SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

EXDENSUR 100 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

EXDENSUR 100 mg solution for injection in pre-filled syringe

Each 1 mL pre-filled syringe contains 100 mg of depemokimab.

Depemokimab is a humanised (IgG1, kappa) monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipients with known effect

EXDENSUR 100 mg solution for injection in pre-filled syringe

Each 1 mL pre-filled syringe contains 0.2 mg polysorbate 80

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection)

Colourless, yellow to brown, clear to opalescent solution, with a pH of 6.0 and an osmolarity of 350 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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 maximum moderate-dose or high-dose inhaled corticosteroids (ICS) plus another asthma controller.

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 control.

4.2 Posology and method of administration

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

Posology

Asthma

Adults and adolescents aged 12 years and over

The recommended dose of depemokimab is 100 mg administered subcutaneously once every 6 months. Dosing at intervals shorter than 6 months is not recommended.

CRSwNP

Adults

The recommended dose of depemokimab is 100 mg administered subcutaneously once every 6 months. Dosing at intervals shorter than 6 months is not recommended.

Missed dose

If a dose is missed, administer as soon as possible. If the missed dose is taken 1 month or longer after the scheduled dose, resume the 6-monthly injection schedule from the date when the missed dose was given.

Special populations

Elderly

No dose adjustment is required for elderly patients aged ≥ 65 years old (see section 5.2).

Renal or hepatic impairment

No dose adjustment is required in patients with renal or hepatic impairment (see section 5.2).

Paediatric population

Asthma

The safety and efficacy of depemokimab in children aged less than 12 years have not yet been established. No data are available.

CRSwNP

The safety and efficacy in children with CRSwNP below the age of 18 years have not been established. No data are available.

Method of administration

The pre-filled syringe must be used for subcutaneous injection only.

EXDENSUR may be self-administered by adult or adolescent patients or administered by a caregiver if their healthcare professional determines that it is appropriate, and only after the patient or caregiver are trained in injection techniques.

For self-administration the recommended injection sites are the abdomen or thigh. A caregiver can also inject EXDENSUR into the upper arm.

Comprehensive instructions for subcutaneous administration of EXDENSUR in a pre-filled syringe are provided in the instructions for use in the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity reactions

Acute and delayed systemic reactions, including hypersensitivity reactions (such as urticaria and pruritus), have occurred following administration of depemokimab. These reactions generally occur within hours of administration, but some had a delayed onset (i.e., days). In the event of a hypersensitivity reaction, appropriate treatment should be initiated and clinical judgement must be used regarding re-administration of depemokimab.

Asthma-related adverse events or exacerbations

Depemokimab must not be used to treat acute asthma symptoms or acute exacerbations.

Asthma-related adverse events or exacerbations may occur during treatment with depemokimab. Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with depemokimab.

Reduction of corticosteroid dosage

Abrupt discontinuation of background medications (including systemic and inhaled corticosteroids) after initiation of depemokimab therapy is not recommended. Reductions in the dosages of background medications, if appropriate, must be gradual and performed under the supervision of a physician.

Parasitic (helminth) infections

Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections were excluded from participation in the clinical programme. Patients with pre-existing helminth infections should be treated for their infection prior to depemokimab therapy. If patients become infected while receiving treatment with depemokimab and do not respond to anti-helminth treatment, consider delaying administration of the next depemokimab dose until the infection resolves.

Excipients

This medicinal product contains polysorbate 80 (see section 2), which may cause allergic reactions.

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg dose, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been conducted with depemokimab.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of depemokimab in pregnanat women. Animal studies targeting IL-5 signalling pathways do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Monoclonal antibodies, such as depemokimab, are expected to be transported across the placenta as pregnancy progresses, therefore, potential exposure to the fetus is likely to be greater during the second and third trimester of pregnancy.

As a precautionary measure, it is preferable to avoid the use of depemokimab during pregnancy. Depemokimab should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus.

Breast-feeding

There are no data regarding the excretion of depemokimab in human or animal milk. However, depemokimab is a humanised monoclonal antibody (immunoglobulin G1

[IgG1] kappa), and immunoglobulin G (IgG) is present in human milk in small amounts.

A decision must be made whether to discontinue breast-feeding or discontinue depemokimab, taking into account the importance of breast-feeding to the infant and the importance of the drug to the mother.

Fertility

There are no fertility data in humans. Animal studies have shown no adverse effects of anti-IL-5 treatment on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

EXDENSUR has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions reported with depemokimab were local injection site reactions (2%).

Tabulated list of adverse reactions

The safety of depemokimab was studied in 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. A total of 773 patients received at least one dose of depemokimab 100 mg in these studies.

Other phase 3 clinical studies include 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 ongoing 52-week study (NIMBLE) involving asthma patients who were previously treated with other anti-IL5/IL-5R biological medicines prior to study entry (n = 538).

Adverse reactions associated with depemokimab are presented in the table below (Table 1).

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000) and very rare (< 1/10 000). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions

System Organ Class	**Adverse reactions**	**Frequency**
Immune system disorders	Hypersensitivity reactions (systemic allergic)[a b]	Uncommon
Skin and subcutaneous tissue disorders	Pruritus	Common
General disorders and administration site conditions	Administration-related systemic reactions (non-allergic)[b c] Local injection site reactions[d]	Common

[a] Observed in a phase 1 study and in an open-label extension study

[b] The majority of events (85%) resolved in ≤7 days, with most events (65%) resolving in ≤2 days from their onset.

[c] Symptoms include headache, fatigue, rash.

[d] Symptoms include pain, erythema, swelling, and itching. The majority of events were mild in intensity and 79% resolved in ≤7 days, with most events (56%) resolving in ≤2 days from their onset.

Paediatric population

A total of fifteen adolescents (aged 12-17) received depemokimab in two placebo-controlled studies for asthma (SWIFT-1 and SWIFT-2) of 52 weeks duration. The safety profile was generally similar to that seen in adults. No additional adverse reactions were identified.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: http://www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no clinical experience with overdose of depemokimab.

There is no specific treatment for an overdose with depemokimab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Further management should be as clinically indicated or recommended by the national poisons centre, where applicable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airways disease, ATC code: R03DX12

Mechanism of action

Depemokimab targets human IL-5 with a high binding affinity of 10.5 pM thereby blocking 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.

IL-5 is a cytokine involved in Type 2 inflammation along with IL-4 and IL-13. IL-5 is responsible for the growth and differentiation of eosinophils in the bone marrow, and recruitment, activation, and survival of eosinophils in the tissue space. Additional cell types that express IL-5R alpha including mast cells, plasma cells, epithelial cells, and fibroblasts, are also involved in inflammation. 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.

Pharmacodynamic effects

Asthma

In placebo-controlled studies involving adult and adolescent patients aged 12 years and older with asthma, a 100 mg dose of depemokimab administered SC every 6 months for 52 weeks reduced blood eosinophils to an adjusted geometric mean count

of 56 cells/mcL at Week 52. This corresponds to a geometric mean reduction of 79% (95% CI: 75.8, 81.8) compared to placebo. This magnitude of blood eosinophil reduction was observed within 2 weeks of treatment (at the first assessment) and was maintained throughout the treatment period.

In a clinical pharmacology study with mild-to-moderate asthma patients, a single 100 mg SC dose of depemokimab produced a rapid reduction in blood eosinophil count. Blood eosinophils were reduced by 54% compared to placebo 24 hours after dosing, which was the first post-dose assessment.

CRSwNP

In placebo-controlled studies involving adult patients with CRSwNP, a 100 mg dose of depemokimab administered SC every 6 months for 52 weeks reduced blood eosinophils to an adjusted geometric mean count of 46 cells/mcL at Week 52. This corresponds to a geometric mean reduction of 85% (95% CI: 82.4, 86.7) compared to placebo. This magnitude of blood eosinophil reduction was observed within 4 weeks of treatment (at the first assessment) and was maintained throughout the treatment period.

Immunogenicity

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.

The percentage of patients who were positive for ADA was 9% (55/622) in a 52-week open-label extension asthma study (AGILE; n = 395 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).

Across the placebo-controlled studies for asthma and CRSwNP indications, and the 52-week open label extension asthma study (AGILE), <1% (N=7) of the patients were positive for neutralising antibodies.

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, efficacy or safety of depemokimab.

Clinical efficacy and safety

Asthma

The efficacy of depemokimab was evaluated in 2 replicate, randomised (2:1 ratio, depemokimab to placebo), double-blind, placebo-controlled, parallel-group, multi-centre clinical studies of 52-weeks treatment duration (SWIFT-1 and SWIFT-2). The two studies enrolled patients aged 12 years and older with asthma with type 2 inflammation characterised by an eosinophilic phenotype. In these studies, depemokimab 100 mg was administered SC once every 6 months for a total of 2 doses in addition to standard of care (SoC) therapy. Patients were required to have 2 or more asthma exacerbations requiring treatment with systemic corticosteroids (SCS) in the last 12 months, while on moderate to high-dose ICS (moderate ICS dose = 500 mcg FP daily metered dose or equivalent; high ICS dose >500 mcg FP daily metered dose or equivalent) plus at least one additional asthma controller (e.g., LABA, long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonist (LTRA), or theophylline). Patients were also required to have a blood eosinophil count of $\geq$150 cells/mcL at screening or $\geq$300 cells/mcL documented in the year prior to study entry and reduced lung function at baseline (pre-bronchodilator forced expiratory volume in 1 second [FEV_1] <80% predicted normal in adults and [FEV_1] <90% or FEV_1:FVC ratio <0.8 in adolescents). Patients were enrolled without requiring a minimum baseline Asthma Control Questionnaire-5 (ACQ-5) score. Depemokimab was administered as add-on to background asthma treatment which continued throughout the duration of the studies. The Full Analysis Set (FAS) population consisted of 762 patients who were randomised and received at least one dose of depemokimab or placebo in the two studies (382 in SWIFT-1 and 380 in SWIFT-2).

The study population in SWIFT-1 and SWIFT-2 comprised adult and adolescent patients, with a mean age of 54 years (SD: 14.2) and 53 years (SD: 16.2), respectively. The majority of participants were female (58% in SWIFT-1 and 63% in SWIFT-2) and predominantly White (83% and 72%, respectively). Patients had a mean pre-bronchodilator % predicted FEV_1 of 62% in both trials (SD: 15.2 in SWIFT-1 and 15.9 in SWIFT-2) and a median eosinophil count of 310 cells/μL in SWIFT-1 and 340 cells/μL in SWIFT-2. The mean number of exacerbations in the previous year was 2.2 in SWIFT-1 and 2.7 in SWIFT-2.

A total of 179 (47%) patients in SWIFT-1 and 154 (41%) patients in SWIFT-2 were on moderate dose ICS treatment (median dose 500 mcg FP daily metered dose or equivalent, range 250-1000 mcg* in both studies) and 203 (53%) patients in SWIFT-1 and 226 (59%) patients in SWIFT-2 were on high dose ICS treatment (median dose 1000 mcg FP daily metered dose or equivalent in both studies, range 250-2000 mcg* in SWIFT 1 and 200-2000 mcg* in SWIFT-2). Additionally, 5% of patients in both trials were on oral corticosteroids (OCS) at baseline.

*There were 7 participants allocated to the high dose ICS stratum whose concomitant medication data suggested there were on an FP equivalent total daily dose of ≤500 mcg and 6 participants in the moderate dose ICS stratum whose concomitant medication data suggested they were on an FP equivalent total daily dose of >500 mcg

Exacerbations

The primary efficacy outcome for SWIFT-1 and SWIFT-2 was the annualised rate of clinically significant exacerbations over the 52-week treatment period. A clinically significant exacerbation was defined as worsening of asthma requiring use of systemic corticosteroids (IV or oral steroids for at least 3 days or a single IM

corticosteroid dose) and/or hospitalisation and/or Emergency Department visit. For patients on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days was required. All patients experiencing an exacerbation were treated with systemic corticosteroids and the majority remained in the study.

In SWIFT-1 and SWIFT-2, the annualised rate of asthma exacerbations was significantly lower in patients receiving depemokimab compared to placebo (Table 2). During the 52-week treatment period, fewer patients experienced exacerbations in the depemokimab groups (32% and 32%) compared with the placebo groups (46% and 50%), in SWIFT-1 and SWIFT-2, respectively. In a pooled analysis from SWIFT-1 and SWIFT-2, the percentage of patients with exacerbations in the depemokimab groups was 31% compared with 48% in the placebo groups.

Table 2. Results of Primary Exacerbation Endpoint (FAS Population)

	SWIFT-1		**SWIFT-2**		**Pooled**	
	Depemokimab N= 250	**Placebo N= 132**	**Depemokimab N= 252**	**Placebo N= 128**	**Depemokimab N= 502**	**Placebo N= 260**
Annualised Asthma Exacerbations Rate						
Exacerbation rate per year	0.46	1.11	0.56	1.08	0.51	1.11
Rate ratio (95% CI) Percent reduction (95% CI)	0.42 (0.30, 0.59) 58% (41, 70)		0.52 (0.36, 0.73) 48% (27, 64)		0.46 (0.36, 0.59) 54% (41, 64)	
p-value	<0.001		<0.001		<0.001*	

FAS = Full Analysis Set

*nominally significant p-value; analysis not multiplicity-controlled

In both studies, a percentage reduction in the annualised rate of clinically significant exacerbations was higher compared with placebo regardless of baseline ICS dose. In the moderate dose ICS population, depemokimab reduced the rate of exacerbations compared with placebo by 64% (RR 0.36 (95% CI: 0.21,0.62)) and 57% (RR 0.43 (95% CI: 0.24,0.77)) in SWIFT-1 and SWIFT-2, respectively. In the high dose ICS population, depemokimab reduced the rate of exacerbations compared with placebo by 54% (RR 0.46 (95% CI: 0.29,0.72)) and 43% (RR 0.57 (95% CI: 0.37,0.88)) in SWIFT-1 and SWIFT-2, respectively.

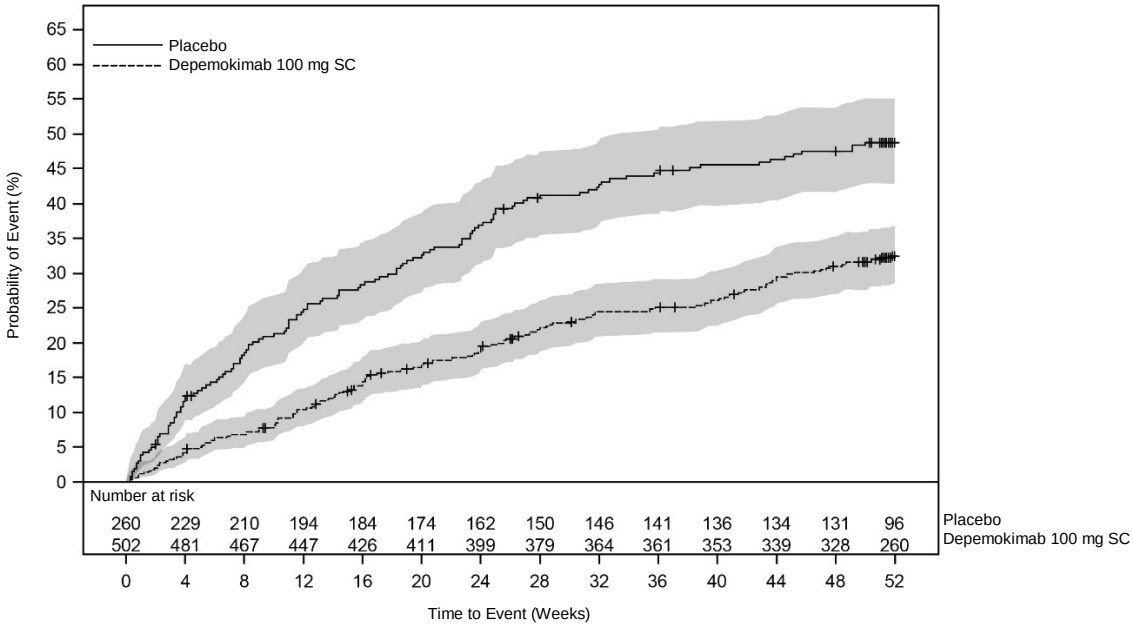
The percentage of patients with exacerbations requiring hospitalisation and/or Emergency Department visit was lower for patients treated with depemokimab compared with placebo. In a pooled analysis of SWIFT-1 and SWIFT-2, the percentage of patients with exacerbations requiring hospitalisation and/or Emergency Department visit over 52 weeks was 3% for depemokimab compared with 9% for placebo. Depemokimab reduced the rate of exacerbations by 72% compared with placebo [Rate Ratio (RR) of 0.28 (95% CI: 0.13, 0.61), p=0.002*].

In a pooled analysis from SWIFT-1 and SWIFT-2, based on the time to first exacerbation analysis, treatment with depemokimab reduced the risk of exacerbation

by 46% compared with placebo [Hazard Ratio (HR) of 0.54 (95% CI: 0.43, 0.69)] p<0.001*] (Figure 1).

*nominally significant p-value; analysis not multiplicity-controlled

Figure 1. Kaplan Meier Curve for Time to First Clinically Significant Exacerbation (Pooled FAS Population)



NOTE: Number (%) of subjects with event(s) in depemokimab group vs. placebo group is 160 (32%) vs. 125 (48%).

Secondary Endpoints

Additional efficacy assessments included health-related quality of life measured with St. George's Respiratory Questionnaire (SGRQ), asthma control measured with Asthma Control Questionnaire (ACQ-5) and lung function (pre-bronchodilator FEV_1).

In both SWIFT-1 and SWIFT-2, all secondary endpoints failed to reach statical significance within the hierarchical testing procedure, after failing to show a statistically significant difference in the change from baseline in SGRO at Week 52.

Table 3 provides the results of these secondary endpoints for the FAS population of SWIFT-1 and SWIFT-2.

Table 3. Results of Secondary Endpoints (FAS Population)

	SWIFT-1		SWIFT-2	
	Depemokimab N = 250	**Placebo N = 132**	**Depemokimab N = 252**	**Placebo N = 128**
St. George's Respiratory Questionnaire (SGRQ) total score at Week 52				
n[a]	224	114	224	116
LS Mean Change from Baseline (SE)	-13.0 (1.11)	-9.7 (1.55)	-14.8 (1.04)	-12.5 (1.46)
Adjusted treatment difference[b]	-3.4		-2.3	
(95% CI)	(-7.1, 0.4)		(-5.8, 1.2)	
p-value [c]	0.080		0.200	
Asthma Control Questionnaire-5 (ACQ-5) score at Week 52				
n[a]	224	114	224	116
LS Mean Change from Baseline (SE)	-0.82 (0.066)	-0.77 (0.091)	-0.81 (0.065)	-0.70 (0.091)
Adjusted treatment difference[b]	-0.04		-0.11	
(95% CI)	(-0.27, 0.18)		(-0.33, 0.11)	
p-value [c]	0.690		0.333	
Pre-bronchodilator FEV_1 (mL) at Week 52				
n[a]	224	115	226	112
LS Mean Change from Baseline (SE)	160 (26.3)	160 (36.4)	240 (28.6)	184 (40.7)
Adjusted treatment difference[b]	-1		56	
(95% CI)	(-89, 88)		(-43, 154)	
p-value [c]	0.991		0.267	

LS = Least Squares, FEV_1 = Forced Expiratory Volume in 1 second

[a] Number of patients with analysable data at the timepoint

[b] Adjusted treatment difference (depemokimab vs. placebo)

[c] statistical significance has not been met

In a pooled analysis from SWIFT-1 and SWIFT-2, the mean change from baseline SGRQ total score at Week 52 was -13.9 and -11.0 in the depemokimab and placebo groups respectively. The adjusted treatment difference was -2.9 (95% CI: -5.4, -0.3), p=0.028* in favour of depemokimab versus placebo.

* nominally significant p-value; analysis not multiplicity-controlled

Responder Analyses

In a pooled analysis of SWIFT-1 and SWIFT-2, the SGRQ responder rate (clinically meaningful improvement defined as a decrease in score of 4 or more) at Week 52 was 65% for depemokimab compared with 61% for placebo with an Odds Ratio (OR) of 1.1 (95% CI: 0.8, 1.5).

In a pooled analysis of SWIFT-1 and SWIFT-2, the ACQ-5 responder rate (clinically meaningful improvement defined as a decrease in score of 0.5 or more) at Week 52

was 54% for depemokimab compared with 54% for placebo with an OR of 1.00 (95% CI: 0.72, 1.38).

Open-label extension study in asthma (AGILE)

Patients who completed either the SWIFT-1 or SWIFT-2 study were able to enrol in an open-label extension study (AGILE) where they all received up to two doses of depemokimab over an additional 52 weeks. The analysis of AGILE (n = 629) showed an annualised exacerbation rate of 0.56 (95% CI: 0.49, 0.65).

Chronic rhinosinusitis with nasal polyps (CRSwNP)

The efficacy of depemokimab in adult patients with CRSwNP was evaluated in 2 replicate, randomised, double-blind, placebo-controlled, parallel-group, multicentre clinical studies of 52-weeks duration (ANCHOR-1 and ANCHOR-2). These studies evaluated the efficacy of 100 mg of depemokimab administered SC once every 6 months for a total of 2 doses in addition to standard of care (SoC) therapy. All patients had been treated with systemic corticosteroids anytime within the past 2 years; and/or had a medical contraindication/intolerance to systemic corticosteroids; and/or had a documented history of prior surgery for nasal polyps (NP) prior to screening. For inclusion, participants were required to have severe symptoms of chronic rhinosinusitis with nasal polyps (defined as symptoms of nasal congestion, blockade or obstruction with moderate or severe severity), and loss of smell or rhinorrhea.

Randomised patients were required to have an endoscopic bilateral NP score of at least 5 out of a maximum score of 8 with a minimum score of 2 in each nasal cavity and a mean nasal obstruction Verbal Response Scale (VRS) score of 2 or greater at baseline.

The demographics and baseline characteristics of the patients in these two studies are provided in Table 4 below:

Table 4. Demographics and Baseline Characteristics (FAS Population)

	ANCHOR-1 N = 271	**ANCHOR-2 N = 257**
Age (y) of patients, mean (SD)	54 (13.4)	50 (12.9)
Female, n (%)	83 (31)	80 (31)
White, n (%)	185 (70)	197 (77)
Duration (y) of CRSwNP, mean (SD)	13 (11.2)	11 (8.7)
Patients with ≥ 1 previous NP surgery, n (%)	171 (63)	162 (63)
SCS use for NP in past 12 months, n (%)	190 (70)	172 (67)
Asthma, n (%)	161 (59)	131 (51)
AERD, n (%)	43 (16)	42 (16)
Blood eosinophil count, cells/mcL, median (min, max)	360 (10, 10 550)	360 (30, 1 670)
Total endoscopic NP score[a b c], mean (SD),	6.0 (1.35)	5.9 (1.29)

maximum score = 8		
Nasal obstruction VRS mean score[a d], mean (SD), maximum score = 3	2.5 (0.48)	2.6 (0.42)
Rhinorrhoea VRS mean score[a d], mean (SD), maximum score = 3	2.2 (0.70)	2.3 (0.67)
Loss of smell VRS mean score[a d], mean (SD), maximum score = 3	2.7 (0.55)	2.8 (0.41)
LMK CT score[a b], mean (SD), maximum score = 24	18.7 (4.08)	18.9 (4.19)
SNOT-22 total score[a e], mean (SD), maximum score = 110	57.4 (22.15)	60.1 (19.95)
Patients with SNOT-22 total score ≥40, n (%)	204 (75)	207 (81)

FAS = full analysis set, CRSwNP = chronic rhinosinusitis with nasal polyps, SCS = systemic corticosteroid, NP = nasal polyps, AERD = aspirin-exacerbated respiratory disease, VRS = verbal response scale, LMK CT = Lund Mackay Computed Tomography, SNOT-22 = Sino-Nasal Outcome Test

[a] Higher scores indicate greater disease severity.

[b] As graded by independent blinded assessors.

[c] NP score is the sum of scores from both nostrils (0-8 scale) where each nostril was graded (0=no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle concha; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha; 4=large polyps causing almost complete congestion/obstruction of the inferior meatus).

[d] Collected daily by patients on a 0 to 3 scale where 0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms.

[e] SNOT-22 is a health-related quality of life assessment tool and includes 22 items in 6 domains of symptoms and impact associated with CRSwNP (nasal, non-nasal, ear/facial, sleep, fatigue, emotional consequences). Higher scores indicate worse health related quality of life.

Total Endoscopic Nasal Polyp Score and Nasal Obstruction VRS Score

The co-primary efficacy endpoints in each study were change from baseline in total endoscopic NP score (0-8 scale) at Week 52 as graded by central blinded readers and change from baseline in mean nasal obstruction VRS score (0-3 scale [0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms]) over Weeks 49 to 52 as self-reported by patients using a daily diary. Patients who received depemokimab had a statistically significant improvement (reduction) in total endoscopic NP score at Week 52 and nasal obstruction VRS score over Weeks 49 to 52 compared with placebo in both ANCHOR-1 and ANCHOR-2. The results for the co-primary endpoints in the individual ANCHOR studies and the results from a pooled analysis from ANCHOR-1 and ANCHOR-2 are presented in Table 5.

Table 5. Results of Co-Primary Endpoints (FAS Population)

	ANCHOR-1		ANCHOR-2		Pooled	
	Depemokimab N = 143	**Placebo N = 128**	**Depemokimab N = 129**	**Placebo N = 128**	**Depemokimab N = 272**	**Placebo N = 256**
Total Endoscopic NP Score at Week 52[a b]						
n[c]	128	120	120	115	248	235
LS Mean (SE)	5.4 (0.14)	6.2 (0.15)	5.4 (0.14)	6.0 (0.15)	5.4 (0.10)	6.1 (0.10)
LS Mean Change from baseline (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)
Adjusted treatment difference[d] (95% CI)	-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[f]	
Nasal Obstruction VRS Mean Score over Weeks 49 to 52[a b]						
n[c]	125	116	119	111	244	227
LS Mean (SE)	1.77 (0.079)	2.00 (0.083)	1.83 (0.076)	2.07 (0.078)	1.80 (0.055)	2.04 (0.057)
LS Mean Change from baseline (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)
Adjusted treatment difference[d] (95% CI)	-0.23 (-0.46, 0.00[e])		-0.25 (-0.46, -0.03)		-0.24 (-0.39, -0.08)	
p-value	0.047		0.025		<0.003[f]	

FAS = Full Analysis Set, NP = Nasal Polyp, LS = Least Squares, VRS = Verbal Response Scale

[a] Patients who had nasal surgery or used disease-modulating medication for CRSwNP prior to the timepoint of interest were assigned the worst possible value of the relevant score for all assessments following surgery or initiation of disease-modulating medication.

[b] Based on Mixed Model Repeat Measures (MMRM) analyses with covariates of treatment, baseline score, log(e) baseline blood eosinophil count, region, previous surgery for nasal polyps, visit and interaction terms for visit by baseline and visit by treatment. For the pooled analysis, study was included as an additional covariate.

[c] Number of patients with analysable data at the timepoint

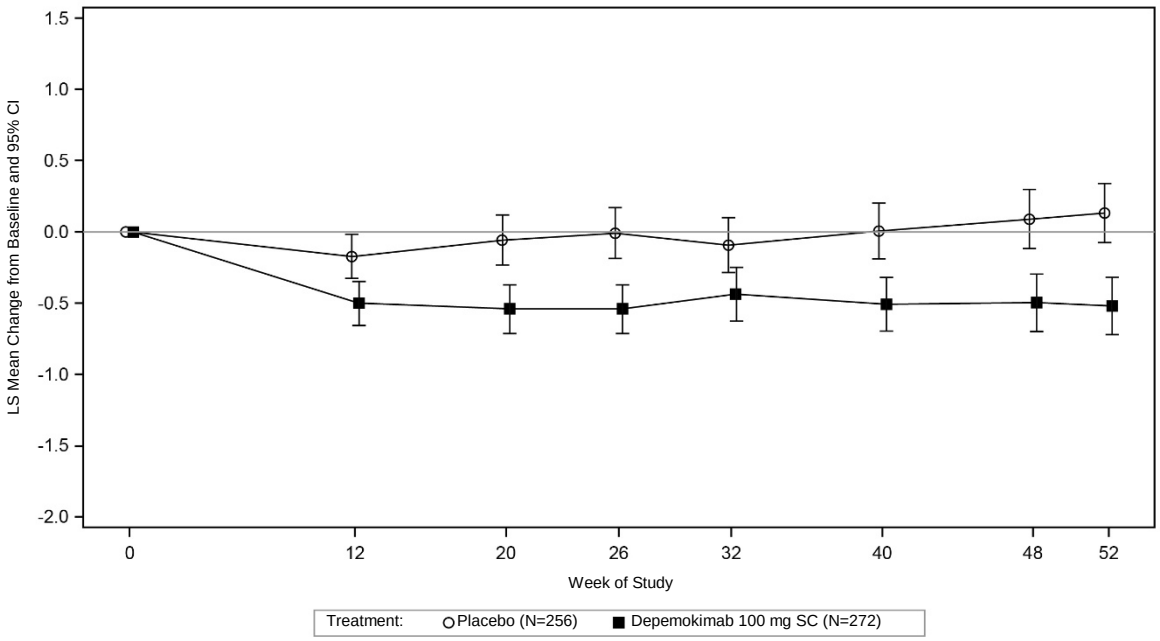
[d] Adjusted treatment difference (depemokimab vs. placebo)

[e] The upper limit of the 95% CI represents a rounded number of -0.003.

[f] nominally significant p-value: analysis not multiplicity-controlled

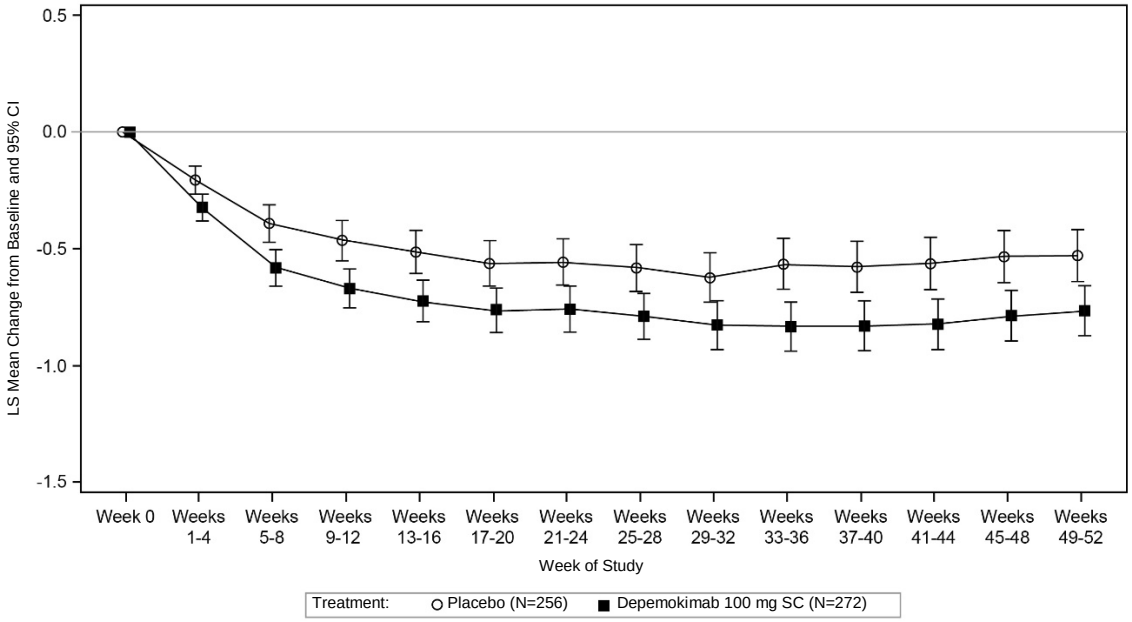
In a pooled analysis from ANCHOR-1 and ANCHOR-2, a treatment difference in favour of depemokimab was observed by Week 12 (first timepoint assessed) for the total endoscopic NP score and by Weeks 1-4 (first timepoint assessed) for the nasal obstruction VRS mean score that was maintained up to Week 52 (Figures 2 and 3).

Figure 2. LS Mean Change from Baseline (95% CI) in Total Endoscopic NP Score up to Week 52 (Pooled FAS Population)



LS = Least Squares; NP = Nasal Polyps; FAS = Full Analysis Set

Figure 3. LS Mean Change from Baseline (95% CI) in Nasal Obstruction VRS Mean Score up to Week 52 (Pooled FAS Population)



LS = Least Squares; VRS = Verbal Response Scale; FAS = Full Analysis Set

In a pooled analysis from ANCHOR-1 and ANCHOR-2, the proportion of total endoscopic NP score responders (≥1 point improvement [decrease] from baseline) at Week 52 was 43% (116/272) for depemokimab compared with 24% (62/256) for placebo with an OR of 2.31 (95% CI: 1.58, 3.38; p<0.001*) and the proportion of nasal obstruction VRS mean score responders (≥1-point improvement [decrease]

from baseline) over Weeks 49 to 52 was 40% (110/272) for depemokimab compared with 29% (75/256) for placebo with an OR of 1.56 (95% CI: 1.07, 2.27; p=0.020*).

* nominally significant p-value; analysis not multiplicity-controlled

In a pooled subgroup analysis of the co-primary endpoints, patients with/without co-morbid asthma, or blood eosinophil counts above or below 300 cells/mcL at baseline showed improvements with depemokimab compared to placebo that were consistent with the overall population.

Secondary endpoints

In both ANCHOR-1 and ANCHOR-2 all secondary endpoints failed to reach statistical significance within the hierarchical testing procedure, after failing to show a statistically significant difference in the change from baseline in rhinorrhoea VRS mean score over weeks 49-52, although the numerical difference was in favour of depemokimab in both studies.

The results for the secondary endpoints in the individual ANCHOR studies and the results of the pooled analysis from ANCHOR-1 and ANCHOR-2 show improvements in favour of depemokimab and are presented in Table 6.

Table 6. Results of Secondary Endpoints (FAS Population)

	ANCHOR-1		**ANCHOR-2**		**Pooled**	
	Depemokimab N = 143	**Placebo N = 128**	**Depemokimab N = 129**	**Placebo N = 128**	**Depemokimab N = 272**	**Placebo N = 256**
Rhinorrhoea VRS Mean Score over Weeks 49 to 52[a b]						
n[c]	125	116	119	111	244	227
LS Mean (SE)	1.46 (0.084)	1.68 (0.087)	1.54 (0.080)	1.72 (0.082)	1.50 (0.058)	1.69 (0.060)
LS Mean change from baseline (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)
Adjusted treatment difference[d] (95% CI)	-0.22 (-0.46, 0.02)		-0.18 (-0.40, 0.05)		-0.19 (-0.36, -0.03)	
p-value	0.074[g]		0.125[g]		0.021[f]	
Loss of Smell VRS Mean Score over Weeks 49 to 52[a b]						
n[c]	125	116	119	111	244	227
LS Mean (SE)	2.24 (0.069)	2.43 (0.072)	2.26 (0.066)	2.52 (0.068)	2.25 (0.048)	2.47 (0.049)
LS Mean change from baseline (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)

Adjusted treatment difference[d] (95% CI)	-0.19 (-0.39, 0.00)		-0.26 (-0.45, -0.07)		-0.22 (-0.35, -0.08)	
p-value	0.055 [g]		0.007 [h]		0.002 [f]	
LMK CT Score at Week 52 [a e]						
n[c]	127	119	121	111	248	230
LS Mean (SE)	15.9 (0.45)	18.0 (0.46)	15.6 (0.42)	18.8 (0.44)	15.8 (0.31)	18.3 (0.32)
LS Mean change from baseline (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)
Adjusted treatment difference[d] (95% CI)	-2.0 (-3.3, -0.8)		-3.2 (-4.4, -2.0)		-2.5 (-3.4, -1.7)	
p-value	0.002 [h]		< 0.001 [h]		<0.001 [f]	
SNOT-22 Total Score at Week 52 [a b]						
n[c]	125	116	119	113	244	229
LS Mean (SE)	44.2 (2.96)	51.0 (3.08)	44.1 (2.83)	54.1 (2.87)	44.3 (2.06)	52.4 (2.12)
LS Mean change from baseline (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)
Adjusted treatment difference[d] (95% CI)	-6.8 (-15.2, 1.6)		-9.9 (-17.9, -2.0)		-8.1 (-13.9, -2.3)	
p-value	0.113[g]		0.015 [h]		0.007[f]	
Nasal Obstruction VRS Mean Score over Weeks 21 to 24 [a b]						
n[c]	133	124	127	118	260	242
LS Mean (SE)	1.79 (0.071)	1.97 (0.074)	1.82 (0.068)	2.05 (0.069)	1.81 (0.049)	2.01 (0.051)
LS Mean change from baseline (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)
Adjusted treatment difference[d] (95% CI)	-0.17 (-0.37, 0.03)		-0.24 (-0.43, -0.04)		-0.20 (-0.34, -0.06)	
p-value	0.094 [g]		0.016 [h]		0.005[f]	
Total Endoscopic NP Score at Week 26 [a b]						
n[c]	132	125	125	120	257	245

LS Mean (SE)	5.3 (0.13)	6.1 (0.13)	5.4 (0.12)	5.7 (0.12)	5.4 (0.09)	5.9 (0.09)
LS Mean change from baseline (SE)	-0.6 (0.13)	0.1 (0.13)	-0.5 (0.12)	-0.1 (0.12)	-0.5 (0.09)	0.0 (0.09)
Adjusted treatment difference[d] (95% CI)	-0.8 (-1.1, -0.4)		-0.3 (-0.7, 0.0)		-0.5 (-0.8, -0.3)	
p-value	<0.001 [h]		0.066 [g]		<0.001 [f]	

FAS = Full Analysis Set; LS = Least Squares; LMK CT = Lund MacKay Computed Tomography; NP = Nasal Polyps; SNOT 22 = Sino Nasal Outcome Test; VRS = Verbal Response Scale

[a] Patients who had nasal surgery or used disease-modulating medication for CRSwNP prior to the timepoint of interest were assigned the worst possible value of the relevant score for all assessments following surgery or initiation of disease-modulating medication.

[b] Based on Mixed Model Repeat Measures (MMRM) analyses with covariates of treatment, baseline score, log(e) baseline blood eosinophil count, region, previous surgery for nasal polyps, visit and interaction terms for visit by baseline and visit by treatment. For the pooled analysis, study was included as an additional covariate.

[c] Number of patients with analysable data at the given timepoint.

[d] Adjusted treatment difference (depemokimab vs. placebo)

[e] Based on analyses of covariance (ANCOVA) with covariates of treatment, baseline score, log(e) baseline blood eosinophil count, region and previous surgery for nasal polyps. For the pooled analysis, study was also included as an additional covariate.

[f] nominally significant p-value; analysis not multiplicity-controlled

[g] statistical significance has not been met

[h] nominally significant p-value following a break in the hierarchy

In a pooled analysis from ANCHOR-1 and ANCHOR-2, the proportion of rhinorrhoea VRS mean score responders (≥1-point improvement [decrease] from baseline) over Weeks 49 to 52 was 39% (105/272) for depemokimab compared with 28% (72/256) for placebo with an OR of 1.67 (95% CI: 1.13, 2.45; p=0.010*) and the proportion of loss of smell VRS mean score responders (≥0.9 points improvement [decrease] from baseline) over Weeks 49 to 52 was 29% (78/272) for depemokimab compared with 15% (39/256) for placebo with an OR of 2.24 (95% CI: 1.45, 3.46; p<0.001*).

In a post-hoc pooled analysis from ANCHOR-1 and ANCHOR-2, the proportion of SNOT-22 responders (≥8.9-point improvement [decrease] from baseline) at Week 52 was 62% (166/266) for depemokimab compared with 50% (126/251) for placebo with an OR of 1.65 (95% CI: 1.15, 2.37; p=0.007*).

*nominally significant p-value; analysis not multiplicity-controlled

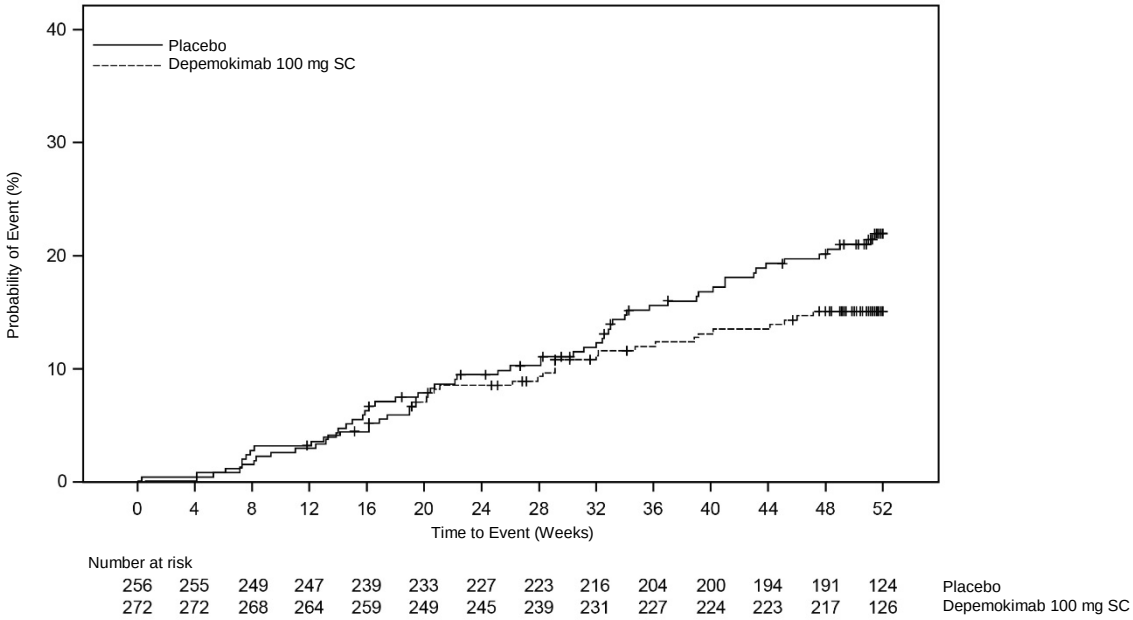
All pooled secondary endpoints failed to reach statistical significance within the hierarchical testing procedure, after failing to show a statistically significant reduction in the risk of requiring nasal surgery (actual or planned) or initiation of disease-modulating medication for CRSwNP up to Week 52, although the results were numerically in favour of depemokimab. The results for the pooled secondary endpoints are presented below.

Nasal Surgery, Systemic Corticosteroid Use, Initiation of Disease-Modulating Medication for CRSwNP

Across the two ANCHOR studies, the proportion of patients who required nasal surgery (actual or planned) or initiated disease-modulating medication for CRSwNP was 16% (44/272) in the depemokimab group and 22% (56/256) in the placebo group (27% risk reduction; HR: 0.735; 95% CI: 0.495, 1.092, ; p=0.128*, Figure 4). The proportion of patients who had nasal surgery or initiated disease-modulating medication for CRSwNP was 12% (33/272) in the depemokimab group, compared with 17% (43/256) in the placebo group, representing a 29% risk reduction (HR: 0.713; 95% CI: 0.453, 1.124; p=0.146*).

*statistical significance has not been met

Figure 4: Kaplan Meier Curve for Time to First Nasal Polyps Surgery (Actual or Planned) or Initiation of Disease-Modulating Medication for CRSwNP up to Week 52 (Pooled FAS Population)



CRSwNP = Chronic Rhinosinusitis with Nasal Polyps; FAS = Full Analysis Set

Across the two ANCHOR studies, the proportion of patients that required at least 1 course of systemic corticosteroids for CRSwNP or disease-modulating medication for CRSwNP or nasal surgery was 26% (72/272) in the depemokimab group compared with 36% (92/256) in the placebo group (OR: 0.58, 95% CI: 0.40, 0.86; p=0.006*). The total number of systemic corticosteroids courses per year (for any indication) was 15% lower in the depemokimab group compared with the placebo group (153 and 180 courses, respectively) and the mean individual annualised total dose (mg) of

systemic corticosteroids (for any indication) was 42% lower in the depemokimab group compared with the placebo group (118.0 mg and 204.8 mg respectively).

*nominally significant p-value following a break in the hierarchy

Patients with Co-morbid Asthma

In a pooled analysis of the secondary endpoint of ACQ-5 score in patients with partially or not well-controlled asthma (ACQ-5 >0.75) at baseline, the mean change from baseline in ACQ-5 score at Week 52 was -0.75 and 0.00 in the depemokimab 100 mg and placebo groups, respectively (treatment difference: -0.75; 95% CI: -1.26, -0.25; p=0.004*). The proportion of ACQ-5 responders (≥0.5-point improvement [decrease] from baseline) at Week 52 was 56% (59/106) with depemokimab compared with 46% (47/103) with placebo (OR: 1.42; 95% CI: 0.79, 2.54; p=0.236**) in this patient population.

*nominally significant p-value following a break in the hierarchy

**statistical significance has not been met

In a post-hoc subgroup analysis across the two ANCHOR studies, depemokimab-treated patients with co-morbid asthma had a 57% reduction in risk of requiring nasal surgery (actual or planned) or initiating disease-modulating medication for CRSwNP compared with the placebo group (11% [16/150] depemokimab vs. 23% [33/142] placebo; HR: 0.432; 95% CI: 0.237, 0.787) and a 75% reduction in risk of having nasal surgery or disease modulating medication for CRSwNP compared with the placebo group (5% [8/150] depemokimab vs. 20% [28/142] placebo; HR: 0.250; 95% CI: 0.114, 0.550).

Paediatric population

Asthma

In the SWIFT-1 and SWIFT-2 studies, there were 30 adolescents (12 to 17 years old), of which 15 received placebo and 15 received depemokimab 100 mg subcutaneously. In a combined analysis of these studies, a 43% reduction in clinically significant exacerbations was observed in adolescents following depemokimab treatment compared to placebo (rate ratio 0.57; 95% CI: 0.15, 2.13).

Chronic rhinosinusitis with nasal polyps (CRSwNP)

There are no clinical data available in children and adolescents aged less than 18 years old.

The licensing authority has waived the obligation to submit the results of studies with EXDENSUR in all subsets of the paediatric population in asthma and CRSwNP (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Depemokimab exhibited approximately dose-proportional pharmacokinetics over a dose range of 10 to 300 mg in patients with asthma following SC administration. Depemokimab pharmacokinetics were consistent in patients with asthma and CRSwNP with an average concentration at steady state of 5.9 mcg/mL and 5.2 mcg/mL, respectively after SC administration of 100 mg depemokimab every 6 months.

Absorption

Following a single subcutaneous (SC) administration (doses ranging from 2 to 300 mg), maximum observed plasma concentrations (C_{max}) were achieved at a median time ranging from 7 to 14 days. Following repeat SC administration once every 6 months there was no accumulation.

Distribution

Following a single SC administration of depemokimab, the mean volume of distribution is 6 to 9 L.

Biotransformation

Depemokimab is a monoclonal antibody which is catabolised by ubiquitous proteolytic enzymes not restricted to hepatic tissue.

Elimination

Following a single SC administration of depemokimab, the geometric mean terminal half-life ranged from 38 to 53 days, with geometric mean apparent clearance values ranging from 0.081 to 0.16 L/day.

Special populations

Gender, race

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

Elderly patients (≥65 years old)

In the population pharmacokinetic analysis, depemokimab pharmacokinetics were consistent between adult patients <65 years and patients aged 65 – 74 years (N = 144) or 75 – 84 years (N = 32). There are limited pharmacokinetics data available in patients ≥ 85 years of age.

Renal impairment

No formal studies have been conducted to investigate the effect of renal impairment on the pharmacokinetics of depemokimab. Based on population pharmacokinetic analyses, no dose adjustment is required in patients with an estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2. Data are limited in patients with an eGFR <60 mL/min/1.73m^2.

Renal impairment is not expected to have a significant impact on clearance as depemokimab is not cleared renally.

Hepatic impairment

No formal studies have been conducted to investigate the effect of hepatic impairment on the pharmacokinetics of depemokimab. Since depemokimab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, changes in hepatic function are unlikely to have any effect on the elimination of depemokimab.

Paediatric population

Asthma

There are limited pharmacokinetic data available in the paediatric population (15 adolescent patients with asthma). The pharmacokinetics of depemokimab in adolescents aged 12 to 17 years were consistent with adults (see section 4.2).

The pharmacokinetics of depemokimab have not been established in paediatric patients with asthma aged less than 12 years of age.

5.3 Preclinical safety data

No genotoxicity or carcinogenicity studies have been conducted.

Fertility

Male and female fertility are unlikely to be affected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys receiving SC dosages up to 100 mg/kg depemokimab for 6 months. Mating and reproductive performance were unaffected in male and female CD-1 mice receiving an analogous antibody, which inhibits the activity of murine IL-5.

Pregnancy

Reproductive toxicology studies have not been conducted with depemokimab. In animal studies with antibodies targeting IL-5 pathways, there were no developmental effects observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine

Histidine monohydrochloride

Trehalose dihydrate

Arginine hydrochloride

Disodium edetate

Polysorbate 80 (E 433)

Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the original carton in order to protect from light.

The pre-filled syringe can be removed from the refrigerator and kept in the unopened carton for up to 7 days at room temperature (up to 30°C), when protected from light. Discard if left out of the refrigerator for more than 7 days.

The pre-filled syringe must be administered within 8 hours once the pack is opened. Discard if not administered within 8 hours.

6.5 Nature and contents of container

1 mL solution in a Type 1 glass syringe with a fixed needle (stainless steel), butyl rubber plunger stopper and passive safety needle guard.

Pack sizes:

1 pre-filled syringe

6.6 Special precautions for disposal

For single-use only.

Do not shake

Before administration, the solution must be inspected visually. The liquid must be colourless, yellow to brown, clear to opalescent. If the solution is cloudy, discoloured or contains particles, the solution must not be used.

After removing the pre-filled syringe from the refrigerator, allow the syringe to reach room temperature for at least 30 minutes before injecting EXDENSUR.

Comprehensive instructions for subcutaneous administration of EXDENSUR in a pre-filled syringe are provided at the end of the package leaflet.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline UK Limited

79 New Oxford Street

London

WC1A 1DG

United Kingdom

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