 | **77.0** | 76.0 | 77.8 | **76.3** | 76.7 | 77.3 | **77.0** |
| Min | 41.1 | 51.0 | **41.1** | 34.6 | 37.7 | **34.6** | 34.6 | 37.7 | **34.6** |
| Max | 152.8 | 154.7 | **154.7** | 161.0 | 139.6 | **161.0** | 161.0 | 154.7 | **161.0** |
| **BMI, kg/m$^2$** | | | | | | | | | |
| Mean | 27.8 | 28.5 | **28.0** | 28.7 | 28.7 | **28.7** | 28.3 | 28.6 | **28.4** |
| SD | 5.6 | 6.5 | **5.9** | 6.1 | 6.7 | **6.3** | 5.9 | 6.6 | **6.1** |
| Median | 27.3 | 27.4 | **27.3** | 27.9 | 28.4 | **28.0** | 27.5 | 27.7 | **27.6** |
| Min | 15.1 | 18.6 | **15.1** | 14.2 | 16.4 | **14.2** | 12.4 | 16.4 | **14.2** |
| Max | 52.6 | 53.1 | **53.1** | 48.8 | 56.6 | **56.6** | 52.6 | 56.6 | **56.6** |

***Asthma history and baseline disease characteristics***

SWIFT-1

Baseline asthma disease state characteristics were generally similar in the depemokimab and placebo groups (Table 16). For the overall population, a total of 47% and 53% of participants were on medium- and high-dose ICS, respectively, with 5% using maintenance OCS. Most participants (91%) had a peripheral blood eosinophil count of ≥150 cells/µL at screening, while 49% of participants had a peripheral blood eosinophil count of ≥300 cells/µL demonstrated in the past 12 months prior to baseline assessment. In addition, baseline exacerbation history and percent predicted pre-dose FEV1 were consistent with the intended, uncontrolled asthma population. The baseline characteristic of ACQ-5 score was not an enrolment criterion in the study, however, most participants were reported with a mean ACQ-5 score of ≥1.5 at baseline. At baseline, the mean (SD) ACQ-5 score was 2.22 (1.12) and 2.34 (1.10) in depemokimab and placebo groups, respectively.

Use of asthma medications prior to treatment was generally similar in the depemokimab and placebo groups (Table 17), with 100% of the participants on ICS, 99% on LABA, and 27% on LAMA. Around 15% of the participants were on triple combination therapy (ICS+LABA+LAMA) prior to treatment.

SWIFT-2

Baseline asthma disease state characteristics were generally similar in the depemokimab and placebo groups (Table 16). For the overall population, a total of 41% and 59% of participants were on medium- and high-dose ICS, respectively, with 5% using maintenance OCS. Most participants (89%) had a peripheral blood eosinophil count of ≥150 cells/µL at screening, while 57% of participants had a peripheral blood eosinophil count of ≥300 cells/µL demonstrated in the past 12 months prior to baseline assessment. In addition, baseline exacerbation history and percent predicted pre-dose FEV1 were consistent with the intended, uncontrolled asthma population. Most participants were reported with a mean ACQ-5 score of ≥1.5 at baseline. At baseline, the mean (SD) ACQ-5 score was 2.20 (1.07) and 2.13 (1.00) in depemokimab and placebo groups, respectively.

Use of asthma medications prior to treatment was generally similar in the depemokimab and placebo groups (Table 17) with 100% of the participants on ICS, 99% on LABA, and 35% on LAMA. Around 29% of the participants were on triple combination therapy (ICS+LABA+LAMA) prior to treatment.

SWIFT-1+2 integrated

More participants experienced ≥3 exacerbations in the past 12 months in SWIFT-2 (27%) compared to SWIFT-1 (14%). Other baseline asthma disease state characteristics were generally consistent between the individual SWIFT studies (Table 17).

More participants were on triple combination therapy (ICS+LABA+LAMA) prior to treatment in SWIFT-2 (29%) compared to SWIFT-1 (15%). Also SABA (79% vs. 62%) and LT receptor antagonists (48% vs. 31%) were used more in SWIFT-2 than in SWIFT-1, respectively. Other asthma medications prior to treatment were generally consistent between the individual studies (Table 17).

**Table 16: Summary of asthma history and baseline disease characteristics (SWIFT-1, SWIFT-2, and SWIFT-1+2 integrated)**

| | SWIFT-1 | | | SWIFT-2 | | | SWIFT-1+2 integrated | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Depem N=250** | **Placeb N=132** | **Total N=382** | **Depem N=252** | **Placeb N=128** | **Total N=380** | **Depem N=502** | **Placeb N=260** | **Total N=762** |
| **Duration of asthma, years** | | | | | | | | | |
| Mean | 23 | 20 | **22** | 26 | 24 | **25** | 24 | 22 | **23** |
| SD | 16.1 | 16.3 | **16.2** | 18.7 | 17.9 | **18.5** | 17.5 | 17.2 | **17.5** |
| Median | 18 | 15 | **17** | 21 | 9 | **20** | 20 | 16 | **18** |
| Min | 2 | 2 | **2** | 2 | 2 | **2** | 2 | 2 | **2** |
| Max | 75 | 71 | **75** | 73 | 78 | **78** | 78 | 75 | **78** |
| **ICS dose level, n (%)** | | | | | | | | | |
| Medium | 118 (47) | 61 (46) | **179 (47)** | 94 (37) | 60 (47) | **154 (41)** | 212 (42) | 121 (47) | **333 (44)** |
| High | 132 (53) | 71 (54) | **203 (53)** | 158 (63) | 68 (53) | **226 (59)** | 290 (58) | 139 (53) | **429 (56)** |
| **Peripheral blood eosinophil count, n (%)** | | | | | | | | | |
| ≥300/µL <12 months | 127 (51) | 61 (46) | **188 (49)** | 151 (60) | 66 (52) | **217 (57)** | 278 (55) | 127 (49) | **405 (53)** |
| ≥150/µL at screening | 224 (90) | 123 (93) | **347 (91)** | 219 (87) | (118 (92) | **337 (89)** | 443 (88) | 241 (93) | **684 (90)** |
| **Eosinophil count, GI/L** | | | | | | | | | |
| Geo. Mean | 0.298 | 0.310 | **0.302** | 0.339 | 0.330 | **0.336** | 0.318 | 0.319 | **0.318** |
| SD Logs | 0.798 | 0.835 | **0.810** | 0.879 | 0.819 | **0.858** | 0.841 | 0.826 | **0.836** |
| Median | 0.310 | 0.315 | **0.310** | 0.345 | 0.320 | **0.340** | 0.330 | 0.320 | **0.320** |
| Min | 0.02 | 0.02 | **0.02** | 0.01 | 0.03 | **0.01** | 0.01 | 0.02 | **0.01** |
| Max | 2.36 | 1.49 | **2.36** | 1.81 | 4.44 | **4.44** | 2.36 | 4.44 | **4.44** |
| **Total IgE, µ/mL** | | | | | | | | | |
| n | 250 | 130 | **380** | 246 | 128 | **374** | 496 | 258 | **754** |
| Geo. Mean | 144 | 180 | **156** | 158 | 189 | **168** | 151 | 185 | **162** |
| SD Logs | 1.5 | 1.5 | **1.5** | 1.5 | 1.4 | **1.4** | 1.5 | 1.5 | **1.5** |
| Median | 181 | 191 | **185** | 167 | 200 | **180** | 177 | 196 | **184** |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Min | 1.9 | 1.9 | **1.9** | 4.8 | 2.2 | **2.2** | 1.9 | 1.9 | **1.9** |
| Max | 12143 | 5266 | **12143** | 16199 | 2702 | **16199** | 16199 | 5266 | **16199** |
| **Maintenance OCS, n (%)** | | | | | | | | | |
| Yes | 8 (3) | 13 (10) | **21 (5)** | 13 (5) | 6 (5) | **19 (5)** | 21 (4) | 19 (7) | **40 (5)** |
| **Required OCS in the past 12 months, n (%)** | | | | | | | | | |
| ≤2 | 210 (84) | 118 (89) | **328 (86)** | 188 (75) | 90 (70) | **278 (73)** | 398 (79) | 208 (80) | **606 (80)** |
| ≥3 | 39 (16) | 14 (11) | **53 (14)** | 64 (25) | 38 (30) | **102 (27)** | 103 (21) | 52 (20) | **155 (20)** |
| **Exacerbations requiring hospitalisation in the past 12 months, n (%)** | | | | | | | | | |
| 0 | 233 (93) | 125 (95) | **358 (94)** | 233 (92) | 111 (87) | **344 (91)** | 466 (93) | 236 (91) | **602 (92)** |
| 1 | 13 (5) | 4 (3) | **17 (4)** | 6 (2) | 12 (9) | **18 (5)** | 19 (4) | 16 (6) | **35 (5)** |
| ≥1 | 4 (2) | 3 (2) | **7 (2)** | 13 (6) | 5 (4) | **18 (4)** | 17 (3) | 8 (3) | **25 (3)** |
| **Pre-bronchodilator FEV1, L** | | | | | | | | | |
| n | 242 | 130 | **372** | 248 | 122 | **370** | 490 | 252 | **742** |
| Mean | 1.90 | 1.84 | **1.88** | 1.80 | 1.79 | **1.80** | 1.85 | 1.82 | **1.84** |
| SD | 0.69 | 0.71 | **0.70** | 0.66 | 0.69 | **0.67** | 0.68 | 0.70 | **0.68** |
| Median | 1.85 | 1.78 | **1.85** | 1.70 | 1.72 | **1.71** | 1.78 | 1.73 | **1.75** |
| Min | 0.50 | 0.43 | **0.43** | 0.61 | 0.65 | **0.61** | 0.50 | 0.43 | **0.43** |
| Max | 4.12 | 3.80 | **4.12** | 3.77 | 4.46 | **4.46** | 4.12 | 4.46 | **4.46** |
| **Pre-bronchodilator FEV1, % predicted** | | | | | | | | | |
| Mean | 62 | 61 | **62** | 63 | 61 | **62** | 60 | 59 | **60** |
| SD | 14.5 | 16.6 | **15.2** | 16.0 | 15.7 | **15.9** | 13.1 | 14.7 | **13.7** |
| **ACQ-5 score** | | | | | | | | | |
| n | 243 | 129 | **372** | 247 | 125 | **372** | 490 | 254 | **744** |
| Mean | 2.22 | 2.34 | **2.26** | 2.20 | 2.13 | **2.17** | 2.21 | 2.24 | **2.22** |
| SD | 1.12 | 1.10 | **1.12** | 1.07 | 1.00 | **1.05** | 1.10 | 1.06 | **1.08** |
| Median | 2.20 | 2.40 | **2.20** | 2.20 | 2.00 | **2.20** | 2.20 | 2.20 | **2.20** |
| Min | 0.0 | 0.0 | **0.0** | 0.0 | 0.0 | **0.0** | 0.0 | 0.0 | **0.0** |
| Max | 5.8 | 5.8 | **5.8** | 4.8 | 4.8 | **4.8** | 5.8 | 5.8 | **5.8** |
| **SGRQ total score** | | | | | | | | | |
| n | 243 | 129 | **372** | 247 | 125 | **372** | 490 | 254 | **744** |
| Mean | 44.7 | 43.6 | **44.3** | 44.7 | 44.0 | **44.5** | 44.7 | 43.8 | **44.4** |
| SD | 20.6 | 21.0 | **20.7** | 18.7 | 18.7 | **18.7** | 19.7 | 19.8 | **19.7** |
| Median | 45.3 | 41.5 | **43.6** | 45.4 | 44.2 | **45.4** | 45.4 | 42.9 | **44.2** |
| Min | 0.4 | 0.0 | **0.0** | 1.3 | 5.7 | **1.3** | 0.4 | 0.0 | **0.0** |
| Max | 90.6 | 93.0 | **93.0** | 97.9 | 95.7 | **97.9** | 97.9 | 95.7 | **97.9** |

**Table 17: Summary of asthma medications taken prior to treatment by respiratory medication class group (SWIFT-1, SWIFT-2, and SWIFT-1+2 integrated)**

| | SWIFT-1 | SWIFT-2 | SWIFT-1+2 integrated |
|---|---|---|---|

| | Depem N=250 | Placeb N=132 | Total N=382 | Depem N=252 | Placeb N=128 | Total N=380 | Depem N=502 | Placeb N=260 | Total N=762 |
|---|---|---|---|---|---|---|---|---|---|
| **Asthma medication, n (%)** | | | | | | | | | |
| **ICS** | 250 (100) | 132 (100) | 382 (100) | 252 (100) | 128 (100) | 380 (100) | 502 (100) | 260 (100) | 762 (100) |
| **LABA** | 247 (99) | 131 (>99) | 378 (99) | 249 (99) | 126 (98) | 375 (99) | 496 (99) | 257 (99) | 753 (99) |
| **LAMA** | 69 (28) | 35 (27) | 104 (27) | 87 (35) | 46 (36) | 133 (35) | 156 (31) | 81 (31) | 237 (31) |
| **ICS+LABA+ LAMA** | 41 (16) | 18 (14) | 59 (15) | 74 (29) | 36 (28) | 110 (29) | 115 (23) | 54 (21) | 169 (22) |
| **OCS** | 8 (3) | 13 (10) | 21 (5) | 13 (5) | 6 (5) | 19 (5) | 21 (4) | 19 (7) | 40 (5) |
| **SABA** | 157 (63) | 78 (59) | 235 (62) | 201 (80) | 101 (79) | 302 (79) | 358 (71) | 179 (69) | 537 (70) |
| **SAMA** | 31 (12) | 17 (13) | 48 (13) | 23 (9) | 12 (9) | 35 (9) | 54 (11) | 29 (11) | 83 (11) |
| **LT receptor antagonist** | 80 (32) | 39 (30) | 119 (31) | 116 (46) | 65 (51) | 181 (48) | 196 (39) | 104 (40) | 300 (39) |
| **Anti-infectives** | 37 (15) | 19 (14) | 56 (15) | 27 (11) | 7 (5) | 34 (9) | 64 (13) | 26 (10) | 90 (12) |
| **Mucolytics** | 23 (9) | 9 (7) | 32 (8) | 19 (8) | 7 (5) | 26 (7) | 42 (8) | 16 (6) | 58 (8) |
| **Xanthine** | 21 (8) | 10 (8) | 31 (8) | 23 (99) | 8 (6) | 31 (8) | 44 (9) | 18 (7) | 62 (8) |
| **Anti-IgE, Anti-IL5** | 0 | 1 (<1) | 1 (<1) | 2 (<1) | 1 (<1) | 3 (<1) | 2 (<1) | 2 (<1) | 4 (<1) |

**Outcomes and estimation**

***Primary outcome: Annualised rate of clinically significant exacerbations over 52 weeks – multiplicity level 1***

SWIFT-1 and SWIFT-2 each met their primary endpoint and demonstrated statistically significant ($P$<0.001) reductions in the annualised rate of clinically significant asthma exacerbations over 52 weeks compared to placebo.

SWIFT-1

The number of subjects who experienced at least 1 clinically significant exacerbation was lower in the depemokimab group compared to placebo, i.e., 32% vs. 46% respectively. At week 52, the annualised exacerbation rate was 0.46 (95% CI: 0.36, 0.58) for depemokimab and 1.11 (95% CI: 0.86, 1.43) for placebo. The rate ratio was 0.42 (95% CI: 0.30, 0.59), $P$<0.001, indicating a 58% (41-70%) reduction in the annualised exacerbation rate (Table 18).

SWIFT-2

Comparable results were observed in the SWIFT-2 study.

The number of subjects who experienced at least 1 clinically significant exacerbation was lower in the depemokimab group compared to placebo, i.e., 32% vs. 50% respectively. At week 52, the annualised exacerbation rate was 0.56 (95% CI: 0.44, 0.70) for depemokimab and 1.08 (95% CI: 0.83, 1.41) for placebo. The rate ratio was 0.52 (95% CI: 0.36, 0.73), $P$<0.001, indicating a 48% (27-64%) reduction in the annualised exacerbation rate (Table 18).

SWIFT-1+2 integrated

Results from the integrated analysis of data from SWIFT-1+2 reflected the results from the individual studies, with a reduction of 54% (rate ratio 0.46; 95% CI: 0.36, 0.59) in the annualised rate of clinically significant exacerbations with depemokimab compared to placebo (Table 19).

**Table 18: Primary analysis of annualised rate of clinically significant exacerbations (SWIFT-1, SWIFT-2, and SWIFT-1+2 integrated)**

| | SWIFT-1 | | SWIFT-2 | | SWIFT-1+2 integrated | |
|---|---|---|---|---|---|---|
| | **Placebo (N=132)** | **Depem 100 mg SC (N=250)** | **Placebo (N=128)** | **Depem 100 mg SC (N=252)** | **Placebo (N=260)** | **Depem 100 mg SC (N=502)** |
| **n** | 132 | 249 | 128 | 252 | 260 | 501 |
| **Annualised exacerbation rate** | **1.11** | **0.46** | **1.08** | **0.56** | **1.11** | **0.51** |
| 95% CI | (0.86, 1.43) | (0.36, 0.58) | (0.83, 1.41) | (0.44, 0.70) | (0.92, 1.33) | (0.43, 0.60) |
| **Depemokimab vs. Placebo** | | | | | | |
| **Rate ratio** | | **0.42** | | **0.52** | | **0.46** |
| 95% CI | | (0.30, 0.59) | | (0.36, 0.73) | | (0.36, 0.59) |
| P-value | | <0.001 | | <0.001 | | <0.001 |
| % reduction in annual rate | | 58% | | 48% | | 54% |
| 95% CI | | (41%, 70%) | | (27%, 64%) | | (41%, 64%) |

Abbreviations: CI = confidence interval; Depem = depemokimab; n = number of participants in analysis; N = number of participants in treatment group; SC = subcutaneous.
Note: Analysis performed using a generalised linear model assuming a negative binomial distribution and covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2 3 4+), geographical region and baseline pre-bronchodilator %predicted FEV1. For the integrated analysis, study (SWIFT-1 and SWIFT-2) was also included as additional covariate.
Note: Percentage reduction in annual rate is calculated as (1-rate ratio)*100

***Secondary outcomes***

The SWIFT studies included six secondary endpoints, of which SGRQ, ACQ-5, FEV1 (secondary endpoints 1-3), and clinically significant exacerbations requiring hospitalisation and/or ED visit (secondary endpoint 6) are presented in the SmPC and described here.

***Change from baseline in SGRQ score at Week 52 – multiplicity level 2***

In the individual studies adjusted for multiplicity, the treatment difference in the change from baseline in SGRQ score did not reach statistical significance at Week 52. This secondary outcome reached statistical significance in the integrated analysis (not adjusted for multiplicity).

Since the SGRQ score failed to show statistical significance in the multiplicity hierarchy in either of the pivotal studies, no statistical inference can be made for the remaining tests in the hierarchy.

SWIFT-1

The mean (SD) baseline SGRQ score was 44.7 (20.6) for depemokimab and 43.6 (21.0) for placebo (Table 16). At Week 52, the LS mean (SD) change from baseline was -13.0 (1.11) for depemokimab and -9.67 (1.55) for placebo. The resulting difference between treatments was -3.36 (95% CI: -7.11, 0.39), *P*=0.080 (Table 19).

SWIFT-2

The mean (SD) baseline SGRQ score was 44.7 (18.7) for depemokimab and 44.0 (18.7) for placebo (Table 20). At Week 52, the LS mean (SD) change from baseline was -14.8 (1.04) for depemokimab and -12.5 (1.46) for placebo. The resulting difference between treatments was -2.31 (95% CI: -5.84, 1.23), *P*=0.200 (Table 19).

SWIFT-1+2 integrated

The mean (SD) baseline SGRQ score was 44.7 (19.7) for depemokimab and 43.8 (19.8) for placebo (Table 20). At Week 52, the LS mean (SD) change from baseline was -13.9 (0.76) for depemokimab and -11.0 (1.06) for placebo. The resulting difference between treatments was -2.88 (95% CI: -5.43, -0.32), *P*=0.028 (Table 19).

**Table 19: Summary of analyses for secondary outcome change from baseline in SGRQ score at Week 52 (SWIFT-1, SWIFT-2, and SWIFT-1+2 integrated)**

| Efficacy endpoints in the study-level multiplicity adjustment plan analyses | SWIFT-1 | | SWIFT-2 | | SWIFT-1+2 integrated | |
|---|---|---|---|---|---|---|
| | Placebo (N=132) | Depem 100 mg SC (N=250) | Placebo (N=128) | Depem 100 mg SC (N=252) | Placebo (N=260) | Depem 100 mg SC (N=502) |
| Change from baseline in SGRQ score at Week 52 [a] | | | | | | |
| Endpoint (statistical hierarchy) | Secondary (multiplicity level 2) | | | | Secondary (not adjusted for multiplicity) | |
| n [b] | 128 | 240 | 124 | 246 | 252 | 486 |
| n [c] | 114 | 224 | 116 | 224 | 230 | 448 |
| LS Mean | 34.64 | 31.29 | 32.10 | 29.80 | 33.42 | 30.54 |
| (SE) | (1.544) | (1.112) | (1.455) | (1.041) | (1.055) | (0.758) |
| LS Mean Change | -9.67 | -13.03 | -12.49 | -14.80 | -11.04 | -13.92 |
| (SE) | (1.544) | (1.112) | (1.455) | (1.041) | (1.055) | (0.758) |
| Difference | -3.36 | | -2.31 | | -2.88 | |
| (95% CI) | (-7.11, 0.39) | | (-5.84, 1.23) | | (-5.43, -0.32) | |
| P-value | 0.080 | | 0.200 | | 0.028 | |

Abbreviations: CI = confidence interval; Depem = depemokimab; LS = least squares; n = number of participants with analysable data at the given timepoint (notes below); N = number in treatment group; SC = subcutaneous; SE = standard error; SGRQ = St. George's Respiratory Questionnaire.
[a] Analysis performed using a repeated measures model with covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, 4+), geographical region, baseline, visit, visit by baseline and visit by treatment group. Pre-bronchodilator percent predicted FEV1 also included for the non-FEV1 endpoints. Study also included for integrated analysis.
[b] Number of participants with analysable data for 1 or more timepoints.
[c] Number of participants with analysable data at the given timepoint.

***Change from baseline in ACQ-5 score at Week 52 – multiplicity level 3***

The treatment difference in the change from baseline in ACQ-5 score did not reach statistical significance at Week 52; neither in the individual studies adjusted for multiplicity nor in the integrated analysis (not adjusted for multiplicity).

SWIFT-1

The baseline mean (SD) ACQ score was 2.22 (1.12) for depemokimab and 2.34 (1.10) for placebo (Table 16). At Week 52, the LS mean (SD) change from baseline was -0.82 (0.066) for depemokimab and -0.77 (0.091) for placebo. The resulting difference between treatments was -0.04 (95% CI: -0.27, 0.18) (Table 20).

SWIFT-2

The baseline mean (SD) ACQ score was 2.20 (1.07) for depemokimab and 2.13 (1.00) for placebo (Table 16). At Week 52, the LS mean (SD) change from baseline was -0.81 (0.065) for depemokimab and -0.70 (0.091) for placebo. The resulting difference between treatments was -0.11 (95% CI: -0.33, 0.11) (Table 20).

SWIFT-1+2 integrated

In both individual studies and the integrated outcome, improvements from baseline in ACQ-5 score were observed, but with no apparent difference between treatment groups (Table 20).

**Table 20: Summary of analyses for change from baseline in ACQ-5 score at Week 52 (SWIFT-1, SWIFT-2, and SWIFT-1+2 integrated)**

| Efficacy endpoints in the study-level multiplicity adjustment plan analyses | SWIFT-1 | | SWIFT-2 | | SWIFT-1+2 integrated | |
|---|---|---|---|---|---|---|
| | Placebo (N=132) | Depem 100 mg SC (N=250) | Placebo (N=128) | Depem 100 mg SC (N=252) | Placebo (N=260) | Depem 100 mg SC (N=502) |
| Change from baseline in ACQ-5 score at Week 52 [a] | | | | | | |
| Endpoint (statistical hierarchy) | Secondary (multiplicity level 3) | | | | Secondary (not adjusted for multiplicity) | |
| n [b] | 129 | 241 | 124 | 246 | 253 | 487 |
| n [c] | 114 | 224 | 116 | 224 | 230 | 448 |
| LS Mean | 1.49 | 1.45 | 1.47 | 1.36 | 1.49 | 1.41 |
| (SE) | (0.091) | (0.066) | (0.091) | (0.065) | (0.064) | (0.046) |
| LS Mean Change | -0.77 | -0.82 | -0.70 | -0.81 | -0.73 | -0.81 |
| (SE) | (0.091) | (0.066) | (0.091) | (0.065) | (0.064) | (0.046) |
| Difference | -0.04 | | -0.11 | | -0.08 | |
| (95% CI) | (-0.27, 0.18) | | (-0.33, 0.11) | | (-0.24, 0.07) | |
| P-value* | 0.690 | | 0.333 | | 0.301 | |

Abbreviations: ACQ-5 = Asthma Control Questionnaire-5; CI = confidence interval; Depem = depemokimab; LS = least squares; n = number of participants with analysable data at the given timepoint (notes below); N = number in treatment group; SC = subcutaneous; SE = standard error.
* In accordance with the statistical testing hierarchy, no statistical inference can be made from this analysis.
[a] Analysis performed using a repeated measures model with covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, 4+), geographical region, baseline, visit, visit by baseline and visit by treatment group. Pre-bronchodilator percent predicted FEV1 also included for the non-FEV1 endpoints. Study also included for integrated analysis.
[b] Number of participants with analysable data for 1 or more timepoints.
[c] Number of participants with analysable data at the given timepoint.

***Change from baseline in pre-bronchodilator FEV1 at Week 52 – multiplicity level 4***

The treatment difference in the change from baseline in pre-bronchodilator FEV1 did not reach statistical significance at Week 52; neither in the individual studies adjusted for multiplicity nor in the integrated analysis (not adjusted for multiplicity).

SWIFT-1

The baseline mean (SD) pre-bronchodilator FEV1 was 1.90 (0.69) L for depemokimab and 1.84 (0.71) L for placebo (Table 16). At Week 52, the LS mean (SD) change from baseline was 0.160 (0.0263) L for depemokimab and 0.160 (0.0364) L for placebo. The resulting difference between treatments was -0.001 L (95% CI: -0.089, 0.088) (Table 21).

SWIFT-2

The baseline mean (SD) pre-bronchodilator FEV1 was 1.80 (0.66) L for depemokimab and 1.79 (0.69) L for

placebo (Table 16). At Week 52, the LS mean (SD) change from baseline was 0.240 (0.0286) L for depemokimab and 0.184 (0.0407) L for placebo. The resulting difference between treatments was 0.056 L (95% CI: -0.043, 0.154) (Table 21).

SWIFT-1+2 integrated

Analysis of data integrated from SWIFT-1+2 showed a treatment difference of 0.028 L (95% CI: -0.038, 0.094 (Table 21). In both individual studies and the integrated outcome, improvements from baseline in pre-bronchodilator FEV1 were observed but with no apparent difference between treatment groups.

**Table 21: Summary of analyses for change from baseline in pre-bronchodilator FEV1 at Week 52 (SWIFT-1, SWIFT-2, and SWIFT-1+2 integrated)**

| Efficacy endpoints in the study-level multiplicity adjustment plan analyses | SWIFT-1 | | SWIFT-2 | | SWIFT-1+2 integrated | |
|---|---|---|---|---|---|---|
| | Placebo (N=132) | Depem 100 mg SC (N=250) | Placebo (N=128) | Depem 100 mg SC (N=252) | Placebo (N=260) | Depem 100 mg SC (N=502) |
| Change from baseline in pre-bronchodilator FEV1 at Week 52 [a] | | | | | | |
| Endpoint (statistical hierarchy) | Secondary (multiplicity level 4) | | | | Secondary (not adjusted for multiplicity) | |
| n [b] | 126 | 236 | 119 | 239 | 245 | 475 |
| n [c] | 115 | 224 | 112 | 226 | 227 | 450 |
| LS Mean | 2.036 | 2.035 | 1.977 | 2.033 | 2.006 | 2.034 |
| (SE) | (0.0364) | (0.0263) | (0.0407) | (0.0286) | (0.0271) | (0.0194) |
| LS Mean Change | 0.160 | 0.160 | 0.184 | 0.240 | 0.172 | 0.200 |
| (SE) | (0.0364) | (0.0263) | (0.0407) | (0.0286) | (0.0271) | (0.0194) |
| Difference | -0.001 | | 0.056 | | 0.028 | |
| (95% CI) | (-0.089, 0.088) | | (-0.043, 0.154) | | (-0.038, 0.094) | |
| P-value* | 0.991 | | 0.267 | | 0.403 | |

Abbreviations: CI = confidence interval; Depem = depemokimab; FEV1 = forced expiratory volume in 1 second; LS = least squares; n = number of participants with analysable data at the given timepoint (notes below); N = number in treatment group; SC = subcutaneous; SE = standard error.
* In accordance with the statistical testing hierarchy, no statistical inference can be made from this analysis.
[a] Analysis performed using a repeated measures model with covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, 4+), geographical region, baseline, visit, visit by baseline and visit by treatment group. Pre-bronchodilator percent predicted FEV1 also included for the non-FEV1 endpoints. Study also included for integrated analysis.
[b] Number of participants with analysable data for 1 or more timepoints.
[c] Number of participants with analysable data at the given timepoint.

***Ratio of the rates of clinically significant exacerbations requiring hospitalisation and/or ED visit – multiplicity level 7***

SWIFT-1

The data did not meet the conditions (total of 20 or more exacerbations requiring hospitalisation and/or ED visit) for conducting the analysis. A numerically smaller percentage of participants in the depemokimab group had an exacerbation that required hospitalisation and/or ED visit (n=3, [1%]) compared to the placebo group (n=11 [8%]).

SWIFT-2

A numerically smaller percentage of participants in the depemokimab group had an exacerbation that required hospitalisation and/or ED visit (n=10, [4%]) compared to the placebo group (n=13 [10%]). The annualised rate of clinically significant exacerbations requiring hospitalisation and/or ED visit over 52 weeks

was 0.05 (95% CI: 0.022, 0.09) for depemokimab and 0.11 (95% CI: 0.05, 0.22) for placebo. The rate ratio was 0.42 (95% CI: 0.16, 1.13) indicating a 58% (95% CI: -13%, 84%) reduction in the annualised exacerbation rate requiring hospitalisation and/or ED visit.

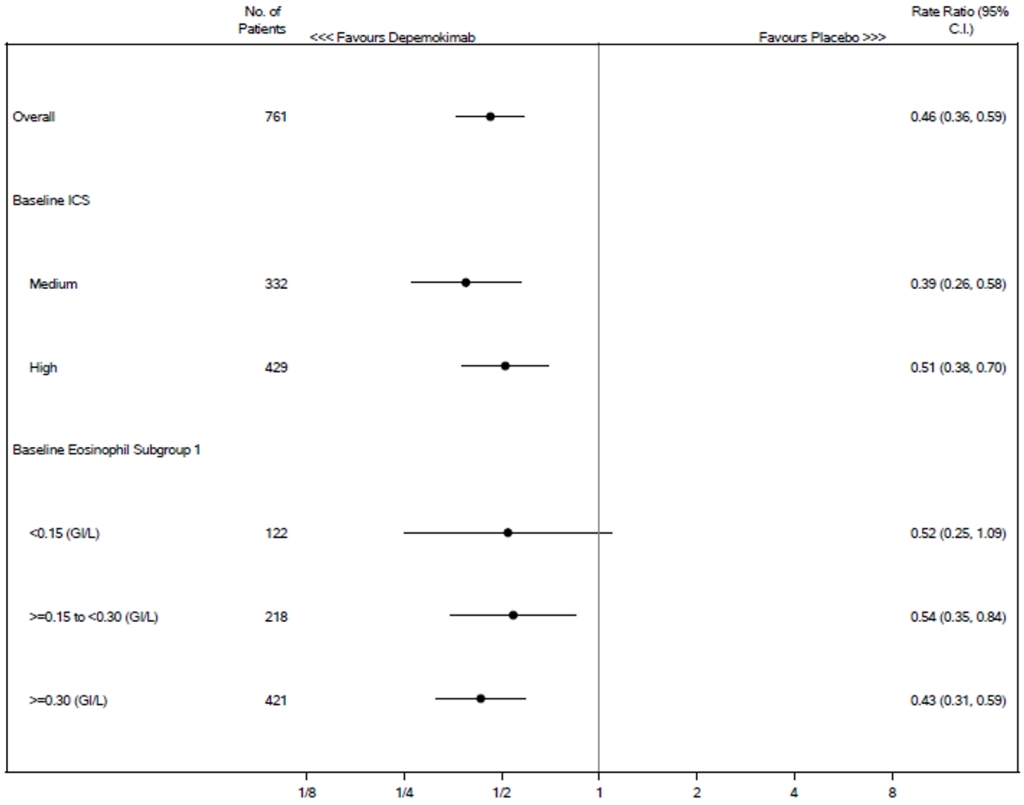
**Pre-defined and post-hoc subgroup analyses**

***Primary outcome: Annualised rate of clinically significant exacerbations over 52 weeks***

SWIFT-1+2 integrated

Results of the subgroup analyses were mostly consistent with the results from the primary analysis. Notably, a reduction in exacerbation rate with depemokimab was observed regardless of whether patients were on medium- or high-dose ICS, and baseline blood eosinophil counts were <150 cells/µL, ≥150 to 300 cells/µL, or >300 cells/µL.

**Figure 17: Forest plot of rate ratios of annualised rate of clinically significant exacerbations by baseline eosinophil count and baseline ICS (pooled FAS population)**




Note: No. of Patients is the number of subjects with analyzable data for the two treatment groups of interest
Note: Analysis performed using a generalized linear model assuming a negative binomial distribution and covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, 4+), geographical region, baseline pre-bronchodilator percent predicted FEV1, study (206713 or 213744), subgroup and subgroup by treatment group. Only subgroup levels with greater than or equal to 20 subjects were included in the statistical analysis.

**Sensitivity analyses**

***Sensitivity analyses primary endpoint***

SWIFT-1

Since the total unobserved/excluded time in the study was <3% of the total study duration, the condition for conducting the analysis was not met. Therefore, the sensitivity analysis using off-treatment imputation was not performed.

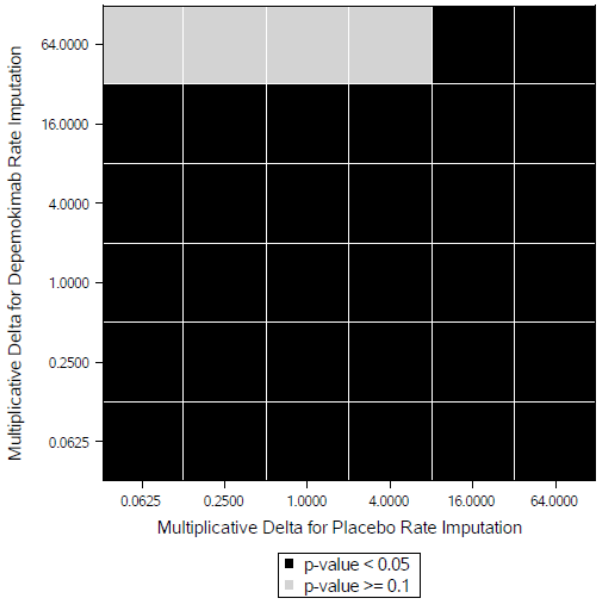
Tipping point analysis was conducted to investigate the impact of missing data by using differing assumptions regarding the exacerbation rate in participants who withdrew from the study. The tipping point sensitivity analysis showed that, even when participants with an unobserved period in the depemokimab group having their exacerbation rate imputed 16 times the 'average' depemokimab rate, there is no change in statistical inference irrespective of the wide range of rates imputed to the placebo group (Figure 18).

SWIFT-2

Since the total unobserved/excluded time in the study was <3% of the total study duration, the condition for conducting the analysis was not met. Therefore, the sensitivity analysis using off-treatment imputation was not performed.

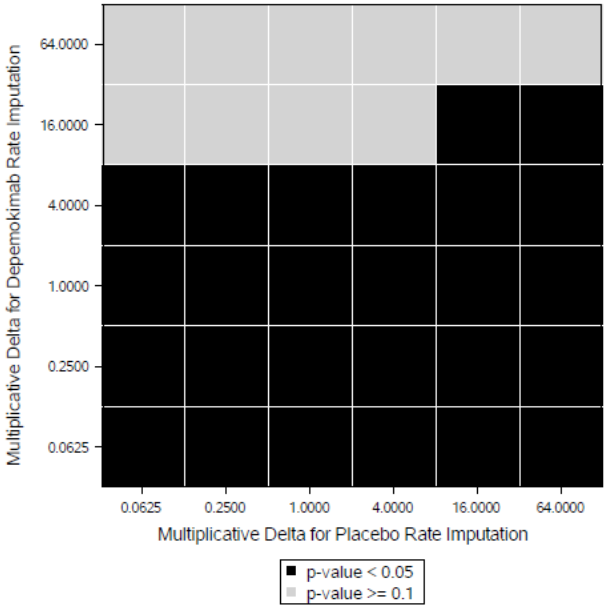
Tipping point analysis was conducted to investigate the impact of missing data by using differing assumptions regarding the exacerbation rate in participants who withdrew from the study. The sensitivity analysis showed that, the tipping point occurs only when participants with an unobserved period in the depemokimab group have their exacerbation rate imputed at least 16 times the 'average' depemokimab rate (Figure 19).

**Figure 18: Tipping point analysis of annualised rate of clinically significant exacerbations (SWIFT-1)**




Note: Analysis performed using a generalised linear model assuming a negative binomial distribution and covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, 4+), geographical region and baseline pre-bronchodilator percent predicted FEV1.
Note: Based on 1,000 iterations.
f_e_rate_exac_tip.sas 11JUN2024 07:03

**Figure 19: Tipping point analysis of annualised rate of clinically significant exacerbations (SWIFT-2)**




Note: Analysis performed using a generalised linear model assuming a negative binomial distribution and covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, 4+), geographical region and baseline pre-bronchodilator percent predicted FEV1.
Note: Based on 1,000 iterations.
f_e_rate_exac_tip.sas 15MAY2024 11:25

**Ancillary analyses**

***PD endpoint of change from baseline in blood eosinophil count***

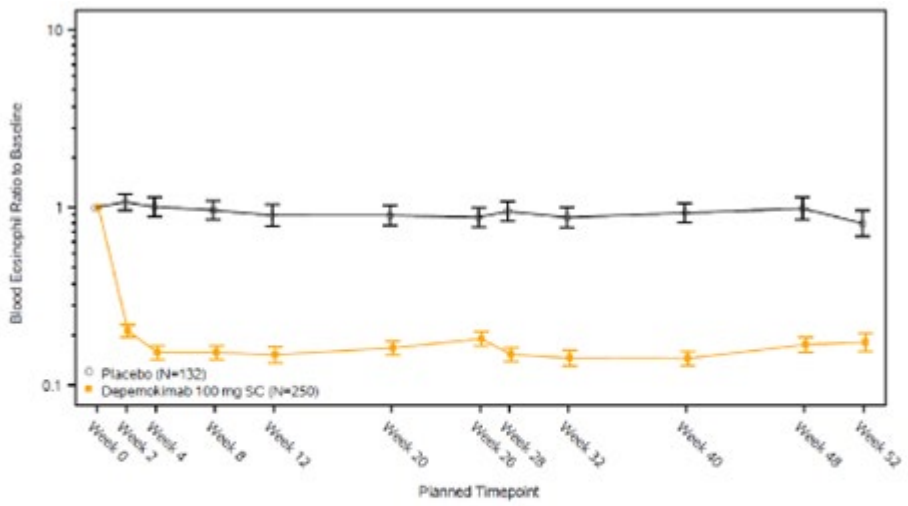
SWIFT-1

The baseline geometric mean blood eosinophil count was 0.298 GI/L for depemokimab and 0.310 GI/L for placebo. No marked change in eosinophil counts was observed in the placebo group, whereas a reduction in eosinophil count was apparent in the depemokimab from as early as 2 weeks and sustained over the study period (Figure 20). Changes in adjusted geometric mean ratios to baseline were larger for depemokimab at every timepoint during the study ($P$<0.001 for all measured timepoints). Of note, the analysis was not adjusted for multiplicity and nominal significance was evaluated in a descriptive manner using a 5% reference level.

SWIFT-2

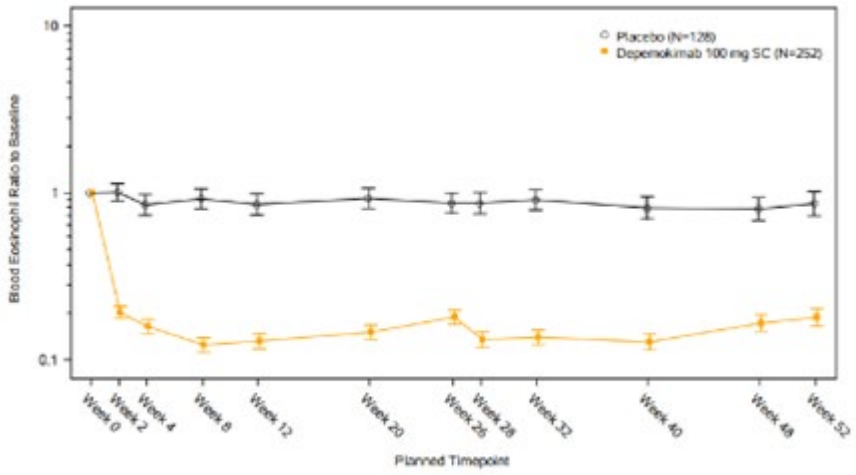
The baseline geometric mean blood eosinophil count was 0.339 GI/L for depemokimab and 0.330 GI/L for placebo. No marked change in eosinophil counts was observed in the placebo group, whereas a reduction in eosinophil count was apparent in the depemokimab from as early as 2 weeks and sustained over the study period (Figure 21). Changes in adjusted geometric mean ratios to baseline were larger for depemokimab at every timepoint during the study ($P$<0.001 for all measured timepoints). Of note, the analysis was not adjusted for multiplicity and nominal significance was evaluated in a descriptive manner using a 5% reference level.

**Figure 20: Adjusted geometric means (95% CI) of ratio to baseline blood eosinophil count (GI/L) (SWIFT-1)**




Note: The loge transformation for values of 0 GI/L will be based on a value of 0.005 GI/L.
Note: Analysis performed using a repeated measures model on loge transformed dependent variable with covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, 4+), geographic region, loge (baseline), visit, visit by loge (baseline) and visit by treatment group.

**Figure 21: Adjusted geometric means (95% CI) of ratio to baseline blood eosinophil count (GI/L) (SWIFT-2)**




Note: The loge transformation for values of 0GI/L will be based on a value of 0.005GI/L.

## 6.3.3. Clinical studies in special populations

**Table 22 Clinical studies in special populations**

| | Controlled Trials | Non-controlled trials |
|---|---|---|
| Renal impairment* patients (Subjects number /total number) | 0/762 | -- |
| Hepatic impairment** patients (Subjects number /total number) | 0/762 | -- |
| Paediatric patients <18 years (Subjects number /total number) | 30/762 | -- |
| Older patients; Age 65-74 (Subjects number /total number) | 161/762 | -- |
| Age 75-84 (Subjects number /total number) | 33/762 | -- |
| Age 85+ (Subjects number /total number) | 0/762 | -- |
| Other (Subjects number /total number) | not defined | -- |

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C

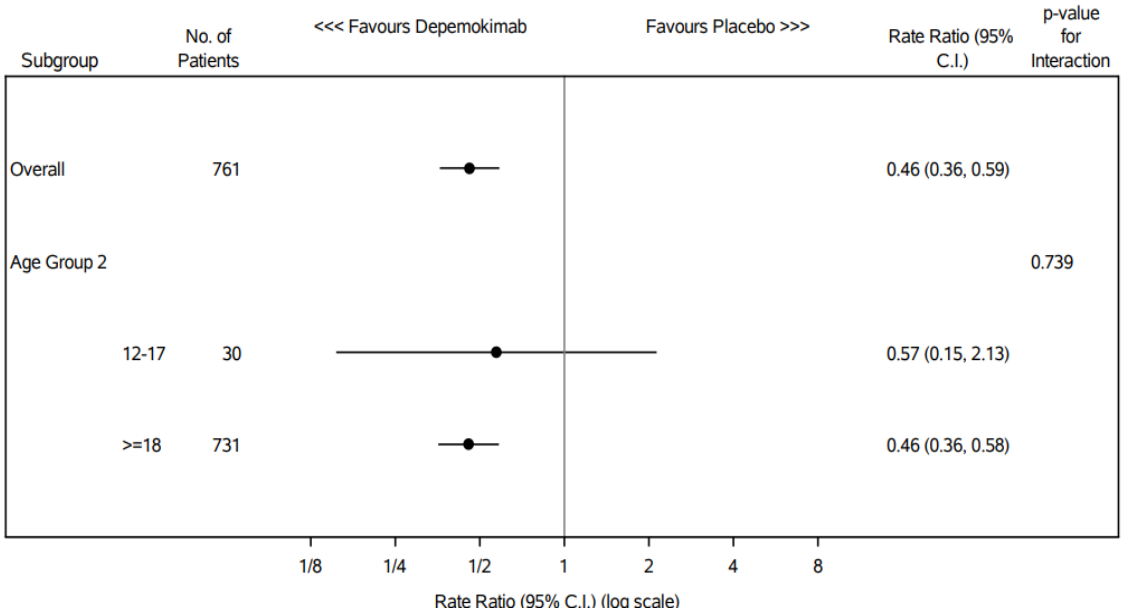
**Elderly**

A total of 194 elderly subjects (n=25%) participated in the SWIFT studies (SWIFT-1+2 integrated). Subgroup analyses of the primary endpoint of annualised rate of clinically significant exacerbations showed consistent results between elderly participants and adults.

**Adolescents**

Subgroup analyses of the primary endpoint of annualised rate of clinically significant exacerbations showed consistent results between adolescents (n=30 participants aged 12 to 17 years) and adults (n=731 participants aged ≥18 years) (Figure 22), with a 43% rate reduction (rate ratio 0.57; 95% 0.15 to 2.13) seen for adolescents and a 54% rate reduction (rate ratio 0.46; 95% CI: 0.36, 0.58) in adults in the depemokimab group, compared to placebo.

**Figure 22: Forest plot of rate ratios of annualised rate of clinically significant exacerbations by age group (SWIFT-1+2 integrated)**




## 6.3.4. Supportive studies

***AGILE study***

**Study title:** A multi-centre, single arm, open-label extension study to evaluate the long-term safety of GSK3511294 (depemokimab) in adult and adolescent participants with severe asthma with an eosinophilic phenotype from studies 206713 or 213744

*Study design*

AGILE was a Phase 3 12-month open-label extension (OLE) study to evaluate the long-term safety, efficacy and immunogenic profile of depemokimab 100 mg SC in adult and adolescent participants who had previously completed the SWIFT-1 or SWIFT-2 studies.

In AGILE, participants received 2 doses of depemokimab 100 mg SC, administered at Weeks 0 and 26. Upon completion of AGILE, participants who received depemokimab in the SWIFT studies had received up to 4 doses of depemokimab over a 104-week (2-year) study period (up to 2 doses for participants who received placebo in the SWIFT studies).

All participants who completed the double-blind study intervention treatment and the exit visit during the SWIFT studies and met none of the AGILE exclusion criteria (including significant health change or malignancy developed during SWIFT study, recent parasitic infection, current vasculitis), were eligible for inclusion. Participants were to be maintained on standard-of-care asthma treatment throughout the study. The maximum number of participants potentially eligible to take part in the AGILE study was approximately 750 (total number of participants enrolled in studies SWIFT-1 or SWIFT-2).

*Demographic and baseline disease state characteristics*

A total of 642 participants were screened, of which 1 participant failed screening. Of the 641 participants who

entered the study, 629 participants were included in the safety analysis set, of which, 602 participants (96%) completed the study and 27 participants (4%) were withdrawn from the study. A total of 419 participants previously received depemokimab in the parent study and 210 participants previously received placebo.

Demographics were generally similar to those of the SWIFT studies, with participants being predominantly white (78%), female (60%), with a median age of 57 years (range: 13 to 83 years). A total of 22 (3%) adolescents participated in the AGILE study.

Disease state characteristics at baseline of the respective parent study were generally similar to those of the SWIFT studies. For the overall population, a total of 43% and 57% of participants were on medium and high dose ICS plus another controller(s), respectively with 4% using maintenance OCS.

At baseline of the AGILE study, mean (SD) pre-bronchodilator FEV1 and percent predicted FEV1 were 2.00 (0.81) L and 66%, respectively in previous placebo and 2.03 (0.77) L and 69%, respectively in previous depemokimab group. On-treatment concomitant asthma medications were used by all the participants (100%). Apart from ICS taken by >99% of participants, most common on-treatment concomitant asthma medications were LABA (97%), leukotriene receptor antagonists (37%), and LAMA (30%).

*Efficacy results*

The annualised rate of clinically significant exacerbations was 0.56 (95% CI: 0.49, 0.65) in the overall population, 0.58 (95% CI: 0.45, 0.73) in the previous placebo group, and 0.55 (95% CI: 0.47, 0.66) in the previous depemokimab group.

The mean (SD) SGRQ total score at baseline in the previous placebo group was 34.5 (21.4) compared to 29.9 (20.2) in the previous depemokimab group. In the previous depemokimab group, mean (SD) change from baseline in SGRQ total score was -2.62 (95% CI: -3.88, -1.36) at Week 26 and -2.33 (95% CI: -3.73, -0.93) at Week 52. In the previous placebo group, mean (SD) change from baseline was -5.00 (95% CI: -6.85, -3.16) at Week 26 and -4.75 (95% CI: -6.79, -2.70).

The mean (SD) ACQ-5 score at baseline was 1.56 (1.15) in previous placebo group and 1.36 (1.10) in previous depemokimab group. The mean (SD) change from baseline in ACQ-5 score was -0.18 (0.79) at Week 26 and -0.19 (0.87) at Week 52 in the previous placebo group and -0.11 (0.85) at Week 26 and -0.09 (0.91) at Week 52 in the previous depemokimab group.

Mean (SD) pre-bronchodilator FEV1 at baseline was 2.00 (0.81) L in the previous placebo group and 2.03 (0.77) L in the previous depemokimab group. The mean (SD) change from baseline in pre-bronchodilator FEV1 was 0.059 (95% CI: 0.018, 0.100) L at Week 26 and 0.036 (95% CI: -0.007, 0.079) L at Week 52 in the previous placebo group and 0.013 (95% CI: -0.015, 0.041) L at Week 26 and -0.004 (95% CI: -0.034, 0.026) L at Week 52 in the previous depemokimab group.

***NIMBLE study***

In the initial MAA, only the safety data from an Interim Analysis (IA Data Cutoff: 15 July 2024) of NIMBLE were included. Upon CHMP's request, the applicant provided a summary of the key efficacy results. The full CSR of the NIMBLE study will be provided post-approval by the end of April 2026.

**Study Title:** A 52-week, randomised, double-blind, double-dummy, parallel group, multi-centre, non-inferiority study assessing exacerbation rate, additional measures of asthma control and safety in adult and adolescent severe asthmatic participants with an eosinophilic phenotype treated with GSK3511294

(depemokimab) compared with mepolizumab or benralizumab.

*Study design*

NIMBLE was a multi-centre, randomised, double-blind, double-dummy, parallel group non-inferiority trial of depemokimab 100 mg SC compared with continuation of mepolizumab or benralizumab treatment in participants with severe asthma with an eosinophilic phenotype.

Participants were randomised 1:1 to either remain on their existing anti-IL-5/5R therapy (mepolizumab or benralizumab) or switch to depemokimab 100 mg. Participants remaining on active comparator treatment (mepolizumab or benralizumab) were to be combined into a single arm with a minimum of 40% of the participants on each treatment. Throughout the study, all participants were to continue their baseline SoC asthma treatment consisting of inhaled corticosteroid (ICS) plus at least 1 other controller, e.g. long-acting beta-2-agonist (LABA), long-acting muscarinic antagonist (LAMA), with or without maintenance OCS. Assessments included the annualised rate of clinically significant exacerbations and measures of lung function, asthma control, and safety. Target for enrolment was 1700 participants (850 per arm).

The primary endpoint was the annualised rate of clinically significant exacerbations over 52 weeks. Secondary endpoints were the weighted mean change from baseline in SGRQ total score, ACQ-5 score, and FEV1, all calculated over 52 weeks. Non-inferiority was assessed on the primary endpoint of annualised rate of clinically significant exacerbations over 52 weeks. The non-inferiority margin was set at 1.28, i.e. non-inferiority would be met if the upper bound for the 95% CI was less than 1.28.

The choice of non-inferiority margin was based on the fixed margin approach.[2] The active control treatment effect was estimated by conducting a random-effects meta-analysis of other anti-IL-5/IL-5R therapies (mepolizumab, benralizumab, reslizumab) compared with placebo. The rate ratio was estimated as 0.51 (95% CI: 0.42, 0.61). Based on an assumption of constancy (the effect of the active control compared with placebo would be similar in this study to that observed in the historical studies), the rate ratio for depemokimab compared with the active comparator arm (mepolizumab / benralizumab) that would result in a placebo-like efficacy for depemokimab is 1/0.61 = 1.64. The upper bound was used because this represents a conservative estimate of the effect the active comparator (mepolizumab / benralizumab) is expected to have. A non-inferiority margin of 1.28 preserves 50% of the active control treatment effect (exacerbation rate ratio) on the loge scale. *Demographic and baseline disease state characteristics*

A total of 1717 participants were randomised (859 in the depemokimab group and 858 in the mepolizumab/benralizumab group), of which 1687 partcipants were included in the FAS population. In the FAS population, 763 (90%) participants in the depemokimab group and 772 (92%) participants in the mepolizumab/benralizumab group completed the study. Demographics were generally similar in both groups, with participants being predominantly white (78%), female (62%), with a median age of 58.6 years (range: 11 to 88 years). A total of 25 (1.5%) adolescents participated in NIMBLE. Disease state characteristics at baseline were balanced between groups. For the overall population, a total of 49% and 51% of participants were on medium and high dose ICS plus another controller(s), respectively, with 4% using maintenance OCS. Most participants (76%) had not experienced an exacerbation that required oral/systemic CS in the past 12 months. A total of 7% of participants had experienced ≥2 exacerbations that required oral/systemic CS in the past 12 months.

[2] FDA Guidance. Non-inferiority clinical trials to establish effectiveness–Guidance for Industry. US Department of Health and Human Services. Washington, DC: Author. 2016. Available at https://www.fda.gov/media/78504/download. Accessed on 14 October 2025.

*Efficacy results*

The annualised rate of clinically significant exacerbations (AER) was 0.57 (95% CI: 0.50, 0.64) in the depemokimab group and 0.49 (95% CI: 0.43, 0.55) in the mepolizumab/ benralizumab group. The exacerbation rate ratio of depemokimab compared with the mepolizumab/benralizumab group was 1.16 (95% CI: 0.98, 1.38). While the 95% confidence interval included 1.0, the upper bound was higher than the pre-specified non-inferiority margin of 1.28, and therefore the primary endpoint did not meet non-inferiority.On both arms of the study, most participants were exacerbation free during the study (64% on depemokimab vs 68% participants on the comparator arm). Furthermore, most participants on both treatment arms did not require asthma-related hospitalisations or ED visits during the study (94% on depemokimab and 95% on the comparator arm).

For the secondary endpoints, minimal changes from baseline were observed over the treatment period in both treatment groups, with minimal treatment differences of 0.17 (95% CI: -0.85, 1.20) for SGRQ, -0.03 (95% CI: -0.09, 0.02) for ACQ-5, and 0.004 (95% CI: -0.016, 0.024) L for FEV1.

A pre-specified analysis of the AER over 52 weeks by subgroup of pre-study biologic treatment (mepolizumab or benralizumab) showed that observed exacerbation rates were similar for participants who remained on mepolizumab (AER 0.48, 95% CI: 0.41, 0.58), benralizumab (AER 0.48, 95% CI: 0.41, 0.58) and those who switched from mepolizumab to depemokimab (AER 0.48, 95% CI: 0.40, 0.57), while a higher value was observed in participants on benralizumab who switched to depemokimab (AER 0.67, 95% CI: 0.57, 0.79). The exacerbation rate ratio was 0.99 (95% CI: 0.78, 1.26) for the mepolizumab subgroup (N=917) and 1.38 (95% CI: 1.09, 1.75) for the benralizumab subgroup (N=770).

### 6.3.5. Healthcare professional engagement

The European Respiratory Society (ERS) was contacted by EMA to provide health care professionals perspective on the target diseases and current treatment landscape. The following input was received:

The standard of care for asthma is well-described in the Global Initiative for Asthma (GINA) report (https://ginasthma.org/). Approximately 5-8% of the population in Europe have asthma of which ~5% have severe asthma. Asthma maintenance treatment includes inhaled corticosteroids (ICS) with long-acting-beta agonist (LABA), with the need in some for add on inhaled long-acting muscarinic antagonists (LAMA) and oral leukotriene receptor antagonists. In those with severe disease that remains poorly controlled with recurrent exacerbations or the need for maintenance systemic corticosteroids biologic therapies are available which include anti-interleukin (IL)5, anti-IL5R, anti-immunoglobulin (IgE), anti-IL4Ralpha and anti-thymic stromal lymphopoietin (TSLP). These are all administered subcutaneously with dosing regimens ranging from bi-weekly to bi-monthly. The biologics are restricted to those with elevated biomarkers of T2-immunity namely blood eosinophils and exhaled nitric oxide with the exception of anti-TSLP that is available independent of the biomarker level. Anti-IL5, anti-IL4Ralpha and anti-TSLP have also demonstrated benefit in those with inadequately controlled chronic rhinosinusitis with nasal polyps (CRSwNP).

The key endpoints in severe asthma are exacerbation reduction and reduction/cessation of maintenance systemic corticosteroids. Improvements in health status and symptoms are particularly important to patients (Core Outcome Measures Sets for Severe Asthma (COMSA) developed by 3TR researchers - European Federation of Allergy and Airways Diseases Patients' Associations (EFA)). Lung function improvements are also important as are related to disease progression and mortality.

The evidence base for biologics for severe asthma in children and adolescents is small and further evidence for depemokimab would be valuable. To date biologics in asthma have not led to adverse effects in pregnancy but this would remain an important consideration.

How to treat patients with asthma driven by non-T2-mediated immunity both pharmacologically and non-pharmacologically, how to alter the trajectory of the disease to prevent severe asthma and how to achieve remission in symptoms, health status and exacerbations remain the challenges for asthma and in particular severe disease.

## 6.3.6. Overall discussion and conclusions on clinical efficacy

### *6.3.6.1. Discussion*

The applicant has developed a new anti-IL-5 treatment, depemokimab. Depemokimab can be administered once every 26 weeks. The applicant requested the following, **updated** indication:

Asthma

*Exdensur is indicated as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by blood eosinophil count in adults and adolescents 12 years and older who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another asthma controller (see section 5.1).*

The clinical development programme was designed to assess whether depemokimab was superior to placebo in adult and adolescent participants ≥12 years with severe eosinophilic asthma with uncontrolled disease despite standard of care.

The clinical development programme comprised three Phase 1 studies (one FTIH, two PK studies), two replicate pivotal Phase 3 RCTs in participants with asthma ≥12 years, and two supportive studies in asthma (an OLE study and a non-inferiority study versus current anti-IL-5 treatment). For the non-inferiority study, an interim analysis was provided for safety and a summary of key study results for efficacy.

The applicant generally followed the obtained scientific advice. The development plan generally supports the proposed indication, which was modified during the review procedure to align with biologicals already approved for severe asthma and the GINA 2025 guideline. It is considered that the updated indication wording proposed for depemokimab, as requested by CHMP, including "characterised by blood eosinophil count" in place of "severe eosinophilic asthma", adequately describes the participants enrolled in the SWIFT studies and is in line with GINA 2025.

**Design and conduct of clinical studies**

Comparator

In principle, placebo-controlled trials in addition to standard of care are in line with the EMA guideline on the clinical investigation of medicinal products for the treatment of asthma (CHMP/EWP/2922/01 Rev.1) and could be considered an adequate approach.

However, anti-IL-5/5R and other biologicals have drastically changed the treatment landscape for uncontrolled asthma in recent years. Therefore, it is also informative to understand how depemokimab compares to marketed anti-IL-5/5R biologicals, which was evaluated in the NIMBLE non-inferiority trial (depemokimab versus mepolizumab/benralizumab).

Dose regimen

No Phase 2 dose-response study was performed. Based on a single ascending dose FTIH study in mild to moderate asthma participants with a blood eosinophil count ≥200 cells/µL, using model-informed drug development (MIDD) principles, the applicant identified 100 mg SC once every 26 weeks as the dose and dosing frequency of depemokimab that matches Phase 3 mepolizumab-like PD response (blood eosinophil count [BEC] suppression of >80%).

Depemokimab and mepolizumab are comparable drug substances with a similar mode of action. Since BEC suppression is a marker of the primary PD response of both drug substances, using the PD target of 80% BEC reduction for dose identification is considered appropriate. In addition, clinical trial simulations demonstrated that a conventional dose-ranging approach was unlikely to provide a more robust and precise estimate of the Phase 3 dose regimen due to the high variability associated with the nature of the primary endpoint and inherent uncertainty with regards to the exacerbation dose response. It was therefore considered unlikely that an alternative dose regimen would have provided a better picture of the optimal clinical response to depemokimab.

Considering the lack of a clear relationship between BEC and clinical outcomes, the question remains unanswered whether a better clinical outcome would have been possible, especially in terms of the secondary outcomes HRQoL and lung function. In absence of such a relationship, modelling based on BEC cannot answer this question. This issue is not pursued considering the positive B/R of 100 mg SC depemokimab once every 6 months in severe eosinophilic asthma.

Duration

The duration of the SWIFT studies was 52 weeks, which was in accordance with the EMA guideline on medicinal products for the treatment of asthma (CHMP/EWP/2922/01 Rev.1). The study period sufficiently captures differences in exacerbation rate in severe uncontrolled asthma, while the dosing regimen of once every 26 weeks justifies the length of the study, as 52 weeks cover two full dose intervals.

Of note, considering the half-life of depemokimab (38-53 days) and dose interval (182 days), a study duration of 52 weeks (2 doses) implies that efficacy and safety have not been established on steady state. However, assuming linear PK over time, predicted PK parameters were shown to remain stable over a simulated two-year period (4 doses). Accumulation ratios remained below 10%, which is not considered clinically relevant. In addition, the safety and efficacy profiles of depemokimab in the AGILE study were generally similar to those observed in the parent studies, with no clear or consistent pattern suggesting efficacy and safety change over time.

Inclusion and exclusion criteria

The SWIFT studies recruited adults and adolescents with uncontrolled severe asthma with an eosinophilic phenotype defined by an elevated BEC ≥300 cells/µL in the past 12 months or ≥150 cells/µL at screening. Inclusion criteria further included a confirmed history of ≥2 asthma exacerbations requiring treatment with systemic corticosteroids (SCS) in the 12 months prior to screening despite regular treatment with medium- to high-dose ICS (≥440 mcg fluticasone propionate [FP] or equivalent) and at least one additional controller medication, persistent airflow obstruction, and evidence of airway reversibility or hyperresponsiveness. The study population therefore concerned a symptomatic asthma population while on maintenance high-dose ICS with an additional controller.

The exclusion criteria excluded patients with a clinically important lung condition other than asthma, current smoking, current diagnosis of vasculitis, prolonged QT interval, recent treatment with another mAb, and previous documented failure with anti-IL-5/5R therapy. Exclusion of participants with vasculitis or prolonged QT interval was based on preclinical safety concerns.

The study population are reflected in Section 4.1. of the SmPC.

Endpoints

The primary objective was to evaluate efficacy of depemokimab versus placebo in terms of a reduction of the exacerbation rate. The secondary objective was to evaluate the effect of depemokimab on health-related quality of life (HRQoL) and additional efficacy assessments.

The SWIFT studies had one primary endpoint and six secondary endpoints included in the hierarchical testing scheme. The primary endpoint was the annualised rate of clinically relevant exacerbations. The applied definition of clinically relevant exacerbations aligns with the EMA guideline on the treatment of asthma (CHMP/EWP/2922/01. Rev1), i.e. "a requirement for systemic corticosteroids or an increase of the maintenance dose of oral corticosteroids for at least three days and/or a need for an emergency visit, hospitalization or death due to asthma."

Most secondary endpoints concerned appropriate patient-reported outcomes, including the well-established St. George's Respiratory Questionnaire (SGRQ) and Asthma Control Questionnaire 5 (ACQ-5), as well as lung function (FEV1). The order of the secondary endpoints was set based on the relevance of quality of life and asthma control as measures of patient experience. Therefore, SGRQ and ACQ-5 were positioned before lung function, which was included to conform with the EMA guideline on asthma.

Estimands

All estimands used the hypothetical strategy for COVID-19 related discontinuation. This is supported, as the interest is in the effect without treatment unrelated (external) events. All estimands (except PD related endpoints) focused on the effect regardless of treatment discontinuation, change of maintenance therapy and concomitant (prohibited or maintenance) medication and this is supported, as this reflects the nett effect seen in clinical practice when starting with depemokimab or not.

Statistical analysis

Generally, the statistical methods were adequate to estimate the estimands. Of note, data not collected after an intercurrent event (e.g., due to treatment withdrawal) may be informative of the outcome and handling them under a missing-at-random assumption may bias the results if the aim is to handle these intercurrent events under a treatment policy strategy. However, the sensitivity analyses prespecified are considered adequate to assess the impact (1) imputing such missing data using data from patients that do have data collected after their intercurrent events; 2) performing tipping point analyses with various values for these missing data).

Change from baseline in SGRQ total score, ACQ-5 score, and pre-bronchodilator FEV1 at Week 52 were analysed using a mixed model for repeated measures, with predictor variables given by treatment, baseline ICS dose, exacerbation history, geographical region, baseline, visit, visit by baseline, and visit by treatment (plus pre-bronchodilator percent predicted FEV1 as a covariate for the non-FEV1 endpoints).

The primary population was the full analysis set (FAS), which consisted of all randomised participants who

received at least 1 dose of study intervention in the SWIFT studies, except for participants excluded due to GCP deviations/data integrity issues. Efficacy analyses were conducted at the individual study level, while the primary and key secondary efficacy endpoints were also assessed in integrated analyses of data from both studies.

**Efficacy data and additional analyses**

Participant flow

In SWIFT-1, a total of 395 participants were randomised. The depemokimab group comprised 259 participants, of whom 257 received the intervention. A total of 250 participants were analysed, while 7 participants were excluded from analysis due to GCP deviations. The placebo group comprised 136 participants, of whom 136 received the intervention. A total of 132 participants were analysed, while 4 participants were excluded from analysis due to GCP deviations.

In SWIFT-2, a total of 397 participants were randomised. The depemokimab group comprised 263 participants, of whom 259 received the intervention. A total of 252 participants were analysed, while 7 participants were excluded from analysis due to GCP deviations. The placebo group comprised 134 participants, of whom 133 received the intervention. A total of 128 participants were analysed, while 5 participants were excluded from analysis due to GCP deviations.

Demographic and disease state characteristics

Baseline demographic and disease state characteristics were generally consistent between the treatment groups and between the two studies, with participants being predominantly White (83% vs. 71%), female (58% vs. 63%), with a median age group of 56.0 years (range: 14 years to 78 years) and 55.5 years (range: 12 – 82 years) in SWIFT-1 and SWIFT-2, respectively. SWIFT-1 included 8 adolescents (3 [1%] in depemokimab group and 5 [4%] in placebo group), while SWIFT-2 included 22 adolescents (12 [5%] in depemokimab group and 10 [8%] in placebo group).

A few differences were observed in the respective study populations. SWIFT-2 enrolled more participants from the US (36% vs. 13% in SWIFT-1) and had a more diverse race distribution with higher percentages of Asian (20%) and Black or African American (7%) participants compared to SWIFT-1 (15% and 2%, respectively).

The SWIFT-2 study population seemed to have a slightly more severe baseline disease state, with more participants who experienced ≥3 exacerbations in the past 12 months (27% vs. 14% in SWIFT-1) and more participants who were on triple combination therapy (ICS+LABA+LAMA) prior to treatment (29% vs. 15% in SWIFT-1). Also, SABA (79% vs. 62%) and LT receptor antagonists (48% vs. 31%) were used more in SWIFT-2 than in SWIFT-1, respectively.

Primary and secondary endpoints

Summary of main efficacy results are presented in SmPC section 5.1.

*Exacerbations*

Both studies showed an improvement in the annualised rate of clinically relevant exacerbations. The rate ratio was 0.42 (95% CI: 0.30, 0.59), indicating a relative 58% (41-71%) reduction in the annualised exacerbation rate in SWIFT-1, and 0.52 (95% CI: 0.36, 0.73), indicating a relative 48% (27-64%) reduction in the annualised exacerbation rate in SWIFT-2. Results from the integrated analysis of data from SWIFT-1+2

reflected the results from the individual studies, with a relative reduction of 54% (rate ratio 0.46; 95% CI: 0.36, 0.59) in the annualised rate of clinically significant exacerbations with depemokimab compared to placebo. These results are comparable to those of other anti-IL-5/5R therapies, for which rate ratios between 0.30 and 0.79 have been reported with a weighted mean of 0.58 (95% CI: 0.51, 0.66)[3], although it is acknowledged that such cross-study comparisons should be interpreted with caution.

*SGRQ total score*

Both studies showed improvements in the patient-reported outcome SGRQ total score for both depemokimab and placebo. The effects were numerically greater in the depemokimab groups, resulting in differences between treatments of -3.36 (95% CI: -7.11, 0.39) for SWIFT-1 and -2.31 (95% CI: -5.84, 1.23) for SWIFT-2, although neither of these reached statistical significance adjusted for multiplicity.

In the integrated analysis, this secondary outcome showed a difference between treatments of -2.88 (95% CI: -5.43, -0.32), reaching statistical significance, but these results were not adjusted for multiplicity and thus are not type I protected

*Other secondary endpoints*

Since the SGRQ score failed to show statistical significance in the multiplicity hierarchy in either pivotal study, no statistical inference can be made for the remaining tests in the hierarchy. Results of the individual studies showed no apparent difference between treatment groups for ACQ-5 score or FEV1. Numerical improvements were observed in both depemokimab and placebo groups. As these endpoints (SGRQ, ACQ-5 and FEV1) are considered to be clinically relevant for healthcare providers, their inclusion in SmPC section 5.1 was ultimately agreed by the CHMP.

Previous studies with biologicals generally showed improvements in both patient-reported outcomes and lung function. Although the SWIFT studies showed an improvement in exacerbation rate, only a numerical improvement in lung function could be observed. However, the treatment landscape of severe uncontrolled asthma has changed with the availability of several biologicals, and many patients with severe asthma already receive treatment. This aspect may have had implications on the study populations recruited for the SWIFT studies, while additionally, it cannot be ruled out that the studied dose regimen (100 mg/Q26W) is not the most appropriate dose regimen for depemokimab. While cross-study comparisons cannot be readily made due to differences in study design and population, the preliminary presented results of the supportive NIMBLE trial may be helpful to determine the relative efficacy of depemokimab versus other anti-IL-5(R) biologicals (refer to supportive studies – NIMBLE below)

Subgroup analyses

In subgroup analyses on the integrated data, results were mostly consistent with the results from the primary analysis. Notably, a reduction in exacerbation rate with depemokimab was observed regardless of whether patients were on medium- or high-dose ICS, and baseline blood eosinophil counts were <150 cells/µL, ≥150 to 300 cells/µL, or >300 cells/µL.

Sensitivity analyses

Since the total unobserved/excluded time in the study was <3% of the total study duration in both SWIFT studies, the condition for conducting the analysis was not met. Therefore, the sensitivity analysis using off-

[3] Kyriakopoulos C, Gogali A, Markozannes G, Kostikas K. Biologic agents licensed for severe asthma: a systematic review and meta-analysis of randomised controlled trials. Eur Respir Rev 2024; 33: 230238

treatment imputation was not performed for either study.

Tipping point analysis was conducted to investigate the impact of missing data by using differing assumptions regarding the exacerbation rate in participants who withdrew from the study. Results of these analyses demonstrated for each SWIFT study that the conclusion from the primary analysis is robust to plausible assumptions about the outcomes for participants with missing data during the 52-week period.

Ancillary analyses

Concerning the PD endpoint of eosinophil blood count, it is well known that biologicals may reduce the number of eosinophils, and this was indeed also observed in the SWIFT studies. Although the reduction in eosinophil count was sustained over the dose interval of 26 weeks, the eosinophil count started to increase between weeks 12 and 20, as well as weeks 40 and 48 in both SWIFT studies, implying a wearing off of the effect of depemokimab on this PD marker. This finding also supports the concern whether the proposed dose regimen is the most optimal for depemokimab.

**Studies in special populations**

Elderly

Elderly subjects were included in the SWIFT studies and comprised a substantial part of the study population (n=194, 25%), which had a median age of 56 years (SWIFT-1+2 integrated data set).

Results in elderly participants (≥65 years) were consistent with the primary analysis (favouring depemokimab) for exacerbations and SGRQ score.

Adolescents

The Paediatric Committee (PDCO) refused the need for a paediatric investigation plan and instead granted a product-specific waiver for depemokimab for all subsets of the paediatric population on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients. The PDCO also advised that the applicant may proceed with the clinical development in adolescents and apply for marketing authorisation in (subsets of) the paediatric population if desired. A limited number of adolescents was included in the SWIFT studies (n=30), of whom a total of 15 participants received depemokimab 100 mg SC. Results of the adolescents subgroup analysis for exacerbations were in line with the primary analysis (favouring depemokimab).

While the mean effect on the primary endpoint was comparable in adults and adolescents, the difference to placebo was not statistically significant in adolescents as the study was not powered to demonstrate efficacy in the adolescent subgroup only. However, results for adolescents can likely be extrapolated from adults, as PK exposure was shown to be comparable between adults and adolescents. The applicant provided results with detailed discussion of a Bayesian dynamic borrowing analysis (BDBA) and the corresponding tipping point analysis (TPA) to substantiate extrapolation of the results of primary endpoint (annualised rate of clinically significant exacerbations over 52 weeks) for depemokimab for the treatment of severe asthma exacerbations from adults (at least 18 years old) to adolescents (12 to 17 years old). Pooled data from SWIFT-1 and SWIFT-2 studies were used.

The overall number of adolescents enrolled in the studies SWIFT-1 and SWIFT-2 was low, and the studies were not powered to demonstrate efficacy in the adolescent subgroup. However, the clinical benefit in favour of depemokimab was evident. This deficiency was overcome by the results of BDBA and the corresponding

TPA.

**Supportive studies**

*AGILE*

In the open-label extension (OLE) study AGILE, the long-term safety, efficacy and immunogenic profile of depemokimab 100 mg SC were evaluated in adult and adolescent participants who had previously completed the SWIFT-1 or SWIFT-2 studies. Participants received two doses of depemokimab 100 mg SC at Weeks 0 and 26. This study showed improved annualised exacerbation rates in previously placebo-controlled participants and supported maintenance of efficacy in participants previously treated with depemokimab.

*NIMBLE*

The non-inferiority study NIMBLE did not meet the statistical criterion for non-inferiority on exacerbation rate ratio between patients who switched from mepolizumab / benralizumab to depemokimab and those who remained on their existing anti-IL-5(R) biological. While the 95% confidence interval included 1.0, the upper bound was higher than the pre-specified non-inferiority margin of 1.28, and therefore the primary endpoint did not meet non-inferiority.

The non-inferiority margin was based on the most conservative consideration for assumed efficacy for the comparator, by using the 95% CI upper bound of the rate ratio of comparator versus placebo (0.61). By using the upper bound, the margin to demonstrate equivalence was narrower and non-inferiority was harder to demonstrate than if the point estimate had been used (0.51), in which case non-inferiority could have been assumed.

The annualised rate of clinically significant exacerbations (AER) in participants treated with depemokimab was low (0.57 [95% CI: 0.50, 0.64]) and comparable to the pooled result observed for the SWIFT-1 and SWIFT-2 studies (0.51 [0.43, 0.60]).

Exacerbation rates were low in the active comparator arm (0.49 [0.43, 0.55]), as expected given the well-established efficacy on this endpoint for both mepolizumab and benralizumab, and comparable to those observed previously for approved anti-IL-5(R) biologicals (weighted mean 0.58 [0.51, 0.66]).

> Although the relative difference between depemokimab and comparator arm appears considerable, i.e. 16% (95% CI: -2%, 38%), the absolute difference is small, i.e. 0.08 exacerbations per year. As the exacerbation rate in each group is small (0.57 vs 0.49) the difference becomes exaggerated when presented as relative difference. Overall, the small absolute difference will likely not result in a clinically relevant difference. This assumption is supported with the overall minimal changes from baseline on other measures of asthma control, SGRQ, ACQ-5 and FEV1.

Subgroup analysis showed that the difference in exacerbation rate was mainly driven by the subgroup of participants on benralizumab who switched to depemokimab. The exacerbation rate ratio between participants who switched to depemokimab and those remaining on their pre-study biological was 0.99 (95% CI: 0.78, 1.26) for the mepolizumab subgroup (N=917) and 1.38 (95% CI: 1.09, 1.75) for the benralizumab subgroup (N=770). Similarly to the overall analysis, annualised exacerbation rates were low in all subgroups (0.67 in the subgroup who switched from benralizumab to depemokimab, 0.48 in the other subgroups), and differences are exaggerated when presented as relative differences.

Moreover, results of these subgroup analyses should be interpreted with caution, as the subgroups were only

stratified by pre-study biologic treatment and not by parameters predictive of exacerbations, such as baseline exacerbation rate, ppFEV1, and eosinophil count. Therefore, imbalances in these parameters may have affected subgroup outcomes.

There is no biological rationale to assume that switching from an anti-IL-5R biological to an anti-IL-5 biological would reduce asthma control. In addition, the presented study is the first formal head-to-head comparison between these biologicals and without replication of results, conclusions are difficult to draw.

Considering that no differences between groups were observed for the secondary endpoints of HRQoL and lung function, overall results of the NIMBLE study do not raise concerns with regards to the efficacy of depemokimab in comparison to other anti-IL-5/5R treatments in patients who have previously shown to benefit from biologicals.

#### *6.3.6.2. Conclusions on the clinical efficacy*

The pivotal phase 3 placebo-controlled trials met their primary endpoint of clinically relevant exacerbations but failed to show any statistically significant effect on the secondary endpoints included in the statistical hierarchy (SGRQ, ACQ-5, FEV1). This lack of statistical significance is in contrast to other anti-IL-5/5R therapies, which generally showed improvements in patient-reported outcomes and/or lung function parameters.

In a direct comparison between depemokimab and approved anti-IL-5 therapies (mepolizumab, benralizumab), the absolute difference in annualised rate of clinically significant exacerbations between the groups was small (0.08 exacerbations/year) and likely not clinically relevant, which is supported by comparable results between groups for the secondary endpoints of HRQoL and lung function. Therefore, although the primary endpoint formally did not meet non-inferiority, results of the NIMBLE study do not raise concerns with regards to the efficacy of depemokimab in comparison to other anti-IL-5/5R treatments in patients who have previously shown to benefit from biologicals.

Depemokimab offers a less frequent dose regimen than the currently approved biologicals for treatment of severe asthma, i.e. once every 6 months instead of once every 2-8 weeks. Less frequent dosing may alleviate treatment burden and improve treatment adherence.

Adults

Overall, the beneficial effect of depemokimab in adults with severe eosinophilic asthma is moderate but clinically relevant considering the reduction in exacerbations.

Adolescents

Although in adolescents, clinical efficacy of similar extent as in adults was demonstrated based on the SWIFT studies, due to few participants aged 12-17 years, the difference to placebo was not statistically significant. However, results for adolescents can be extrapolated from adults based on comparable PK exposure between adults and adolescents and supportive Bayesian analysis. Therefore, the beneficial effect of depemokimab in adults with severe eosinophilic asthma can be extrapolated to adolescents with severe eosinophilic asthma.

## CRSwNP

## 6.3.7. Main studies

## 6.3.8. ANCHOR-1 and ANCHOR-2

#### 6.3.8.1.1. Study title ANCHOR-1 and ANCHOR-2

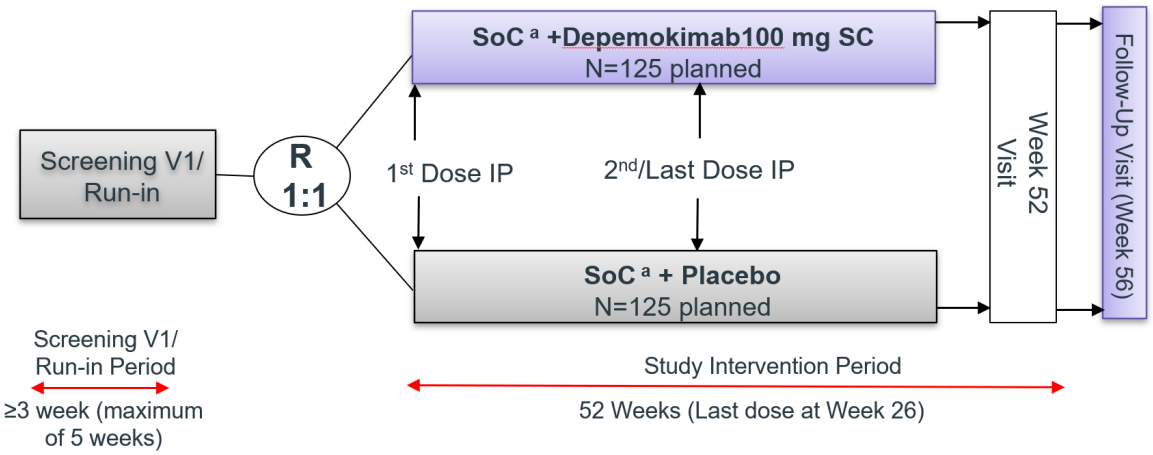
A randomised, double-blind, parallel group Phase III study to assess the efficacy and safety of 100 mg SC depemokimab in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) – (depemokimAb iN CHrOnic Rhinosinusitis) - ANCHOR-1 and ANCHOR-2.

#### 6.3.8.1.2. Study design

ANCHOR-1 and ANCHOR-2 were replicate, double-blind, placebo-controlled, parallel-group, Phase 3 studies of depemokimab 100 mg + SoC in adults with CRSwNP assessing the efficacy and safety to support the CRSwNP indication.

The studies included a 4-week run-in period followed by randomisation to a 52-week treatment period and a 4-week follow-up period. The total study duration (treatment period and follow-up period) was approximately 56 weeks.

**Figure 23: Study schematic – ANCHOR-1 and ANCHOR-2**




Abbreviations: INCS = intranasal corticosteroid; IP = investigational product (depemokimab or placebo); N = number of participants planned to be randomised to each treatment arm; QoL = quality of life; R = randomization; SC = subcutaneous; SoC = standard of care; V = visit.

a. SoC = saline washes, INCS and (for severe symptoms, when short term relief is required) intermittent courses of systemic corticosteroids [EPOS, 2020]. Antibiotic courses may also be required for intercurrent sinus infection, and progression to surgery as a result of severe symptoms and disruption to QoL.

**Treatment**

All participants were required to be on standard of care (SoC). Depending on local practice, SoC could include intranasal corticosteroids (INCS), saline nasal douching, occasional short courses of systemic corticosteroids (except during the run-in period), and/or antibiotics.Throughout the study, intranasal corticosteroids were required to be consistently taken (with the exception of Japan were this treatment is not approved).

Short courses of systemic corticosteroids (e.g., systemic corticosteroids for treatment of CRSwNP) were allowed as rescue medication.

During the trial, participants received one of the following study treatments, i.e.:

- Depemokimab subcutaneous (SC) injection, 100 mg/mL; 1 mL SC injection PFS once every 26 weeks (Week 0) and Week 26.
- Sterile 0.9% (w/v) sodium chloride solution; 1 mL SC injection of placebo PFS once every 26 weeks (Week 0) and Week 26.

**Randomisation**

Participants eligible to enter the study were assigned to treatment randomly via an interactive response technology system. Randomisation was stratified based on the occurrence of previous surgery for nasal polyps (NP) and country.

**Blinding**

This study was blinded for the sponsor, assessor, investigator, caregiver, and participant.

To maintain the blind, data on IL-5 levels and haematology data (absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes) from post randomisation samples were not to be reported to the site or the central study team, prior to the unblinding of the study.

**Patient population**

The study population included adults (≥18 years) with severe CRSwNP. Participants had symptoms of chronic rhinosinusitis while on SoC, as described by at least two different symptoms for at least 12 weeks prior to the start of study, one of which should be either nasal blockage/obstruction/congestion with moderate or severe severity or nasal discharge (anterior/posterior nasal drip), plus facial pain/pressure and/or reduction or loss of smell for at least 12 weeks prior to visit 1.

Participants were also required to have had prior treatment with systemic CS on at least 3 consecutive days within the past 2 years (unless contraindication or intolerant), and/or a documented history of prior surgery for CRSwNP at screening.

At randomisation, participants were required to have a total endoscopic nasal polyp score of ≥5 (out of a maximum score of 8 combined across both nasal cavities), with a score of ≥2 in each nasal cavity, and a mean nasal obstruction score of ≥2 over the previous 7 days (VRS scale, 0 to 3).

Key exclusion criteria

The key exclusion criteria were known vasculitis, immunodeficiency and eosinophilic diseases, of if QTcF ≥450 msec or QTcF ≥480 msec for participants with bundle branch block in the 12-lead ECG.

The study also excluded participants who had an acute sinusitis or upper respiratory tract infection in the 2 weeks prior to screening or randomisation, underwent intranasal or sinus surgery within the previous 6 months or were on a waiting list for nasal surgery.
In addition, specific washout periods were defined for participants that could have used medication to treat the inflammation response of CRS, e.g. mepolizumab, reslizumab, or benralizumab within 12 months; dupilumab, omalizumab within 130 days.

#### 6.3.8.1.3. Objectives and estimands

The aim of the twin studies was to assess the efficacy and safety over a 52-week treatment period of depemokimab 100 mg SC given once every 26 weeks as add-on therapy to participants with CRSwNP.

**Primary objective**

The study is designed to test the superiority of depemokimab 100 mg SC vs. placebo (both in addition to SoC) in two co-primary endpoints. The co-primary endpoints were selected to capture both an objective assessment of obstruction (endoscopic Nasal Polyp Score (NPS) and the participant's experience of a cardinal symptom of CRSwNP (mean nasal obstruction Verbal Response Scale (VRS) symptom score).

**Estimands for the primary objective**

**Table 23: Estimands for primary objective**

| | |
|---|---|
| **Population** | Adult patients with uncontrolled severe CRSwNP despite the SoC. |
| **Treatment condition** | Assignment to Depemokimab+ SOC compared to assignment to Placebo + SoC |
| **Endpoint (variable)** | LS mean change from baseline in total endoscopic Nasal Polyp score at |

| | |
|---|---|
| | Week 52 (centrally read)<br>LS mean change from baseline in mean nasal obstruction score VRS from Week 49 through to Week 52 |
| **Population-level summary** | Difference in means between treatment groups - depemokimab 100 mg SC + SoC versus placebo + SoC |
| **Intercurrent events and strategy to handle them** | |
| Surgery[a] | **Composite strategy** incorporating occurrence of the event into the definition of the endpoint.<br>Specifically, participants who underwent surgery were assigned the worst possible value of the relevant score for all assessments following surgery (i.e., the worst value that it is possible to select a given scale), i.e. total Nasal Polyp score of 8. |
| Initiation of medication that modulate the course of CRSwNP by reduction of blood eosinophils or type 2 inflammation | **Composite strategy** by incorporating the occurrence of the event into the definition of the endpoint.<br>Specifically, participants who started a medication that may modulate the disease course of CRSwNP (e.g. some biologicals, chronic CS and INCS) were assigned the worst possible value of the relevant score for all assessments following the start of the medication (i.e., the worst value that is possible to select on the given scale, e.g. nasal obstruction VRS score of 3). |
| Premature discontinuation of study treatment | Treatment policy strategy |
| Systemic CS usage[b] | Treatment policy strategy |
| COVID-19 related events | Treatment policy strategy |
| Prohibited therapy | Treatment policy strategy |
| All other changes in background therapy | Treatment policy strategy |

[a] Surgery, which includes any procedure involving instruments resulting in incision and removal of tissue from the nasal cavity (e.g., polypectomy and endoscopic sinus surgery (ESS))

[b]Systemic course for CRSwNP were applied according local practices and local standard or care. A systemic course of SCS had a predefined end of treatment. A chronic course of systemic treatments had a duration ≥ 21 days and was given as maintenance treatment.

**Supplementary estimand strategy for co-primary endpoints**

In addition, the intercurrent event (ICE) for all changes in background medication or start of medication that could modulate the disease course of CRSwNP was handled under the treatment policy strategy and was considered as a supplementary estimand to the primary estimand.

**Statistical methods for estimation and sensitivity analysis on primary estimands**

The primary population for the primary endpoint analysis was the FAS, which consisted of all randomised participants who received at least 1 dose of study intervention in the ANCHOR studies, except for participants recruited to sites with GCP deviations.

Co-primary endpoint analyses were conducted at the individual study level (for each of ANCHOR-1 and ANCHOR-2) and in an integrated analysis of data from both studies.

The co-primary endpoints were analysed using a Mixed Models Repeated Measures (MMRM) model, with covariates of treatment group, baseline score, log(e) baseline blood eosinophil count, region, previous surgery for nasal polyps, visit and interaction terms for visit by baseline score and visit by treatment group. For the integrated analysis, study was also included as an additional covariate.

The same co-primary endpoint analyses were performed using the FAS-Modified analysis set (i.e., FAS criteria but without excluding participants recruited to sites with GCP deviations). In addition, the same analyses were performed with the intercurrent event strategy described under the supplementary estimand.

Intercurrent events were handled following different strategies, depending on the type of event (Table 24).

Sensitivity analyses were to be conducted to investigate the impact of missing data and to examine the robustness of the analyses of the primary endpoints to departures from the assumption that missing data were missing at random.

On request, *post-hoc* additional sensitivity analyses were provided (a) intercurrent events were handled according to the treatment policy (b) putting on the NP waiting list was used as a intercurrent event handled by the composite strategy.

**Secondary objective**

Individual studies ANCHOR-1 and ANCHOR-2

In support of the co-primary endpoints, additional secondary efficacy endpoints were collected to demonstrate the superiority of depemokimab over placebo in CRSwNP by means of showing improvement in other symptoms associated with CRSwNP (rhinorrhoea, loss of smell), objective improvements (Lund MacKay CT score), and quality of life (SNOT-22) and improvement of the co-primary endpoints at an earlier stage (week 26).

Pooled studies (ANCHOR-1 and ANCHOR-2)

A predefined pooled analysis of ANCHOR-1 and ANCHOR-2 investigated the avoidance of systemic corticosteroids (CS) use and avoidance of nasal polyp surgery (NP-surgery), where NP-surgery referred to any procedure involving instruments resulting in incision and removal of tissue from the nasal cavity (e.g., polypectomy and endoscopic sinus surgery [ESS]). The systemic use of corticosteroids and NP-surgery are events that occur with a relatively low incidence over the course of 1 year, and the individual studies would likely not adequately assess the reduction of these events.

**Estimands for the secondary objectives**

**Table 24: Secondary estimands individual studies ANCHOR-1 and ANCHOR 2**

| | |
|---|---|
| Population | Adult patients with uncontrolled severe CRSwNP despite the SoC |
| Treatment condition | Assignment to Depemokimab + SoC compared to assignment to Placebo + SoC |
| Endpoint (variable) | LS mean change from baseline in mean symptom score for rhinorrhoea (runny nose) (VRS) from Week 49 through to Week 52<br><br>LS mean change from baseline in mean symptom score for loss of smell (VRS) from Week 49 through to Week 52 |

| | |
|---|---|
| | LS mean change from baseline in Lund Mackay CT score at Week 52<br>LS mean change from baseline in SNOT-22 total score at Week 52<br>LS mean change from baseline in mean nasal obstruction score (VRS) from Week 21 through to Week 24<br>LS mean change from baseline in total endoscopic NP score at Week 26 |
| Population-level summary | Difference in LS means between treatment groups - depemokimab 100 mg SC + SoC versus placebo + SoC |
| Intercurrent events and strategy to handle them | |
| Surgery[a] | **Composite strategy** incorporating occurrence of the event into the definition of the endpoint.<br>Specifically, participants who underwent surgery were assigned the worst possible value of the relevant score for all assessments following surgery (i.e., the worst value that it is possible to select a given scale), i.e. total NP score of 8. |
| Initiation of medication that modulate the course of CRSwNP by reduction of blood eosinophils or type 2 inflammation | **Composite strategy** by incorporating the occurrence of the event into the definition of the endpoint.<br>Specifically, participants who started a medication that may modulate the disease course of CRSwNP (e.g. some biologicals, chronic CS and INCS)[c] were assigned the worst possible value of the relevant score for all assessments following the start of the medication (i.e., the worst value that is possible to select on the given scale, e.g. nasal obstruction VRS score of 3). |
| Premature discontinuation of study treatment | Treatment policy strategy |
| Other background medication or prohibited medication | Treatment policy strategy |
| Covid related events | Treatment policy strategy |
| Course of systemic CS for any reason[b] | Treatment policy strategy |

[a] Surgery, which includes any procedure involving instruments resulting in incision and removal of tissue from the nasal cavity (e.g., polypectomy and endoscopic sinus surgery (ESS))

[b]Systemic course pf corticosteroids were applied according local policy.

[c] The wording "modulate the disease course of CRSwNP" is used in the document, in the SmPC this has been reworded to "initiation of other maintenance treatment impacting type 2 inflammation".

**Table 25: Pre-specified Secondary estimands of the pooled analyses of ANCHOR-1 and ANCHOR 2**

| | |
|---|---|
| Population | Patients with a diagnosis of CRSwNP (endpoint 1, 2, 3) |

| | |
|---|---|
| | Participants with a diagnosis of CRSwNP and partially or not well controlled with an ACQ-5 score >0.75 at baseline (endpoint 4) |
| Treatment condition | Assignment to Depemokimab+ SOC compared to assignment to Placebo + SoC |
| Endpoint (variable) | 1. Time to first nasal surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP up to Week 52.<br>2. Time to first nasal surgery (actual) or initiating disease modulating medication for CRSwNP up to Week 52<br>3. Requiring at least 1 course of systemic CS[a] or disease modulating medication or nasal surgery (actual) for CRSwNP during the Week 52 treatment period<br>4. LS mean change from baseline in ACQ score at week 52 |
| Population-level summary | Endpoint 1 and 2: Hazard ratio between depemokimab 100 mg SC + SoC and placebo + SoC<br>Endpoint 3: Odds ratio between depemokimab 100 mg SC + SoC and placebo + SoC<br>Endpoint 4: LS mean difference between depemokimab 100 mg SC + SoC and placebo + SoC |
| Intercurrent events and strategy to handle them | |
| Surgery[b] | **Composite strategy** incorporating occurrence of the event into the definition of the endpoint i.e. Participants who undergo surgery (or enter its waiting list if included in the endpoint) will be counted as event (endpoint 1 and 2) and as requiring systemic CS during the week 52 treatment period (endpoint 3).<br>For endpoint 4, participants who underwent surgery were assigned a score of 6, the worst possible value of ACQ-5 for all assessments following surgery. |
| Initiation of medication that may modulate the course of CRSwNP by reduction of blood eosinophils or type 2 inflammation | **Composite strategy** by incorporating the occurrence of the event into the definition of the endpoint i.e. surgery (endpoint 1 and 2) or requiring a course of systemic CS during the week 52 treatment period (endpoint 3).<br>For endpoint 4, participants who underwent surgery were assigned a score of 6, the worst possible value of ACQ-5 for all assessments following initiation of medication. |
| Premature discontinuation of study treatment | Treatment policy strategy |

| | |
|---|---|
| Other background medication or prohibited medication | Treatment policy strategy |
| COVID-19 related events | Treatment policy strategy |
| Course of systemic CS for any reason | Treatment policy strategy (endpoint 1,2,4)<br>Composite strategy (endpoint 3) |

[a] Systemic course for CRSwNP were applied according local practices and local standard or care. A systemic course of SCS had a predefined end of treatment. A chronic course of systemic treatments had a duration ≥ 21 days and was given as maintenance treatment.

[b] Surgery, which includes any procedure involving instruments resulting in incision and removal of tissue from the nasal cavity (e.g., polypectomy and endoscopic sinus surgery (ESS))

Supplementary estimand strategy for pooled secondary endpoints related to nasal surgery

• **Supplementary estimand 1:** In addition, the intercurrent event for all changes in background medication or start of medication (including those medications that may modulate the disease course of CRSwNP) to be handled under the treatment policy strategy was considered as a supplementary estimand to the primary estimand.

In addition, a post-hoc analyses was requested where NP surgery on the waiting list was handled as an intercurrent event by the composite strategy.

• **Supplementary estimand 2:** In addition, ICE for initiation of a medication that may modulate the disease course of CRSwNP by reduction of blood eosinophils or type 2 inflammation was handled under the hypothetical strategy.
Medications that may modulate the disease course were selected either based on published evidence or mechanism of action, and included the initiation of some biologics, chronic systemic CS and INCS. All other changes in background medication or start of a prohibited medication were handled using treatment policy strategy.

**Statistical methods for estimation and sensitivity analysis on the secondary estimand**

Statistical analyses for the change from baseline in Lund Mackay CT score at Week 52 was performed using an analysis of covariance (ANCOVA) model with covariates of treatment group, baseline score, log(e) baseline blood eosinophil count, region and previous surgery for nasal polyps.

For the time to first nasal surgery or disease-modulating medication for CRSwNP, a Cox proportional hazards model was used with covariates of treatment group, baseline total endoscopic nasal polyps score, baseline nasal obstruction score (VRS), log(e) baseline blood eosinophil, region, study, and previous surgery for nasal polyps.

For the secondary endpoint of requiring at least 1 course of systemic CS or disease-modulating medication for CRSwNP or nasal surgery, a logistic regression model was used with covariates of treatment group, number of courses of systemic corticosteroids in 12 months prior to screening for Nasal Polyps Score (0,

1, >1 as ordinal), log(e) baseline blood eosinophil count, baseline total endoscopic score, baseline nasal obstruction (VRS), region, study and previous surgery for nasal polyps.

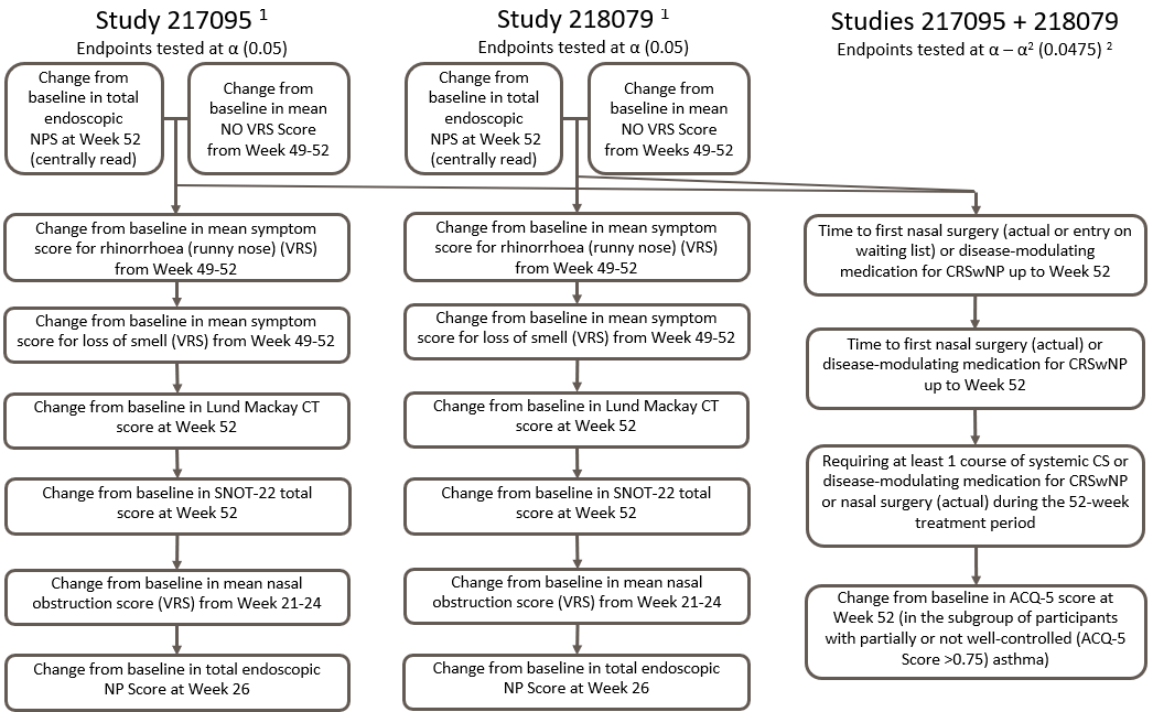
All other secondary endpoints were analysed in the same way as the corresponding nasal obstruction-VRS or Nasal Polyp Score co-primary endpoints.

Statistical testing strategy

To account for multiplicity, a statistical testing strategy was applied. Within each study, the co-primary endpoints were tested first and if both comparisons were significant at the 2-sided 5% level, testing continued within the study according to the testing procedure.

If statistical significance was achieved for both co-primary endpoints within each study, the protocol-pre-specified pooled secondary endpoints were tested in a closed-testing manner using the pre-defined hierarchy and a significance level of $\alpha - \alpha^2$ (4.75%) dependent on statistical significance having been achieved for the previous endpoint in the hierarchy.

**Figure 24 Conceptualisation of statistical testing strategy across the ANCHOR-1 and ANCHOR-2 studies[1]**




Abbreviations: ACQ = Asthma Control Questionnaire; CS = corticosteroid; CT = computerised tomography; NO = nasal obstruction; NPS = nasal polyp score; SNOT = Sino-nasal Outcome Test; VRS = verbal response scale.

1. Study 217095 is ANCHOR-1, Study 218079 is ANCHOR-2. With regards to the estimand strategy, for the primary and secondary endpoints, the intercurrent events (ICE) of nasal surgery (actual) and initiation of disease-modulating medications for CRSwNP were handled using a composite strategy by assigning the worst possible value of the relevant score for all assessments following the ICE. All other ICEs were handled using a treatment policy strategy.
2. If the hierarchy is broken, then nominal significance will be evaluated in a descriptive manner using a 5% reference level.

**Sample size determination**

The sample size for this study is based on the co-primary efficacy endpoints of total endoscopic nasal polyps score at Week 52 and mean nasal obstruction VRS symptoms score from Week 49 through to Week

52, and a pre-specified pooled analysis of data from study ANCHOR-1 (this study) and ANCHOR-2 for the key secondary endpoint of time to first nasal surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP.

Approximately 250 participants were planned to be randomised into this study in a ratio of 1:1, giving 125 randomised participants per group. This sample size allowed for up to 5% of randomised participants to be non-evaluable, providing a minimum of 118 evaluable participants per group in the analyses of primary and secondary endpoints.

The co-primary endpoint of total endoscopic Nasal Polyp score (NPS) at Week 52 had >99% power assuming a true population difference of −1.10 between depemokimab and placebo. This assumed a standard deviation of 1.665 with significance declared at the 2-sided 5% significance level. The smallest observed effect which was predicted to result in a statistically significant difference between depemokimab 100 mg SC + SoC and placebo + SoC was a treatment difference of −0.42.

For the co-primary endpoint nasal obstruction VRS mean score during Week 49 to Week 52, the study had >99% power assuming a true population difference of −0.70 between depemokimab and placebo. This assumed a standard deviation of 0.84 with significance declared at the 2-sided 5% significance level. The smallest observed effect which was predicted to result in a statistically significant difference between depemokimab 100 mg SC + SoC and placebo + SoC was a treatment difference of −0.21.

The overall power for both co-primary endpoints is >99%.

Pooled analyses

For the pooled secondary endpoint, the proportion of participants in the pooled placebo group expected to require surgery or disease-modulating medication for CRSwNP was 23%.

Assuming a true population hazard ratio of 0.38 (62% reduction in risk of required surgery) this pooled analysis had >90% power to observe statistical significance at the 2-sided 4.75% level.

In the pooled analysis, the smallest observed effect that was predicted to result in a statistically significant difference between depemokimab 100 mg SC + SoC and placebo + SoC was a hazard ratio of 0.64 (36% reduction in risk of surgery).

The overall power for both co-primary endpoints and the pre-specified pooled analysis of time to requiring first nasal surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP using data from this study (ANCHOR-1) and ANCHOR-2 is >90%.

#### 6.3.8.1.4. Results

**Participant flow and numbers analysed**

ANCHOR-1

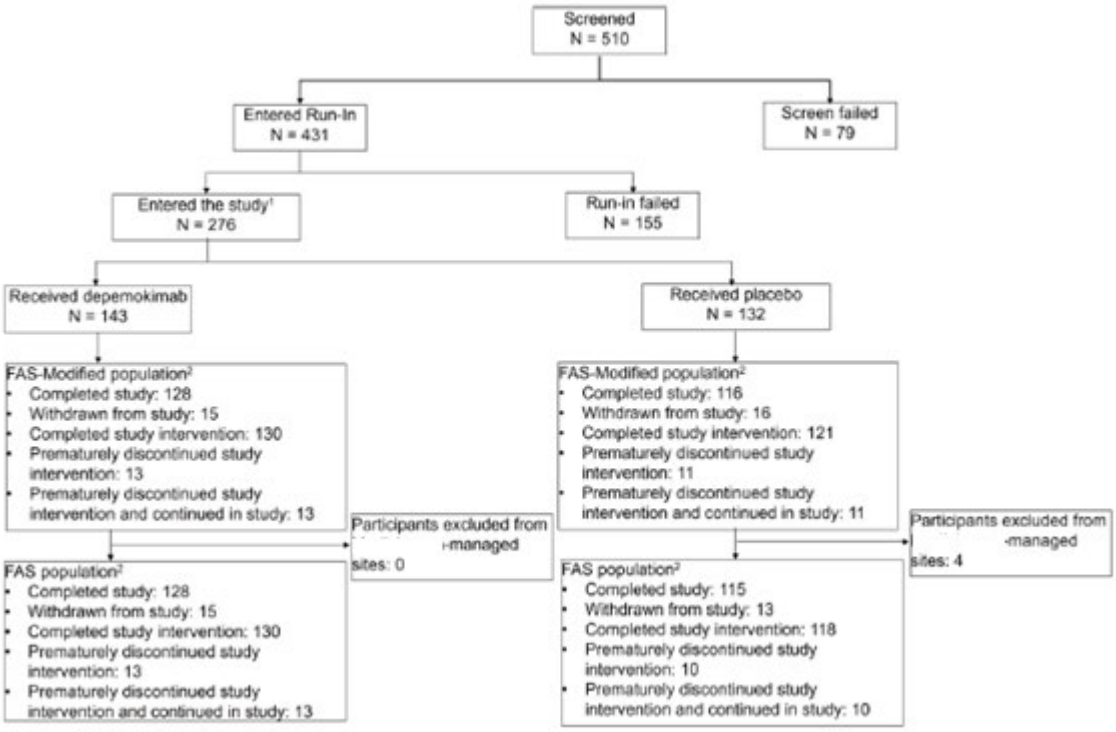
The first participant was enrolled on 22 April 2022; the last patient last visit was on 27 Aug 2024.

A total of 271 participants were randomised. A total of 4 participants were not included in the FAS because of site-specific GCP deviations. Most participants completed the study (90%) receiving a total of 2 doses (92%) (Figure 25)

Geographic locations: Asia (China, Japan); Europe (Belgium, France, Germany, Netherlands, Spain, United Kingdom); North America (Canada, The United States of America [US]); South America (Argentina)

Database lock: 20 September 2024.

**Figure 25: Participant flow of the ANCHOR-1 study**




1 A total of 276 participants entered the study and were randomised; a total of 275 received study treatment.
2 the FAS excluded data from 2 sites with GCP deviations i.e. n=0 patients randomised to depemokimab and 4 patients randomised to placebo. These data were not included before database lock. This data is included in the FAS-modified population

ANCHOR-2

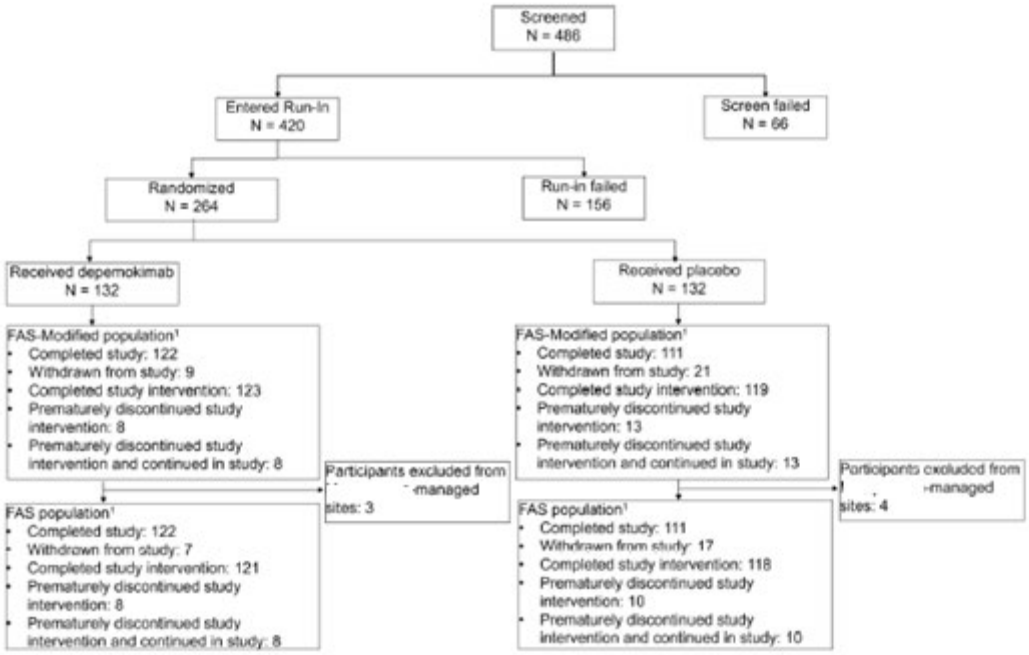
The first participant was enrolled on 18 April 2022; the last participant last visit was on 6 Aug 2024.

A total of 264 participants were randomised. A total of 7 participants were not included in the FAS because of site-specific GCP deviations. Most participants (90%) completed the study receiving a total of 2 doses (93%).

Geographic locations: Asia (China, Japan, Turkey); Europe (Italy, Poland, Romania, Spain, Sweden); and North America (US).

Database lock: 26 Aug 2024.

**Figure 26 Participant flow ANCHOR-2**




the FAS excluded data from 2 sites with GCP deviations i.e. n=3 patients randomised to depemokimab and n=4 randomised to placebo. These data were not included before data base lock. This data is included in the FAS-modified population

**Deviations from study plan**

The ANCHOR-1 and ANCHOR-2 studies were dated November 2021. The studies had a total of 5 amendments that were implemented in the study protocol. These amendments were made before database lock (ANCHOR-1 20 Sept 2024: ANCHOR-2: unknown.

Amendment 1 (09 February 2022) and amendment 2 (October 2022) refer to clarifications of the protocol. Amendment 3 (17/18 October 2023), amendment 4 (12 March 2024) and amendment 5 (26 June 2024) affected the strategical testing hierarchy and/or statistical analyses of the data. There was also one Statistical Analyses plan (SAP) amendment (15 July 2024).

Protocol Amendment 5 (dated 26 June 2024)

- The primary estimand strategy was updated to handle the initiation of medications that may modulate the disease course of CRSwNP intercurrent event with a composite strategy in alignment with US FDA guidelines.
- Co-primary and key secondary outcomes: addition of tipping point sensitivity analyses for the coprimary endpoints was added to explore the impact of missing data
- Power calculations were updated to account for the updated estimand strategy
- Changed name of modified Intent- To-Treat (mITT) analysis set to Full Analysis Set (FAS), and definition changed to remove site 255403 and 255387 based on site related GCP deviations.

Protocol Amendment 4 (12 March 2024)

- Changing the pooled analysis endpoint of time to first NP-surgery (actual) from 'Other' to 'Secondary'

Protocol Amendment 3 (18 October 2023 ANCHOR-1, 17 October 2023 (ANCHOR-2)

- To update the statistical testing hierarchy.
- Updating the definition of the NP-surgery secondary endpoint from actual only, to include entry on waiting list
- Including the ACQ-5 score endpoint in the pooled analysis statistical hierarchy instead of in the individual study level

**SAP** amendment 1 (15 Jul 2024)

- The protocol defined reference level for alpha for the testing of the other pooled efficacy endpoints is described as 4.75% (α – α2). However, the reference level that is used after a break in the pooled testing hierarchy for the remaining pooled secondary endpoints and other pooled efficacy endpoints, conducted without multiplicity adjustment, is at the 5% reference level.

**Intercurrent events**

Intercurrent events were pre-defined events that occurred after treatment initiation and either precluded observation of the endpoint or affected its interpretation.

Table 26 shows that the ANCHOR-1 and ANCHOR-2 show a comparable number of intercurrent events in the treatment arms while on study, including the follow-up period. During the 52-week observation period, the number of Nasal surgeries was n=29 (11%) for depemokimab and n=42 (16%) for placebo.

In both studies, surgery was numerically more prevalent in both placebo arms.
In the ANCHOR-1 study, more patients initiated a disease modulating therapy in the depemokimab arm (n=8) compared to the placebo arm (n=5), while the opposite was observed for the ANCHOR-2 study, in the pooled analyses, a comparable number of patients received disease modulating treatments.

**Table 26: Summary of ICEs, FAS population, ANCHOR-1 study, ANCHOR-2 and integrated analyses**

| ICE category | ANCHOR-1 | | ANCHOR-2 | | ANCHOR-1+2 | |
|---|---|---|---|---|---|---|
| | Depemokimab 100 mg SC (N=143) | Placebo (N=128) | Depemokimab 100 mg SC (N=129) | Placebo (N=128) | Depemokimab 100 mg SC (N=272) | Placebo (N=256) |
| | Number (%) of participants with ICE | | | | | |
| **Surgery resulting in incision or removal of nasal cavity tissue** | 14 (10) | 23 (18) | 15 (12) | 19 (15) | 29 (11) | 42 (16) |
| **Initiation of a medication that may modulate disease course of CRSwNP [a]** | 8 (6) | 5 (4) | 1 (<1) | 4 (3) | 9 (3) | 9 (4) |

| ICE category | ANCHOR-1 | | ANCHOR-2 | | ANCHOR-1+2 | |
|---|---|---|---|---|---|---|
| | Depemokimab 100 mg SC (N=143) | Placebo (N=128) | Depemokimab 100 mg SC (N=129) | Placebo (N=128) | Depemokimab 100 mg SC (N=272) | Placebo (N=256) |
| | Number (%) of participants with ICE | | | | | |
| **Premature discontinuation of study treatment** | 13 (9) | 10 (8) | 8 (6) | 10 (8) | 21 (8) | 20 (8) |
| **Any other changes in background medication or start of a prohibited medication** | 0 | 1 (<1) | 0 | 1 (<1) | 0 | 2 (<1) |
| **COVID-19-related events** | 13 (9) | 11 (9) | 12 (9) | 12 (9) | 25 (9) | 23 (9) |
| **Course(s) of systemic CS for any reason** | 42 (29) | 60 (47) | 41 (32) | 47 (37) | 83 (31) | 107 (42) |

a. Disease-modulating medications included biologics targeting Type 2 inflammation, continuous use of CS, and initiation of INCS in Japanese participants

Note: For primary estimand, composite strategy is used on the ICE of 'surgery resulting in incision or removal of nasal cavity tissue' and 'Initiation of a medication that may modulate disease course of CRSwNP'.

Treatment policy strategy is used for other ICEs listed in the table.

Note: For supplementary estimand, composite strategy is used on the ICE of 'surgery resulting in incision or removal of nasal cavity tissue'. Treatment policy strategy is used for other ICEs listed in the table.

**Numbers to be analysed**

The FAS included All-randomised participants who took at least 1 dose of study intervention excluding participants from with GCP deviations (1 site ANCHOR-1, 2 sites ANCHOR-2). This data was included in the FAS modified (Table 27).

**Table 27: Summary of study populations – ANCHOR-1, ANCHOR-2 and integrated**

| Population | ANCHOR-1 | | | | ANCHOR-2 | | | | Integrated | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | No treatment (n, %) | Depe (n, %) | Pla (n, %) | Total (n, %) | No treatment (n, %) | Depe (n, %) | Pla (n, %) | Total (n, %) | Depe (n, %) | Pla (n, %) | Total (n, %) |
| Screened | 234 (100) | 143 (100) | 133 (100) | 510 (100) | 222 (100) | 132 (100) | 132 (100) | 486 (100) | | | |
| Enrolled | 0 | 143 (100) | 133 (100) | 276 (54) | 0 | 132 (100) | 132 (100) | 264 (54) | | | |
| Randomized[1] | 0 | 143 (100) | 133 (100) | 276 (54) | 0 | 132 (100) | 132 (100) | 264 (54) | 275 (100) | 265 (100) | 540 (100 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Full Analyses Set (FAS)[2] | | 143 (100) | 128 (96) | 271 (53) | | 129 (96) | 128 (97) | 257 (53) | 272 (98.9) | 256 (96.6) | 528 (97) |
| FAS-Modified[2] | | 143 (100) | 132 (>99) | 275 (54) | | 132 (100) | 132 (100) | 264 (54) | | | |

FAS: All randomised participants who took at least 1 dose of study intervention excluding participants from the site with GCP deviations. The excluded patients are included in the FAS-modified

1. A total of 276 participants entered the study and were randomized; however, 275 participants received either depemokimab or placebo (i.e. one patient allocated to placebo did not receive treatment)
2. Confirmed GCP deviations in several sites overviewed by one CRO.

**Baseline data**

Demographics

Demographic characteristics were generally similar between the depemokimab and placebo groups in both studies.

ANCHOR-1

The participants in the study were predominantly white (70%), male (69%) and had a mean age of 53.5 years (Table 28).

ANCHOR-2

The participants in the study were predominantly white (77%), male (69%) and had a mean age of 50.4 years (Table 28).

ANCHOR-1 vs ANCHOR-2

The ANCHOR-2 study included mainly patients from Europe (65%), while the main population of ANCHOR-1 (56%) was included outside the EU or USA (rest of world).

**Table 28: Summary of demographic characteristics, FAS population (ANCHOR-1, ANCHOR-2, and Integrated Population)**

| | **ANCHOR-1** | | | **ANCHOR-2** | | | **Integrated** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Dep N=143** | **Pla N=128** | **Total N=271** | **Dep N=129** | **Pla N=128** | **Total N=257** | **Dep N=272** | **Pla N=256** | **Total N=528** |
| **Sex** | | | | | | | | | |
| Female, n (%) | 45 (31) | 38 (30) | **83 (31)** | 40 (31) | 40 (31) | **80 (31)** | 85 (31) | 78 (30) | **163 (31)** |
| Male, n (%) | 98 (69) | 90 (70) | **188 (69)** | 89 (69) | 88 (69) | **177 (69)** | 187 (69) | 178 (70) | **365 (69)** |
| **Age (years)** | | | | | | | | | |

| | ANCHOR-1 | | | ANCHOR-2 | | | Integrated | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Dep N=143** | **Pla N=128** | **Total N=271** | **Dep N=129** | **Pla N=128** | **Total N=257** | **Dep N=272** | **Pla N=256** | **Total N=528** |
| Mean | 54.1 | 52.9 | **53.5** | 50.5 | 50.4 | **50.4** | 52.4 | 51.6 | **52.0** |
| SD | 13.37 | 13.49 | **13.42** | 12.95 | 12.98 | **12.94** | 13.27 | 13.27 | **13.26** |
| Median | 55 | 55 | **55** | 50 | 50 | **50** | 53.0 | 52.0 | **52.0** |
| Min | 20 | 19 | **19** | 20 | 23 | **20** | 20 | 19 | **19** |
| Max | 93 | 78 | **93** | 83 | 78 | **80** | 93 | 78 | **93** |
| **Age -group (years)** | | | | | | | | | |
| 18-64, n (%) | 113 (79) | 101 (79) | **214 (79)** | 110 (85) | 104 (81) | **214 (83)** | 223 (82) | 205 (80) | **428 (81)** |
| ≥65, n (%) | 30 (21) | 27 (21) | **57 (21)** | 19 (15) | 24 (19) | **43 (17)** | 49 (18) | 51 (20) | **100 (19)** |
| **High level race** | | | | | | | | | |
| Asian, n (%) | 37 (27) | 30 (24) | **67 (25)** | 27 (21) | 26 (20) | **53 (21)** | 64 (24) | 56 (22) | **120 (23)** |
| Black or African American, n (%) | 4 (3) | 2 (2) | **6 (2)** | 2 (2) | 3 (2) | **5 (2)** | 6 (2) | 5 (2) | **11 (2)** |
| White, n (%) | 97 (70) | 88 (71) | **185 (70)** | 99 (77) | 98 (77) | **197 (77)** | 196 (73) | 186 (74) | **382 (73)** |
| **Region** | | | | | | | | | |
| Europe, n (%) | 51 (36) | 46 (36) | **97 (36)** | 83 (64) | 83 (65) | **166 (65)** | 134 (49) | 129 (50) | **263 (50)** |
| US, n (%) | 11 (8) | 10 (8) | **21 (8)** | 10 (8) | 10 (8) | **20 (8)** | 21 (8) | 20 (8) | **41 (8)** |
| Rest of world, n (%) | 81 (57) | 72 (56) | **153 (56)** | 36 (28) | 35 (27) | **71 (28)** | 117 (43) | 107 (42) | **224 (42)** |
| **Height (cm)** | | | | | | | | | |
| Mean | 171.22 | 171.91 | **171.55** | 171.26 | 172.09 | **171.68** | 171.24 | 172.00 | **171.61** |
| SD | 9.961 | 10.052 | **9.99** | 9.330 | 8.792 | **0.058** | 9.649 | 9.425 | **9.540** |
| Median | 172.00 | 172.00 | **172.00** | 171.00 | 172.00 | **172.00** | 172.00 | 172.00 | **172.00** |
| Min. | 149.0 | 148.0 | **148.0** | 147.00 | 145.00 | **145** | 147.0 | 145.0 | **145.0** |

| | ANCHOR-1 | | | ANCHOR-2 | | | Integrated | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Dep N=143** | **Pla N=128** | **Total N=271** | **Dep N=129** | **Pla N=128** | **Total N=257** | **Dep N=272** | **Pla N=256** | **Total N=528** |
| Max. | 197.0 | 196.0 | **197.0** | 191.0 | 190.0 | **191** | 197.0 | 196.0 | **197.0** |
| **Weight (kg)** | | | | | | | | | |
| Mean | 79.10 | 79.80 | **79.43** | 78.96 | 79.92 | **79.44** | 79.04 | 79.86 | **79.44** |
| SD | 15.944 | 16.520 | **16.19** | 16.045 | 18.928 | **17.513** | 79.04 | 17.730 | **16.832** |
| Median | 78.20 | 77.85 | **78.10** | 77.00 | 76.90 | **77.00** | 77.90 | 77.55 | **77.65** |
| Min. | 47.5 | 40.0 | **40.0** | 45.9 | 42.4 | **42.4** | 45.9 | 40.0 | **40.0** |
| Max. | 121.0 | 148.9 | **148.9** | 145 | 140.6 | **145** | 145.0 | 148.9 | **148.9** |
| **BMI (kg/m$^2$)** | | | | | | | | | |
| Mean | 26.91 | 26.91 | **26.91** | 26.78 | 26.80 | **26.79** | 26.85 | 26.86 | **26.85** |
| SD | 4.681 | 4.668 | **26.91** | 4.240 | 5.189 | **4.726** | 4.470 | 4.924 | **4.691** |
| Median | 26.30 | 26.72 | **26.54** | 26.49 | 25.86 | **26.31** | 26.39 | 26.43 | **26.41** |
| Min. | 18.1 | 17.5 | **17.5** | 18.4 | 17.4 | **17.4** | 18.1 | 17.4 | **17.4** |
| Max. | 42.7 | 42.7 | **42.7** | 43.3 | 44.9 | **44.9** | 43.3 | 44.9 | **44.9** |

Dep is depemokimab, Pla = placebo, SD is standard deviation, N= Min. is minimum. Max = maximum, US is USA

Disease characteristics

ANCHOR-1

At baseline, the disease characteristics between the depemokimab and placebo group were generally comparable, although a slightly higher proportion of participants in the depemokimab received a course of systemic corticosteroids (CS) in the preceding year (73% vs 66%), and suffered from asthma related respiratory disease (AERD) 18% vs 13%. The mean (SD) visual analogue scores (VAS) for nasal obstruction were > 7 in both treatment groups (Table 29).

At baseline, the median duration of CRSwNP was 12.93 (11.20) years. Most patients n=205 (98%) used intra-nasal corticosteroids and had received prior surgery n=171(63%). A total of patients n=205 (76%) had received oral corticosteroids to treat the nasal polyps, while n= 161 (59%) had co-morbid asthma and n= 43 (16%) had AERD (Table 29).

At baseline, the geometric mean blood eosinophil count was 0.337 GI/L (Table 29), mean (SD) total endoscopic Nasal Polyp score was 6.0 (1.35), and mean (SD) nasal obstruction VRS score was 2.54 (0.479).

ANCHOR-2

At baseline, the disease characteristics between the depemokimab and placebo group were generally comparable, although a slightly higher proportion of participants in the depemokimab received a course of systemic corticosteroids (CS) in the preceding year (70% vs 63%), while the depemokimab group also showed a higher geometric mean (SD) compared to placebo Geo Mean (SD logs 0.375 (0.6) U/L vs 0.288 (0.82) U/L.

At baseline, the median duration of CRSwNP was 11.13 (8.71) years. Most patients n= 249 (97%) used intra-nasal corticosteroids and had received prior surgery n=62 (63%). A total of patients n=172 (76%) had received oral corticosteroids in the previous 2 years to treat the nasal polyps, while n= 131 (51%) had co-morbid asthma and n= 42 (16%) had Aspirin related respiratory diseases (Table 29).

At baseline, the geometric mean blood eosinophil count was 0.329 GI/L (Table 29), mean (SD) total endoscopic Nasal Polyp score was 5.9 (1.29), and mean (SD) nasal obstruction VRS score was 2.60 (0.422). The mean (SD) visual analogue scores (VAS) for nasal obstruction were > 7 in both treatment groups (Table 29).

**Table 29: Summary of CRSwNP disease history and characteristics and asthma status at baseline, FAS population (ANCHOR-1, ANCHOR-2 and Integrated Population)**

| | **Anchor -1** | | | **Anchor-2** | | | **Integrated** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Depe** | **Pla** | **Total** | **Depe** | **Pla** | **Total** | **Depe** | **Pla** | **Total** |
| | **(N=143)** | **(N=128)** | **(N=271)** | **(N=129)** | **(N=128)** | **(N=257)** | **(N=272)** | **(N=256)** | **(N=528)** |
| **Duration CRSwNP , years** | | | | | | | | | |
| **Mean (SD)** | 13.45 (12.12) | 12.34 (10.09) | **12.93 (11.20)** | 11.25 (8.48) | 11.02 (8.98) | **11.13 (8.71)** | 12.40 (10.59) | 11.68 (9.55) | **12.05 (10.09)** |
| **Duration of chronic rhinosinusitis, years** | | | | | | | | | |
| **Mean (SD)** | 14.24 (11.49) | 15.51 (14.13) | **14.91 (12.94)** | 11.62 (8.54) | 12.15 (10.14) | **11.89 (9.36)** | 13.67 (11.95) | 13.20 (10.86) | **13.44 11.44** |
| **Number of previous surgeries for NP, n (%)** | | | | | | | | | |
| **n=0** | 53 (37) | 47 (37) | **100 (37)** | 49 (38) | 46 (36) | **95 (37)** | 99 (36) | 96 (38) | **195(37)** |
| **n≥ 1** | 90 (63) | 81 (63) | **171 (63)** | 80 (62) | 82 (64) | **162(63)** | 173 (64) | 160 (63) | **333(63)** |
| **Participant used at least 3 consecutive days of systemic CS in the previous 2 years, n (%)** | | | | | | | | | |
| **Yes** | 109 (76) | 96 (75) | **205 (76)** | 97 (75) | 97 (72) | **189 (74)** | 206 (76) | 188 (74) | **394 (75)** |
| **Participant medically unsuitable or intolerant to systemic CS, n (%)** | | | | | | | | | |
| Yes | 5 (3) | 6 (5) | **11 (4)** | 8 (6) | 5 (4) | **13 (5)** | 13 (5) | 11 (4) | **24 (5)** |
| **No of Courses of systemic CS for NP in the previous 12 months, n (%)** | | | | | | | | | |
| **0** | 38 (27) | 43 (34) | **81 (30)** | 38 (29) | 47 (37) | **85 (33)** | 76 (28) | 90 (35) | **166(31)** |
| **1** | 74 (52) | 48 (38) | **122 (45)** | 62 (48) | 57 (45) | **119(46)** | 136 (50) | 105 (41) | **241(46)** |
| **2** | 17 (12) | 18 (14) | **35 (13)** | 12 (10) | 12 (9) | **25 (10)** | 30 (11) | 30 (12) | **60 (11)** |
| **≥ 2** | 14 (10) | 19 (15) | **33 (12)** | 16 (12) | 12 (9) | **28 (11)** | 30 (11) | 31 (12) | **61 (12)** |
| **Total IgE, U/mL** | | | | | | | | | |
| **Geo Mean (SD logs)** | 142.94 (1.49) | 139.88 (1.26) | **141.48 (1.39**) | 114.58 (1.22) | 116.28 (1.25) | **115.42 (1.24)** | 128.61 (1.372) | 127.58 (1.260) | **128.11 1.318)** |
| **Baseline eosinophils, GI/L** | | | | | | | | | |
| **Geo Mean (SD logs)** | 0.319 (0.923) | 0.359 (0.853) | **0.337 (0.891)** | 0.375 (0.657) | 0.288 (0.822) | **0.329 (0.754)** | 0.344 (0.81) | 0.322 (0.84) | **0.333 (0.83)** |
| **INCS use at baseline, n (%)** | | | | | | | | | |
| **Yes** | 139 (97) | 126 (98) | **265 (98)** | 126 (98) | 123 (96) | **249 (97)** | 265 (97) | 249 (97) | **514 (97)** |
| **Aspirin related respiratory disease (AERD), n (%)** | | | | | | | | | |
| **Yes** | 26 (18) | 17 (13) | **43 (16)** | 23 (18) | 19 (15) | **42 (16)** | 49 (18) | 36 (14) | **85 (16)** |
| **Asthma, n (%)** | | | | | | | | | |
| **Yes** | 82 (57) | 79 (62) | **161 (59)** | 68 (53) | 63 (49) | **131 (51)** | 150 (54) | 142 (55) | **292 (55)** |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Total endoscopic NP score (mean (SD))** | | | | | | | | | |
| **Mean (SD)** | 5.9 (1.35) | 6.0 (1.37) | **6.0 (1.35)** | 5.9 (1.37) | 5.8 (1.37) | **5.9 (1.29)** | 5.9 (1.27) | 5.9 (1.37) | **NP** |
| **Nasal obstruction VRS score** | | | | | | | | | |
| **Mean (SD)** | 2.55 (0.487) | 2.53 (0.472) | **2.54 (0.479)** | 2.62 (0.426) | 2.57 (0.418) | **2.60 (0.422)** | 2.58 (0.460) | 2.55 (0.446) | **NP** |
| **Rhinorrhoea VRS score** | | | | | | | | | |
| **Mean SD** | 2.16 (0.697) | 2.18 (0.711) | **2.17 (0.702)** | 2.25 (0.689) | 2.27 (0.648) | **2.26 (0.668)** | 2.20 (0.693) | 2.22 (0.680) | **NP** |
| **Loss of smell (VRS) score** | | | | | | | | | |
| **mean (SD)** | 2.70 (0.547) | 2.74 (0.564) | **2.72 (0.554)** | 2.85 (0.388) | 2.77 (0.421) | **2.81 (0.406)** | 2.77 (0.483) | 2.76 (0.497) | **NP** |
| **Lund Mack Kay CT score** | | | | | | | | | |
| **mean (SD)** | 18.4 (4.15) | 19.0 (3.99) | **18.7 (4.08)** | 19.6 (3.75) | 18.2 (4.51) | **18.9 (4.19)** | 19.0 (3.99) | 18.6 (4.27) | **NP** |
| **SNOTT-22 total score** | | | | | | | | | |
| **mean (SD)** | 58.2 (22.60) | 56.6 (21.70) | **57.4 (22.15)** | 60.1 (21.51) | 60.1(18.34) | **60.1 (19.95)** | 59.1 (22.07) | 58.3 (20.12) | **NP** |
| **Patients with SNOT-22 total score ≥ 40** | | | | | | | | | |
| **n (%)** | **109 (76)** | **95 (74)** | **204 (75)** | **99 (77)** | **108 (84)** | **207 (81)** | **208 (76)** | **203 (81)** | **411 (78)** |

CS: corticosteroids, Depem: depemokimab, CRSwNP: Chronic rhinosinusitis with nasal polyps, SD: standard deviation
Note: Percentages were calculated based on "n. NP= not provided

Prohibited medication

Prohibited medication was defined as any medication that could modulate the disease course of CRSwNP by reduction of blood eosinophils or type 2 inflammation i.e. like biologicals targeting type 2 inflammation, systemic corticosteroids or intranasal corticosteroids (Japan only).
In the ANCHOR-1 trial, more patients in the depemokimab groups started one of these medications (n=8 (6%) vs n=5 (4%), while the opposite was observed in the ANCHOR-2 trial (n=1 (<1%) vs n=4 (3%). Overall, the number of patients starting one of these treatments were comparable (n=9 both treatments).

**Table 30: Number of Participants Initiating a Disease-Modulating Medication or Any Other Changes in Background Medication or Prohibited Medication (FAS Population)**

| | **Anchor 1** | | **Anchor 2** | | **Pooled analyses** | |
|---|---|---|---|---|---|---|
| | **Depemokimab 100 mg SC** | **Placebo** | **Depemokimab 100 mg SC** | **Placebo** | **Depemokimab 100 mg SC** | **Placebo** |
| **N** | **143** | **128** | **129** | **128** | **272** | **256** |
| **Initiation of a medication that may modulate the disease course of CRSwNP, n (%)** | **8 (6%)** | **5 (4%)** | **1 (<1%)** | **4 (3%)** | **9 (3.3 %)** | **9 (4.5%)** |
| Biologics which may modulate the course of CRSwNP | 3 | 5 | 1 | 1 | 4 (1.5 %) | 6 (2.3%) |
| Chronic SCS | 2 | 0 | 0 | 0 | 2 (0.7%) | 0 (0%) |
| Initiation of INCS | 3 | 0 | 0 | 3 | 3 (1.2%) | 3 1.1%) |
| **Any other changes in background medication or start of a prohibited medication (not considered disease-modulating)** | **0** | **1 (<1%)** | **0** | **1 (<1%)** | **0 (0%)** | **1 (0.7%)** |

| | | | | | | |
|---|---|---|---|---|---|---|
| Allergen immunotherapy | 0 | 1 | 0 | 0 | 0 (0%) | 1 (0.4%) |

Note, the table has been modified by the Assessor to facilitate a comparison between the two trials, while in addition, a pooled analyses was added

**Outcomes and estimation**

***Summary of the outcome measures***

Individual studies

The baseline efficacy scores were comparable between treatments and trials (Table 31).

In the FAS population of both studies, both co-primary endpoints achieved statistical significance at the 2-sided 5% significance level in favour of the depemokimab group compared with the placebo group.

Regarding the individual studies, in both studies the testing hierarchy was broken at the first secondary endpoint i.e. running nose, as statistical significance was not achieved. Therefore, this null hypothesis and subsequent null-hypothesis could not be rejected, and p-values should be considered as descriptive only (Table 31).

ANCHOR-1: For the remaining secondary endpoints, the treatment differences favoured the depemokimab arm, reaching a statistical nominal significance the LUND MacKay CT score at week 52.
ANCHOR-2: The remaining secondary endpoints, the treatment difference was nominally significant in favour of depemokimab compared with placebo in the hierarchy except for the change from baseline in the total endoscopic Nasal Polyp score at Week 26 (Table 31).

Pooled analyses

In addition to the study-level analyses summarised above, multiplicity-adjusted analyses of pooled endpoints was pre-specified in the study protocols.

Statistical significance was not achieved for the key secondary endpoint of the pooled analyses, i.e. the Time to first NP surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP up to Week 52 (see Table 32). Therefore, this null hypothesis and subsequent null-hypothesis could not be rejected, and p-values should also be considered as descriptive only (Table 32).

**Table 31: Summary of results for co-primary and secondary efficacy endpoints; FAS population, ANCHOR-1 and ANCHOR-2 and integrated analyses**

| | **ANCHOR-1** | | **ANCHOR-2** | | **Integrated** | |
|---|---|---|---|---|---|---|
| **LS mean (SE) change from baseline** | **Dep (N=143)** | **Placebo) (N=128)** | **Dep (N=129)** | **Pla (N=128)** | **Dep) (N=272)** | **Placebo (N=256)** |
| **Total endoscopic Nasal Polyp score (co-primary endpoint)** | | | | | | |
| Baseline, mean (SD) | 5.9 (1.34) | 6.0 (1.37) | 5.9 (1.21) | 5.8 (1.37) | 5.9 (1.27) | 5.9 (1.37) |
| LS mean change (SE) | -0.6 (0.14) | 0.2 (0.15) | -0.5 (0.14) | 0.1 (0.15) | -0.5 (0.10) | 0.1 (0.10) |
| Adj. mean dif. (95% CI), p value | -0.7 (-1.1, -0.3) | | -0.6 (-1.0, -0.2) | | -0.7 (-0.9, -0.4) | |
| p-value | <0.001 | | 0.004 | | <0.001[b] | |
| **The nasal obstruction VRS mean score over Week 49 to Week 52 (CO-primary endpoint)** | | | | | | |
| Baseline, mean (SD) | 2.55 (0.487) | 2.53 (0.472) | 2.62 (0.426) | 2.57 (0.418) | 2.58 (0.460) | 2.55 (0.446) |

| | ANCHOR-1 | | ANCHOR-2 | | Integrated | |
|---|---|---|---|---|---|---|
| **LS mean (SE) change from baseline** | **Dep (N=143)** | **Placebo) (N=128)** | **Dep (N=129)** | **Pla (N=128)** | **Dep) (N=272)** | **Placebo (N=256)** |
| LS mean change (SE) | -0.76 (0.079) | -0.53 (0.083) | -0.77 (0.076) | -0.53 (0.078) | -0.77 (0.055) | -0.53 (0.057) |
| Adj. mean dif. (95% CI) | -0.23 (-0.46, 0.00[a]) | | -0.25 (-0.46, -0.03) | | -0.24 (-0.39, -0.08) | |
| p-value | 0.047 | | 0.025 | | 0.003[b] | |
| **Rhinorrhoea (runny nose) VRS mean score over Week 49 to Week 52 (Sec endpoint)** | | | | | | |
| Baseline, mean (SD) | 2.16 (0.697) | 2.18 (0.711) | 2.25 (0.689) | 2.27 (0.648) | 2.20 (0.693) | 2.22 (0.680) |
| LS mean change, (SE) | -0.71 (0.084) | -0.49 (0.087) | -0.72 (0.080) | -0.54 (0.082) | -0.71 (0.058) | -0.52 (0.060) |
| Adj. mean dif. (95% CI) | -0.22 (-0.46, 0.02) | | -0.18 (-0.40, 0.05); | | -0.19 (-0.36, -0.03); | |
| p-value | 0.074 | | 0.125 | | 0.021[6] | |
| **Loss of smell VRS mean score over Week 49 to Week 52 (Sec endpoint)** | | | | | | |
| Baseline, mean (SD) | 2.70 (0.547) | 2.74 (0.564) | 2.85 (0.388) | 2.77 (0.421) | 2.77 (0.483) | 2.76 (0.497) |
| LS mean change, (SE) | -0.48 (0.069) | -0.29 (0.072) | -0.56 (0.066) | -0.30 (0.068) | -0.52 (0.048) | -0.30 (0.049) |
| Adj. mean dif. (95% CI) | -0.19 (-0.39, 0.00) | | -0.26 (-0.45,-0.07) | | -0.22 (-0.35, -0.08); | |
| p-value | 0.055 | | 0.007[b] | | 0.002[b] | |
| **Lund Mackay CT score at Week 52 (Sec endpoint)** | | | | | | |
| Baseline, mean (SD) | 18.4 (4.15) | 19.0 (3.99) | 19.6 (3.75) | 18.2 (4.51) | 19.0 (3.99) | 18.6 (4.27) |
| LS mean change, (SE) | -2.8 (0.45) | -0.8 (0.46) | -3.5 (0.42) | -0.3 (0.44) | -3.1 (0.31) | -0.6 (0.32) |
| Adj. mean dif. (95% CI) | -2.0 (-3.3, -0.8) | | -3.2 (-4.4, -2.0); | | -2.5 (-3.4, -1.7) | |
| p-value | 0.002[b] | | <0.001[b] | | <0.001[b] | |
| **SNOT-22 total score at Week 52 (Sec endpoint)** | | | | | | |
| Baseline, mean (SD) | 58.2 (22.60) | 56.6 (21.70) | 60.1 (21.51) | 60.1 (18.34) | 59.1 (22.07) | 58.3 (20.12) |
| LS mean change, (SE) | -13.3 (2.96) | -6.5 (3.08) | -15.9 (2.83) | -6.0 (2.87) | -14.4 (2.06) | -6.3 (2.12) |
| Adj. mean dif. (95% CI) | -6.8 (-15.2, 1.6) | | -9.9 (-17.9, -2.0) | | -8.1 (-13.9, -2.3) | |
| p-value | 0.113 | | 0.015[b] | | 0.007 [b] | |
| **nasal obstruction VRS mean score over Week 21 to Week 24 (Sec endpoint)** | | | | | | |
| Baseline, mean (SD) | 2.55 (0.487) | 2.53 (0.472) | 2.62 (0.426) | 2.57 (0.418) | 2.58 (0.460) | 2.55 (0.446) |
| LS mean change, (SE) | -0.74 (0.071) | -0.57 (0.074) | -0.78 (0.068) | -0.54 (0.069) | -0.76 (0.049) | -0.56 (0.051) |
| Adj. mean dif. (95% CI) | -0.17 (-0.37, 0.03) | | -0.24 (-0.43, -0.04) | | -0.20 (-0.34, -0.06); | |
| p-value | 0.094 | | 0.016[b] | | 0.005[b] | |
| **Total endoscopic Nasal Polyp score at Week 26 (Sec endpoint)** | | | | | | |

| | ANCHOR-1 | | ANCHOR-2 | | Integrated | |
|---|---|---|---|---|---|---|
| **LS mean (SE) change from baseline** | **Dep (N=143)** | **Placebo) (N=128)** | **Dep (N=129)** | **Pla (N=128)** | **Dep) (N=272)** | **Placebo (N=256)** |
| Baseline, mean (SD) | 5.9 (1.34) | 6.0 (1.37) | 5.9 (1.21) | 5.8 (1.37) | 5.9 (1.27) | 5.9 (1.37) |
| LS mean change, (SE) | -0.6 (0.13) | 0.1 (0.13) | -0.5 (0.12) | -0.1 (0.12) | -0.5 (0.12) | -0.1 (0.12) |
| Adj. mean dif. (95% CI) | -0.8 (-1.1, -0.4) | | -0.3 (-0.7, 0.0) | | -0.3 (-0.7, 0.0) | |
| p-value | <0.001[b] | | 0.066 | | 0.066 | |

Abbreviations: CI = confidence interval; CT = computed tomography; FAS = Full Analysis Set; LS = least squares;; SD= standard deviation; SE = standard error; SNOT-22 = sino-nasal outcome test; VRS = verbal response scale.

'* endpoints are measured as the change from baseline to the mentioned endpoint

b. The upper limit of the 95% CI for Weeks 49 to 52 represents a rounded value of -0.003408994.

Nominal significance (i.e., p<0.05 without multiplicity control) was achieved. However, statistical significance was not achieved due to a break in the multiplicity-controlled testing hierarchy.

Note: Gray shaded rows indicate those endpoints for which the null hypothesis could not be rejected, and p-values should be considered as descriptive only.

**Table 32: Summary of results for pooled primary and secondary efficacy endpoints (Pooled ANCHOR-1+2)**

| **Endpoints** | **Depemokimab LS mean change (SE) (N=272)** | **Placebo LS mean change (SE) (N=256)** | **Adjusted mean difference (depemokimab – placebo); 95% CI; p-value** |
|---|---|---|---|
| **Co-primary endpoints** | | | |
| LS mean (SE) Change from baseline in the total endoscopic Nasal Polyp score at Week 52 | -0.5 (0.10) | 0.1 (0.10) | -0.7 (-0.9, -0.4); p<0.001[a] |
| LS mean (SE) Change from baseline in the nasal obstruction VRS mean score over Week 49 to Week 52 | -0.77 (0.055) | -0.53 (0.057) | **-0.24 (-0.39, -0.08); p=0.003[a]** |
| **Secondary endpoints (pooled analyses)** | | | |
| **Time to first NP-surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP up to Week 52** | | | |
| Hazard ratio (95% CI). p-value | | 0.735 (0.495, 1.092). 0.128 | |
| **Time to first NP-surgery (actual) or disease-modulating medication for CRSwNP up to Week 52** | | | |
| Hazard ratio (95% CI). p-value | | 0.713 (0.453, 1.124) 0.146 | |
| **Requiring at least 1 course of systemic CS or disease-modulating medication for CRSwNP or NP-surgery (actual) during the 52-week treatment period** | | | |
| Odds ratio (95% CI) p-value | | 0.58 (0.40, 0.86) 0.006[a] | |
| **Change from baseline in ACQ-5 score at Week 52 in participants with partially or not well-controlled asthma** | | | |
| Difference (depemokimab - placebo) (95% CI) p-value | | -0.75 (-1.26, -0.25) 0.004[a] | |

Abbreviations: ACQ-5 = asthma control questionnaire-5; CI = confidence interval; CRSwNP = chronic rhinosinusitis with nasal polyps; CS = corticosteroids; NP-surgery = refers to any procedure involving instruments resulting in incision and removal of tissue from the nasal cavity (e.g., polypectomy and endoscopic sinus surgery).

a. Nominal significance (i.e., p<0.05 without multiplicity control) was achieved. However, statistical significance was not achieved due to a break in the multiplicity-controlled testing hierarchy.

Note: Gray shaded rows indicate those endpoints for which the null hypothesis could not be rejected, and p-values should be considered as descriptive only

***Co-primary endpoint 1: change from baseline in total endoscopic NP score at week 52 (centrally read)***

ANCHOR-1

At baseline, the mean (SD) total endoscopic Nasal Polyp score was 5.9 (1.34) for depemokimab and 6.0 (1.37) for placebo. At week 52, the LS mean change from baseline (SE) was -0.6 (0.14) for depemokimab and 0.2 (0.15) for placebo, resulting in a -0.7 (95% CI -1.1, -0.3) difference, p<0.001 (Table 31).

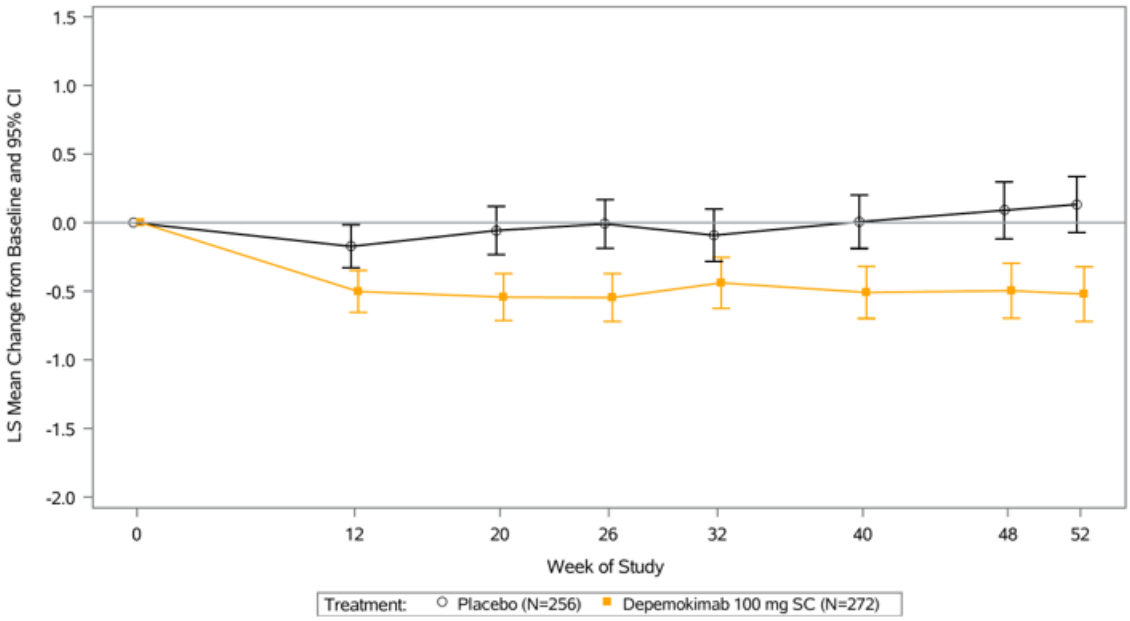
ANCHOR-2

At baseline, the mean (SD) total endoscopic Nasal Polyp score was 5.9 (1.21) for depemokimab and 5.8 (1.37) for placebo. At week 52, the LS mean (SE) change from baseline was -0.5 (0.14) for depemokimab and 0.1 (0.15) for placebo, resulting in a -0.6 (95% CI -1.0, -0.2) difference, p<0.004 (Table 31).

Integrated analysis

At week 52, the LS mean (SE) change from baseline was for -0.5 (0.10) depemokimab and 0.1 (0.10) for placebo, resulting in a -0.7 (95% CI -0.9, -0.4) difference, nominal p<0.001 (Table 31, Figure 27 ).

**Figure 27: Line plot of analysis of change from baseline in total endoscopic Nasal Polyp score (Integrated ANCHOR-1+2)**




Abbreviations: CI = confidence interval; LS = least squares; SC = subcutaneous.

Note: Participants with nasal surgery or initiation of a medication that may modulate the disease course of CRSwNP were assigned the worst possible total endoscopic Nasal Polyp score for all visits after surgery or initiation of medication.

Note: Analysis performed using a repeated measures model with covariates of study, treatment group, baseline score, log(e) baseline blood eosinophil count, region, previous surgery for nasal polyps, visit, visit by baseline, and visit by treatment group

***Co-primary endpoint 2: Change from baseline in mean nasal obstruction score (VRS) from Week 49 through to Week 52***

ANCHOR-1

At baseline, the mean (SD) nasal obstruction VRS score was 5.9 (1.34) for depemokimab and 6.0 (1.37) for placebo. At week 52, the LS mean change from baseline -0.76 (0.079) for depemokimab and -0.53 (0.083) for placebo, resulting in a -0.23 (95% CI -0.46, 0.00) difference, p=0.047 (Table 31).

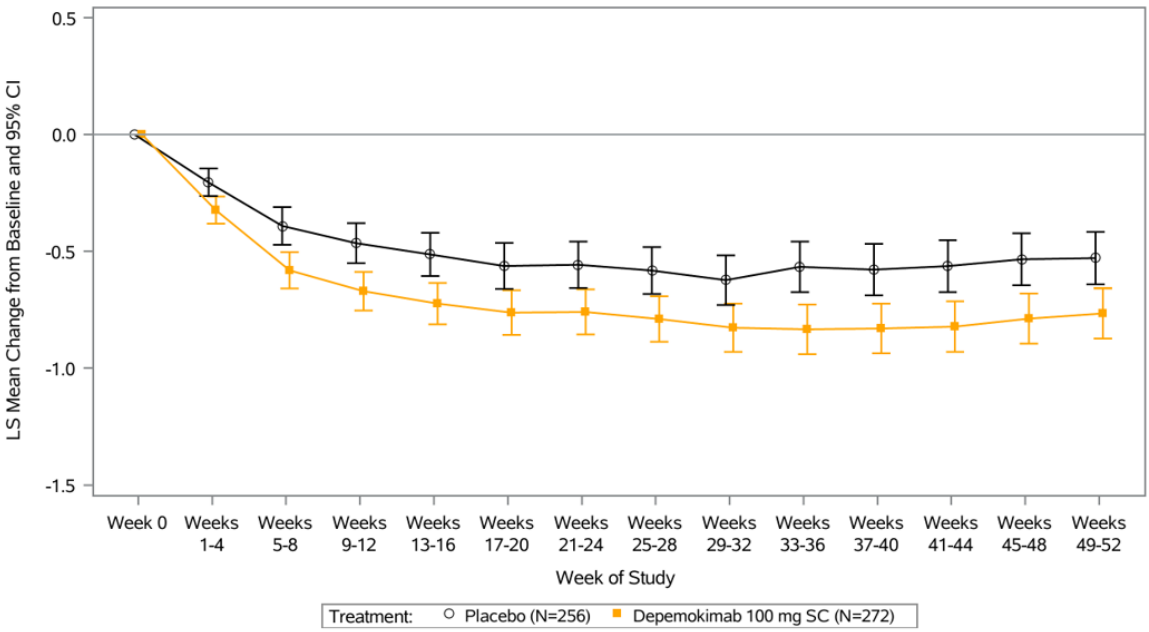
ANCHOR-2

At baseline, the mean (SD) nasal obstruction VRS score was 2.62 (0.443) for depemokimab and 2.57 (0.42) for placebo. At week 52, the LS mean (SE) change from baseline was -0.77 (0.076) for depemokimab and -0.53 (0.078) for placebo, resulting in a -0.25 (95% CI -0.46, -0.03) difference, p= 0.025 (Table 31).

Integrated analysis

At week 52, the LS mean (SE) change from baseline was -0.77 (0.055) for depemokimab and -0.53 (0.057) for placebo, resulting in a -0.24 (95% CI -0.39, -0.03) difference, nominal p= 0.003 (Table 31, Figure 28).

**Figure 28: Line plot of analysis of change from baseline in nasal obstruction VRS mean score (Integrated ANCHOR-1+2)**




Abbreviations: CI = confidence interval; LS = least squares; SC = subcutaneous; VRS = verbal response scale.

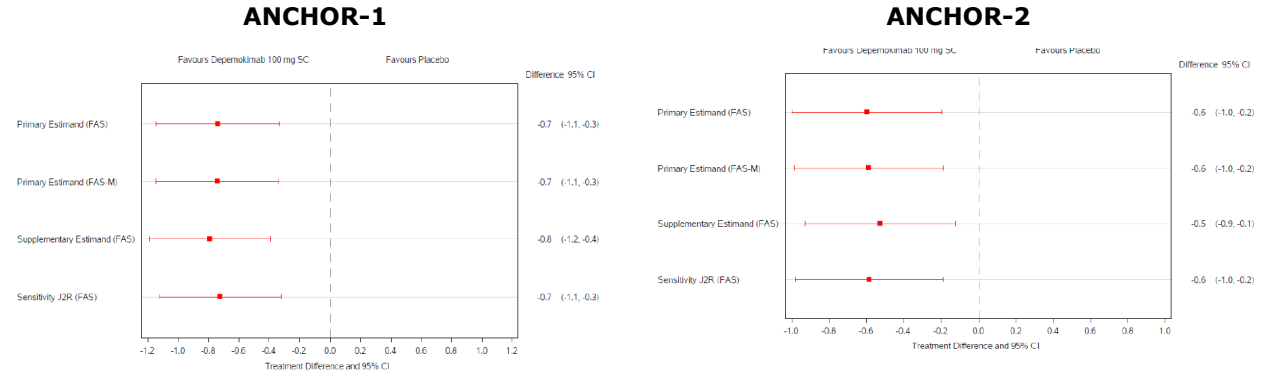
Note: Participants with nasal surgery or initiation of a medication that may modulate the disease course of CRSwNP were assigned the worst possible mean nasal obstruction VRS score for all visits after surgery or initiation of medication.

Note: Analysis performed using a repeated measures model with covariates of study, treatment group, baseline score, log(e) baseline blood eosinophil count, region, previous surgery for nasal polyps, visit, visit by baseline, and visit by treatment group.

***Sensitivity analyses co-primary endpoints***

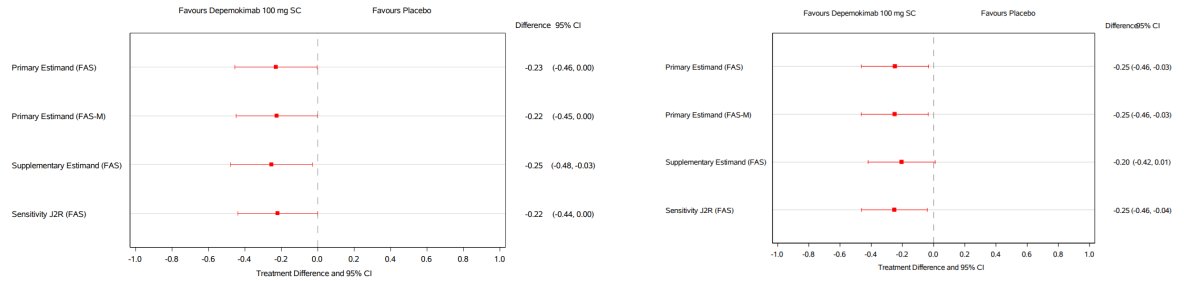
Sensitivity analyses confirmed the robustness of the primary analyses for both co-primary endpoints for both studies ( Figure 29 and Figure 30), including the Nasal Obstruction -VRS score over week 49 to week 52 in ANCHOR-1. The results for modified FAS and sensitivity analysis given by jump-to-reference approach for missing data imputation were almost identical with results of primary analysis regarding borderline results. More specifically, modified FAS led to estimated treatment difference between depemokimab 100 mg SC and placebo -0.22 point with corresponding 95% CI (-0.45 point, -0.00014 point) and estimated treatment difference between depemokimab 100 mg SC and placebo -0.22 points with corresponding 95% CI (-0.44 point, -0.00127 point).

**Figure 29: Forest plot of LS mean (95% CI) treatment difference in change from baseline for primary and sensitivity analyses for in the Nasal Polyp -score over week 49 to week 52 -ANCHOR 1 and ANCHOR-2 studies.**




**Analyses model depemokimab 100 mg SC vs placebo change in baseline differences with 95% CI are displayed**

**Figure 30: Forest plot of LS mean (95% CI) treatment difference in change from baseline for primary and sensitivity analyses for in the Nasal obstruction CRS score over week 49 to week 52 -ANCHOR 1 and ANCHOR-2 studies.**

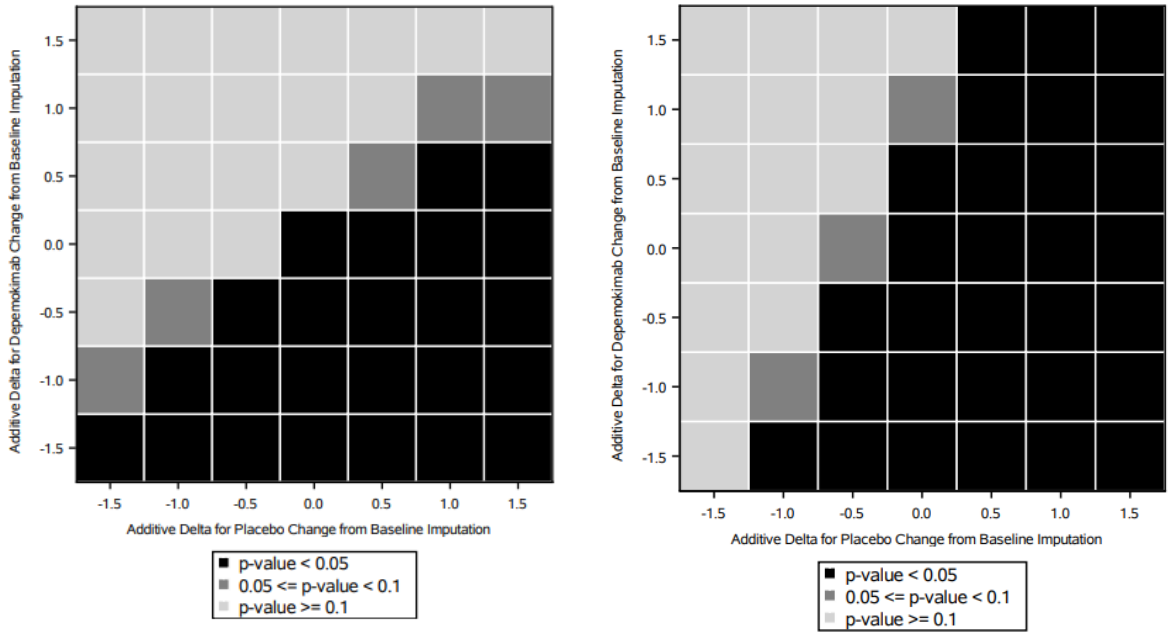



Note: Analysis model depemokimab 100 mg SC vs. placebo change in baseline differences with 95% CIs are displayed.
Note: The upper limit of the 95% CI for Primary Estimand (FAS) represents a rounded value from -0.003408994. The upper limit of the 95% CI for Primary Estimand (FAS-M) represents a rounded value from -0.001415878. The upper limit of the 95% CI for Sensitivity J2R (FAS) represents a rounded value from -0.001271444.

Additional tipping point analyses showed the robustness of the Nasal Polyp-score in both trials and Nasal Obstrucion VRS score in both trials (Figure 31).

**Figure 31: Sensitivity analysis of change from baseline in nasal obstruction VRS mean score over time week 49 to week 52 using tipping point, FAS population, ANCHOR-1 study**

**ANCHOR-1** **ANCHOR-2**




Tipping point analysis was conducted to investigate the impact of missing data by using differing assumptions regarding the total endoscopic Nasal Polyp score. For each treatment group, the imputed values varied separately by a value of delta, where delta represented a change in endoscopic Nasal Polyp score for each imputed timepoint.Note: Participants with nasal surgery or initiation of a medication that may modulate the disease course of CRSwNP are assigned the worst possible mean NO VRS score for all visits after surgery or initiation of medication.
Note: Analysis performed using an analysis of covariance model with covariates of treatment group, baseline score, log(e) baseline blood eosinophil count, region, previous surgery for Nasal Polyps. Based on 1000 imputations.
Source: Figure 2.2.36 (02JUL2025 04:03) ANCHOR-1 CSR erratum; m5.3.5.1)
Source: Figure 2.2.37 (02JUL2025 12:45) ANCHOR-2 CSR erratum; m5.3.5.1

Note: Participants with nasal surgery or initiation of a medication that may modulate the disease course of CRSwNP are assigned the worst possible mean Nasal Obstruction VRS score for all visits after surgery or initiation of medication.
Note: Analysis performed using an analysis of covariance model with covariates of treatment group, baseline score, log(e) baseline blood eosinophil count, region, previous surgery for NP. Based on 1000 imputations.

The post-hoc requested analyses where all intercurrent events were handled according to the treatment strategy supported the primary analyses.

**Secondary outcomes**

***First secondary endpoint (Sec-1): Change from baseline in mean symptom score for rhinorrhoea (VRS) from Week 49 through to Week 52***

ANCHOR-1

At baseline, the mean (SD) symptom score for rhinorrhoea VRS was 2.16 (0.697) for depemokimab and 2.18 (0.711) for placebo.
The LS mean (SE) change from baseline in the rhinorrhoea VRS mean score over Week 49 to Week 52 was

-0.71 (0.084) for depemokimab and -0.49 (0.087) for placebo, resulting in a -0.22 (95% CI: -0.046, 0.02) difference, p=0.074 (Table 31).

ANCHOR-2

At baseline, the mean (SD) symptom score for rhinorrhoea (VRS) was 2.25 (0.689) for depemokimab and 2.27 (0.648) for placebo.
The LS mean (SE) change from baseline over week 49 to week 52 in the rhinorrhoea VRS score was -0.72 (0.080) for depemokimab and -0.54 (0.082) for placebo, resulting in a -0.18 (95% CI -0.40, 0.05) difference, p=0.125 (Table 31).

ANCHOR-1 and ANCHOR-2

The LS mean (SE) change from baseline over week 49 to week 52 in the rhinorrhoea VRS score was -0.71 *(0.058)* for depemokimab and -0.52 *(0.06)* for placebo, resulting in a -0.19 (95% CI -0.36, -0.03) difference, nominal p=0.021 (Table 31).

The hierarchy was broken and treatment differences with p<0.05 for any subsequent endpoint are indicated as nominally significant.

***Sec-2: Change from baseline in mean symptom score for loss of smell (VRS) from Week 49 through to Week 52.***

ANCHOR-1

At baseline, the mean (SD) symptom score for loss of smell VRS score was 2.70 (0.547) for depemokimab and 2.74 (0.547) for placebo.

The LS mean (SE) change in symptom score for loss of smell (VRS) from baseline to Week 49 through to Week 52 was -0.48 (0.069) for depemokimab and -0.29 (0.072) for placebo, resulting in a -0.19 (95% CI 0.39, 0.00) difference, p=0.05 (Table 31).

ANCHOR-2

At baseline, the mean (SD) symptom score for loss of smell VRS score was 2.85 (.388) for depemokimab and 2.77 (0.421) for placebo.

The LS mean (SE) change in loss of smell (VRS) score from baseline to Week 49 through to Week 52 was for -0.56 (0.066) depemokimab and -0.30 (0.068) for placebo, resulting in a -0.26 (95% CI -0.45, -0.07) difference, nominal p=0.007 (Table 31).

Integrated analysis

The LS mean (SE) change in loss of smell (VRS) score from baseline to Week 49 through to Week 52 was for -0.52 (0.048) depemokimab and -0.30 (0.049) for placebo, resulting in a -0.22 (95% CI -0.35, -0.08) difference, nominal p=0.002 (Table 31).

***Sec-3: Change from baseline in Lund Mackay CT score at Week 52***

At baseline, the mean Lund Mackay CT scores were comparable between the treatments and across studies. Both studies showed a nominally significant improvement.

ANCHOR-1

At baseline, the mean (SD) Lund MacKay CT score was 18.4 (4.15) for depemokimab and 19.0 (3.99) for placebo.

At week 52, the LS mean change from baseline (SE) was -2.8 (0.45) for depemokimab and -0.8 (0.46) for placebo, resulting in a -2.0 (95% CI -3.3, -0.8) difference, nominal p=0.002 (Table 31).

ANCHOR-2

At baseline, the mean (SD) Lund MacKay CT score was 19.6 (3.75) for depemokimab and 18.2 (4.51) for placebo.

At week 52, the LS mean (SE) change from baseline was -3.5 (0.42) for depemokimab and -0.3 (0.068) for placebo, resulting in a -3.2 (95% CI -4.4, -2.0) difference, nominal p <0.001 (Table 31).

Integrated analysis

At week 52, the LS mean (SE) change from baseline was -3.1 (0.31) for depemokimab and -0.6 (0.32) for placebo, resulting in a -2.5 (95% CI -3.4, -1.7) difference, nominal p<0.001 (Table 31).

***Sec-4: Change from baseline in SNOT-22 total score at Week 52***

ANCHOR-1

At baseline, the mean (SD) SNOT-22 score was 56.6 (21.70) for depemokimab and 58.2 (22.60) for placebo.

At week 52, the LS mean (SE) change from baseline was -13.3 (2.96) for depemokimab and -6.5 (3.08) for placebo, resulting in a -6.8 (95% CI -15.2, 1.6) difference, nominal p=0.113 (Table 31).

ANCHOR-2

At baseline, the mean (SD) SNOT-22 score was 60.1 (21.51) for depemokimab and 60.1 (18.34) for placebo.

At week 52, the LS mean (SE) change from baseline was for -15.9 (2.83) for depemokimab and -6.0 (2.87) for placebo, resulting in a -9.9 (95% CI -17.9, -2.0) difference, nominal p=0.015 (Table 31).

Integrated analysis

At week 52, the LS mean (SE) change from baseline was for -14.4 (2.06) for depemokimab and -6.5 (2.12) for placebo, resulting in a -8.1 (95% CI -13.9, -2.3) difference, nominal p =0.007 (Table 31).

***Sec-5: Change from baseline in mean nasal obstruction score (VRS) from Week 21 through to Week 24***

ANCHOR-1

At baseline, the mean (SD) in the nasal obstruction score (VRS) was 2.55 (0.487) for depemokimab and 2.53 (0.472) for placebo.

The LS mean (SE) change in the nasal obstruction VRS score from baseline to week 21 through to 24 was -0.74 (0.071) for depemokimab and -0.57 (0.074) for placebo, resulting in a -0.17 (95% CI -0.37, 0.03) difference, p=0.09 (Table 31).

ANCHOR-2

At baseline, the mean (SD) in nasal obstruction score (VRS) was 2.62 (0.426) for depemokimab and 2.57 (0.418) for placebo.

The LS mean (SE) change in the nasal obstruction VRS score from baseline to week 21 through to 24 was -0.78 (0.068) for depemokimab and -0.54 (0.069) for placebo, resulting in a -0.24 (95% CI -0.43, -0.04) difference, nominal p=0.016 (Table 31).

Integrated analysis

The LS mean (SE) change in the nasal obstruction VRS score from baseline to week 21 through to 24 was -0.76 (0.049) for depemokimab and -0.56 (0.051) for placebo, resulting in a -0.20 (95% CI -0.34, -0.06) difference, nominal p=0.005 (Table 31).

***Sec-6: Change from baseline in total endoscopic Nasal Polyp score at Week 26***

ANCHOR-1

At baseline, the mean (SD) total endoscopic Nasal Polyp score was for 5.9 (1.34) depemokimab and for 6.0 (1.37) placebo.

At week 26, the LS mean (SE) change from baseline was -0.6 (0.13) for depemokimab and 0.1 (0.13) for placebo, resulting in a -0.8 (95% CI -1.1, -0.4) difference, nominal p<0.001 (Table 31).

ANCHOR-2

At baseline, the mean (SD) total endoscopic Nasal Polyp score was 5.9 (1.21) for depemokimab and 5.8 (1.37) for placebo.

At week 26, the LS mean (SE) change from baseline was -0.5 (0.12) for depemokimab and -0.1 (0.12) for placebo, resulting in a -0.3 (95% CI 0.7, 0.00) difference, p=0.066 (Table 31).

Integrated analysis

The LS mean (SE) change from baseline in total endoscopic Nasal Polyp score at week 26 was -0.5 (0.12) for depemokimab and -0.1 (0.12) for placebo, resulting in a -0.3 (95% CI -0.7, 0.0) difference, nominal p=0.06 (Table 31).

**Other endpoints**

In addition to the secondary outcome measurements, responder analyses were also conducted at week 52. Responders did not undergo nasal polyp surgery and did not start disease-modulating medication during the trial, while they showed an improvement from baseline ≥ minimal clinically important difference at week 52.

The results for the various co-primary and secondary endpoints of the ANCHOR-1, ANCHOR-2 and integrated analyses are provided in the Table 33. The results were consistently higher for the depemokimab treatment arm.

**Table 33: Summary responder analyses -individual studies and integrated analyses.**

| | ANCHOR-1 | | ANCHOR-2 | | Integrated | |
|---|---|---|---|---|---|---|
| | **Depemokimab (N=143)** | **Placebo (N=128)** | **Depemokimab (N=129)** | **Placebo (N=128)** | **Depemokimab (N=272)** | **Placebo (N=256)** |
| **Nasal polyp size** | | | | | | |
| **Responders in total endoscopic Nasal Polyp score (defined as at least 1 point reduction [improvement] from baseline) at Week 52 – other endpoint [a]** | | | | | | |
| Responders; n (%) | 63 (44) | 31 (24) | 53 (41) | 31 (24) | 116 (43) | 62 (24) |
| Odds ratio (95% CI); | 2.68 (1.56, 4.61) | | 2.07 (1.19, 3.59) | | 2.31 (1.58, 3.38) | |
| p-value | <0.001[b] | | 0.010[b] | | p<0.001[b] | |
| **Responders in nasal obstruction VRS mean score (defined as at least 1 point reduction [improvement] from baseline) over Weeks 49 to 52 – other endpoint [a]** | | | | | | |
| Responders; n (%) | 51 (36) | 38 (30) | 59 (46) | 37 (29) | 110 (40) | 75 (29) |
| Odds ratio (95% CI) | 1.30 (0.77, 2.20) | | 1.92 (1.10, 3.37) | | 1.56 (1.07, 2.27) | |
| p-value | 0.317 | | 0.022[b] | | 0.020[b] | |
| **Responders for rhinorrhea (runny nose) VRS mean score (defined as at least 1 point reduction [improvement] from baseline) over Weeks 49 to 52 – other endpoint [a]** | | | | | | |
| Responders; n (%) | 49 (34) | 37 (29) | 56 (43) | 35 (27) | 105 (39) | 72 (28) |
| Odds ratio (95% CI); | 1.44 (0.83, 2.52) | | 2.03 (1.16, 3.53) | | 1.67 (1.13, 2.45) | |
| p-value | 0.196 | | 0.013[b] | | 0.010[b] | |
| **Responders for rhinorrhea (runny nose) VRS mean score (defined as at least 0.9 points reduction [improvement] from baseline) over Weeks 49 to 52 – other endpoint [a]** | | | | | | |
| Responders; n (%) | 39 (27) | 18 (14) | 39 (30) | 21 (16) | 78 (29) | 39 (15) |
| Odds ratio (95% CI) | 2.36 (1.25, 4.46) | | 2.23 (1.21, 4.12) | | 2.24 (1.45, 3.46) | |
| p-value | 0.009[b] | | 0.011[b] | | <0.001[b] | |
| **Responders for loss of smell VRS mean score (defined as at least 0.9 points reduction [improvement] from baseline) over Weeks 49 to 52 – other endpoint [a]** | | | | | | |
| Responders; n(%) | 39 (27) | 18 (14) | 39 (30) | 21 (16) | 78 (29) | 39 (15) |
| Odds ratio (95% CI) | 2.36 (1.25, 4.46) | | 1.23 (1.21, 4.12) | | 2.24 (1.45, 3.46) | |
| p-value | 0.009 | | 0.011 | | <0.001 | |
| **Responders for SNOT-22 total score (defined as at least 8.9-point reduction [improvement] from baseline) at Week 52 – other endpoint [a]** | | | | | | |
| Responders; n (%) | 81 (58) | 68 (54) | 85 (67) | 58 (46) | 166 (62) | 126 (50) |
| Odds ratio (95% CI) | 1.13 (0.67, 1.89) | | 2.62 (1.53, 4.48) | | 1.65 (1.15, 2.37) | |
| p-value | 0.650 | | <0.001[b] | | 0.007[c] | |

Abbreviations: CI=confidence interval. CRSwNP=chronic rhinosinusitis with nasal polyps. FAS=full analysis set. LMK CT = Lund Mackay computerised tomography. NO=nasal obstruction. NP=nasal polyps. OR=odds ratio. SC = subcutaneous. SNOT-22 = 22-item sino-nasal outcomes test. VRS = verbal response scale.
[1] Number of participants with analysable data at the given timepoint.
[2] Analysis performed using a generalised linear mixed model with a logit link function and covariates of treatment group, baseline score, log(e) baseline blood eosinophil count, region, previous surgery for nasal polyps, visit, visit by baseline, and visit by treatment group. For the integrated analysis, study was also included as a covariate.
[3] Binomial model with identity link function by visit with same covariates as main analysis.
* Response is defined as:

- NPS: a reduction of at least 1 point in Nasal Polyp score compared to baseline.
- NO: a reduction of at least 1 point in NO VRS score compared to baseline.
- Rhinorrhoea: a reduction of at least 1 point in rhinorrhoea VRS score compared to baseline.
- Loss of smell: a reduction of at least 0.9 points in loss of smell VRS score compared to baseline.
- LMK CT score: a reduction of at least 4 points in LMK CT score compared to baseline.
- SNOT-22: a reduction of at least 8.9 points in SNOT-22 compared to baseline.

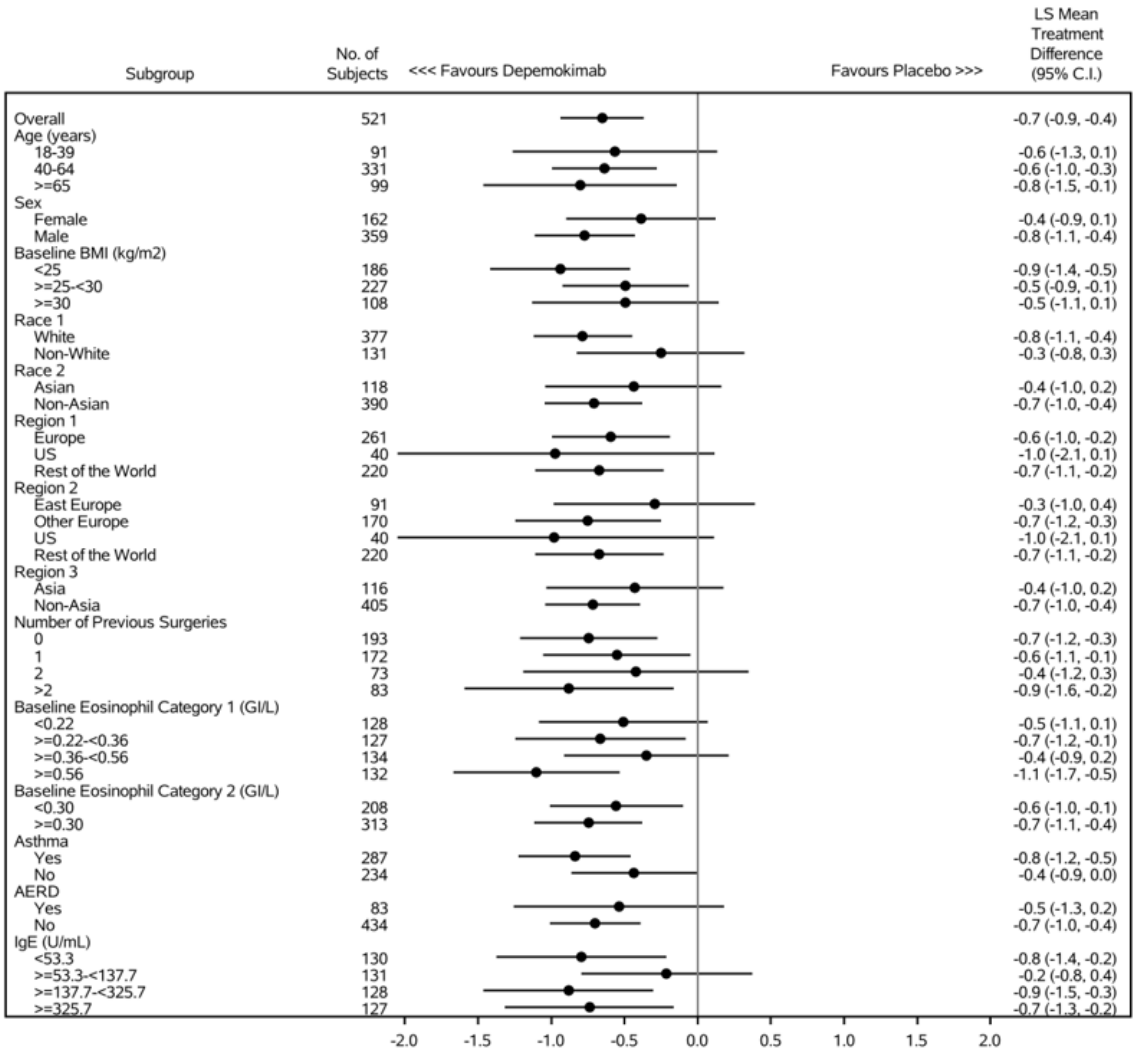
Participants were considered non-responders if they didn't achieve the endpoint specified point reduction from baseline, or had nasal surgery (actual) prior to visit, or initiated disease modulating medication for CRSwNP or had missing data.
†Nominally significant p-value; analysis not multiplicity-adjusted.
^The integrated analyses for SNOT-22 was conducted as post-hoc.

### Pre-defined and post-hoc subgroup analyses

#### *Primary endpoints*

Results of the subgroup analyses of the total endoscopic Nasal Polyp Score at Week 52 were consistent between ANCHOR-1 And ANCHOR-2. Figure 32 and Figure 33 provide the integrated analyses showing the consistency of the subgroup analyses with the primary analyses for both co-primary endpoints.

**Figure 32: Forest plot of least square mean (95% CI) treatment difference in change from baseline in total endoscopic Nasal Polyp Score at Week 52 by subgroup (Integrated ANCHOR-1+2)**

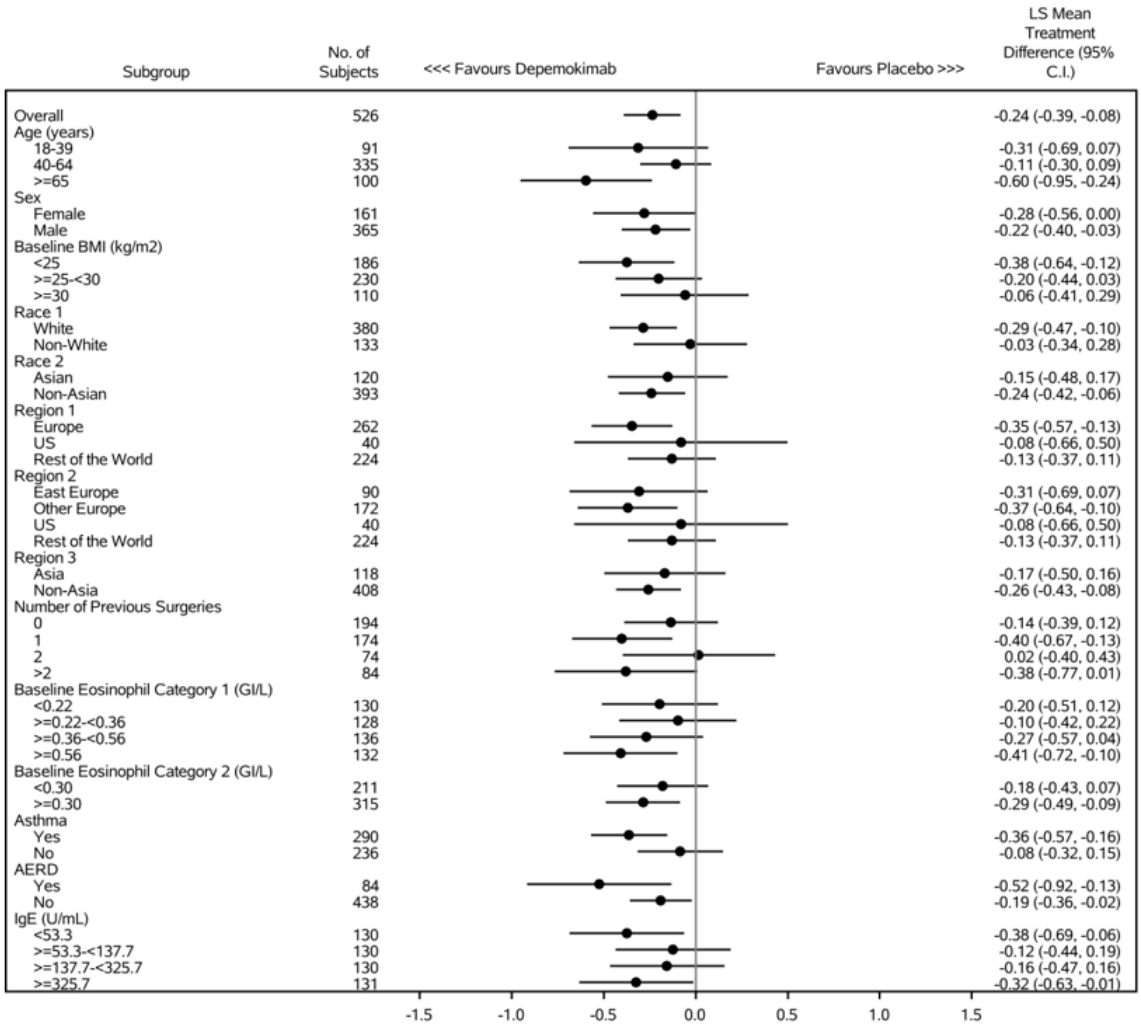



Abbreviations: AERD = aspirin-exacerbated respiratory disease; BMI = body mass index; CI = confidence interval; IgE = immunoglobulin E; LS = least squares.

Note: Number of participants is the number of participants with analyzable data for one or more timepoints for the 2 treatment groups of interest.

Note: Analysis performed using a repeated measures model with covariates as per corresponding analysis table.

**Figure 33: Forest plot of least square mean (95% CI) treatment difference in change from baseline in mean nasal obstruction VRS score over Weeks 49 to 52 by subgroup (Integrated ANCHOR-1+2)**




Abbreviations: AERD = aspirin-exacerbated respiratory disease; BMI = body mass index; CI = confidence interval; IgE = immunoglobulin E; LS = least squares.

Note: Number of participants is the number of participants with analyzable data for one or more timepoints for the 2 treatment groups of interest.

Note: Analysis performed using a repeated measures model with covariates as per corresponding analysis table.

**Ancillary analyses**

Pharmacodyamic endpoint of change from baseline in blood eosinophil count at Week 52.

ANCHOR-1

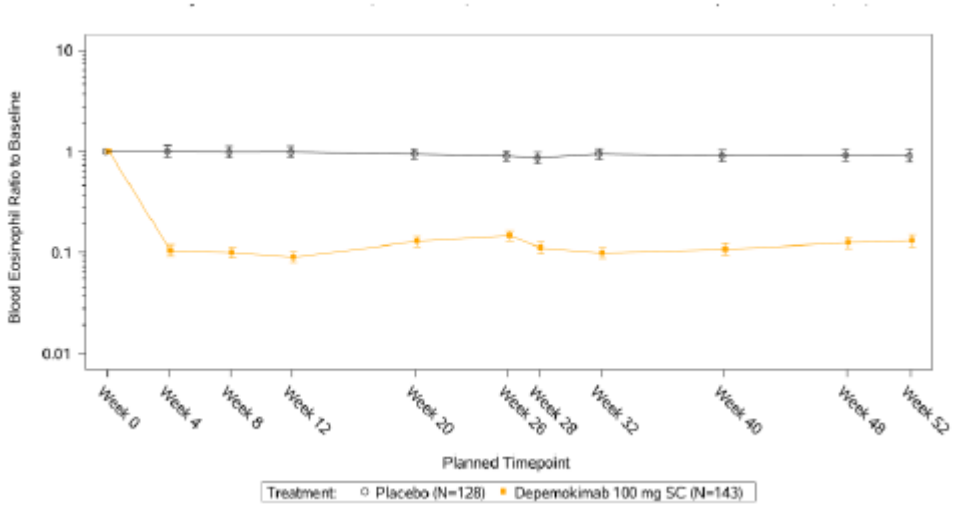
The baseline geometric mean blood eosinophil count was 0.319 GI/L for depemokimab and 0.359 GI/L for placebo. No marked change in eosinophil counts was observed in the placebo group, whereas a reduction in eosinophil count was apparent in the depemokimab from as early as 4 weeks (first assessment point post dosing) and sustained over the study period (Figure 34). Changes in adjusted geometric mean ratios to

baseline were larger for depemokimab at every timepoint during the study (nominal *P*<0.001 for all measured timepoints).

ANCHOR-2

The baseline geometric mean blood eosinophil count was 0.375 GI/L for depemokimab and 0.288 GI/L for placebo. No marked change in eosinophil counts was observed in the placebo group, whereas a reduction in eosinophil count was apparent in the depemokimab from as early as 4 weeks (first assessment point post dosing) and sustained over the study period (Figure 35). Changes in adjusted geometric mean ratios to baseline were larger for depemokimab at every timepoint during the study (nominal P<0.001 for all measured timepoints, not adjusted for nominal significance).

**Figure 34: Line polot of Adjusted geometric means (and 95% CIs) of ratio to blood eosinophil count data (GI/L), FAS population, ANCHOR-1 study**



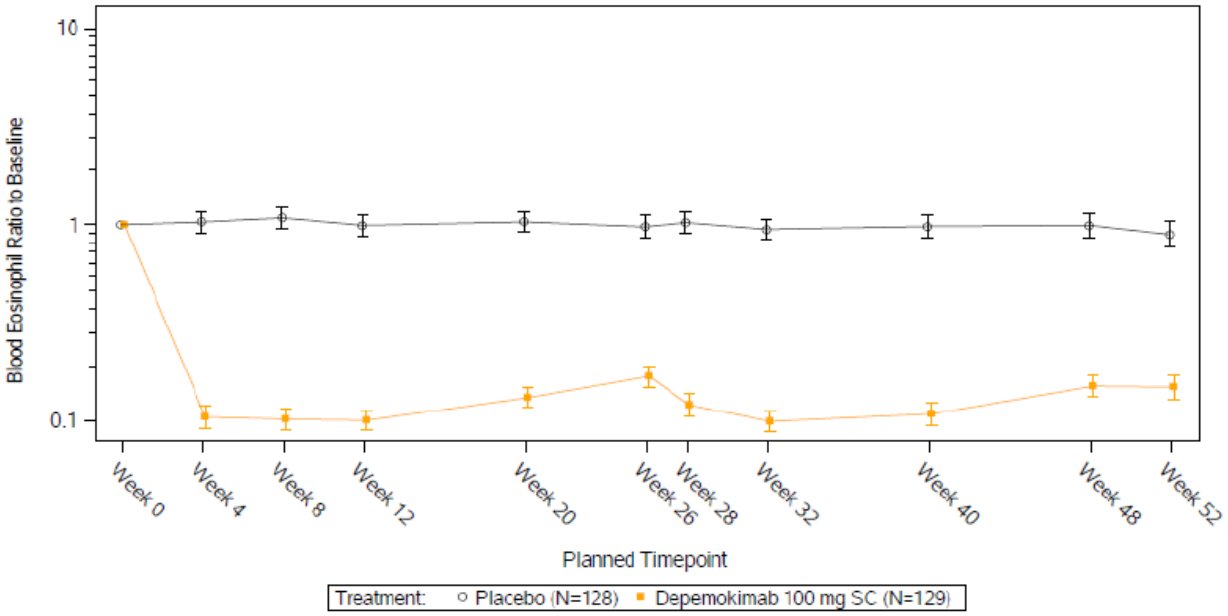

Note: The log(e) transformation for values of 0 GI/L are imputed with a value of 0.005 GI/L.

Note: All PD data while on-treatment are included in the analysis.

Note: Data after initiation of a medication that may modulate the disease course of CRSwNP are not summarized.

Note: Analysis performed using a repeated measures model on log(e) transformed dependent variable with covariates of treatment group, log(e) baseline, region, previous surgery for Nasal Polyps, visit, visit by log(e) baseline and visit by treatment group.

**Figure 35: Line plot of adjusted geometric means (and 95% CIs) of ratio to blood eosinophil count data (GI/L), FAS population, ANCHOR-2 study**




Note: The values of 0 GI/L are imputed with a value of 0.005 GI/L prior to log(e) transformation.

Note: All PD data while on-treatment are included in the analysis.

Note: Note: Data after initiation of a medication that may modulate the disease course of CRSwNP are not summarized.

Note: Analysis performed using a repeated measures model on log(e) transformed dependent variable with covariates of treatment group, loge(baseline), region, previous surgery for Nasal Polyps, visit, visit by log(e) baseline and visit by treatment group.

## 6.3.9. Clinical studies in special populations

**Table 34: Clinical studies in special populations**

| | Controlled Trials | Non-controlled trials |
|---|---|---|
| Renal impairment* patients (Subjects number /total number) | 3/528 | None |
| Hepatic impairment** patients (Subjects number /total number) | 0/528 | None |
| Paediatric patients <18 years (Subjects number /total number) | 0/528 | None |
| Age 65-74 (Subjects number /total number) | 78/528 | None |
| Age 75-84 (Subjects number /total number) | 21/528 | None |

| | | |
|---|---|---|
| Age 85+<br>(Subjects number /total number) | 1/528 | None |
| Other<br>(Subjects number /total number) | NA | NA |

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition).
** Hepatic impairment is defined as having Child-Pugh score B or C.
Note: Total number of participants includes participants both in the placebo and depemokimab groups.

## 6.3.10. Analysis performed across trials (pooled analyses and meta-analysis)

**Pooled analyses**

Treatment goals for chronic rhinosinusitis with nasal polyps (CRSwNP) include the reduction of systemic corticosteroids (CS) use and avoidance of NP-surgery.
These efficacy outcomes occur with relatively low incidence. Also, the number of participants with partially controlled or not well-controlled asthma was anticipated to be low in each of the 2 studies.

Analyses of efficacy endpoints related to NP-surgery, systemic CS or other disease modulating medications, and asthma were pre-specified to be included as *secondary outcomes* to be performed on the pooled data from the ANCHOR-1 and ANCHOR-2 studies.

The pooled study included a total of 3 key secondary endpoints related to CRSwNP, and a 4$^{th}$ secondary endpoint relating to asthma control. The randomised population included a total of 275 patients randomised to depemokimab and 265 patients to placebo. The FAS included a total of 272 depemokimab treated patients and 256 placebo treated patients, as the patients with GCP deviations were excluded (Table 35).

**Table 35: Summary of study populations, ANCHOR-1, and ANCHOR-2**

| Population | ANCHOR-1 | | ANCHOR-2 | | Pooled analyses | |
|---|---|---|---|---|---|---|
| | Depemokimab n (%) | Placebo n (%) | Depemokimab n (%) | Placebo n (%) | Depemokimab n (%) | Placebo n (%) |
| **Randomized** | 143 (100) | 133(100) | 132 (100) | 132(100) | 275(100) | 265 (100) |
| **FAS**1,2 | 143 (100) | 128 (96) | 129 (98) | 128 (97) | 272(98.9) | 256 (96.6) |

1. Patients with confirmed GCP deviations in several studies involving a site management organization, refers to Participants (ANCHOR-1: placebo 4 participants and depemokimab: 0 participant; ANCHOR-2: placebo 4 participants and depemokimab: 3 participants. These patients were excluded from the FAS population.
2. In the placebo group, 1 participant in the placebo group entered the ANCHOR-1 study and was randomised but did not receive placebo. The participant was not included in the FAS population.

First key secondary estimand from the pooled analyses (Key pooled Sec-1): Pooled First key secondary outcome: Time to first NP surgery (actual or entry on waiting list) or disease- modulating medication for CRSW NP up to 52 weeks

In both ANCHOR studies, the proportion of participants-who- required- NP-surgery-(defined-as- actual surgery-or-entry- on-a-waiting-list-for-surgery)-or-disease-modulating- medication-for-CRSwNP- by-

Week 52, was lower in the depemokimab group (n=44, 16%) compared with the placebo group (n=56, 22%).

Although there was differentiation between curves in the Kaplan-Meier plot, the difference between treatment groups over the 52 Week period was not statistically significant (HR 0.735 95% CI 0.495, 1.092), p = 0.128 (Figure 36).

**Table 36: Summary of pooled secondary endpoints results. Analysis of time to first NP surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP up to Week 52, FAS population, secondary estimand, ANCHOR-1 and ANCHOR-2 studies and pooled analysis**

| | ANCHOR-1 | | ANCHOR-2 | | Pooled | |
|---|---|---|---|---|---|---|
| | Depemokimab 100 mg SC (N=143) | Placebo (N=128) | Depemokimab 100 mg SC (N=129) | Placebo (N=128) | Depemokimab 100 mg SC (N=272) | Placebo (N=256) |
| **Surgery** | | | | | | |
| **Time to first NP- surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP up to Week 52 – pooled secondary endpoint[b]** | | | | | | |
| n | 143 | 128 | 129 | 128 | 272 | 256 |
| Number (%) of participants with endpoint event | 23 (16) | 28 (22) | 21 (16) | 28 (22) | 44 (16) | 56 (22) |
| NP surgery (actual) | 0 | 1 (<1) | 2 (2) | 2 (2) | 2 (<1) | 3 (1) |
| Entry on waiting list | 16 (11) | 24 (19) | 18 (14) | 23 (18) | 34 (13) | 47 (18) |
| Initiation of disease-modulating medication | 7 (5) | 4 (3) | 1 (<1) | 4 (3) | 8 (3) | 8 (3) |
| Adjusted probability of event, % (95% CI) | 14.5 (9.6, 21.5) | 20.7 (14.6, 29.0) | 15.7 (10.4, 23.3) | 23.3 (16.7, 31.9) | 15.0 (11.3, 19.9) | 21.9 (17.2, 27.7) |
| Reduction in risk (95% CI) | 32% (-19%, 61%) | | 29% (-26%, 61%) | | 27% (-9%, 51%) | |
| Hazard ratio (95% CI) | 0.681 (0.390, 1.189) | | 0.707 (0.395, 1.264) | | 0.735 (0.495,1.092 | |
| p-value | 0.177 | | 0.243 | | 0.128 | |
| **Time to first I NP-surgery (actual) or disease-modulating medication for CRSwNP up to Week 52 – pooled secondary endpoint[b]** | | | | | | |
| N | 143 | 128 | 129 | 128 | 272 | 256 |
| Number (%) of participants with endpoint event | 18 (13) | 23 (18) | 15 (12) | 20 (16) | 33 (12) | 43 (17) |
| NP surgery | 11 (8) | 20 (16) | 14 (11) | 16 (13) | 25 (9) | 36 (14) |
| Initiation of disease-modulating medication | 8 (6) | 4 (3) | 1 (<1) | 4 (3) | 9 (3) | 8 (3) |

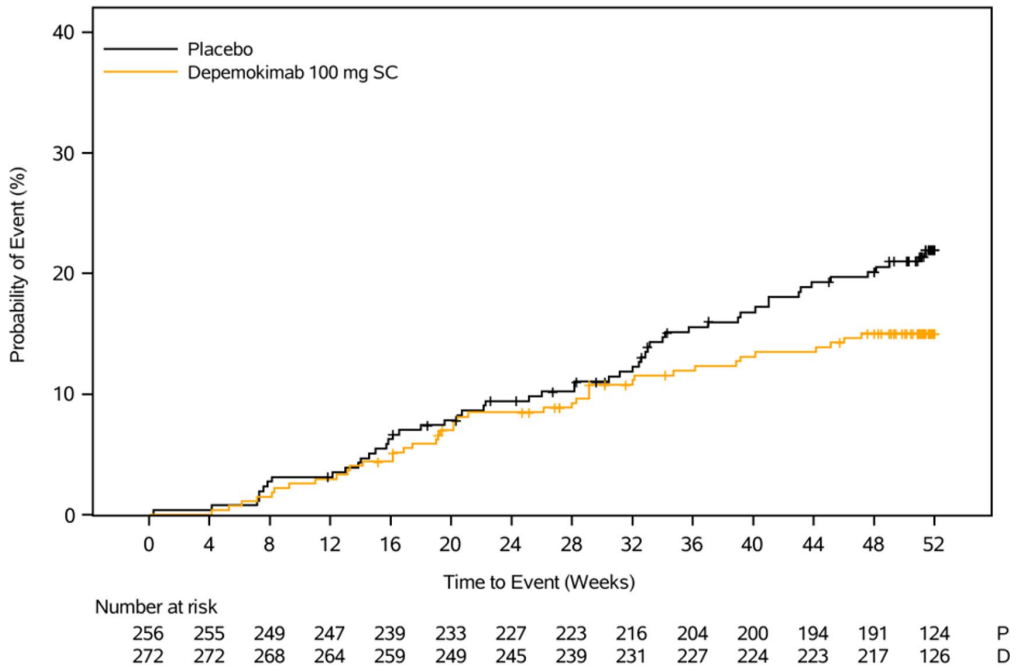
| | ANCHOR-1 | | ANCHOR-2 | | Pooled | |
|---|---|---|---|---|---|---|
| | **Depemokimab 100 mg SC (N=143)** | **Placebo (N=128)** | **Depemokimab 100 mg SC (N=129)** | **Placebo (N=128)** | **Depemokimab 100 mg SC (N=272)** | **Placebo (N=256)** |
| Adjusted probability of event, % (95% CI) | 12.5 (7.9, 19.3) | 16.7 (11.2, 24.4) | 11.8 (7.3, 18.9) | 16.8 (11.1, 24.9) | 12.2 (8.8, 16.8) | 16.7 (12.6, 22.0) |
| Reduction in risk (95% CI) | 34% (-23%, 65%) | | 30% (-39%, 65%) | | 29% (-12%, 55%) | |
| Hazard ratio (95% CI) | 0.661 (0.355, 1.232) | | 0.700 (0.352, 1.394) | | 0.713 (0.453, 1.124) | |
| p-value | 0.193 | | 0.311 | | 0.146 | |
| **Systemic CS use** | | | | | | |
| **Requirement for at least 1 course of systemic CS, disease-modulating medication for CRSwNP, or NP-surgery (actual) during the Week 52 treatment period – pooled secondary endpoint[c]** | | | | | | |
| n | 143 | 128 | 129 | 128 | 272 | 256 |
| Requiring systemic CS, n (%) | 38 (27) | 49 (38) | 34 (26) | 43 (34) | 72 (26) | 92 (36) |
| Took systemic SC | 26 (18) | 39 (30) | 28 (22) | 31 (24) | 54 (20) | 70 (27) |
| Surgery and no prior systemic CS use | 5 (3) | 7 (5) | 5 (4) | 9 (7) | 10 (4) | 16 (6) |
| Initiation of medication and no prior systemic CS use | 6 (4) | 3 (2) | 1 (<1) | 3 (2) | 7 (3) | 6 (2) |
| Surgery and initiation of medication with no prior systemic CS use | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| Not requiring systemic CS, n(%) | 105 (73) | 79 (62) | 95 (74) | 85 (66) | 200 (74) | 164 (64) |
| OR (95% CI); | 0.59 (0.35, 1.01) | | 0.59 (0.33, 1.05) | | 0.58 (0.40, 0.86) | |
| P value | p=0.055 | | p=0.073 | | p=0.006[a] | |

Abbreviations: ACQ-5 = asthma control questionnaire; CI = confidence interval; CRSwNP = chronic rhinosinusitis with nasal polyps; CS = systemic corticosteroids; LS = least squares; MMRM = mixed model repeated measures; NC = not conducted; NP = nasal polyps; OR = odds ratio; SC = subcutaneous; SE = standard error; VRS = visual response scale.

a. Nominal significance (i.e., $p<0.05$ without multiplicity control) was achieved. However, statistical significance was not achieved due to a break in the multiplicity-controlled testing hierarchy. b. Surgery endpoints analysed using a Cox Proportional Hazards Model with covariates of treatment, baseline total endoscopic NPS, baseline nasal obstruction score (VRS), log(e) baseline blood eosinophil count, region, study (removed for individual study analysis), and previous surgery for CRSwNP.

c. Systemic CS endpoint analysed using logistic regression with covariates of treatment, number of courses of systemic corticosteroids in 12 months prior to screening for Nasal Polyps (0, 1, >1), log(e) baseline blood eosinophil count, baseline total endoscopic nasal polyps score, baseline nasal obstruction score (VRS), region, study and previous surgery for nasal polyps. The covariate for study is removed for the individual-study analyses.

**Figure: 36 Kaplan-Meier plot of time to first nasal surgery (actual or entry on waiting list) or disease-modulating medication for CRSwNP up to Week 52 (Pooled ANCHOR-1+2)**

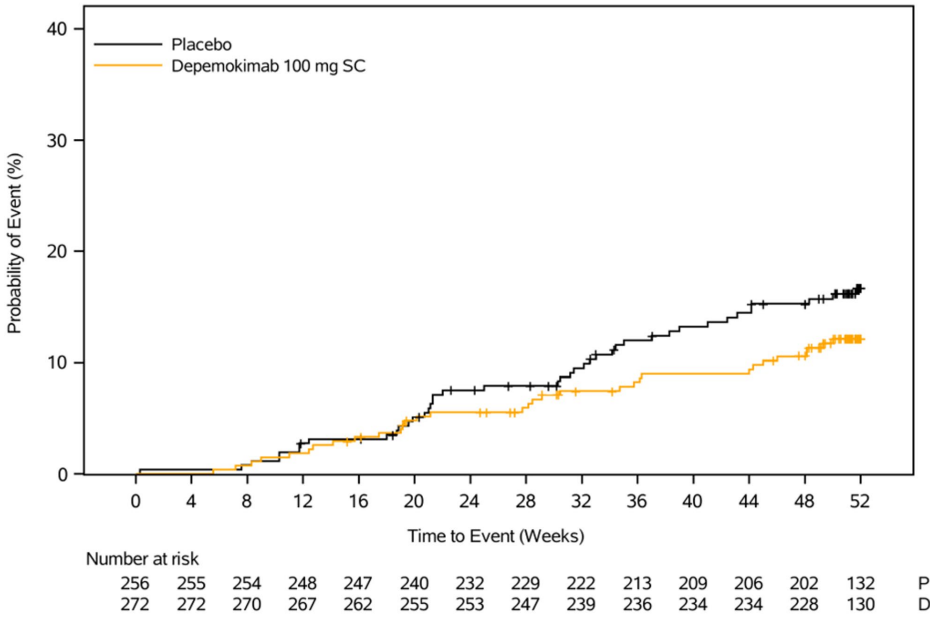



Abbreviations: CRSwNP = chronic rhinosinusitis with nasal polyps; D = Depemokimab; P = Placebo; SC = subcutaneous.
Note: Initiation of a medication that may modulate the disease course of CRSwNP was counted as requiring nasal surgery at the start of the medication.

Key pooled Second key secondary outcome: Time to first nasal surgery (actual) or disease modulating medication for CRSwNP up to 52 weeks

In addition, the proportion of participants-who-required- NP- surgery-(defined- as-actual-surgery) or disease-modulating-medication-for-CRSwNP-by-Week 52, was lower in the depemokimab group (n=33, 12%) compared with the placebo group (n= 43, 17%). This second key secondary outcome of the pooled analyses did also no reach statistical significance. (HR=0.713 (95% CI: 0.453, 1.124), p=0.146 not type one protected (Figure 37).

**Figure 37: Kaplan-Meier plot of time to first nasal surgery (actual) or disease-modulating medication for CRSwNP up to Week 52 (Pooled ANCHOR-1+2)**




Abbreviations: CRSwNP = chronic rhinosinusitis with nasal polyps; D = Depemokimab; P = Placebo; SC = subcutaneous.
Note: Initiation of a medication that may modulate the disease course of CRSwNP was counted as requiring nasal surgery at the start of the medication.

S3 pooled analyses Third key secondary outcome: Requiring at least 1 course of systemic CS or disease-modulating medication for CRSwNP or NP-surgery (actual) during the 52-week treatment period

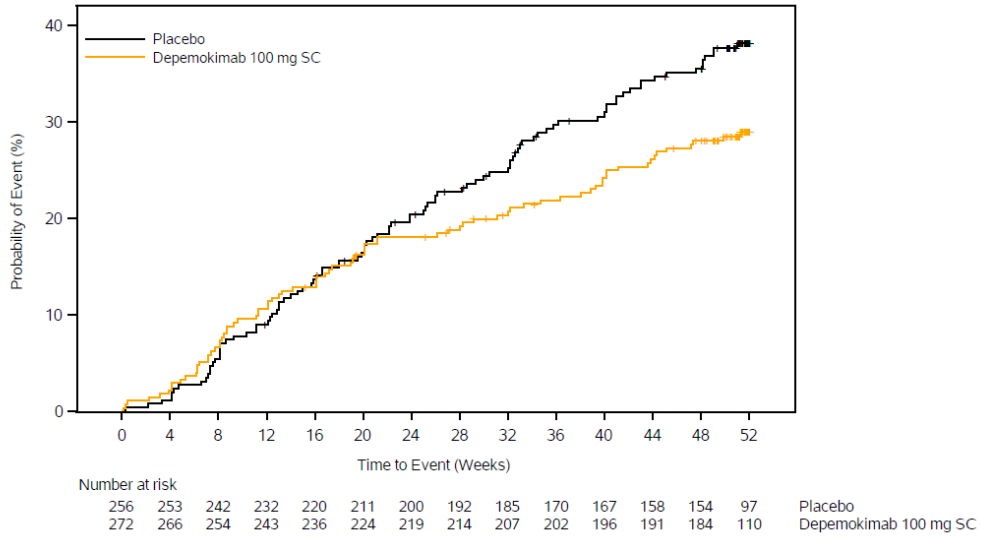
In the pooled analysis, the proportion of participants-requiring-at-least-1-course-of- systemic-CS- or disease-modulating-medication- for-CRSwNP-or-NP-surgery-(actual)-up-to Week 52 was lower in the depemokimab group (n=72 (26%) than in the placebo group (n= 92 (36%). The corresponding odds ratio was 0.58 (95% CI: 0.40, 0.86; p=0.006) which was nominally significant in favour of depemokimab.

Other outcomes pooled analyses

Other outcome: Time to first nasal surgery (actual or entry on waiting list) or course of steroids, or disease modulating medication for CRSwNP up to 52 weeks.

In the pooled analysis, the proportion of participants-who-required-NP-surgery-(actual-or-entry-on waiting-list)-or-course-of-systemic-CS-or-disease-modulating-medication- for- CRSwNP-by-Week- 52 was lower in the depemokimab group (n=81 (30%) than in the placebo group (n=96 (38%). The corresponding hazard ratio was 0.750 (95% CI: 0.557 to 1.009) p=0.058, see Figure 38 below).

**Figure 38: Kaplan-Meier plot of time to first NP-surgery (actual or entry on waiting list) or course of systemic CS or disease-modulating medication for CRSwNP, FAS population, pooled (ANCHOR-1 and ANCHOR-2)**




Note: Initiation of a medication which may modulate the disease course of CRSwNP was counted as requiring NP surgery or systemic CS at the start of the medication.

Systemic CS for CRSwNP

*Proportion of patients using systemic CS-for- CRSwNP*

In the ANCHOR-1 study, the proportion of subjected requiring a ≥ 1 course of systemic CS- for- CRSwNP up-to-week-52 was n=28 (20%) for depemokimab and n=40 (31%) for placebo, resulting in a treatment difference of 11 %; in the ANCHOR-2 these numbers were n=29 (22%) and n=32(25%) respectively, resulting in a treatment difference of 3%.

In the integrated analyse, the number of subjects requiring a ≥ 1 course of systemic- CS- for- CRSwNP up to week 52 was n=57 (21%) for depemokimab and n=72 (85%) for placebo i.e. a treatment difference of 7%.

Systemic course of CS regardless of indication

*Proportion of patients using systemic CS regardless indication*

In the ANCHOR-1 study the proportion of subjected requiring a ≥ 1 course- of- systemic CS- regardless indication- up- to- week 52 was n=42 (29%) for depemokimab and n=58 (45%%) for placebo, resulting in a treatment difference of 16 %; in the ANCHOR-2 these numbers were n=40 (31%) and n=47 (37%) respectively, resulting in a treatment difference of 6%.

In the integrated analyse, the number of subjects requiring a ≥ 1 course of systemic CS regardless indication was n=82 (30%) for depemokimab and n=105 (41%) for placebo i.e. a treatment difference of 11 %.

**Subgroup analyses (*post-hoc*)**

Subgroup analyses of the ANCHOR key pooled secondary endpoints have been provided according to baseline blood eosinophil count (BEC) (<300 or ≥300 cells/µL) and concomitant asthma (yes or no, see Figure 39,below .

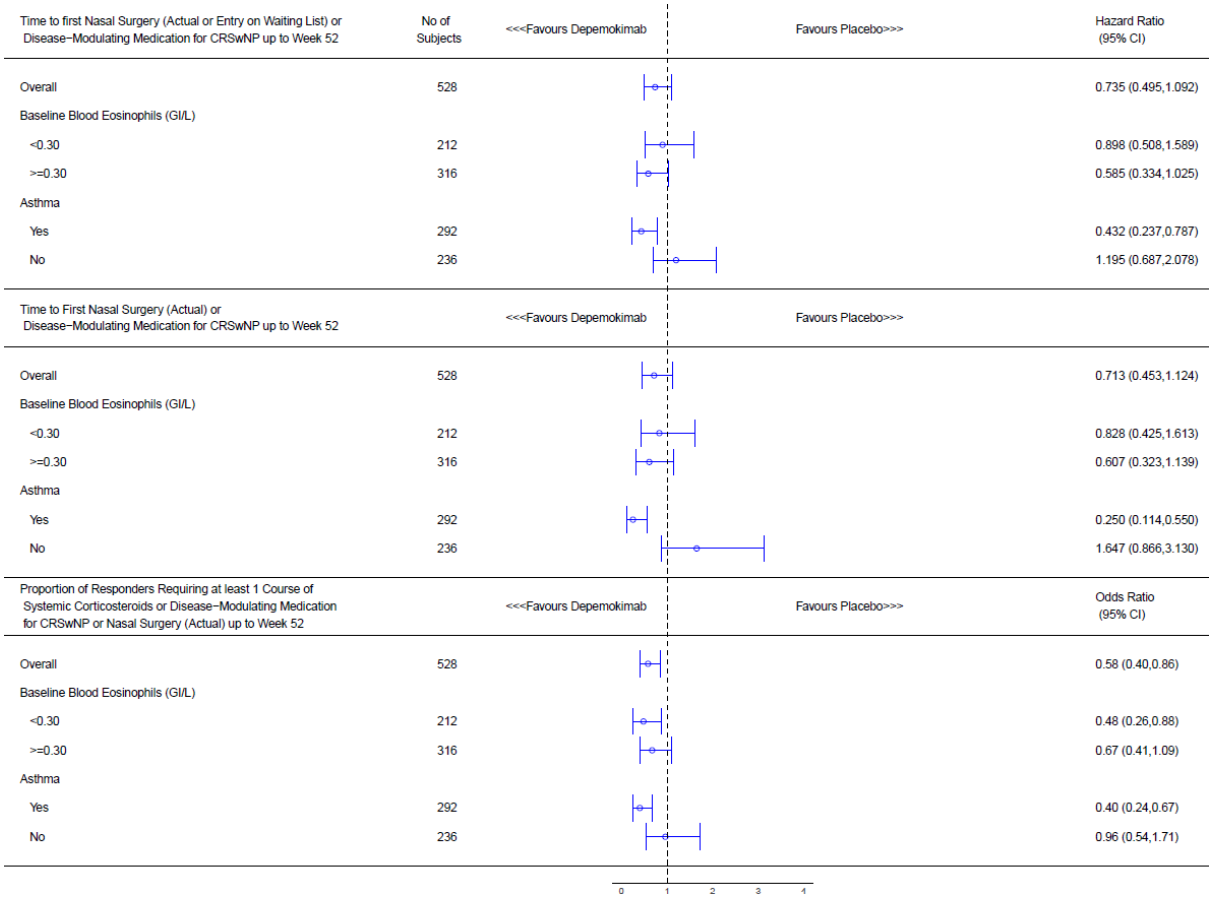
Hazard ratios in favour of depemokimab over placebo were shown for the two time to first surgery endpoints (i.e., 'actual + waitlist', and 'actual'):

- Regardless of baseline BEC.
- For participants with concomitant asthma.

An odds ratio in favour of depemokimab over placebo was shown for the endpoint of "participants requiring at least 1 course of SCS or disease-modulating medication for CRSwNP or nasal surgery (actual)":

- Regardless of baseline BEC.
- Regardless of concomitant asthma.

**Figure 39: Post−Hoc: Forest plot of the Pooled Secondary Endpoints of Surgery and SCS Use by Subgroup (Integrated FAS Population)**



## 6.3.11. Healthcare professional engagement

Please refer to 6.3 Healthcare professional engagement for input received from the European Respiratory Society.

## 6.3.12. Overall discussion and conclusions on clinical efficacy

### *6.3.12.1. Discussion*

The applicant requested the following **updated** indication to correctly reflect the included population, as per CHMP request:

*Exdensur is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control*.

Dose

No formal dose response study was performed in adult patients with chronic rhinosinusitis with nasal polyps (CRSwNP). The dose regimen was selected based on the FIH and additional modeling in the depemokimab program and mepolizumab program including the FIH study 205722. The investigated posology in the two pivotal phase 3 trials (ANCHOR-1 and ANCHOR-2) was 100 mg depemokimab subcutaneous (SC) every 26 weeks.

The PD data demonstrated that depemokimab 100 mg SC in adult patients with CRSwNP resulted in a marked reduction in blood eosinophils early in treatment. This reduction was sustained throughout both ANCHOR studies, although blood eosinophil count started to increase during the dosing interval from week 12-20 weeks post-dose onwards.

Design and conduct of the clinical studies

The two pivotal twin studies were well designed, multinational, replicate, randomised double blind placebo-controlled trials (ANCHOR-1 and ANCHOR-2) to show the superior efficacy of depemokimab 100 mg SC over placebo when used as add-on treatment to the standard of care according to local policy in patients with CRSwNP. Randomisation was stratified based on the occurrence of previous surgery for nasal polyps (NP) and country. These stratification criteria can be clarified by different manifestations of the severity of disease and regional variability in the treatment of CRSwNP. Despite the CHMP Scientific advise, patients were not stratified according to baseline eosinophil count but this did not raise any issue.

Study population - inclusion criteria

The inclusion criteria defined a study population of patients with severe symptomatic CRSwNP suffering from uncontrolled, severe disease despite standard of care including intranasal corticosteroids[4] (all countries, except Japan). Patients were required to have moderate to severe symptoms despite prior treatment with systemic corticosteroid (CS) within the past 2 years, and/or a documented history of prior surgery for CRSwNP or having contra-indications for these treatments, which is reflected in the requested updated indication. Patients were excluded if they were already on maintenance treatment targeting type 2 inflammation i.e. mepolizumab, dupilumab, systemic corticosteroids, etc.

[4] https://doi.org/10.1016/j.jaci.2020.11.013

The ANCHOR-1 and ANCHOR-2 study did not use a specific inclusion threshold for baseline eosinophil count, because of the absence of an association between CRSwNP and allergic rhinitis [5] , while no clear definition exits for type 2 inflammation in CRSwNP.

Control arm

The placebo control was considered scientifically useful and feasible (Scientific advice (EMA/SA/00000059022). The placebo control is acceptable for a troublesome, but not life-threatening disease, while other approved biologicals for CRSwNP had not been broadly adopted as SoC. The less frequent dose administration (6 monthly in stead of monthly/ 2 monthly) may result in a lower treatment burden and better treatment adherence.

Blinding

During the study, the blind was sufficiently ensured as the syringes had a similar appearance. In addition, prior to the unblinding of the study, the data on IL-5 levels and haematology data from post randomization samples was not reported to the site or the central study team.

Duration

The trial duration of 52 weeks could be considered acceptable to provide the long-term efficacy in term of symptoms improvement and nasal polyp improvement.

Endpoints

Summary of main efficacy results are presented in SmPC section 5.1.

The two co-primary endpoints refer to an *objective* endpoint measurement, i.e. reduction in NP score, and a *subjective* patient-derived outcome measure referring to an improvement of a cardinal symptom of CRSwNP, i.e. reduction in nasal obstruction score over week 49-52 using by means of the Verbal response system (VRS) using a 4 point Likert score (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms).

The use of the Nasal Polyp-score to show the reduction in NP size is consistent with other procedures. The use of a verbal rating system is suggested by the FDA guideline[6].

The co-primary endpoints using a combination of an objective and subjective endpoint is endorsed, as an improvement in both outcomes would substantiate a treatment effect. Furthermore, the severity of disease is primarily based on symptoms rather than polyp size.
The secondary outcome measures of the individual trials referred to different outcome domains including the score of symptoms associated with CRSwNP, QoL (SNOT 22 score), and CT scores. The use of various efficacy domains to demonstrate efficacy supports a treatment effect when improvements are observed in all domains favouring treatment,

Additional responder rates were provided for co-primary and secondary outcomes to contextualise the results. Response rates were provided for the proportion of patients that showed a response ≥ MCID and did not undergo NP-surgery and/or a started maintenance treatment with a disease modulating drug. Responder rates were provided for both trials and the integrated analyses.

[5] Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology 2020; 58 (Suppl S29):1-464.
[6] Chronic Rhinosinusitis with Nasal Polyps: Developing Drugs for Treatment | FDA

Key secondary outcome of the Pooled analyses

The first key secondary outcome of the pooled analyses refers to time-to-event outcomes for the need for additional treatment to provide sufficient symptomatic control, i.e. need for NP surgery, need for additional maintenance treatment targeting type 2 inflammation. These events occur with relative low incidence over the course of the 1-year study; therefore, the pooling of the replicate twin studies was anticipated and the sample size adjusted to increase the number of participants to evaluate these events.

The first and second pooled key secondary outcomes differ in the assessment of the time to surgery, as the first endpoint used the NP surgery actual or on waiting list, while for the second the time to actual NP surgery was taken.

The third pooled key secondary outcome refers to the proportion of patients that need additional treatments to provide adequate symptom control. In this definition, the need for additional treatment is extended with the number of patients that need a course of oral corticosteroids to provide symptom control.

Note that although these three secondary key outcomes refer to the need for intensification of therapy, they define the need for intensification of therapy differently. Therefore, they may refer to different parts of the study population.

The fourth pooled secondary endpoint refers to a large post-randomisation subgroup, i.e. patients with asthma. Although this refers to a large post-randomisation subgroup (55%), the results of this endpoint refer to a concomitant disease for which an additional indication is sought (see section 6.3.2 to section 6.3.8)

**Conduct of the studies**

Heterogeneous population

The included CRSwNP population can be considered heterogeneous. The trials recruited patients across 16 countries in different geographical regions with varying clinical practices (including the use of nasal surgery), and a different prevalence of CRSwNP with a type 2 inflammation. These studies also included Chinese patients, where more mixed endotypes predominate. Although this might improve the study recruitments, efficacy results might become compromised. A heterogeneous population improves the external validity of the trial but add to the variability of observed effects making it harder to demonstrate statistically significant differences.

Amendments

The study included various amendments made before database lock and unblinding of the trial results. The first two amendments had no large impact on trial design. Amendment 3-4 might have impacted hierarchy and amendment 5 affected the analyses of the primary and secondary estimands. With amendment 5, an additional composite, initiation of additional maintenance therapy to treat symptoms, was added to the key pooled secondary time-to-event outcome.

Amendment 5 was made following new published FDA guideline on the investigation of CRSwNP (July 2023)[7]. The amendment occurred late in the trial (26 June 2024, last patient last visit: August 2024). In principle, late changes in the analyses/estimands before the database lock are possible without affecting trial integrity if it can be assured that they are not data driven. As the request came from FDA and the

trials were double blind, this might be possible. However, as these events would likely occur more in the placebo arm, the late decision to handle these events with a composite strategy may have favoured the depemokimab arm, although still no statistical difference was demonstrated for the key secondary endpoint.

The key secondary endpoint Time-to nasal surgery was amended twice. Amendment 3 included the composite NP-surgery on waiting list and amendment 5 the need for additional maintenance treatments to treat type 2 inflammation. These amendments could make the trial more sensitive to show a difference with placebo. From a clinical point of view, these modifications can be supported as they refer to an insufficient treatment effect.

Statistical analyses

The applicant used a predefined hierarchical test structure to analyse the co-primary endpoints, key secondary and secondary outcomes. This approach is supported

Intercurrent events

Interpretation of all selected efficacy endpoints can be affected by intercurrent events like the initiation of treatments that may modulate the disease course of CRSwNP, courses of systemic steroid for any indication, antibiotics, surgery and treatment discontinuation.

The applicant used the intercurrent events (i) NP-surgery[8] and (ii) initiation of a disease modulating medication for CRSwNP as a composite strategy in the analyses of the primary and (key secondary outcome measures) i.e. the outcome scores will be assigned to the worst possible value following the start of these intercurrent events. This composite analysis provides a distinct answer to the question of the treatment effect of depemokimab vs placebo on top of standard care in the provided study population. *Post-hoc* analyses were provided were the intercurrent events were analysed according to the treatment policy.

According to the statistical analysis plan for the pooled analyses of time to nasal surgery (actual or waiting list) or disease modulating drugs, patients withdrawing before week 52 without nasal surgery (actual or waiting list) or disease modulation drugs, were to be censored. According to the patient flow, 15/143 (depemokimab) vs 13/132 (placebo) withdrew in ANCHOR-1 and 7/132 vs 17/132 in ANCHOR-2. In analysis considering these patients would have an event, the impact of these potentially informative censorings was shown to be minimal. Similarly, the analysis considering treatment discontinuation as an event for the endpoint systematic CS use, showed similar results as the original analysis for systematic CS use (which already considered disease modulating medication and nasal surgery as events).

**Results**

Study population

The study included uncontrolled, severe symptomatic patients with CRSwNP despite the use of inhaled corticosteroid and nasal surgery in the past 2 years. As expected, more males than females were included (69% vs 31%), with a mean (SD) age of 52 (13.26) years. Frequently reported co-morbidities were asthma (55%) and aspirin-related respiratory disease (16%).

[7] Chronic Rhinosinusitis With Nasal Polyps Developing Drugs for Treatment
[8] NP surgery refers tos any procedure involving instruments restulsin in incision or removal of tissue from the nasal cavity (E.g. polypectomy and endoscopic sinus sugergy

The baseline demographics and disease characteristics were comparable between the two twin studies with the exception of region. The ANCHOR-2 included predominantly European patients (65%), while the EU-population was in minority in the ANCHOR-1 (35%). The comparability in study design and included patient population supports pooling of the results.

Endpoints

*Individual studies – co-primary endpoints*

Both pivotal studies met their co-primary endpoints by demonstrating a statistically significant improvement showing the superiority over placebo in both an objective endpoint (i.e. improvement of nasal obstruction score) as well as subjective improvement i.e. "nasal obstruction" as measures by the VRS Likert scale, although the effect on the VRS nasal obstruction score was borderline statistically significant in the ANCHOR-1 study. Nevertheless, subgroup analyses and additional sensitivity analyses including jump to reference analyses supported the primary efficacy analyses. The subgroup analyses for the primary endpoints aligned with previous reported data showing the higher treatment responses in patients suffering from type 2 inflammation, i.e. baseline eosinophil count ≥ 300 cell/µL or with asthma, compared to patients with baseline eosinophil count <300 µL and without a concomitant diagnosis of asthma.

For both trials, the hierarchical testing was broken as the first secondary outcome failed to show a statistically significant improvement i.e. symptoms improvement in the runny nose. Nevertheless, both trials showed at least numerically improvements in all secondary outcome measures. These improvements reached nominal statistical significance when the results were pooled. However, as these endpoints were not type I protected, they will not be included in the SmPC, although the overall numerical favourable effect in all these outcomes support a treatment effect.

The co-primary and secondary endpoints were supported with responder analyses to contextualise the results. The co-primairy endpoint NP-score showed an absolute response rate of 43% vs 24%, which correlates to an odds ratio (OR) of 2.31, 95% CI: (1.58, 3.38), p-value < 0.001). This responser rate shows a 2.21 higher response, a response that can be considered clinically relevant.

For the Nasal Obstruction VRS Likert score, the reported response rates were 40% vs 29% resulting in an OR of 1.56 (5% CI 1.07, 157). This OR rate is somewhat lower compared with the NP-score, but patient-reported measures have a higher variability and therefore, this improvement can be considered clinically relevant; particularly when supported by relevant improvements in secondary outcome measures with improved responder rates over the various efficacy domains i.e. symptomatic improvement, QoL and CT score. Overall, these data show a clinically relevant treatment effect, which is supported with at least numerical improvement in the key secondary outcome measures from the pooled analyses.

Key secondary outcomes

The key secondary outcome of the pooled analyses measures showed numerical improvements. The lack of achieving statistical significance of these pooled secondary outcomes is partly explained by the lower number than expected surgeries (i.e. the number of lower than previously reported in the mepolizumab trials). Nevertheless, numerically a lower proportion of depemokimab patients received type 2 modifying treatments like a course of systemic corticosteroids for CRSwNP (21% vs 28%), a course of steroids regardless indication (30% vs 41%), or Nasal Polyp-surgery (10% vs 14%).

Overall, it can be considered that depemokimab demonstrated a clinically relevant improvement over placebo. The efficacy of depemokimab on objective measures of the total endoscopic NP score was clearly demonstrated. With respect to patient-reported outcomes, improvements over placebo are observed in various domains although the indirects study comparisons suggest that these primary and secondary measurements are somewhat smaller than observed in previous studies for other similar medicinal products. However, the lack of a head-to-head comparison preclude firm conclusions, considering amongst others the regional differences in the treatment and aetiology of CRSwNP, other symptoms score measurement, lower than expected number of nasal surgeries, various analyses etc.
In addition, the cross-study comparison is further impaired with the availability of biologicals targeting type 2 inflammation in some countries. This may have impacted the included study population, as it can assumed that many severely symptomatic patients already receive Type 2 inflammatory treatment while these patients might be less willing to participate in a placebo-controlled trial, with the risk of being randomised to placebo. However, like in previous studies[9] [10], the largest effect was observed in patients harbouring more intense Type 2 inflammation. In this respect, a head-to head comparison with another biological targeting type 2 inflammation would have been more conclusive, although a relevant improvement over placebo has been demonstrated.

However, the low dosing frequency ie. twice annually, is a treatment benefit, as it is associated with a low treatment burden and may theoretically be associated with a better treatment adherence.

**Studies in special populations**

No data are available in adolescents with renal or hepatic impairment as these were excluded from participation in the ANCHOR studies. This is adequately addressed in the proposed SmPC text.

Elderly

Elderly subjects (aged ≥ 65) were included in the ANCHOR studies and comprised (n= 78/528, 15%). Results in elderly participants (≥65 years) were consistent with the primary analysis (favouring depemokimab).

### *6.3.12.2. Conclusions on the clinical efficacy*

Depemokimab is administer twice annually. Therefore, it has a low treatment burden with associated assumption of good treatment adherence.

Depemokimab showed a clinically relevant improvement in the co-primary endpoints over placebo. Furthermore, the integrated analyses of secondary outcomes showed nominal statistical improvement and responder rates in various efficacy domains. These results were supported with at least numerical reduction of need of treatment intensification (pooled key secondary outomes). Overall, a clinically relevant treatment effect of depemokimab over placebo has been demonstrated in adult patients with severe, symptomatic CRsWNP despite the SoC.

[9] Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2021; 9: 1141–53
[10] Bachert C, Han JK, Desrosiers MY, et al. Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: a randomized, placebo-controlled trial. J Allergy Clin Immunol 2022; 149: 1309–17.e12

## *6.4. Clinical safety*

Refer to the table of studies in section 6.3.2.

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

### 6.4.1. Safety data collection

The pivotal safety data of depemokimab is derived from a clinical development programme in adult and adolescent patients aged 12 years and older with asthma (SWIFT-1 and SWIFT-2 studies) and in adult patients with CRSwNP (ANCHOR-1 and ANCHOR-2 studies). In these 4 randomised, 52-week, placebo-controlled, multicentre studies, patients received either subcutaneous (SC) depemokimab or placebo once every 6 months. For details regarding study designs and baseline patient characteristics, please refer to the efficacy section of this report.

The replicate SWIFT studies were pooled to support the asthma indication (**SWIFT pool**), as were the replicate ANCHOR studies to support the CRSwNP indication (**ANCHOR pool**; Figure 40). Safety data were also evaluated from a larger pool of all 4 Phase 3 placebo-controlled studies with depemokimab in both the asthma and CRSwNP indications (the "**placebo-controlled pool**").

Supportive safety data is derived from 2 phase 3 clinical studies:

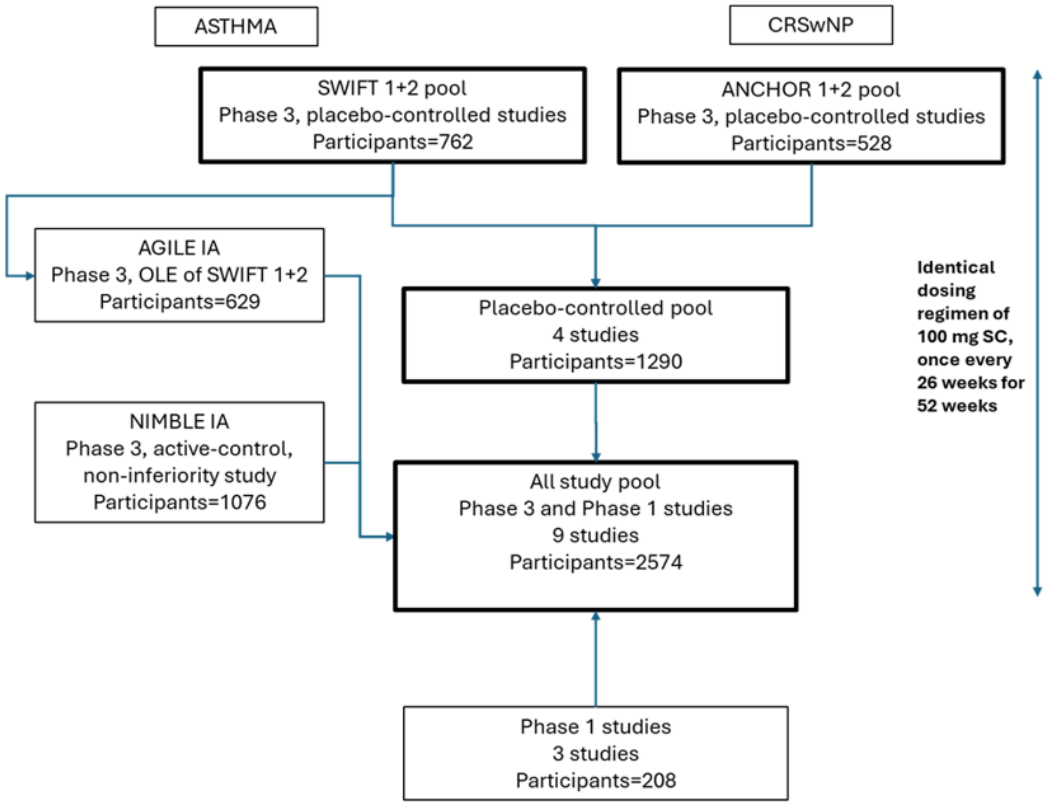
- an open-label 52-week extension study (**AGILE**) involving asthma patients (n = 629) who had previously completed either of the two asthma studies (SWIFT-1 or SWIFT-2), and
- an interim analysis of an ongoing 52-week active controlled study (**NIMBLE**) involving asthma patients aged 12 years and older who were previously treated with other anti-IL5/IL-5R biological medicines prior to study entry (n = 538). Patients received depemokimab 100 mg SC every 26 weeks or an active comparator according to the treatment prior to randomisation (mepolizumab every 4 weeks or benralizumab every 8 weeks). Both groups also received a placebo matching the other treatment group.

To further support analysis of rare events, integrated summaries of exposure, SAEs, and deaths were evaluated from a pool of all 9 clinical studies (the 6 Phase 3 studies described above and 3 dose finding

Phase 1 studies described in the clinical efficacy section of this report) in asthma, CRSwNP and healthy participants (the "**all study pool**").

Analyses of the safety data were performed on the safety population defined as all participants who received at least 1 dose of randomised study intervention. Due to concerns about data integrity and GCP deviations, data from two sites (56 patients) participating in the depemokimab studies were excluded from the primary analyses by the applicant.

**Figure 40: Safety data populations**




Notes: Participants in AGILE are not counted in the all study pool since they were previously enrolled in SWIFT. There were 4 participants in NIMBLE who only received placebo matching or unknown doses (depemokimab or mepolizumab/benralizumab). Of those, 2 were randomized to depemokimab and 2 were randomized to mepolizumab/benralizumab. These 4 participants are not included in the depemokimab or mepolizumab/benralizumab exposure summaries. But all 4 participants are included in the AE summary tables under their randomized treatment groups. Furthermore, 1 participant in SWIFT-2 was randomized to receive depemokimab but received placebo.

## 6.4.2. Patient exposure

### Asthma studies

SWIFT pool

In the SWIFT pool (n=762), a total of 501 participants received at least 1 dose of depemokimab 100 mg

SC plus SoC, and 261 participants received placebo plus SoC.

A total of 92% (n=464) participants in the depemokimab group and 92% (n=239) participants in the placebo group completed treatment and study and so received 2 doses of study intervention and were followed for 52 weeks.

The mean (SD) exposure was 11.7 (1.4) months for the depemokimab group and 11.8 (1.2) months for the placebo group.

AGILE – OLE asthma

At the data cut-off for the final analysis (9 June 2025), in the AGILE safety population (n=629), 419 participants had received depemokimab 100 mg SC plus SoC in the previous SWIFT study, and 210 had received placebo plus SoC. A total of 98% (n=409) participants in the previous depemokimab group and 96% (n=201) participants in the previous placebo group had completed treatment and study at the time of the final data cut-off.

During the AGILE study, the mean (SD) treatment exposure was 12.0 months in both the previous depemokimab group and previous placebo group.

The 409 participants who received depemokimab in the previous SWIFT study and who had completed AGILE received 4 doses of depemokimab 100 mg SC in total and were followed for 104 weeks.

NIMBLE – active control asthma

At the data cut-off for IA (15 July 2024), in the NIMBLE safety population (n=1076), 536 received depemokimab 100 mg SC plus SoC and 536 received mepolizumab/benralizumab plus SoC. Four participants (2 randomised to depemokimab 100 SC plus SoC and 2 randomised to mepolizumab/benralizumab plus SoC) only received placebo matching or unknown doses.

A total of 87% (n=468) participants in the depemokimab group have completed the treatment and study, received 2 doses of depemokimab 100 mg SC and were followed for 52 weeks. A total of 89% (n=479) participants in the mepolizumab/benralizumab group completed treatment and study and were followed for 52 weeks.

The total mean (SD) treatment exposure was 11.6 (1.7) months for the depemokimab group versus 11.8 (2.5) months for the mepolizumab/benralizumab group.

**ANCHOR pool – CRSwNP**

In the ANCHOR pool (n=528), 272 participants received at least 1 dose of depemokimab 100 mg SC plus SoC and 256 participants received placebo plus SoC. A total of 92% (n=249) participants in the depemokimab group and 87% (n=222) in the placebo group completed the treatment and study and so received 2 doses study intervention and were followed for 52 weeks.

The mean (SD) exposure was 11.6 (1.6) months for the depemokimab group and 11.6 (1.6) months for the placebo group.

**All study pool**

A total of 1715 participants were exposed to depemokimab across all clinical trials (all doses; Table 37). This included 1283 participants from the asthma indication and 272 from the CRSwNP indication.

A total of 1678 participants were exposed to a dose of 100 mg SC depemokimab. This included 1256 participants with asthma, 272 with CRSwNP, and 150 healthy volunteers.

**Table 37. Summary of subjects in safety population by indication and dose (all study pool)**

| | Placebo | Depemokimab | | | | | (Mepo 100/ Benra 30) mg SC[2] | All Doses[3] | Total |
|---|---|---|---|---|---|---|---|---|---|
| | | 2 mg SC | 10 mg SC | 30 mg SC | 100 mg SC[1] | 300 mg SC | | | |
| **All** | **529** | **6** | **6** | **9** | **1678** | **16** | **536** | **1715** | **2780** |
| **Asthma, n (%)** | **273 (52)** | **6 (100)** | **6 (100)** | **9 (100)** | **1256 (75)** | **6 (38)** | **536 (100)** | **1283 (75)** | **2092 (75)** |
| Severe asthma | 261 (49) | 0 | 0 | 0 | 1247 (74) | 0 | 536 (100) | 1247 (73) | 2044 (74) |
| Mild to moderate asthma | 12 (2) | 6 (100) | 6 (100) | 9 (100) | 9 (<1) | 6 (38) | 0 | 36 (2) | 48 (2) |
| **Chronic rhinitis with nasal polyps, n (%)** | **256 (48)** | **0** | **0** | **0** | **272 (16)** | **0** | **0** | **272 (16)** | **528 (19)** |
| **Healthy volunteers, n (%)** | **0** | **0** | **0** | **0** | **150 (9)** | **10 (63)** | **0** | **160 (9)** | **160 (6)** |

Benra=benralizumab; mepo=mepolizumab; SC=subcutaneous.
1. 2 participants randomized to depemokimab 100 mg SC in NIMBLE received only placebo matching or unknown doses and are not included in this table but are included in the safety population.
2. 2 participants randomized to (mepo 100/benra 30) mg SC in NIMBLE received only placebo matching or unknown doses and are not included in this table but are included in the safety population.
3. All doses includes unique subjects in all depemokimab treatment arm. Patients in AGILE were counted twice in total column when their SWIFT treatment was placebo.

At the time of the data cut-off, 349 participants have received 4 doses of depemokimab in total (2 doses in the SWIFT studies and a further 2 doses in AGILE; Table 38). Median exposure was 11.99 months (min, max 5.98, 25.89) for the depemokimab 100 mg SC group (n=1680).

**Table 38: Summary of exposure (therapeutic coverage) to depemokimab by dose (all study pool)**

| | Depemokimab 2 mg SC (N=6) | Depemokimab 10 mg SC (N=6) | Depemokimab 30 mg SC (N=9) | Depemokimab 100 mg SC (N=1680) | Depemokimab 300 mg SC (N=16) | Total (N=1717) |
|---|---|---|---|---|---|---|
| **Number of dose(s)** | | | | | | |
| n | 6 | 6 | 9 | 1678 | 16 | 1715 |
| 1, n (%) | 6 (100) | 6 (100) | 9 (100) | 295 (18) | 16 (100) | 332 (19) |
| 2, n (%) | 0 | 0 | 0 | 964 (57) | 0 | 964 (56) |
| 3, n (%) | 0 | 0 | 0 | 70 (4) | 0 | 70 (4) |
| 4, n (%) | 0 | 0 | 0 | 349 (21) | 0 | 349 (20) |
| **Exposure (months)** | | | | | | |
| n | 6 | 6 | 9 | 1678 | 16 | 1715 |
| Mean | 5.980 | 5.980 | 5.980 | 13.721 | 5.980 | 13.554 |
| SD | 0.0000 | 0.0000 | 0.0000 | 5.9277 | 0.0000 | 5.9703 |
| Median | 5.980 | 5.980 | 5.980 | 11.992 | 5.980 | 11.959 |
| Min | 5.98 | 5.98 | 5.98 | 5.98 | 5.98 | 5.98 |
| Max | 5.98 | 5.98 | 5.98 | 25.89 | 5.98 | 25.89 |
| **Total subject-years** | | | | | | |
| Exposure[1] | 2.99 | 2.99 | 4.48 | 1918.57 | 7.97 | 1937.01 |

SC=subcutaneous; SD=standard deviation.
1. Total subject-years exposure was calculated as duration of exposure (days) divided by 365.25.
Two participants from depemokimab arm only received placebo matching or unknown doses and are therefore not included. For AGILE patients who were previously on depemokimab, the duration of exposure is calculated between the dates of first dose in SWIFT and last dose in AGILE.

## 6.4.3. Adverse events

**Asthma studies**

SWIFT pool

*Overview of adverse events*

In the SWIFT pool, the proportion of participants with any AE was similar in both treatment groups (72% in the depemokimab group versus 76% in the placebo group; Table 39). The proportion of participants with an SAE was lower in the depemokimab group compared with the placebo group (7% versus 13%). There were no fatal SAEs.

**Table 39: Overview of all on-treatment adverse events (SWIFT pool)**

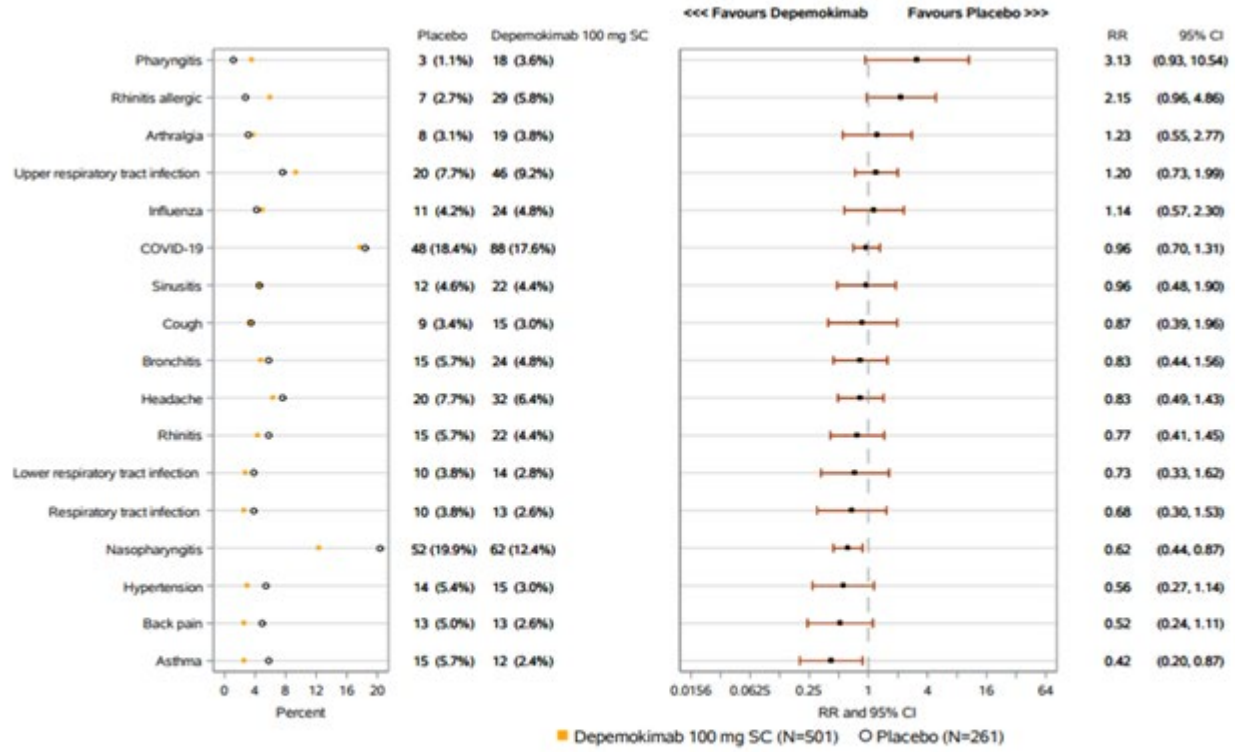
| | Placebo (N=261) | | Depemokimab (N=501) | |
|---|---|---|---|---|
| | n (%) | Rate | n (%) | Rate |
| **Any AE** | **198 (76)** | **1797** | **362 (72)** | **1539** |
| AEs related to study treatment | 6 (2) | 24 | 19 (4) | 41 |
| AEs leading to permanent discontinuation of study treatment or withdrawal from study | 3 (1) | 12 | 5 (<1) | 10 |
| AEs leading to dose interruption/delay | 0 | | 1 (<1) | 2 |
| **Any SAE** | **35 (13)** | **149** | **33 (7)** | **71** |
| SAEs related to study treatment | 0 | | 0 | |
| Fatal SAEs | 0 | | 0 | |
| Fatal SAEs related to study treatment | 0 | | 0 | |

AE=adverse event; SAE=serious adverse event.
Note: Rate is incidence rate per 1000 subject-years, calculated as: (total number of subjects with AE)/(total exposure duration/365.25)*1000. If an AE belonging to the category being summarized occurs during the exposure period, then that subject's exposure ends at the start of the first occurrence of the AE.
Note: n=Number of subjects.

*Common adverse events*

The most commonly reported AEs (those reported for ≥10% participants in either treatment group) were COVID 19 (reported for 17.6% participants in the depemokimab group versus 18.4% participants in the placebo group) and nasopharyngitis (12.4% versus 19.9%; Figure 41). There were no notable differences in the AE profile over time (0 to <4 weeks vs. 4 to <12 weeks vs. 12 to <26 weeks) for either the depemokimab group or placebo group.

**Figure 41: Plot of common (≥3%) adverse events and CMH-adjusted RR (SWIFT pool)**




AE=adverse event; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; RR=relative risk.
Note: A common AE is an AE where the incidence is greater than or equal to 3% in any of the treatment groups.

*Adverse events by severity*

The majority of participants in both arms had an AE with a maximum intensity of mild (~27%) or moderate (~42%).

AEs with a maximum intensity of severe were reported for 3% participants in the depemokimab group and 8% in the placebo group. The most frequently reported AEs with a maximum intensity of severe (those reported for ≥1% participants in any given treatment group) were pneumonia (<1% in the depemokimab group versus 1% in the placebo group) and asthma (<1% versus 3%).

*Drug-related adverse events*

In the SWIFT pool, the proportion of patients with an AE related to study treatment, as assessed by the investigator, was 4% in the depemokimab group and 2% in the placebo group (Table 40). No individual PT was reported for ≥1% participants.

**Table 40: Summary of on-treatment drug-related adverse events by SOC and PT (SWIFT pool)**

| | Placebo (N=261) | | Depemokimab (N=501) | |
|---|---|---|---|---|
| | n (%) | Rate | n (%) | Rate |
| **Any AE** | **6 (2)** | **24** | **19 (4)** | **41** |
| **General disorders and administration site conditions** | | | | |
| Any event | 2 (<1) | 8 | 5 (<1) | 10 |
| Injection site reaction | 0 | | 4 (<1) | 8 |
| Asthenia | 0 | | 1 (<1) | 2 |
| Chills | 1 (<1) | 4 | 0 | |
| Fatigue | 0 | | 1 (<1) | 2 |
| Influenza like illness | 0 | | 1 (<1) | 2 |
| Injection site pain | 1 (<1) | 4 | 0 | |
| Pyrexia | 1 (<1) | 4 | 0 | |
| **Nervous system disorders** | | | | |
| Any event | 1 (<1) | 4 | 5 (<1) | 10 |
| Headache | 1 (<1) | 4 | 4 (<1) | 8 |
| Anosmia | 0 | | 1 (<1) | 2 |
| Dysgeusia | 0 | | 1 (<1) | 2 |
| Migraine | 0 | | 1 (<1) | 2 |
| **Infections and infestations** | | | | |
| Any event | 2 (<1) | 8 | 1 (<1) | 2 |
| Bronchitis | 1 (<1) | 4 | 0 | |
| Herpes zoster | 1 (<1) | 4 | 0 | |
| Nasopharyngitis | 1 (<1) | 4 | 0 | |
| Oral candidiasis | 0 | | 1 (<1) | 2 |
| Upper respiratory tract infection | 1 (<1) | 4 | 0 | |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Any event | 0 | | 3 (<1) | 6 |
| Dry throat | 0 | | 1 (<1) | 2 |
| Epistaxis | 0 | | 1 (<1) | 2 |
| Oropharyngeal pain | 0 | | 1 (<1) | 2 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Any event | 0 | | 3 (<1) | 6 |
| Erythema | 0 | | 1 (<1) | 2 |
| Rash | 0 | | 1 (<1) | 2 |
| Urticaria | 0 | | 1 (<1) | 2 |

AGILE – OLE asthma

*Overview of adverse events*

An overview of the safety profile of depemokimab in AGILE at the time of the final analysis is presented in Table 41.

**Table 41: Overview of all on-treatment adverse events (AGILE final analysis)**

| | Depemokimab 100 mg SC | | | | | |
|---|---|---|---|---|---|---|
| | Previous Placebo (N=210) | | Previous Depemokimab 100 mg SC (N=419) | | Total (N=629) | |
| | n (%) | Rate | n (%) | Rate | n (%) | Rate |
| **Phase: on- and post-treatment** | | | | | | |
| Any AE, n (%) | 147 (70) | 1292 | 301 (72) | 1389 | 448 (71) | 1356 |
| AEs related to study treatment, n (%) | 5 (2) | 23 | 15 (4) | 35 | 20 (3) | 31 |
| AEs leading to permanent discontinuation of study treatment or withdrawal from study, n (%) | 2 (<1) | 9 | 2 (<1) | 5 | 4 (<1) | 6 |
| AEs leading to dose interruption/delay, n (%) | 1 (<1) | 5 | 2 (<1) | 5 | 3 (<1) | 5 |
| Any SAE, n (%) | 21 (10) | 100 | 38 (9) | 90 | 59 (9) | 94 |
| SAEs related to study treatment, n (%) | 0 | | 0 | | 0 | |
| Fatal SAEs, n (%) | 0 | | 0 | | 0 | |
| Fatal SAEs related to study treatment, n (%) | 0 | | 0 | | 0 | |

Note: Rate is incidence rate per 1000 subject-years, calculated as: (Total number of participants with AE)/(Total exposure duration/365.25)*1000. If an AE belonging to the category being summarized occurs during the exposure period, then that participant's exposure ends at the start of the first occurrence of the AE.
Note: n=Number of participants.

*Common adverse events*

The proportion of participants with any AE was similar in both treatment groups (~70%;Table 42). The most common AEs (those reported for ≥10% of either treatment group) were nasopharyngitis (14% in the previous depemokimab group vs. 10% in the previous placebo group) and upper respiratory tract infection (11% vs. 12%, respectively).

**Table 42: Summary of common (⩾3%) on-treatment adverse events by overall frequency (CMH-adjusted) (AGILE final analysis)**

| | Depemokimab 100 mg SC | | | | | |
|---|---|---|---|---|---|---|
| | Previous Placebo (N=210) | | Previous Depemokimab 100 mg SC (N=419) | | Total (N=629) | |
| Preferred Term | n (%) | Rate | n (%) | Rate | n (%) | Rate |
| Any event, n (%) | 146 (70) | 1344 | 297 (71) | 1430 | 443 (70) | 1400 |
| Nasopharyngitis, n (%) | 21 (10) | 110 | 58 (14) | 151 | 79 (13) | 138 |
| Upper respiratory tract infection, n (%) | 25 (12) | 132 | 45 (11) | 117 | 70 (11) | 122 |
| COVID-19, n (%) | 16 (8) | 82 | 28 (7) | 71 | 44 (7) | 74 |
| Bronchitis, n (%) | 7 (3) | 35 | 23 (5) | 58 | 30 (5) | 50 |
| Headache, n (%) | 7 (3) | 35 | 18 (4) | 45 | 25 (4) | 42 |
| Pharyngitis, n (%) | 8 (4) | 40 | 15 (4) | 37 | 23 (4) | 38 |
| Rhinitis, n (%) | 8 (4) | 40 | 13 (3) | 32 | 21 (3) | 35 |
| Lower respiratory tract infection, n (%) | 6 (3) | 30 | 14 (3) | 35 | 20 (3) | 33 |
| Pneumonia, n (%) | 5 (2) | 25 | 14 (3) | 35 | 19 (3) | 32 |
| Respiratory tract infection, n (%) | 3 (1) | 15 | 16 (4) | 40 | 19 (3) | 31 |
| Influenza, n (%) | 7 (3) | 35 | 9 (2) | 22 | 16 (3) | 26 |

*Adverse events by severity*

The majority of participants had an AE with a maximum intensity of mild or moderate (24% and 40% for the previous depemokimab group, versus 27% and 35% for the previous placebo group, respectively). AEs with a maximum intensity of severe were reported for 6% participants in the previous depemokimab

group versus 8% participants in the previous placebo group. Overall, severe AEs reported in more than 1 participant included pneumonia (5 participants (,1%)), asthma (5 participants (<1%)), atrial fibrillation (2 participants (<1%)), bronchitis (2 participants (<1%)), fall (2 participants (<1%)), head injury (2 participants (<1%)), and intervertebral disc protrusion (2 participants (<1%)). The remainder of the severe AEs were reported in single participants.

*Drug-related adverse events*

The overall proportion of participants with an AE related to study treatment, as assessed by the investigator, was 4% for the previous depemokimab group and 2% for the previous placebo group. The AEs assessed by the investigator as related to study treatment that were reported for >1 participant in either the previous depemokimab and previous placebo groups were headache, ALT increased, AST increased, injection site reaction and nausea. No individual PT was reported for ≥1% participants.

NIMBLE – active control asthma

*Overview of adverse events*

An overview of the safety profile of depemokimab in NIMBLE at the time of the IA is presented in Table 43.

**Table 43: Overview of all on-treatment adverse events (NIMBLE IA)**

| | Depemokimab (N=538) | | Mepo/Benra (N=538) | |
|---|---|---|---|---|
| Phase: On-treatment | n (%) | Rate | n (%) | Rate |
| Any AE | 448 (83) | 2310 | 435 (81) | 2101 |
| AEs related to study treatment | 47 (9) | 98 | 43 (8) | 87 |
| AEs leading to permanent discontinuation of study treatment or withdrawal from study | 7 (1) | 14 | 12 (2) | 23 |
| AEs leading to dose interruption/delay | 8 (1) | 16 | 15 (3) | 29 |
| Any SAE | 46 (9) | 94 | 43 (8) | 85 |
| SAEs related to study treatment | 0 | | 2 (<1) | 4 |
| Fatal SAEs | 0 | | 0 | |
| Fatal SAEs related to study treatment | 0 | | 0 | |

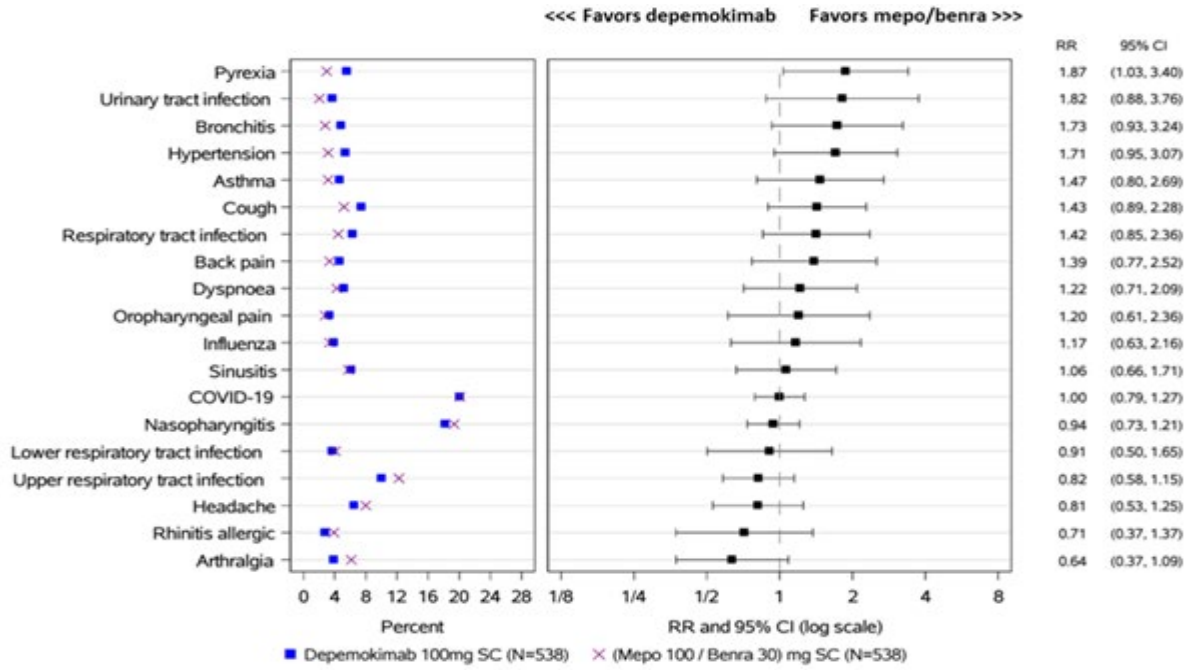
AE=adverse event; benra=benralizumab; IA=interim analysis; mepo=mepolizumab.
Note: Rate is event rate per 1000 subject-years, calculated as: (total number of subjects with AE)/(total exposure duration/365.25)*1000. If an AE belonging to the category being summarized occurs during the exposure period then that subject's exposure ends at the start of the first occurrence of the AE.

*Common adverse events*

The proportion of participants with any AE was similar between groups (83% in the depemokimab group versus 81% in the mepolizumab/benralizumab group).

The most common AEs (those reported for ≥10% of either treatment group) were (by PT) COVID-19 (20% in both groups), nasopharyngitis (18% in the depemokimab group versus 19% in the mepolizumab/benralizumab group), and upper respiratory tract infection (10% vs. 12%). The CMH-adjusted RR between depemokimab and mepolizumab/benralizumab for each common AE is displayed in Figure 42. There were no notable differences in the AE profile over time (0 to <4 weeks vs. 4 to <12 weeks vs. 12 to <26 weeks) for either the depemokimab group or placebo group.

**Figure 42. Plot of common (≥3%) adverse events and CMH-adjusted RR (NIMBLE IA)**




AE=adverse event; benra=benralizumab; CI=confidence interval; IA=interim analysis; mepo=mepolizumab; RR=relative risk.
Note: A common AE is an AE where the incidence is greater than or equal to 3% in any of the treatment groups.

*Adverse events by severity*

The majority of participants had an AE with a maximum intensity of mild or moderate (34% and 42% in the depemokimab group and 36% and 38% in the mepolizumab/benralizumab group, respectively). AEs with a maximum intensity of severe were reported for 7% participants in both treatment groups. The only AE with a maximum intensity of severe reported for ≥1% participants in either treatment group was asthma (2% versus 1%)

*Drug-related adverse events*

The proportion of participants with an AE assessed by the investigator as related to study treatment was similar between groups (9% of participants in the depemokimab group and 8% of participants in the mepolizumab/benralizumab group). The only AE assessed by the investigator as related to study treatment that was reported for ≥1% participants was injection site reaction (2% in both treatment groups).

**ANCHOR pool – CRSwNP**

*Overview of adverse events*

In the ANCHOR pool, the proportion of participants with any AE was similar in both treatment groups (75% in the depemokimab group and 79% in the placebo group; Table 44).

The proportion of participants with an SAE was 3% in the depemokimab group and 6% in the placebo group. None were assessed by the investigator as related to study treatment, and there were no fatal SAEs.

**Table 44. Overview of all on-treatment adverse events (ANCHOR pool)**

| | Placebo (N=256) | | Depemokimab (N=272) | |
|---|---|---|---|---|
| | n (%) | Rate | n (%) | Rate |
| **Any AE** | **203 (79)** | **2064** | **203 (75)** | **1690** |
| AEs related to study treatment | 9 (4) | 38 | 17 (6) | 68 |
| AEs leading to permanent discontinuation of study treatment or withdrawal from study | 3 (1) | 12 | 0 | |
| AEs leading to dose interruption/delay | 1 (<1) | 4 | 0 | |
| **Any SAE** | **16 (6)** | **68** | **9 (3)** | **35** |
| SAEs related to study treatment | 0 | | 0 | |
| Fatal SAEs | 0 | | 0 | |
| Fatal SAEs related to study treatment | 0 | | 0 | |

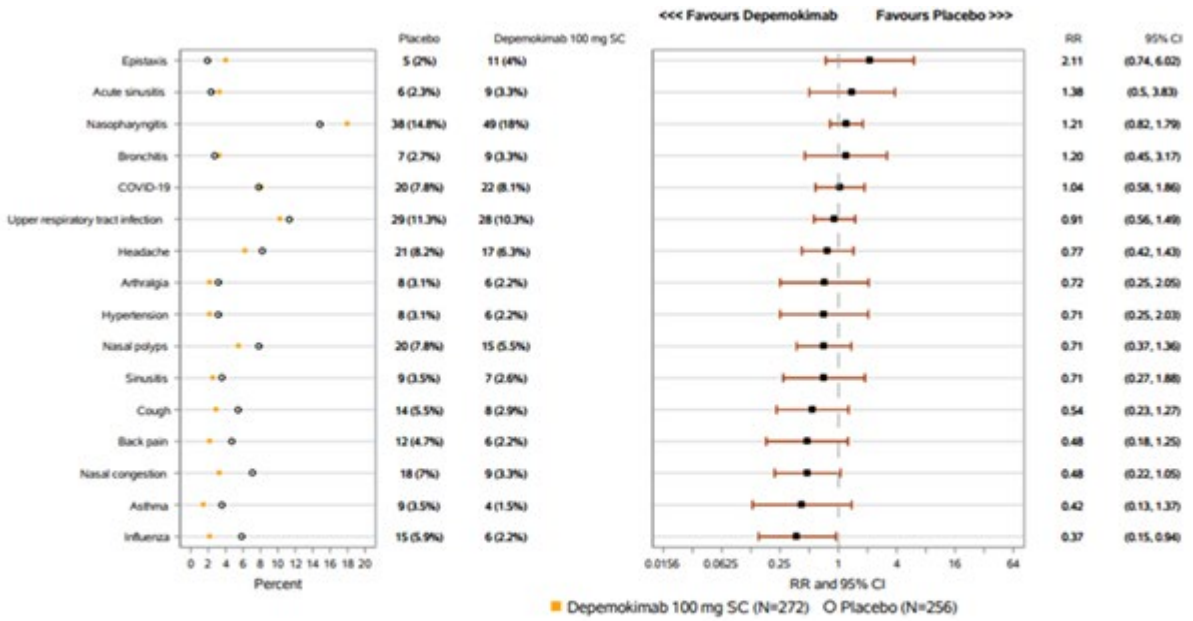
AE=adverse event; SAE=serious adverse event.
Note: Rate is incidence rate per 1000 subject-years, calculated as: (total number of subjects with AE)/(total exposure duration/365.25)*1000. If an AE belonging to the category being summarized occurs during the exposure period, then that subject's exposure ends at the start of the first occurrence of the AE.
Note: n=Number of subjects.

*Common adverse events*

The most commonly reported AEs (those reported for ≥10% participants in either treatment group) were nasopharyngitis (reported for 18.0% participants in the depemokimab group vs. 14.8% participants in the placebo group) and upper respiratory tract infection (10.3% versus 11.3%).

Overall, the proportion of participants with common AEs was similar between the treatment groups with the exception of influenza; this was more common in the placebo group than the depemokimab group. The CMH-adjusted RR between depemokimab and placebo for each common AE is displayed in Figure 43.

**Figure 43: Plot of common (≥3%) on-treatment AEs and CMH-adjusted RR (ANCHOR pool)**




AE=adverse event; CMH=Cochran-Mantel-Haenszel; RR=relative risk.
Note: A common AE is an AE where the incidence is greater than or equal to 3% in any of the treatment groups. RR is non-estimable when there are zero events in one treatment group.

*Adverse events by severity*

The majority of participants had an AE with a maximum intensity of mild or moderate (33% and 38% in the depemokimab group and 36% and 34% in the placebo group, respectively).

AEs with a maximum intensity of severe were reported for 4% participants in the depemokimab group and 9% in the placebo group. The most frequently reported AE with a maximum intensity of severe (the only AE reported for ≥1% participants in any treatment group) was nasal polyps (<1% in the depemokimab group versus 2% in the placebo group).

*Drug-related adverse events*

The proportion of participants with an AE assessed by the investigator as related to study treatment was 6% in the depemokimab group and 4% in the placebo group (Table 45). No individual PT was reported for ≥1% of participants.

**Table 45: Summary of on-treatment drug related adverse events by SOC and PT (ANCHOR pool)**

| | Placebo (N=256) | | Depemokimab (N=272) | |
|---|---|---|---|---|
| | n (%) | Rate | n (%) | Rate |
| **Any AE** | **9 (4)** | **38** | **17 (6)** | **68** |
| **General disorders and administration site conditions** | | | | |
| Any event | 1 (<1) | 4 | 5 (<1) | 19 |
| Fatigue | 0 | | 2 (<1) | 8 |
| Administration site haematoma | 0 | | 1 (<1) | 4 |
| Administration site inflammation | 0 | | 1 (<1) | 4 |
| Injection site pain | 1 (<1) | 4 | 0 | |
| Injection site reaction | 0 | | 1 (<1) | 4 |
| Local reaction | 0 | | 1 (<1) | 4 |
| **Investigations** | | | | |
| Any event | 2 (<1) | 8 | 3 (1) | 12 |
| Alanine aminotransferase increased | 1 (<1) | 4 | 2 (<1) | 8 |
| Protein urine | 1 (<1) | 4 | 0 | |
| White blood cell count increased | 0 | | 1 (<1) | 4 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Any event | 0 | | 4 (1) | 16 |
| Eczema | 0 | | 1 (<1) | 4 |
| Fixed eruption | 0 | | 1 (<1) | 4 |
| Papule | 0 | | 1 (<1) | 4 |
| Pruritus | 0 | | 1 (<1) | 4 |
| Rash | 0 | | 1 (<1) | 4 |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Any event | 2 (<1) | 8 | 1 (<1) | 4 |
| Pain in extremity | 2 (<1) | 8 | 0 | |
| Myalgia | 0 | | 1 (<1) | 4 |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Any event | 2 (<1) | 8 | 1 (<1) | 4 |
| Cough | 1 (<1) | 4 | 0 | |
| Epistaxis | 1 (<1) | 4 | 0 | |
| Nasal congestion | 0 | | 1 (<1) | 4 |
| **Ear and labyrinth disorders** | | | | |
| Any event | 1 (<1) | 4 | 1 (<1) | 4 |
| Deafness | 1 (<1) | 4 | 0 | |
| Ear discomfort | 1 (<1) | 4 | 0 | |
| Ear pain | 0 | | 1 (<1) | 4 |

| | Placebo (N=256) | | Depemokimab (N=272) | |
|---|---|---|---|---|
| | n (%) | Rate | n (%) | Rate |
| **Infections and infestations** | | | | |
| Any event | 1 (<1) | 4 | 1 (<1) | 4 |
| Pneumonia | 0 | | 1 (<1) | 4 |
| Sinusitis | 1 (<1) | 4 | 0 | |
| **Cardiac disorders** | | | | |
| Any event | 1 (<1) | 4 | 0 | |
| Defect conduction intraventricular | 1 (<1) | 4 | 0 | |
| **Eye disorders** | | | | |
| Any event | 1 (<1) | 4 | 0 | |
| Erythema of eyelid | 1 (<1) | 4 | 0 | |
| Lacrimation increased | 1 (<1) | 4 | 0 | |
| **Gastrointestinal disorders** | | | | |
| Any event | 0 | | 1 (<1) | 4 |
| Abdominal pain lower | 0 | | 1 (<1) | 4 |
| **Metabolism and nutrition disorders** | | | | |
| Any event | 0 | | 1 (<1) | 4 |
| Abnormal loss of weight | 0 | | 1 (<1) | 4 |
| **Nervous system disorders** | | | | |
| Any event | 0 | | 1 (<1) | 4 |
| Headache | 0 | | 1 (<1) | 4 |

AE=adverse event; PT=preferred term; SOC=system organ class.
Note: Rate is incidence rate per 1000 subject-years, calculated as: (total number of subjects with AE)/(total exposure duration/365.25)*1000. If an AE belonging to the category being summarized occurs during the exposure period, then that subject's exposure ends at the start of the first occurrence of the AE.
Note: n=Number of subjects.

#### *6.4.3.1. Adverse drug reactions*

The totality of evidence was considered from the placebo-controlled pool and the all-study pool to evaluate the AE profile.

Identification of potential ADRs was performed using quantitative criteria to triage AEs from the placebo-controlled pool (a primary dataset) for further qualitative analyses. Safety data from AGILE IA, NIMBLE IA and Phase I studies were supplementary.

Medical judgement was used in determining if there was sufficient evidence of a causal association for AEs identified through quantitative analyses. The ADRs proposed for inclusion in the SmPC by the applicant are shown in Table 46.

**Table 46: Adverse reactions proposed for inclusion in SmPC by the applicant**

| System Organ Class | Adverse reactions | Frequency |
|---|---|---|
| Skin and subcutaneous tissue disorders | Pruritus | Common |
| General disorders and administration site conditions | Administration-related systemic reactions (non-allergic) | Common |
| | Local injection site reactions | Common |

## 6.4.4. *Adverse events* of special interest, serious adverse events and deaths, other significant events

***Allergic reactions (including anaphylaxis or other systemic reactions)***

**Asthma studies**

SWIFT pool

A summary of on-treatment SAEs and AESIs in the SWIFT pool is presented in Table 47. No patients were reported to have an AESI of allergic (Type I hypersensitivity) reaction or anaphylactic reaction, as assessed by the investigator.

Other systemic reactions were reported in 2% of patients in the depemokimab group vs. <1% in the placebo group. All the events reported by the investigator as other systemic reactions were non-serious and considered to be either mild or moderate in intensity. A total of 8 events/7 participants in the depemokimab group and 3/2 in the placebo group were assessed by the investigator as related to study treatment. One event in 1 patient (<1%) in the depemokimab group was reported as not recovered/ not resolved.

**Table 47: Summary of on-treatment SAEs and AESIs: incidence (CMH adjusted) RR and risk difference (SWIFT pool)**

| | Placebo (N=261) | Depemokimab (N=501) | CMH-adjusted Relative Risk (95% CI) | % Risk Difference (Exact 95% CI) |
|---|---|---|---|---|
| **Risks** | | | | |
| Serious adverse events, n (%) | 35 (13) | 33 (7) | 0.49 (0.31, 0.77) | -6.8 (-11.9, -1.6) |
| Allergic (type I hypersensitivity) reactions, n (%) | 0 | 0 | Non-est | 0 |
| Anaphylaxis, n (%) | 0 | 0 | Non-est | 0 |
| Other systemic reactions, n (%) | 2 (<1) | 8 (2) | 2.08 (0.44, 9.84) | 0.8 (-1.3, 2.5) |
| Type III hypersensitivity/vasculitis, n (%) | 0 | 0 | Non-est | 0 |
| Local injection site reactions, n (%) | 2 (<1) | 7 (1) | 1.82 (0.38, 8.71) | 0.6 (-1.5, 2.3) |

AESI=adverse event of special interest; CMH=Cochran-Mantel-Haenszel; non-est=non-estimated; RR=relative risk; SAE=serious adverse event.
Note: A RR of 1 = no difference in risk between treatments, <1 favors depemokimab and >1 favors placebo.
Note: A risk difference of 0 = no difference in risk between treatments, <0 favors depemokimab and >0 favors placebo.

AGILE – OLE asthma

One participant in the previous placebo group had an event considered by the investigator to represent an allergic (Type I hypersensitivity) reaction. The event (PT: pruritus) was considered as non-serious, mild in intensity and related to the study treatment by the investigator. No participants reported an AESI event of anaphylaxis.

Three participants in the previous depemokimab group were reported with AEs of (PT) drug hypersensitivity (verbatim text: Paxlovid allergy) and hypersensitivity (verbatim text: episode of increased allergy). The outcome of the events was reported as resolved in 2 participants, and as not recovered in 1 participant. All these eventswere considered as not related to the study treatment by the investigator, and not classified as AESIs.

Events considered by the investigator to represent other systemic reactions were reported for

4 participants (<1%) overall. The events (by PT headache [4 events], nausea, and malaise) were considered as non-serious and mild in intensity by the investigator. A total of 4 events in 3 participants were assessed by the investigator as related to study treatment.

NIMBLE – active control asthma

The proportion of participants who experienced events considered by the investigator to represent allergic (Type I hypersensitivity) reaction was <1% in the depemokimab group and none in the mepolizumab/benralizumab group.

One participant in the depemokimab group experienced an AESI of rash. This event was reported by the investigator as related to study treatment, and it corresponded to the administration of placebo.

Under the Immune system disorders SOC, the following AEs (by PT) were reported: drug hypersensitivity (3 participants in the depemokimab group versus 1 participant in the mepolizumab/benralizumab group) and hypersensitivity (3 versus 3, respectively). These events were not classified as AESIs and were assessed by the investigator as not related to study treatment. Among these, 1 event (PT: drug hypersensitivity) was reported as an SAE for a participant in the depemokimab group. The event was associated with nitrofurantoin and not related to study treatment.

There were no AESIs reported by the investigator as anaphylaxis. A total of 2 SAEs of anaphylaxis (PT: anaphylactic reaction) were reported for a participant in the depemokimab group. These events were not classified as AESIs and were assessed by the investigator as not related to study treatment. One of these anaphylactic reactions was related to peanut allergy and the other had unknown trigger.

The proportion of participants who experienced events considered by the investigator to represent other systemic reactions was 2% (n=11) in the depemokimab group and <1% (n=3) in the mepolizumab/benralizumab group. All the events representing other systemic reactions were considered as related to study treatment by the investigator and reported to be either mild or moderate in intensity. Other systemic reactions reported were related to active injection in 9 and 2 participants and were related to placebo injection in 4 and 2 participants in the depemokimab and mepolizumab/benralizumab groups respectively. Of the 9 participants who reported systemic reactions related to active injection in depemokimab group, 3 participants were treated with mepolizumab, and 6 participants were treated with benralizumab prior to this study.

The allergic or other systemic reactions reported for the active depemokimab arm were dizziness, headache, paraesthesia, fatigue, malaise, erythema, myalgia, hypoaesthesia oral, and paraesthesia oral (<1% each).

**ANCHOR pool – CRSwNP**

No participants were reported to have an event considered by the investigator to represent allergic (Type I hypersensitivity) reaction or anaphylactic reaction. One participant (<1%) in the depemokimab group had an event considered by the investigator to represent other systemic reaction (SOC skin and subcutaneous disorders – PT fixed eruption). This event was considered non-serious and moderate in intensity. It was assessed by the investigator to be related to study treatment. No events were reported in the placebo group.

***Type III hypersensitivity***

There were no events reported by the investigator as Type III hypersensitivity reaction in the clinical studies reflected in the SWIFT pool, AGILE and NIMBLE studies, ANCHOR pool or FTIH study.

***Local injection site reactions***

**Asthma studies**

SWIFT pool

Injection site reactions were reported for 7 (1%) patients in the depemokimab group and 2 (<1%) patients in the placebo group. All the events reported as local site injection site reactions were non-serious and considered to be mild in intensity by the investigator. All events were assessed by the investigator as related to study treatment.

AGILE – OLE asthma

Local injection site reactions were reported for 6 participants (<1%), all in the previous depemokimab group. The events representing local injection site reactions were considered as non-serious, mild in intensity and related to the study treatment by the investigator.

NIMBLE – active control asthma

The proportion of participants who experienced local injection site reactions was 3% in the depemokimab group and 4% in the mepolizumab/benralizumab group. All the events were considered as mild or moderate in intensity by the investigator. A total of 22 events/17 participants in the depemokimab group and 30/20 in the mepolizumab/benralizumab group were assessed by the investigator as related to study treatment. Local injection reactions were reported as related to active injection in 8 participants in the depemokimab group and 17 participants in the mepolizumab/benralizumab group, and to placebo in 9 and 3 participants, respectively.

**ANCHOR pool – CRSwNP**

The proportion of participants who experienced local injection site reactions was 1% in the depemokimab group and <1% in the placebo group. All the events were considered as non-serious and reported to be mild in intensity by the investigator apart from 1 event in the placebo group which was reported to be moderate in intensity. A total of 5 events/3 participants in the depemokimab group and 2 events/2 participants in the placebo group were assessed by the investigator as related to study treatment.

***QTc prolongation***

**Asthma studies**

SWIFT pool

At worst case post-baseline, the proportions of participants with potentially clinically significant changes in ECG from baseline were similar between treatment groups (3% in depemokimab group and 4% in placebo group). Mean changes from baseline in ECG parameters, including QTcF, were similar between treatment groups over time.

No participant met the protocol-specified QTcF stopping criteria (QTcF >500 msec or QTcF ≥530 msec for

participants with underlying bundle branch block and baseline QTcF 450 to 480 msec, uncorrected QT interval >600 msec or increase from baseline >60 msec). One participant in the depemokimab group in SWIFT-1 had an increase in QTcF >500 msec (513 msec; <60 msec above baseline) recorded at Week 28, with a baseline QTcF of 459 msec. Reportedly, the participant had a pacemaker with underlying bundle branch block and did not meet protocol defined QTc stopping criteria for participants with bundle branch block (≥530 msec).

No AEs of QT/QTc prolongation were reported. Two events of MedDRA SMQ Broad 'Torsade de pointes/QT prolongation' were reported in the depemokimab arm that were not considered related to treatment by the investigator: one non-serious event of syncope and one moderate event of seizure.

AGILE – OLE asthma

At worst case post-baseline, the proportion of participants with potentially clinically significant changes in ECG from baseline was 4% in previous depemokimab group and 2% in previous placebo group.

Mean changes from baseline in ECG parameters, including QTcF, were similar between the previous placebo group and the previous depemokimab group over time. One participant had QTcF interval increase to 512 msec (a change from baseline in QTcF >60 msec) at Week 52. During the study, the participant reported an SAE of atrial fibrillation. The event was of moderate intensity, was resolved, and was assessed by the investigator as not related to study treatment.

Analysis of AEs under Cardiac disorders SOC did not indicate an effect on QT interval. AEs under the MedDRA SMQ Broad "Torsade de pointes/QT Prolongation" were reported in 3 participants: 1 participant (<1%) in the previous placebo group and 2 participants (<1%) in the previous depemokimab group:

- The participant from the previous placebo group reported a non-serious AE of electrocardiogram QT prolonged (QTcF value 456 msec). The event was mild in intensity, was resolved, and was assessed by the investigator as not related to the study treatment.
- In the previous depemokimab group, one participant reported an SAE of seizure (moderate in intensity). Another participant reported a non-serious AE of syncope (mild in intensity). Both events were resolved and were assessed by the investigator as not related to the study treatment.

NIMBLE – active control asthma

At worst case post-baseline, the proportions of participants with potentially clinically significant changes in ECG from baseline were comparable between depemokimab (3%) and mepolizumab/benralizumab (2%) groups.

Mean changes from baseline in ECG parameters, including QTcF, were similar between the treatment groups over time.

No participants in the depemokimab group met the protocol-specified QTcF stopping criteria. One participant in the mepolizumab/benralizumab group had a maximum increase from baseline of >60 msec in QTcF to 404 msec on study Day 364 (exit visit).

Analysis of AEs under Cardiac disorders SOC did not indicate an effect on QT interval.

AEs under the MedDRA SMQ Broad "Torsade de pointes/QT Prolongation" were reported in 6 participants: 4 (<1%) participants in depemokimab group and 2 (<1%) participants in mepolizumab/benralizumab

group. None of the events were of apparent cardiac origin:

- Four participants in depemokimab group and 1 participant in mepolizumab/benralizumab group reported a non-serious AE of syncope. All events were mild or moderate in intensity, were resolved, and were considered by the investigator as not related to the study treatment.
- One participant in mepolizumab/benralizumab group reported a non-serious AE of 'loss of consciousness'. The event was mild in intensity, was resolved, and was considered by the investigator as not related to the study treatment.

ECG-related AEs under Investigations SOC were reported in 1 participant in depemokimab group (PT: electrocardiogram T wave inversion) and 2 participants in mepolizumab/benralizumab group (PT: electrocardiogram T wave abnormal and electrocardiogram abnormal).

**ANCHOR pool – CRSwNP**

In the ANCHOR pool, abnormal ECG findings were reported in similar proportions of participants in depemokimab group and placebo group at worst case post-baseline (29% versus 27%).

Mean changes from baseline in ECG parameters, including QTcF, were similar between treatment groups over time.

One participant in the placebo arm in ANCHOR-2 met the protocol-specified QTcF stopping criteria.

Analysis of AEs under Cardiac disorders SOC did not indicate a treatment effect on QT interval.

AEs under the MedDRA SMQ Broad "Torsade de pointes/QT Prolongation" were reported in 2 participants (<1%) in placebo group and none in depemokimab group.

**SAEs**

**Asthma studies**

SWIFT pool

The proportion of participants with an SAE was lower in the depemokimab group compared with the placebo group (7% versus 13%). Those affecting ≥2% participants in either treatment group were asthma (2% in the depemokimab group versus 4% in the placebo group) and pneumonia (<1% versus 2%).

None of the reported SAEs were considered as related to the study treatment by the investigator.

AGILE – OLE asthma

The proportion of participants with an SAE was similar in the previous depemokimab group and the previous placebo group (9%). The most common on-treatment SAE was asthma (1% in each arm). None of the reported SAEs were related to study treatment, as assessed by the investigator.

NIMBLE – active control asthma

The proportion of participants with an SAE was similar in both groups (9% versus 8%). The only SAE affecting ≥2% participants in either treatment group was asthma (2% in both treatment groups). None of the reported SAEs were considered as related to the study treatment by the investigator in the depemokimab group. Two participants in the mepolizumab/benralizumab group had on-treatment SAEs considered as related to study treatment by the investigator (preferred term (PT): thunderclap headache

and atrial fibrillation).

**ANCHOR pool – CRSwNP**

The proportion of participants with an SAE was lower in the depemokimab group compared with the placebo group (3% versus 6%). No individual PT was reported for ≥1% participants. The on- and post-treatment SAE profile was similar to the on-treatment SAE profile (4% versus 6%).

There were no SAEs assessed by the investigator as related to study treatment.

**All study pool**

In the all study pool, the proportion of participants with SAEs was similar in the depemokimab 100 mg SC group and the placebo group (8% versus 10%). The only SAE PTs that were reported for ≥1% participants were asthma (2% in both groups) and pneumonia (<1% in the depemokimab group versus 1% in the placebo group).

SAEs were also analysed by incidence rate per 1000 patient-years, calculated as total number of participants with AE/(total exposure duration/365.25)*1000. This was done on a dose basis. The most frequently reported SAEs by rate (those with a rate of ≥5 per 1000 patient-years) were asthma (16 in the depemokimab group versus 26 in the placebo group), pneumonia (6 versus 12), and COVID-19 (5 versus 4).

**Deaths**

**Asthma and CRSwNP studies**

There were no deaths in the SWIFT pool, AGILE OLE study or ANCHOR pool in CRSwNP.

AGILE – OLE asthma

No fatal SAEs were reported in the study. However, one participant in the previous placebo group reported with hypokalaemia, cerebral infarction, and COVID-19 during the post-treatment period died due to COVID-19 at a later date after withdrawal from the study. None of the SAEs were considered related to study treatment by the investigator.

NIMBLE – active control asthma

One participant in the mepolizumab/benralizumab group had an SAE (PT: metastatic malignant melanoma) with a fatal outcome reported during the post-treatment period. This event was assessed by the investigator as not related to the study treatment. No on-treatment fatal SAEs were reported in the study.

**All depemokimab studies**

There were no deaths reported in any of the completed studies with depemokimab. There were 3 deaths reported in ongoing studies, of which 1 within the all study pool in the requested target population (in the NIMBLE study, see details above).

In other depemokimab studies in different target populations, 2 deaths were reported:

- 1 death in DESTINY (PT: cardio-respiratory arrest), a study in HES.
- 1 death in OCEAN (PT: myocardial infarction), a study in EGPA.

Both events were considered not related to study treatment by the investigator. It is unknown which treatment these participants received as these studies are still ongoing and data remain blinded.

**Other significant events**

*Malignancy*

A similar incidence of events under Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC (hereafter malignancy AEs) was observed between placebo and depemokimab (both 1%) in a pool of 4 placebo-controlled studies, across two indications of asthma and CRSwNP. Of these, 7 were SAEs (<1% in each group). In asthma OLE study AGILE at interim analysis, malignancy AEs were reported by 6/629 (<1%) participants. Of these, 3 were SAEs (3/629 [<1%]). In asthma non-inferiority study (NIMBLE) at interim analysis, malignancy AEs were reported by 22 participants (7/538 [1%] in the mepolizumab/benralizumab group; 15/538 [3%] in the depemokimab group). Of these, 7 were considered SAEs (<1% in each group).

Across all studies, the types of malignancies reported varied and were those that are common in the general population and included breast cancer, adenocarcinoma of the colon, ovarian cancer, prostate cancer, bronchial carcinoma, thyroid cancer, basal cell carcinoma, squamous cell carcinoma and malignant melanoma. There were no participants that received depemokimab who reported a malignancy that resulted in a fatal outcome.

*Infections*

In the placebo-controlled pool of SWIFT and ANCHOR studies, infections were reported for 53% of patients in the depemokimab group and 56% of patients in the placebo group. There were no on-treatment AEs related to bacterial, viral, fungal or parasitic/nematode infections reported with ≥2% higher incidence in the depemokimab group compared to placebo.

*Safety observations related to medical device or device/drug combination*

There were no safety observations related to the medical device (pre-filled safety syringes assembled to a syringe safety device or autoinjector depending on study) or the device/drug combination. No AEs related to the use of the investigational medical device/the device/drug combination were reported.

## 6.4.5. Discontinuation due to adverse events

**Asthma studies**

SWIFT pool

In the SWIFT pool, the proportion of participants with an AE leading to permanent discontinuation of study treatment or withdrawal from study was <1% in the depemokimab group and 1% in the placebo group (Table 48). No event occurred in more than 2 participants. The only AE to be reported for >1 participant was ALT increased (2 participants, <1%) in the depemokimab group.

Of the AEs that led to permanent discontinuation of study treatment or withdrawal from study, 1 was assessed by the investigator as related to study treatment – this was the AE of herpes zoster in the placebo group.

**Table 48: Summary of on-treatment AEs leading to permanent discontinuation of study treatment or withdrawal from study by SOC and PT (SWIFT pool)**

| | Placebo (N=261) | | Depemokimab (N=501) | |
|---|---|---|---|---|
| | n (%) | Rate | n (%) | Rate |
| **Any AE** | **3 (1)** | **12** | **5 (<1)** | **10** |
| **Investigations** | | | | |
| Any event | 0 | | 2 (<1) | 4 |
| ALT increased | 0 | | 2 (<1) | 4 |
| ALT abnormal | 0 | | 1 (<1) | 2 |
| Blood bilirubin abnormal | 0 | | 1 (<1) | 2 |
| **Neoplasms benign, malignant, and unspecified (incl cysts and polyps)** | | | | |
| Any event | 1 (<1) | 4 | 1 (<1) | 2 |
| Breast cancer | 1 (<1) | 4 | 0 | |
| Metastases to peritoneum | 0 | | 1 (<1) | 2 |
| Ovarian cancer | 0 | | 1 (<1) | 2 |
| **Psychiatric disorders** | | | | |
| Any event | 1 (<1) | 4 | 1 (<1) | 2 |
| Depression | 1 (<1) | 4 | 0 | |
| Grief reaction | 0 | | 1 (<1) | 2 |
| **Infections and infestations** | | | | |
| Any event | 1 (<1) | 4 | 0 | |
| Herpes zoster | 1 (<1) | 4 | 0 | |
| **Nervous system disorders** | | | | |
| Any event | 0 | | 1 (<1) | 2 |
| Myasthenia gravis | 0 | | 1 (<1) | 2 |

AE=adverse event; PT=preferred term; SOC=system organ class.
Note: Rate is incidence rate per 1000 subject-years, calculated as: (Total number of subjects with AE)/(Total exposure

AGILE – OLE asthma

The proportion of participants with an AE leading to permanent discontinuation of study treatment or withdrawal from study was <1% in both previous treatment groups. No event occurred in more than 1 participant, and no AE that led to permanent discontinuation of study treatment or withdrawal from study was related to study treatment, as assessed by the investigator.

NIMBLE – active control asthma

The proportion of participants with an AE leading to permanent discontinuation of study treatment or withdrawal from study was low in both groups (1% versus 2%). AEs that led to permanent discontinuation of study treatment or withdrawal from the study assessed by the investigator as related to study treatment were rash, Bell's palsy, and cough in the depemokimab group, and ecchymosis, atrial fibrillation, oedema peripheral, and blood urea increased in the mepolizumab/benralizumab group.

**ANCHOR pool – CRSwNP**

The proportion of participants with an AE leading to permanent discontinuation of study treatment or withdrawal from study was none in the depemokimab and 1% in the placebo group (Table 49). None were considered related to treatment.

**Table 49: Summary of on-treatment AEs leading to permanent discontinuation of study treatment or withdrawal from study by SOC and PT (ANCHOR pool)**

| | Placebo (N=256) | | Depemokimab (N=272) | |
|---|---|---|---|---|
| | n (%) | Rate | n (%) | Rate |
| **Any AE** | **3 (1)** | **12** | **0** | **0** |
| **Immune system disorders** | | | | |
| Any event | 1 (<1) | 4 | 0 | |
| Drug hypersensitivity | 1 (<1) | 4 | 0 | |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Any event | 1 (<1) | 4 | 0 | |
| Asthma | 1 (<1) | 4 | 0 | |
| **Skin and subcutaneous tissue disorders** | | | | |
| Any event | 1 (<1) | 4 | 0 | |
| Urticaria | 1 (<1) | 4 | 0 | |

AE=adverse event; PT=preferred term; SOC=system organ class.
Note: Rate is incidence rate per 1000 subject-years, calculated as: (Total number of subjects with AE)/(Total exposure duration/365.25)*1000. If an AE belonging to the category being summarized occurs during the exposure period, then that subject's exposure ends at the start of the first occurrence of the AE.
Note: n=Number of subjects.

## 6.4.6. Safety in special populations

Data were analysed based on intrinsic factors age, sex, and race and extrinsic factor geographical region for both the asthma and CRSwNP indications. In addition, the safety profile of adolescent patients with asthma in the SWIFT 1+2 pool and the NIMBLE study was analysed. Data from AGILE were not analysed, which is acceptable.

The overall incidences of AEs across the depemokimab group and placebo group in the age, sex, race, and region sub-groups were generally similar with no apparent treatment related effects in the placebo-controlled studies in asthma and CRSwNP. The analyses at study level were generally consistent with those in the pooled analyses.

Safety in adolescents - asthma

Safety in adolescents 12-17 years old is supported by data from the SWIFT 1+2 pool and NIMBLE. In both the SWIFT 1+2 pool, and NIMBLE, the overall mean exposure in adolescents (12.0 months with depemokimab) was similar to that in adults over 18 years old (11.7 months). The safety profile of the adolescent participants in both studies is shown in Table 50 and Table 51.

**Table 50: Exposure and on-treatment AE data by SOC and PT for adolescent and adult patients (SWIFT pool)**

| | Adolescents (12-17 years old) | | Adults (over 18 years old) | |
|---|---|---|---|---|
| | Placebo (N=15) | Depemokimab (N=15) | Placebo (N=246) | Depemokimab (N=486) |
| **Exposure** | | | | |
| Mean (SD), months | 11.6 (1.6) | 12.0 (0.1) | 11.8 (1.2) | 11.7 (1.4) |
| **AEs n (%)** | | | | |
| Any event | 9 (60) | 11 (73) | 189 (77) | 351 (72) |
| **Infections and infestations** | | | | |
| Any event | 6 (40) | 10 (67) | 147 (60) | 270 (56) |
| COVID-19 | 0 | 1 (7) | 48 (20) | 87 (18) |
| Nasopharyngitis | 1 (7) | 2 (13) | 51 (21) | 60 (12) |
| Pharyngitis | 0 | 3 (20) | 3 (1) | 15 (3) |
| Upper respiratory tract infection | 1 (7) | 2 (13) | 19 (8) | 44 (9) |
| Gastroenteritis | 2 (13) | 0 | 2 (<1) | 2 (<1) |
| Influenza | 2 (13) | 0 | 9 (4) | 24 (5) |
| Pharyngitis streptococcal | 0 | 2 (13) | 0 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Any event | 6 (40) | 2 (13) | 38 (15) | 83 (17) |
| Asthma | 2 (13) | 0 | 13 (5) | 12 (2) |
| Cough | 2 (13) | 0 | 7 (3) | 15 (3) |
| Dyspnoea | 2 (13) | 0 | 2 (<1) | 12 (2) |
| **Investigations** | | | | |
| Any event | 4 (27) | 1 (7) | 9 (4) | 20 (4) |
| Weight increased | 2 (13) | 0 | 0 | 1 (<1) |
| **Nervous system disorders** | | | | |
| Any event | 4 (27) | 1 (7) | 27 (11) | 62 (13) |
| Headache | 4 (27) | 1 (7) | 16 (7) | 31 (6) |

AE=adverse event; PT=preferred term; SD=standard deviation; SOC=system organ class.

Note: n=number of subjects. If an AE belonging to the category being summarized occurs during the exposure period, then that subject's exposure ends at the start of the first occurrence of the AE.

Note: AEs are summarized for those reported for >10% participants in either treatment group for the adult groups, and for ≥2 participants in either treatment group for adolescent participants

**Table 51: Exposure and on-treatment AE data by SOC and PT for adolescent and adult patients (NIMBLE IA)**

| | Adolescents (12-17 years) | | Adults (18-64 years) | | Adults (≥65 years) | |
|---|---|---|---|---|---|---|
| | Mepo/ benra (N=7) | Depe (N=7) | Mepo/ benra (N=336) | Depe (N=363) | Mepo/ benra (N=193) | Depe (N=166) |
| **Exposure** | | | | | | |
| Mean (SD), months | 11.7 (2.3) | 12.0 (0.1) | 11.7 (2.6) | 11.7 (1.6) | 11.9 (2.1) | 11.5 (1.8) |
| **AEs** | | | | | | |
| **Any event n (%)** | 6 (86) | 6 (86) | 223 (66) | 230 (63) | 154 (79) | 140 (84) |
| **Infections and infestations** | 3 (43) | 6 (86) | 72 (21) | 83 (23) | 103 (53) | 101 (61) |
| Rhinitis | 2 (29) | 2 (29) | 11 (3) | 11 (3) | 1 (<1) | 3 (2) |
| Upper respiratory tract infection | 1 (14) | 2 (29) | 48 (14) | 39 (11) | 17 (9) | 13 (8) |
| COVID-19 | 1 (14) | 1 (14) | 72 (21) | 83 (23) | 35 (18) | 24 (14) |
| Nasopharyngitis | 1 (14) | 1 (14) | 74 (22) | 65 (18) | 29 (15) | 32 (19) |
| **Respiratory, thoracic and mediastinal disorders** | 5 (71) | 3 (43) | 84 (25) | 95 (26) | 47 (24) | 42 (25) |
| Cough | 2 (29) | 2 (29) | 16 (5) | 27 (7) | 10 (5) | 11 (7) |
| Asthma | 2 (29) | 1 (14) | 11 (3) | 18 (5) | 4 (2) | 6 (4) |
| Oropharyngeal pain | 2 (29) | 0 | 11 (3) | 13 (4) | 2 (1) | 5 (3) |
| **Gastrointestinal disorders** | 2 (29) | 2 (29) | 47 (14) | 51 (14) | 22 (11) | 28 (17) |
| Abdominal pain | 0 | 2 (29) | 5 (1) | 1 (<1) | 2 (1) | 3 (2) |
| **General disorders and administration site conditions** | 2 (29) | 1 (14) | 52 (15) | 58 (16) | 34 (18) | 29 (17) |
| Pyrexia | 2 (29) | 1 (14) | 8 (2) | 16 (4) | 6 (3) | 13 (8) |

AE=adverse event; benra=benralizumab; depe=depemokimab; mepo=mepolizumab; PT=preferred term; SD=standard deviation; SOC=system organ class.
Note: n=number of subjects. If an AE belonging to the category being summarized occurs during the exposure period, then that subject's exposure ends at the start of the first occurrence of the AE.
Note: AEs are summarized for those reported for >10% participants in either treatment group for the adult groups, and for ≥2 participants in either treatment group for adolescent participants.

**Hepatic and renal impairment**

No formal studies have been conducted to investigate the effect of hepatic or renal impairment on the pharmacokinetics of depemokimab.

**Pregnancy and lactation**

As of the data cut-off for this submission, 11 pregnancies were reported for 10 female participants receiving investigational product in the completed and ongoing depemokimab studies (all indications), and 1 pregnancy reported for the partner of a male participant while he was receiving treatment.

Of the 11 pregnancies, 7 were reported in participants who received depemokimab. The reported outcomes of these pregnancies were 1 live birth, 2 elective terminations, 1 report of a spontaneous abortion at less than 22 weeks gestation, 2 reports of spontaneous abortion within approximately 1 month, all with no apparent congenital anomaly, and 1 ongoing pregnancy. The partner of the male participant reported a live birth with no apparent congenital anomaly present.

There have been no reports of depemokimab exposure during lactation in any of the studies in the depemokimab program. However, depemokimab is a humanised mAb (IgG1 kappa), and IgG is present in human milk in small amounts.

**Drug abuse and overdose**

There is no evidence for patient abuse of depemokimab.

The dose of depemokimab considered to be an overdose has not been defined. Single doses of up to 300 mg have been administered SC without evidence of dose related toxicities. There is no known antidote and a specific treatment in the event of a suspected overdose is not recommended.

**Withdrawal and rebound**

AE data from the follow-up post-treatment periods in the SWIFT and ANCHOR studies (i.e., from participants who discontinued treatment and remained in a study or from participants who were followed for 4 weeks after Week 52) did not support a return of symptoms (or acute exacerbations in the case of the SWIFT studies) in greater incidence after cessation of treatment.

**Effects on ability to drive and use machines**

There have been no studies to investigate the effect of depemokimab on driving performance or the ability to operate machinery. No or negligible influence of depemokimab on the ability to drive and use machines is expected based on the type of AEs observed throughout the clinical development program.

## 6.4.7. Immunological events

**Asthma studies**

SWIFT pool

A total of 89% post-baseline ADA positive participants (n=39/44, which included 2 NAb positive participants) experienced at least 1 AE compared with 71% ADA negative participants (n=323/455) in the depemokimab treatment group. The most frequently reported SOC was Infections and infestations, with AEs being reported by ADA positive participants (77% [34/44], AEs reported/ADA positive participants) more often than ADA negative participants reporting AEs (54% [246/455], AEs reported/ADA negative participants). COVID-19 and upper respiratory tract infections were reported more often in ADA positive participants (39% and 23%) than by ADA negative participants (16% and 8%, respectively). The incidence of nasopharyngitis was higher with ADA negative participants than ADA positive participants (13% versus 7%, respectively). Oropharyngeal discomfort and dermatitis were the only AEs reported by ≥2 ADA positive participants which were not reported by any ADA negative participants.

Two study participants were NAb positive. One participant was NAb positive at Week 52 and reported AEs of rhinorrhoea, conjunctivitis, headache, and 2 events of cough, which were all resolved by Week 35. The second participant was NAb positive only at Week 26 (subsequent visits were ADA negative) and reported AEs of tonsillitis, allergic conjunctivitis, dry eye, injection site reaction after seconddose, and another tonsillitis, which all resolved.

AGILE – OLE asthma

In the overall population, on-treatment AEs were reported by 84% (46/55) ADA positive participants and 70% (395/567) ADA negative participants. The most commonly reported AEs were nasopharyngitis (13%) and upper respiratory tract infection (11%), in the ADA positive and ADA negative participants. None of the ADA positive participants reported with AESIs.

NIMBLE – active control asthma

The ADA incidence was 3% (17/531) for participants receiving depemokimab, and all these participants were negative for NAb.

Post-baseline, study participants continuing to receive mepolizumab or benralizumab were not evaluated for immunogenicity.

For the depemokimab group, reporting of AEs in ADA positive participants (89%, 16/18) was similar to those of ADA negative participants (84%, 431/514). The most common AEs overall were in the SOC of Infections and infestations, with the most common AEs (by PT) being COVID-19 (28% vs. 20%),nasopharyngitis (28% vs. 18%), upper respiratory tract infections (17% vs. 10%), and sinusitis (17% vs. 6%) in ADA positive versus ADA negative participants, respectively. Injection site reactions (PT: rash) were reported for 2% of ADA negative participants and for no ADA positive participants.

**ANCHOR pool – CRSwNP**

In the depemokimab treatment group, there were 272 participants with a post baseline ADA assay result. Of these, 21 participants were ADA positive and 251 were ADA negative. A total of 71% (15/21) ADA positive participants were reported to have at least 1 AE compared with 75% (188/251) ADA negative participants.

The most frequently reported SOC was Infections and infestations, with AEs being reported by ADA positive participants (62%, 13/21) more often than ADA negative participants (47%, 117/251). The most common AEs overall (those reported for ≥10% participants in either ADA category) were (by PT), upper respiratory tract infection (29% vs. 9%), nasopharyngitis (10% vs. 19%), diarrhoea (14% vs. 2%), bronchitis (10% vs. 3%), epistaxis (10% vs. 4%), cough (10% vs. 2%), oropharyngeal pain (10% vs. 2%), pyrexia (10% vs. 1%) in in ADA positive participants versus ADA negative participants, respectively.

## 6.4.8. Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted.

## 6.4.9. Vital signs and laboratory findings

For the majority of chemistry laboratory results, haematological laboratory results and vital signs, there was no evidence of treatment effect. Linked to the mechanism of action, an effect on eosinophils was noted.

***Liver chemistry***

In the SWIFT pool, serum ALT elevations ≥3×ULN occurred in a higher proportion of participants in the depemokimab group (2% [12/501]) compared to placebo (0.38% [1/261]; Table 52). Of these, 5 participants in the depemokimab group met protocol-defined liver stopping criteria, and 6 participants in the depemokimab group and 1 in the placebo group met criteria for increased liver monitoring. A similar numerical imbalance in liver chemistry events was observed in the placebo-controlled pool.

**Table 52: Summary of hepatobiliary laboratory abnormalities including central and local laboratory data (SWIFT pool)**

| Laboratory Criteria, n (%)[1, 2]<br>Overall | Placebo<br>(N=261) | Depemokimab<br>(N=501) |
|---|---|---|
| n<br>ALT ≥3xULN and BIL ≥2xULN[3] | 258<br>0 | 500<br>3 (<1) |
| n<br>ALT ≥3xULN and INR >1.5[4] | 1<br>0 | 8<br>0 |
| n<br>ALT ≥3xULN and BIL ≥2xULN[3] and (ALP <2xULN) | 258<br>0 | 500<br>2 (<1) |
| n<br>Hepatocellular injury[5] | 258<br>1 (<1) | 500<br>7 (1) |
| n<br>Hepatocellular injury[5] and BIL ≥2xULN[3, 5] | 258<br>0 | 500<br>2 (<1) |
| n<br>ALT ≥3xULN[6]<br>ALT ≥5xULN<br>ALT ≥8xULN<br>ALT ≥10xULN<br>ALT ≥20xULN | 261<br>1 (<1)<br>1 (<1)<br>0<br>0<br>0 | 501<br>12 (2)<br>4 (<1)<br>4 (<1)<br>4 (<1)<br>2 (<1) |

1. Participants may be counted in more than one category.
2. ALT=alanine aminotransferase; ALP=alkaline phosphatase; BIL=total bilirubin; INR=international normalized ratio; ULN=upper limit of normal.
3. If direct bilirubin is available, then direct bilirubin as a portion of total bilirubin must be >35% when total bilirubin is ≥2xULN, in order to satisfy the criteria. Bilirubin value is on or up to 28 days after ALT value.
4. INR value is on or up to 28 days after ALT value.
5. Hepatocellular injury is defined as ((ALT/ALT ULN)/(ALP/ALP ULN)) ≥5 and ALT ≥3xULN. ALT and ALP values must occur on the same day.
6. The total number of participants in the depemokimab group with ALT ≥3xULN includes one participant with ALT ≥3xULN at baseline.

A detailed review of the ALT changes for participants with liver chemistry events (protocol-defined increased liver monitoring/ stopping events) revealed no consistent patterns in the timing of their occurrence in relation to dosing. The increases in ALT were mostly transient, asymptomatic, and most events resolved spontaneously without intervention, despite the continued presence of depemokimab, and/ or were associated with other underlying causes.

Three participants in the depemokimab group had ALT >3xULN accompanied by an increase in total bilirubin >2xULN. All had identified underlying etiologies (including acute hepatitis A, cholelithiasis, and autoimmune hepatitis with potential confounding from gallstone related symptoms) and none of these cases triggered Hy's Law.

In AGILE, serum ALT elevations ≥3×ULN occurred in 2% (11/629) participants. In the ANCHOR pool, serum ALT elevations ≥3×ULN occurred in 1.47% (4/272) participants in the depemokimab group and 0.78% (2/256) participants in the placebo group. Results from the NIMBLE IA showed that the proportion of participants with ALT ≥3xULN in the depemokimab group (0.37% [2/538] was lower than in the active comparator (mepolizumab/ benralizumab) group (1.67% [9/538]).

A review of changes from baseline for liver function parameters from an integrated analyses across indications did not reveal an imbalance with shifts from baseline relative to the normal range, which occurred with comparable incidence in both the depemokimab and placebo groups. Mean changes from baseline were

comparable between the groups.

The proportion of participants with liver-related AEs reported under the Hepatobiliary disorders SOC and Investigations SOC was generally similar between treatment groups in the placebo-controlled pool. Under the Infections and infestations SOC, there were 4 events of viral hepatitis reported in the depemokimab group. None of the events of viral hepatitis were considered related to study treatment by the investigators.

## 6.4.10. Post marketing experience

Not applicable

## 6.4.11. Overall discussion and conclusions on clinical safety

### *6.4.11.1. Discussion*

#### 6.4.11.1.1. Overall assessment of available safety data

The main safety data is derived from 1037 patients with asthma (n=501 in SWIFT pool and n=536 in NIMBLE) and 272 patients with CRSwNP, participating in Phase III controlled studies. A total of 936 asthma patients (n=464 in SWIFT pool and n=472 in NIMBLE) and 249 CRSwNP patients completed the treatment and thereby received 2 doses of depemokimab. The median exposure to depemokimab 100 mg SC across all studies was 12 months. Across all studies, a total of 964 patients received at least 2 doses of depemokimab 100 mg SC, corresponding to 1 year of treatment and 349 patients received 4 doses (i.e. 2 years of treatment).

The size and extent of the overall safety data base is acceptable. Nevertheless, the safety database in CRSwNP is relatively limited with regard to the number of patients and duration of exposure (n=272; 12 months). As discussed in scientific advice (EMA/SA/0000158669), support can be derived from safety data in asthma patients, considering the similar safety profile (see below). The acceptable safety profile of the approved medicinal product mepolizumab is also supportive for the safety profile of depemokimab, given the similar mode of action.

In both target populations, the proportion of patients with AEs was similar between the depemokimab (72-75%) and placebo (76-79%). The most common AEs were generally similar in both arms. In the asthma SWIFT pool, only allergic rhinitis occurred slightly more frequent (>3%) in the depemokimab arm (5.8% vs. 2.7% with placebo). In the ANCHOR pool of CRSwNP patients, this was only the case for nasopharyngitis (18% vs. 14.8% with placebo).

Drug related AEs were reported with 2% difference compared to placebo across both indications: 4% with depemokimab vs. 2% with placebo in the SWIFT pool and 6% vs. 4%, respectively, in the ANCHOR pool. Only injection site reaction (n=4, <1% vs. 0) and headache (n=4, <1% vs. n=1, <1%) were reported in more than 1 patient in the depemokimab group of the SWIFT pool. In the ANCHOR pool, fatigue (n=2, <1% vs. 0) and ALT increased (n=2, <1% vs. n=1, <1%) were the only related AEs reported in more than 1 patient in the depemokimab group. Severe AEs were reported less frequently with depemokimab (3-4%) compared to placebo (8-9%) in the two main safety pools.

In the main safety pools, the incidence of SAEs in patients treated with depemokimab was similar or even slightly lower frequency compared to the placebo group. Across all depemokimab studies, asthma (2% in

depemokimab and placebo groups) and pneumonia (<1% with depemokimab and 1% with placebo) were the only SAEs reported for ≥1% of patients. No SAEs were considered related to treatment by the investigator. There were no deaths reported in any of the completed studies with depemokimab.

The proportion of participants with an AE leading to permanent discontinuation of study treatment or withdrawal from study was low across the main safety pools and similar or even lower compared to the proportion of placebo treated patients. The only event leading to permanent discontinuation reported for more than 1 patient was ALT increased/abnormal (n=2, <1%).

Safety data of long-term treatment in asthma is derived from open label extension (OLE) study AGILE. At the final analysis of this study, patients who previously received 12 months of depemokimab treatment in the parent SWIFT studies, were exposed to depemokimab for another 12 months (i.e. two additional doses). The safety profile of depemokimab was generally similar to the parent SWIFT studies, regardless of whether participants had previously received depemokimab or placebo. These final results support a tolerable long-term (up to 104 weeks) safety profile for depemokimab.

When compared to the existing anti-IL5/5R biologicals mepolizumab and benralizumab in the interim analysis of the NIMBLE study, the safety profile of depemokimab was generally similar. No clinically relevant differences in common (related) AEs and severity of AEs were observed and the overall safety profile of depemokimab in the NIMBLE study resembles the profile observed in the SWIFT studies.

Based on the data presented, no formal comparison of depemokimab with approved biologicals in CRSwNP can be made. As discussed in the efficacy section and previous obtained scientific advice (EMA/SA/0000059022), this is acceptable. At the time of study initiation, there existed two approved biologicals for CRSwNP, but these products were not broadly adopted as standard of care. The novel advantage of a biologic requiring 6-monthly dosing and the nature of this condition, troublesome but not life-threatening, further support a placebo-controlled study design.

Final comparative safety data in asthma will become available post-approval with final results of active controlled study NIMBLE. The applicant agreed to present the full CSR including final safety data of this study post-authorisation by the end of April 2026 (PAM-REC).

Based on the mode of action and administration method, hypersensitivity reactions (type I and III, as well as anaphylaxis or other systemic reactions) and local injection site reactions were selected as AESI. Based on non-clinical data, QTc prolongation was defined as an AESI as well.

No related anaphylactic reactions were observed in the asthma and CRSwNP patients treated with depemokimab and type I hypersensitivity (AE of rash) was reported for 1 patient on depemokimab in the NIMBLE study. There were no events reported by the investigator as Type III hypersensitivity reaction in the asthma or CRSwNP patients. Other systemic reactions were more frequently observed, but generally non-serious and mostly resolving within a few days of onset.

As could be expected with a drug delivered by SC injection, injection site reactions were commonly observed after depemokimab administration in the asthma and CRSwNP trials (~1-3%), the majority of mild intensity and resolving in a few days. This is adequately reflected in the adverse reactions table and description of selected ARs of SmPC section 4.8.

Preclinically, QTc prolongation has been observed in the 6-month repeat dose monkey study administered 100 mg/kg every 3 months (2 doses). In the FTIH study, the predicted increase in mean QTcF change from

baseline with depemokimab plasma concentrations point estimates remained below 10 msec up to concentrations of 100 ug/mL, but the 95% CI did not exclude 10 msec. For further analysis of QTc prolongation in the FTIH study, and some outstanding issues raised as other concerns, please refer to the PK/PD section of this report. Thorough ECG analyses and analysis of AEs were performed for all clinical studies. Patients with a QT interval corrected by Fridericia's method QTc(F) ≥450 msec or QTc(F) ≥480 msec (for participants with Bundle Branch Block) were excluded from the main pivotal Phase 3 trials. It is reassuring that review of safety data from the depemokimab clinical development program (including completed studies and ongoing studies with interim analyses) has not identified a clinical cardiac safety signal.

Infections were not defined as AESI, but eosinophils may be involved in the immunological response to some helminth infections. There is no imbalance observed in bacterial, viral, fungal or parasitic/nematode infections between depemokimab and placebo treated patients in the placebo controlled pool of SWIFT and ANCHOR studies. The proposed warning in SmPC section 4.4 is nevertheless acceptable.

Genotoxicity studies have not been conducted with depemokimab as in vitro and in vivo assays. While not defined as AESI, a summary of AEs related to malignancy has been presented by the applicant. Similar incidences of events under SOC Neoplasms benign, malignant and unspecified were observed between placebo and depemokimab (1%) in a pool of the 4 pivotal placebo-controlled studies. Of these, 7 were SAEs (2/517 [<1%] in the placebo group; 5/773 [<1%] in the depemokimab group). At the interim analysis of asthma non-inferiority study NIMBLE, events under the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC were reported by 22 participants (7/538 [1%] in the mepolizumab/benralizumab group; 15/538 [3%] in the depemokimab group). Frequencies of new malignancies in long-term studies of benralizumab, mepolizumab and reslizumab are generally consistent with expectations based on characteristics of the study population. However, it is known that an increased incidence of malignancy may only become apparent over a longer time especially for rarer and slower-growing malignancies. The applicant was asked to discuss the observed higher incidence of malignancies in the non-inferiority study (NIMBLE) and provide brief narratives with causality assessment of the observed cases. The provided discussion does not signal any safety pattern in the observed malignancies; thus no safety concerns is raised at this time. Furthermore, the applicant committed to provide the full CSR, including final safety results, of the active controlled study NIMBLE by the end of April 2026. The occurrence of malignancies will also be followed as part of the PSURs submissions.

The overall incidences of AEs across the depemokimab group and placebo group in the age, sex, race, and region sub-groups were generally similar with no apparent clinically relevant treatment related effects in the placebo-controlled studies in asthma and CRSwNP. The analyses at study level were generally consistent with those in the pooled analyses. No significant impact of hepatic or renal impairment on clearance of depemokimab is expected. No patients with hepatic impairment were included in the studies. In the placebo-controlled studies, 7 patients with renal impairment were included who received depemokimab treatment. Although some differences in incidences between the respective comparator groups were noted, numbers were very small prohibiting final conclusions in this special population. This also applies to the special population of pregnant patients.

Overall, 33 adolescent participants (aged 12-17) with asthma were involved in the SWIFT studies, NIMBLE and AGILE study and exposed to depemokimab, corresponding to 2.6% (33/1247) of the study population in these three studies. All age groups of adolescents (12-17) were included in the studies, which is considered adequate. The safety profile seen in adolescent patients with asthma was generally similar to that seen in

adult patients. SAEs were reported in 2 adolescent participants in the depemokimab group. 1 participant in the SWIFT 1+2 pool experienced abdominal pain and 1 participant in the NIMBLE IA experienced asthma, diabetes mellitus, and diabetic metabolic decompensation. All SAEs were considered unrelated to the study treatment by the investigator and did not lead to discontinuation of study treatment. No new safety concern was identified in the adolescent participants. Depemokimab is not intended to be indicated for paediatric or adolescent CRSwNP patients, and absence of safety data in this population is therefore acceptable.

For the majority of chemistry laboratory results, haematological laboratory results, and liver function tests there was no evidence of treatment effect. An effect on eosinophils was noted, which is expected and linked to the mechanism of action of depemokimab. In the SWIFT pool, serum ALT elevations ≥3×ULN occurred in a higher proportion of participants in the depemokimab group (2.20%) compared to placebo (0.38%). In general, the increases in ALT were transient, asymptomatic, and most events resolved spontaneously without intervention, despite the continued presence of depemokimab, and/ or were associated with other underlying causes. Based on the presented review of liver function tests, it is acknowledged that there is no signal for severe liver toxicity. In the placebo controlled (ANCHOR + SWIFT) pool, hepatobiliary disorders were reported with similar incidences between the depemokimab and group. 4 cases of viral hepatitis were reported in the depemokimab arm and none in the placebo group. However, none of the events of viral hepatitis were considered related to the study treatment by investigators, and no clustering of events was noted by the applicant. Two of the observed hepatitis cases describe potential confounders. No safety trend is noted and the higher number is considered to be an incidental finding at this time.

In some safety populations (SWIFT and OLE study AGILE) AEs were reported more frequently in ADA positive patients, compared to ADA negative patients. The most common AEs being more frequently reported were in the SOC of Infections and Infestations. Despite some differences in frequencies, these AEs were reported commonly in the ADA negative patients as well. Hence, no clinically relevant impact of immunogenicity on safety is observed. The AEs reported in patients with NAbs were also reported in ADA negative patients. The number of NAb positive patients is too limited to draw firm conclusions, but available data suggest that there is no clear association between AEs and NAb positivity.

There were no safety observations related to the medical device or the device/drug combination. The safety profile of depemokimab is acceptable for self-administration at home by adult and adolescent patients, if their health care provider determines it appropriate.

Safety data supports claims in sections 4.3., 4.4., 4.6., 4.7., and 4.9., of the SmPC.

#### 6.4.11.1.2. Adverse drug reactions in the SmPC

The ADRs proposed by the applicant for inclusion in SmPC section 4.8. are described in section 6.4.3.1 above.

**Table 53: ADRs proposed for inclusion in the SmPC by the Rapporteur**

| | |
|---|---|
| ***Skin and subcutaneous tissue disorders*** | |
| ***Pruritus*** | Common (1%) |
| ***General disorders and administration site conditions*** | |
| ***Administration-related systemic reactions (non-allergic)*** | Common (2%) |
| ***Local injection site reactions*** | Common (2%) |

The proposed ADRs pruritus, administration-related systemic reactions [non-allergic] and local injection site reactions) are supported. In addition to these ADRs, headache and fatigue were also reported as related AEs in more than 1 patient. It is acknowledged that these adverse reactions have been described as symptoms of administration-related systemic reactions in a subsection Description of selected adverse reactions.

Hypersensitivity reactions (systemic, allergic) were proposed by the applicant based on 2 AEs. 1 AE was observed in the Phase 1 PK comparability study [214099] – Type I Hypersensitivity classified by the investigator as systemic reaction reported under the PT "injection site urticaria". Another AE was observed in the AI AGILE, however based on the study protocol the reported PT term was pruritus (which is proposed to be included to section 4.8 of SmPC as a separate term). Allergic reactions including anaphylaxis were monitored as AESI. In the placebo-controlled studies no systemic allergic reactions (type I hypersensitivity) and no AESI of anaphylactic reaction were reported. Therefore, the addition of the ADR Hypersensitivity reactions (systemic, allergic) based on the referred evidence is not supported. In line with

Guideline on summary of product characteristics - Revision 2 (SmPC) September 2009, the section 4.8 will be regularly reviewed (e.g. as part of the PSUR evaluations) and, if necessary, updated with the aim to ensure appropriate information to health care professionals on the safety profile of the product. Furthermore, subsection C of Section 4.8 of the SmPC could generally inform on adverse reactions with very low frequency which may not have been observed in relation to the product, but which are considered to be related to the same therapeutic, chemical or pharmacological class. In conclusion, information on potential hypersensitivity reactions (systemic allergic) is described in subsection Description of selected adverse reactions.

While inclusion of administration-related systemic reactions (non-allergic) as ADR is endorsed, it was not specified how many of each of the PT terms (headache, fatigue, rash) were reported and the provided total number of cases (n=19) was not clearly elucidated taking into consideration the ISS PostHoc Outputs. The applicant was requested to provide information on each included PT term from the stated Administration-related systemic reactions separately (e.g. number of reported cases, source. A total of 24 events were reported in these 19 participants. Among these, 12 participants were reported with Preferred Terms (PTs) of headache (9), fatigue (3), and rash (1). Additionally, rash and fatigue were reported as symptoms associated with AEs of erythema (1), fixed drug eruption (1), and malaise (1) (PT level) in 3 other participants. Section 4.8 of the SmPC was amended and describes additional information regarding the frequency of observed risks. Nasopharyngitis was observed throughout all studies as one of the most commonly reported AEs (36% in FTIH study, in pooled ANCHORs it was reported for 18.0% participants in the depemokimab group versus 14.8% participants in the placebo group, SWIFTs pool 12.4% in depemokimab versus 19.9% in placebo, AGILE 10 %, NIMBLE (18% and 19%, depemokimab versus mepolizumab/benralizumab groups). The applicant was requested to discuss the relevance of inclusion of nasopharyngitis in section 4.8 of the SmPC. The subsequently provided pooled data showed that nasopharyngitis did not meet the prespecified quantitative thresholds as it occurred more frequently in the placebo group (90/517, 17%) than the depemokimab group (111/773, 14%) in a pool of 4 pivotal placebo-controlled studies. It is therefore agreed to not include this ADR in SmPC section 4.8 at this stage

#### *6.4.11.2. Conclusions on clinical safety*

Overall, treatment with depemokimab was well tolerated in the study population of asthma and CRSwNP patients, as reflected in the short list of generally mild adverse reactions. The safety profile seen in adolescent patients with asthma was generally similar to that seen in adult patients. Final analyses of active

compared study NIMBLE in asthma patients will be submitted post approval by the end of April 2026 (PAM-REC).

# 7. Risk management plan

## *7.1. Safety specification*

### 7.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

**Table 54: Summary of safety concerns in the proposed RMP**

| ***Summary of safety concerns*** | |
|---|---|
| ***Important identified risks*** | None |
| ***Important potential risks*** | None |
| ***Missing information*** | Use in pregnant patients |

### 7.1.2. Discussion on proposed safety specification

The proposed summary of safety concerns in the RMP is acceptable. In line with the PRAC outcome at D166 (see section 7.6), the 'use in breastfeeding patients' is deleted as missing information from the proposed safety concerns.

Three biologics targeting IL-5 or its receptor (mepolizumab, reslizumab, and benralizumab) are approved globally for the treatment of severe asthma with an eosinophilic phenotype. The appropriate Important potential risks described for them are malignancies and alteration in cardiovascular safety. The risk of QTc prolongation was closely monitored throughout studies. No treatment effect on the QT interval was observed in patients treated with depemokimab across both asthma and CRSwNP programs at the recommended clinical dose of 100 mg SC. No severe clinical outcomes such as torsade de pointes, ventricular tachycardia, ventricular fibrillation, ventricular flutter, or sudden deaths were reported. Thus, it is endorsed that the risk does not have to be classified as the safety concern in the RMP.

Malignancy- Genotoxicity studies have not been conducted with depemokimab as in vitro and in vivo assays. As for the applicant, depemokimab is not believed to possess a carcinogenic potential since monoclonal antibodies are not considered to be associated with cancer risks unless they cause significant immunosuppression, which depemokimab does not. The applicant stated that published literature is not in agreement if the IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumour rejection or eosinophil infiltration into tumours can promote tumour growth. Similar incidence of events under SOC Neoplasms benign, malignant and unspecified was observed between placebo (6/517 [1%]) and depemokimab (10/773 [1%]) in a pool of 4 pivotal placebo-controlled studies. Of these, 7 were SAEs (2/517 [<1%] in the placebo group; 5/773 [<1%] in the depemokimab group). In asthma non-inferiority study (206785) at interim analysis, events under the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC were reported by 22 participants (7/538 [1%] in the mepolizumab/benralizumab

group; 15/538 [3%] in the depemokimab group). Frequencies of new malignancies in long-term studies of benralizumab, mepolizumab and reslizumab are generally consistent with expectations based on characteristics of the study population. However, it is known that an increased incidence of malignancy may only become apparent over a longer time especially for rarer and slower-growing malignancies. (Jackson et al, 2023). It could generally be agreed not to include the risk as Important Potential Risk in the RMP, however further enhanced monitoring is considered needed. Thus, the applicant was asked to follow this concern as part of the PSURs submissions. This request was endorsed by the applicant.

While other (potential) risks have been reported with depemokimab treatment, they are not considered to impact the benefit risk balance to a large extent. As such, it is agreed that there are no other important identified or potential risks to be included in the safety specifications of the RMP.

Severe hypersensitivity reactions is a known risk for Mepolizumab and Reslizumab (IPR). As there have been no severe cases observed in the current clinical program, it is recommended to include the risk of "Severe hypersensitivity reactions, including anaphylactic or anaphylactoid" to safety concerns of the PSUR, in order to monitor the risk post-marketing

## *7.2. Pharmacovigilance plan*

### 7.2.1. Proposed pharmacovigilance plan.

Routine pharmacovigilance activities

There are no activities beyond adverse reaction reporting and signal detection.

Specific adverse reaction follow-up questionnaires

None

Other forms of routine pharmacovigilance activities

None

Additional pharmacovigilance activities

The applicant did not propose any additional pharmacovigilance activities.

### 7.2.2. Discussion on the Pharmacovigilance Plan

#### *7.2.2.1. Routine pharmacovigilance activities*

The applicant proposed to address the missing information of use in pregnancy only by routine pharmacovigilance activities in the form of enhanced data collection. Key maternal pregnancy information (e.g. relevant maternal medical history) and pregnancy outcome information are foreseen to be collected in this enhanced data collection. However, no information on how the data will be collected and, on the process, to identify patients was provided. Additional pharmacovigilance activities to investigate use during pregnancy was performed for mepolizumab, however, due to low recruiting no final conclusion could be made after finalization of this study. Therefore, it seems that additional pharmacovigilance activities might not be suitable to analyse the safety of use in pregnant women. In general, enhanced data collection to obtain more

information in treated pregnant women is endorsed. However, more information on the enhanced data collection needs to be provided. The applicant was asked to describe the process of the enhanced data collection that is foreseen in detail, including how patients will be identified, how information will be inquered and collected and which information will be inquered specifically. With the responses, the applicant presented details of the foreseen enhanced data collection process. However, it is considered that the enhanced data collection does not entail additional information to the routine data collection process for pregnancy that is described in GVP module Product- or Population-Specific Considerations III: Pregnant and breastfeeding women. The applicant was therefore requested to remove the enhanced data collection from Part III.1 of the RMP and to update all other parts of the RMP accordingly. These changes were implemented in the final RMP version 1.0.

The missing information for depemokimab is "Use in pregnant and lactating patients". Pregnant patients are addressed by enhanced data collection; however, no proposal was made to address use during breastfeeding. The applicant was asked to propose measures how use during breastfeeding will be further investigated. With the responses, the applicant discussed that depemokimab is a humanised IgG1 monoclonal antibody and systemic absorption of IgG in neonates/infants is considered negligible. The applicant therefore concluded that routine pharmacovigilance activities are sufficient to address the use of depemokimab in breastfeeding patients. This is endorsed.

#### *7.2.2.2. Additional pharmacovigilance activities*

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product and no adidirional pahracovigilance activities are needed.

## *7.3. Plans for post-authorisation efficacy studies*

No PAES studies have been proposed and included in the RMP

## *7.4. Risk minimisation measures*

### 7.4.1. Proposed risk minimisation measures

**Table 55: Planned routine risk minimisation measures**

| Safety concern | Routine risk minimisation activities |
|---|---|
| Missing Information: Use in pregnant patients | **Routine risk communication:**<br><br>SmPC Section 4.6, Fertility, Pregnancy and Lactation, of the SmPC advises prescribers on the non-clinical reproductive toxicity data available relating to Exdensur which states that there are no or limited amount of data from the use of depemokimab in pregnant women. As a precautionary measure, it is preferable to avoid the use of Exdensur during pregnancy.<br><br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br><br>Not applicable |

| | |
|---|---|
| | **Other routine risk minimization measures beyond the Product Information:**<br>Not applicable |

The applicant did not propose any additional risk minimisation measures.

### 7.4.2. Discussion on the risk minimisation measures

#### *7.4.2.1. Routine risk minimisation measures*

The PRAC having considered the data submitted was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

#### *7.4.2.2. Additional risk minimisation measures*

No additional risk minimisation measures are proposed, which is accepted by the PRAC.

## *7.5. RMP Summary and RMP Annexes overall conclusion*

The RMP Part VI and the RMP Annexes are acceptable.

## *7.6. PRAC Outcome*

PRAC discussed and agreed the following comments and recommendations:

**Summary of safety concerns**

PRAC recommended to keep use in pregnant patients as missing information but not the use in breastfeeding.

Routine pharmacovigilance activities and routine risk minimisation measures are considered sufficient.

RMP version 0.2 is acceptable provided that the enhanced data collection is removed from Part III.1 of the RMP with submission of the final RMP at the end of the application procedure.

## *7.7. Overall conclusion on the Risk Management Plan*

The CHMP and PRAC Rapporteur consider that the risk management plan version 1.0 is acceptable.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

# 8. Pharmacovigilance

## *8.1. Pharmacovigilance system*

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

## *8.2. Periodic Safety Update Reports submission requirements*

The active substance is not included in the EURD list and a new entry will be required. The new list of Union

reference dates (EURD list) entry uses the European birth date (EBD) or the international birth date (IBD) to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the IBD. The IBD is 29th August 2017.

# 9. Product information

## *9.1. Summary of Product Characteristics (SmPC)*

See attached edited product information including both Rapporteur and Co-Rapporteur assessment.

### 9.1.1. SmPC section 4.1 justification

Asthma

The pivotal asthma studies SWIFT-1 and SWIFT-2 included adults and adolescents with uncontrolled severe eosinophilic asthma with regular treatment with medium- to high-dose ICS (≥440 mcg FP or equivalent) and at least one additional asthma controller medication. The updated proposed indication adequately reflects the population included in the replicate pivotal studies: *Exdensur is indicated as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by blood eosinophil count in adults and adolescents 12 years and older who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another asthma controller (see section 5.1).*

CRSwNP

The pivotal CRSwNP studies ANCHOR-1 and ANCHOR-2 included adults with uncontrolled severe CRSwNP using intra-nasal corticosteroids and with a history of systemic corticosteroids and nasal surgery. The requested proposed updated indication reflects the included study population properly i.e. *Exdensur is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.*

*SmPC section 5.1 justification*

Asthma

The applicant proposed to include the primary endpoint exacerbations and the secondary endpoints SGRQ score, ACQ-5 score, and pre-bronchodilator FEV1. Despite the failed statistical testing at level 2 in the multiplicity hierarchy (SGRQ score) in either pivotal study, inclusion of these secondary endpoints is endorsed since this provides important information to healthcare providers.

CRSwNP

Section 5.1 presents the baseline characteristics and the co-primary endpoints of the two pivotal studies. The baseline characteristics also include the basal VRS smell score and QoL scores because these characteristics are mentioned as inclusion criteria in the EUFOREA guideline for the initiation of a biological treatment for CRSwNP. Section 5.1 also presents the results of the co-primary endpoints over time to align with other approved biologicals for CRSwNP.

The results of the secondary outcome measures were deleted as they are not type I protected.

Although the results of the pooled key secondary outcomes did not show statistical difference and as such were also not type I protected, they are included in the SmPC as they provide important information for healthcare providers in the treatment of CRSwNP with biologicals like depemokimab.

A difference in approach for the SmPC may be perceived between the asthma and CRSwNP indication with regard to the acceptance of secondary endpoints that failed to show statistical significance in the hierarchical testing scheme. In CRSwNP, both co-primary endpoints were met, but as the first secondary endpoint failed to show statistical significance, all other outcomes are not Type I protected anymore and are therefore not considered to be included in the SmPC. The key secondary endpoints on the pooled analysis also failed to show significance but are included in the SmPC as they provide important information to prescribers in the treatment fo CRSwNP to initiate treatment with biologicals. Therefore, the presentation of the first key secondary endpoint (nasal surgery) is accepted as well as the proportion of CRSwNP patients using SCS (third key secondary endpoint). With these presented endpoints, prescribers will be well informed on both objective and subjective endpoints. Other results are included in the EPAR, which can be used for cross-study comparison to other products.

In the asthma indication (SWIFT studies), only the primary endpoint (exacerbations) was met. Here it is considered that presentation of three secondary endpoints (on HRQoL and lung function) is important to allow prescribers to make a well-informed decision on therapy.

## *9.2. Labelling*

### 9.2.1. Package leaflet (PL)

See attached edited product information including assessment.

### 9.2.2. User consultation

**Conclusion from the checklist for the review of user consultation**

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

## *9.3. Additional monitoring*

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Exdensur (depemokimab)) is included in the additional monitoring list since it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU..

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 10. Benefit-risk assessment

## *10.1. Therapeutic context*

Depemokimab targets human IL-5, thereby blocking the binding to the IL-5 receptor alpha expressed on the cell surface *in vitro*. IL-5 is a core cytokine in Type 2 inflammation along with IL-4 and IL-13. Type 2 inflammation driven by IL-5 is an important component in the pathogenesis of asthma and CRSwNP. IL-5 is

the major cytokine responsible for the growth and differentiation of eosinophils in the bone marrow, and recruitment, activation, and survival of eosinophils in the tissue space.

Following CHMP assessment, the agreed indications are:

Asthma

*Exdensur is indicated as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by blood eosinophil count in adults and adolescents 12 years and older who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another asthma controller (see section 5.1).*

Chronic rhinosinusitis with nasal polyps (CRSwNP)

*Exdensur is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.*

The proposed posology for both indications is 100 mg, administered subcutaneously once every 6 months.

## 10.1.1. Disease or condition, therapeutic indication

For a detailed description, please see section 3.1 of this document.

**Asthma**

Asthma is a chronic heterogeneous lung disease characterised by inflammation, airway hyperresponsiveness and variable airflow obstruction. Symptoms vary over time and in intensity and can include wheezing, shortness of breath, chest tightness, and cough.

There are more than 300 million people with asthma worldwide, of whom up to 10% of adult patients and 2.5% of paediatric patients have severe asthma characterised by a reduced quality of life and increased risk of fixed airflow limitation, exacerbations, hospitalisation, and death.[11]

Type 2 inflammation is the underlying pathology for more than 80% of people with severe asthma. Uncontrolled eosinophilic inflammation, reflective of IL-5 driven disease, is a recognised risk factor for severe disease exacerbations, airway remodelling and lung function decline in asthma.

**CRSwNP**

Nasal polyps are a chronic inflammation outgrow of the paranasal sinus mucosa and present bilaterally among the middle and superior nasal meatus. Nasal polyps are associated with chronic rhinosinusitis. The inflammation in CRSwNP is often characterised by an eosinophilic (type 2 inflammation), which also plays a role in asthma.

It is estimated that 4% of the global population suffer from CRSwNP. It is a disease of the middle age and occurs more frequently in males. Frequent comorbidities are asthma and aspirin related respiratory disease.

Symptoms of CRSwNP are nasal obstruction, loss of smell, facial pain, and facial pression. Symptoms are of variable intensity and may have a detrimental effect on quality of life.

[11] Brusselle GG, Koppelman GH. Biologic Therapies for Severe Asthma. N Engl J Med 2022;386:157-71. DOI: 10.1056/NEJMra2032506

## 10.1.2. Available therapies and unmet medical need

For a detailed description, please see section 3.1 of this document.

**Asthma**

The standard of care (SoC) for severe eosinophilic asthma is treatment with inhaled corticosteroids (ICS) and other controller medications, including short-acting and long-acting beta agonists (SABA, LABA), short-acting and long-acting muscarinic antagonists (SAMA, LAMA), and leukotriene antagonists. Exacerbations usually necessitate short-term treatment with systemic corticosteroids (CS).

Add-on targeted therapy with biologicals is recommended in case of frequent exacerbations and/or poor symptom control. Several biologicals targeting type 2 inflammation have been approved for uncontrolled severe eosinophilic asthma, including three biologicals targeting IL-5. While these biologicals reduce the need for systemic CS and enhance patient outcomes, difficulties in adhering to the dosing schedule or maintaining long-term treatment persistence could potentially negatively impact these benefits.

**CRSwNP**

The SoC for CRSwNP in adults is a treatment with intranasal corticosteroid (INCS), and nasal saline irrigation. For severe symptoms, intermittent use of oral corticosteroids can be supplied, when fast and short relief is required.

Surgery to remove the tissue of the nasal cavity (NP-surgery) can be indicated in patients with severe uncontrolled CRSwNP despite the SoC, particularly when oral corticosteroids are frequently needed to relief symptoms. However, without control of the underlying inflammation, nasal polyps have a strong tendency to recur. Since 2019, various biologicals, targeting the type 2 inflammation have been approved as add-on therapy to SoC in adult patients with CRSwNP, which all require dosing once every 2-4 weeks. While these biologicals reduce the need for systemic CS and surgery, and improve patient outcomes, difficulties in adhering to the dosing schedule or maintaining long-term treatment persistence could potentially negatively impact these benefits.

## *10.2. Main clinical studies*

For a detailed description of the main clinical studies supporting this application, please refer to sections 6.3.2 (Asthma) and 6.3.8 (CRSwNP).

The pivotal efficacy and safety data of depemokimab is derived from a clinical development programme in adult and adolescent patients aged 12 years with severe, esosinophilic, uncontrolled asthma despite SOC treatment (SWIFT-1 and SWIFT-2 studies) and in adult patients with severe, uncontrolled CRSwNP despite SoC treatment (ANCHOR-1 and ANCHOR-2 studies). In these 4 randomised, 52-week, placebo-controlled, multicentre Phase 3 studies, patients received either subcutaneous (SC) depemokimab or placebo once every 6 months.

For review of safety data, the replicate SWIFT studies were pooled to support the asthma indication (**SWIFT pool**), as were the replicate ANCHOR studies to support the CRSwNP indication (**ANCHOR pool**).

Main supportive data is derived from2 phase 3 clinical studies in asthma:

- Efficacy and safety results from an open-label 52-week extension study (**AGILE**) involving asthma patients (n = 629) who had previously completed either of the two asthma studies (SWIFT-1 or SWIFT-2), and

- Safety results from an interim analysis (n = 538) and a summary of key efficacy results of a 52-week active controlled study (**NIMBLE**) involving asthma patients aged 12 years and older who were previously treated with other anti-IL5/IL-5R biological medicines prior to study entry (n = 1687). Patients received depemokimab 100 mg SC every 26 weeks or an active comparator according to the treatment prior to randomisation (mepolizumab every 4 weeks or benralizumab every 8 weeks). Both groups also received a placebo matching the other treatment group.

## *10.3. Favourable effects*

Depemokimab has a long elimination half-life of 38 to 53 days, which enable twice-a-year dosing.

Throughout the pivotal studies, a sustained decrease in eosinophils was observed. Eosinophil count started to increase again 12-20 weeks post-dose but remained below baseline values for the entire dose interval of 26 weeks.

**Asthma**

SWIFT studies

Both pivotal SWIFT studies met their primary endpoint of clinically relevant exacerbations. The rate ratio was 0.42 (95% CI: 0.30, 0.59), indicating a relative 58% (41-71%) reduction in the annualised exacerbation rate in SWIFT-1, and 0.52 (95% CI: 0.36, 0.73), indicating a relative 48% (27-64%) reduction in the annualised exacerbation rate in SWIFT-2. Results from the integrated analysis of data from SWIFT-1+2 reflected the results from the individual studies, with a reduction of 54% (rate ratio 0.46; 95% CI: 0.36, 0.59) in the annualised rate of clinically significant exacerbations with depemokimab compared to placebo.

For several patient-reported outcomes (SGRQ score, ACQ-5 score) and lung function (FEV1), numerical improvements from baseline were observed at Week 52 in both depemokimab and placebo groups. For SGRQ score, these improvements were numerically greater for depemokimab than for placebo.

Subgroup analyses support the primary endpoint, with improved outcomes in exacerbation rate regardless of baseline ICS dose, eosinophil count, or ACQ-5 score.

Results in elderly participants (≥65 years; n=194) were consistent with the primary analysis for exacerbations and SGRQ score (favouring depemokimab). For adolescents (12-17 years; n=30), results for the primary endpoint of exacerbations were in line with the primary analysis (favouring depemokimab).

AGILE study

Interim efficacy data showed that the effects of depemokimab on exacerbations (rate ratio 0.46 [95% CI: 0.38, 0.56]; n=419) and SGRQ total score (mean [SD] change from AGILE baseline -0.94 [14.1] at Week 52; n=218) were maintained following further dosing in participants who received depemokimab in the parent studies.

NIMBLE study

In a direct comparison between depemokimab and approved anti-IL-5 therapies (mepolizumab, benralizumab), the annualised rate of clinically significant exacerbations was 0.57 (95% CI: 0.50, 0.64) in the depemokimab group and 0.49 (95% CI: 0.43, 0.55) in the mepolizumab/benralizumab group, resulting in an exacerbation rate ratio of 1.16 (95% CI: 0.98, 1.38).

**CRSwNP**

ANCHOR studies

Both pivotal ANCHOR studies met their co-primary endpoints by showing a statistically significant difference in (i) the LS mean decrease in the nasal polyps score at week 52 (centrally read) and (ii) improvement from baseline in the mean nasal obstruction score verbal response scale (VRS) from week 49 through week 52. The adjusted mean differences in the LS mean (95% CI) NP score at week 52 were -0.7 (95% CI -1.1, -0.3), p<0.001 and -0.6 (95% CI -1.0, -0.2), p=0.004 for ANCHOR-1 and ANCHOR-2 respectively, while the adjusted mean differences in VRS nasal obstruction were -0.23 (95% CI -0.46, 0.00), p=0.047 and -0.25 (95% CI-0.46, -0.03), p=0.025, respectively.

In the pooled analyses, the first key secondary outcome showed a numerical improvement in the time to first NP-surgery (actual or entry on waiting list) or disease modulating medication for CRSwNP up to Week 52, hazard ratio 0.735 (95% CI 0.495, 1.092; p=0.128).

The other time-to-event endpoint of the pooled analyses referring to the total need of rescue therapy (i.e. NP surgery (actual or on waiting lists, initiation of disease modulating drugs for CRSwNP or systemic CS courses for CRSwNP) almost showed a statistically significant difference (HR 0.750 (95% CI: 0.557, 1.009; p=0.058 [not type I protected]). In the overall pooled analyses, numerical treatment differences favouring depemokimab were observed in the number- of-patients-needing NP- surgery- (actual- or- on- waiting- list)- or-"disease-modulating medication" (treatment difference [n=12, 8%]).

The proportion of participants requiring at least 1 course of systemic CS or disease-modulating medication for CRSwNP or NP surgery (actual) up to Week 52 was lower in the depemokimab group (n=72 [26%]) than in the placebo group (n=92 [36%]). The corresponding odds ratio was 0.58 (95% CI: 0.40, 0.86; p=0.006) which was nominally significant in favour of depemokimab.

Various additional sensitivity analyses support the reported outcome of the primary analyses. Subgroup analyses support the overall co-primary endpoints, with improved outcomes in (i) patients with asthma compared to non-asthma and (ii) high eosinophil count (≥300 cells/µL) vs low eosinophil count.

## 10.3.1. Uncertainties and limitations about favourable effects

The proposed posology might not be the most optimal proposal as symptom control and effects on blood eosinophil count appear to decrease towards the end of the dose interval in both indications. Considering that no other posology was studied, it currently remains an uncertainty whether a more optimal posology may exist, but this can be accepted considering the positive B/R for depemokimab 100 mg SC Q26W in both indications.

At high body weights (140-160 kg), exposure to depemokimab may be decreased 2-fold. Although exposure-response analyses demonstrated that subgroups with the lowest BEC reductions in both asthma and CRSwNP were consistent with the estimated treatment differences observed in the overall population, reduced efficacy cannot be excluded in obese patients.

**Asthma**

Both SWIFT studies failed to show any statistically significant effect on the secondary endpoints included in the statistical hierarchy. Since the hierarchical testing for multiplicity was broken at the first secondary outcome, all secondary endpoints are not type I protected. Nevertheless, both studies showed numerical

improvements in all secondary outcome measures. These improvements reached nominal statistical significance for SGRQ score when the results were pooled.

For the patient-reported secondary endpoints, subgroups that may be reflective of less severe disease (i.e. baseline eosinophil count <0.15 GI/L, baseline ACQ-5 score <1.5) exhibited a smaller or even negative treatment effect (favouring placebo), although these results were not statistically significant.

Only 30 participants <18 years were enrolled in the SWIFT studies combined, of whom a total of 15 participants received depemokimab 100 mg SC. Data in adolescents are therefore limited. While the mean effect on the primary endpoint was comparable in adults and adolescents, the difference to placebo was not statistically significant in adolescents due to these low numbers of patients 12-17 years. However, results for adolescents can be extrapolated from adults, as PK exposure was shown to be comparable between adults and adolescents. To further support extrapolation, additional Bayesian analysis was performed.

In the NIMBLE non-inferiority study, which compared depemokimab to approved anti-IL-5 therapies (mepolizumab, benralizumab), the primary endpoint did not meet non-inferiority. While the 95% confidence interval included 1.0, the upper bound was higher than the pre-specified non-inferiority margin of 1.28. However, the number of exacerbations was low in both groups, which may exaggerate the relative difference. The absolute difference between the groups was small (0.08 exacerbations/year) and not clinically relevant, which is supported by comparable results between groups for the secondary endpoints of HRQoL and lung function. Therefore, results of the NIMBLE study do not raise concerns with regard to the efficacy of depemokimab in comparison to other anti-IL-5/5R treatments in patients who have previously shown to benefit from biologicals.

**CRSwNP**

Both studies failed to show a statistically significant improvement in the first secondary outcome (Change from baseline in rhinorrhoea VRS score over week 49 to week 52). Nominally statistically significant results at the 5% significance level without control for multiplicity were not concluded for the secondary endpoints in hierarchy in both ANCHOR studies, although they reached nominal statistical significance when the results were pooled.

Biologicals are typically administered in CRSwNP to prevent surgery, while the "initiation of disease modifying drugs" can be interpreted as a surrogate for surgery. Biologicals are also initiated to prevent systemic courses of corticosteroids. These endpoints are included in the time-to-event key pooled secondary endpoints. These the time-to-events outcomes failed to show statistically significance.

Although the study showed a nominal statistically significant Odds ratio for the overall proportion of patients that needed intensification of treatment by means of surgery, initiation of disease-modulating treatment, or systemic corticosteroids to treat CRSwNP, the absolute actual difference with placebo is modest (10%).

## *10.4. Unfavourable effects*

Safety data is available for 1037 patients with asthma (n=501 in SWIFT pool/AGILE and n=536 in NIMBLE) and 272 patients with CRSwNP, participating in Phase III controlled studies. A total of 936 asthma patients (n=464 in SWIFT pool and n=472 in NIMBLE) and 249 CRSwNP patients completed the treatment and thereby received 2 doses.

The median exposure to depemokimab 100 mg SC across all studies was 12 months. Overall, a total of 964 patients received at least 2 doses of depemokimab 100 mg SC, corresponding to 1 year of treatment and 349

patients received 4 doses (i.e. 2 years of treatment).

Asthma

- In the SWIFT pool, the proportion of patients with AEs was similar in the depemokimab group (72%) and placebo group (76%).* The most common AEs were generally similar in both arms. Only allergic rhinitis occurred slightly more frequent (>3%) in the depemokimab arm (5.8% vs. 2.7% with placebo).
- Drug related AEs were reported in 4% and 2%, respectively. Only injection site reaction (n=4, <1% vs. 0) and headache (n=4, <1% vs. n=1, <1%) were reported in more than 1 patient in the depemokimab group.

CSRwNP

- In the ANCHOR pool, the proportion of patients with AEs was similar in the depemokimab (75%) and placebo group (79%).* The most common AEs were generally similar in both arms. Only nasopharyngitis occurred slightly more frequent (>3%) in the depemokimab arm (18% vs. 14.8% with placebo).
- Drug related AEs were reported in 6% and 4%, respectively. Only fatigue (n=2, <1% vs. 0) and ALT increased (n=2, <1% vs. n=1, <1%) were reported in more than 1 patient in the depemokimab group.

Both indications - AESI and laboratory findings

- Injection site reactions were commonly observed after depemokimab administration in the asthma and CRSwNP main safety pools (~1-3%). These events were non-serious, mild in intensity and generally resolved in a few days.
- Type I hypersensitivity (AE of rash) was reported for 1 patient on depemokimab in the NIMBLE study (non-serious, rash). No related anaphylactic reactions were observed in the asthma and CRSwNP patients treated with depemokimab, but 'other systemic reactions' were more frequently observed in asthma (2% vs. <1%; SWIFT pool) and CRSwNP patients (<1% vs. 0). These were generally non-serious and mostly resolving within a few days of onset.
- Serum ALT elevations ≥3×ULN were observed with depemokimab treatment (~1-2% vs. <1% with placebo in the main safety pools). The increases in ALT were mostly transient, asymptomatic, and most events resolved spontaneously without intervention. A review of changes from baseline for liver function parameters from an integrated analyses across indications did not reveal a sign of severe liver toxicity.

* Of note: in the main safety pools of asthma as well as CRSwNP patients, the incidence of severe AEs and SAEs in patients treated with depemokimab was similar or even slightly lower frequency compared to the placebo group. Across all depemokimab studies, asthma (2% in depemokimab and placebo groups) and pneumonia (<1% with depemokimab and 1% with placebo) were the only SAEs reported for ≥1% of patients. No SAEs were considered related to treatment by the investigator. There were no deaths reported in any of the completed studies with depemokimab.

### 10.4.1. Uncertainties and limitations about unfavourable effects

- The exposure of adolescent patients was limited with 33 patients exposed to depemokimab 100mg.

- Safety of depemokimab treatment in adults with CRSwNP has been compared to placebo, but not to safety of other active therapies, such as biologicals approved in this indication. Final safety results of the active controlled study NIMBLE in asthma will be presented post-authorisation by the end of April 2026 (PAM-REC).

- The safety database in CRSwNP is relatively limited with regard to the number of treated patients and duration of exposure (n=272; of whom n=249 received 2 doses, i.e. 12 months treatment). As discussed in scientific advice (EMA/SA/0000158669), support can be derived from safety data in asthma patients, considering the similar safety profile.

- Considering that two doses were given in the pivotal studies, safety has not been established on steady state in either indication. However, in additional 2-year simulations, the PK parameters remained relatively stable, with accumulation ratio below 10%, which is not considered clinically relevant.

- A higher incidence of malignancies in the interim analysis of non-inferiority study (NIMBLE) has been observed. Narratives with causality assessment of the observed cases do not signal any safety pattern in the observed malignancies. Similar incidences of events under SOC Neoplasms benign, malignant and unspecified were observed between placebo and depemokimab in a pool of 4 pivotal placebo-controlled studies. Thus, no safety concern is raised. The full CSR, including final safety results, of the active controlled study NIMBLE will be provided post-approval (by the end of April 2026). Moreover, the occurrence of malignancies will be followed as part of the PSURs submissions.

## *10.5. Effects Table*

**Table 56: Efects Table for Exdensur in severe uncontrolled eosinophilic asthma and severe uncontrolled CRSwNP**
**Asthma data cut-off: 10DEC2023 (SWIFT-1), 07MAY2024 (SWIFT-2)**
**CRSwNP data cut-off: 20SEP2024 (ANCHOR-1), 26AUG2024 (ANCHOR-2)**

| *Effect (short description)* | *Depemokimab 100 mg SC* | *Placebo* | *Uncertainties/ Strength of evidence* | *Ref* |
|---|---|---|---|---|
| **Favourable Effects** | | | | |
| **Asthma** | | | | |
| Annualised exacerbation rate (95% CI; primary endpoint) | 0.46 (0.36, 0.58) | 1.11 (0.86, 1.43) | **SoE:** Comparable, statistically significant effect observed in replicate studies; Tipping point analysis demonstrated robustness of conclusion of the primary analysis in either study | SWIFT-1 |
| | 0.56 (0.44, 0.70) | 1.08 (0.83, 1.41) | | SWIFT-2 |

| *Effect (short description)* | *Depemokimab 100 mg SC* | *Placebo* | *Uncertainties/ Strength of evidence* | *Ref* |
|---|---|---|---|---|
| LS mean (SE) change from baseline in SGRQ score at week 52 (secondary endpoint) | -13.0 (1.11) | -9.7 (1.55) | **SoE:** Comparable effect observed in replicate studies<br>**Unc:** Individual studies failed to show significant differences, statistical hierarchy broken | SWIFT-1 |
| | -14.8 (1.04) | -12.5 (1.46) | | SWIFT-2 |
| **CRSwNP** | | | | |
| LS mean (SE) change from baseline in the total endoscopic NP score at week 52 (co-primary endpoint) | -0.6 (0.14) | 0.2 (0.15) | **SoE:** Comparable and statistically significant effect observed in replicate studies | ANCHOR-1 |
| | -0.5 (0.14) | 0.1 (0.15) | | ANCHOR-2 |
| LS mean (SE) change from baseline nasal obstruction VRS score over week 49 to week 52 (co-primary endpoint) | -0.76 (0.079) | -0.53 (0.083) | **SoE:** Comparable and statistically significant effect observed in replicate studies | ANCHOR-1 |
| | -0.77 (0.076) | -0.53 (0.078) | | ANCHOR-2 |
| Time to first NP surgery (actual or entry on waiting list) or disease-modulating medication up to week 52 (key secondary endpoint pooled analysis) | 44 (16%) | 56 (22%) | **SoE:** Pooled analyses HR 0.735 (0.495, 1.092), p=0.128 = not statistically significant; statistical hierarchy broken<br>**Unc:** Actual number of surgeries lower than expected | Pooled ANCHOR studies |
| **Unfavourable Effects** (asthma and CRSwNP pooled) | | | | |
| Drug related AEs | 5% | 3% | **SoE:** No individual PT was reported for ≥1% patients. Similar safety profile in asthma SWIFT pool and CRSwNP ANCHOR pool<br>**Unc:** Limited safety database in CRSwNP (n=272). No active controlled or long term (>12 months) treatment data in CRSwNP patients | Placebo controlled pool |

| *Effect (short description)* | *Depemokimab 100 mg SC* | *Placebo* | *Uncertainties/ Strength of evidence* | *Ref* |
|---|---|---|---|---|
| Local injection site reactions* | ~1-3% | <1% | **SoE:** Generally non-serious and resolving in a few days | All Phase III studies |
| Administration related systemic reactions (non-allergic)** | 1% | <1% | **SoE:** Generally non-serious and resolving in a few days | All Phase III studies |

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence.
*Symptoms include pain, erythema, swelling, itching. ** Symptoms include headache, fatigue, rash.

## *10.6. Benefit-risk assessment and discussion*

### 10.6.1. Importance of favourable and unfavourable effects

**Dose regimen**

Depemokimab offers a reduced dosing schedule (twice per year) compared to currently approved biologicals, which all require more frequent dosing, i.e. every 2-8 weeks. Less frequent dosing may alleviate treatment burden as less frequent therapeutic interventions are needed. Based on observations in other diseases, this may provide greater patient satisfaction and improved quality of life.

It was noted that the proposed posology might not be the most optimal proposal as symptom control and effects on blood eosinophil count appear to decrease towards the end of the dose interval in both indications. Considering that no other posology was studied, it currently remains an uncertainty whether a more optimal posology may exist, but this can be accepted considering the positive B/R for depemokimab 100 mg SC Q26W in both indications.

**Asthma**

SWIFT-1 and SWIFT-2 were well designed, multicentre, randomised, placebo-controlled trials that aimed to show superiority of depemokimab over placebo as add-on treatment in patients with severe eosinophilic asthma with uncontrolled disease despite standard of care, including medium- to high-dose ICS (≥440 mcg FP or equivalent) and at least one asthma controller.

Both SWIFT studies met their primary endpoint of exacerbations. The observed relative reduction in annualised rate of clinically significant exacerbations (54% for the integrated analysis) compared to placebo was comparable to those of other anti-IL-5/5R therapies (21-70%).

However, both SWIFT studies failed to show any statistically significant effect on the secondary endpoints included in the statistical hierarchy. For several patient-reported outcomes (SGRQ score, ACQ-5 score) and lung function (FEV1), improvements from baseline were observed at Week 52 in both depemokimab and placebo groups. Only for SGRQ score, these improvements were numerically greater for depemokimab than for placebo and statistically significant in the integrated analysis, although this analysis was not controlled for multiplicity.

This lack of statistical significance on HRQoL and lung function is in contrast to other anti-IL-5/5R therapies, which generally showed improvements in patient-reported outcomes and/or lung function parameters. However, the treatment landscape of severe uncontrolled asthma has changed with the availability of several biologicals, and many patients with severe asthma already receive treatment. This may have had implications on the study populations recruited for the SWIFT studies, while additionally, it cannot be ruled out that the studied dose regimen (100 mg/Q26W) is not the most appropriate dose regimen for depemokimab.

In a direct comparison between depemokimab and approved anti-IL-5 therapies (mepolizumab, benralizumab), the annualised rate of clinically significant exacerbations was 0.57 (95% CI: 0.50, 0.64) in the depemokimab group and 0.49 (95% CI: 0.43, 0.55) in the mepolizumab/benralizumab group, resulting in an exacerbation rate ratio of 1.16 (95% CI: 0.98, 1.38). While the 95% confidence interval included 1.0, the upper bound was higher than the pre-specified non-inferiority margin of 1.28, and therefore the primary endpoint did not meet non-inferiority.

The number of exacerbations was low in both groups, however, which may exaggerate the relative difference. The absolute difference between the groups was small (0.08 exacerbations/year) and not clinically relevant, which is supported by comparable results between groups for the secondary endpoints of HRQoL and lung function. Therefore, results of the NIMBLE study do not raise concerns with regard to the efficacy of depemokimab in comparison to other anti-IL-5/5R treatments in patients who have previously shown to benefit from biologicals.

**Adolescents**

Only few adolescents were included in the SWIFT studies (n=30), of whom a total of 15 received depemokimab 100 mg SC.

While clinical efficacy of similar extent was demonstrated between adults and adolescents based on the subgroup analyses of the primary endpoint, the number of adolescents included in both studies is low. However, results for adolescents can be extrapolated from adults, as PK exposure was shown to be comparable between adults and adolescents. Additional Bayesian analysis was performed, which supports the extrapolation of results from adults to adolescents.

Overall, the beneficial effect of depemokimab in both adults and adolescents with severe eosinophilic asthma is moderate but clinically relevant considering the reduction in exacerbations.

**CRSwNP**

The pivotal studies ANCHOR-1 and ANCHOR-2 were both well designed, multicentre, randomised, placebo-controlled trials of 52-week duration that showed a replication of efficacy when depemokimab was added to the standard of care. Both trials met their co-primary endpoint by showing statistically significant improvements in both the objective co-primary endpoint (Nasal Polyp score) as well as a subjective improvement in the nasal obstruction VRS Likert symptom score, with nasal obstruction being a cardinal symptom of CRSwNP. These co-primary endpoints were supported with various sensitivity analyses including Jump to reference analyses. The secondary outcomes of both trials also showed numerical improvements across various efficacy domains, i.e symptomatic improvement, quality of life and CT-score. These secondary outcome measures reached nominal statistical significance when results were combined.

The pooled key secondary outcome showed a numerical delay to the timepoint when intensification of treatment was needed by means of need for nasal surgery (actual or on waiting list) or additional

maintenance treatment to target type 2 inflammation; however, a nominal lower proportion of patients needed additional treatments including coursed or oral corticosteroids to achieve sufficient symptom control.

The overall treatment effects over various domains support the clinical relevance of the efficacy. The cross-study comparisons suggests that overall treatment effects are somewhat smaller than observed in previous pivotal studies. However, the lack of a head-to-head comparison preclude firm conclusions, considering amongst others the regional differences in the treatment and aetiology of CRSwNP, symptom measurement, statistical analyses etc, while the number of nasal surgeries was lower than expected. The comparison with previous studies is impaired because of the availability of other biologicals targeting type 2 inflammation. It can assumed that many severely symptomatic patients already receive Type 2 inflammatory treatment, while trial participation harbours the risk of being randomised to placebo. Like in previous studies the largest effect was observed in patients harbouring more intense Type 2 inflammation.

Nevertheless, the overall efficacy data robustly show a treatment effect, which is considered clinically relevant when compared to placebo.

For both indications, the low dosing frequency of twice annually adds to the treatment benefit as it has a low treatment burden and may theoretically be associated with a better treatment adherence.

**Safety**

Treatment with depemokimab was well tolerated in the study population of asthma and CRSwNP patients, as reflected in the short list of generally mild adverse reactions and similar or lower incidence of severe AEs and SAEs compared to placebo. Only a limited number of adolescent participants (33 in total) were exposed to depemokimab sin the clinical studies. However, no new safety concern was identified in this population. The safety profile seen in adolescent patients with asthma was generally similar to that seen in adult patients.

The safety database in CRSwNP patients is relatively limited, and there is no active-controlled data for this target population. Safety data could be partly extrapolated from the asthma study population, where a similar safety profile is observed. The acceptable safety profile of the approved anti-IL-5 biological mepolizumab, with a similar mode of action, provides further support for safety of depemokimab in CRSwNP.

### 10.6.2. Balance of benefits and risks

Depemokimab offers a reduced dosing schedule (twice per year) compared with currently approved biologicals, i.e. every 2 to 8 weeks. This treatment scheme could lead to better adherence.

**Asthma**

For the indication asthma, both replicate pivotal studies met their primary endpoint of clinically significant exacerbations. The rate ratio of depemokimab versus placebo for clinically significant exacerbations was comparable to the rate ratios of other anti-IL-5/5R biologicals versus placebo. In contrast to other anti-IL-5/5R biologicals, which generally showed improvements in patient-reported outcomes and lung function, the pivotal studies failed to show any statistically significant effect on these secondary endpoints.

A direct comparison between depemokimab and approved anti-IL-5 therapies (mepolizumab, benralizumab) did not raise concerns with regard to the efficacy of depemokimab in comparison to other anti-IL-5/5R treatments in patients who have previously shown to benefit from biologicals.

Overall, in adults with severe uncontrolled eosinophilic asthma, the extent of the effect of depemokimab is considered moderate but the benefit outweighs the risks of this treatment given its low toxicity as shown in the clinical trials. Therefore, the benefit/risk balance is considered positive.

In adolescents with severe uncontrolled eosinophilic asthma, efficacy comparable to adults was demonstrated in the SWIFT studies, but the difference to placebo was not statistically significant due to few participants aged 12-17 years. Results for adolescents can nevertheless be extrapolated from adults, as PK exposure was shown to be comparable between adults and adolescents. An additional Bayesian analysis was performed to further support the extrapolation from adults to adolescents.

The initially proposed wording of the indication has been adjusted to correctly reflect the included study population, i.e. Exdensur *is indicated as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by blood eosinophil count in adults and adolescents 12 years and older who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another asthma controller (see section 5.1).*

**CRSwNP**

For the indication CRSwNP, both replicate pivotal studies met their co-primary endpoint, supported with at least numerical improvements in the secondary and key secondary outcome measures, improvements achieved with twice annual dosing. No direct comparison was made with other anti-IL-5/5R biologicals, but the overall effect over placebo was considered clinically relevant and the benefit outweighs the risks of this treatment given its low toxicity as shown in the clinical trials. Therefore, the benefit/risk balance is considered positive.

The initially proposed wording of the indication has been adjusted to correctly reflect the included study population, i.e. *Exdensur is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.*

**Additional considerations on the benefit-risk balance**

The European Respiratory Society (ERS) was contacted by EMA to provide healthcare professionals perspective on the target diseases and current treatment landscape. The ERS summarised the current treatment landscape in asthma and CRSwNP and indicated that a reduced frequency in exacerbations is beneficial to patients, carers and healthcare providers. It was noted that the key endpoints in severe asthma are exacerbation reduction and reduction/cessation of maintenance systemic corticosteroids. According to the ERS, improvements in health status and symptoms are particularly important to patients. Lung function improvements were also considered important as they are related to disease progression and mortality.

It was furthermore noted that the evidence base for biologics for severe asthma in children and adolescents is small and further evidence for depemokimab would be valuable. To date biologics in asthma have not led to adverse effects in pregnancy but this would remain an important consideration. How to treat patients with asthma driven by non-T2-mediated immunity both pharmacologically and non-pharmacologically, how to alter the trajectory of the disease to prevent severe asthma and how to achieve remission in symptoms, health status and exacerbations remain the challenges for asthma and in particular severe disease, according to the ERS

## *10.7. Benefit-risk conclusions*

### 10.7.1. CHMP conclusions

**Asthma**

The overall benefit-risk balance of Exdensur in asthma is positive.

**CRSwNP**

The overall benefit-risk balance of Exdensur in CRSwNP is positive.