18 September 2025
EMADOC-1700519818-2093764
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tezspire

International non-proprietary name: Tezepelumab

Procedure No. EMEA/H/C/005588/EMAVR0000245013

Note

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

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List of abbreviations

Abbreviation or special term	Explanation
ADA	Anti-drug antibody(ies)
ADR	Adverse drug reaction
AE	Adverse event
AERD	Aspirin exacerbated respiratory disease
AESI	Adverse events of special interest
AI	Autoinjector
ANCOVA	Analysis of covariance
APFS	Accessorised pre-filled syringe
BD	Bronchodilator
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CRSwNP	Chronic rhinosinusitis with nasal polyps
CSR	Clinical Study Report
CT	Computed tomography
DAE	Discontinuation of investigational product due to an AE
DBL	Database lock
DCO	Data cut-off
DSS	Difficulty with sense of smell
EAIR	Exposure-adjusted incidence rate
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
GCP	Good clinical practice
GINA	Global Initiative for Asthma
HRQoL	Health related quality of life
IAC	Independent Adjudication Committee
Ig	Immunoglobulin

IL	Interleukin
INCS	Intranasal corticosteroid
IND	Investigational New Drug
IP	Investigational product
LMK	Lund-Mackay (score)
LS	Least squares
MACE	Major adverse cardiovascular event
MFNS	Mometasone furonate nasal spray
MTP	Multiple testing procedure
N	Number of subjects per category, number of subjects in analysis
N	Number of subjects (per treatment group)
NC	Nasal congestion
NCS	Nasal congestion score
NCT	National Clinical Trial
NP	Nasal polyp(s)
NPS	Nasal polyp(osis) score
NPSD	Nasal Polyposis Symptom Diary
NSAID-ERD	Nonsteroidal anti-inflammatory drug exacerbated respiratory disease
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamic
PK	Pharmacokinetics
PRO	Patient-reported outcome
PT	Preferred term
PY	Person years
Q2W	Every 2 weeks
Q4W	Every 4 weeks
SA	Scientific Advice
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCS	Systemic corticosteroids
SMO	Site management organisation
SMP	Study may proceed
SNOT-22	SinoNasal Outcome Test, 22 item
SOC	System Organ Class
Teze	Tezepelumab

Th	T helper
TSLP	Thymic stromal lymphopoietin
TSS	Total Symptom Score
US	United States
V	Visit
Wk	Week

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 8 January 2025 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIB and A

Extension of indication to include treatment of Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) for Tezspire, based on results from study WAYPOINT (D5242C00001); this is a global, multicentre, randomised, double-blind, parallel-group, placebo-controlled study that evaluated the efficacy and safety of tezepelumab compared with placebo in the treatment of CRSwNP. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 4.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes and to update the PI and the Package Leaflet in accordance with the latest EMA excipients guideline.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0378/2020 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH received Scientific Advice (SA) on the development of tezepelumab as add-on therapy for treatment of severe CRSwNP from the CHMP on 30 April 2020 (EMEA/H/SA/3593/2/2020/II). The SA pertained to the following clinical aspects:

- The overall design of the phase 3 study, namely the acceptability of the proposed co-primary and key secondary endpoints, the choice of primary estimand, the analyses for the co-primary and secondary endpoints, the proposed testing strategy for confirmatory endpoints and the clinical significance of the secondary endpoint 'proportion of patients who achieve a maximum NPS of 1 (NPS $\leqslant$ 1) in each nostril at Week 52'.

- The adequacy of the safety data collected in the phase 3 study, combined with data gathered from the use of tezepelumab in other indications.
- The use of a single phase 3 pivotal study to support an MAA for this indication.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Finbarr Leacy Co-Rapporteur: Ewa Balkowiec Iskra

Timetable	Actual dates
Submission date	8 January 2025
Start of procedure:	26 January 2025
CHMP Rapporteur Assessment Report	24 March 2025
PRAC Rapporteur Assessment Report	28 March 2025
CHMP Co-Rapporteur Assessment	4 April 2025
PRAC Outcome	10 April 2025
CHMP members comments	14 April 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 April 2025
Request for supplementary information (RSI)	25 April 2025
MAH's responses submitted to the CHMP on	23 May 2025
CHMP Rapporteur Assessment Report	24 June 2025
PRAC Rapporteur Assessment Report	27 June 2025
PRAC members comments	n/a
PRAC Outcome	10 July 2025
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	17 July 2025
Request for supplementary information (RSI)	24 July 2025
MAH's responses submitted to the CHMP on	19 August 2025
PRAC Rapporteur Assessment Report	25 August 2025
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	28 August 2025
CHMP Rapporteur Assessment Report	3 September 2025
PRAC Outcome	4 September 2025
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	n/a
CHMP Opinion	18 September 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is characterised by inflammation of the nasal mucosa and paranasal sinuses with inflammatory hyperplastic growths that protrude into the nasal passages (i.e., nasal polyps). The inflammatory profile of CRSwNP is heterogeneous and can include type 1, type 2, and type 3 inflammation. Patients with CRSwNP often experience significant nasal obstruction and congestion, nasal discharge, facial pain or pressure, and impaired sense of smell, symptoms that can have a profound impact on quality of life and function.

CRSwNP affects up to 4% of the general population and is more common in males than females. The prevalence of CRSwNP increases with age, with age of onset typically from 40 to 60 years. In patients with CRSwNP, asthma is a common inflammatory co-morbidity, affecting 40% to 67% of patients with CRSwNP, with severe asthma being most common (57% to 62%). Conversely, approximately 41% of patients with severe asthma have nasal polyps, indicative of the high co-morbid rates between CRSwNP and asthma.

Claimed therapeutic indication

The therapeutic indication sought by the MAH is as follows: 'Tezspire 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.'

Management

Standard-of-care options for CRSwNP include intranasal corticosteroids (INCS) and systemic corticosteroids (SCS), long-term antibiotics, and nasal polyp removal surgery (also referred to as sinonasal surgery). Treatment of CRSwNP involves a stepwise approach, progressing from INCS to SCS and eventually surgical procedures such as implantation of a corticosteroid-eluting stent, polypectomy, or endoscopic sinus surgery. These treatments may provide symptomatic relief but do not address the underlying inflammatory processes, leading to frequent recurrence, and the treatments are associated with side effects.

In addition, the biologic treatments dupilumab (Dupixent), omalizumab (Xolair), and mepolizumab (Nucala) are available as add-on therapy for CRSwNP with insufficient symptom control from treatments described above. However, some patients do not respond to these treatments due to persistent tissue fibrosis and non-type 2-mediated disease. As a result, many patients still rely on SCS treatment despite the associated drawbacks.

2.1.2. About the product

Tezepelumab is a human monoclonal antibody that binds to thymic stromal lymphopoietin (TSLP), an upstream inflammatory cytokine that regulates several inflammation pathways.

Tezepelumab is currently approved as an add-on maintenance treatment in patients with severe asthma 12 years of age and older. The approved dosage for asthma is 210 mg SC Q4W.

2.2. Quality aspects

A rationale for not providing an updated Notified Body Opinion for the CRSwNP extension of indication was provided by the MAH. The justification was based on the fact that there are no changes to the device or device instructions for use and this was evident in the updated PI provided. Furthermore, the MAH has stated the expanded user population are expected to be similar with no impact on potential use errors and risk mitigations and this is supported. The MAH's conclusion that the addition of the CRSwNP indication is a non-substantial device change is supported, and thus a new notified body opinion is not required.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

Tezepelumab is a human monoclonal antibody, and as such is a protein, and is considered a natural substance. It is expected to be extensively metabolised to amino acid residues which will be recycled or further degraded, and therefore the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, tezepelumab is not expected to pose a risk to the environment.

2.3.2. Discussion and conclusion on non-clinical aspects

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, tezepelumab is not expected to pose a risk to the environment.

The current extension of indication in CRSwNP is considered approvable from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

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

- Tabular overview of clinical studies

Study number (acronym) Sponsor EudraCT Number NCT number	Study title	Co-primary objectives	Co-primary endpoints	Treatments, doses, regimen, route of administration, and number of randomised participants	Participant population	Duration
D5242C00001 (WAYPOINT) EudraCT No: 2020-003062-39 NCT No: NCT04851964	A Multicentre, Randomised, Double-Blind, Parallel-Group, Placebo-Controlled Phase 3 Efficacy and Safety Study of Tezepelumab in Participants with Severe Chronic Rhinosinusitis with Nasal Polyposis (WAYPOINT)	To evaluate the effect of tezepelumab on NPS To evaluate the effect of tezepelumab on participant-reported NC	Change from baseline in total NPS evaluated by nasal endoscopy at Week 52 and change from baseline in bi-weekly mean NCS evaluated as part of the NPSD at Week 52	Tezepelumab 210 mg SC Q4W (N = 204) Placebo SC Q4W (N = 206)	Female or male adults with physician-diagnosed CRSwNP at least 12 months prior to Screening Visit 1, NCS ≥ 2, NPS consistent with need for surgery (total NPS ≥ 5 with at least 2 for each nostril), SNOT-22 total score ≥ 30, and documented treatment of NP exacerbation with SCS within the past 12 months but not within the last 3 months prior to Visit 1 and/or any history of NP surgery	A 52-week double-blind, placebo-controlled treatment period, followed by a 24-week or 12-week follow-up period [a]

[a] A 24-week follow-up period was planned for the first 200 randomised participants and a 12-week follow-up period for all other participants.

CRSwNP Chronic rhinosinusitis with nasal polyps; N Number of subjects; NC Nasal congestion; NCS Nasal congestion score; NCT National Clinical Trial; NP Nasal polyp(s); NPS Nasal polyp score; NPSD Nasal Polyposis Symptom Diary; Q4W Every 4 weeks; SC Subcutaneous; SCS Systemic corticosteroids; SNOT-22 SinoNasal Outcome Test, 22 item.

2.4.2. Pharmacokinetics

The WAYPOINT study was conducted with the evaluation of pharmacokinetic (PK) and immunogenicity of tezeplumab as a secondary objective.

Samples for tezepelumab PK (trough serum concentrations) and immunogenicity (anti-drug antibodies - ADA and neutralising antibodies - nAb) were taken at baseline, and pre-dose at Week 4, Week 12, Week 24, Week 36, Week 52, and Week 64.

The PK analysis set contained all participants in the FAS who received active (tezepelumab) treatment and had at least one detectable tezepelumab serum concentration from a sample collected post-treatment that is assumed not to be affected by factors such as protocol deviations.

PK results

Tezepelumab trough serum concentrations are summarised by time in Table 1. During treatment, the serum trough concentrations were above the LLOQ (0.01 µg/mL) in all participants who received tezepelumab. After administration of tezepelumab, the mean serum trough concentration increased over time, approaching steady state by Week 12 and maintained through Week 52.

Table 1. Serum concentration (µg/mL) of tezepelumab over time (PK set)

	Result								
Group Timepoint	**n**	**n < LLOQ**	**Arithmetic mean**	**Arithmetic SD**	**Geometric mean**	**Geometric CV%**	**Median**	**Min**	**Max**
Teze 210 mg Q4W N = 203									
Baseline	189	189	NQ	NC	NQ	NC			
Week 4	183	0	12.885	4.331	12.165	35.9	12.531	4.134	29.489
Week 12	175	0	23.170	9.081	21.496	40.8	21.788	6.982	58.010
Week 24	171	0	26.056	10.776	23.994	43.0	25.280	8.422	73.479
Week 36	167	0	27.571	11.497	25.237	45.4	25.743	7.435	65.585
Week 52	167	0	26.489	10.978	24.352	43.7	25.223	7.281	66.004
Week 64	184	0	3.417	3.234	2.449	103.1	2.473	0.153	28.495

CV% Coefficient of variation; LLOQ Lower limit of quantification (µg/mL); Max Maximum; Min Minimum; n Number of observations in analysis; N Number of subjects per treatment group; NC Not calculated; ND Not determined; NQ Not quantified; Q4W Every 4 weeks; SD Standard deviation; Teze Tezepelumab

Immunogenicity results

The ADA prevalence (testing positive for ADA at any time) and the ADA incidence (testing positive for TE-ADA) were low in the tezepelumab group (5.7% and 3.7%, respectively). The ADA prevalence and ADA incidence were 11.1% and 7.4%, respectively, in the placebo group.

Confirmed ADA-positive participants were tested for the prevalence and incidence of nAb, which were both low for both treatment groups (1.1% and 0.6% for tezepelumab and 1.2% and 1.2% for placebo group).

The number of participants with TE-ADA was too low to formally assess the potential impact of ADA on efficacy, PK, or safety. Tezepelumab serum concentrations at different timepoints in TE-ADA-positive participants in the tezepelumab group were generally within the range of those in ADA-negative participants.

Table 2 summarises the ADA responses seen through the study.

Table 2. Summary of anti-drug antibody responses during the on-study period (Safety set) – non-China participants

ADA category	Statistics	Teze 210 mg N = 174	Placebo N = 171
ADA positive at baseline and/or post-baseline (ADA prevalence)	n/Na (%)	10/174 (5.7)	19/171 (11.1)
	Maximum titre		
	Min	67.2	67.2
	Q1	67.20	67.20
	Median	67.20	67.20
	Q3	67.20	67.20
	Max	268.8	2150.4
ADA positive at baseline only	n/Nb (%)	2/164 (1.2)	1/162 (0.6)
	Maximum titre		
	Min	67.2	67.2
	Q1	67.20	67.20
	Median	67.20	67.20
	Q3	67.20	67.20
	Max	67.2	67.2
Treatment-induced ADA positive [a]	n/Nd (%)	6/164 (3.7)	12/162 (7.4)
	Maximum titre		
	Min	67.2	67.2
	Q1	67.20	67.20
	Median	67.20	67.20
	Q3	67.20	67.20
	Max	134.4	134.4
Treatment-boosted ADA positive [a]	n/Nd (%)	0/164	0/162
Treatment emergent ADA (ADA incidence) [a]	n/Nd (%)	6/164 (3.7)	12/162 (7.4)
	Maximum titre		
	Min	67.2	67.2
	Q1	67.20	67.20
	Median	67.20	67.20
	Q3	67.20	67.20
	Max	134.4	134.4

Both baseline and at least one post-baseline ADA positive	n/Nd (%)	2/164 (1.2)	4/162 (2.5)
	Maximum titre		
	Min	67.2	67.2
	Q1	67.20	67.20
	Median	168.00	100.80
	Q3	268.80	1142.40
	Max	268.8	2150.4
ADA persistently positive [b]	n/Nc (%)	4/174 (2.3)	11/171 (6.4)
	Maximum titre		
	Min	67.2	67.2
ADA category	Statistics	Teze 210 mg N = 174	Placebo N = 171
	Q1	67.20	67.20
	Median	67.20	67.20
	Q3	67.20	134.40
	Max	67.2	2150.4
ADA transiently positive [b]	n/Nc (%)	4/174 (2.3)	7/171 (4.1)
	Maximum titre		
	Min	67.2	67.2
	Q1	67.20	67.20
	Median	100.80	67.20
	Q3	201.60	67.20
	Max	268.8	67.2
TE-ADA positive with maximum titre > median of maximum titres [c]	n/Nd (%)	1/164 (0.6)	2/162 (1.2)
	Maximum titre		
	Min	134.4	134.4
	Q1	134.40	134.40
	Median	134.40	134.40
	Q3	134.40	134.40
	Max	134.4	134.4
ADA positive at baseline (regardless of post- baseline)	n/Nb (%)	4/164 (2.4)	5/162 (3.1)
	Maximum titre		
	Min	67.2	67.2
	Q1	67.20	67.20

	Median	67.20	67.20
	Q3	168.00	134.40
	Max	268.8	2150.4
Any post-baseline ADA positive	n/Nc (%)	8/174 (4.6)	18/171 (10.5)
	Maximum titre		
	Min	67.2	67.2
	Q1	67.20	67.20
	Median	67.20	67.20
	Q3	100.80	67.20
	Max	268.8	2150.4
nAb positive at baseline and/or post-baseline (nAb prevalence)	n/Na (%)	2/174 (1.1)	2/171 (1.2)
	Maximum titre		
	Min	67.2	67.2
	Q1	67.20	67.20
	Median	100.80	67.20
	Q3	134.40	67.20
	Max	134.4	67.2
Treatment-induced nAb positive (nAb incidence) [d]	n/Nd (%)	1/164 (0.6)	2/162 (1.2)
	Maximum titre		
	Min	134.4	67.2
	Q1	134.40	67.20
	Median	134.40	67.20
	Q3	134.40	67.20
	Max	134.4	67.2

Baseline is the last non-missing value prior to administration of the first dose of investigational product.
On-study includes assessments starting on the date of first dose of IP and ending on the study completion or withdrawal date.
[a] Treatment emergent-ADA positive is defined as the sum of treatment-induced ADA positive (ADA negative at baseline and post-baseline ADA positive) and treatment-boosted ADA positive (ADA positive at baseline and boosted to 4-fold or higher during the study period).
[b] ADA persistently positive is defined as ADA positive at > = 2 post-baseline assessments (with > = 16 weeks between first and last positive) or ADA positive at last post-baseline assessment. ADA transiently positive is defined as having at least one post-baseline ADA positive assessment and not fulfilling the conditions of ADA persistently positive.
[c] The median of maximum titres is calculated based on the maximum titre for each ADA positive subject within each treatment group (including both baseline and post-baseline measurements).
[d] nAb incidence is defined as nAb negative at baseline (or ADA negative at baseline) and nAb positive at any post-baseline visit.
If a subject has more than 1 non-missing titre during the study, the maximum titre for each subject is summarised.
Titre values of positive ADA samples reported as ≤ limit of detection are imputed as limit of detection.

ADA Anti-Drug Antibody; IP = Investigational product. Max Maximum; Min Minimum; N Number of subjects in treatment group; n Number of subjects satisfying the conditions of the specified ADA category; Na = Number of subjects with any ADA assessment at baseline and/or post-baseline; nAb Neutralising antibodies; Nb = Number of subjects with an ADA assessment at baseline; Nc = Number of subjects with at least one post- baseline ADA

assessment; Nd = Number of subjects with an ADA assessment at baseline and at least one post- baseline assessment; Q1 Lower quartile; Q3 Upper quartile; TE Treatment emergent;

2.4.3. Pharmacodynamics

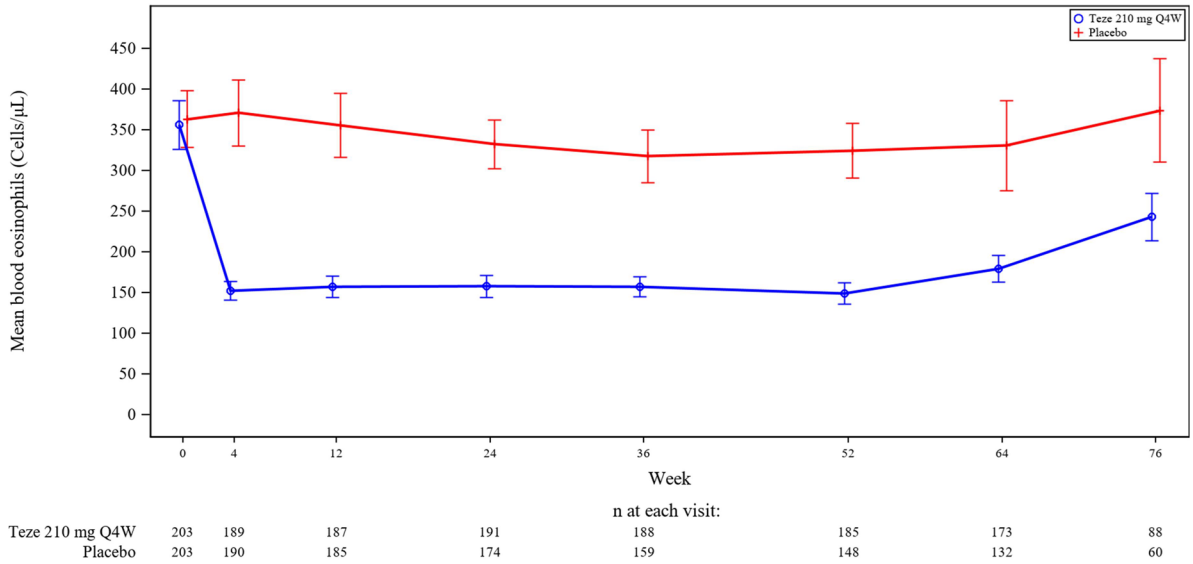
In the WAYPOINT study, the pharmacodynamics (PD) was evaluated in patients with CRSwNP as an exploratory objective.

The PD endpoints reported in this study were the peripheral blood eosinophil counts, total serum IgE, and fractional exhaled nitric oxide (FeNO) in participants with Co-Morbid Asthma/aspirin exacerbated respiratory disease (AERD)/Nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD).

Results

A reduction in mean blood eosinophil count was observed the tezepelumab group, from the first post-baseline assessment at Week 4 (Figure 1). The reduction was maintained through Week 52 (EOT). During the off-treatment period, the mean blood eosinophil counts in the tezepelumab group gradually increased but had not returned to baseline level by Week 76.

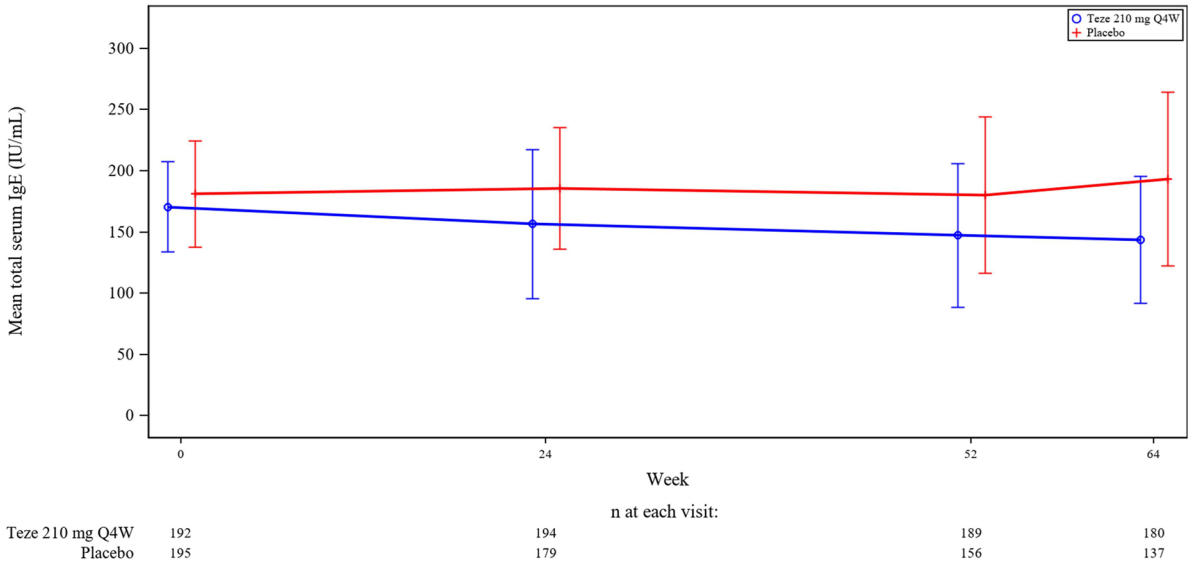
Figure 1. Peripheral blood eosinophil counts (Cells/µL) by timepoint up to week 76 (FAS)



The line points are mean. The upper and lower bars are the 95% CI. CI Confidence interval; n Number of subjects in analysis.

A reduction in mean total serum IgE was observed in the tezepelumab group, from the first post-baseline assessment at Week 24 through Week 52 (Figure 2). During the off-treatment period, IgE levels in the tezepelumab group continued to decrease up to Week 64.

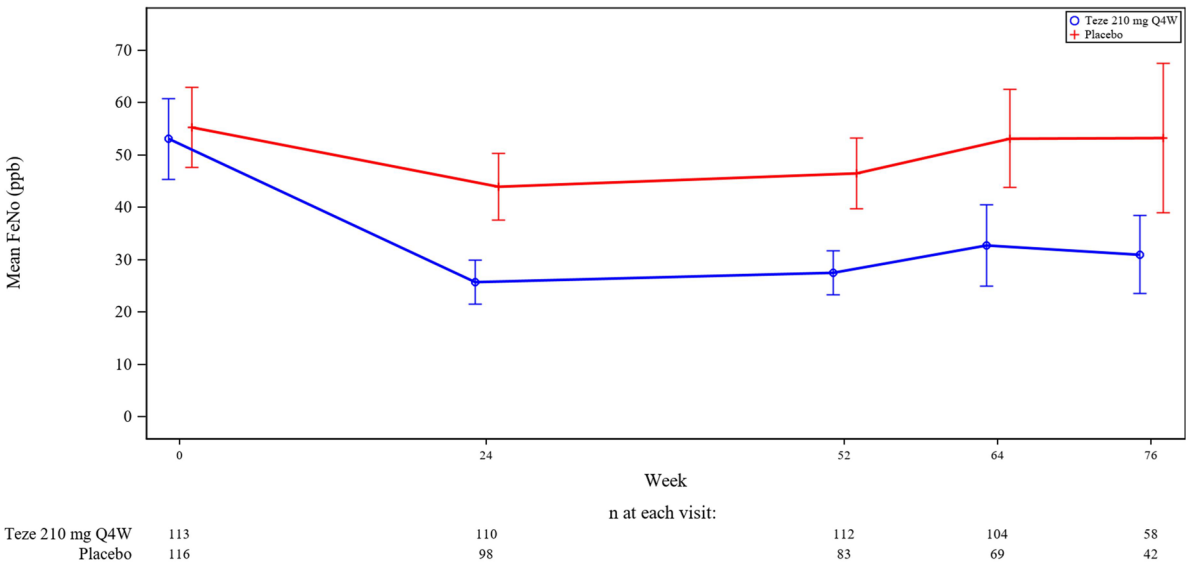
Figure 2. Total serum IgE (IU/mL) by timepoint up to week 64 (FAS)



The line points are mean. The upper and lower bars are the 95% CI.
CI Confidence interval; IgE Immunoglobulin E; n Number of subjects in analysis; Q4W Every 4 weeks; Teze Tezepelumab.

Change in FeNO was evaluated in the subgroup of participants with co-morbid asthma/AERD/NSAID-ERD. The mean FeNO level decreased over time in the tezepelumab group, observed from the first post-baseline assessment at Week 24 and was maintained through Week 76.

Figure 3. FeNO (ppb) by timepoint up to week 76 (co-morbid asthma/AERD/NSAID-ERD subset)



The line points are mean. The upper and lower bars are the 95% CI.
CI Confidence interval; FeNO Fractional Exhaled Nitric Oxide; n Number of subjects in analysis; NSAID-ERD Nonsteroidal Anti-Inflammatory Drug Exacerbated Respiratory Disease; Q4W Every 4 weeks; Teze Tezepelumab

2.4.4. PK/PD modelling

Population Pharmacokinetic analysis of tezepelumab in participants with severe CRSwNP (WAYPOINT)

The purpose of this analysis was to characterise the PK of tezepelumab in patients with CRSwNP. Prior to the current analysis, an asthma popPK model of tezepelumab in adolescents and adults was previously established (D5180C00007 popPK 2021) using data collected from 8 clinical studies conducted in healthy volunteers and patients with asthma, including the Phase 3 study NAVIGATOR (D5180C00007), Phase 2b study PATHWAY (CD-RI- MEDI9919-146/D5180C00001), and Phase 1 studies 20070620 (Study 0620), 20080390 (Study 0390), 20101183 (Study 1183), D5180C00002 (Study 0002, non-Chinese adolescents with asthma), D5180C00003 (Study 0003), and D5180C00012 (PATH-BRIDGE). A *post-hoc* analysis of patients with comorbid nasal polyps in the PATHWAY population revealed that 15.2% of the subjects had comorbid CRSwNP. Asthma patients with NP treated with tezepelumab demonstrated improvement in AERR, FEV1 and ACQ-6 and T2 inflammatory biomarkers relative to placebo to an equivalent extent as non-NP asthma patients. These finding support the rationale of a broad effect of tezepelumab in asthma and potential efficacy in CRSwNP.

Population PK analysis

Prior experience

A 2-compartment linear disposition model with first order absorption and elimination adequately described tezepelumab PK following IV or SC administration in adolescents and adults with asthma and healthy adult subjects (D5180C00007 popPK 2021). Body weight on CL, Vc, CLD, and Vp; ICS dose level (no/low versus medium/high dose) on CL and Vc; race (Asian versus non-Asian) on CL; formulation (Clinical Process 1 versus Clinical Process 2) on CL; and age on Vc were identified as statistically significant covariates on the PK of tezepelumab.

The PK parameter estimates for the final popPK model of tezepelumab in adolescent and adult asthma patients and in healthy adult subjects are presented in Table 3.

Table 3. Summary of final tezepelumab asthma popPK parameters

Parameter	Parameter Description	Estimate (% RSE)	95% CI from Bootstrapping	Shrinkage (%)
$exp(\theta_1)$	Clearance (CL) (L/day)	0.172 (3.89%)	(0.159, 0.186)	--
θ_7	Influence of body weight on CL	1.01 (4.28%)	(0.915, 1.09)	--
θ_{11}	Influence of no or low ICS dose level on CL	-0.168 (11.0%)	(-0.203, -0.133)	--
θ_{13}	Influence of Asian race on CL	0.0867 (24.1%)	(0.0444, 0.127)	--
θ_{15}	Influence of Clinical Process 1 formulation on CL	0.0955 (14.7%)	(0.0671, 0.127)	--
$exp(\theta_2)$	Central volume, V_c (L)	3.91 (5.68%)	(3.47, 4.32)	--
θ_8	Influence of body weight on V_c	0.963 (11.8%)	(0.677, 1.21)	--
θ_{12}	Influence of no or low ICS dose level on V_c	-0.102 (26.9%)	(-0.161, -0.0402)	--
θ_{14}	Influence of age on V_c	0.195 (14.7%)	(0.132, 0.261)	--
$exp(\theta_3)$	Inter-compartmental clearance (Q) (L/day)	0.568 (4.95%)	(0.506, 0.647)	--
θ_9	Influence of body weight on Q	0.588 (48.8%)	(3.42e-6, 1.19)	--
$exp(\theta_4)$	Peripheral volume, V_p (L)	2.17 (3.46%)	(1.98, 2.37)	--
θ_{10}	Influence of body weight on V_p	0.609 (20.5%)	(0.346, 0.895)	--
$exp(\theta_5)$	Absorption rate constant, k_a (1/day)	0.316 (3.41%)	(0.292, 0.34)	--
$exp(\theta_6)/(1+exp(\theta_6))$	Bioavailability after SC administration, F (%)	76.8 (3.61% [a])	(71.6, 82.7)	--
ω_{CL}	IIV for CL (CV%)	29.9 (2.13%)	(28.2, 31.7)	2.67
ω_{Vc}	IIV for V_c (CV%)	35.8 (3.87%)	(32.2, 40.0)	17.2
ω_Q	IIV for Q (CV%)	47.9 (9.66%)	(32.5, 64.6)	62.1
ω_{Vp}	IIV for V_p (CV%)	13.1 (13.1%)	(8.15, 16.3)	67.4
$\Omega_{CL\sim Vc}$	Covariance (CL~V_c)	0.0734 (6.81%)	(0.0608, 0.0879)	--
σ_a	Additive residual error (µg/mL)	0.0191 (12.5%)	(3.30e-6, 0.0298)	11.3
σ_p	Proportional residual error (%)	13.9 (0.774%)	(13.3, 14.5)	11.3

[a] The relative standard error for the original non-transformed bioavailability estimate (RSE_F) was calculated from the standard error of the logit transformed parameter θ_6 (SE_θ_6) by linear approximation using the following equation: RSE_F = (1-F) × SE_θ_6 × 100%.

Methodology

The popPK analysis was performed using the nonlinear mixed effects modelling approach. Model parameter estimation and evaluation were implemented with NONMEM 7, Version 7.5 or higher, PsN Version 5.2, and R version 4.1.3. All models were fitted using the First Order Conditional Estimation method with Interaction (FOCEI). In addition, ADVAN6/13 subroutines were applied when PK models are coded with ordinary differential equations.

A stepwise approach was applied to characterise the PK behaviour of tezepelumab in the severe CRSwNP population (from study D5242C00001), using a popPK approach.

The model for the current analysis was built using the previously developed asthma popPK model for tezepelumab (D5180C00007 popPK 2021) as a base model, including covariates established in the asthma model. The data set for the current analysis included the pooled data from the eight studies used to develop the previous asthma model, and the sparse data from the PATHWAY study in patients with CRSwNP.

Model development was guided by plausibility of the estimates, visual inspection of diagnostic plots, the reliability and precision of model parameter estimates, reduction in inter-individual variability and residual errors, and reduction in objective function value (OFV). A model was declared superior to an alternative nested model at the levels of significance of 1 % when OFV is reduced by ≥ 6.63. In addition, the shrinkage, which should be below 30%-40%, was determined for all random effects to ensure that there is no overfit (ε-shrinkage) and to inform about the relevance of employing empirical Bayesian estimations during covariate analysis (η-shrinkage).

The covariate relationships may explain part of the interindividual variability estimated in tezepelumab PK parameters of the popPK base model. Covariate/parameter relationships to evaluate were prespecified in Table 4. These were selected based on prior knowledge of previous popPK analysis, physiological plausibility, and clinical relevance. A full covariate modelling approach emphasising parameter estimation rather than stepwise hypothesis testing was implemented.

Table 4. Covariates tested in the tezepelumab popPK models

Covariates included in previous asthma popPK	CL	V_c	Q	V_p	k_a	F
Body weight (BWT)	+	+	+	+	n/a	n/a
Age	+	+	n/a	n/a	n/a	n/a
Race (Asian/White/Black/Other)	+	+	n/a	n/a	n/a	n/a
Inhaled corticosteroid (ICS) dose (no/low/medium/high)	+	+	n/a	n/a	n/a	n/a
Drug formulation (Clinical Process 1 or 2)	+	+	n/a	n/a	+	+
Aspartate aminotransferase (AST)	+	n/a	n/a	n/a	n/a	n/a
Creatinine clearance (CRCL)	+	n/a	n/a	n/a	n/a	n/a
Baseline blood eosinophil count (EOS)	+	+	n/a	n/a	n/a	n/a
Disease status (healthy/asthma/CRSwNP)	+	+	n/a	n/a	n/a	n/a
Ethnicity (Japanese / Chinese/Other)	+	+	n/a	n/a	n/a	n/a
Sex (male/female)	+	+	n/a	n/a	n/a	n/a
Anti-drug antibodies (ADA)	+	+	n/a	n/a	n/a	n/a

Results

Observed data

In total, 13634 observations (1090 from WAYPOINT) from 1575 subjects (203 subjects from WAYPOINT) were used for parameter estimation in the popPK model.

The Inhaled corticosteroid (ICS) level for the WAYPOINT study was not recorded in the popPK dataset, as the clinical sample cut-off for PK only allowed a limited access to clinical database. ADA positives were only found in 5 subjects in the WAYPOINT study, providing a low overall percentage of ADA positive (2.16%). The summary statistics of the different covariates showed consistency across patient

populations in the WAYPOINT study and previous studies, except for those associated with disease markers in patients with CRSwNP (CRP, FeNO, eosinophils and IgE). As anticipated, the disease markers in patients with CRSwNP exhibited elevated blood eosinophils and FeNO, as well as decreased CRP and IgE levels. However, as FeNO, IgE, and CRP levels were not available in a significant proportion of the subjects (approximately 30% or more), these covariates were omitted from the analysis. Upon CHMP's request, the MAH provided a *post-hoc* analysis including the FeNO, IgE, and CRP data from the WAYPOINT pooled dataset. Overall, these covariates did not have a significant impact on the PK of tezepelumab and their exclusion from the updated model was accepted.

Disease status (healthy, asthma, or CRSwNP) was included as a categorical covariate.

Figure 4 below shows concentrations *vs* time after last dose (TALD) by study and dose in the studies that make up the dataset. The MAH also provided figures showing the individual serum tezepelumab concentrations *vs* time or TALD (semilog), stratified by study, ADA, age, weight, sex, ethnicity, disease status and ICS groups. There were no signs of evident differences in the systemic exposure of tezepelumab across the different groups, suggesting similar PK behaviour between disease status (patients with asthma and patients with CRSwNP) (Figure 5). The lack of substantial PK differences across studies indicates that all clinical studies can be pooled together for popPK analysis.

Figure 4. Tezepelumab concentration vs time after last dose by study and dose

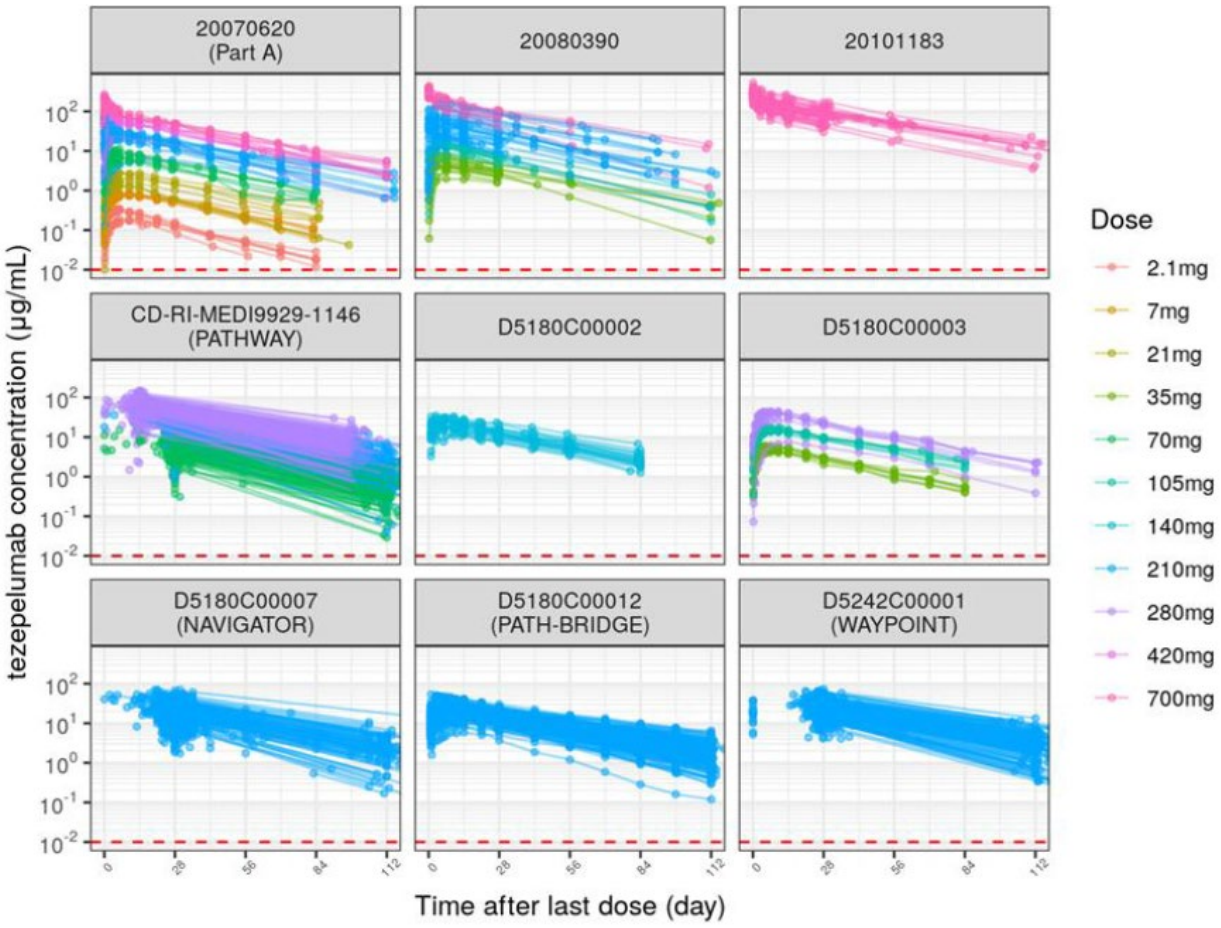
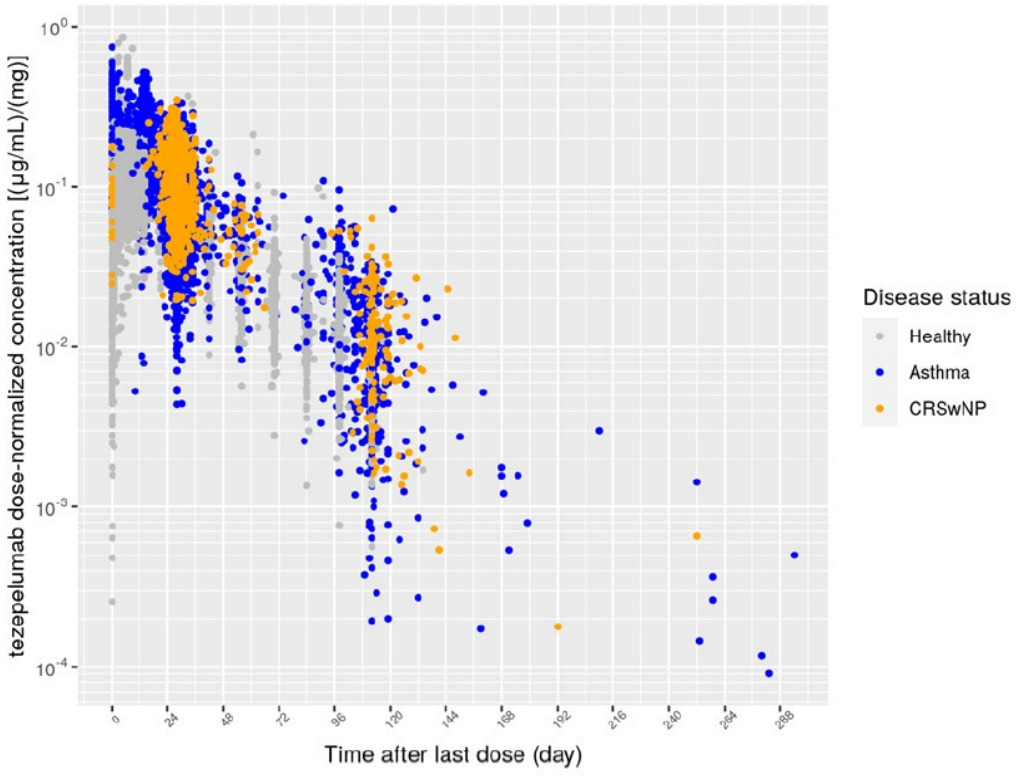


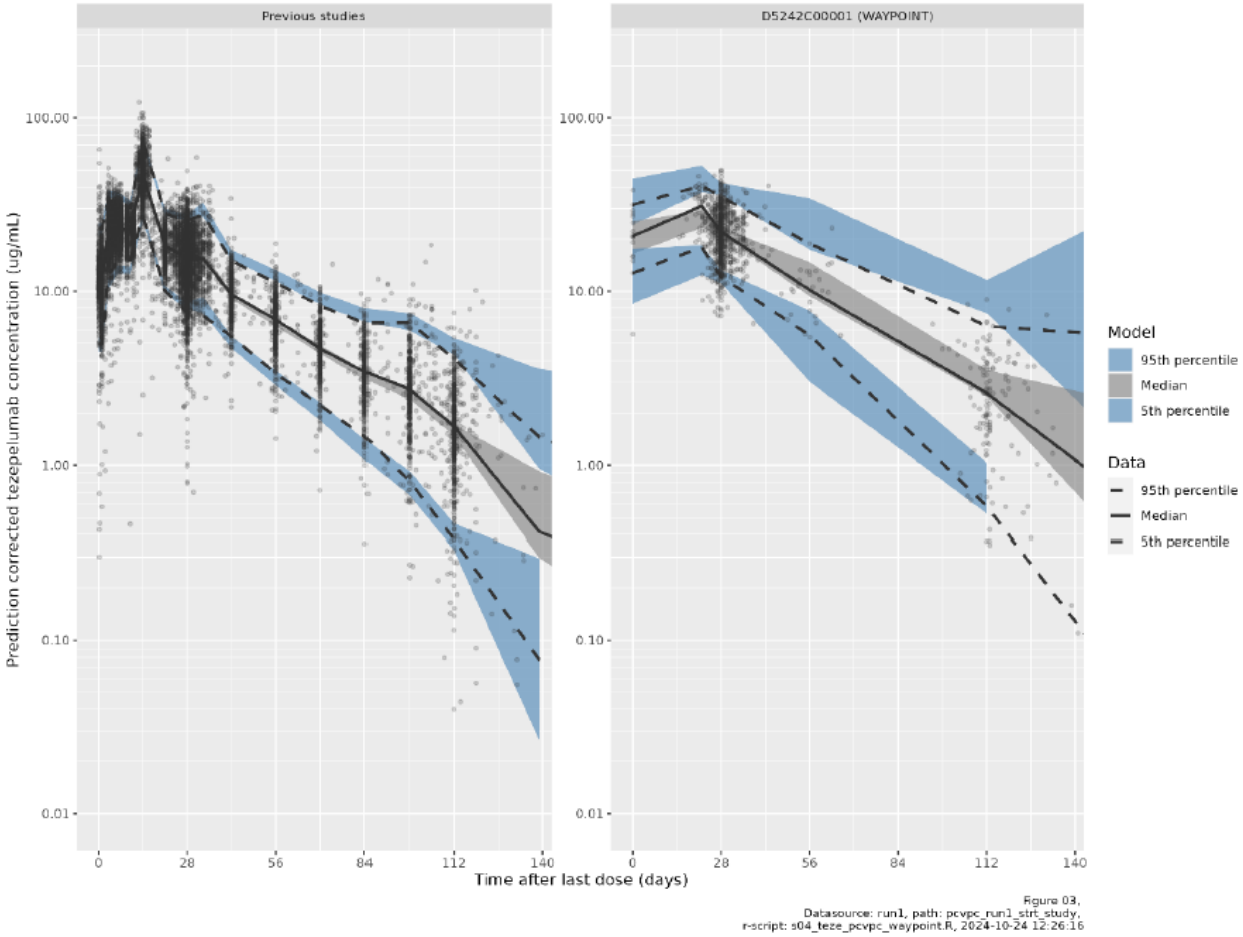
Figure 5. Dose-normalised tezepelumab concentration vs time after last dose grouped by disease status



Covariate model development

The first step of model development consisted of evaluating the feasibility of reproducing the same popPK results that were obtained in the previous well-established asthma popPK model (D5180C00007 popPK 2021). Thus, an external validation by means of prediction corrected visual predictive check (pcVPC) methodology was used to evaluate if the previous asthma popPK model was able to predict the PK data from patients with CRSwNP enrolled in the WAYPOINT study (Figure 6). Considering that the asthma popPK model was able to reproduce the PK data from subjects with CRSwNP (n=203), it was considered that tezepelumab exhibits similar PK behaviour in both CRSwNP and asthma patients. The previously developed asthma popPK model was selected as the base model.

Figure 6. Prediction-corrected visual predictive check plot for external evaluation of asthma popPK model using PK data from patients with CRSwNP (from study D5242C00001)



Solid and dashed lines = the median, 5th, and 95th percentiles of the observations, respectively; shaded grey and blue areas = the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model.

For the assessment of base model covariate relationships, IIV on bioavailability and residual was shown to be significant, and so this was retained for the other estimated parameters (ka, CL, Vc, Q, and Vp). The adequacy of the error model was demonstrated. It was demonstrated that all covariates in the base model were significant in CRSwNP except for body weight (BWT) on Q (with an increase of 8.5 points). However, based on allometric scaling theory, it was decided to retain BWT in all disposition PK parameters (CL, Vc, Q and Vp). Formulation was not retained as a covariate on CL as it was deemed CL was unlikely to be affected by formulation effect. All other covariates from the base model were retained.

In the following step, correlation between continuous and categorical covariates and intersubject variability were plotted. No clear trends were observed suggesting these covariates had little effect on tezepelumab exposure. In summary, for the key covariate of disease status (patients with CRSwNP vs patients with asthma), the popPK analysis results showed that disease status did not influence tezepelumab PK. No statistically significant disease effect was identified on CL, Vc, Q, Vp, ka and F using popPK analysis. No other covariates tested (Japanese or Chinese ethnicity, AST, sex, ADA status, or formulation) demonstrated any significance except the relation of CRCL on CL however the inclusion of CRCL was not retained due to the small impact on CL. The covariance effects from the base model were deemed adequate.

Tezepelumab final popPK model for CRSwNP

The final model consisted of:

- Two-compartmental distribution model with first-order absorption and elimination.
- Inter-subject variability (IIV) was characterised on absorption rate constant (ka), bioavailability (F), clearance (CL), central volume (Vc), distribution clearance (Q), peripheral volume (Vp) and residual.
- A combination of proportional and additive residual error model.
- Body weight (BWT), inhaled corticosteroid dose level (ICS) and race as statistically significant covariates on CL.
- BWT, ICS and age had a statistically significant impact on Vc.
- BWT as statistically significant covariate on intercompartmental clearance (CL_D) and Vp.

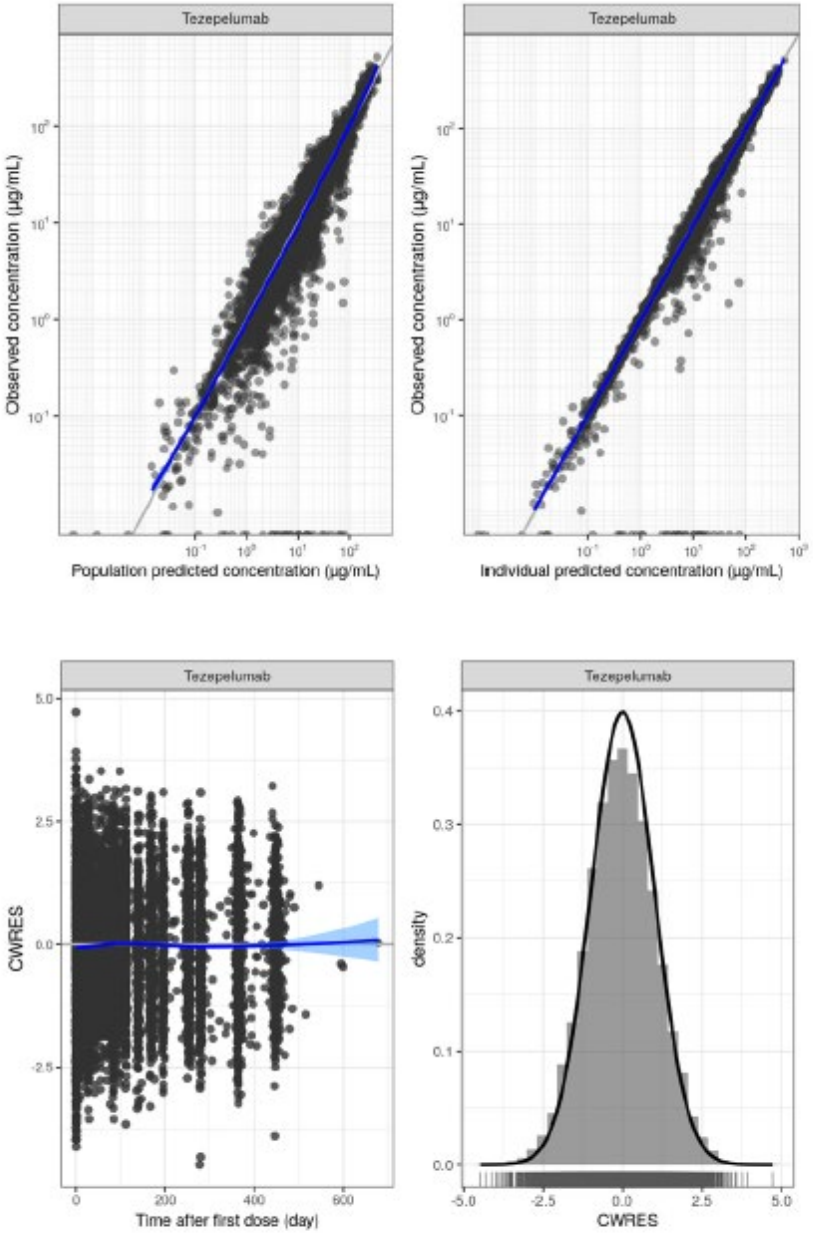
The parameter estimates for the final CRSwNP updated popPK model are reported in Table 5.

Table 5. PopPK model parameters estimates from CRSwNP updated popPK model (run39.mod)

Parameter	Estimate	RSE (%)	bootstrap median	bootstrap 95%CI	Shrink. (%)	Unit
Population Parameter						
K_a	0.327	2.56	0.327	[0.304 ; 0.356]	--	1/day
Bioavailability after SC admin. (F)	81.9	7.54	81.3	[74.4 ; 95.6]	--	%
CL	0.188	1.42	0.186	[0.171 ; 0.221]	--	L/day
$V_{central}$	4.23	2.57	4.19	[3.76 ; 5.22]	--	L
$Q_{intercompartmental}$	0.572	6.93	0.572	[0.499 ; 0.649]	--	L/day
$V_{peripheral}$	2.21	2.58	2.20	[1.98 ; 2.42]	--	L
Covariate						
Influence of body weight on CL	0.979	3.69	0.979	[0.905 ; 1.05]	--	--
Influence of no or low ICS dose level on CL	-0.192	8.27	-0.190	[-0.218 ; -0.163]	--	--
Influence of Asian race on CL	0.0944	18.2	0.0930	[0.0632 ; 0.127]	--	--
Influence of body weight on V_c	0.797	10.6	0.790	[0.542 ; 1.03]	--	--
Influence of no or low ICS dose level on V_c	-0.120	19.0	-0.117	[-0.161 ; -0.0754]	--	--
Influence of age on V_c	0.238	9.21	0.239	[0.183 ; 0.297]	--	--
Influence of body weight on Q	0.716	31.0	0.702	[0.102 ; 1.33]	--	--
Influence of body weight on Vp	0.729	11.4	0.717	[0.404 ; 1.06]	--	--
Interindividual Variability						
IIV for CL	23.5	6.26	23.5	[21.5 ; 27.5]	11.7	%
Covariance CL-V_c	0.0267	15.7	0.0267	[0.0144 ; 0.0562]	-	--
IIV for V_c	20.8	14.6	21.0	[14.7 ; 29.4]	44.0	%
IIV for Q	60.2	9.81	59.6	[49.4 ; 70.4]	48.6	%
IIV for V_p	11.1	21.7	10.8	[3.88 ; 15.4]	66.9	%
IIV for K_a	42.1	6.74	41.7	[37.4 ; 45.7]	47.8	%
IIV for Bioavailability (F)	11.0	8.81	11.1	[9.23 ; 5.42]	33.3	%
IIV for Res	44.9	4.40	44.8	[41.9 ; 47.3]	3.67	%
Residual Variability						
Proportional component	11.9	1.31	11.9	[11.6 ; 12.3]	3.32	%
Additive component	0.0283	9.24	0.0287	[0.00611 ; 0.0443]	3.32	µg/mL

Standard GOF plots (Figure 7) showed good agreement between the model prediction and the observed tezepelumab serum concentration when pooling all data. There was no apparent bias or trend in the CWRES over chronological time, suggesting time invariant PK. There were no identified potential outliers (observations with absolute values of the CWRES > 5). Distribution of CWRES showed random normal scatter around zero for all data with no specific pattern, indicating the appropriateness of the residual model.

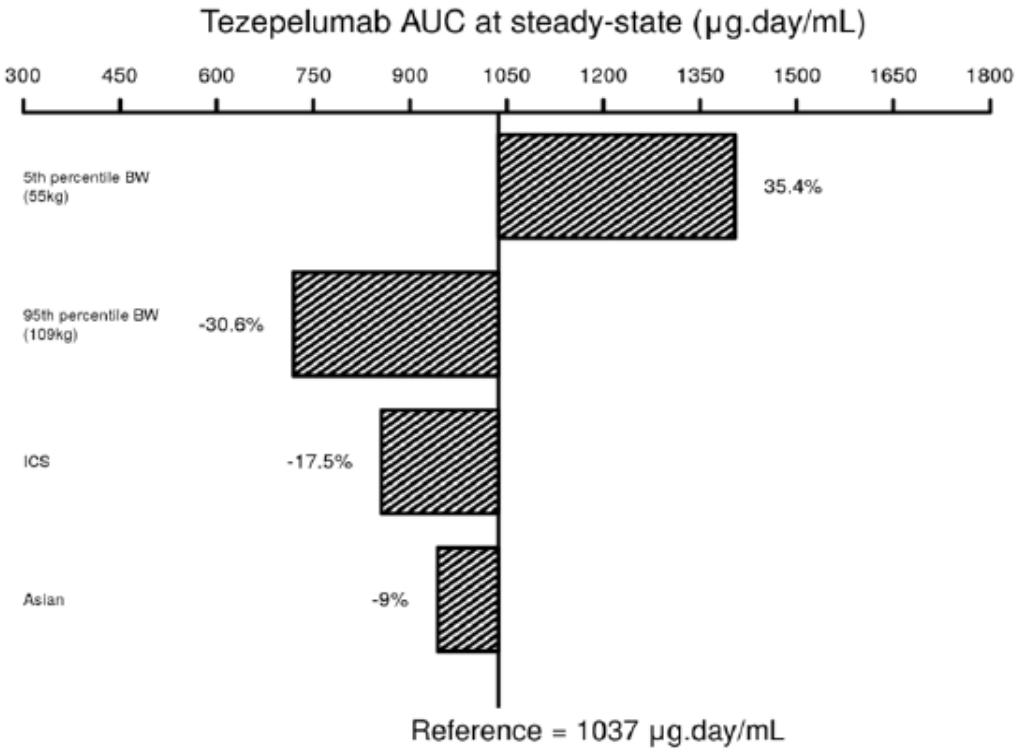
Figure 7. Basic goodness of fit plots for final CRSwNP updated popPK model (run39.mod)



Blue line = a trend line through the data points; Blue area = the 95% confidence interval around it.

The impact of the selected covariates on steady-state exposure parameters (AUCss [Figure 8], Cmax,ss [Figure 9] and Cmin,ss [Figure 10]) based on a univariate assessment are presented as tornado plots from Figure 8 to Figure 10, using covariate range from clinical study D5242C00001 following 12 consecutive SC administrations of 210 mg every 4 weeks (Q4W). The reference values for tezepelumab exposure were 1037 µg·d/mL for AUCss, 47 µg/mL for Cmax,ss and 26 µg/mL for Cmin,ss. For all tested covariates (body weight, age, race and ICS), only body weight showed a significant impact on tezepelumab exposure (>|30%|). Body weight was shown to be the most influential covariate on tezepelumab exposure parameters with a maximum change of up to 39% for the 5th percentile of observed BWT (55 kg) in subjects with CRSwNP included in study WAYPOINT. The impact of all other tested covariates (age, race and ICS) on tezepelumab exposure parameters was minimal (<|~20%|) and can be regarded of minor clinical relevance in patients with CRSwNP, as considered by the MAH. Similar results were observed in tornado plots for CL and Vss.

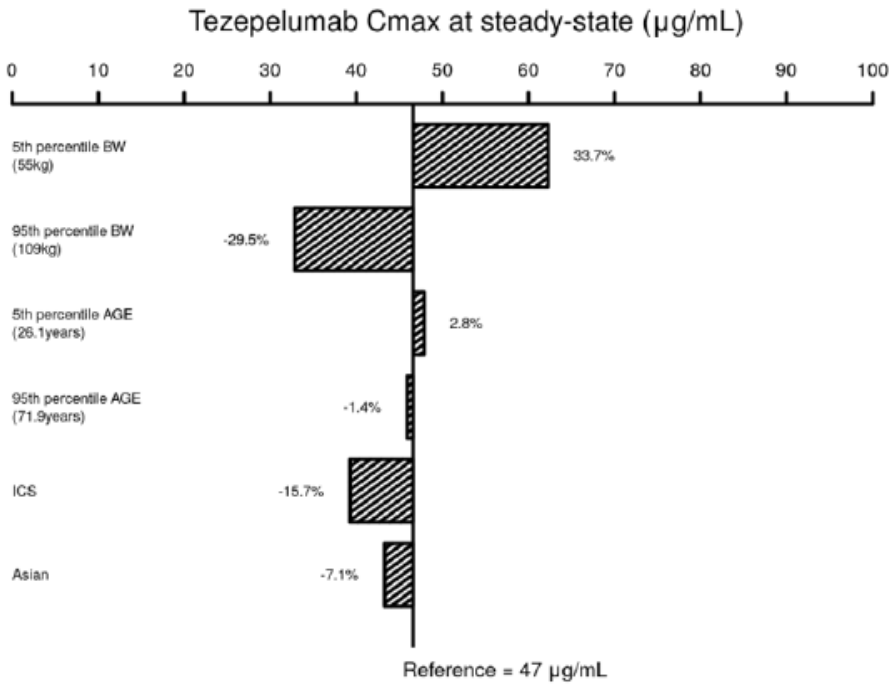
Figure 8. Impact of covariates on tezepelumab AUCss – Tornado plot



Reference: Male, Patient with CRSwNP, No/Low ICS, no-Asian, median covariates
Bars represent the relative change (%) from the reference
Dosing regimen: Tezepelumab 210 mg

Dashed area = the percentage change of model parameter for the 5th and 95th percentile of the relevant covariates relative to the median parameter estimates (for continuous covariates), or relative to the most frequent category (for categorical covariates).

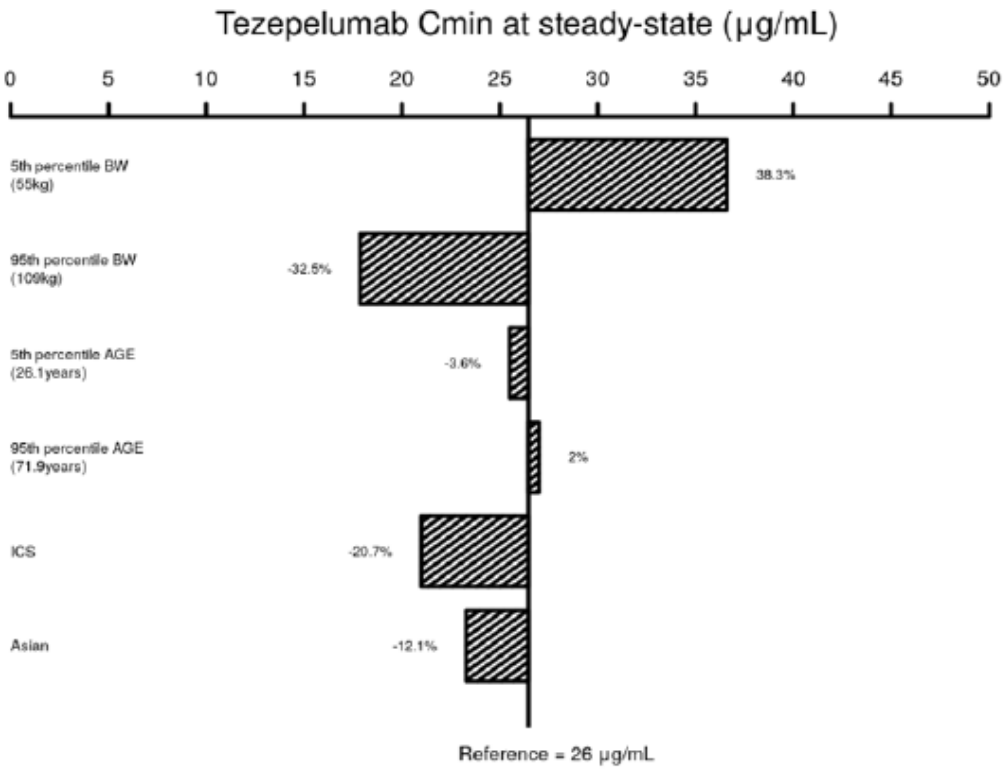
Figure 9. Impact of covariates on tezepelumab Cmax,ss – Tornado plot



Reference: Male, Patient with CRSwNP, No/Low ICS, no-Asian, median covariates
Bars represent the relative change (%) from the reference
Dosing regimen: Tezepelumab 210 mg

Dashed area = the percentage change of model parameter for the 5th and 95th percentile of the relevant covariates relative to the median parameter estimates (for continuous covariates), or relative to the most frequent category (for categorical covariates).

Figure 10. Impact of covariates on tezepelumab Cmin,ss – Tornado plot

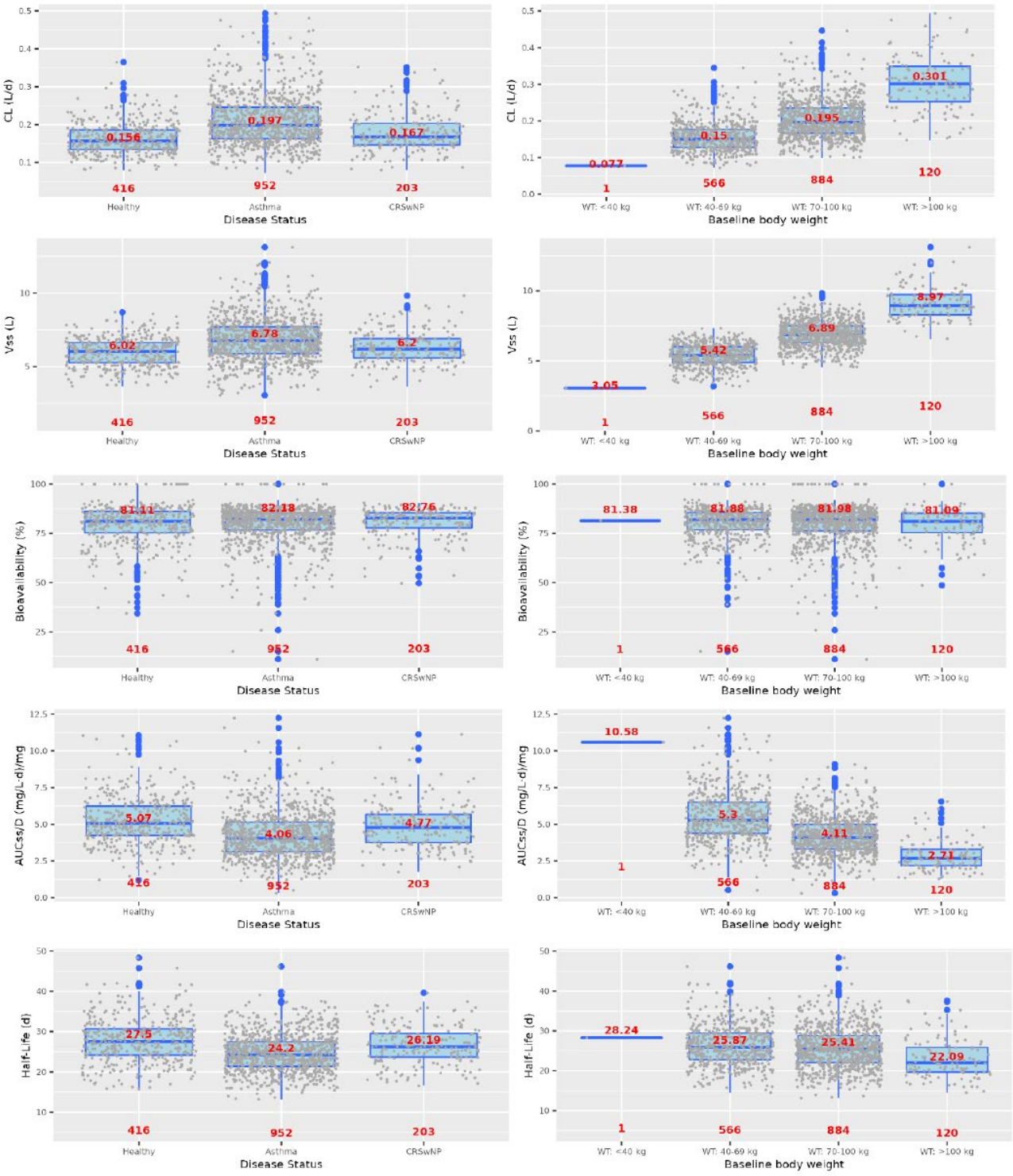


Reference: Male, Patient with CRSwNP, No/Low ICS, no-Asian, median covariates
Bars represent the relative change (%) from the reference
Dosing regimen: Tezepelumab 210 mg

Dashed area = the percentage change of model parameter for the 5th and 95th percentile of the relevant covariates relative to the median parameter estimates (for continuous covariates), or relative to the most frequent category (for categorical covariates)

The evaluation of the impact of covariates on tezepelumab PK was also conducted by means of *post-hoc* analysis using the individual PK parameters across the entire population. Potential differences in tezepelumab systemic exposure between different sub-groups (disease status, body weight, ICS, race, age, ADA, sex and ethnicity) were evaluated by comparing individual *post-hoc* model predicted PK parameters (CL, Vss, F, AUCss/D and t1/2). Figure 11 below highlights the impact of disease status and body weight on the model predicted parameters. No meaningful difference in tezepelumab CL, Vss, F, AUCss/D or t1/2 was observed between patients with CRSwNP and patients with asthma. Body weight demonstrated a substantial impact on CL, Vss, and AUCss/D.

Figure 11. Tezepelumab CL, Vss, F, AUCss/D and t1/2 stratified on disease status and body weight



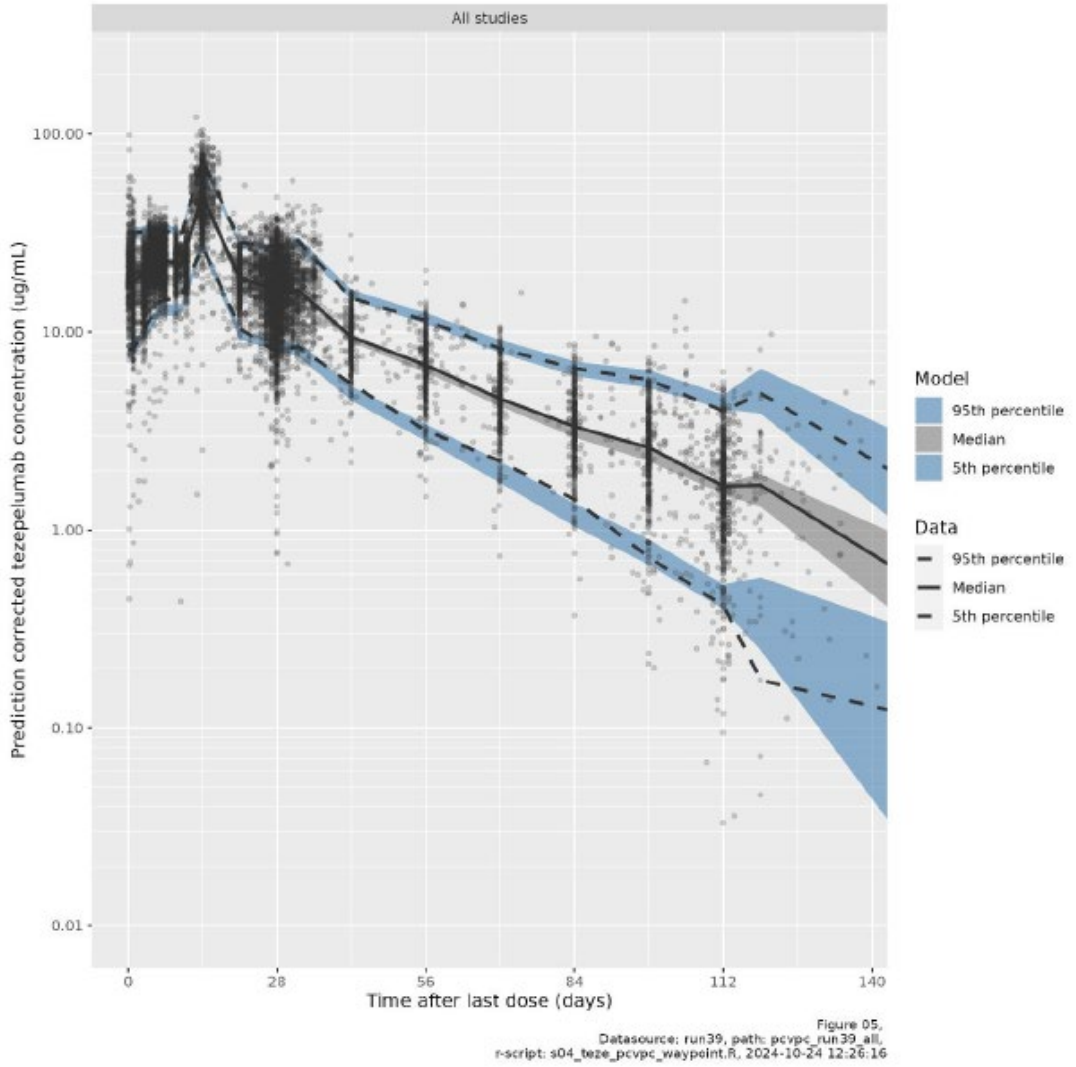
To further evaluate the impact of disease status and ethnicity on tezepelumab drug exposure, an evaluation of the individual AUCss (calculated as F·Dose/CL) was performed in subjects only treated with 210 mg Q4W (Table 6). These results confirmed that there was no meaningful difference in tezepelumab exposure between patients with asthma and with CRSwNP. Specifically, the AUCss in patients with CRSwNP was only 16.4% higher than that in patients with asthma.

Table 6. Descriptive Statistics for Individual Tezepelumab AUCss in Subjects Treated with 210 mg Q4W Grouped by Disease Status

Groups	n	AUCss Mean *(µg/mL·d)*	AUCss cv *(%)*	AUCss Q1 *(µg/mL·d)*	AUCss Q2 *(µg/mL·d)*	AUCss Q3 *(µg/mL·d)*	AUCss Q4 *(µg/mL·d)*	AUCss Diff. *(%)*
Asthma	**651**	**885.8**	**36**	**653.7**	**858.0**	**1,082.7**	**2,136.8**	**0.0**
CRSwNP	203	1,031.1	32	789.1	1,002.0	1,190.5	2,336.5	16.4
Healthy	6	890.6	39	667.6	809.5	1,118.3	1,395.6	0.5

The ability of the final CRSwNP updated popPK model to reproduce the central tendency and variability of the tezepelumab concentration data over time was evaluated using pcVPC based on 1000 simulated replicates of the popPK dataset. The pcVPC including data for all studies (Figure 12) demonstrated a strong agreement between the model prediction and the observed tezepelumab serum concentration, indicating that the developed model was appropriate in describing the time course of tezepelumab and its variability in a heterogeneous population, encompassing healthy subjects, patients with asthma and patients with CRSwNP.

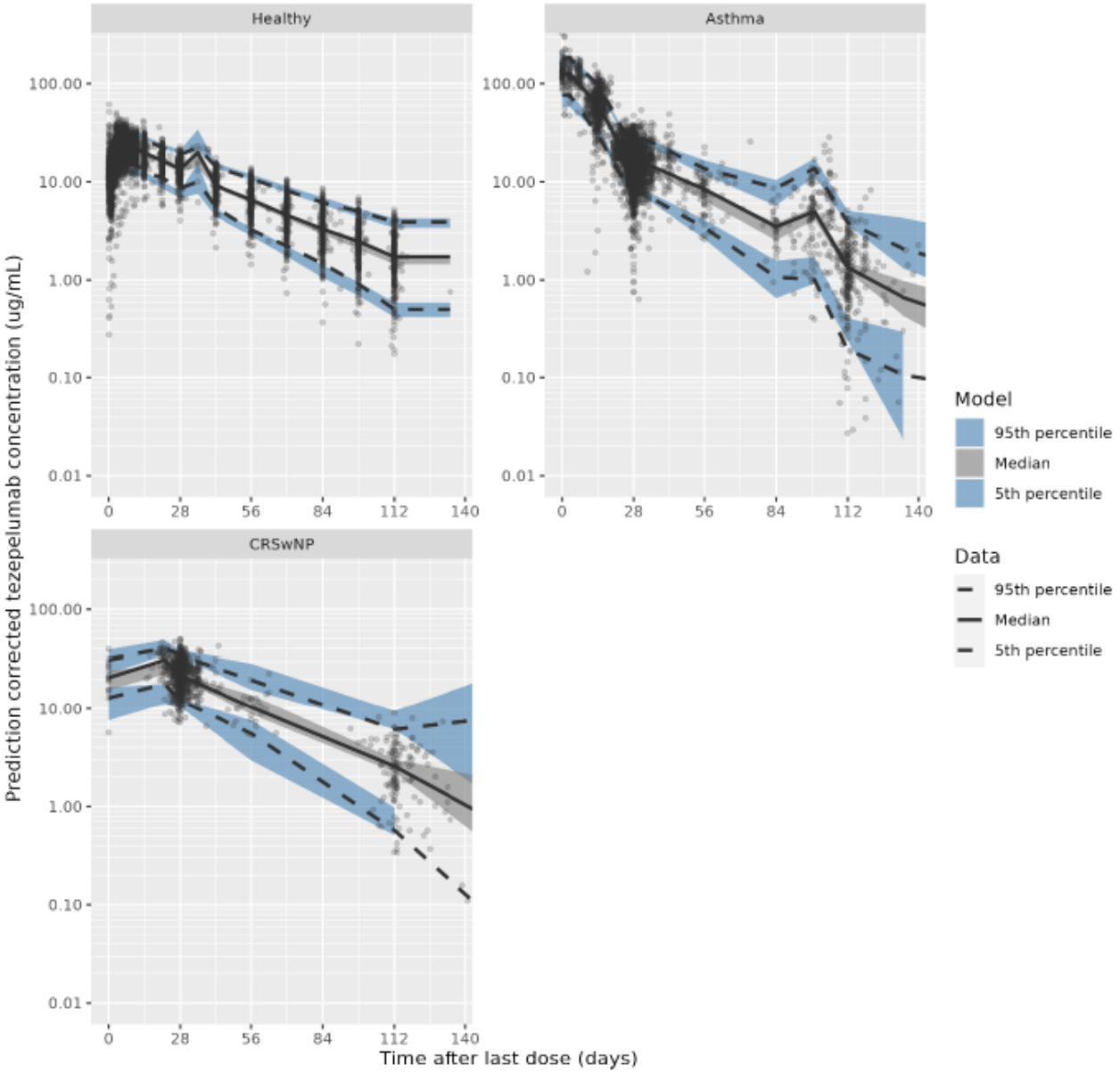
Figure 12. pcVPC of the CRSwNP updated popPK model (run39.mod) vs time after last dose



Solid and dashed lines = the median, 5th, and 95th percentiles of the observations, respectively; shaded grey and blue areas = the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model

The disease-stratified pcVPCs are presented in Figure 13. This pcVPC plot illustrates the adequate model performance describing PK data across different disease status, thereby indicating that the CRSwNP updated popPK model adequately described tezepelumab PK in healthy volunteers, in patients with asthma and in patients with CRSwNP.

Figure 13. pcVPC of CRSwNP updated popPK model vs time after last dose – stratified by disease status



Solid and dashed lines = the median, 5th, and 95th percentiles of the observations; shaded grey and blue areas = the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model.

2.4.5. Discussion on clinical pharmacology

Pharmacokinetics (PK)

The MAH has provided PK data evaluated in the WAYPOINT study by summarising the plasma concentrations of tezepelumab throughout the study.

The serum concentration results from the WAYPOINT study in patients with CRSwNP show a similar trend to the results from the NAVIGATOR and SOURCE studies, which used the same treatment regimen of 210 mg tezepelumab every 4 weeks in patients with asthma, with steady state

concentrations being reached between Week 12 and Week 24. It is noted that the mean (arithmetic and geometric) concentrations observed in the WAYPOINT study were similar but higher than in both the NAVIGATOR and SOURCE studies at each time-point. The WAYPOINT mean concentrations would still be contained within the variability seen in the SOURCE and NAVIGATOR studies, thus this is still considered acceptable overall.

The immunogenicity results observed in the WAYPOINT study demonstrated an overall low incidence of treatment induced ADAs and nAbs. These results were adequately added to SmPC section 5.1. These results are in line with both the asthma NAVIGATOR and SOURCE studies, where incidence of treatment emergent ADAs and nAbs was also low and comparable to placebo. The low number of patients with ADAs makes it difficult to draw a meaningful conclusion on the impact of ADAs on tezepelumab PK in the CRSwNP population, however as the results are similar to what was seen in the asthma population this is considered acceptable overall.

Overall, the presented PK and immunogenicity results from the WAYPOINT study suggest that the PK and immunogenicity in the CRSwNP patient population is similar to that seen in patients with asthma. The PK of tezepelumab in the CRSwNP population is also discussed below, under PopPK analysis.

Pharmacodynamics (PD)

The PD evaluation was considered an exploratory endpoint in the WAYPOINT study. As a result, only a small number of parameters were reported.

In general, for the three PD parameters reported, there was a decrease in the measured values (eosinophils counts, total IgE, and FeNO) compared to baseline in the tezepelumab group, which was maintained throughout the treatment period (Week 0-52).

This is in line with the results reported for these parameters in the SOURCE study (in asthma). This suggests that the PD for tezepelumab are similar in CRSwNP and asthma for the reported parameters.

PopPK analysis

The purpose of the PopPK model was to characterise the PK of tezepelumab in patients with CRSwNP.

The popPK analysis was performed using the pooled data set of eight studies from the previously developed model, and the data from the WAYPOINT study in patients with CRSwNP. The previously developed model was used as the base model for model development. This is considered appropriate as the data from the WAYPOINT study demonstrated that there are similar trends in the PK of tezepelumab between patients with CRSwNP (WAYPOINT) and asthma (NAVIGATOR, SOURCE).

The preparation of the analysis data set, and the handling of missing data, erroneous data and outliers was adequately explained by the MAH. The strategy described to characterise the popPK of tezepelumab in the CRSwNP population is also acceptable. The steps described in model building indicate good modelling practice.

For the covariate model, the criteria for significance for changes in nested models (changes in the OFV of ≥ 6.63) is considered acceptable and is in line with standard practice. The acceptance criteria for shrinkage are also considered acceptable. The overall protocol for the exclusion of existing covariates or inclusion of potential covariates of interest is acceptable as well.

The steps for model evaluation were described in sufficient detail and are considered acceptable to evaluate whether the model describes the data from patients with CRSwNP well. Overall, the methods described for the model development for the current analysis are considered acceptable.

Based on the description and analysis of the observed data, it is agreed that the data from the WAYPOINT study can be pooled with the data from the previous studies for parameter estimation in

the popPK model. There were no substantial differences in PK trends across the different studies or disease states. FeNO, IgE, and CRP levels were not available for a proportion of observations (>30%) and these covariates were omitted from the analysis. Nevertheless, these covariates are not expected to have a significant impact on the PK of tezepelumab, therefore this is considered acceptable.

For the categorical covariate for disease status, comorbid asthma and CRSwNP was not accounted for in the analysis i.e. no subjects from previous studies were categorised with CRSwNP and no subjects from WAYPOINT categorised with asthma. In the previous asthma studies a proportion of subjects had comorbid CRSwNP (e.g. 14% in NAVIGATOR), and in the WAYPOINT study a significant proportion (>50%) of subjects had comorbid asthma. To understand the impact of these categories, the categorical covariate disease status was tested as a potential covariate on CL in the WAYPOINT population PK model including 3 additional parameters in covariate test model. The inclusion of these 4 categories of disease status in the clearance model resulted in a non-significant reduction in the objective function by 4.8 points. The differences between the covariate test and reference models were minimal for all parameters, with prediction errors of less than 5%, except for the covariate effect of inhaled corticosteroid on CL, which was less than 20%. The potential influence of disease status (individuals with asthma without CRSwNP, individuals with asthma and CRSwNP, and individuals without asthma and with CRSwNP) on CL compared to healthy volunteers, showed an increase of less than 6% in all cases, suggesting that disease state has minimal impact on clearance. It is thus accepted that the evaluated disease statuses do not have a significant impact on the PK of tezepelumab.

The previous popPK model (D5180C00007 popPK 2021) was used as the base model for this popPK model development. The data from the WAYPOINT study in CRSwNP subjects was used to perform an external validation on the base model and was able to adequately reproduce the CRSwNP data, demonstrating that it was an acceptable base model.

The MAH applied the methodology for testing of covariates on parameters as described, and the stepwise approach could be followed logically. All covariates from the base model were found to be significant in the CRSwNP population except for body weight on Q, however the MAH chose to retain this in the model based on allometric scaling theory. This is considered acceptable. In the following step, each additional covariate of interest (including disease status) tested did not show any statistically significant impact on estimated parameters. CrCL demonstrated significance on clearance, however as the impact to CL was minimal this was not retained in the model. Considering tezepelumab is a human monoclonal antibody it is not expected that renal clearance plays any role in elimination of the drug, therefore this is considered acceptable.

The description of the final popPK model for CRSwNP is considered acceptable. For the final model, the final parameters and covariate effects are well estimated (RSE ranging from 1.31 – 31%). The estimated parameters are slightly different than what was reported for the asthma popPK parameters, however the difference is relatively minimal (<10% for majority) that is not considered a concern. Shrinkage for the IIV is overall higher than was seen for the asthma popPK parameters, however the majority of parameters are within an acceptable range (<50%) except for the Vp. This is in line with the asthma popPK parameters and is considered acceptable. The magnitude of IIV is overall in line with what was reported for the asthma popPK parameters. The standard GOF plots demonstrated good agreement of the observed data with the population and individual predicted concentrations, and the CWRES plots demonstrate no trends of concern.

Overall, the covariates included in the model had a statistically insignificant impact on tezepelumab AUC, Cmax, and Cmin in CRSwNP, except for body weight. Body weight was the most influential covariate on tezepelumab exposure. Compared with a typical participant with body weight of 70 kg, participants with body weight at the 5th and 95th percentiles of the WAYPOINT population were

expected to have 35.4%, 33.7%, and 38.3% higher and 30.6%, 29.5%, and 32.5% lower steady state exposures (AUC,ss, Cmax,ss and Cmin,ss), respectively. No impact to the efficacy or safety profile was seen in the WAYPOINT study, and these results are in line with what was seen in the asthma population. Therefore, based on analyses of efficacy and safety data provided by the MAH upon CHMP's request, no dose adjustment based on body weight is deemed needed.

The MAH has provided a number of pcVPCs including a pcVPC for all data and one stratified by disease state. Based on the presented pcVPCs, the predictive performance of the final PopPK model for the CRSwNP has improved compared to the base model. The predictive performance of the final popPK model is overall acceptable.

The final popPK model presented by the MAH demonstrates precise parameter estimation and acceptable predictive performance of tezepelumab plasma concentrations based on pcVPCs. Disease state, as implemented in the model, appeared to have no significant impact on any of the predicted PK parameters or plasma concentration parameters. It is overall accepted that the CRSwNP popPK model demonstrates that the PK of tezepelumab is similar in patients with asthma and CRSwNP, as outlined in Section 5.2 of the SmPC.

2.4.6. Conclusions on clinical pharmacology

The CHMP concludes that the clinical pharmacology of tezepelumab is similar in patients with asthma and CRSwNP; and is sufficiently characterised.

2.5. Clinical efficacy

2.5.1. Dose response studies

No dose response studies in CRSwNP were performed by the MAH.

Given the similarity of the underlying inflammatory pathophysiology of asthma and nasal polyps and significant overlap in patient populations, the MAH considered that the approved asthma dose of 210 mg Q4W SC was expected to effectively target the inflammatory pathways relevant to both diseases and show efficacy in CRSwNP. The 210 mg Q4W dosing regimen was thus selected for WAYPOINT based on the efficacy, safety, and exposure-response analysis from the Phase IIb Study PATHWAY in asthma, which demonstrated that the 210 mg Q4W dose led to improved clinical efficacy compared with 70 mg Q4W, whereas the 280 mg Q2W dose did not further increase efficacy compared with 210 mg Q4W, and the safety profiles were similar across the 3 doses.

In addition, a 210 mg Q4W dosing regimen was used in the Phase III NAVIGATOR study, in which improvements in SNOT-22 scores were observed in a *post-hoc* analysis of participants with nasal polyps.

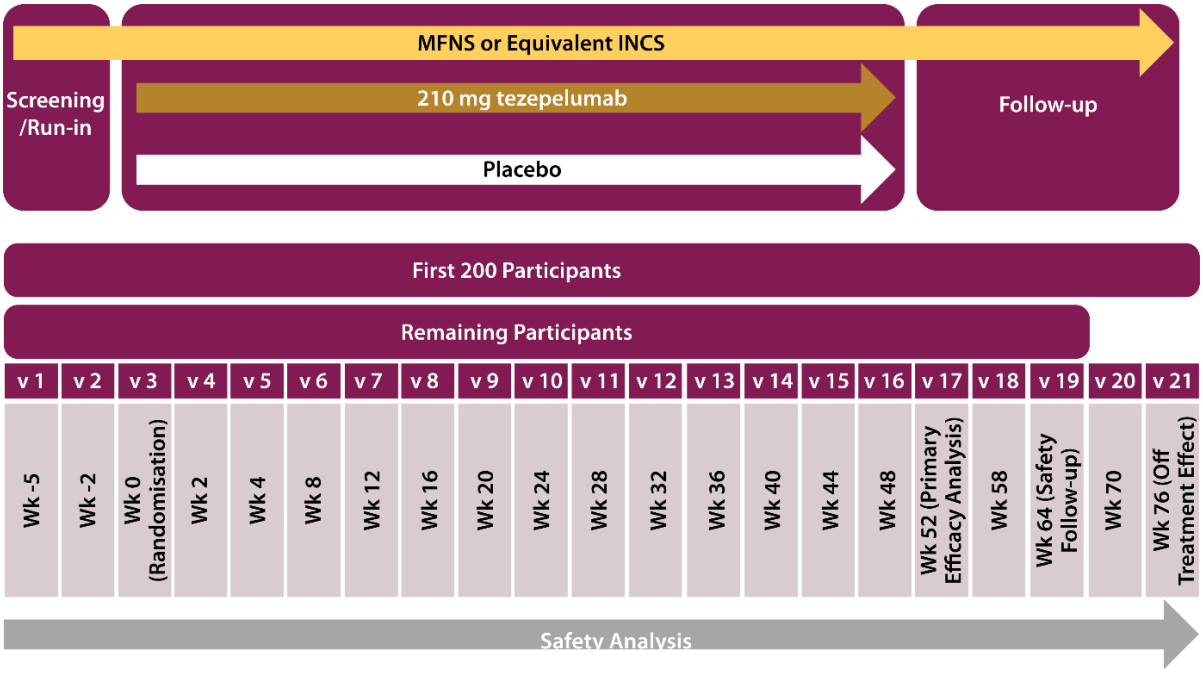
2.5.2. Main study

A multicentre, randomised, double-blind, parallel-group, placebo-controlled phase 3 efficacy and safety study of tezepelumab in participants with severe chronic rhinosinusitis with nasal polyposis (WAYPOINT)

Methods

This was a Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of tezepelumab 210 mg administered subcutaneously (SC) once every 4 weeks (Q4W) using the accessorised pre-filled syringe (APFS), versus placebo, in participants with CRSwNP.

Figure 14. Flow Chart of WAYPOINT Study Design



INCS intranasal corticosteroid; MFNS mometasone furoate nasal spray; v visit; Wk week.

Study participants

Key inclusion criteria:

- Participant had to be 18 years of age or older at the time of signing the informed consent.
- Participants with physician-diagnosed CRSwNP for at least 12 months prior to Visit 1 that had:
    - Severity consistent with need for surgery as defined by total Nasal Polyp Score (NPS) ≥ 5 (at least 2 for each nostril) at screening, as determined by the central reader
    - Nasal Congestion Score (NCS) ≥ 2 at Visit 1
    - Ongoing documented NP symptoms for > 8 weeks prior to screening such as rhinorrhoea and/or reduction or loss of smell.

- SinoNasal Outcome Test, 22 item (SNOT-22) total score ≥ 30 at screening (Visit 1).
- Any standard of care for treatment of CRSwNP provided the participant was stable on that treatment for at least 30 days prior to Visit 1.
- Documented treatment of NP exacerbation with SCS for at least 3 consecutive days or one intramuscular depo-injectable dose (or contraindications/intolerance to) within the past 12 months prior to Visit 1 but not within the last 3 months prior to Visit 1 and/or any history of NP surgery (or contraindications/intolerance to).

Participants had to meet the following criteria at the randomisation visit (Visit 3):

- Confirmed central reading total NPS ≥ 5 (at least 2 for each nostril) at Visit 2.
- The below Inclusion criterion was replaced with Amendment 3:
    - At randomisation visit (Visit 3), a bi-weekly mean NCS ≥ 2 (baseline bi-weekly score collected from study Day -13 to study Day 0).
    - Original inclusion criterion 15: NCS ≥ 2 at Visit 3.
- SNOT-22 score ≥ 30 at randomisation (Visit 3).

Key exclusion criteria:

Medical Conditions

- Any clinically important co-morbidities other than asthma that could confound interpretation of clinical efficacy results.
- Any disorder, including but not limited to cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that was not stable in the opinion of the Investigator or Sponsor and could:
    - Affect the safety of the participant throughout the study
    - Influence the findings of the studies or their interpretations
    - Impede the participant's ability to complete the entire duration of study.
- Sinus surgery within 6 months of screening visit OR any sinus surgery in the past which changed the lateral wall of the nose making NPS evaluation impossible.
- Participants with conditions or concomitant disease that makes them non-evaluable for the primary efficacy endpoint such as:
    - Antrochoanal polyps
    - Nasal septal deviation that occluded at least one nostril
    - Acute sinusitis, nasal infection, asthma exacerbation, or upper respiratory infection at screening or in the 2 weeks before screening; or Churg-Strauss syndrome (also known as eosinophilic granulomatosis with polyangiitis), Young's syndrome or Kartagener's syndrome.
- Major surgery within 8 weeks prior to Visit 1 or planned NP surgery during the conduct of the study.

Prior/Concomitant Therapy

- Regular use of decongestants (topical or systemic) at enrolment was not allowed unless used for endoscopic procedure.
- Use of corticosteroid-eluting intranasal stents within 6 months prior to Visit 1 and during the study period.
- Recent aspirin desensitisation within 6 months of enrolment.

Treatments

Description	**Tezepelumab**	**Placebo**
Intervention Name	Tezepelumab	Placebo
Type	Biologic, combination product	Placebo, combination product
Unit Dose Strength(s)	210 mg	NA
Dosage Level(s)	210 mg Q4W	Placebo Q4W
Route of Administration	SC injection	SC injection
Use	Experimental	Placebo
IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	Study treatment will be provided in an APFS with 1.91 mL fill volume. Each syringe will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. The labels will be translated into the local language where applicable.	Study treatment will be provided in an APFS with 1.91 mL fill volume. Each syringe will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. The labels will be translated into the local language where applicable.

Objectives

The objectives were to evaluate the efficacy and safety of tezepelumab 210 mg administered subcutaneously (SC) once every 4 weeks (Q4W) using the accessorised pre-filled syringe (APFS), versus placebo, in participants with CRSwNP.

Outcomes/endpoints

Co-primary endpoints:

- Change from baseline in total NPS evaluated by nasal endoscopy at Week 52.
- Change from baseline in bi-weekly mean NCS evaluated as part of the NPSD at Week 52.

Key secondary endpoints:

- Change from baseline in bi-weekly mean loss of smell evaluated as part of the NPSD at Week 52.
- Change from baseline in SNOT-22 scores at Week 52.
- Change from baseline in LMK score evaluated by CT at Week 52.
- Time to surgery decision and/or SCS for NP up to Week 52.
- Time to NP surgery decision up to Week 52.
- Time to SCS for NP up to Week 52.
- Change from baseline in bi-weekly mean NPSD TSS at Week 52.
- Change from baseline in pre-BD FEV1 at Week 52 in participants with co-morbid asthma/AERD/NSAID-ERD.

Other secondary endpoints

- Change from baseline over time in NPS evaluated by nasal endoscopy through Week 52.
- Change from baseline over time in bi-weekly mean NCS evaluated as part of the NPSD through Week 52.
- Exposure of SCS over 52 weeks (a course of SCS was defined as SCS for at least 3 consecutive days for treatment of NP. An SCS course was considered as a new course if the start date was at least 7 days after the end date of the last SCS use for NP course).
- Change from baseline in ACQ-6 at Week 52 in participants with co-morbid asthma/ AERD/NSAID-ERD.

Exploratory endpoints (selected)

- Change from baseline in total NPS and bi-weekly mean NCS through the post-treatment period (up to week 76)
- EQ-5D-5L
- Patient Global Impression of Severity (PGI-S)
- Patient Global Impression of Change (PGI-C

Sample size

The WAYPOINT study was sized to provide persuasive statistical evidence for the co-primary endpoints (change in NPS and NCS) and the key secondary endpoints of change in loss of smell, LMK score, and SNOT-22 (considering a significance level of 0.01 in the sample size calculations), and to provide sufficient power to assess the composite endpoint of time to NP surgery and/or SCS for NP treatment (2-sided level of 1%). This sample size was considered to allow for assessment of the effect of tezepelumab versus placebo on NPS and NCS in key subgroups and provided a reasonably sized safety database.

Assuming a population SD of 2.25 in total NPS change and 1.22 in NCS change from baseline to Week 52, a sample size of 200 participants per treatment group would provide at least 95% total power to observe a statistically significant difference at a 2-sided 1% level on both co-primary endpoints if the true effect of tezepelumab was -1.8 and -0.87 change from baseline in total NPS and NCS,

respectively. The assumptions of population SDs and true effects were based on reported estimates and CIs for the corresponding endpoints in the dupilumab Phase III nasal polyp studies. Assuming that 50% to 70% of participants would have co-morbid asthma, this sample size would provide > 80% power for the co-primary endpoints at a 2-sided 5% significance level in the co-morbid asthma/AERD/NSAID-ERD subgroup.

Randomisation

Patients were randomised 1:1 to either tezepelumab or matching placebo. To further ensure a study population representative of the target population, participants were stratified by region (China, Japan, and rest of the world), prior NP surgery, and co-morbid asthma/AERD/NSAID-ERD. Randomisation was monitored to ensure that 50% to 70% of the study population had co-morbid asthma/AERD/NSAID-ERD, and at least 50% had prior surgery for CRSwNP.

Blinding (masking)

This was a double-blind study in which tezepelumab and placebo were not visually distinct from each other. All packaging and labelling of IP was done in such way as to ensure blinding for all sponsor and investigational site staff. Neither the participant nor any of the Investigators or sponsor staff who were involved in the treatment or clinical evaluation and monitoring of the participants were to be aware of the treatment received. Since tezepelumab and placebo were not visually distinct, IP was handled by a qualified person (e.g., pharmacist or study nurse) at the site.

Statistical methods

The co-primary analysis compared the effect of tezepelumab versus placebo in the change from baseline in NPS at Week 52 and the change from baseline in the bi-weekly mean NCS at Week 52. Efficacy analyses were based on the full analysis set (FAS) according to the randomised treatments.

Description of co-primary efficacy endpoints

The total NPS is the sum of the right and left nostril scores (maximum of 8), as evaluated by nasal endoscopy. The left and right score was based on a central read with a scale from 0 to 4 as listed in the Table 7 below. Each nasal endoscopy was evaluated by two independent physician reviewers. The process of evaluation differed between confirmation of eligibility criteria and collection of scores for efficacy analysis. As a consequence, the NPS scores were derived differently for eligibility and efficacy use.

Table 7. Description of the co-primary endpoint NPS scale

Polyp score	Polyp size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate
3	Polyps reaching the lower border of the inferior turbinate or a middle meatal polyp with a score of 2 with any additional polyp medial to the middle turbinate
4	Large polyps causing complete or near-complete obstruction of the inferior nasal cavity i.e. touching the floor of the nose

NPS score derivation to confirm eligibility criteria at Visit 2: If polyp scores for left and right nostril (maximum of 4 per each nostril) provided by two reviewers were:

- exactly the same, then the NPS score was the sum of right and left nostril scores provided by one reviewer,
- different for right and/or left nostril but the sum for each reviewer is >5, then the NPS score was calculated as the mean of right and left nostril scores provided by both reviewers,
- different for right and/or left nostril and the sum for one reviewer is <5, then the nasal endoscopy was evaluated by an independent adjudicator. The NPS score was the sum of left and right nostril scores provided by the reviewer selected by adjudicator.

NPS score derivation for efficacy analysis use: If polyp scores for left and right nostril provided by two reviewers at the same visit were:

- exactly the same, then the NPS score was the sum of right and left nostril scores provided by one reviewer at this visit,
- different for right and/or left nostril, then the nasal endoscopy was evaluated by an independent adjudicator. The NPS score at this visit was calculated as the sum of scores for left and/or right nostril selected by adjudicator, ie. there was no requirement the right and left nostril scores selected by adjudicator are provided by the same reviewer.

Participant reported nasal congestion (NC) were evaluated as part of the NPSD. The NCS (nasal congestion score) is captured by one item in the NPSD asking participants to rate the severity of their worst NC over the past 24 hours using the following response options: 0 – None; 1 – Mild; 2 – Moderate; 3 – Severe. Baseline was the mean of daily responses from Day -13 to Day 0. Bi-weekly (14-day) mean NCS was calculated if at least 8 days in each 14-day period has evaluable data; otherwise, the bi-weekly mean was set to missing. The NCS and the changes from baseline at Week 52 were calculated for the co-primary efficacy endpoint.

Analysis of co-primary efficacy endpoints

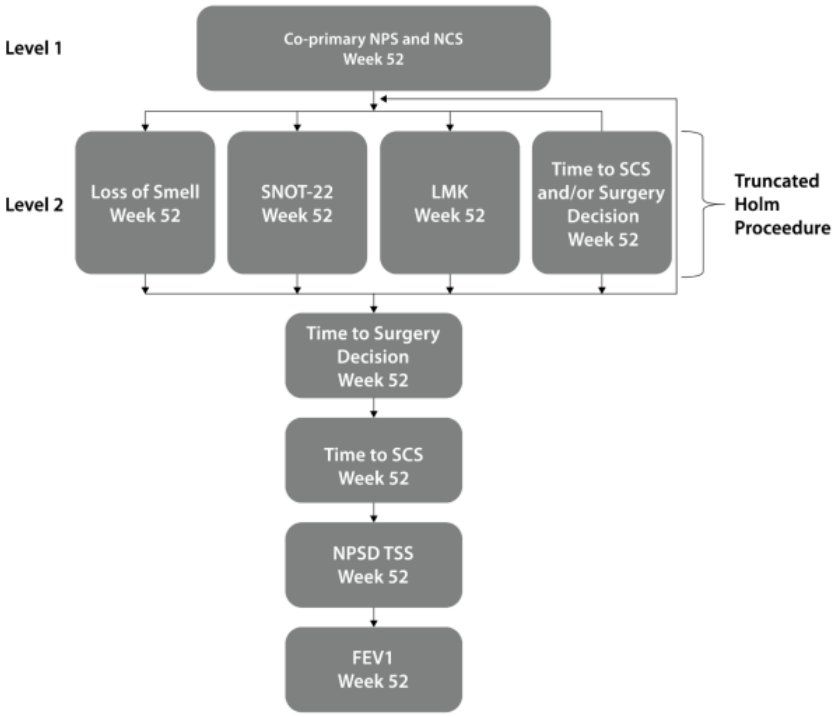
Both co-primary efficacy endpoints were analysed using an analysis of covariance model. For the primary estimand co-primary endpoint analyses, an ANCOVA model was used with the baseline value as a covariate, and treatment group, baseline co-morbid asthma status, prior NP surgery status, and region as factors. Sensitivity analyses were performed to examine the missing at random assumption.

Differences in least square means and the corresponding 95% confidence intervals (CIs) were provided along with the p-values. The analyses were performed for the primary estimand and supplementary estimands.

Both primary endpoints were tested at 2-sided 5% level. If both endpoints were significant at 5%, then testing was to proceed to the key secondary endpoints. The type I error across primary and key secondary endpoints was controlled at 5% according to the multiple testing strategy shown in the Figure 15 below. The co-primary and key secondary endpoints were also tested at the 1% level to further demonstrate persuasive statistical significance for this single, Phase III study.

Supportive, sensitivity, and subgroup analyses were performed on the co-primary efficacy endpoints.

Figure 15. Multiple Testing Procedure for Co-primary and Key Secondary Endpoints (Tezepelumab 210 mg Q4W versus Placebo)



FEV1 forced expiratory volume in 1 second; LMK Lund-Mackay score, NCS nasal congestion score; NPS nasal polyp score; NPSD nasal polyposis symptom diary; Q4W every 4 weeks; SCS systemic corticosteroids; SNOT22 Sino-Nasal Outcome Test 22 item; TSS total symptom score.

Primary Estimand

The primary estimand is described as follows:

- Treatment: Randomised treatment of tezepelumab 210 mg Q4W or placebo.
- Population of interest: Adult participants with severe CRSwNP (total NPS $\geq$ 5) and an inadequate response to standard-of-care therapy, based on their randomised treatment and receiving at least one dose of IP.
- Endpoints of interest: Change from baseline in co-primary endpoints: NPS and bi-weekly mean NCS at Week 52.
- Population level summary for the endpoint: Difference in means between tezepelumab and placebo treatment groups.
- Handling of intercurrent events:

  – NP surgery: Composite variable - worst possible score (ie, 8 for NPS and 3 for NCS) was used for the post-surgery scores.

  – SCS for NP: Composite variable Worst Observation Carried Forward (WOCF)

  – Treatment discontinuation: Treatment policy

  – Adherence to background MFNS or an equivalent INCS and IP: Treatment policy

  – Biologic use for NP: Composite variable – WOCF

  – Steroids or biologic use for co-morbid conditions: Treatment policy

– COVID-19 related: Treatment policy

Supplementary Estimand

Composite variable strategy was used for SCS for NP, biologic use for NP, and treatment discontinuation: the worst possible score was used after the ICEs.

The key secondary and other secondary efficacy endpoints used the same strategies for the ICEs unless noted otherwise.

Table 8. Definitions of analysis sets

Population/Analysis set	Description
Enrolled analysis set	All participants who signed the ICF.
Randomised analysis set	All participants randomised to study treatment (irrespective of whether IP was subsequently taken).
Full analysis set	All participants randomised to study treatment who received at least one dose of IP, irrespective of their protocol adherence, and continued participation in the study.
Co-morbid asthma/AERD/NSAID-ERD subset	All participants in full analysis set with co-morbid asthma/AERD/NSAID-ERD at baseline.
Safety set	All participants who received at least one dose of IP.
PK analysis set	All participants in the full analysis set who received active (tezepelumab) treatment and had at least one detectable tezepelumab serum concentration from a sample collected post-treatment that is assumed not to be affected by factors such as protocol deviations.
Additional follow-up analysis set	Includes the approximately first 200 participants who have a 24-week follow-up period after end of treatment (participants who completed the Week 76 visit or withdrew from the study after Week 64 visit).

Efficacy analyses were based on the full analysis set (defined above) with the exceptions of the endpoints of change in pre-BD FEV1, ACQ-6, and FeNO, which were based on the co-morbid asthma/AERD/NSAID-ERD subset.

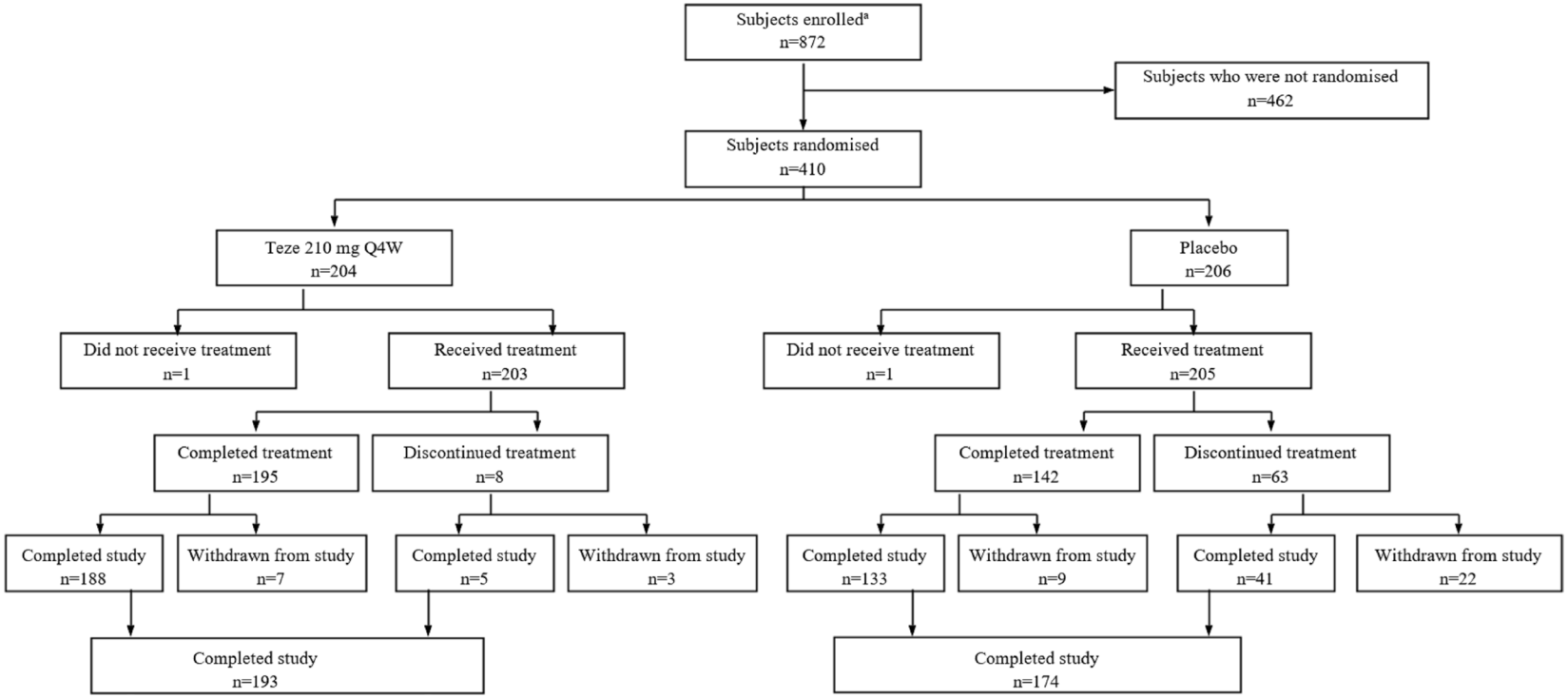
Results

Participant flow

The study was conducted in 112 sites (with enrolled participants), of which 104 sites randomised at least one participant, in 10 countries. Three sites were closed during the study due to GCP compliance issues and were not included in the disposition summaries.

Participant disposition is summarised in Figure 16 and Table 9.

Figure 16. Subject Disposition (Enrolled Analysis Set)



[a] Informed consent received.
n Number of subjects per category; Q4W Every 4 weeks; Teze Tezepelumab

Table 9. Subject Disposition (Enrolled Analysis Set)

	Teze 210 mg Q4W		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects enrolled [a]					872	
Subjects not randomized					462	
Lost to follow-up					2	
Screen failure					443	
Withdrawal by subject					15	
Other					2	
Subjects randomized	204		206		410	
Subjects randomised, not treated	1		1		2	
Withdrawal by subject	1		0		1	
Other	0		1		1	
Subjects received treatment	203	(100)	205	(100)	408	(100)
Subjects completed treatment	195	(96.1)	142	(69.3)	337	(82.6)
Subjects discontinued treatment	8	(3.9)	63	(30.7)	71	(17.4)
Subject decision	4	(2.0)	43	(21.0)	47	(11.5)
Adverse event	1	(0.5)	4	(2.0)	5	(1.2)
Severe non-compliance to protocol	1	(0.5)	1	(0.5)	2	(0.5)
Development of study specific discontinuation criteria	0		0		0	
Subject lost to follow-up	0		1	(0.5)	1	(0.2)
Pregnancy	0		0		0	
Other	2	(1.0)	14	(6.8)	16	(3.9)
Subjects discontinued treatment but completed study	5	(2.5)	41	(20.0)	46	(11.3)
Option 1 [b]	2	(1.0)	20	(9.8)	22	(5.4)
Option 2 [c]	1	(0.5)	2	(1.0)	3	(0.7)
Option 3 [d]	2	(1.0)	19	(9.3)	21	(5.1)
Subjects entered 24-week follow-up period	90	(44.3)	73	(35.6)	163	(40.0)
Subjects completed 24-week follow-up period [e]	90	(100)	70	(95.9)	160	(98.2)
Subjects withdrawn from study during 24-week follow-up period [e]	0		3	(4.1)	3	(1.8)
Withdrawal by subject	0		2	(2.7)	2	(1.2)
Other	0		1	(1.4)	1	(0.6)
Subjects only entered 12-week follow-up period	103	(50.7)	76	(37.1)	179	(43.9)
Subjects completed 12-week follow-up period [e]	98	(95.1)	73	(96.1)	171	(95.5)
Subjects withdrawn from study during 12-week follow-up period [e]	5	(4.9)	3	(3.9)	8	(4.5)
Withdrawal by subject	5	(4.9)	3	(3.9)	8	(4.5)
Subjects who completed treatment and study	188	(92.6)	133	(64.9)	321	(78.7)

Subjects completed study	193	(95.1)	174	(84.9)	367	(90.0)
Subjects withdrawn from study	10	(4.9)	31	(15.1)	41	(10.0)
Death	0		1	(0.5)	1	(0.2)
Lost to follow-up	2	(1.0)	2	(1.0)	4	(1.0)
Withdrawal by subject	8	(3.9)	23	(11.2)	31	(7.6)
Other	0		5	(2.4)	5	(1.2)

Percentages are based on the number of randomised subjects who received at least one dose of IP.
[a] Informed consent received.
[b] Subject(s) returned for all regular clinic visits and performed all scheduled assessments (excluding IP administration) until the EOT visit at Week 52 (+ /-5 days).
[c] Subject(s) offered to be followed up on a monthly basis via telephone calls while continuing ePRO data collection on the handheld device at home until the subject completed the EOT visit at Week 52 (+ /-5 days). The UPSIT assessment were not completed at home after IPD visit until the subject returned back to the site at the EOT visit.
[d] Subject(s) contacted by Investigator only at 52 weeks post randomisation. No study assessments performed prior to this contact.
[e] The denominator for the percentage is the number of subjects who entered to the corresponding follow-up period.
DBL Database lock; n Number of subjects per category; Q4W Every 4 weeks; Teze Tezepelumab; IP Investigational Product.

Recruitment

First subject enrolled: 22 April 2021

Last subject last visit: 11 December 2024

Conduct of the study

There were 5 amendments to the protocol; none affected the integrity of the trial. Amendments 3, 4, and 5 were considered substantial and are summarised below:

- Co-primary, key secondary, and other secondary endpoints related to NPSD scores and inclusion Criterion for NCS were updated from 'change from baseline' to 'change from baseline in bi-weekly mean' to ensure correct evaluation of endpoints between baseline and Week 52; medical device sections were updated to align with new International Organization for Standardization 14155 and European Medical Device Regulation (Amendment 3).
- NP surgery endpoint updated to use the date of decision for surgery (versus actual date of surgery), due to COVID-19-related delays in scheduling. Risk assessment aligned with updated investigator brochure, and assessment of pre-specified events by an IAC added (Amendment 4).
- Two key secondary objectives 'resolution/near complete resolution of nasal polyps', and 'resolution/near complete resolution of nasal polyps and NPSD TSS responses' were moved to exploratory objectives, and the estimands for another health authority and multiplicity testing procedure for secondary endpoints were modified to align with health authority guidance (Amendment 5).

Important Protocol Deviations

Important protocol deviations are summarised in Table 10. The types of important protocol deviations reported were not considered to have a meaningful impact on the interpretation of the results.

There were few participants with important protocol deviations related to country-specific COVID-19 public health restrictions; the impact of the COVID-19 pandemic on the conduct of the study is therefore considered to be minimal.

Table 10. Important Protocol Deviations (Randomised Analysis Set)

	Teze 210 mg Q4W N = 204 n (%)	**Placebo N = 206 n (%)**	**Total N = 410 n (%)**
Subjects with at least one important protocol deviation	37 (18.1)	62 (30.1)	99 (24.1)
Did not fulfil key eligibility criteria	13 (6.4)	17 (8.3)	30 (7.3)
Discontinuation criteria for study treatment met but participant not withdrawn from study treatment	1 (0.5)	1 (0.5)	2 (0.5)
Discontinuation criteria for overall study withdrawal met but patient not withdrawn from study	0	0	0
Investigational product deviation	4 (2.0)	1 (0.5)	5 (1.2)
Excluded medications taken	1 (0.5)	5 (2.4)	6 (1.5)
Receipt of any marketed or investigational biologic treatment within 4 months or 5 half-lives prior to Visit 1, throughout the screening and treatment period.	1 (0.5)	5 (2.4)	6 (1.5)
Deviations to study procedure	1 (0.5)	0	1 (0.2)
Other important deviations	21 (10.3)	50 (24.3)	71 (17.3)
If the following assessments were missed at IP Discontinuation visit or EOT visit: CT; Nasal endoscopy (NPS); NCS;	21 (10.3)	50 (24.3)	71 (17.3)
Subjects with at least one important protocol deviation due to global/country situation study disruption	5 (2.5)	1 (0.5)	6 (1.5)
Subjects with at least one important protocol deviation excluding global/country situation study disruption related important protocol deviation	33 (16.2)	61 (29.6)	94 (22.9)

The same subject may have more than one important protocol deviation.
Global/country situation includes COVID-19 pandemic only.
Percentages are based on the number of subjects in each treatment group (N) as denominator.
COVID-19 Corona Virus Disease 2019; n Number of subjects per category; N Number of subjects per treatment group; Q4W Every 4 weeks; Teze Tezepelumab.

Treatment Compliance

Treatment compliance to IP administration was monitored via clinic visits. Mean compliance to IP was high and similar between groups (97.51% and 98.25% in the tezepelumab and placebo groups, respectively). Few participants had < 80% compliance (3.0% and 0.5% in the tezepelumab and placebo groups, respectively).

Background medication (INCS/MFNS) compliance was high and similar between groups. The overall mean compliance with the INCS/MFNS was 84.31%.

NPSD daily diary overall compliance was high and similar between groups. The overall mean compliance was 85.72%.

Baseline data

The demographic and key baseline characteristics are summarised in Table 11. Demographic and key baseline characteristics were generally balanced between the treatment groups.

Table 11. Demographic and Key Baseline Characteristics

Characteristics and category	Statistic	Teze 210 mg Q4W N = 203	Placebo N = 205	Total N = 408
Demographic Characteristics				
Age at screening visit(years)	n	203	205	408
	Mean	50.1	49.4	49.7
	SD	13.60	13.69	13.63
	Min	18	18	18
	Q1	40.0	37.0	39.0
	Median	51.0	51.0	51.0
	Q3	60.0	59.0	59.0
	Max	81	75	81
Age group at screening visit (years)				
< 65 years	n (%)	174 (85.7)	179 (87.3)	353 (86.5)
> = 65 years	n (%)	29 (14.3)	26 (12.7)	55 (13.5)
Gender at screening visit				
Female	n (%)	77 (37.9)	65 (31.7)	142 (34.8)
Male	n (%)	126 (62.1)	140 (68.3)	266 (65.2)
Race				
Black or African American	n (%)	3 (1.5)	3 (1.5)	6 (1.5)
White	n (%)	150 (73.9)	149 (72.7)	299 (73.3)
Native Hawaiian or other Pacific Islander	n (%)	0	0	0
American Indian or Alaska Native	n (%)	0	0	0
Asian	n (%)	46 (22.7)	51 (24.9)	97 (23.8)
Other	n (%)	4 (2.0)	2 (1.0)	6 (1.5)
Not reported	n (%)	0	0	0
Race group				
White	n (%)	150 (73.9)	149 (72.7)	299 (73.3)
Non-white	n (%)	53 (26.1)	56 (27.3)	109 (26.7)
Ethnicity group				
Hispanic or Latino	n (%)	11 (5.4)	11 (5.4)	22 (5.4)
Not Hispanic or Latino	n (%)	192 (94.6)	194 (94.6)	386 (94.6)
Region group 1				
China	n (%)	29 (14.3)	34 (16.6)	63 (15.4)
Japan	n (%)	17 (8.4)	16 (7.8)	33 (8.1)

ROW	n (%)	157 (77.3)	155 (75.6)	312 (76.5)

Characteristics and category	**Statistic**	**Teze 210 mg Q4W N = 203**	**Placebo N = 205**	**Total N = 408**
Region group 2				
Asia Pacific (including China and Japan)	n (%)	46 (22.7)	50 (24.4)	96 (23.5)
Europe	n (%)	110 (54.2)	116 (56.6)	226 (55.4)
North America	n (%)	47 (23.2)	39 (19.0)	86 (21.1)
Key Baseline Characteristics				
Height (cm)	n	203	205	408
	Mean	170.36	171.92	171.14
	SD	9.676	9.329	9.524
	Q1	164.00	165.00	165.00
	Median	170.00	172.00	171.50
	Q3	177.00	179.50	178.00
Weight (kg)	n	203	205	408
	Mean	77.55	80.97	79.27
	SD	16.162	16.446	16.375
	Q1	66.80	69.00	68.00
	Median	74.60	79.40	76.10
	Q3	89.00	89.90	89.35
BMI (kg/m^2) [a]	n	203	205	408
	Mean	26.604	27.306	26.956
	SD	4.468	4.621	4.553
	Q1	23.529	24.167	23.875
	Median	25.952	26.673	26.340
	Q3	28.720	30.104	29.713
BMI group 1				
< 25 kg/m^2	n (%)	81 (39.9)	69 (33.7)	150 (36.8)
> = 25 to < 30 kg/m^2	n (%)	82 (40.4)	82 (40.0)	164 (40.2)
> = 30 kg/m^2	n (%)	40 (19.7)	54 (26.3)	94 (23.0)

Characteristics and category	Statistic	Teze 210 mg Q4W N = 203	Placebo N = 205	Total N = 408
BMI group 2				
< 30 kg/m^2	n (%)	163 (80.3)	151 (73.7)	314 (77.0)
> = 30 kg/m^2	n (%)	40 (19.7)	54 (26.3)	94 (23.0)

[a] Body mass index = weight(kg)/[height(m)]^2.
Percentages are based on the number of subjects in each treatment group (N) as denominator.
BMI Body Mass Index; Max Maximum; Min Minimum; n Number of subjects per category; N Number of subjects per treatment group; Q1 Lower quartile; Q3 Upper quartile; Q4W Every 4 weeks; ROW Rest of the world; SD Standard deviation; Teze Tezepelumab.

Disease characteristics are summarised in Table 12. Disease characteristics were generally similar in both treatment groups.

Table 12. Nasal Polyposis Disease Characteristics at Baseline (Full Analysis Set)

	Statistic	Teze 210 mg Q4W N = 203	Placebo N = 205	Total N = 408
Baseline blood eosinophil count (cells/uL)	n	203	203	406
	Mean	356.4	363.3	359.8
	SD	217.20	252.40	235.19
	Min	10	0	0
	Q1	180.0	190.0	190.0
	Median	320.0	310.0	310.0
	Q3	450.0	470.0	460.0
	Max	1130	1430	1430

	Statistic	Teze 210 mg Q4W N = 203	Placebo N = 205	Total N = 408
Baseline blood eosinophil count group				
< 150 cells/uL	n (%)	29 (14.3)	25 (12.2)	54 (13.2)
> = 150 to < 300 cells/uL	n (%)	59 (29.1)	74 (36.1)	133 (32.6)
> = 300 cells/uL	n (%)	115 (56.7)	104 (50.7)	219 (53.7)
Missing	n (%)	0	2 (1.0)	2 (0.5)
Baseline total serum IgE (IU/mL)	n	194	195	389
	Mean	171.17	181.23	176.21
	SD	259.251	308.504	284.684
	Min	1.3	1.3	1.3
	Q1	26.30	31.70	29.80
	Median	82.20	68.90	78.40
	Q3	191.20	188.30	190.10
	Max	1778.6	2393.7	2393.7

Baseline perennial specific IgE status				
Positive	n (%)	72 (35.5)	78 (38.0)	150 (36.8)
Negative	n (%)	123 (60.6)	120 (58.5)	243 (59.6)
Unknown	n (%)	8 (3.9)	7 (3.4)	15 (3.7)
Baseline seasonal specific IgE status				
Positive	n (%)	76 (37.4)	60 (29.3)	136 (33.3)
Negative	n (%)	117 (57.6)	136 (66.3)	253 (62.0)
Unknown	n (%)	10 (4.9)	9 (4.4)	19 (4.7)
Baseline NPS (efficacy)	n	202	205	407
	Mean	6.1	6.1	6.1
	SD	1.23	1.25	1.24
	Min	3.0	3.0	3.0
	Q1	5.0	5.0	5.0
	Median	6.0	6.0	6.0
	Q3	7.0	7.0	7.0
	Max	8	8	8
Baseline bi-weekly mean NCS	n	203	203	406
	Mean	2.59	2.55	2.57
	SD	0.469	0.539	0.505
	Min	1.1	0.0	0.0

	Statistic	**Teze 210 mg Q4W N = 203**	**Placebo N = 205**	**Total N = 408**
	Q1	2.14	2.07	2.08
	Median	2.85	2.83	2.85
	Q3	3.00	3.00	3.00
	Max	3.0	3.0	3.0
Baseline loss of smell	n	203	203	406
	Mean	2.9	2.8	2.9
	SD	0.40	0.38	0.39
	Min	0	1	0
	Q1	3.0	3.0	3.0
	Median	3.0	3.0	3.0
	Q3	3.0	3.0	3.0
	Max	3	3	3
Baseline SNOT-22	n	203	205	408
	Mean	68.2	69.2	68.7
	SD	18.44	18.39	18.40
	Min	32	31	31
	Q1	56.0	57.0	56.0

	Median	66.0	71.0	68.0
	Q3	82.0	81.0	81.0
	Max	110	110	110
Baseline LMK	n	200	204	404
	Mean	18.9	18.5	18.7
	SD	3.74	3.85	3.80
	Min	4	10	4
	Q1	16.0	15.0	16.0
	Median	19.5	19.0	19.0
	Q3	22.0	21.5	22.0
	Max	24	24	24
Baseline JESREC [a]				
	Nobs [a]	29	34	63
> = 11	n (%)	22 (75.9)	27 (79.4)	49 (77.8)
< 11	n (%)	7 (24.1)	7 (20.6)	14 (22.2)

	Statistic	**Teze 210 mg Q4W N = 203**	**Placebo N = 205**	**Total N = 408**
Baseline NPSD TSS	n	203	203	406
	Mean	16.3	16.4	16.3
	SD	4.05	4.51	4.28
	Min	6	6	6
	Q1	13.0	13.3	13.1
	Median	16.1	16.1	16.1
	Q3	19.3	19.8	19.4
	Max	24	24	24
Baseline NPIF	n	198	197	395
	Mean	98.5	91.3	94.9
	SD	88.19	83.11	85.66
	Min	5	3	3
	Q1	41.0	39.0	40.0
	Median	72.0	65.0	67.0
	Q3	130.0	117.0	124.0
	Max	584	581	584
Allergic rhinitis				
Yes	n (%)	28 (13.8)	29 (14.1)	57 (14.0)
No	n (%)	175 (86.2)	176 (85.9)	351 (86.0)
Co-morbid asthma/AERD/NSAID-ERD [b]				
Yes	n (%)	122 (60.1)	126 (61.5)	248 (60.8)

No	n (%)	81 (39.9)	79 (38.5)	160 (39.2)
AERD/NSAID-ERD				
Yes	n (%)	34 (16.7)	37 (18.0)	71 (17.4)
No	n (%)	169 (83.3)	168 (82.0)	337 (82.6)
Age at NP diagnosis (years)	n	203	205	408
	Mean	37.5	36.7	37.1
	SD	13.05	13.97	13.51
	Min	9	4	4
	Q1	28.0	26.0	27.0
	Median	37.0	36.0	36.5
	Q3	47.0	47.0	47.0
	Max	77	70	77

	Statistic	**Teze 210 mg Q4W N = 203**	**Placebo N = 205**	**Total N = 408**
Time since NP diagnosis (years)	n	203	205	408
	Mean	12.71	12.80	12.75
	SD	10.429	10.336	10.370
	Min	1.2	1.1	1.1
	Q1	4.60	5.10	5.00
	Median	9.70	10.60	10.20
	Q3	18.50	17.00	17.75
	Max	63.0	59.1	63.0
Prior surgery for NP status				
Yes	n (%)	144 (70.9)	147 (71.7)	291 (71.3)
No	n (%)	59 (29.1)	58 (28.3)	117 (28.7)
Number of prior NP surgery	n	203	205	408
	Mean	1.4	1.6	1.5
	SD	1.42	3.05	2.38
	Min	0	0	0
	Q1	0.0	0.0	0.0
	Median	1.0	1.0	1.0
	Q3	2.0	2.0	2.0
	Max	8	40	40
Number of prior NP surgeries				
0	n (%)	59 (29.1)	58 (28.3)	117 (28.7)
1	n (%)	73 (36.0)	77 (37.6)	150 (36.8)
2 or more	n (%)	71 (35.0)	70 (34.1)	141 (34.6)
Time since last NP surgery (years)	Nobs [c]	144	147	291
	Mean	7.71	7.68	7.70

	SD	6.536	6.242	6.378
	Min	0.2	0.5	0.2
	Q1	3.30	3.50	3.40
	Median	6.30	6.50	6.30
	Q3	9.90	9.90	9.90
	Max	42.7	36.8	42.7
Time since last NP surgery	Nobs [c]	144	147	291
< 3 years	n (%)	32 (22.2)	33 (22.4)	65 (22.3)

	Statistic	Teze 210 mg Q4W N = 203	Placebo N = 205	Total N = 408
> = 3 years	n (%)	112 (77.8)	114 (77.6)	226 (77.7)
Any prior SCS use for NP				
Yes	n (%)	130 (64.0)	137 (66.8)	267 (65.4)
No	n (%)	73 (36.0)	68 (33.2)	141 (34.6)
Number of SCS treatment for NP in past 12 months	n	203	205	408
	Mean	0.7	0.7	0.7
	SD	0.67	0.91	0.80
	Min	0	0	0
	Q1	0.0	0.0	0.0
	Median	1.0	1.0	1.0
	Q3	1.0	1.0	1.0
	Max	4	7	7
Number of SCS treatment for NP in past 12 months				
0	n (%)	83 (40.9)	90 (43.9)	173 (42.4)
1	n (%)	101 (49.8)	90 (43.9)	191 (46.8)
2 or more	n (%)	19 (9.4)	25 (12.2)	44 (10.8)
Baseline staphylococcus aureus colonization in nasal culture				
Yes	n (%)	74 (36.5)	58 (28.3)	132 (32.4)
No	n (%)	104 (51.2)	119 (58.0)	223 (54.7)
Missing	n (%)	25 (12.3)	28 (13.7)	53 (13.0)

[a] JESREC score is assessed only for China participants. Nobs is number of subjects from China. The JESREC percentages are based on Nobs.

[b] Yes indicates subjects with a diagnosis of asthma or AERD or NSAID-ERD. 3 subjects (1 in placebo and 2 in tezepelumab) with AERD/NSAID-ERD but without diagnosis of asthma reported.

[c] Subjects with any prior NP surgery.

Percentages are based on the number of subjects in each treatment group (N) as denominator.

NPSD data from 2 subjects are excluded due to critical data quality issue.

IgE oriental cockroach considered in perennial specific IgE status applied only for Rest of World participants for whom this allergen was tested.

AERD Aspirin Exacerbated Respiratory Disease; BMI Body Mass Index; LMK Lund-Mackay Score; Max Maximum; Min Minimum; n Number of subjects per category; N Number of subjects per treatment group; NCS Nasal Congestion Score; NP Nasal polyposis; NPIF Nasal Peak Inspiratory Flow (L/min); NPS Nasal polyposis Score; NPSD Nasal Polyposis Symptom Diary; NSAID-ERD: Nonsteroidal Anti-Inflammatory Drug Exacerbated Respiratory Disease; Q1 Lower quartile; Q3 Upper quartile; Q4W Every 4 weeks; SD Standard deviation; SNOT-22 Sino-nasal Outcome Test; SCS Systemic corticosteroid; Teze Tezepelumab; TSS Total Symptom Score.

In total, 3.7% of study participants had used biologics for asthma and/or NP at least once prior to study entry. The most commonly reported allowed concomitant medications included: intranasal corticosteroids (R01AD) (as expected given these are study background INCS); asthma medications 'adrenergics in combination with corticosteroids or other drugs excluding anticholinergics' (R03AK) and selective beta-2-adrenoreceptor agonists (R03AC); and anilides (N02BE). Use of these medications was similar between treatment groups.

Use of disallowed concomitant medications during the treatment period was reported in no participants in the tezepelumab group and 2 (1.0%) participants in the placebo group. The disallowed concomitant medications were biologics including dupilumab and omalizumab (one participant each in the placebo group). Confirmed cases of prohibited medication use anytime during the study were reported as important protocol deviations.

Numbers analysed

The analysis sets and the number of participants in each analysis set are summarised in Table 13. The 6 participants randomised at the 3 study centres in Japan that were closed due to GCP issues were not included in any analysis sets. In addition, data from 2 patients is excluded due to a critical data quality issue identified at one site in China.

Table 13. Analysis sets

Analysis set	**Teze 210 mg Q4W**	**Placebo**	**Total**
Randomised analysis set	204	206	410
Safety set	203	205	408
Excluded from Safety set	1	1	2
Did not receive at least one dose of investigational product	1[a]	1	2
Full analysis set	203	205	408
Excluded from Full analysis set	1	1	2
Randomised without at least one dose of investigational product	1[a]	1	2
PK analysis set	203	0	203
Excluded from PK analysis set	1	206	207
Did not have at least one detectable tezepelumab serum concentration from a sample collected post-treatment	1[a]	206	207
Additional FU analysis set	90	73	163
Excluded from additional FU analysis set	114	133	247
Randomised but not follow-up	31	72	103
Did not complete week 64 visit	83	61	144

Co-morbid Asthma/AERD/NSAID-ERD subset	122	126	248
Excluded from Co-morbid Asthma/AERD/NSAID-ERD subset	82	80	162
Participants who do not have comorbid asthma/AERD/NSAID-ERD at baseline	82	80	162

[a] This participant was randomised but never dosed and was therefore excluded from PK analysis set, safety set, and full analysis set.

The same subject could have been excluded from an analysis set for more than one reason.
AERD: Aspirin Exacerbated Respiratory Disease; FU follow up; n Number of subjects per category; NSAID- ERD: Nonsteroidal Anti-Inflammatory Drug Exacerbated Respiratory Disease; PK Pharmacokinetic; Q4W Every 4 weeks; Teze Tezepelumab.

Outcomes and estimation

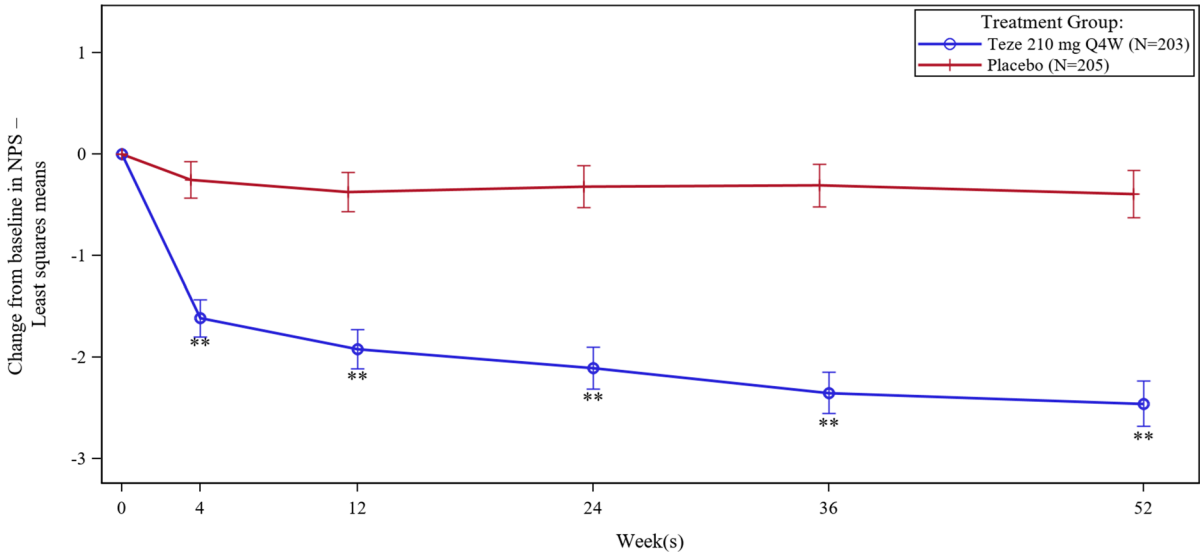
Co-primary Endpoint: Change in Total Nasal Polyp Score (NPS)

Primary Estimand

The total NPS change from baseline at Week 52 was statistically significantly improved in the tezepelumab group compared with the placebo group: -2.458 versus -0.380, respectively (LS mean difference -2.078 [95% CI: -2.399 to -1.757], p < 0.0001).

The improvement in the tezepelumab group in total NPS, compared with placebo, was observed from Week 4 and maintained throughout Week 52 (Figure 17).

Figure 17. Change from Baseline in Total NPS by Timepoint, Primary Estimand, ANCOVA (Full Analysis Set)



* denotes unadjusted p<0.05 and ** denotes unadjusted p<0.01 for Teze 210 mg Q4W vs Placebo treatment comparison.

Error bars represent 95% confidence intervals. P-values are based on the ANCOVA model at each timepoint.
ANCOVA Analysis of covariance; NPS Nasal polyposis score; Q4W Every 4 weeks; Teze Tezepelumab.

Supplementary Estimand Analyses

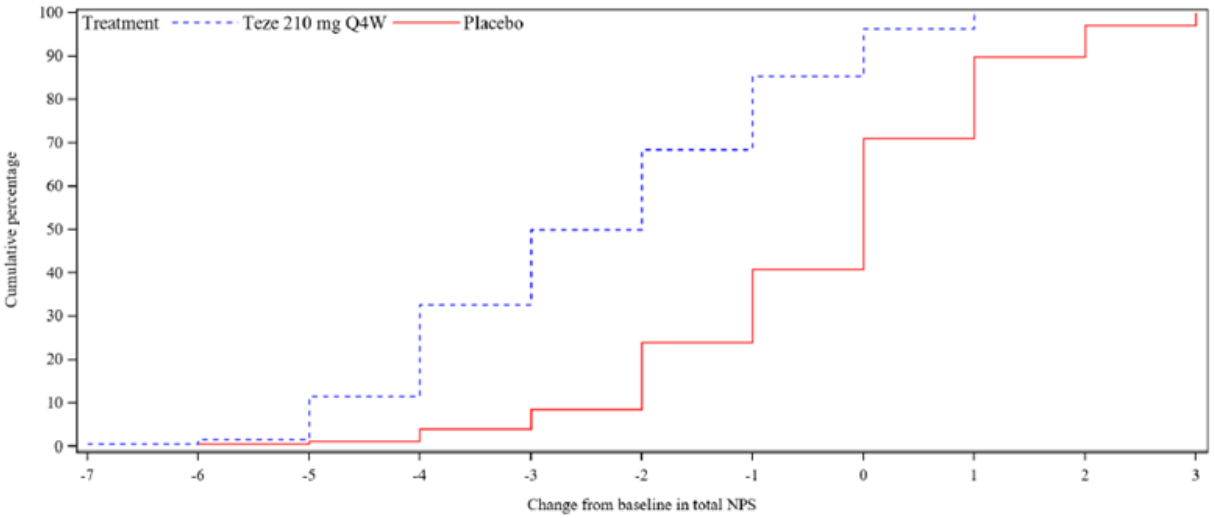
The supplementary estimand analysis using composite strategy for NP surgery, SCS for NP, biologics for NP, and treatment discontinuation, where NPS after the ICEs were replaced with worst possible

score, showed consistent results with the primary estimand analysis. The supplementary estimand analysis using a hypothetical strategy for COVID-19 infection also showed consistent results.

Supportive Analyses

The cumulative distribution function curves of the change from baseline in total NPS at Week 52 showed separation between the tezepelumab and placebo groups across the curve, with a consistently greater proportion of tezepelumab-treated participants with improvements on NPS versus placebo-treated participants across all changes.

Figure 18. Cumulative distribution function of change from baseline in total NPS at Week 52, supportive analysis (Full analysis set)



Participants who have missing data at Week 52 without a preceeding surgery or SCS/biologics for NP are excluded from this analysis.
Data after NP surgery are set to WPS and after SCS/biologic use for NP are set to WOCF.
NP Nasal polyposis; SCS Systemic corticosteroids; NPS Nasal polyposis score; Q4W Every 4 weeks; Teze Tezepelumab; WPS Worst possible score; WOCF Worst observation carried forward

Sensitivity Analyses

A consistent efficacy of tezepelumab compared with placebo was observed for all sensitivity analyses conducted on total NPS change from baseline.

Subgroup Analyses

The efficacy of tezepelumab measured by total NPS change from baseline, compared with placebo, was consistent across all pre-specified subgroups based on demographic variables and baseline disease characteristics, including subgroups with and without prior NP surgery and with and without co-morbid asthma/AERD/NSAID-ERD. However, the CIs for the Japan subgroup did not exclude zero.

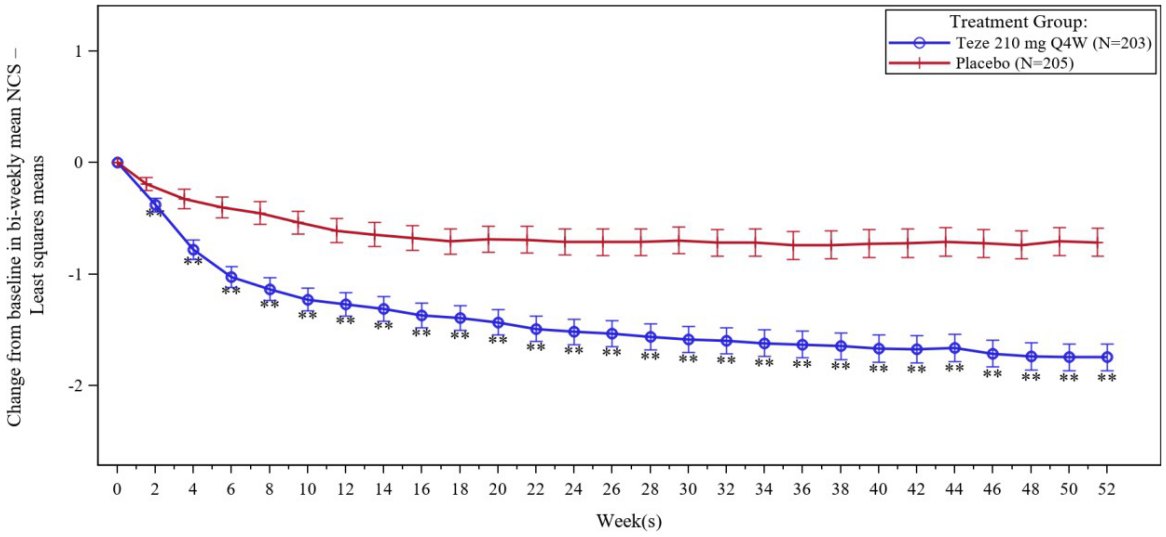
Co-primary Endpoint: Change in Nasal Congestion Score (NCS)

Primary Estimand Analysis

The bi-weekly mean NCS change from baseline at Week 52 was statistically significantly improved in the tezepelumab group compared with the placebo group: -1.743 versus -0.703, respectively (LS mean difference -1.039 [95% CI: -1.214 to -0.865], $p < 0.0001$).

The improvement in the tezepelumab group, compared with placebo in bi-weekly mean NCS was observed early (Week 2) and maintained through Week 52 (Figure 19).

Figure 19. Change from Baseline in Bi-weekly Mean NCS by Timepoint, Primary Estimand, ANCOVA (Full Analysis Set)



* denote unadjusted p<0.05 and ** denote unadjusted p<0.01 for Teze 210 mg Q4W vs Placebo treatment comparison.
Error bars represent 95% confidence intervals. P-values are based on the ANCOVA model at each timepoint.
ANCOVA Analysis of covariance; NCS Nasal congestion score; Q4W Every 4 weeks; Teze Tezepelumab.

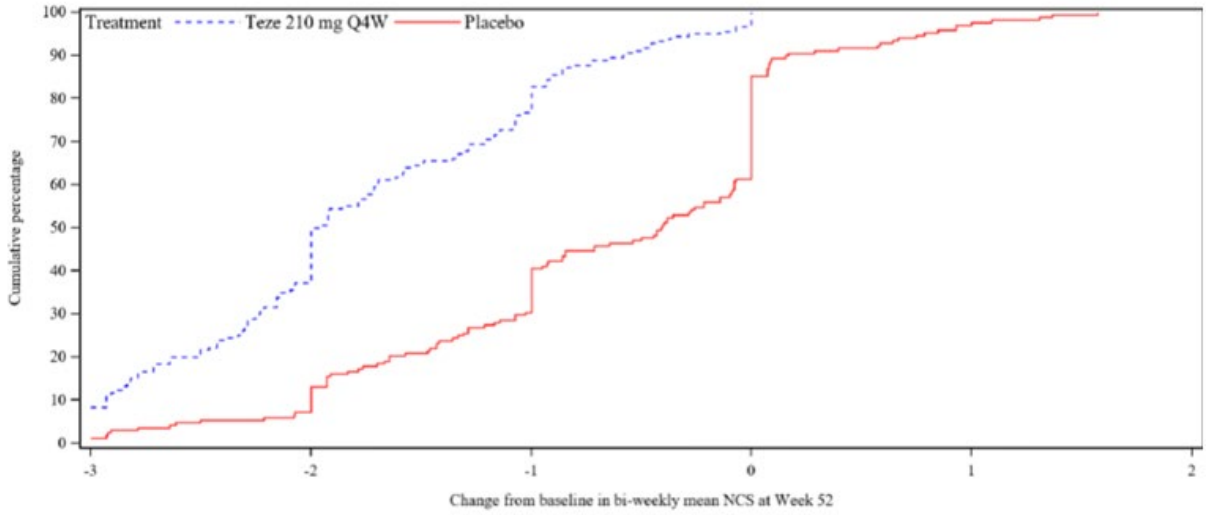
Supplementary Estimand Analyses

The supplementary estimand analysis using composite strategy for NP surgery, SCS for NP, biologics for NP, and treatment discontinuation, where NCS after the ICEs were replaced with worst possible score, showed consistent results with the primary estimand analysis. The supplementary analyses using ANCOVA with hypothetical strategy for COVID-19 infections showed results consistent with the primary NCS analysis.

Supportive Analyses

The cumulative distribution function curves of the change from baseline in bi-weekly mean NCS at Week 52 showed separation between the tezepelumab and placebo groups across the curve, with a consistently greater proportion of tezepelumab-treated participants with improvements on NCS versus placebo-treated participants across all changes.

Figure 20. Cumulative distribution function of change from baseline in bi-weekly mean NCS at Week 52, supportive analysis (Full analysis set)



Participants who have missing data at Week 52 without a preceeding surgery or SCS/biologics for NP are excluded from this analysis.
Data after NP surgery are set to WPS and after SCS/biologic use for NP are set to WOCF.
A negative value of change from baseline indicate improvement.
NP Nasal polyposis; SCS Systemic corticosteroids; NPS Nasal congestion score; Q4W Every 4 weeks; Teze Tezepelumab; WPS Worst possible score; WOCF Worst observation carried forward

Sensitivity Analyses

A consistent efficacy of tezepelumab compared with placebo was observed for all sensitivity analyses conducted on bi-weekly mean NCS change from baseline at Week 52.

Subgroup Analyses

The efficacy of tezepelumab measured by bi-weekly mean NCS change from baseline, compared with placebo, was consistent across all pre-specified subgroups based on demographic variables and baseline disease characteristics, including subgroups with and without prior NP surgery and with and without co-morbid asthma/AERD/NSAID-ERD. However, the CIs for the Japan subgroup did not exclude zero.

Key secondary endpoints

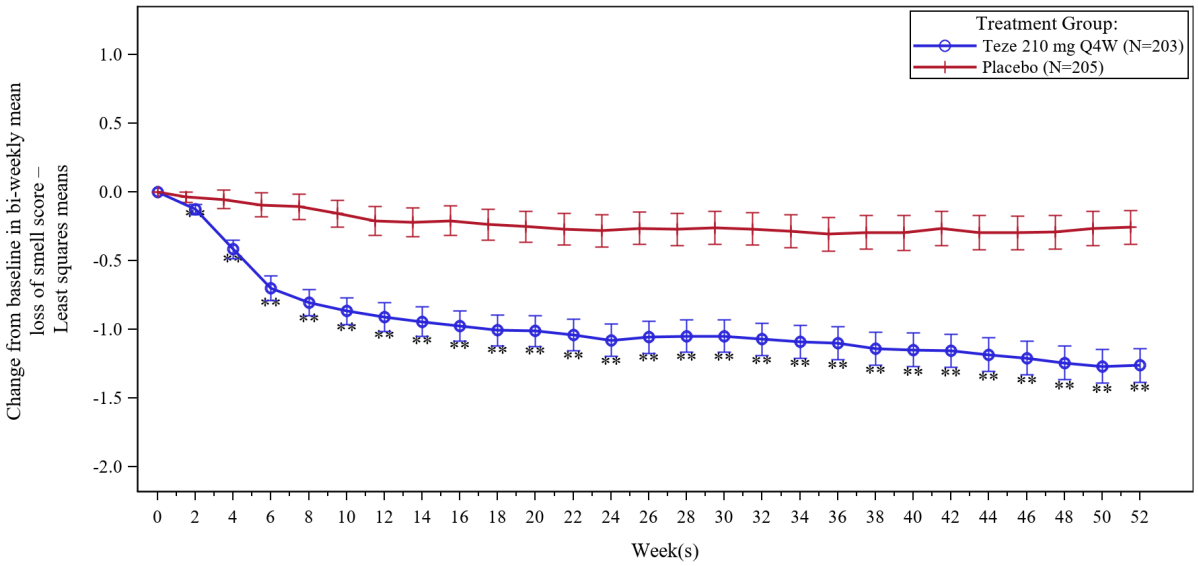
All key secondary endpoint analyses in this section are based on the primary Estimand.

Loss of Smell

Change from baseline in loss of smell, evaluated as bi-weekly mean NPSD difficulty with sense of smell item score, was statistically significantly improved in the tezepelumab group at Week 52 compared with the placebo group: -1.261 versus -0.255, respectively (LS mean difference -1.005 [95% CI: -1.177 to -0.834], $p < 0.0001$).

The improvement in the tezepelumab group compared with the placebo group was observed as early as Week 2 and maintained throughout the treatment period (Figure 21).

Figure 21. Change from Baseline in Bi-weekly Mean Loss of Smell Score by Timepoint, Primary Estimand, ANCOVA (Full Analysis Set)



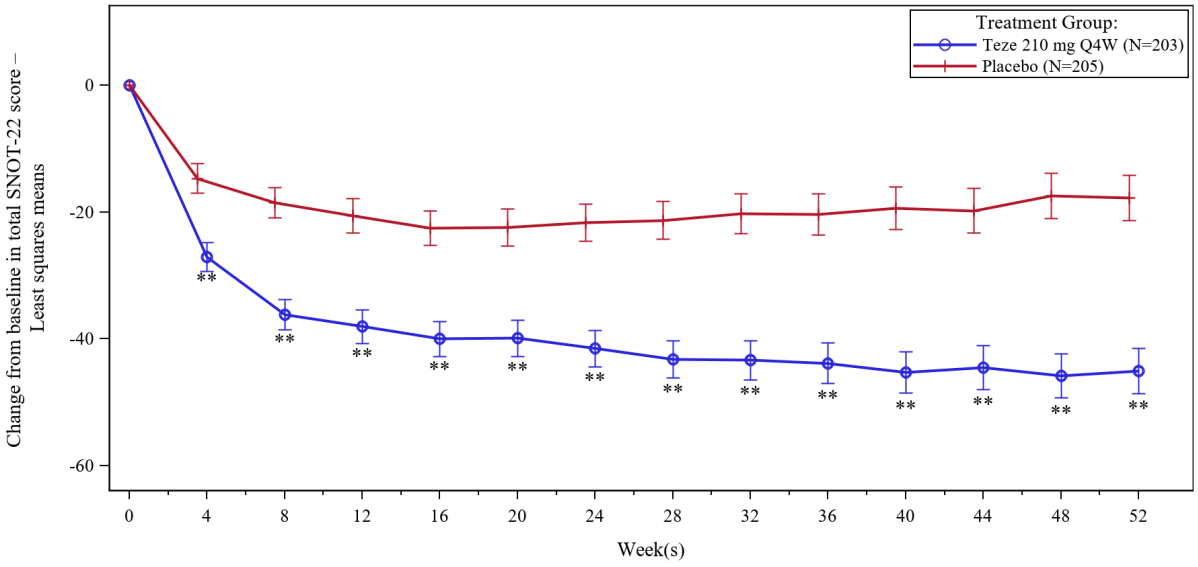
* denote unadjusted p<0.05 and ** denote unadjusted p<0.01 for Teze 210 mg Q4W vs Placebo treatment comparison.
Error bars represent 95% confidence intervals. P-values are based on the ANCOVA model at each timepoint.
ANCOVA Analysis of covariance; Q4W Every 4 weeks; Teze Tezepelumab.

Change in SNOT-22 Score

The change from baseline in SNOT-22 score at Week 52 was statistically significantly improved in the tezepelumab group compared with the placebo group: -45.022 versus -17.580, respectively (LS mean difference -27.441 [95% CI: -32.512 to -22.370], p < 0.0001). The improvement was observed as early as Week 4 and maintained throughout the treatment period (Figure 22).

The proportion of responders at Week 52 based on SNOT-22 score (defined as ≥ 8.9 point reduction from baseline), evaluated as a supporting analysis, was higher in the tezepelumab group compared with placebo.

Figure 22. Change from Baseline in Total SNOT-22 Score by Timepoint, Primary Estimand, ANCOVA (Full Analysis Set)



* denote unadjusted p<0.05 and ** denote unadjusted p<0.01 for Teze 210 mg Q4W vs Placebo treatment comparison.
Error bars represent 95% confidence intervals. P-values are based on the ANCOVA model at each timepoint.
ANCOVA Analysis of covariance; SNOT-22 SinoNasal Outcome Test, 22 items; Q4W Every 4 weeks; Teze Tezepelumab.

Change in LMK Score

The change from baseline at Week 52 in sinus opacification, evaluated by CT and measured by LMK score, showed statistically significant improvement in the tezepelumab group compared with the placebo group: -6.270 versus -0.569, respectively (LS mean difference -5.700 [95% CI: -6.371 to -5.030], p < 0.0001).

Time to Nasal Polyp Surgery Decision and/or Systemic Corticosteroid Treatment for Nasal Polyps

Note that the endpoint time to NP surgery is defined as the time to NP surgery decision.

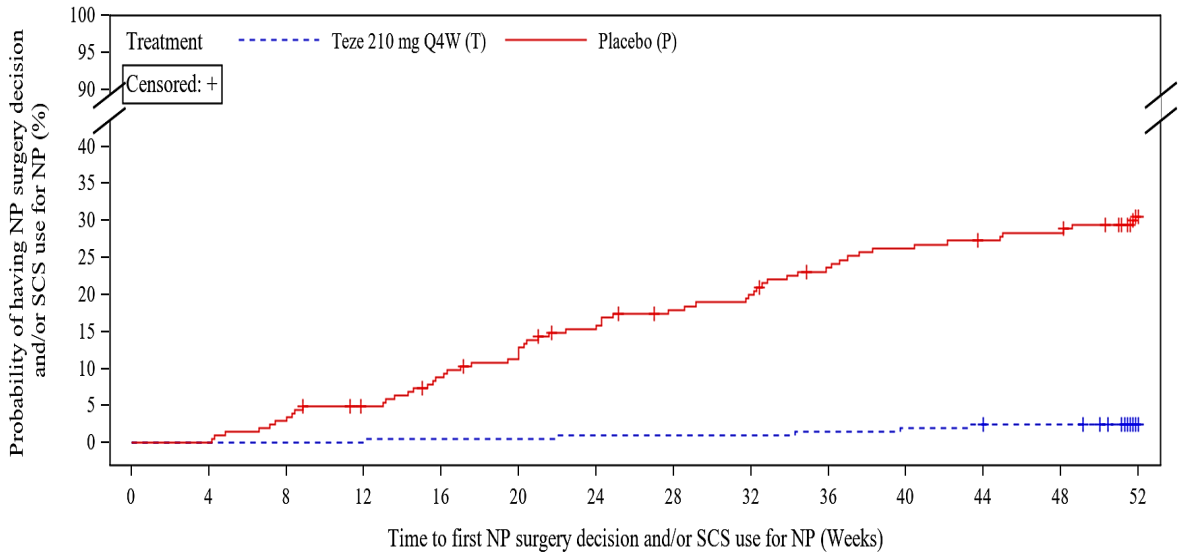
Tezepelumab statistically significantly reduced the proportion of participants with the need for NP surgery and/or SCS for NP over 52 weeks compared with placebo: 5.7% versus 31.4%, respectively (HR 0.08 [95% CI: 0.03 to 0.16], p < 0.0001). Additionally, tezepelumab statistically significantly reduced the need for NP surgery and need for SCS for NP (individual component endpoints).

A separation in Kaplan-Maier incidence curves was observed early and increased throughout the treatment period (Figure 23).

Tezepelumab statistically significantly reduced the proportion of participants requiring NP surgery compared with placebo over 52 weeks: 0.5% versus 22.0%, respectively (HR 0.02 [95% CI: 0.00 to 0.09, p < 0.0001]).

Tezepelumab statistically significantly reduced the proportion of participants requiring SCS for NP compared with placebo over 52 weeks: 5.2% versus 19.3%, respectively (HR 0.11 [95% CI: 0.04 to 0.25, p < 0.0001]).

Figure 23. Time to First NP Surgery Decision and/or SCS for NP, Kaplan-Meier Cumulative Incidence Curve (Full Analysis Set)



At risk

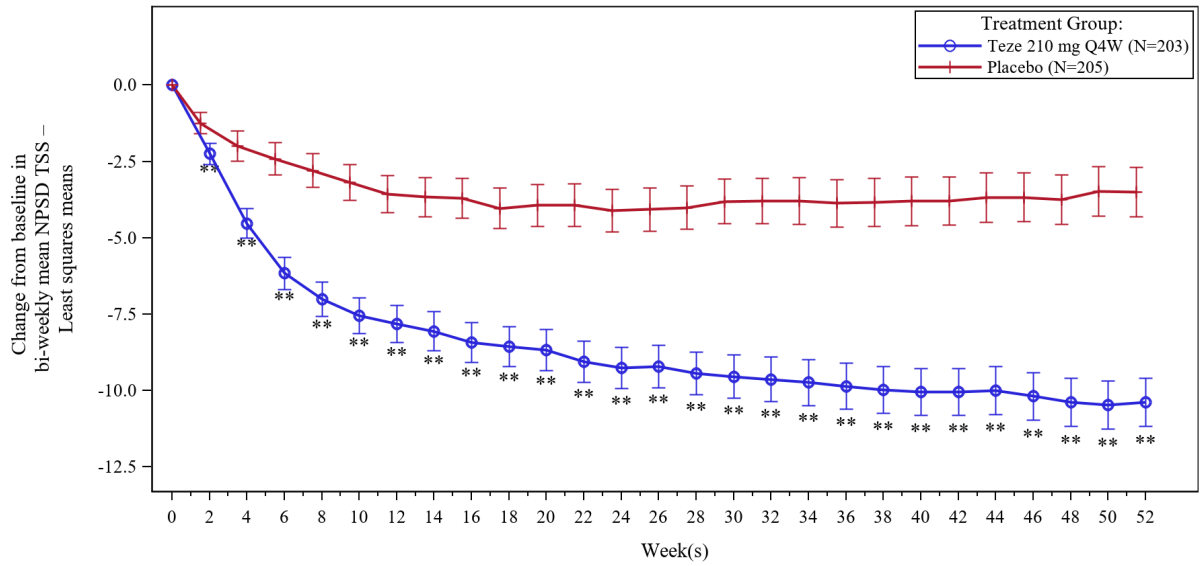
T: n=	203	203	203	203	202	202	201	201	201	200	199	198	197	167
P: n=	205	205	199	192	183	177	166	159	155	146	141	138	136	113

Time to first NP surgery decision and/or SCS use for NP (days) = Earliest of (date of first NP surgery decision, Start of first SCS use for NP) - date of randomisation + 1.
Censoring rule for time to first event: For subjects who do not have surgery decision or SCS use for NP, the time to event is censored at the earlier of the date of the Week 52 visit or study withdrawal date (for subjects not followed up until Week 52).
n Number of subjects in analysis; NP Nasal polyposis; Q4W Every 4 weeks; SCS Systemic corticosteroids; Teze Tezepelumab.

NPSD Total Symptom Score

The change from baseline in bi-weekly mean NPSD TSS at Week 52 was statistically significantly improved in the tezepelumab group compared with the placebo group: -10.388 versus -3.429, respectively (LS mean difference -6.959 [95% CI: -8.085 to -5.833], $p < 0.0001$). A decrease (improvement) in NPSD TSS was observed in the tezepelumab group from Week 2 and maintained through Week 52 (Figure 24).

Figure 24. Change from Baseline in Bi-weekly Mean NPSD TSS by Timepoint, Primary Estimand, ANCOVA (Full Analysis Set)



* denote unadjusted p<0.05 and ** denote unadjusted p<0.01 for Teze 210 mg Q4W vs Placebo treatment comparison.
Error bars represent 95% confidence intervals. P-values are based on the ANCOVA model at each timepoint.
ANCOVA Analysis of covariance; NPSD Nasal polyps symptom diary; Q4W Every 4 weeks; Teze Tezepelumab; TSS Total symptom score.

Pre-Bronchodilator FEV_1 in Participants with Co-morbid Asthma/ AERD/NSAID-ERD

Mean baseline pre-BD FEV_1 was 2.865 L (SD: 0.933) in the tezepelumab group and 2.915 L (SD: 0.845) in the placebo group. Mean percent predicted pre-BD FEV_1 at baseline was 87.246% (SD: 16.713) in the tezepelumab group and 84.374% (SD: 16.064) in the placebo group.

No difference versus placebo was observed in pre-BD FEV_1 at Week 52 in participants with co-morbid asthma/AERD/NSAID-ERD. The change from baseline in pre-BD FEV_1 at Week 52 was 0.022 L in the tezepelumab group and 0.027 L in the placebo group (LS mean difference -0.005 L [95% CI: -0.121 to 0.111], p = 0.9362).

Since this was not an asthma-specific trial, disease severity and airway reversibility were not evaluated at the time of randomisation. The mean baseline pre-BD FEV_1 and mean percent predicted pre-BD FEV_1 were higher than anticipated, indicating that the co-morbid asthma/AERD/NSAID-ERD trial population did not exhibit significant impairment in terms of pre-BD FEV_1.

Other secondary endpoints

Nasal Polyp Score Evaluated by Nasal Endoscopy Through Week 52 and NPS Responders

At Week 52, 63.5% in the tezepelumab group and 19.0% in the placebo group had a ≥ 2 points reduction in NPS compared with baseline (odds ratio 8.25 [95% CI: 5.10 to 13.35], difference in responder rates 45.33 [95% CI: 36.78 to 53.88]). The proportions of participants with ≥ 1 point reduction from baseline at Week 52 were 79.3% and 31.2% in the tezepelumab and placebo groups, respectively, with an odds ratio of 8.87 (95% CI: 5.39 to 14.60). The difference in responder rates was 45.18 (95% CI: 36.59 to 53.77).

Change from Baseline over Time in Bi-weekly Mean NCS Evaluated by NPSD Through Week 52 and NCS Responders

At Week 52, 73.4% in the tezepelumab group and 32.7% in the placebo group had a ≥ 1 point reduction in NCS compared with baseline (odds ratio 6.93 [95% CI: 4.27 to 11.24], difference in responder rates 40.41 [95% CI: 31.73 to 49.09]).

Loss of Smell Evaluated by UPSIT Test

The mean change in loss of smell, evaluated by UPSIT test from baseline at Week 52, was 9.310 in the tezepelumab group and -0.192 in the placebo group with a treatment difference of 9.503 (95% CI: 7.844 to 11.162).

Sinus Opacification - Modified Lund-MacKay (Zinreich) Score

The mean change in sinus opacification on CT, evaluated by modified LMK score (Zinreich Score), from baseline at Week 52 was -17.520 in the tezepelumab group and -1.106 in the placebo group with a treatment difference of -16.413 (95% CI: -18.096 to -14.731).

Sinus Severity Score

The mean change in sinus severity score, evaluated by quantitative CT assessment, from baseline at Week 52 was -32.754 in the tezepelumab group and -1.978 in the placebo group with a treatment difference of -30.776 (95% CI: -34.020 to -27.531).

Systemic Corticosteroid Use

The annualised number of courses of SCS for NP was reduced in the tezepelumab group compared with the placebo group (rate ratio: 0.1138 [95% CI: 0.0481 to 0.2693]).

Change from Baseline by Domain of NPSD

Overall, improvements were observed throughout the treatment period in the tezepelumab group compared with placebo.

Nasal Peak Inspiratory Flow

The mean change in NPIF, evaluated by nasal inspiratory measurements, from baseline through Week 52 showed improvement in the tezepelumab group compared with placebo. At Week 52, the change from baseline was 22.857 in the tezepelumab group and 0.504 in the placebo group with a treatment difference of 22.353 (95% CI: 6.272 to 38.434).

Asthma Control in Participants with Co-morbid Asthma/AERD/NSAID-ERD

In the subgroup of participants with co-morbid asthma/AERD/NSAID-ERD, participants in the tezepelumab group showed improvement in ACQ-6 scores at Week 52 compared with participants in the placebo group (LS mean difference -0.388 [95% CI: -0.585 to -0.190]).

In CRSwNP participants with co-morbid asthma/AERD/NSAID-ERD, tezepelumab improved asthma symptom control compared with participants in the placebo group, as measured by an improvement in ACQ-6 score of at least 0.5. The responder rate in the tezepelumab group at Week 52 was 67.2% versus 41.3% in the placebo group (odds ratio 2.52 [95% CI: 1.21 to 5.27]).

Exploratory endpoints

Off-treatment Effects on NPS and NCS

Change in total NPS and bi-weekly NCS, and changes from baseline through the post-treatment period were analysed using the additional follow-up analysis set to explore the post-treatment effect of tezepelumab.

The improvement in the tezepelumab group over the placebo group was present through Week 76 although reduced gradually during the off-treatment period.

Patient-Reported Quality of Life Outcomes

EQ-5D-5L

The mean change from baseline in total EQ-5D-5L score at Week 52 was -2.5 (SD: 3.40) in the tezepelumab group and -2.2 (SD: 3.97) in the placebo group. A higher percentage of participants in the tezepelumab group reported 'no problem' in the 5 dimensions of EQ-5D-5L: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression at Week 52 compared with placebo. Larger changes from baseline in visual analogue scale and health state index scores at Week 52 were also observed in tezepelumab compared with placebo.

PGI-S and PGI-C

A greater proportion of participants in the tezepelumab group (76.5%) perceived (PGI-S) that they had mild to no symptoms at Week 52, compared with the placebo group (41.6%).

PGI-C showed improvements over time in the tezepelumab group compared with placebo, both by category and improvement response.

Ancillary analyses

Not applicable.

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14. Summary of Efficacy for trial D5242C00001 (WAYPOINT)

Title: A Multicentre, Randomised, Double-Blind, Parallel-Group, Placebo-Controlled Phase 3 Efficacy and Safety Study of Tezepelumab in Participants with Severe Chronic Rhinosinusitis with Nasal Polyposis (WAYPOINT)	
Study identifier	D5242C00001; WAYPOINT EudraCT Number: 2020-003062-39 NCT Number: NCT04851964
Design	Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group

	Duration of main phase: Duration of run-in phase: Duration of extension phase:		52-week treatment period 5-week screening/run-in period 24-week follow-up period planned for the first 200 randomised participants and a 12-week follow-up for all other participants
Hypothesis	Superiority		
Treatment groups	Tezepelumab		Tezepelumab 210 mg every 4 weeks (Q4W) subcutaneously (SC), 204 participants randomised
	Placebo		Placebo Q4W SC, 206 participants randomised
Endpoints and definitions	Co-primary endpoint	Nasal polyp score (NPS)	Change from baseline in total NPS evaluated by nasal endoscopy at Week 52.
	Co-primary endpoint	Nasal Congestion Score (NCS)	Change from baseline in bi-weekly mean NCS evaluated as part of the nasal polyposis symptom diary (NPSD) at Week 52.
	Key secondary	Loss of smell	Change from baseline in bi-weekly mean loss of smell evaluated as part of the NPSD at Week 52.
	Key secondary	SinoNasal Outcome Test, 22 item (SNOT-22)	Change from baseline in SNOT-22 scores at Week 52.
	Key secondary	Lund-Mackay (LMK) score	Change from baseline in LMK score, evaluated by sinus computed tomography at Week 52.
	Key secondary	Nasal polyp(s) (NP) surgery and/or systemic corticosteroids (SCS) for NP	Time to first surgery decision and/or SCS for NP up to Week 52. Time to first NP surgery decision up to Week 52. Time to first SCS for NP up to Week 52.
	Key secondary	NPSD total symptom score (TSS)	Change from baseline in bi-weekly mean NPSD TSS at Week 52.
	Key secondary	Pre-bronchodilator (Pre-BD) forced expiratory volume in 1 second (FEV_1)	Change from baseline in pre-BD FEV_1 in participants with co-morbid asthma/aspirin exacerbated respiratory disease (AERD)/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD) at Week 52.

	Other secondary	SCS use for NP	Exposure of SCS over 52 weeks (a course of SCS was defined as SCS for at least 3 consecutive days for treatment of NP. An SCS course was considered as a new course if the start date was at least 7 days after the end date of the last SCS use for NP course).
Notes	Endpoints included in the multiple testing procedure: NPS, NCS, loss of smell, SNOT-22, LMK score, time to first SCS for NP and/or surgery decision, time to first surgery decision, time to first SCS for NP, NPSD TSS, pre-BD FEV_1		
Database lock (DBL)	29 October 2024 (primary DBL); data cut-off 23 September 2024		

Results and Analysis				
Analysis description	**Primary analysis: NPS**			
Analysis population and time point description	Full analysis set (FAS); Week 52			
Descriptive statistics and estimate variability	Treatment group		Tezepelumab	Placebo
	Number of participants		203	205
	NPS (least squares mean [LSMean] change from baseline)		-2.458	-0.380
	95% Confidence Interval (CI)		(-2.681, -2.234)	(-0.611, -0.148)
Effect estimate per comparison	NPS	Comparison groups	Tezepelumab versus placebo	
		LSMean difference	-2.078	
		95% CI	(-2.399, -1.757)	
		p-value (analysis of covariance [ANCOVA])	< 0.0001** ** statistically significant at 0.01 level under the multiple testing strategy	
Notes	The improvement in the total NPS in the tezepelumab group, compared with placebo, was observed from Week 4 and maintained throughout Week 52. Supplementary and sensitivity analyses all showed consistent results. Subgroup analyses were consistent across all pre-specified subgroups, including subgroups with and without prior NP surgery and with and without co-morbid asthma/AERD/NSAID-ERD.			
Analysis description	**Primary analysis: NCS**			
Analysis population and time point description	FAS; Week 52			
	Treatment group		Tezepelumab	Placebo
	Number of participants		203	205

Descriptive statistics and estimate variability	NCS (LSMean change from baseline)		-1.743	-0.703
	95% CI		(-1.864, -1.622)	(-0.830, -0.577)
Effect estimate per comparison	NCS	Comparison groups	Tezepelumab versus placebo	
		LSMean difference	-1.039	
		95% CI	(-1.214, -0.865)	
		p-value (ANCOVA)	< 0.0001** ** statistically significant at 0.01 level under the multiple testing strategy	
Notes	The improvement in bi-weekly mean NCS in the tezepelumab group, compared with placebo, was observed early (Week 2) and maintained throughout Week 52. Supplementary and sensitivity analyses all showed consistent results. Subgroup analyses were consistent across all pre specified subgroups, including subgroups with and without prior NP surgery and with and without co-morbid asthma/AERD/NSAID-ERD.			
Analysis description	**Key secondary analysis: Loss of smell**			
Analysis population and time point description	FAS; Week 52			
Descriptive statistics and estimate variability	Treatment group		Tezepelumab	Placebo
	Number of participants		203	205
	Loss of smell (LSMean change from baseline)		-1.261	-0.255
	95% CI		(-1.382, -1.139)	(-0.378, -0.133)
Effect estimate per comparison	Loss of smell	Comparison groups	Tezepelumab versus placebo	
		LSMean difference	-1.005	
		95% CI	(-1.177, -0.834)	
		p-value (ANCOVA)	< 0.0001** ** statistically significant at 0.01 level under the multiple testing strategy	
Notes	The improvement in the tezepelumab group compared with the placebo group was observed as early as Week 2 and maintained throughout the treatment period.			
Analysis description	**Key secondary analysis: SNOT-22**			
Analysis population and time point description	FAS; Week 52			
	Treatment group		Tezepelumab	Placebo
	Number of participants		203	205

Descriptive statistics and estimate variability	SNOT-22 (LSMean change from baseline)		-45.022	-17.580
	95% CI		(-48.572, -41.472)	(-21.189, -13.971)
Effect estimate per comparison	SNOT-22 score	Comparison groups	Tezepelumab versus placebo	
		LSMean difference	-27.441	
		95% CI	(-32.512, -22.370)	
		p-value (ANCOVA)	< 0.0001** ** statistically significant at 0.01 level under the multiple testing strategy	
Notes	The improvement in SNOT-22 score was observed as early as Week 4 and maintained throughout the treatment period. The proportion of responders at Week 52 based on SNOT-22 score (defined as ≥ 8.9 point reduction from baseline), evaluated as a supporting analysis, was higher in the tezepelumab group compared with placebo.			
Analysis description	**Key secondary analysis: LMK score**			
Analysis population and time point description	FAS; Week 52			
Descriptive statistics and estimate variability	Treatment group		Tezepelumab	Placebo
	Number of participants		203	205
	LMK score (LSMean change from baseline)		-6.270	-0.569
	95% CI		(-6.740, -5.799)	(-1.046, 0.093)
Effect estimate per comparison	LMK score	Comparison groups	Tezepelumab versus placebo	
		LSMean difference	-5.700	
		95% CI	(-6.371, -5.030)	
		p-value (ANCOVA)	< 0.0001** ** statistically significant at 0.01 level under the multiple testing strategy	
Analysis description	**Key secondary analysis: Time to first surgery decision and/or SCS for NP**			
Analysis population and time point description	FAS; Week 52			
Descriptive statistics and estimate variability	Treatment group		Tezepelumab	Placebo
	Number of participants		203	205
	Proportion of participants with NP surgery decision and/or SCS for NP (Kaplan-Meier estimate [%])		5.7	31.4
	95% CI		(1.3, 15.0)	(25.0, 38.0)
		Comparison groups	Tezepelumab versus placebo	

Effect estimate per comparison	Time to first surgery decision and/or SCS for NP	Hazard ratio (HR)	0.08
		95% CI	(0.03, 0.16)
		p-value (Cox regression)	< 0.0001** ** statistically significant at 0.01 level under the multiple testing strategy
Notes	A separation in Kaplan-Maier incidence curves was observed early.		
Analysis description	**Key secondary analysis: Time to first NP surgery decision**		
Analysis population and time point description	FAS; Week 52		
Descriptive statistics and estimate variability	Treatment group		Tezepelumab / Placebo
	Number of participants		203 / 205
	Proportion of participants with NP surgery decision (Kaplan-Meier estimate [%])		0.5 / 22.0
	95% CI		(0.0, 2.5) / (16.4, 28.2)
Effect estimate per comparison	Time to first NP surgery decision	Comparison groups	Tezepelumab versus placebo
		Hazard ratio (HR)	0.02
		95% CI	(0.00, 0.09)
		p-value (Cox regression)	< 0.0001** ** statistically significant at 0.01 level under the multiple testing strategy
Analysis description	**Key secondary analysis: Time to first SCS for NP**		
Analysis population and time point description	FAS; Week 52		
Descriptive statistics and estimate variability	Treatment group		Tezepelumab / Placebo
	Number of participants		203 / 205
	Proportion of participants with SCS for NP (Kaplan-Meier estimate [%])		5.2 / 19.3
	95% CI		(1.1, 14.7) / (14.1, 25.1)
Effect estimate per comparison	Time to first SCS for NP	Comparison groups	Tezepelumab versus placebo
		Hazard ratio (HR)	0.11
		95% CI	(0.04, 0.25)
		p-value (Cox regression)	< 0.0001** ** statistically significant at 0.01 level under the multiple testing strategy

Analysis description	**Key secondary analysis: NPSD TSS**			
Analysis population and time point description	FAS; Week 52			
Descriptive statistics and estimate variability	Treatment group		Tezepelumab	Placebo
	Number of participants		203	205
	NPSD TSS (LSMean change from baseline)		-10.388	-3.429
	95% CI		(-11.174, -9.601)	(-4.241, -2.617)
Effect estimate per comparison	NPSD TSS	Comparison groups	Tezepelumab versus placebo	
		LSMean difference	-6.959	
		95% CI	(-8.085, -5.833)	
		p-value (ANCOVA)	< 0.0001** ** statistically significant at 0.01 level under the multiple testing strategy	
Notes	A decrease (improvement) in NPSD TSS was observed in the tezepelumab group from Week 2 and maintained through Week 52.			
Analysis description	**Key secondary analysis: Pre-BD FEV_1**			
Analysis population and time point description	Co-morbid asthma/AERD/NSAID-ERD subset; Week 52			
Descriptive statistics and estimate variability	Treatment group		Tezepelumab	Placebo
	Number of participants		122	126
	Pre-BD FEV_1 (liters [L]) (LSMean change from baseline)		0.022	0.027
	95% CI		(-0.065, 0.108)	(-0.055, 0.108)
Effect estimate per comparison	Pre-BD FEV_1	Comparison groups	Tezepelumab versus placebo	
		LSMean difference	-0.005	
		95% CI	(-0.121, 0.111)	
		p-value (ANCOVA)	0.9362	
Notes	Mean baseline pre-BD FEV_1 was 2.865 L (standard deviation [SD]: 0.933) in the tezepelumab group and 2.915 L (SD: 0.845) in the placebo group. Mean percent predicted pre-BD FEV_1 at baseline was 87.246% (SD: 16.713) in the tezepelumab group and 84.374% (SD: 16.064) in the placebo group.			
Analysis description	**Other secondary analysis: SCS use for NP**			
Analysis population and time point description	FAS; Week 52			
	Treatment group		Tezepelumab	Placebo

Descriptive statistics and estimate variability	Number of participants		203	205
	Annual courses of SCS for NP	Number of courses	9	59
		Total time at risk (years)	205.2	195.7
		Crude rate	0.04	0.30
Effect estimate per comparison	Annual courses of SCS for NP	Comparison groups	Tezepelumab versus placebo	
		Rate ratio	0.1138	
		95% CI	(0.0481, 0.2693)	
		p-value (negative binomial model)	< 0.0001	

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Dose response study

No dose response studies in CRSwNP were performed by the MAH. The selected 210mg dose, administered every 4 weeks, is in line with the currently approved posology for tezepelumab in asthma.

The 210 mg Q4W dosing regimen was selected for the phase III WAYPOINT study based on the efficacy, safety, and exposure-response analysis from the Phase IIb study PATHWAY in asthma, which demonstrated that the 210 mg Q4W dose led to improved clinical efficacy compared with 70 mg Q4W, whereas the 280 mg Q2W dose did not further increase efficacy compared with 210 mg Q4W, and the safety profiles were similar across the 3 doses. In addition, a 210 mg Q4W dosing regimen was used in the Phase III NAVIGATOR study in asthma, in which improvements in SNOT-22 scores were observed in a *post hoc* analysis of participants with nasal polyps.

It is noted that concerns regarding dose selection were expressed as part of the CHMP SA: the MAH was recommended to conduct a proof-of-concept and dose-ranging study as CHMP considered that it was not certain that CRSwNP and asthma patients would respond in a similar way to the same dose of tezepelumab. Nevertheless, the MAH considered that the approved asthma dose of 210 mg Q4W SC should effectively target the inflammatory pathways relevant to both diseases and therefore show efficacy in CRSwNP, given the similarity of the underlying inflammatory pathophysiology of asthma and nasal polyps and significant overlap in patient populations. This is agreed by CHMP.

Main study

The MAH has performed a single pivotal phase III, randomised, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of tezepelumab in participants with CRSwNP. The general trial design is endorsed, patients were to receive active treatment for 48 weeks, a sufficient duration to assess efficacy at week 52, while the follow-up period up to week 76 is important to examine maintenance of the effect while off treatment and longer-term safety effects. Placebo controlled trials were also performed for approved biologics with the same indication.

After enrolment, the background intranasal corticosteroid (INCS) therapy was standardised to total 400µg daily mometasone furoate nasal spray (MFNS) or equivalent INCS. The standardisation of background therapy is advantageous to minimise the background variation between patients.

The MAH clarified that there was one case of NP exacerbation during the screening/run in period which should not be considered as caused by INCS therapy. No exacerbation of symptoms due to standardisation of therapy was observed during the screening/run-in period.

Data from 6 patients is excluded from the CSR due to significant deviations from GCP identified by the Japanese regulatory agency. In addition, data from 2 patients is excluded due to a critical data quality issue identified at one site in China. The number of patients whose data is excluded from the report (total n=8) is low. The MAH provided further information on the nature of the significant deviations from GCP identified in Japan and on the critical data quality issue identified at one site in China. The exclusion of this data is appropriate and does not affect the efficacy conclusion.

Study population

The proposed indication is '*Tezspire is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids, and/or surgery do not provide adequate disease control'.* The inclusion criteria of persistent signs (NPS ≥ 5) and symptoms (NCS ≥2) meet the requirements for severe disease. It is agreed that patients with a history of surgery and systemic corticosteroids (SCS) can be considered as inadequate responders. The study enrolled patients both with and without asthma which tezepelumab is also indicated for and which is a common comorbidity with CRSwNP. The study aimed to enroll 50% to 70% of participants with co-morbid asthma. Eligibility criteria were overall acceptable.

Study endpoints

The co-primary endpoints are change in baseline in nasal polyp(osis) score (NPS, by nasal endoscopy) and nasal congestion score (NCS, as part of NPSD) evaluated at week 52. NPS is a robust objective endpoint measurement evaluated by central review by two independent physicians, in contrast NCS is a subjective endpoint based on patient diary symptoms. A limitation of these endpoints is the lack of established minimal clinically important differences (MCID), nonetheless both endpoints are appropriate and clinically relevant endpoints. NCS daily scores were to be summarised as 14-day means which will minimise the effects of missing diary entries and as per SAP, participants with change from baseline in bi-weekly mean NCS ≤ -1.0 would be defined as NCS responders. NPS was a co-primary endpoint for the approval of other biologics in the same setting, although the timepoint for primary analysis was week 24 for some of the already approved medicinal products. In addition, NCS was also a co-primary endpoint for other approved biologicals in CRSwNP.

Secondary endpoints include analysis of the co-primary endpoints over time therefore covering 24 weeks of treatment also. The co-primary endpoint at 24 week was considered acceptable during the SA procedure however an endpoint at 52 is also accepted and in line with other approved biologics.

Other secondary endpoints are acceptable and include change from baseline in loss of smell, SNOT-22 scores, LMK scores, NPSD and pre-BD FEV1 at week 52, and time to surgery and/or use of SCS up to week 52. The secondary endpoints adequately cover other patient reported symptoms apart from NC.

Sample size

The sample size which aimed to include approximately 200 participants per treatment group appears adequate. The trial was randomised and stratified for geographical region, prior NP surgery, and co-morbid asthma/AERD/NSAID-ERD. Blinding and randomisation measures helped to reduce any inherent bias in the study, blinding procedures appear reasonable. As per CHMP SA, the MAH was advised to power this single pivotal study to conclude on the treatment effect in both subsets of asthmatic and the more heterogeneous non-asthmatic subpopulations.

The MAH has adequately described the primary estimand and strategies for handling the intercurrent events (ICE) along with additional supplementary estimands and sensitivity analyses.

Efficacy data and additional analyses

A total of 872 participants were enrolled in the pivotal phase III study, with a total of 410 subsequently randomised from 101 sites in 10 countries. Participants were randomised to either tezepelumab 210 mg (204 participants) or placebo (206 participants) treatment. It is noted that less than 50% of subjects enrolled in the study were included. The MAH clarified that a total of 462 enrolled participants were not randomised in the study. Two participants were lost to follow-up, 15 withdrew, and 2 were not randomised due to other reasons; 443 participants were screen failures. The most common reasons for screen failure were related to the inclusion criteria for CRSwNP disease characteristics. A total of 182 did not meet inclusion criterion. A total of 102 did not meet inclusion criterion regarding required confirmed central reading toral NPS $\geq$ 5 (at least 2 for each nostril) at Visit 2.

There was a large difference in the number of patients discontinuing treatment between arms, 4% versus 31% for tezepelumab compared to the placebo group. While most discontinuations were due to 'subject decision', it is possible that worsening/no improvement of symptoms played a part and may be suggestive of treatment effect in the tezepelumab arm.

All but 1 patient in each arm were included in the full analysis set (FAS) for the efficacy analyses, these 2 patients were excluded due to not receiving any treatment which is accepted.

The final protocol and SAP amendments occurred before the primary database lock for the efficacy analyses. The MAH confirmed that almost half of patients were recruited before a modification to the inclusion criteria in relation to NCS baseline mean scores, however this did not substantially affect the baseline data with minimal differences to bi-weekly mean NCS scores before and after the amendment, 2.47 (2.71) and 2.66 (2.92) respectively. There were a lower number of protocol deviations in the tezepelumab arm compared to the placebo arm (18% versus 30%). The most common reasons for protocol deviations were due to missing NPS or NCS assessments at the IP Discontinuation visit or EOT visit, the EOT visit does not impact the co-primary analyses. If IP discontinuation occurred prior to the co-primary analyses, this would be managed by handling of the ICE (treatment policy).

Background inhaled corticosteroids (INCS) medications (400µg MFNS daily) were standardised for at least 4 weeks before the start of IMP dosing, and compliance with this was high (>83%) across both treatment groups. As participants were dosed with the IMP under medical supervision, at the site by the Investigator/designee or at home by a healthcare professional, there were few issues with treatment compliance, which was >95% across both treatment groups.

Compliance with daily completion of the NPSD symptom diary was also high at >85% in both treatment groups. The MAH clarified that bi-weekly (14-day) mean score was calculated by averaging the daily scores in a 14-day period, if at least 8 days in the 14-day period had evaluable data (ie, > 50% diary entries evaluable); otherwise, the bi-weekly mean in that period was set to missing. Moreover, since the NPSD was completed by participants via ePRO, individual items could not be skipped. The overall mean compliance with the NPSD daily diary completion was 85.72% and can be considered high. Overall, 78.9%, 17.9%, 2.9%, and 0.2% participants had 0 to < 25%, 25 to < 50%, 50 to < 75%, and $\geq$75% missing diary entries during the study, respectively.

Overall, the demographics, baseline characteristics and concomitant therapies were well balanced between the treatment arms. Patients were predominantly <65 years old, male and white. Given the common pathophysiology globally for CRSwNP, it is considered that data collected are applicable to all regions. Mean baseline disease characteristics were similar for NPS, 6.3 and 6.2, and NCS, 2.59 and 2.55 for tezepelumab and placebo treated patients. 60% and 62% of tezepelumab and placebo treated patients also had asthma/AERD/NSAID/NSAID-ERD, consistent with literature findings that CRSwNP is commonly associated with other inflammatory co-morbidities. 71% and 72% of tezepelumab and placebo treated patients received prior surgery for NP while 64% and 67% of tezepelumab and placebo

treated patients had prior use of SCS confirming that these patients were inadequate responders to prior treatments. The study population was representative of the intended target population, as outlined in the inclusion/exclusion criteria.

Co-primary endpoints

Results demonstrated statistically significant results for the co-primary endpoints of NPS and NCS when comparing tezepelumab to placebo treated patients. These results are presented in SmPC section 5.1. Specifically, the mean difference in NPS change from baseline at Week 52 was -2.078 in favour of tezepelumab. Similar results were also obtained with the supplementary estimand analyses (different handling of ICE strategies), supportive analyses (cumulative distribution function curves) and sensitivity analyses (rank ANCOVA, control-based with DRMI, tipping point analysis). Subgroup analyses on a wide range of subgroups also demonstrated similar results, with the exception of the Japan subgroup, however patient numbers were too low to allow robust conclusion in this subgroup (n=17 and n=16 for tezepelumab and placebo groups, respectively). Subgroup analysis on subjects with and without co-morbid asthma/AERD/NSAID-ERD demonstrated similar LS mean differences between treatment groups for NPS (-2.237 and -1.832) in favour of tezepelumab.

The mean difference in NCS change from baseline at Week 52 was -1.039 in favour of tezepelumab. Again, similar results were also obtained with the supplementary estimand analyses, supportive analyses, sensitivity analyses and subgroup analyses, with the exception of the Japan sub-group. Subgroup analysis on subjects with and without co-morbid asthma/AERD/NSAID-ERD demonstrated similar LS mean differences between treatment groups for NCS (-1.152 and -0.865) in favour of tezepelumab.

Overall, the supplementary, supportive, sensitivity and subgroup analyses for both NPS and NCS provide reassurance of the primary estimand for both co-primary endpoints.

The frequency of ICE which occurred during the study was provided on request by the CHMP. A higher proportion of participants in placebo group had NP surgery, SCS/biologics for NP, treatment discontinuation, steroids/biologics for co-morbid conditions compared to the tezepelumab group, this is consistent with the efficacy of tezepelumab. A similar proportion of participants in both treatment groups had nonadherence to background MFNS/INCS, nonadherence to IP, and COVID-related ICEs.

The efficacy results at week 76, reflecting the off-treatment effect, after treatment ended at week 48, demonstrated maintained but diminishing treatment effects.

Secondary and exploratory endpoints

Results for secondary endpoints demonstrated a greater reduction in negative outcomes including loss of smell, SNOT-22 questionnaire scores, LMK scores for sinus opacification evaluated by CT scan, sinus severity scores and a greater reduction in NPSD Total Symptom Score at week 52 when comparing tezepelumab to placebo treated patients. The proportion of patients needing SCS and/or surgery decision for NP up to week 52 was 6% and 31% of tezepelumab and placebo treated patients.

Similarly, a greater increase in positive outcomes including nasal peak inspiratory flow scores and no/low symptom scores in the EQ-5D-5L, PGI-S and PGI-C QoL questionnaires was observed at week 52 when comparing tezepelumab to placebo treated patients. Overall, the secondary endpoints support the positive treatment effects of tezepelumab as demonstrated by the co-primary endpoints in patients with CRSwNP.

In the subgroup of patients with co-morbid asthma/AERD/NSAID-ERD, there was a greater decrease in ACQ-6 asthma questionnaire scores at Week 52 when comparing tezepelumab to placebo treated patients however no difference was observed in pre-BD FEV1 at week 52.

Some patients with comorbid CRSwNP were enrolled as part of the asthma clinical development programme. The MAH has presented data from two asthma studies where patients also had a history of nasal polyps. While a direct comparison is difficult due to the different trial designs and type of patients involved, both trials reported one endpoint in common with the WAYPOINT trial, SNOT-22 scores at week 52. In the NAVIGATOR trial, results demonstrated a substantial reduction in SNOT-22 scores in patients treated with tezepelumab compared to patients treated with placebo (LSMean difference of -10.58) adding additional support to the proposed extension of indication in CRSwNP. In the other trial, DIRECTION, results demonstrated only minimal effects when comparing tezepelumab to placebo treated patients.

2.5.4. Conclusions on the clinical efficacy

Overall, the clinical efficacy results support the use of tezepelumab in CRSwNP patients.

The proposed posology of 210mg dose, administered every 4 weeks, is accepted and in line with the currently approved posology for tezepelumab in asthma.

2.6. Clinical safety

Introduction

To support this extension of indication in adults with CRSwNP, the MAH has presented safety data from the WAYPOINT single pivotal phase III study.

Safety assessments in WAYPOINT included review of AEs (including SAEs, discontinuations of investigational product due to adverse events (DAEs), and AESIs), clinical laboratory tests, ECGs, vital signs measurements, and physical examinations.

Safety analyses were performed using the safety set, which included all participants who received at least one dose of IP.

'On-treatment period' includes adverse events with onset date on or after the date of the first dose of IP up and including minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal).

'On-study period' includes adverse events with onset date on or after the date of the first dose of IP up and including date of study completion or date of study withdrawal.

Patient exposure

A total of 408 participants were included in the Safety Set, with 203 being in the treatment group and 205 being in the placebo group. One randomised patient from each treatment group was excluded from the safety set as they did not receive any dose of IP.

As the Safety and FAS sets are identical, the baseline characteristics of the FAS population are presented in section 2.5 'Clinical efficacy'.

Duration of Exposure

The mean duration of exposure to IP was longer in the tezepelumab group (mean 367.7 days [range: 97 to 554]) compared with the placebo group (mean 313.4 days [range: 34 to 433]). The lower duration of exposure in the placebo group reflects the lower number of participants completing treatment compared with the tezepelumab group.

Adverse events

The overall incidences of AEs, SAEs, and DAEs, respectively, were generally similar in the tezepelumab and placebo treatment groups. There were no AEs of fatal outcome in the tezepelumab group in this study; one AE with fatal outcome occurred in the placebo group during the on-study period.

Table 15. Overall Summary of Adverse Events - On-study (Safety Set)

	Teze 210 mg Q4W N = 203			Placebo N = 205			
AE Category	**n (%)**	**Exposure years**	**EAIR (Per 100 PY)**	**n (%)**	**Exposure years**	**EAIR (Per 100 PY)**	**EAIR difference to Placebo (95% CI)**
Any AE	166 (81.8)	99.3	167.2	165 (80.5)	88.4	186.6	-19.3 (-58.1, 18.7)
Any SAE (including events with outcome = death)	11 (5.4)	263.7	4.2	14 (6.8)	236.4	5.9	-1.8 (-6.2, 2.3)
Any AE with outcome of death	0	270.8	0	1 (0.5)	247.6	0.4	-0.4 (-2.3, 1.0)
Any AE leading to discontinuation of IP (DAE)	1 (0.5)	270.4	0.4	4 (2.0)	245.8	1.6	-1.3 (-3.9, 0.6)

EAIR per 100 PY (Person years) for each treatment is calculated as the number of subjects in that treatment group reporting the AE divided by the total time at risk in that treatment group, where time at risk is the time to the first event for a subject who experienced the event during the analysis period and time during the analysis period for a subject who didn't experience the event, multiplied by 100.
The EAIR difference is based on the Miettinen and Nurminen method comparing the difference in EAIR per 100 person years between treatment groups.
An EAIR difference below zero favours active treatment.
On-study: The table includes adverse events with onset date on or after the date of the first dose of IP up and including date of study completion or date of study withdrawal.
Subjects with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.
CI Confidence interval; EAIR Exposure-adjusted incidence rate, on a scale of 100 person-years; IP Investigational product; n Number of subjects per category; N Number of subjects per treatment group; Q4W Every 4 weeks; Teze Tezepelumab.

Common Adverse Events by System Organ Class and Preferred Term

Common Adverse Events by SOC

During the on-study period, the most commonly reported AEs by SOC in the tezepelumab group were Infections and infestations SOC (65.0%), Respiratory, thoracic and mediastinal disorders SOC (23.2%), and Musculoskeletal and connective tissue disorders SOC (17.2%), with corresponding EAIR of 88.3, 20.3, and 14.5 per 100 participant-years, respectively. For participants in the placebo group, AEs were most commonly reported in Infections and infestations SOC (57.1%), Respiratory, thoracic and mediastinal disorders SOC (38.5%), and Nervous system disorders SOC (13.7%), with corresponding exposure-adjusted incidence of 79.7, 42.2, and 12.5 per 100 participant-years, respectively.

AEs in the Respiratory, thoracic and mediastinal disorders SOC were reported with a lower exposure-adjusted incidence in the tezepelumab group than in the placebo group (EAIR of 20.3 versus 42.2 per 100 participant-years [23.2% and 38.5% of participants], respectively). This difference was mostly due to AEs with the PT chronic rhinosinusitis with nasal polyps and PT asthma that were reported more frequently in participants who received placebo. No other clinically relevant imbalances in the incidence of AEs by SOC were observed.

Common Adverse events by PT

During the on-study period, the 4 most commonly reported AEs in the tezepelumab group were COVID-19 (27.1%), nasopharyngitis (22.2%), upper respiratory tract infection (11.3%), and headache (9.4%). In the placebo group, the most commonly reported AEs were chronic rhinosinusitis with nasal polyps (27.3%), COVID-19 (21.5%), nasopharyngitis (11.2%), and headache (7.8%).

Incidences of the most common AEs in the on-study period were generally similar across both treatment groups, except for events of chronic rhinosinusitis with nasal polyps and asthma, which were reported with lower incidence in the tezepelumab group compared with the placebo group, and events of pharyngitis (a known ADR for tezepelumab) which were reported with a higher incidence in the tezepelumab group (5.4 %) compared with the placebo group (0.5%).

Adverse Events by Intensity

Most of the AEs reported on treatment by participants in both the tezepelumab and placebo groups, respectively, had a maximum intensity of mild or moderate.

Severe AEs were reported in 17 (8.4%) participants in the tezepelumab group and 18 (8.8%) participants in the placebo group based on data available at the final DBL. The most frequently reported severe AE PT in the tezepelumab group was COVID-19 (2 [1.0%] participants), and the most frequently reported severe AE PT in the placebo group was chronic rhinosinusitis with nasal polyps (6 [2.9%] participants). It is also noted that the incidences of moderate and severe events of PT asthma were both lower in the tezepelumab group compared with placebo.

Adverse Events by Causality

The majority of AEs in the tezepelumab and placebo treatment groups reported during the on-study period were not considered causally related to IP by the Investigator. AEs considered related to IP, as judged by the Investigator, were reported on treatment by 28 (13.8%) participants in the tezepelumab group and 21 (10.2%) in the placebo group.

There were no AE PTs considered related to IP by the Investigator with > 3% incidence in the tezepelumab group. The most frequently reported AE PTs considered related to IP by the Investigator in the tezepelumab group were headache, and injection site pain, reported in 6 (3.0%) and 6 (3.0%) participants, respectively; corresponding incidences in the placebo group were 4 (2.0%), and 3 (1.5%) participants, respectively.

Small numerical differences were observed between the treatment groups for the most common AEs considered causally related by the Investigator in the on-study period, but no specific trends or pattern could be identified.

Serious adverse events/deaths/other significant events

Serious Adverse Events

The overall incidence of SAEs during the on-study period was similar between the tezepelumab (5.4%) and placebo (6.8%) groups. For participants in the tezepelumab group, SAEs were most commonly reported in the Infections and infestations SOC (3.0%). No SAE PT was reported in more than one tezepelumab-treated participant.

There were no clinically relevant imbalances between the tezepelumab and placebo groups in SAEs at the SOC or at the PT level.

In the tezepelumab group, one of the SAEs (PT pulmonary tuberculosis) was considered by the Investigator to be causally related to IP. In the placebo group, 3 SAEs (PT atrial fibrillation, PT myopericarditis, and PT anaphylactic shock) were considered by the Investigator to be causally related to treatment. There was one SAE (PT squamous cell carcinoma of the skin) that was reported for a participant in the placebo group. This malignancy occurred on treatment but was reported to the Investigator after the DCO for the primary DBL; the event resolved on treatment and was not considered by the Investigator to be causally related to IP.

Deaths

There were no AEs of fatal outcome in the tezepelumab group in this study.

One AE (PT: bacterial sepsis) with fatal outcome occurred in the placebo group during the on-treatment period but was considered to be unrelated to the IP by the investigator.

Adverse Events of Special Interest

Serious Infections

The incidence of serious infections in the on-treatment period was similar between the tezepelumab and placebo groups. No apparent trends in serious infections were noted. One event (0.5%) of serious infection (PT: pulmonary tuberculosis) occurring in the tezepelumab group on treatment was considered causally related to IP by the Investigator.

The incidence of serious infections in the on-study period was similar to the on-treatment period with events reported for 6 (3.0%) in the tezepelumab group, and 4 (2.0%) in the placebo group. A single additional event of serious infection, PT arthritis bacterial (1 [0.5%]), was reported in the tezepelumab group in the on-study period; this event was not considered causally related to IP by the Investigator.

Serious Cardiac Events

The incidence of serious cardiac events in the on-treatment period was similar between the tezepelumab and placebo groups. No apparent trends in serious cardiac events were noted. Two of the serious cardiac events were considered causally related to IP by the Investigator; both events (PT atrial fibrillation, PT myopericarditis) were reported in the placebo group.

In accordance with the protocol, some AEs were referred to the IAC for adjudication. The number of events submitted for adjudication on treatment was low in both treatment groups.

A total of 2 (1.0%) participants in the tezepelumab group and 3 (1.5%) in the placebo group had any AE sent for serious cardiac event adjudication. The IAC agreed with the Investigator-reported verbatim term for the events in the tezepelumab group.

Malignancy

Malignancies AESIs occurred in 1.0% of participants in the tezepelumab group and 0.5% of participants in the placebo group.

There were 2 events of malignancy in the tezepelumab group (PT invasive lobular breast carcinoma, and PT malignant melanoma) in the on-treatment period and one event (PT squamous cell carcinoma of the skin) in the placebo group. Neither of the events of malignancies were considered causally related to IP by the Investigator. No additional malignancies were reported in the on-study period.

Serious Hypersensitivity Reactions

There were no events of serious hypersensitivity in the tezepelumab group and 2 events in the placebo group (one event was considered causally related to IP by the investigator, the other was not considered causally related to IP by the investigator).

Helminth Infection

There were no confirmed events of helminth infection reported in this study.

Guillain-Barré Syndrome

There were no events of Guillain-Barré Syndrome reported in this study.

Adjudicated Events

An IAC provided an external independent assessment of blinded data to confirm the diagnosis and causality to IP of serious cardiac events, MACE (defined in the IAC charter), and deaths, as well as the diagnosis of malignancies that occurred from randomisation until the end of the follow-up period of this study.

The number of events submitted for adjudication on treatment was low in both treatment groups:

- A total of 2 (1.0%) participants in the tezepelumab group and 3 (1.5%) in the placebo group had any AE sent for serious cardiac event adjudication. The IAC agreed with the Investigator reported verbatim term for the events in the tezepelumab group.
- A total of 2 (1.0%) participants in the tezepelumab group and none in the placebo group had any AE sent for MACE adjudication. For both participants in the tezepelumab group the events were adjudicated as MACE.
- A total of 2 (1.0%) participants in the tezepelumab group and one (0.5%) in the placebo group had any AE sent for malignancy adjudication; all events were adjudicated as non-fatal new malignancies.
- In the placebo group, the death was confirmed as a non-cardiovascular death. There were no deaths in the tezepelumab group.
- For those events for which the IAC was meant to provide a causality assessment (all except malignancy), the IAC did not consider any adjudicated events as causally related to IP.

No additional events were submitted for adjudication in the on-study period.

Safety in Subgroups by Age, Gender, Race, BMI, and Geographical Region

The AE profile of tezepelumab during the on-treatment period was generally similar across subgroups by age group (≥ 18 to < 65, and ≥ 65 years), by gender (Male, Female), by race (White, Non-White), by BMI (< 25.0, ≥ 25 to < 30, ≥ 30 kg/m^2), and by geographical region (Asia Pacific including China and Japan, Europe, North America).

Laboratory findings

No new safety concerns regarding clinical laboratory evaluations were identified for tezepelumab in this study.

During the on-study period, there were no clinically meaningful trends in laboratory parameters, except for the recognised PD effect of tezepelumab treatment on lowering blood eosinophil counts.

There were no clinically significant differences or trends in AEs related to laboratory parameters between the tezepelumab and placebo treatment groups.

No new safety concerns regarding vital signs, ECGs, physical findings, or other observations related to safety were identified for tezepelumab in this study. During the on-study period, there were no clinically meaningful trends in vital signs or ECGs over time and no notable differences were observed between the treatment groups.

Safety in special populations

No additional information on the safety of tezepelumab in special populations has been generated as part of this development in CRSwNP. The current position that no dose adjustment is required in special populations for tolerability reasons, remains valid.

Discontinuation due to adverse events

The overall incidence of DAEs on treatment was low and similar between the tezepelumab (0.5%) and placebo (1.5%) groups. There was no pattern in the DAEs reported.

Immunogenicity

The ADA prevalence (testing positive for ADA at any time) and the ADA incidence (testing positive for TE-ADA) were low in the tezepelumab group (5.7% and 3.7%, respectively). The ADA prevalence and ADA incidence were 11.1% and 7.4%, respectively, in the placebo group. Confirmed ADA-positive participants were tested for the prevalence and incidence of nAb, which were both low for both treatment groups (1.1% and 0.6% for tezepelumab and 1.2% and 1.2% for placebo group).

The number of participants with TE-ADA was too low to formally assess the potential impact of ADA on safety. Tezepelumab serum concentrations at different timepoints in TE-ADA-positive participants in the tezepelumab group were generally within the range of those in ADA-negative participants.

Post marketing experience

There is no post-marketing experience with the use of tezepelumab in patients with CRSwNP.

Tezepelumab is approved as an add-on maintenance treatment for severe asthma.

Based on evaluation of post-marketing data since first approval, the event of anaphylaxis was added to the list of ADRs for tezepelumab. No other significant actions relating to safety were taken and no new safety concerns or ADRs have been identified during subsequent reporting periods.

2.6.1. Discussion on clinical safety

Tezepelumab is currently authorised as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

The MAH has performed a single phase III, randomised, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of tezepelumab in participants with CRSwNP.

A total of 408 participants were included in the Safety set, with 203 being in the treatment group and 205 being in the placebo group.

Overall, the rate of AEs was similar across both groups. During the study period, the most commonly reported AEs by SOC in the tezepelumab group were Infections and infestations SOC (65.0%), Respiratory, thoracic and mediastinal disorders SOC (23.2%), and Musculoskeletal and connective tissue disorders SOC (17.2%), with corresponding EAIR of 88.3, 20.3, and 14.5 per 100 participant-years, respectively. For participants in the placebo group, AEs were most commonly reported in Infections and infestations SOC (57.1%), Respiratory, thoracic and mediastinal disorders SOC (38.5%), and Nervous system disorders SOC (13.7%%), with corresponding exposure-adjusted incidence of 79.7, 42.2, and 12.5 per 100 participant-years, respectively.

During the on-study period, the 4 most commonly reported AEs in the tezepelumab group were COVID-19 (27.1%), nasopharyngitis (22.2%), upper respiratory tract infection (11.3%), and headache (9.4%). In the placebo group, the most commonly reported AEs were chronic rhinosinusitis with nasal polyps (27.3%), COVID-19 (21.5%), nasopharyngitis (11.2%), and headache (7.8%).

The frequencies of different types of infections, including COVID-19, nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, influenza and pharyngitis were numerically higher in the tezepelumab group as compared to the placebo group. These differences persisted when adjusted for the difference in exposure between treatment and placebo groups. It is noted that pharyngitis is already listed as an ADR in SmPC section 4.8 with frequency 'common'. Given the mechanism of action of the product (blockade of thymic stromal lymphopoietin (TSLP), these and other types of infections could also be related to tezepelumab.

The MAH clarified that there was a numerical imbalance in the overall incidence of AEs in the Infections and infestations SOC in the tezepelumab group compared with placebo in the on-treatment period (61.1% versus 51.7% [EAIRs 98.2 versus 92.1 per 100 participant years, respectively]), although the EAIR difference was small with broad 95% CI (EAIR difference 6.1, 95% CI -18.8 to 30.9). However, nasopharyngitis and URTIs are the main AEs driving the difference between the treatment groups. In a pooled analysis of AE data from 8 completed Phase II and III clinical studies of 210 mg tezepelumab administered SC Q4W in patients with severe asthma, the incidence rate for subjects with SAEs within the Infections and infestations SOC was comparable between tezepelumab 210 mg and placebo groups, with incidence rates of 2.21 per 100 subject-years (N = 1114; 31 [2.8%] of subjects) and 2.31 per 100 subject-years (N = 837; 23 [2.7%] of subjects), respectively. Of note, serious infections are listed as important potential risks in the RMP.

In the SmPC for tezepelumab, pharyngitis, rash, arthralgia and injection site reaction are listed as ADRs with the frequency 'common' whereas hypersensitivity is listed as ADR with frequency 'not known'.

In the WAYPOINT study, pharyngitis occurred in the treatment and placebo arms at rates of 5.4% and 0.5% respectively, arthralgia at rates of 3.9% and 1.5% respectively, and injection site pain at rates of 3.4% and 1.5% respectively. Rash was not reported at significant rates in the study. The rates of these AEs are similar to those seen in patients with asthma.

It was noted that the incidence of asthma AEs was lower in the treatment group than in the placebo group, and this difference is plausible given the mechanism of action of the product and its authorisation for use in that condition.

Upon CHMP's request, the MAH conducted an in-depth review of data from the WAYPOINT study to assess the cases of epistaxis that occurred in the study. The MAH stated that, although there was a slightly higher reported incidence of epistaxis in the tezepelumab group (5.9%; n=12) compared to placebo (3.4%; n=7) in the on-treatment period, the overall number of epistaxis events was low, none were serious, and all were of mild intensity. An examination of subject characteristics, concomitant medications, and time to onset revealed no clear trends or confounding factors that would suggest any causal relationship. The individual cases of epistaxis, including the one deemed "possibly related," were mild and resolved without significant intervention. In addition, the exposure-adjusted incidence rate difference was small. The MAH concluded that, based on the available data, there is insufficient evidence to include epistaxis in Section 4.8 of the SmPC, and this can be supported. Routine safety surveillance to continue to monitor epistaxis will be carried out by the MAH, which too is supported.

The AE of back pain had a higher incidence in the treatment group than in the placebo group. To assess the relationship between the IP and back pain, the MAH reviewed the data from the WAYPOINT study, as well as data from the asthma development. In the WAYPOINT study, a numerical imbalance in events was reported in the tezepelumab group (10 [4.9%]) compared with placebo (5 [2.4%]) in the on-treatment period; however, no events were considered serious, and none were considered by the Investigator to be possibly related to the IMP. In addition, the MAH reviewed data from PSURs from December 2022 to June 2024. These reports included information from 8 phase II and phase III clinical trials. Cumulatively, 1114 participants received tezepelumab while 837 participants received placebo. Back pain events were found to be similar between the active treatment and placebo arms, with 3.42 per 100 subject-years in the tezepelumab group (48 [4.3%] subjects) and 3.41 per 100 subject-years in the placebo group (34 [4.1%] subjects). In addition, no back pain events were reported as serious, and neither the investigators nor the MAH considered any back pain events to be causally related to tezepelumab. A review of post-marketing data for that period did not support a causal relationship to the drug. Overall, the conclusion of the MAH that back pain should not be added to section 4.8 of the SmPC is supported.

Adverse Events by Intensity

Most of the AEs reported on treatment by participants in both the tezepelumab and placebo groups, respectively, had a maximum intensity of mild or moderate.

Severe AEs were reported in 17 (8.4%) participants in the tezepelumab group and 18 (8.8%) participants in the placebo group during the on-study period. The most frequently reported severe AE PT in the tezepelumab group was COVID-19 (2 [1.0%] participants), and the most frequently reported severe AE PT in the placebo group was CRSwNP (6 [2.9%] participants). It is also noted that the incidences of moderate and severe events of PT asthma were both lower in the tezepelumab group compared with placebo.

Adverse Events by Causality

The majority of AEs in the tezepelumab and placebo treatment groups reported during the on-treatment period were not considered causally related to IP by the Investigator. AEs considered related

to IP, as judged by the Investigator, were reported on treatment by 28 (13.8%) participants in the tezepelumab group and 21 (10.2%) in the placebo group.

There were no AE PTs considered related to IP by the Investigator with > 3% incidence in the tezepelumab group. The most frequently reported AE PTs considered related to IP by the Investigator in the tezepelumab group were headache, and injection site pain, reported in 6 (3.0%) and 6 (3.0%) participants, respectively; corresponding incidences in the placebo group were 4 (2.0%), and 3 (1.5%) participants, respectively.

Small numerical differences were observed between the treatment groups for the most common AEs considered causally related by the Investigator in the on-treatment period, but no specific trends or patterns could be identified.

That said, it is noted that there was a case of pulmonary tuberculosis in the treatment arm. The MAH has stated that there is no evidence to suggest that the IP was causal in this regard.

The MAH further provided data from the asthma development programme in which a patient was diagnosed with tuberculosis, but this was considered non-related by the investigator in that clinical trial.

Data from post-marketing surveillance totalling 73400 patient years has shown that 2 cases of tuberculosis have been gathered in that period up to November 2024. This also is supportive of the MAH's position that tezepelumab is not causally associated with the development of tuberculosis.

Tuberculosis is a serious infection and as serious infections are a known risk that is associated with the use of tezepelumab the MAH is committed to maintaining this under close surveillance.

Serious adverse event/deaths/other significant events

The overall number of SAEs reported in both treatment and placebo groups in the WAYPOINT study was small and similar between groups (5.4% vs 6.8% in the treatment arm and placebo arm respectively) suggesting that treatment with tezepelumab was generally well tolerated with respect to this aspect. There were no clinically relevant imbalances between the tezepelumab and placebo groups in SAEs at the SOC or at the PT level.

There was one death in the clinical trial; this occurred in the placebo group during the on-treatment period and was considered to be unrelated to the IP by the investigator.

Adverse Events of Special Interest

The incidence of the AESI of serious infections in the on-treatment period was similar between the tezepelumab and placebo groups. One event (0.5%) of serious infection (PT: pulmonary tuberculosis) occurring in the tezepelumab group on treatment was considered causally related to IP by the Investigator.

The incidence of the AESI of serious cardiac events in the on-treatment period was similar between the tezepelumab and placebo groups.

Two of the serious cardiac events were considered causally related to IP by the Investigator; both events (PT atrial fibrillation, PT myopericarditis) were reported in the placebo group.

The incidence of the AESI of malignancy in the on-treatment period was similar between the tezepelumab and placebo groups. A total of 2 (1.0%) participants in the tezepelumab group and one (0.5%) in the placebo group had any AE sent for malignancy adjudication; none of these events were adjudicated as non-fatal new malignancies.

An independent adjudication committee (IAC) did not consider any adjudicated events as causally related to IP.

Both malignancy and acute cardiac events are listed as important safety concerns in the RMP. While data currently available do not raise immediate concerns in this regard, the MAH should continue to monitor these events as previously requested and in line with the current RMP.

There were no events of serious hypersensitivity in the tezepelumab group and 2 events in the placebo group.

There were no confirmed events of helminth infection or Guillain-Barré Syndrome reported in this study.

The AE profile of tezepelumab during the on-treatment period was generally similar across subgroups by age group (≥ 18 to < 65, and ≥ 65 years), by gender (Male, Female), by race (White, Non-White), by BMI (< 25.0, ≥ 25 to < 30, ≥ 30 kg/m2), and by geographical region (Asia Pacific including China and Japan, Europe, North America).

Laboratory findings

No significant safety concerns related to laboratory values, physical examinations, or other observations were seen in this trial.

Discontinuation due to adverse events

The overall incidence of DAEs on study was low and similar between the tezepelumab (0.5%) and placebo (1.5%) groups based on data available at the final DBL. There was no pattern in the DAEs reported.

No firm conclusions can be drawn from the pattern of discontinuation that was observed in the WAYPOINT trial due to the small number of instances that occurred in the trial. Adverse events that led to discontinuation of the medicine should continue to be monitored and reported in accordance with existing pharmacovigilance requirements.

Immunogenicity

Overall, the immunogenicity of tezepelumab that was observed in the WAYPOINT clinical trial was low and similar to that previously seen in patients with asthma.

Pooled analyses

To further clarify the safety characteristics of tezepelumab in patients who have comorbid asthma and CRSwNP, the MAH assessed pooled data from several placebo-controlled asthma studies, which included subjects with medical history of nasal polyps.

The MAH's assertion that the safety profile of tezepelumab in the patients with comorbid asthma and CRSwNP was generally similar to the established safety profile of tezepelumab, and that no new safety concerns regarding AEs in this subgroup are evident is supported.

Overall, the safety profile of tezepelumab in patients with CRSwNP as observed in the WAYPOINT study is reassuring.

2.6.2. Conclusions on clinical safety

The overall conclusion of the safety assessment is that tezepelumab was well tolerated in patients receiving treatment for CRSwNP, with a safety profile consistent with that previously observed in asthma.

2.6.3. PSUR cycle

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

2.7. Risk management plan

The MAH submitted an updated RMP version 6.2 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

The CHMP endorsed this advice without changes.

Safety concerns

Important identified risks	None
Important potential risks	Serious infections Serious cardiac events Malignancy
Missing information	Use in pregnant and breastfeeding women

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Not applicable				
Category 2 – Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Study D5180R00010: Database study of the use (and safety) of tezepelumab in women with severe asthma during pregnancy. Ongoing	To evaluate the risk of adverse pregnancy, foetal, and infant outcomes in pregnant women with severe, uncontrolled asthma taking tezepelumab compared with a suitably matched unexposed population using real-world data.	Use in pregnancy	Study Protocol submission	17Mar2023
			Interim Report 1	31Mar2028
			Interim Report 2	31Mar2031
			Final Study Report submission	March 2034
Study D5180C00024 (SUNRISE): Phase III study to evaluate the	To demonstrate the ability of tezepelumab, compared with placebo, to reduce OCS use in adults with severe	Serious infections, serious cardiac events, malignancy	Study Protocol	07Feb2022

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
efficacy and safety of tezepelumab in reducing OCS use in adults with OCS-dependent asthma Ongoing	asthma being treated with maintenance OCS in combination with high dose ICS and LABA with or without other asthma controller therapies, while maintaining asthma control.		Final Study Report (abbreviated)	Q1 2026
Study D5180R00024: Serious cardiac events post-authorisation safety study. Ongoing	To compare the incidence of serious cardiac events between patients with severe, uncontrolled asthma who are newly exposed to tezepelumab and suitably matched patients who are unexposed to tezepelumab.	Serious cardiac events	Study Protocol submission	19Sep2023
			Interim Report 1	30Apr2026
			Interim Report 2	30Apr2028
			Final Study Report submission	31May 2030

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None	Not applicable	Not applicable
Important potential risks		
Serious infections	Routine risk minimisation measures: SmPC Section 4.4 and Package Leaflet Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Post-marketing targeted ADR follow-up questionnaires Additional pharmacovigilance activities: Study D5180C00024 - 28-week OCS-reduction study in severe asthma
Serious cardiac events	Routine risk minimisation measures: SmPC Section 4.4 and Package Leaflet Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Post-marketing targeted ADR follow-up questionnaires Additional pharmacovigilance activities: Study D5180C00024 - 28-week OCS-reduction study in severe asthma Study D5180R00024 - Serious cardiac events post authorisation safety study

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Malignancy	Routine risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Post-marketing targeted ADR follow-up questionnaires Additional pharmacovigilance activities: Study D5180C00024 - 28-week OCS-reduction study in severe asthma
Missing information		
Use in pregnancy and breastfeeding	Routine risk minimisation measures: SmPC Section 4.6 and Package Leaflet Section 2	Additional pharmacovigilance activity: Study D5180R00010 (PASS) - Database study of the use (and safety) of tezepelumab in women with severe asthma during pregnancy

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Changes were also made to the PI to bring it in line with the latest EMA excipients guideline which were reviewed and accepted by the CHMP.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: there have not been revisions that significantly affect the overall readability and design of the package leaflet.

Therefore, it is justified to consider the Package Leaflet User Testing report provided during the review of the initial MAA procedure as relevant for this application, and that no new testing is considered needed for this submission.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

CRSwNP is characterised by inflammation of the nasal mucosa and paranasal sinuses with inflammatory hyperplastic growths that protrude into the nasal passages (i.e., nasal polyps). Patients with CRSwNP often experience significant nasal obstruction and congestion, nasal discharge, facial pain or pressure, and impaired sense of smell, symptoms that can have a profound impact on quality of life and function.

CRSwNP affects up to 4% of the general population and is more common in males than females. The prevalence of CRSwNP increases with age, with age of onset typically from 40 to 60 years. In patients

with CRSwNP, asthma is a common inflammatory co-morbidity, affecting 40% to 67% of patients with CRSwNP, with severe asthma being most common (57% to 62%). Conversely, approximately 41% of patients with severe asthma have nasal polyps, indicative of the high co-morbid rates between CRSwNP and asthma.

3.1.2. Available therapies and unmet medical need

Standard-of-care options for CRSwNP include INCS and SCS, long-term antibiotics, and nasal polyp removal surgery (also referred to as sinonasal surgery). Treatment of CRSwNP involves a stepwise approach, progressing from INCS to SCS and eventually surgical procedures. These treatments may provide symptomatic relief but do not address the underlying inflammatory processes, leading to frequent recurrence, and the treatments are associated with side effects.

In addition, biologic treatments are available as add-on therapy for CRSwNP with insufficient symptom control from treatments described above. However, some patients do not respond to these treatments due to persistent tissue fibrosis and non-type 2-mediated disease. As a result, many patients still rely on SCS treatment despite the associated drawbacks.

3.1.3. Main clinical studies

The CRSwNP clinical development programme consists of a single global, multicentre, Phase III, double-blind, randomised study to evaluate the efficacy and safety of tezepelumab 210 mg Q4W SC compared with placebo for treatment of patients with CRSwNP (WAYPOINT).

3.2. Favourable effects

Results demonstrated statistically significant results ($p < .0001$) for the co-primary endpoints of nasal polyp(osis) score (NPS) and nasal Congestion Score (NCS) when comparing tezepelumab to placebo treated patients with CRSwNP. Specifically, the mean difference in NPS and NCS change from baseline at Week 52 was -2.078 (95% CI -2.399, -1.757) and -1.039 (95% CI -1.214, -0.865) in favour of tezepelumab. Improvements were seen as early as week 4. Similar results were also obtained with supplementary estimand, supportive, sensitivity and most subgroup analyses including in patients with and without co-morbid asthma, providing reassurance of the primary estimand for both co-primary endpoints. The off-treatment effect demonstrated maintained but diminishing treatment effects.

The secondary endpoints also support the positive treatment effects of tezepelumab demonstrated by the co-primary endpoints in patients with CRSwNP. Specifically, results demonstrated a mean change from baseline at week 52 of -1.005 (-1.177, -0.834) in loss of smell, -27.441 (-32.512, -22.370) in SNOT-22 scores, -5.700 (-6.371, -5.030) in Lund Mackay scores (LMK), -6.959 (-8.085, -5.833) in Total Symptom Score (TSS) and a 92% reduction, HR 0.08 [95% CI: 0.03 to 0.16] for the time to first sino-nasal surgery decision and/or SCS for NP.

3.3. Uncertainties and limitations about favourable effects

There are no remaining uncertainties and limitations about favourable effects.

3.4. Unfavourable effects

During the on-treatment period, the most commonly reported AEs by SOC in the tezepelumab group were Infections and infestations SOC (65.0%), Respiratory, thoracic and mediastinal disorders SOC (23.2%), and Musculoskeletal and connective tissue disorders SOC (17.2%), with corresponding EAIR of 88.3, 20.3, and 14.5 per 100 participant-years, respectively. For participants in the placebo group, AEs were most commonly reported in Infections and infestations SOC (57.1%), Respiratory, thoracic and mediastinal disorders SOC (38.5%), and Nervous system disorders SOC (13.7%), with corresponding exposure-adjusted incidence of 79.7, 42.2, and 12.5 per 100 participant-years, respectively.

During the on-treatment period, the 4 most commonly reported AEs in the tezepelumab group were COVID-19, nasopharyngitis, upper respiratory tract infection, and headache. In the placebo group, the most commonly reported AEs were chronic rhinosinusitis with nasal polyps, COVID-19, nasopharyngitis, and headache. The rate of adverse events was similar between the treatment and placebo groups, with any difference being clinically insignificant.

3.5. Uncertainties and limitations about unfavourable effects

There are no remaining uncertainties and limitations about favourable effects.

3.6. Effects Table

Table 16. Effects Table for Tezspire for Chronic Rhinosinusitis with Nasal Polyps:

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Nasal polyps	Change from baseline in NPS score	NPS score, range 0-8	-2.46	-0.38	p <.0001	Phase 3 clinical trial WAYPOINT
Nasal congestion	Change from baseline in NCS score	NCS score, range 0-3	-1.74	-0.7	p <.0001	
Loss of smell	Change from baseline in DSS (difficulty with sense of smell)	DSS score, range 0-3	-1.26	-0.26	p <.0001	
HRQoL symptom	Change from baseline in SNOT-22	SNOT-22 score, range 0-110	-45.02	-17.58	p <.0001	
LMK score	Change from baseline in LMK	LMK score, range 0-24	-6.27	-0.57	p <.0001	
Reduction in need of SCS/surgery	Proportion of patients needing SCS/surgery decision for NP up to week 52	% of patients	5.7	31.4	p <.0001	
Unfavourable Effects						
Any AE (on-study)		N (%)	166 (81.8%)	165 (80.5%)		Phase 3 clinical trial WAYPOINT
Pharyngitis		N (%)	11 (5.4%)	1 (0.5%)		Phase 3 clinical trial WAYPOINT
Arthralgia		N (%)	8 (3.9)	3 (1.5)		Phase 3 clinical trial WAYPOINT
Injection site pain		N (%)	7 (3.4)	3 (1.5)		Phase 3 clinical trial WAYPOINT
Asthma		N (%)	1 (0.5%)	14		Phase 3

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
				(6.8%)		clinical trial WAYPOINT

Abbreviations: NPS - Nasal polyp(osis) score, NCS - Nasal Congestion Score, DSS - Difficulty with sense of smell, HRQoL Health related quality of life, SNOT-22 - SinoNasal Outcome Test, 22 item, LMK - Lund-Mackay (score), SCS - Systemic corticosteroids, NP - Nasal polyp(s)

Notes: N/A

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, the efficacy results are positive, all primary endpoints were met, demonstrated statistical significance and were supported by positive results on several key secondary endpoints. The observed improvements on the co-primary NPS and NCS endpoints are considered clinically relevant.

Overall, the observed safety profile in the studied CRSwNP population was comparable with that in the asthma population. The rate of AEs was similar across both groups. There was a significant increase in the incidence of pharyngitis in the tezepelumab group, while there was a significant reduction in the incidence of asthma in this group. This latter finding is in keeping with the mechanism of action of tezepelumab and so is not unexpected.

3.7.2. Balance of benefits and risks

The efficacy data presented by the MAH show clinically relevant effects and therefore supports the extension of indication to CRSwNP in adult patients.

The overall safety profile observed in patients with CRSwNP is generally consistent with that observed in the approved asthma population.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Tezspire is positive in the following indication: 'Tezspire 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. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIB and A

Extension of indication to include treatment of Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) for Tezspire, based on results from study WAYPOINT (D5242C00001); this is a global, multicentre, randomised, double-blind, parallel-group, placebo-controlled study that evaluated the efficacy and safety of tezepelumab compared with placebo in the treatment of CRSwNP. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. In addition, the Marketing authorisation holder took the opportunity to implement editorial changes and to update the PI and the Package Leaflet in accordance with the latest EMA excipients guideline. Version 6.2 of the RMP is agreed.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the RMP are recommended.

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

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

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Tezspire-H-C-5588-II- EMAVR0000245013'

Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 18 September 2025.