21 May 2026
EMADOC-1700519818-2988231
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Nucala

mepolizumab

Procedure no: EMA/PAM/0000336241

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	28 April 2026	28 April 2026
☐	CHMP comments	11 May 2026	n/a
☐	Updated CHMP Rapporteur AR	13 May 2026	n/a
☒	CHMP outcome	21 May 2026	21 May 2026

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Table of contents

1. Introduction

On 9 March 2026, the MAH submitted an Interim report for paediatric Study 206785 for Nucala, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are not submitted as part of specific EU obligations and Study 206785 is not part of any Paediatric Investigation Plan. No amendments to the Product Information are foreseen by the MAH as a result of the conclusions from the study.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Nucala (mepolizumab) is a monoclonal antibody targeting interleukin-5 (IL-5). It acts by specifically inhibiting IL-5 signalling, a central cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. In patients with type 2 inflammation–driven disease, IL-5 plays a key role in the pathogenic mechanisms underlying various inflammatory conditions, including asthma.

Nucala was first authorised in the EU on 02-December-2015 as an *"add-on therapy for the treatment of severe refractory eosinophilic asthma (SUA) in adults, adolescents and children aged 6 years and older".*

The recommended dose of mepolizumab for adults and adolescents aged 12 years and over is 100 mg administered subcutaneously once every 4 weeks. The recommended dose of mepolizumab for children aged 6 to 11 years old is 40 mg administered subcutaneously once every 4 weeks.

Study 206785

The MAH has stated that Study 206785 (NIMBLE) is part of the Depemokimab clinical development programme. The marketing authorisation application consisting of the full relevant data package (i.e. containing several studies) has been submitted and Exdensur (depemokimab) has received marketing authorisation on the 12th of February 2026, EMEA/H/C/006446/0000.

An interim report for Study 206785 has been submitted as part of this procedure (IA Data Cutoff: 15 July 2024). Data from participants for whom the study is still ongoing were not included in this interim report. This interim report has been reviewed as part of the marketing authorisation application for Exdensur, depemokimab. A recommendation has been made within the Exdensur marketing authorisation procedure (EMEA/H/C/006446/0000), that *"for the 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."*

This post-authorisation measure procedure, submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, for Nucala will therefore review updated clinical data from the interim report for Study 206785, in terms of clinical outcomes for Nucala (mepolizumab) only.

2.2. Information on the pharmaceutical formulation used in the study

- Depemokimab 100 mg SC administered every 26 weeks and placebo SC treatment matching the active comparator (participant's anti-IL-5/5R treatment prior to randomisation: either placebo matching mepolizumab every 4 weeks or placebo matching benralizumab every 8 weeks).

- Active comparator according to the participant's treatment prior to randomisation (either mepolizumab every 4 weeks or benralizumab every 8 weeks) and placebo SC matching depemokimab administered every 26 weeks.

Injections related to depemokimab and its matching placebo at randomisation and Week 26 were administered in the clinic via a PFS.

See CSR for batch and lot numbers for the treatments administered in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted an interim report for:

- Study 206785 (NIMBLE), data cut-off date 15 July 2024

2.3.2. Clinical study

Study 206785 (NIMBLE). Non-inferiority study of GSK3511294 (depemokimab) compared with mepolizumab or benralizumab in participants with severe asthma with an eosinophilic phenotype.

Description

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.

ClinicalTrials.gov:	NCT04718389
EudraCT:	2020-003612-28
EudraCT, CTIS:	2023-510230-84-00
IND:	146742

Depemokimab was developed as a long-acting subcutaneous (SC) injectable anti-IL-5, that can be administered on a less frequent basis to currently available IL-5 antagonists. The aim of the study was to investigate whether depemokimab 100 mg SC given every 26 weeks is noninferior on maintaining the rate of clinically significant exacerbations in participants with severe asthma with an eosinophilic phenotype, to current available IL-5 antagonist (mepolizumab) or IL-5 receptor antagonist (IL-5R, benralizumab) treatment, over a 52-week treatment period.

Number of Study Centre(s) and Countries:

As of interim data cut-off date (15 July 2024), 1090 participants were randomised in 404 sites across 20 countries.

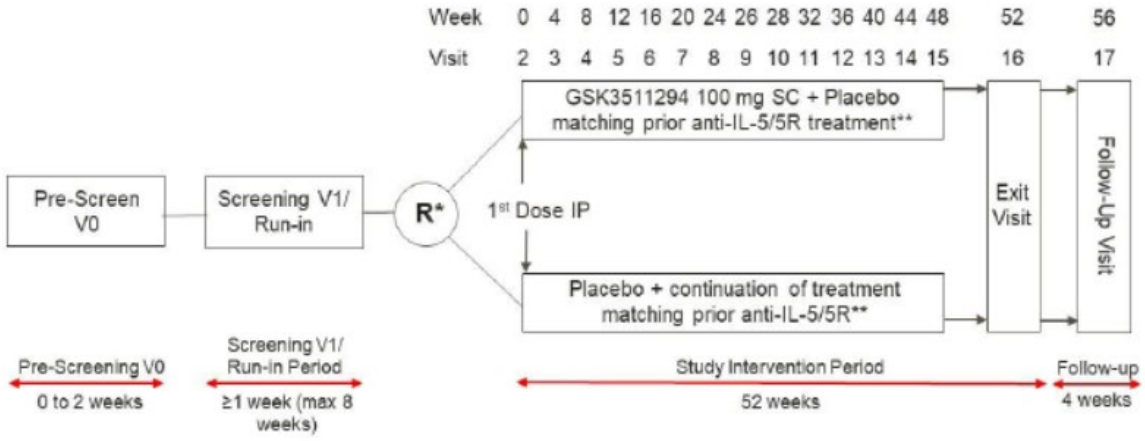
Study Period:

Study initiation date: 26 January 2021

Interim data cut-off date: 15 July 2024

Database lock date: 12 August 2024

Figure 1: Study Schema



** R = Randomisation*
*** Participants randomised to GSK3511294 will receive placebo treatment matching their prior anti-IL-5/5R medication while subjects randomised to receive placebo matching GSK3511294 will receive active treatment matching their prior anti-IL-5/5R (either mepolizumab 100 mg every 4 weeks or benralizumab 30 mg every 8 weeks). All injections will be administered by a prefilled safety syringe (PFS)*

Methods

Study participants

The study recruited adults and adolescents ≥12 years of age, at the time of signing the informed consent (≥18 years of age for Germany, United Kingdom, and Norway; ≥16 years for Austria) and who had a documented physician diagnosis of asthma for ≥2 years that met the National Heart, Lung, and Blood Institute (NHLBI) or Global Initiative for Asthma (GINA) guidelines, who were receiving:

a. Either mepolizumab 100 mg SC or benralizumab 30 mg SC for at least 12 months prior to Screening. Eligible participants had to have a documented benefit to their anti-IL-5/IL-5R therapy assessed by either ≥50% reduction in exacerbation frequency since initiating treatment, ≥50% reduction in maintenance OCS use since initiating treatment, or no exacerbations in the past 6 months while receiving antiIL-5/IL-5R therapy and an ACQ-5 score of ≤1.5 at Screening.

   AND

b. A SoC regimen of medium to high dose ICS and at least 1 other controller medication. Participants had to have a requirement for regular treatment with medium to high dose ICS in the 12 months prior to Visit 1 with or without maintenance OCS. The maintenance ICS dose must have been ≥440 mcg fluticasone propionate (FP) hydrofluoroalkane product (HFA) daily, or clinically comparable. All participants were required to be on at least one additional controller medicine besides ICS (e.g. LABA, LAMA). Those on medium dose ICS were required to be on a long- acting beta-2-agonist (LABA). At Visit 2 (Week 0), those participants who met the randomisation eligibility criteria were to be randomised in a 1:1 ratio to one of the following groups:

   - Depemokimab 100 mg SC and placebo SC matching the participant's prior anti- IL-5/5R medication (either placebo matching mepolizumab or placebo matching benralizumab)

     OR

- Active comparator matching the participant's prior anti-IL-5/5R medication (either active mepolizumab 100 mg SC via pre-filled syringe or active benralizumab 30 mg SC) and placebo SC matching depemokimab.

Key exclusion criteria:

Participants with presence of a known pre-existing, clinically important lung condition other than asthma were excluded. Participants who had other conditions that could lead to elevated eosinophils such as hyper-eosinophilic syndrome (HES), eosinophilic granulomatosis with polyangiitis (EGPA), or eosinophilic esophagitis were also excluded.

Additional exclusion criteria included current malignancy or previous history of cancer in remission for less than 12 months prior to Screening. Participants with high clinical suspicion of vasculitis at Screening were evaluated and current vasculitis were excluded prior to enrolment.

Participants who had received omalizumab (Xolair), dupilumab (Dupixent) or reslizumab (Cinqair/Cinqaero) or tezepelumab (Tezspire) within 130 days prior to Visit 1 and those who had received any other monoclonal antibody (mAb) within 5 half-lives of Visit 1 were also excluded.

Participants who had QTcF ≥450 msec or QTcF ≥480 msec (for participants with bundle branch block in the central over-read 12-lead ECG) at Screening Visit 1 were excluded.

Participants with cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices, and persistent jaundice were excluded. An alanine aminotransferase (ALT) >2 x upper limit normal (ULN) or total bilirubin >1.5 x ULN were excluded. Isolated hyperbilirubinemia was allowed if direct fraction was <35%.

Current smokers or former smokers with a smoking history of ≥20 pack years; current or previous use of cigars, pipe smoking, electronic cigarettes/vaping was exclusionary. Participants with allergy/intolerance to a mAb or biologic or any of the excipients of the investigational products were also excluded.

Treatments

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.

At the end of the run-in period (Visit 2), participants who met the randomisation eligibility criteria were randomised in a 1:1 ratio to receive 1 of the following treatments:

- Depemokimab 100 mg SC administered every 26 weeks and placebo SC treatment matching the active comparator (participant's anti-IL-5/5R treatment prior to randomisation: either placebo matching mepolizumab every 4 weeks or placebo matching benralizumab every 8 weeks).
- Active comparator according to the participant's treatment prior to randomisation (either mepolizumab every 4 weeks or benralizumab every 8 weeks) and placebo SC matching depemokimab administered every 26 weeks.

Injections related to depemokimab and its matching placebo at randomisation and Week 26 were administered in the clinic via a PFS.

Objectives

Primary, secondary, and other efficacy endpoints were not evaluated in this interim report. Only safety endpoints were evaluated.

The primary endpoint included the annualised rate of clinically significant exacerbations over 52 weeks. Secondary endpoints included the St. George's Respiratory Questionnaire (SGRQ), Asthma Control Questionnaire-5 (ACQ-5), and change in forced expiratory volume in one second (FEV1) over 52 weeks, as well as safety endpoints.

Outcomes/endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of depemokimab 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab in participants with severe asthma with an eosinophilic phenotype who have previously benefited from anti-IL-5/5R therapy	• Annualized rate of clinically significant exacerbations[a] over 52 weeks

Objectives	Endpoints
Secondary	
• To evaluate depemokimab 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab on health-related quality of life (HRQoL) and additional efficacy assessments	• Weighted mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score calculated over 52 weeks • Weighted mean change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score calculated over 52 weeks • Weighted mean change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) calculated over 52 weeks

Other	
• To investigate depemokimab 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab on incidence of hospitalization and/or Emergency Department (ED) visit and measures of asthma control, night sleep and lung function	• Annualized rate of exacerbations requiring hospitalization and/or ED visit over 52 weeks • Time to first clinically significant exacerbation[a] • Change from baseline in the percentage of nights free from awakenings due to asthma symptoms requiring rescue medication use over 2-week periods • Change from baseline in morning peak expiratory flow (PEF) 2-week mean • Change from baseline in daily asthma symptom scores 2-week mean • Change from baseline in percentage of rescue medication-free 24-hour periods over 2-week periods • Mean number of days with oral corticosteroid (OCS) usage over 52 weeks • Change from baseline in SGRQ total score at discrete timepoints during the 52-week period • Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period • Change from baseline in pre-bronchodilator FEV_1 at discrete timepoints during the 52-week period
• To investigate depemokimab versus maintaining existing treatment with either mepolizumab or benralizumab on o patient- and clinician-rated response to therapy o patient global impression of asthma severity and its change from baseline	• Patient-rated response to therapy at discrete timepoints during the 52-week period • Clinician-rated response to therapy at discrete timepoints during the 52-week period • Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period • Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during the 52-week period
• To investigate the pharmacodynamics (PD) effects of depemokimab	• Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period

Objectives	Endpoints
Safety	
• To evaluate the safety and tolerability of depemokimab 100 mg (SC) every 26 weeks versus maintaining existing treatment with either mepolizumab or benralizumab in participants with severe asthma with an eosinophilic phenotype who have previously benefited from anti-IL-5/5R therapy	• Incidence of adverse events (AEs)/serious adverse events (SAEs) • Laboratory parameters, including hematological and clinical chemistry parameters • Vital signs including blood pressure (BP), body temperature, and pulse rate • Electrocardiogram (ECG) assessments • Incidence of immunogenicity as measured by the presence of anti-drug antibody (ADA)/neutralizing antibody (NAb) to depemokimab

1. Clinically significant exacerbations will be defined as worsening of asthma requiring systemic corticosteroids (CSs) (intramuscular (IM), intravenous (IV) or oral) and/or hospitalization and/or ED visit (see Protocol Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

Sample size

Planned Number of Participants

Approximately 2650 participants with severe asthma with an eosinophilic phenotype currently benefitting from anti-IL-5/5R therapy (mepolizumab or benralizumab) were planned to be screened to achieve a target global randomisation of approximately 1700 participants (850 participants per arm).

Randomisation and blinding (masking)

At Visit 2 (Week 0), those participants who meet the randomisation eligibility criteria were to be randomised in a 1:1 ratio 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.

Statistical Methods

Statistical Hypotheses

The treatment comparison of depemokimab + standard of care (SoC) with active comparator (mepolizumab or benralizumab) + SoC on the primary endpoint of annualised rate of clinically significant exacerbations was to be made in order to assess the primary objective of non-inferiority. The null hypothesis that the exacerbation rate ratio for depemokimab + SoC compared with active comparator (mepolizumab or benralizumab) + SoC is at least 1.28 was to be tested at the one-sided 2.5% significance level, i.e. non-inferiority will be met if the upper bound for the 95% confidence interval (CI) is less than 1.28. Should non-inferiority be met, the primary endpoint was then to be tested for superiority at the 5% two-sided significance level.

Sample Size Determination

The sample size of 850 participants per arm (equal allocation) was based on sufficient power to conclude non-inferiority with a margin of 1.28 using a one-sided 2.5% significance level. The maximum treatment effect (i.e. observed rate ratio of depemokimab + SoC compared to active comparator (mepolizumab or benralizumab) + SoC estimated to result in a conclusion of non-inferiority is 1.11.

Results

Participant flow

The interim report includes data from participants who have completed the study as of the interim data cut-off date of 15 July 2024 except for 1 participant who was excluded as the data could not be cleaned in time due to operational challenges.

As of 15 July 2024, a total of 1313 participants were screened, 1090 participants were randomised, and 1076 were included in the interim analysis (IA) including 972 participants who had completed the study. Data from participants who have withdrawn, were screen failures or run-in failures in the study as of 14 June 2024, were also included in this report.

Of the 1313 screened participants, 153 (12%) failed screening, 1160 (88%) entered the run-in. The majority of the screen failures (112 [9%] participants) were due to not meeting inclusion or exclusion criteria. Of the 1160 participants who entered the run-in, 1090 (94%) completed the run-in period, 70 (6%) participants failed, of which 49 (4%) did not meet the continuation criteria at the end of the run-in period.

Recruitment

A total of 1717 participants were randomised, of which 1687 were included in the full analysis set (FAS) of the *total population* (839 in the mepolizumab/benralizumab group [457 received mepolizumab 100 mg and 382 received benralizumab 30 mg], and 848 in the depemokimab group). Data from participants for whom the study is still ongoing were not included in Study 206785 interim report. For the recruitment in relation to the completed population (FAS) at interim analysis see the Participant flow section.

Baseline data

Based on the Clinical Expert Statement, data was presented on the total population, the average age was 58.6 years overall, with **11 participants (1%) between ages 12-17 and 1 (<1%) participant <12 years of age in the mepolizumab/benralizumab group**. There were 13 participants (2%) between ages 12-17 in the depemokimab group.

As per Study 206785 Interim CSR, the baseline data in the table below were presented. Data from participants for whom the study is still ongoing were not included in this interim report.

Table 1: Summary of Study Population Results (FAS Population)

Study Population Characteristics	Depemokimab 100 mg SC	(Mepo 100 / Benra 30) mg SC
Disposition (Majority of the participants completed the study in both groups)	• Total number of participants =538 • 480 participants completed the study, 58 participants discontinued the study, of which 4 participants completed the study treatment	• Total number of participants=538 • 492 participants completed the study, 46 participants discontinued the study, of which 4 participants completed the study treatment
Demographics (Generally similar in both the groups)	• Gender: Female (62%), Male (38%) • Median Age: 59.0 years (range:12-88) • Age group: o 18-64 years (68%) o ≥65 years (31%) o 12-17 years (1%) • Race: White/Caucasian/European heritage (76%)	• Gender: Female (64%), Male (36%) • Median Age: 61.0 years (range: 13-88) • Age group: o 18-64 years (63%) o ≥65 years (36%) o 12-17 years (1%) • Race: White/Caucasian/European heritage (76%)
Baseline Disease Characteristics (Generally similar in both the groups)	• Median duration of asthma: 18.0 years • Medium to high ICS dose o Medium dose ICS (50%) o High dose ICS (50%) • Maintenance OCS at baseline: 5%	• Median duration of asthma 18.0 years • Medium to high ICS dose o Medium dose ICS (49%) o High dose ICS (51%) • Maintenance OCS at baseline: 4%
Asthma Exacerbation History (The distribution of number of exacerbations over the previous 12 months [overall and by type of medical intervention] was similar in both the groups)	• History of asthma exacerbations that required oral/systemic corticosteroids in the past 12 months o 73% of participants had 0 exacerbation o 17% of participants had 1 exacerbation o 6% of participants had 2 exacerbations o 2% of participants had 3 exacerbations o 1% of participants had 4 exacerbations	• History of asthma exacerbations that required oral/systemic corticosteroids in the past 12 months o 75% of participants had 0 exacerbation o 17% of participants had 1 exacerbation o 5% of participants had 2 exacerbations o 1% of participants had 3 exacerbations o <1% of participants had 4 exacerbations
Screening and Baseline Lung Function Test (Baseline mean clinic lung function values were generally similar in both the groups)	• Mean (SD) pre-bronchodilator FEV_1: 2.197 (0.7907) L • Mean pre-bronchodilator percent predicted FEV_1: 80.30% • Mean (SD) pre-bronchodilator FVC: 3.268 (1.0319) L • Mean Pre-bronchodilator FEV_1/FVC ratio: 0.675	• Mean (SD) pre-bronchodilator FEV_1: 2.179 (0.8337) L • Mean pre-bronchodilator percent predicted FEV_1: 80.04% • Mean (SD) pre-bronchodilator FVC: 3.206 (1.0419) L • Mean Pre-bronchodilator FEV_1/FVC ratio: 0.677
Prior and Concomitant Medications (The proportion of participants receiving each medication class was generally similar in both the groups)	• Prior to Screening, >99% of the participants were receiving ICS and 96% were receiving LABA asthma maintenance therapies. • >99% of participants used asthma concomitant medications, LABA (94%) as the most common on-treatment concomitant asthma medication, apart from ICS (>99%) • 95% of participants used non-asthma concomitant medications, most common was paracetamol (31%)	• Prior to Screening, >99% of the participants were receiving ICS and 96% were receiving LABA asthma maintenance therapies. • >99% of participants used asthma concomitant medications, LABA (95%) as the most common on-treatment concomitant asthma medication, apart from ICS (>99%) • 96% of participants used non-asthma concomitant medications, most common was paracetamol (31%)

Number analysed

Data from participants for whom the study is still ongoing were not included in this interim report.

Table 2: Summary of Study Populations (Screened)

Population, n (%)	No Treatment (N=223)	Depemokimab 100mg SC (N=543)	(Mepo 100 / Benra 30) mg SC (N=547)	Total (N=1313)
Screened	223 (100)	543 (100)	547 (100)	1313 (100)
Enrolled	70 (31)	543 (100)	547 (100)	1160 (88)
Randomized	0	543 (100)	547 (100)	1090 (83)
Full analysis set (FAS)	0	538 (>99)	538 (98)	1076 (82)
FAS-Japan	0	76 (14)	77 (14)	153 (12)
FAS-non-Japan	0	462 (85)	461 (84)	923 (70)
FAS-modified	0	543 (100)	544 (>99)	1087 (83)
Safety	0	538 (>99)	538 (98)	1076 (82)
Safety-Japan	0	76 (14)	77 (14)	153 (12)
Safety-non-Japan	0	462 (85)	461 (84)	923 (70)
Safety-modified	0	543 (100)	544 (>99)	1087 (83)

Note: 3participants were randomized in error but not dosed with study treatment.
Participant ID was randomized twice in error but this participant is counted only once

Full Analysis Set Population

A total of 1090 participants were randomised (543 in the depemokimab group and 547 participants mepolizumab/benralizumab group), of which 1076 participants were included in the FAS population. Of the 14 participants who were excluded from the FAS, 11 participants randomised at sites 250366 and 250886 were excluded from the FAS population due to concerns about data integrity and GCP violations, and 3 participants were randomised in error but did not receive any study intervention and were therefore not included.

In the FAS population, 480 (89%) participants in the depemokimab group and 492 (91%) participants in the mepolizumab/benralizumab group completed the study. A total of 58 (11%) participants in the depemokimab group and 46 (9%) participants in the mepolizumab/benralizumab group were withdrawn from the study. Of the withdrawn participants, 4 (<1%) participants each in the depemokimab and mepolizumab/benralizumab groups completed the study treatment. The most common reasons for withdrawal from study were withdrawal by subject (27 [5%] participants in the depemokimab group and 31 [6%] participants in the mepolizumab/benralizumab group) and lost to follow-up (10 [2%] participants in the depemokimab group and 4 (<1%) participants in the mepolizumab/benralizumab group).

In the FAS population, 472 (88%) participants in the depemokimab group and 483 (90%) participants in the mepolizumab/benralizumab group completed the study treatment. A total of 66 (12%) participants in the depemokimab group and 55 (10%) participants in the mepolizumab/benralizumab group discontinued treatment prematurely.

A total of 27 (5%) participants in the depemokimab group and 23 (4%) participants in the mepolizumab/benralizumab group were prematurely discontinued treatment and study at same time. The most common primary reasons for treatment discontinuation were withdrawal by subject (25 [5%] participants and 30 [6%] participants) and lack of efficacy (12 [2%] participants and 3 [<1%] participants) in the depemokimab and mepolizumab/benralizumab groups, respectively.

Safety population included 1076 participants (excluding 11 participants randomised at 2 specific sites due to concerns about data integrity and GCP violations and 3 participants who were randomised in error but did not receive any study intervention).

Efficacy results

As per Study 206785 Interim CSR, efficacy data was not analysed and evaluated for the interim report.

Exposure

For the participants included in this interim analysis, the median exposure was 364.0 (range: 182 to 501) days in depemokimab group and 369.5 (range: 28 to 580) days in mepolizumab/benralizumab group (Table below). The median exposure to the study intervention was generally similar across the age groups of 12-17 years, 18-64 years and ≥65 years in the depemokimab and mepolizumab/benralizumab groups.

Table 3: Summary of Exposure to Study Treatment (Full Analysis Set)

	Depemokimab 100mg SC (N=538)	Mepolizumab 100mg SC (N=288)	Benralizumab 30mg SC (N=250)	(Mepo 100 / Benra 30) mg SC (N=538)
Time on study treatment (days)[1]				
n	536	287	249	536
Mean (SD)	353.3 (50.33)	347.3 (70.60)	369.1 (79.52)	357.4 (75.59)
Median	364.0	364.0	392.0	369.5
Min.	182	28	56	28
Max.	501	580	450	580
Total subject-years exposure[2]				
	518.48	272.88	251.64	524.52

1. Only includes time on the active treatment a participant was randomized to.
2. Total subject-years exposure will be calculated as duration of exposure (days) divided by 365.25.
Note: 4 participants only received placebo matching or unknown doses and are therefore not included.

<u>As per the Clinical Expert Statement</u>

Annualised rate of clinically significant exacerbations over 52 weeks (primary endpoint)

The annualised rate of clinically significant exacerbations was 0.57 (95% CI: 0.50, 64) in depemokimab group and 0.49 (95% CI: 0.43, 0.55) in mepolizumab/benralizumab group.

The resulting exacerbation rate ratio (1.16 [95% CI: 0.98, 1.38]) did not meet the primary non-inferiority objective of the study (the upper bound of the 95% CI exceeded 1.28), despite the CI including 1.

In both arms of the study, the majority of participants were exacerbation-free during the study (64% in depemokimab group vs 68% participants in mepolizumab/benralizumab group). Furthermore, most participants in both treatment groups did not require asthma exacerbation-related hospitalizations or ED visits during the study (94% in depemokimab group and 95% in the mepolizumab/benralizumab group).

Exacerbation rates were low in the active comparator arm (AER 0.49) as expected given the well-established efficacy on this endpoint for both mepolizumab and benralizumab. The exacerbation rate in those participants treated with depemokimab was also low (AER 0.57) and similar to the pooled result observed for the SWIFT-1 and SWIFT-2 studies (AER 0.51), as well as those observed with other approved biologic therapies. The absolute difference in the annualised exacerbation rate between the two arms of the study was 0.08, which is not considered clinically meaningful.

Given the small numbers of participants under 18 years of age as a proportion of the overall study population/FAS, it would not be possible to obtain a meaningful treatment estimate for the primary and key secondary efficacy endpoints for this subgroup.

Annualised Rate of Clinically Significant Exacerbations Over 52 weeks by Subgroup of Pre-Study Biologic Treatment (mepolizumab/benralizumab)

A pre-specified sub-group analysis of the primary endpoints by pre-study biologic treatment (mepolizumab or benralizumab) showed that for participants with mepolizumab as pre-study biologic, the annualised rate of clinically significant exacerbations were the same in both depemokimab (0.48 [95%CI: 0.40, 0.57]) and mepolizumab (0.48 [95%CI: 0.41, 0.58]) groups, with corresponding rate ratio of 0.99 [95%CI: 0.78, 1.26]. In participants with benralizumab as pre-study biologic, the annualised rate of clinically significant exacerbations was 0.67 [95%CI: 0.57, 0.79] in depemokimab group and 0.48 [95%CI: 0.41, 0.58] in benralizumab group, with corresponding rate ratio of 1.38 [95%CI: 1.09, 1.75]. The absolute difference in the annualised exacerbation rate between the four subgroups is again not considered clinically meaningful.

Secondary endpoints, including SGRQ, ACQ-5, and FEV1

Secondary endpoints were generally consistent between the two treatment groups. Over 52 weeks, the weighted mean change from baseline in SGRQ total score showed a LS mean change (standard error [SE]) of -0.69 (0.476) in the depemokimab group compared to -0.86 (0.486) in the mepolizumab/benralizumab group, with a treatment difference of 0.17 (95% CI: -0.85, 1.20). For the ACQ-5 score, the LS mean change (SE) was 0.03 (0.026) for depemokimab and 0.06 (0.026) for mepolizumab/benralizumab, with a treatment difference of -0.03 (95% CI: -0.09, 0.02). For pre-bronchodilator FEV1, the LS mean change (SE) was -0.014 L (0.0093) for depemokimab versus -0.018 L (0.0095) for mepolizumab/benralizumab, resulting in a treatment difference of 0.004 L (95% CI: -0.016, 0.024).

Minimal changes from baseline were observed over the treatment period in the secondary endpoints including measures of quality of life (SGRQ), asthma control (ACQ-5) and lung function (FEV1), indicating no loss of asthma control or quality of life from baseline whether switching to depemokimab or remaining on existing therapy.

Safety results

Immunogenicity

Post-baseline, study participants who continued receiving mepolizumab or benralizumab were not evaluated for immunogenicity.

Safety results, as per Study 206785 Interim CSR:

The safety results evaluated and included in Study 206785 Interim CSR report were for participants who have completed the study as of the interim data cut-off date of 15 July 2024 (except for 1 participant who was excluded due to operational challenges in cleaning data of this participant in time) and the participants who have withdrawn, were screen failures or run-in failures in the study as of 14 June 2024. Data from participants who are still ongoing in the study were not evaluated.

The proportion of participants with AEs was similar between groups (83% of participants in the depemokimab group and 81% of participants in the mepolizumab/benralizumab group) (Table below). Overall, the mean changes in clinical laboratory values and vital signs were similar across the study groups.

Table 4: Overview of All Adverse Events (Safety)

Overall	Depemokimab 100mg SC (N=538)		(Mepo 100/ Benra 30) mg SC (N=538)	
Phase: On- and post- treatment	**n (%)**	**Rate**	**n (%)**	**Rate**
Any AE, n (%)	**449 (83)**	**2292**	**435 (81)**	**2060**
AEs related to study treatment	47 (9)	96	43 (8)	85
AEs leading to permanent discontinuation of study treatment or withdrawal from study[1]	7 (1)	13	13 (2)	24
AEs leading to dose interruption/delay	8 (1)	15	15 (3)	28
Any SAE, n (%)	**49 (9)**	**99**	**46 (9)**	**89**
SAEs related to study treatment	0		2 (<1)	4
Fatal SAEs	0		1 (<1)	2
Fatal SAEs related to study treatment	0		0	

1. One participant in the mepolizumab/benralizumab group experienced AE leading to permanent discontinuation of the study treatment or withdrawal from study after 81 days of the last dose date of mepolizumab. Thus, this AE was considered to have occurred in the post-treatment period.

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.

Overall summary of on-treatment AEs

The proportion of participants with an on-treatment AE was generally similar between groups (83% of participants in the depemokimab group and 81% of participants in the mepolizumab/benralizumab group).

On-treatment AEs leading to permanent discontinuation of study treatment or withdrawal from study were reported in 7 (1%) participants in the depemokimab group and 12 (2%) participants in the mepolizumab/benralizumab group. A total of 8 (1%) participants in the depemokimab group and 15 (3%) participants in the mepolizumab/benralizumab group had at least 1 AE leading to dose interruption or delay.

The most frequently reported on-treatment AEs by preferred term (PT) were COVID-19 (20% in both groups), nasopharyngitis (18% and 19%), upper respiratory tract infection (10% and 12%), and headache 7% and 8%) in the depemokimab versus mepolizumab/benralizumab groups, respectively. Overall, the proportion of participants with these AEs was generally similar between the treatment groups.

The proportion of participants with treatment-related AEs as reported by the investigator was similar between groups (9% of participants in the depemokimab group and 8% of participants in the mepolizumab/benralizumab group).

The most frequently reported treatment-related AEs by PT were injection site reaction (11 [2%] vs. 13 [2%]), headache (5 [<1%] in both groups), fatigue (4 [<1%] in both groups), pruritus (4 [<1%] versus 3 [<1%]), and asthenia (3 [<1%] vs. 1 [<1%]) in the depemokimab vs mepolizumab/benralizumab groups, respectively.

The proportion of participants with mild, moderate, and severe AEs was generally similar in both treatment groups. In the depemokimab group, 226 (42%) participants had moderate AEs, 185 (34%) had mild AEs, and 37 (7%) had severe AEs. In the mepolizumab/benralizumab group, 206 (38%) participants had moderate AEs, 193 (36%) had mild AEs, and 36 (7%) had severe AEs.

Overall, the most frequently reported severe AEs by System Organ Class (SOC) were Infections and infestations (14 [3%] versus 15 [3%]) and Respiratory, thoracic, and mediastinal disorders (10 [2%] vs. 9 [2%]) in the depemokimab versus mepolizumab/benralizumab groups, respectively.

The most frequently reported severe AEs by PT in the Infections and infestations SOC were pneumonia (5 [<1%] versus 3 [<1%]), and COVID-19 (4 [<1%] in both groups) in the depemokimab versus mepolizumab/benralizumab groups, respectively.

The most frequently reported severe AEs by PT in the Respiratory, thoracic, and mediastinal disorders SOC was asthma (9 [2%] participants in the depemokimab group and 6 [1%] in the mepolizumab/benralizumab group).

Summary of post-treatment AEs

During post-treatment, AEs were reported in 67 (12%) participants in the depemokimab group and 44 (8%) in the mepolizumab/benralizumab group. One participant in each group had an AE considered to be related to study treatment by the investigator and 3 participants in each group had at least 1 SAE. One participant in the mepolizumab/benralizumab group had an SAE with a fatal outcome (PT: metastatic malignant melanoma) which was considered as not related to study treatment.

The overall interpretation of the cumulative on- and post-treatment AE profile was consistent with that of the on-treatment phase.

Serious adverse events and other significant AEs

The overall proportion of participants with on-treatment SAEs was generally similar in both groups. A total of 46 (9%) participants in the depemokimab group and 43 (8%) participants in the mepolizumab/benralizumab group had an on-treatment SAE. The most frequently reported on-treatment SAE by PT was asthma in both depemokimab and mepolizumab/benralizumab 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 (PT: thunderclap headache and atrial fibrillation). One participant in mepolizumab/benralizumab group died due to post-treatment SAE (PT: metastatic malignant melanoma).

AEs leading to treatment discontinuation or study withdrawal were reported in 7 (1%) participants in the depemokimab group and 13 (2%) participants in the mepolizumab/benralizumab group. AEs leading to treatment discontinuation or study withdrawal were reported in 7 participants (8 non-fatal events) in the depemokimab group. Treatment-related AEs (as considered by the investigator) by PT leading to permanent discontinuation of study treatment or withdrawal from study in the depemokimab group were rash, Bell's palsy, and cough.

One participant with a fatal AE and 12 other participants with non-fatal AEs discontinued study treatment or withdrawn from the study in mepolizumab/benralizumab group. Treatment-related AEs (as considered by the investigator) leading to permanent discontinuation of study treatment or withdrawal from study by PT in the mepolizumab/benralizumab group were ecchymosis, atrial fibrillation, edema peripheral, and blood urea increased.

Adverse events of special interest (AESIs)

Adverse events of special interest for the study were allergic (Type I hypersensitivity) reactions including anaphylaxis or other systemic reactions, Type III hypersensitivity (immune complex disease/vasculitis), local injection site reactions, and QTc prolongation.

One participant in depemokimab group (PT: rash) and no participants in the mepolizumab/benralizumab group reported an AESI of allergic (Type I hypersensitivity) reaction, as assessed by the investigator. This event was reported by the investigator as being related to study

intervention, which corresponds to placebo administration. This participant was on treatment with benralizumab prior to this study.

No AESI of anaphylaxis were reported in either of the treatment groups in the study. Events considered by the investigator to represent other systemic reactions were reported in 11 (2%) participants in the depemokimab group and 3 (<1%) participants in the mepolizumab/benralizumab group.

The relative risk for other systemic reactions in depemokimab group compared to mepolizumab/benralizumab group was 3.67 (95% CI: 1.03 to 13.07). 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 injections in 9 and 2 participants and were related to placebo injections 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. In the mepolizumab/benralizumab group, 2 participants who reported systemic reactions were treated with mepolizumab prior to this study.

No events of Type III hypersensitivity reactions (immune complex disease/vasculitis) were reported in either of the treatment groups in the study. Local injection site reactions were reported in 17 (3%) participants in the depemokimab group and 20 (4%) participants in the mepolizumab/benralizumab group. Local injection reactions reported were related to active injections in 8 and 17 participants and were related to placebo injections in 9 and 3 participants in the depemokimab and mepolizumab/benralizumab groups respectively.

Among the 8 participants who reported local injection site reaction to active injection in the depemokimab group, 4 participants were treated with mepolizumab, and 4 participants were treated with benralizumab prior to this study. In the mepolizumab/benralizumab group, of the 17 participants who reported local injection site reaction to active injection, 15 participants were treated with mepolizumab and 2 participants were treated with benralizumab prior to this study.

The relative risk for local injection reactions in the depemokimab group compared to mepolizumab/benralizumab group was 0.85 (95% CI: 0.45 to 1.60). The events representing local injection site reactions were considered as related to study treatment, and mild or moderate in intensity by the investigator.

AEs by PT reported under the Medical Dictionary for Regulatory Activities (MedDRA) broad Standardized MedDRA Query (SMQ) of Torsade de pointes/QT prolongation were syncope (4 [<1%] participants in depemokimab and 1 [<1%] participant in mepolizumab/benralizumab group) and loss of consciousness (1 [<1%] participant in mepolizumab/benralizumab group).

Clinical laboratory parameters and other safety evaluations

Overall, the mean changes from baseline in vital signs, ECG, and clinical laboratory results were similar between the groups. Changes to outside the normal range in laboratory results were generally comparable in incidence in both groups.

Cumulatively, 5 participants met liver stopping criteria (1 from depemokimab group and 4 from mepolizumab/benralizumab group), and 6 participants met increased liver monitoring criteria that never reached stopping criteria (1 from depemokimab group and 5 from mepolizumab/benralizumab group). No liver function-related SAEs were reported in participants that met the increased liver

monitoring criteria. Three liver function-related SAEs of PT ALT increased, transaminases increased and cholecystitis were reported in participants that met the liver stopping criteria. All the 3 events were considered as not related to the study treatment by the investigator. The liver function-related reported AEs were considered as non-serious and not related to the study treatment by the investigator.

Analysis of AEs under Cardiac disorders SOC and those derived from the SMQ of Torsade de pointes/QT prolongation did not indicate an effect on QT interval. No AEs of QT/QTc prolongation were reported. 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).

Safety results, as per the Clinical Expert Statement

The proportion of all participants with an on-treatment AE was similar between groups (84% of participants in the depemokimab group and 82% of participants in the mepolizumab/benralizumab group). The proportion of all participants with on-treatment SAEs was same in both groups (8% of participants in both depemokimab and mepolizumab/benralizumab groups).

For participants under the age of 18, a post-hoc analysis focused on safety data was performed (post-hoc Tables were included with this submission). In the age 12-17 group, the number of participants with any on-treatment AE was similar between treatment groups, with 10/13 (77%) participants in the depemokimab group and 9/11 (82%) in the mepolizumab/benralizumab group. The types of AEs were generally balanced between the two treatment groups, although the small numbers of participants in this age group limits meaningful comparison. The most frequently reported on-treatment AEs by SOC were Infections and infestations (10/13 [77%] versus 6/11 [55%] participants) and Respiratory, thoracic and mediastinal disorders (4/13 [31%] versus 7/11 [64%] participants) in the depemokimab versus mepolizumab/benralizumab group, respectively. Two of thirteen (15%) participants age 12-17 in the depemokimab group had an AE related to study treatment (as reported by the investigator), and zero participants age 12-17 in the mepolizumab/benralizumab group had an AE related to study treatment. No participants in the age 12-17 group had an AE leading to permanent discontinuation of study treatment or withdrawal from study.

The one participant with a reported age of <12 was in the mepolizumab/benralizumab group and was treated with mepolizumab. This participant reported one single nonserious AE of PT:COVID-19 in the trial. The AE was considered as not related to study treatment, and did not lead to permanent discontinuation of study treatment or withdrawal from study.

Across the study, no fatal SAEs were reported during the on-treatment period. In the age 12-17 group, 1/13 (8%) participant in the depemokimab group and 3/11 (27%) participants in the mepolizumab/benralizumab group experienced at least one SAE. Of the participants who received mepolizumab during the study, participant experienced 2 SAEs, which included an SAE of PT: suicide attempt (requiring hospitalisation; life threatening) 97 days after first dose of study drug, and a separate SAE of PT: asthma (requiring hospitalization) 198 days after the first dose of study drug. Neither SAE was considered related to the investigational product by the investigator or sponsor. The other 2 participants in the mepolizumab/benralizumab group who experienced SAEs received benralizumab during the study.

Adverse events of special interest (AESI) for this study were allergic (Type I hypersensitivity) reactions including anaphylaxis or other systemic reactions, Type III hypersensitivity reactions (immune complex disease/vasculitis), local injection site reactions, and QTc prolongation. No participants under 18 years of age who received mepolizumab in the study reported an AESI.

Cumulatively, 5 participants (1 participant from depemokimab group and 4 participants from mepolizumab/benralizumab group) met liver stopping criteria, none of whom were under 18 years of age. No participants under 18 years of age met increased liver monitoring criteria that never reached stopping criteria.

2.3.3. Discussion on clinical aspects

Study participants

Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older. As per the EU Nucala product information Section 5.1, the eosinophilic phenotype definition is defined as an elevated peripheral blood eosinophil count of ≥300/µL or ≥150/µL that is related to asthma, depending on symptom duration.

Study 206785 enrolled adults and adolescents ≥12 years of age and who had a documented physician diagnosis of asthma for ≥2 years with an eosinophilic phenotype who have previously benefited from anti-IL-5/5R therapy. The population is comparable to the existing authorised Nucala indication.

Participants who met the randomisation criteria entered the 52-week treatment period and were randomised to double-blinded treatment in a 1:1 ratio to receive placebo with either Depemokimab 100 mg SC or the participant's prior anti-IL-5/5R medication (either active mepolizumab 100 mg SC or active benralizumab 30 mg SC) on the active comparator arm.

Exposure

Study 206785 interim report includes data from participants who have completed the study as of the interim data cut-off date of 15 July 2024 except for 1 participant who was excluded as the data could not be cleaned in time due to operational challenges.

As of 15 July 2024, a total of 1313 participants were screened, 1090 participants were randomised, and 1076 were included in the interim analysis (IA) including 972 participants who had completed the study.

Based on the total population, the average age was 58.6 years overall, with 11 participants (1%) between ages 12-17 and 1 (<1%) participant <12 years of age in the mepolizumab/benralizumab group. There were 13 participants (2%) between ages 12-17 in the depemokimab group.

Effectiveness

The primary endpoint was to evaluate the efficacy of depemokimab. Primary, secondary, and other efficacy endpoints were not evaluated in Study 206785 interim report. Only safety endpoints were evaluated. The Clinical Expert Statement included a summary of efficacy results however this is not relevant for this procedure and has been assessed as per the Exdensur marketing authorisation procedure (EMEA/H/C/006446/0000).

Safety

The safety results evaluated and included in Study 206785 Interim CSR report were for participants who have completed the study as of the interim data cut-off date of 15 July 2024. Data from participants who are still ongoing in the study were not evaluated; however, as part the Exdensur marketing authorisation procedure (EMEA/H/C/006446/0000) the MAH has committed to submitting the final safety results.

The Clinical Expert Statement presents a summary of safety data by total number enrolled in the trial, with data from ongoing patients however the results are comparable to the Interim CSR data for the

overall population and are not focused on in this procedure. For participants under the age of 18, a post-hoc analysis focused on safety data was performed and contributed to the analysis for this procedure.

To note, the safety data is presented for Nucala together with benralizumab safety outcomes. Subjects who were administered mepolizumab (n= 288), had a marginally higher number enrolled than benralizumab (n= 250), total subject-years exposure were comparable (272.88, 251.64 respectively) therefore imbalances of reporting for benralizumab is not expected to overly skew outcomes. Both medicinal products have a similar mechanism of action and safety profiles however the safety results for Nucala should be interpreted under this limitation.

Another limitation for the interpretation of the Nucala safety profile, was that the results in Study 206785 Interim CSR report were presented as a comparison between the depemokimab versus mepolizumab/benralizumab groups. For the purpose of this report, the mepolizumab/benralizumab group will be assessed in comparison to the known safety profile of Nucala.

Immunogenicity

Post-baseline, study participants who continued receiving mepolizumab or benralizumab were not evaluated for immunogenicity.

Study 206785 Interim CSR report

The most frequently reported on-treatment AEs by preferred term (PT) were COVID-19 (20% in both groups), nasopharyngitis (18% and 19%), upper respiratory tract infection (10% and 12%), and headache 7% and 8%) in the depemokimab versus mepolizumab/benralizumab groups, respectively.

The most frequently reported treatment-related AEs by PT were injection site reaction (11 [2%] vs. 13 [2%]), headache (5 [<1%] in both groups), fatigue (4 [<1%] in both groups), pruritus (4 [<1%] versus 3 [<1%]), and asthenia (3 [<1%] vs. 1 [<1%]) in the depemokimab vs mepolizumab/benralizumab groups, respectively.

For Nucala, in placebo-controlled studies in adult and adolescent patients with severe refractory eosinophilic asthma, the most commonly reported adverse reactions during treatment were headache (20%), injection site reactions (8%) and back pain (6%).

The most frequently reported severe AEs by PT were pneumonia and COVID-19 (<1% in both groups). Two participants in the mepolizumab/benralizumab group had on-treatment SAEs considered as related to study treatment by the investigator (PT: thunderclap headache and atrial fibrillation). Post-treatment, one participant in the mepolizumab/benralizumab group had an SAE with a fatal outcome (PT: metastatic malignant melanoma) which was considered as not related to study treatment.

Treatment-related AEs by PT reported in Study 206785 Interim CSR report were consistent with the known safety profile, it is noted that known ADRs were reported at lower frequency. SAEs were low. No new AEs were reported.

Adverse events of special interest for the study were allergic (Type I hypersensitivity) reactions including anaphylaxis or other systemic reactions, Type III hypersensitivity (immune complex disease/vasculitis), local injection site reactions, and QTc prolongation.

One participant in depemokimab group (PT: rash) and no participants in the mepolizumab/benralizumab group reported an AESI of allergic (Type I hypersensitivity) reaction. No AESI of anaphylaxis were reported in either of the treatment groups in the study. Events considered by the investigator to represent other systemic reactions were reported in 3 (<1%) participants in the mepolizumab/benralizumab group.

In the mepolizumab/benralizumab group, 2 participants who reported systemic reactions were treated with mepolizumab prior to this study. No events of Type III hypersensitivity reactions were reported in either of the treatment groups in the study. Local injection site reactions were reported in 20 (4%) participants in the mepolizumab/benralizumab group.

AEs by PT reported under MedDRA SMQ of Torsade de pointes/QT prolongation were syncope (4 [<1%] participants in depemokimab and 1 [<1%] participant in mepolizumab/benralizumab group) and loss of consciousness (1 [<1%] participant in mepolizumab/benralizumab group).

ECG findings were unremarkable.

Hypersensitivity reactions (systemic allergic) and anaphylaxis are included ADRs in Section 4.8 of the Nucala SmPC.

Overall, it can be concluded that treatment-related AEs by PT reported in Study 206785 Interim CSR report were consistent with the known safety profile of Nucala, known ADRs were reported at lower frequency. SAEs were low. No new AEs were reported. AESI and vital signs and laboratory findings yielded no inconsistencies compared to the Nucala safety profile. No inconsistencies in the safety data were noted, to warrant specific analysis of the participants receiving mepolizumab in the mepolizumab/benralizumab group.

Clinical Expert Statement- post-hoc analysis of safety data for participants under the age of 18

The Clinical Expert Statement includes a post-hoc analysis focused on safety data for participants under the age of 18. Again, this post-hoc safety data is presented for Nucala together with benralizumab safety outcomes. Another limitation for the interpretation of the Nucala safety profile, was that the results were presented as a comparison between the depemokimab versus mepolizumab/benralizumab groups, rather than comparative analysis between age groups. In addition, the number of participants under the age of 18 years is low (1 participant enrolled at < 12 years in the mepolizumab/benralizumab group; the 12-17 age group: n=13/848 in the depemokimab group and n=11/839 in the mepolizumab/benralizumab group). All safety data relating to the post-hoc analysis should be interpreted considering these limitations and are descriptive in nature.

In participants under 18 years of age, on-treatment AEs were similar to adult age group AEs, AEs were consistent with the underlying disease or the known safety profile of Nucala. No AESIs were reported. One participant under 18 years of age who received mepolizumab reported 2 SAEs, both of which were assessed as unrelated to the study treatment. Within the context of the small number of participants under 18 years of age, no new safety signals for mepolizumab were detected in the mepolizumab/benralizumab group for participants under 18 years of age.

3. CHMP overall conclusion and recommendation

Study 206785 (NIMBLE) is part of the Depemokimab clinical development programme. The marketing authorisation application consisting of the full relevant data package (i.e. containing several studies) has been submitted and Exdensur (depemokimab) has received marketing authorisation on the 12th of February 2026, EMEA/H/C/006446/0000.

An interim report for Study 206785 has been submitted as part of this post-authorisation measure procedure (IA Data Cutoff: 15 July 2024). Data from participants for whom the study is still ongoing were not included in this interim report. This interim report has also been reviewed as part of the marketing authorisation application for Exdensur, depemokimab. A recommendation has been made within the Exdensur marketing authorisation procedure (EMEA/H/C/006446/0000), that "for the 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."

This post-authorisation measure procedure, submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, for Nucala will therefore review updated clinical data from the interim report for Study 206785, in terms of clinical outcomes for Nucala (mepolizumab) only.

Study 206785 interim report includes data from participants who have completed the study as of the interim data cut-off date of 15 July 2024. A total of 1313 participants were screened, 1090 participants were randomised, and 1076 were included in the interim analysis (IA) including 972 participants who had completed the study.

Based on the total population, the average age was 58.6 years overall, with 11 participants (1%) between ages 12-17 and 1 (<1%) participant <12 years of age in the mepolizumab/benralizumab group. There were 13 participants (2%) between ages 12-17 in the depemokimab group.

Study 206785 is a well-designed double-blind, double-dummy, parallel group, multi-centre, non-inferiority study which enrolled a population which is relevant to the existing authorised Nucala indication in severe refractory eosinophilic asthma. The primary endpoint was to evaluate the efficacy of depemokimab and therefore efficacy is not assessed as part of this procedure.

Several limitations in interpreting the safety data with respect to Nucala existed due to the study design focused on depemokimab outcomes, including safety outcomes presented for participants receiving mepolizumab together with participants receiving benralizumab, also results were presented as a comparison between the depemokimab versus mepolizumab/benralizumab groups.

Overall, however it can be concluded that treatment-related AEs by PT reported in Study 206785 Interim CSR report were consistent with the known safety profile of Nucala. Known ADRs were reported at lower frequency. SAEs were low. No new AEs were reported. AESI and vital signs and laboratory findings yielded no inconsistencies compared to the Nucala safety profile.

The MAH's proposal that the data provided in Study 206785 Interim CSR report does not alter existing data in the product information, is agreed.

In addition, a post-hoc analysis focusing on safety data for participants under the age of 18 was carried out. Results should be interpreted with caution considering the small sample size of paediatric patients and the limitations discussed above, results are therefore descriptive in nature.

On review of the post-hoc analysis for participants under the age of 18, on-treatment AEs were similar to AEs reported in the adult age group. AEs were consistent with the underlying disease or the known safety profile of Nucala. No AESIs were reported. One participant under 18 years of age who received mepolizumab reported 2 SAEs, both of which were assessed as unrelated to the study treatment. Within the context of the small number of participants under 18 years of age, no new safety signals for mepolizumab were detected in the mepolizumab/benralizumab group for participants under 18 years of age.

The MAH has concluded that safety outcomes reported in Study 206785 Interim report are in line with the approved product information for mepolizumab in the European Union (EU). Therefore, no changes to the Summary of Product Characteristics (SmPC) for mepolizumab have been proposed.

Based on the submitted data and taking into account the strengths and the limitations of the data, it is agreed that the product information does not warrant further updates.

☒ **Fulfilled:**

No regulatory action required.