▼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 pen
EXDENSUR 100 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for injection contains 100 mg of depemokimab.

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

Excipients with known effect

Each mL of solution for injection 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 osmolality of 350 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of administration

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

Posology

This medicinal product is intended for long-term treatment. A decision to continue the therapy should be made at least annually based on the patient's level of disease control.

Asthma

Adults and adolescents aged 12 years and over

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

CRSwNP

Adults

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

Missed dose

If a dose is missed, it should be administered as soon as possible. If the missed dose is taken 1 month or longer after the scheduled dose, the 6-monthly injection schedule should be resumed 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

There is no relevant use of depemokimab in the paediatric population for the treatment of CRSwNP.

Method of administration

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

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

For self-administration the recommended injection sites are the abdomen or thigh, except for the 5 cm around the navel. A caregiver can also inject the solution into the upper arm. It should not be injected into areas where the skin is bruised, tender, erythematous, or hardened.

Comprehensive instructions for administration are provided in the instructions for use at the end of 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

Hypersensitivity reactions, such as anaphylaxis and angioedema, may occur following administration of depemokimab (see section 4.8). These reactions may occur within hours of administration, but some may have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, appropriate treatment as clinically indicated, is recommended. Upon re-administration of depemokimab monitoring to detect signs of recurring hypersensitivity reactions is recommended. In case of a severe or recurring hypersensitivity reaction, permanent discontinuation of depemokimab should be considered.

Acute asthma exacerbations

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

Asthma-related adverse symptoms or exacerbations may occur during treatment with depemokimab. It is recommended that patients be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with depemokimab.

Corticosteroids

Abrupt discontinuation of background treatments (including systemic and inhaled corticosteroids) after initiation of depemokimab therapy is not recommended. Reductions in the doses of background treatments, 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 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, delaying administration of the next depemokimab dose until the infection resolves should be considered.

Excipients with known effect

Polysorbates
This medicinal product contains 0.2 mg of polysorbate 80 per 100 mg dose (see section 2). Polysorbates may cause allergic reactions.

Sodium
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 interaction studies have been performed. The potential for drug-drug interactions is considered to be low as depemokimab is catabolised 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of depemokimab in pregnant 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 in a linear fashion as pregnancy progresses.

As a precautionary measure, it is preferable to avoid the use of EXDENSUR during pregnancy.

Breast-feeding

It is unknown whether depemokimab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, EXDENSUR could be used during breast-feeding if clinically needed.

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 are local injection site reactions (2%).

Tabulated list of adverse reactions

Adverse reactions reported during clinical trials 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
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

Description of selected adverse reactions

Systemic reactions (allergic)

Hypersensitivity reactions, such as anaphylaxis and angioedema, have been reported with other monoclonal antibodies that target IL-5 or its receptor. These reactions may occur based on the experience with the class (see section 4.4).

Systemic reactions (non-allergic)

Administration-related non-allergic reactions (e.g., headache, fatigue, rash) were reported in 1% of patients receiving depemokimab in the entire clinical development programme. In the 52-week placebo-controlled studies in asthma and CRSwNP, systemic non-allergic reactions were reported in < 1% of patients receiving depemokimab.

Systemic reactions (non-allergic) reported with depemokimab were non-serious and were either mild or moderate in intensity. The majority of events were transient: 88% of events resolved ≤ 7 days from onset whereas, 67% of events resolved ≤ 2 days from their onset.

Local injection site reactions

Local injection site reactions (e.g., pain, erythema, swelling, itching) were reported in 2% of patients receiving depemokimab in the entire clinical development programme. The reactions reported with depemokimab were non-serious, mild in intensity and were transient (79% resolved in ≤ 7 days, with most events (56%) resolving in ≤ 2 days from their onset).

In the placebo-controlled studies in asthma and CRSwNP, local injection site reactions were reported in 1% of patients receiving depemokimab compared to < 1% of patients who received placebo.

Paediatric population

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Single doses of up to 300 mg have been administered subcutaneously without evidence of dose-related toxicities.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Depemokimab targets human IL-5 with a 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.

IL-5 is a pleiotropic cytokine with established impact on eosinophils and other immune and structural cells. 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

In a clinical pharmacology study with mild-to-moderate asthma patients, a single 100 mg subcutaneous 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.

In the asthma and CRSwNP phase 3 studies, these reductions were sustained over the treatment period and blood eosinophil count reductions at week 52 were 79% and 85% compared to placebo, respectively.

Immunogenicity

In patients who received at least one 100 mg dose of depemokimab administered subcutaneously 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).

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

Anti-drug antibodies (ADA) were commonly detected. No evidence of ADA impact on pharmacokinetics, pharmacodynamics, efficacy or safety was observed; however, data are still limited.

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 subcutaneously 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 medium- to high-dose ICS (≥ 440 mcg fluticasone propionate or equivalent) plus at least one additional asthma controller. Patients were also required to have a blood eosinophil count of ≥150 cells/mcL at screening or ≥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 demographics and baseline characteristics of the patients in these 2 studies are provided in Table 2.

Table 2. Demographics and baseline characteristics (FAS population)

	SWIFT-1 (N = 382)	**SWIFT-2 (N = 380)**
Age (y) of patients, mean (SD)	54 (14.2)	53 (16.2)
Patients aged ≥ 65 years, n (%)	98 (26)	96 (25)
Female, n (%)	223 (58)	241 (63)
White, n (%)	316 (83)	272 (72)
Duration of asthma, years, mean (SD)	22 (16.2)	25 (18.5)
Mean pre-bronchodilator % predicted FEV_1 (SD)	62 (15.2)	62 (15.9)
Mean % reversibility (SD)	17 (15.3)	18 (17.4)
Mean number of exacerbations in previous year (SD)	2.2 (0.69)	2.7 (1.92)
Eosinophil count, cells/mcL, median (min, max)	310 (20, 2 360)	340 (10, 4 440)
Total IgE, U/mcL, median (min, max)	185 (1.9, 12 142)	180 (2.2, 16 198)
Mean SGRQ total score (SD), range 0-100	44.3 (20.70)	44.5 (18.69)
Patients with ACQ ≥1.5 at baseline, n (%)	280 (75)	279 (75)
Medium-dose ICS use, n (%)[a]	179 (47)	154 (41)
High-dose ICS use, n (%)[a]	203 (53)	226 (59)
ICS + LAMA + LABA use, n (%)	95 (25)	127 (33)
Maintenance OCS use, n (%)	21 (5)	19 (5)

FAS = Full Analysis Set, FEV_1 = Forced Expiratory Volume in 1 second, IgE = immunoglobulin E, SGRQ = St. George's Respiratory Questionnaire, ACQ-5 = Asthma Control Questionnaire, ICS = inhaled corticosteroid, OCS = oral corticosteroid
[a] Medium-dose ICS = 440 mcg FP daily or equivalent; High-dose ICS > 440 mcg FP daily or equivalent

Exacerbations

The primary efficacy endpoint 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 SCS (intravenous or oral steroids for at least 3 days or a single intramuscular corticosteroid dose) and/or hospitalisation and/or emergency department visit. For patients on maintenance SCS, at least double the existing maintenance dose for at least 3 days was required. All patients experiencing an exacerbation were treated with SCS. The majority of patients (95% and 92% for SWIFT-1 and SWIFT-2, respectively) completed the studies.

In SWIFT-1 and SWIFT-2, the annualised rate of asthma exacerbations was significantly lower in patients receiving depemokimab compared to placebo (Table 3). The percentage of patients with exacerbations requiring hospitalisation and/or emergency department visit was lower for patients treated with depemokimab (1% and 4%) compared with placebo (8% and 10%) in SWIFT-1 and SWIFT-2, respectively.

Table 3. Results of primary exacerbation endpoint (FAS population)

	SWIFT-1		**SWIFT-2**	
	Depemokimab N = 250	**Placebo N = 132**	**Depemokimab N = 252**	**Placebo N = 128**
Annualised asthma exacerbations rate				
Percent of patients with an exacerbation	32%	46%	32%	50%
Exacerbation rate per year	0.46	1.11	0.56	1.08
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)	
p-value	<0.001		<0.001	

FAS = Full Analysis Set

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). Table 4 provides the results of these secondary endpoints for the FAS population of SWIFT-1 and SWIFT-2.

Table 4. 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)	

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)	
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)	

FAS = Full Analysis Set, 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)

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 subcutaneously once every 6 months for a total of 2 doses in addition to standard of care (SoC) therapy. Patients had been treated with systemic corticosteroids (SCS) anytime within the past 2 years; and/or had a medical contraindication/intolerance to SCS; and/or had a documented history of prior surgery for nasal polyps (NP) prior to screening. 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. Other than nasal obstruction, there were no other entry requirements for symptoms or for quality of life at randomisation. A total of 528 patients (271 in ANCHOR-1 and 257 in ANCHOR-2) were included in the Full Analysis Set (FAS) population.

The demographics and baseline characteristics of the patients in these two studies are provided in Table 5 below:

Table 5. 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)
Patients aged ≥ 65 years, n (%)	57 (21)	43 (17)
Female, n (%)	83 (31)	80 (31)
White, n (%)	185 (70)	197 (77)
Duration (y) of CRSwNP, mean (SD)	13 (11.2)	11 (8.7)
Blood eosinophil count, cells/mcL, median (min, max)	360 (10, 10 550)	360 (30, 1 670)
Intranasal corticosteroid use, n (%)	265 (98)	249 (97)
Patients with ≥ 1 previous NP surgery, n (%)	171 (63)	162 (63)
SCS use for NP in past 12 months, n (%)	190 (70)	172 (67)

Medical contraindication/intolerance to SCS, n (%)	11 (4)	13 (5)
Asthma, n (%)	161 (59)	131 (51)
AERD, n (%)	43 (16)	42 (16)
Total endoscopic NP score[a b c], mean (SD), maximum score = 8	6.0 (1.35)	5.9 (1.29)
Nasal obstruction VRS mean score[a d], mean (SD), maximum score = 3	2.5 (0.48)	2.6 (0.42)
Loss of smell VRS mean score[a d], mean (SD), maximum score = 3	2.7 (0.55)	2.8 (0.41)
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 polyp, AERD = aspirin-exacerbated respiratory disease, VRS = Verbal Response Scale, 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. The results for the co-primary endpoints in the ANCHOR-1 and ANCHOR-2 studies are presented in Table 6.

Table 6. Results of co-primary endpoints (FAS population)

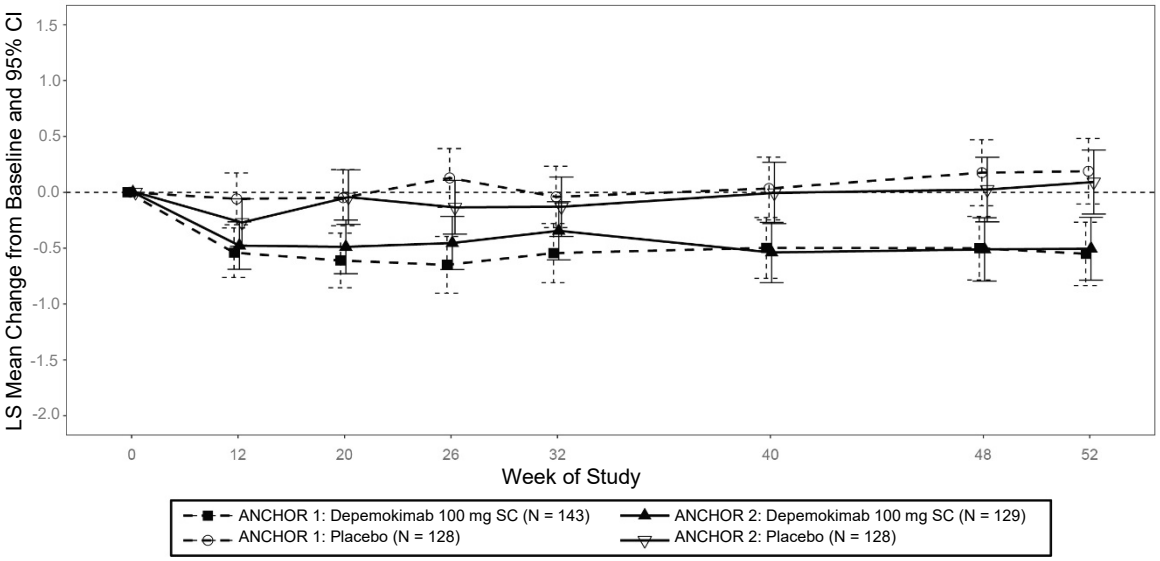
	ANCHOR-1		**ANCHOR-2**	
	Depemokimab N = 143	**Placebo N = 128**	**Depemokimab N = 129**	**Placebo N = 128**
Total endoscopic NP score at Week 52[a b]				
n[c]	128	120	120	115
LS mean (SE)	5.4 (0.14)	6.2 (0.15)	5.4 (0.14)	6.0 (0.15)
LS mean change from baseline (SE)	-0.6 (0.14)	0.2 (0.15)	-0.5 (0.14)	0.1 (0.15)
Adjusted treatment difference[d] (95% CI)	-0.7 (-1.1, -0.3)		-0.6 (-1.0, -0.2)	
p-value	<0.001		0.004	
Nasal obstruction VRS mean score over Weeks 49 to 52[a b]				
n[c]	125	116	119	111

LS mean (SE)	1.77 (0.079)	2.00 (0.083)	1.83 (0.076)	2.07 (0.078)
LS mean change from baseline (SE)	-0.76 (0.079)	-0.53 (0.083)	-0.77 (0.076)	-0.53 (0.078)
Adjusted treatment difference[d] (95% CI)	-0.23 (-0.46, 0.00[e])		-0.25 (-0.46, -0.03)	
p-value	0.047		0.025	

FAS = Full Analysis Set, NP = nasal polyp, LS = Least Squares, VRS = Verbal Response Scale
[a] Patients who had nasal surgery or used other maintenance treatment impacting type 2 inflammation (including biologics indicated for CRSwNP, chronic use of systemic corticosteroids and intranasal corticosteroids) prior to the timepoint of interest were assigned the worst possible value of the relevant score for all assessments following surgery or initiation of other maintenance treatment impacting type 2 inflammation.
[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.
[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.

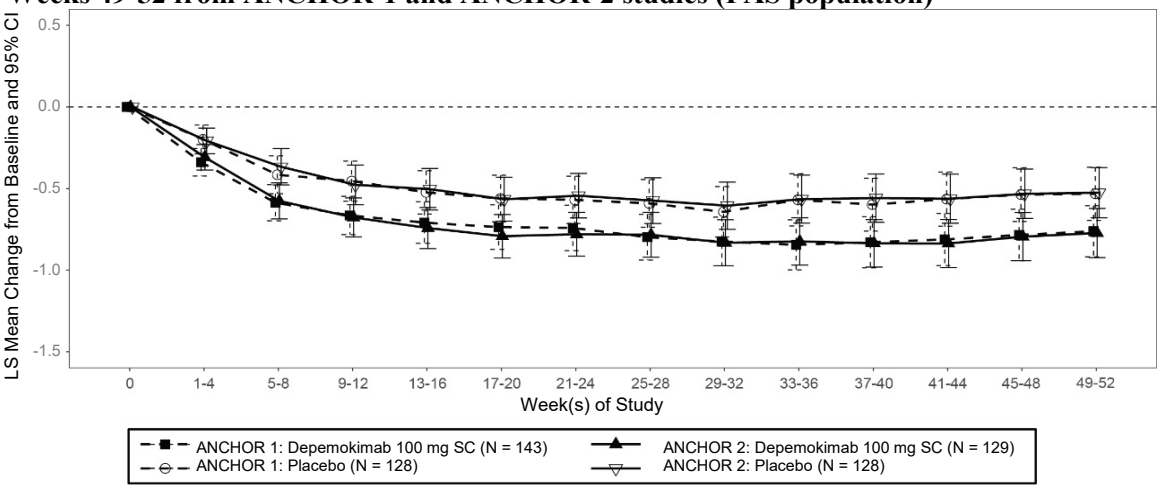
In analyses from the individual studies ANCHOR-1 and ANCHOR-2, a treatment difference in favour of depemokimab was observed by Week 12 (first timepoint assessed) for the total endoscopic NP score and by Weeks 1-4 (first timepoint assessed) for the nasal obstruction VRS mean score that was maintained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

Figure 1. LS mean change from baseline (95% CI) in total endoscopic NP score up to Week 52 from ANCHOR-1 and ANCHOR-2 studies (FAS population)



LS = Least Squares; NP = nasal polyp; FAS = Full Analysis Set

Figure 2. LS mean change from baseline (95% CI) in nasal obstruction VRS mean score up to Weeks 49-52 from ANCHOR-1 and ANCHOR-2 studies (FAS population)

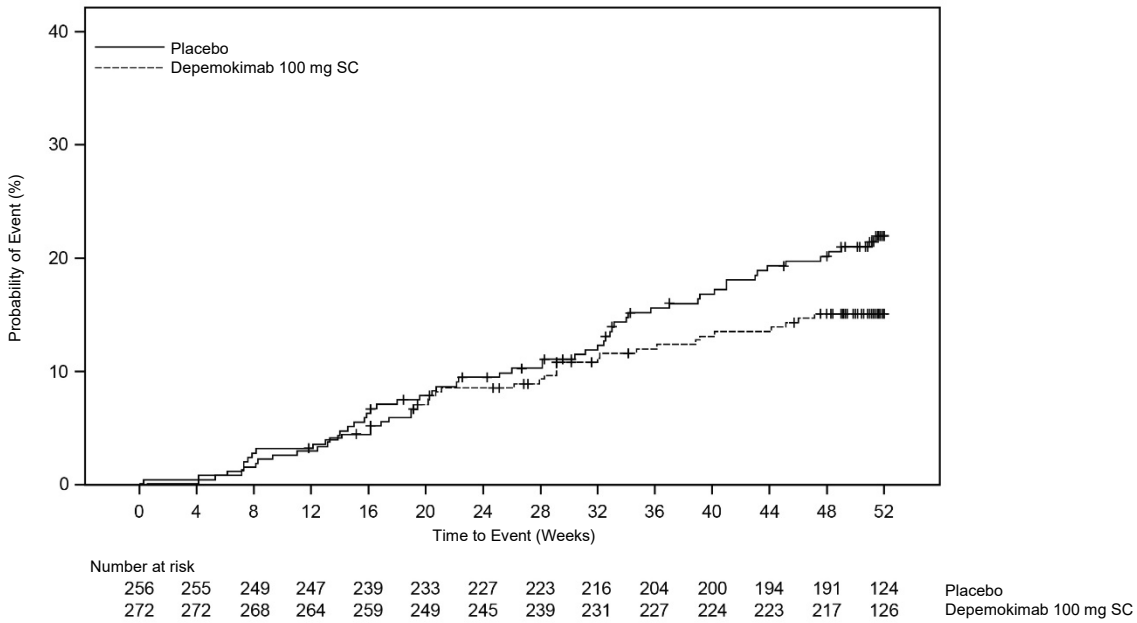


LS = Least Squares; VRS = Verbal Response Scale; FAS = Full Analysis Set

Nasal surgery, systemic corticosteroid use, initiation of other maintenance treatment impacting type 2 inflammation for CRSwNP

Across the two ANCHOR studies, the key secondary endpoint of the proportion of patients who required nasal surgery (actual or planned) or initiated other maintenance treatment impacting type 2 inflammation (including biologics indicated for CRSwNP, chronic use of systemic corticosteroids and intranasal corticosteroids) 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, Figure 3). The proportion of patients who had nasal surgery or initiated other maintenance treatment impacting type 2 inflammation 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).

Figure 3: Kaplan Meier curve for time to first nasal polyps surgery (actual or planned) or initiation of other maintenance treatment impacting type 2 inflammation[1] for CRSwNP up to Week 52 (pooled FAS population)



CRSwNP = chronic rhinosinusitis with nasal polyps; FAS = Full Analysis Set

[1]Other maintenance treatment impacting type 2 inflammation includes biologics indicated for CRSwNP, chronic use of systemic corticosteroids and intranasal corticosteroids.

Across the two ANCHOR studies, the proportion of patients that required at least 1 course of SCS for CRSwNP or other maintenance treatment impacting type 2 inflammation 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).

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 European Medicines Agency 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 subcutaneous administration. After subcutaneous administration of 100 mg depemokimab every 6 months, the average concentrations (%CV) at steady state were 5.9 mcg/mL (28%) and 5.2 mcg/mL (27%) in asthma and CRSwNP patients, respectively. The Week 26 trough concentrations were 1.2 mcg/mL (37%) and 1.0 mcg/mL (36%) in asthma and CRSwNP patients, respectively.

Absorption

Following a single subcutaneous administration (doses ranging from 2 to 300 mg), maximum observed plasma concentrations (C_{max}) were achieved at a median time ranging from 8 to 14 days. After a single subcutaneous administration of 100 mg depemokimab, the average C_{max} (%CV) was 12.2 mcg/mL (16%).
Following two repeat subcutaneous administrations once every 6 months, achieving steady-state conditions, the depemokimab accumulation was negligible (< 10%).

Distribution

Following a single subcutaneous administration of depemokimab, the mean apparent 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 subcutaneous 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

Body weight

Population pharmacokinetic analyses indicated that exposure to depemokimab decreases with increasing body 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 5th to 95th percentiles), the difference in all exposure metrics was less than 1.3-fold. Thus, the magnitude of effect of body weight on depemokimab exposure is not considered clinically relevant within this body weight range. At high body weights (140-160 kg) the exposure may be decreased 2-fold. For such patients, reduced efficacy cannot be excluded.

Gender, ethnicity

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

Elderly

Available pharmacokinetic data in elderly patients (≥ 65 years old, N = 176) across all clinical studies showed that depemokimab pharmacokinetics were similar between adult patients and patients aged 65 years and older (up to 93 years), based on the population pharmacokinetic analysis.

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 impaired renal function. Data are limited (n = 2) in patients with an eGFR < 30 mL/min/1.73m^2, but CL/F values of these two patients fell within the range of patients with normal renal function.

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. Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) had no clinically relevant effect on depemokimab apparent clearance.

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 similar to adults (see section 4.2) and key pharmacokinetics parameters are presented in Table 7.

Table 7. Derived secondary pharmacokinetics parameters in patients who received depemokimab 100 mg subcutaneously every 26 weeks in the pooled SWIFT-1 and SWIFT-2 studies

Parameter - geometric mean (%CV)	Adolescents N = 15	Adults N = 479	Overall N = 494
$AUC_{tau, ss}$ (mcg*day/mL)	1051 (31)	1082 (28)	1081 (28)
$C_{av, ss}$ (mcg /mL)	5.8 (31)	5.9 (28)	5.9 (28)
$C_{max, 26-52}$ (mcg/mL)	14.6 (30)	13.6 (28)	13.6 (28)
$T_{max, 26-52}$ (day)	10.8 (9)	13.7 (18)	13.6 (18)
$C_{trough, week52}$ (mcg/mL)	1.1 (39)	1.3 (38)	1.3 (38)
$t_{1/2}$ (days)	44.7 (9)	48.7 (10)	48.6 (10)

$AUC_{tau,ss}$; area under the concentration-time curve during a dosing interval at steady state, $C_{av,ss}$; average concentration during a dosing interval, $C_{max, 26-52}$; maximum concentration during the second dosing interval, $T_{max, 26-52}$; time to maximum concentration during the second dosing interval, $C_{trough, week 52}$; trough concentration at the end of the second administration, $t_{1/2}$; half-life

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

Pharmacokinetic/pharmacodynamic relationship

There is a clear relationship between depemokimab pharmacokinetics and reduction in blood eosinophil counts (pharmacodynamics) with maximum achievable reduction of around 85% and a half-maximal effective concentration (EC_{50}) of 0.19 mcg/mL. The concentration associated with 90% of maximal effect (EC_{90}) was 0.75 mcg/mL.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity with safety pharmacology endpoints.

No genotoxicity, carcinogenicity or reproductive toxicology studies have been conducted with depemokimab.

In animal studies targeting IL-5 signaling pathways (e.g. knockout animal data and class effects), there were no developmental effects observed.

Male and female fertility are unlikely to be affected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys at exposures sufficiently in excess of the maximum human exposure. 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.

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

30 months

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not shake.
Store in the original carton in order to protect from light.

The pre-filled pen and 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 pen or pre-filled syringe must be administered within 8 hours once the carton is opened. Discard if not administered within 8 hours.

6.5 Nature and contents of container

EXDENSUR 100 mg solution for injection in pre-filled pen

1 mL solution in a Type 1 glass syringe with a fixed needle (stainless steel) in a pre-filled pen.

Pack size:
1 pre-filled pen

EXDENSUR 100 mg solution for injection in pre-filled syringe

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

Pack size:
1 pre-filled syringe

6.6 Special precautions for disposal and other handling

Before administration, the solution must be inspected visually. If the solution is cloudy, discoloured or contains particles, the solution must not be used.

After removing the pre-filled pen or pre-filled syringe from the refrigerator, the pen or syringe should be allowed to reach room temperature for at least 30 minutes before injecting the solution.

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus

Dublin 24
D24 YK11
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EXDENSUR 100 mg solution for injection in pre-filled pen

EU/1/25/2007/001

EXDENSUR 100 mg solution for injection in pre-filled syringe

EU/1/25/2007/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 February 2026

10. DATE OF REVISION OF THE TEXT

08 May 2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.