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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

TEZSPIRE

International non-proprietary name:	tezepelumab
Pharmaceutical form:	solution for injection in a pre-filled syringe
Dosage strength(s):	210 mg
Route(s) of administration:	subcutaneous use
Marketing authorisation holder:	AstraZeneca AG
Marketing authorisation no.:	68454
Decision and decision date:	extension of therapeutic indication approved on 20 November 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, definitions, abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
ADR	Adverse drug reaction
AE	Adverse event
AERD	Aspirin-exacerbated respiratory disease
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BD	Bronchodilator
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
COVID-19	Coronavirus disease 2019
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyps
CRSwNP	Chronic rhinosinusitis with nasal polyps
CT	Computed tomography
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
FESS	Functional endoscopic sinus surgery
FEV1	Forced expiratory volume in 1 second
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INCS	Intranasal corticosteroids
INN	International non-proprietary name
IP	Investigational product
ITT	Intention-to-treat
LoQ	List of Questions
LS	Least squares
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NC	Nasal congestion
NCS	Nasal congestion score
NP	Nasal polyp(s)
NPS	Nasal polyp(osis) score
NPSD	Nasal Polyposis Symptom Diary
NO(A)EL	No observed (adverse) effect level
NSAID-ERD	Nonsteroidal anti-inflammatory drug-exacerbated respiratory disease
PBPK	Physiology-based pharmacokinetics

PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
PT	Preferred term
Q4W	Every 4 weeks
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous
SCS	Systemic corticosteroids
SNOT-22	Sino-Nasal Outcome Test, 22 items
SwissPAR	Swiss Public Assessment Report
TBC	Tuberculosis
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved indication in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Chronic rhinosinusitis with nasal polyps (CRSwNP)
TEZSPIRE is indicated as an add-on to maintenance treatment in adult patients with CRSwNP.

2.2.2 Approved indication

Chronic rhinosinusitis with nasal polyps (CRSwNP)
TEZSPIRE is indicated as an add-on therapy with intranasal corticosteroids in adults with severe CRSwNP that cannot be adequately controlled with systemic corticosteroids and/or surgical intervention.

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended dose is 210 mg of TEZSPIRE by subcutaneous injection every 4 weeks.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	4 February 2025
Formal control completed	28 February 2025
List of Questions (LoQ)	3 June 2025
Response to LoQ	18 July 2025
Preliminary decision	12 September 2025
Response to preliminary decision	13 October 2025
Final decision	20 November 2025
Decision	approval

3 Medical context

Chronic rhinosinusitis (CRS) is defined as a complex inflammatory condition involving the paranasal sinuses and linings of the nasal passages that lasts 12 weeks or longer. CRS is divided into CRS with nasal polyps (CRSwNP) and CRS without NP (CRSsNP), which are distinguished by the presence or absence of nasal polyps. Symptoms associated with CRSwNP include loss of the sense of smell (anosmia), nasal obstruction or blockage, anterior or posterior nasal drainage, and facial pressure.

The estimated prevalence of CRS is between 5 and 12 percent of the general population. CRSwNP accounts for 20 to 33 percent of CRS cases. CRS occurs in both children and adults, although it is typically diagnosed in young or middle-aged adults. In several studies of adults, the mean age at diagnosis was 39 years. Females were disproportionately affected in some studies, although this finding is not consistent.

Initial treatment is with intranasal corticosteroids (INCS). Functional endoscopic sinus surgery (FESS), rather than biologic therapy, is the recommended next step in treatment for patients who require additional therapy. Biologic agents are a reasonable alternative to FESS for patients with severe or uncontrolled concomitant asthma who also need biologic therapy for their asthma, those with other conditions that could be simultaneously treated with a specific biologic, and those who refuse or cannot safely undergo surgery. The choice of treatment for acute exacerbations (oral glucocorticoids, antibiotics, or a temporary change to a more intense form of INCS) depends on the clinical scenario.

In addition to various local nasal medicinal products containing corticosteroids, three products have been approved for the systemic treatment of CRSwNP (dupilumab, omalizumab and mepolizumab).

4 Nonclinical aspects

The applicant did not submit any new nonclinical studies to support the requested new indication, which is considered acceptable. The new indication is unlikely to result in any significant risk to the environment. From the nonclinical point of view, there are no objections to the approval of the requested new indication.

5 Clinical aspects

5.1 Clinical pharmacology

The available tezepelumab PK data in the new population of patients with chronic rhinosinusitis with nasal polyps (CRSwNP) comprised PK data from one phase 3 study (WAYPOINT). This was analysed using a PopPK approach. An asthma PopPK model that had previously been developed for tezepelumab was able to predict the PK data for patients with CRSwNP who were enrolled in the WAYPOINT study. In addition, the PopPK model was updated with the new PK data, and the re-estimated PK parameters were similar to the estimates of the previous asthma PopPK model. In summary, subcutaneous administration of 210 mg tezepelumab every 4 weeks in patients with CRSwNP resulted in comparable exposures to those seen in patients with asthma.

5.2 Dose finding and dose recommendation

No dedicated clinical dose-finding studies were provided for the CRSwNP indication. The applicant supports using the same dosing regimen as for asthma, citing similarities in the underlying inflammatory pathophysiology. While this rationale is understandable, conducting a specific dose-finding study for this indication would have been preferable, as CRSwNP is still a different disease.

5.3 Efficacy

One pivotal study (WAYPOINT) was submitted. This was a phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of tezepelumab 210 mg subcutaneous (SC) every 4 weeks (Q4W) versus placebo in participants with CRSwNP. The study included a run-in period of 5 weeks, followed by a 52-week treatment period that was followed by a 24-week (open to the first 200 randomised participants) or 12-week (all other participants) safety follow-up period. Patients were on background INCS medication.

The co-primary endpoints were NP size (change from baseline in total nasal polyp(osis) score (NPS) evaluated by nasal endoscopy at week 52) and nasal congestion (change from baseline in bi-weekly mean nasal congestion score (NCS) at week 52). These co-primary endpoints of NPS and NCS are in line with the FDA CRSwNP guideline. The relevant key secondary endpoints included patient-reported loss of smell, patient-reported symptom scores for nasal polyp-related quality of life (SNOT-22), surgery and/or systemic corticosteroid (SCS) use, and sinus opacification as assessed by CT imaging.

Participants were adults 18 years of age and older with CRSwNP. CRSwNP severity had to be consistent with need for surgery despite documented treatment with SCS (within the past year but not within the last 3 months prior to Visit 1) and/or any history of prior NP surgery, ongoing NP symptoms for at least 2 months prior to enrolment, and moderate-to-severe self-reported nasal congestion (NCS ≥ 2 at Visit 1). These inclusion criteria are considered to adequately reflect the targeted patient population.

Overall, 410 participants were randomised, 204 to tezepelumab and 206 to placebo. A significantly higher percentage of patients discontinued study treatment in the placebo group (30.7%) compared to the tezepelumab group (3.9%). In the placebo group, this was mostly due to subject decision (21%) and other reasons (6.8%). More detailed reasons for treatment discontinuation were provided in response to the LoQ. The most common reasons for study treatment discontinuation were NP surgery (1 participant on tezepelumab and 24 participants on placebo), followed by participants who perceived

the investigational product (IP) to be ineffective (2 participants on tezepelumab and 19 participants on placebo). These numbers support the efficacy of tezepelumab.

Baseline demographic and disease characteristics were generally balanced between the two treatment groups, and the study population was representative of the target CRSwNP population.

Both co-primary endpoints were met, and the differences between tezepelumab and placebo are also considered clinically relevant. The total NPS change at week 52 was a statistically significant improvement from baseline in the tezepelumab group compared with the placebo group: -2.458 versus -0.392, respectively (LS mean difference -2.065 [95% CI: -2.389 to -1.742], $p < 0.0001$). The bi-weekly mean NCS change from baseline at week 52 was statistically significantly improved in the tezepelumab group compared with the placebo group (LS mean difference -1.028 [95% CI: -1.201 to -0.855], $p < 0.0001$).
Furthermore, all key secondary endpoints were also met except for change from baseline in pre-BD FEV1 in participants with co-morbid asthma/AERD/NSAID-ERD.

Overall, it can be concluded that the efficacy of tezepelumab as add on therapy to INCS was demonstrated in CRSwNP patients. The 52-week duration of this pivotal study was also acceptable for a treatment for a chronic disease. However, no data for efficacy in CRSwNP patients are available beyond 52 weeks, nor are there plans to collect any.

The indication wording initially proposed by the applicant was considered too broad. In response to the LoQ, it was adjusted to more adequately reflect the included study population, in particular regarding disease severity.

5.4 Safety

As only one pivotal study was conducted in CRSwNP, no pooled safety analysis was provided. Overall, the safety database for asthma can be considered supportive for this indication, and the post-marketing data are supportive as well. However, the safety database for CRSwNP alone is considered rather small for this not-so-rare disease.

Overall, the percentages of patients experiencing AEs were similar (78.3% in the tezepelumab group compared to 77.1% in the placebo group). During the on-treatment period, the four most commonly reported AEs in the tezepelumab group were COVID-19, nasopharyngitis, upper respiratory tract infection, and headache. Incidences of the most common AEs in the on-treatment period were generally similar across both treatment groups, except for nasopharyngitis, the reported incidence of which was higher in the tezepelumab group (22.2%) compared with the placebo group (11.2%). This difference of 11% is considered clinically relevant, and the fact that one case of nasopharyngitis was considered as possibly related to the IP by the investigator further substantiates that this is an adverse drug reaction (ADR), and it was included in the Information for healthcare professionals as such.

There were no AEs with a fatal outcome in the tezepelumab group in this study.
The percentage of SAEs was slightly higher in the placebo group (5.9%) compared to the tezepelumab group (4.9%). No SAE PT was reported in more than one tezepelumab-treated participant.

The incidence of serious infections on treatment was slightly higher in the tezepelumab group (2.5%) compared to the placebo group (2.0%). The Information for healthcare professionals already contains a warning about infections. However, a new clinically relevant severe infection – TBC – occurred in the WAYPOINT study, and this is now also mentioned under serious infections in the warnings and precautions section.

The Information for healthcare professionals contains a warning regarding a potential risk for serious cardiac events. The data from the WAYPOINT study did not raise any concerns, as the incidence of serious cardiac events was lower in the tezepelumab group (1.0%) compared to the placebo group (1.5%). Two malignancies were reported in the tezepelumab group (invasive lobular breast carcinoma and malignant melanoma) compared to none in the placebo group. Given the limited safety base, this may not be sufficient to draw any conclusions. The Information for healthcare professionals already contains a warning about malignancies.

Anaphylaxis was added to the list of ADRs for Tezepelumab on the basis of post-marketing data. No other significant actions relating to safety were taken, and no new safety concerns or ADRs have been identified in the post-marketing setting.

5.5 Final clinical benefit risk assessment

The PK of tezepelumab in patients with CRSwNP was sufficiently characterised and was similar to that in the patient population covered by the previous approval.
The efficacy of tezepelumab as add-on therapy to INCS compared to placebo was demonstrated in patients with severe CRSwNP over 52 weeks. The safety profile was acceptable and did not reveal any new prohibitive safety concerns to the already known safety profile in asthma patients. Therefore, the benefit-risk is considered positive for tezepelumab as add-on therapy to INCS in adult patients with severe CRSwNP.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for TEZSPIRE was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

TEZSPIRE®

Composition

Active substances

Tezepelumab, produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipients

Solution for injection in pre-filled syringe and pre-filled pen

Acetic acid 99%, proline, polysorbate 80, sodium hydroxide (for pH adjustment), water for injections ad solutionem pro 1.91 ml.

Pharmaceutical form and active substance quantity per unit

Solution for injection in pre-filled syringe

Solution for injection in pre-filled syringe (injection) for subcutaneous use.
Each single-use pre-filled syringe contains 210 mg tezepelumab (110 mg/mL).
Clear to opalescent, colourless to yellowish solution.

Solution for injection in pre-filled pen

Solution for injection in pre-filled pen (injection) for subcutaneous use.
Each single-use pre-filled pen contains 210 mg tezepelumab (110 mg/mL).
Clear to opalescent, colourless to yellowish solution.

Indications/Uses

Asthma

TEZSPIRE is indicated in addition to inhaled maintenance therapy in adults with severe asthma who meet the following criteria:

- inadequate asthma control and at least one severe exacerbation in the past 12 months despite concomitant treatment with inhaled corticosteroids and long-acting bronchodilators.
- systemic corticosteroids are not used as long-term therapy for asthma control.

Details about the patient populations studied: see “Properties/Effects”.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

TEZSPIRE is indicated as an add-on therapy with intranasal corticosteroids in adults with severe CRSwNP that cannot be adequately controlled with systemic corticosteroids and/or surgical intervention.

Dosage/Administration

TEZSPIRE treatment should be initiated by physicians experienced in the diagnosis and treatment of severe asthma or CRSwNP.

Usual dosage

Adults

Asthma

The recommended dose is 210 mg of TEZSPIRE by subcutaneous injection every 4 weeks (see “Properties/Effects”).
A decision to continue the therapy should be made at least annually based on the patient's level of asthma control.

CRSwNP

The recommended dose is 210 mg of TEZSPIRE by subcutaneous injection every 4 weeks.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Patients with hepatic disorders

No dose adjustment is required for patients with hepatic impairment (see “Pharmacokinetics”).

Patients with renal disorders

No dose adjustment is required for patients with renal impairment (see “Pharmacokinetics”).

Elderly patients

No dose adjustment is required for elderly patients age 65 or older (see “Pharmacokinetics”).

Children and adolescents

TEZSPIRE is not authorised for use in the paediatric population.
The safety and efficacy of TEZSPIRE in children and adolescents under 18 years of age for the treatment of asthma have not been established. Only limited data are available (see “Properties/Effects”).
The safety and efficacy of TEZSPIRE in children under 18 years of age for the treatment of CRSwNP have not been established.

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, the patient can resume dosing on the scheduled day of administration. If the next dose is already due, then administer as planned. A double dose must not be administered.

Mode of administration

TEZSPIRE is administered as a subcutaneous (SC) injection.
A patient may self-inject TEZSPIRE or the patient's caregiver may administer TEZSPIRE after training in SC injection technique. Proper training should be provided to patients and/or caregivers on the preparation and administration of TEZSPIRE prior to use according to the "Instructions for Use".
TEZSPIRE should be injected into the thigh or abdomen, except for the 5 cm around the navel. If a healthcare professional or caregiver administers the injection, the upper arm can also be used. A patient should not self-inject in the arm. TEZSPIRE should not be injected into areas where the skin is tender, bruised, erythematous, or hardened. It is recommended to rotate the injection site with each injection.
Comprehensive instructions for administration using the pre-filled syringe/pre-filled pen is provided in the "Instructions for Use".

Contraindications

TEZSPIRE is contraindicated in patients who have known hypersensitivity to tezepelumab or any of its excipients.

Warnings and precautions

General

TEZSPIRE should not be used to treat acute asthma exacerbations.
Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment.
Abrupt discontinuation of oral corticosteroids after initiation of TEZSPIRE therapy is not recommended. Reduction in oral corticosteroid doses, if appropriate, should be gradual and performed under the supervision of a physician.

Hypersensitivity reactions

Hypersensitivity reactions (e.g. anaphylaxis, rash) may occur following administration of TEZSPIRE (see "Undesirable effects"). These reactions may occur within hours of administration, but in some instances have a delayed onset (i.e. days).
In the event of a hypersensitivity reaction, appropriate treatment as clinically indicated should be initiated.

Parasitic (helminth) infection

TSLP may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if TEZSPIRE may influence a patient's response against helminth infections.
Patients with pre-existing helminth infections should be treated before initiating therapy with TEZSPIRE. If patients become infected while receiving treatment with TEZSPIRE and do not respond to anti-helminth treatment, treatment with TEZSPIRE should be discontinued until infection resolves.

Serious infections

Immunomodulatory drugs might increase the risk for serious infections (including tuberculosis). The size of the control group, the limited duration of the controlled periods and the exclusion of patients at specific risk in TEZSPIRE studies to date do not allow reliable conclusions to be drawn in this regard.

Serious cardiac events

In a long-term clinical study, a numerical imbalance in serious cardiac adverse events was observed in patients treated with tezepelumab compared to placebo. No causal relationship between tezepelumab and these events has been established, nor has a patient population at increased risk of these events been identified.
Patients should be advised of signs or symptoms indicative of a cardiac event (such as chest pain, dyspnoea, malaise, light headedness or fainting) and to consult a doctor immediately if such symptoms occur. If patients develop a serious cardiac event during tezepelumab treatment, therapy with tezepelumab should be discontinued until the acute event stabilises.
There is currently no data on resumption of treatment in patients who develop a serious cardiac event or serious infection.

Vaccinations

The use of live attenuated vaccines is not recommended during or immediately before TEZSPIRE therapy. Prior to initiation of TEZSPIRE therapy, it is recommended to bring the patient's vaccination status up to date. If live vaccination is considered prior to TEZSPIRE therapy, the time interval between live vaccination and treatment with TEZSPIRE must comply with current vaccination guidelines for immunomodulatory drugs.

Malignant tumours

Immunomodulatory drugs might increase the risk for tumours. The size of the control group and the limited duration of the controlled periods in TEZSPIRE studies to date do not allow reliable conclusions to be drawn in this regard.

Interactions

No formal drug interaction studies have been performed. See "Pharmacokinetics".

In a randomised, double-blind, parallel-group study of 70 patients aged between 12 and 21 years with moderate to severe asthma, tezepelumab treatment did not appear to affect the humoral antibody responses induced by seasonal quadrivalent influenza vaccination.
The use of live attenuated vaccines should be avoided in patients receiving TEZSPIRE.
The expression of hepatic CYP450 enzymes can be altered by certain pro-inflammatory cytokines in systemic inflammatory diseases. There is a potential risk that TEZSPIRE could modify the formation of CYP450 expression upon initiation of treatment with TEZSPIRE.
Therefore, patients taking medicinal products whose dose is titrated individually and that are metabolised by CYP450 3A4, 1A2 or 2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporin or benzodiazepines) should be monitored at the start and end of TEZSPIRE therapy and have their dose adjusted if necessary.
Based on the population pharmacokinetic analysis, commonly co-administered asthma medications (including leukotriene receptor antagonists, theophylline/aminophylline, and oral corticosteroids (OCS)) had no effect on tezepelumab clearance.

Pregnancy, lactation

Pregnancy

The data on pregnancy exposure from the clinical studies are insufficient to inform on drug-associated risk. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see “Preclinical data”).
Human IgG antibodies, such as tezepelumab, are transported across the placenta barrier; therefore, TEZSPIRE may be transmitted from the mother to the developing foetus.
As a precautionary measure**,** it is preferable to avoid the use of TEZSPIRE during pregnancy unless the expected benefit to the pregnant mother is greater than any possible risk to the foetus.

Lactation

It is unknown whether tezepelumab is excreted in human milk. However, IgG antibodies are known to be present in human milk. Risk to the breast-fed child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from using TEZSPIRE, taking into account the benefit and risk of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data in humans. Animal studies showed no adverse effects of tezepelumab treatment on fertility (see “Preclinical data”).

Effects on ability to drive and use machines

The effects of TEZSPIRE on the ability to drive and use machines have not been studied.

Undesirable effects

Summary of the safety profile

Asthma

In clinical studies in patients with severe asthma, the most commonly reported adverse reactions during treatment were arthralgia and pharyngitis.
A total of 739 patients with uncontrolled, severe asthma received at least one dose of TEZSPIRE in 3 randomised, placebo-controlled, multicentre trials of 48 to 52 weeks duration (PATHWAY, NAVIGATOR, and SOURCE). The pooled safety data from PATHWAY and NAVIGATOR consists of 665 adults and adolescents who received at least one dose of TEZSPIRE during these two placebo-controlled clinical studies of 52 weeks duration (Table 1). The adverse reactions with TEZSPIRE seen in SOURCE were similar to the pooled safety data from PATHWAY and NAVIGATOR.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

In a clinical study in patients with CRSwNP, the most commonly reported adverse reaction during treatment was pharyngitis.
The safety profile for a total of 203 patients with CRSwNP who received TEZSPIRE during the randomised, placebo-controlled, multicentre trial of 52 weeks duration (WAYPOINT), was generally similar with the established safety profile of TEZSPIRE. The incidence of adverse reactions was similar to those reported in asthma.

List of adverse reactions

The adverse reactions should be arranged according to MedDRA system organ classes and the conventional frequencies as follows:
"very common" (≥1/10)
"common" (≥1/100, <1/10)
"uncommon" (≥1/1,000, <1/100)
"rare" (≥1/10,000, <1/ 1,000)
"very rare" (<1/10,000)
"not known" (frequency cannot be estimated from the available data)

Table 1 Adverse drug reactions

System organ class	Adverse reactions	Frequency
Infections & infestations	Nasopharyngitis[a] Pharyngitis[b]	Very common Common
Skin and subcutaneous tissue disorders	Rash[c]	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Common
General disorders and administration site conditions	Injection site reaction	Common

[a] Nasopharyngitis was observed only in the CRSwNP study (WAYPOINT).

[b] Pharyngitis was defined by the following grouped preferred terms: pharyngitis, pharyngitis bacterial, pharyngitis streptococcal and viral pharyngitis

[c] Rash was defined by the following grouped preferred terms: rash, rash pruritic, rash erythematous, rash maculo-papular, rash macular

Undesirable effects from the post-marketing phase

There have been post-marketing reports of anaphylactic reactions in connection with TEZSPIRE.

Description of specific adverse reactions

Injection site reactions

In the asthma pooled safety data from PATHWAY and NAVIGATOR, injection site reactions (e.g. injection site erythema, injection site swelling, injection site pain) occurred at a rate of 3.8% in patients treated with tezepelumab 210 mg SC every 4 weeks (Q4W) compared with 3.1% in patients treated with placebo.

Paediatric population (not authorised in Switzerland)

A total of 82 adolescents aged 12 to 17 with severe, uncontrolled asthma were enrolled in the 52-week Phase 3 NAVIGATOR study (see “Properties/Effects”). The safety profile in adolescents described in this study was generally similar to the overall study population.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In clinical trials, doses of up to 280 mg were administered subcutaneously every 2 weeks (Q2W) and doses of up to 700 mg were administered intravenously every 4 weeks (Q4W) to patients with asthma without evidence of dose-related toxicities.

Treatment

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

Properties/Effects

ATC code

R03DX11

Mechanism of action

Tezepelumab is a human monoclonal antibody directed against thymic stromal lymphopoietin (anti-TSLP antibody, IgG2λ) that binds to human TSLP and prevents its interaction with the heterodimeric TSLP receptor. TSLP, an epithelial cell-derived cytokine, is involved in inflammatory cascades and plays a role in the initiation and persistence of airway and mucosal inflammation in asthma and CRSwNP. TSLP regulates immunity at the epithelium by influencing dendritic cells and other innate and adaptive immune cells and inflammatory processes as well as bronchial hyper-responsiveness. In addition, it has been shown that TSLP may have indirect effects on airway structural cells (e.g. fibroblasts and airway smooth muscle) and increased levels of TSLP mRNA and protein are found in the airways of patients with asthma as well as in nasal polyp tissue. In asthma and CRSwNP, both allergic and non-allergic triggers induce TSLP production. Blocking TSLP with tezepelumab influences a broad spectrum of biomarkers and cytokines associated with inflammation (e.g. blood eosinophils, IgE, FeNO, IL-5, and IL-13).

Pharmacodynamics

Effect on blood eosinophils, inflammatory biomarkers and cytokines

In asthma clinical trials, administration of tezepelumab 210 mg SC Q4W reduced inflammatory biomarkers and cytokines from baseline compared with placebo with an onset of effect by 2 weeks and sustained reduction to 52 weeks for blood eosinophil counts, FeNO, serum IL-5 concentration, and serum IL-13 concentration. Tezepelumab caused a progressive reduction in serum total IgE concentration, with levels continuing to decrease throughout treatment.
In a CRSwNP trial, administration of tezepelumab 210 mg SC Q4W resulted in reductions of inflammatory biomarkers (blood eosinophils and serum IgE) which were consistent with reductions observed in the asthma trials.

Effect on eosinophils in the airway submucosa

In a clinical trial, administration of tezepelumab 210 mg SC Q4W reduced submucosal eosinophil counts by 89% compared with a 25% reduction with placebo. Reduction was consistent regardless of baseline inflammatory biomarkers.

Immunogenicity

In NAVIGATOR, anti-drug antibodies (ADA) were detected in patients with asthma at any time in 26 (4.9%) out of 527 patients who received tezepelumab at the recommended dosing regimen during the 52-week study period. Of these 26 patients, 10 patients (1.9% of patients treated with tezepelumab) developed treatment-emergent antibodies and 1 patient (0.2% of patients treated with tezepelumab) developed neutralising antibodies. ADA titres were generally low and often transient. There were too few patients with treatment-emergent ADAs or neutralizing antibodies to assess the impact on pharmacokinetics, pharmacodynamics, efficacy and safety of TEZSPIRE. The immunogenicity profile of tezepelumab was maintained over 76 weeks of treatment in DESTINATION for severe asthma patients originally enrolled in NAVIGATOR (n=415) and was also maintained over 104 weeks in those subjects who subsequently enrolled in the extended follow-up phase of DESTINATION (n=289).
In patients with CRSwNP (WAYPOINT), a treatment-emergent ADA response developed in 5 (3%) out of 164 patients treated with tezepelumab 210 mg SC Q4W during the 52-week treatment period. Neutralising antibody activity was detected in 1 of the ADA positive patients. While there was no apparent impact of ADA on pharmacokinetics, pharmacodynamics, efficacy, or safety, there were insufficient numbers of patients with treatment emergent ADA to make a formal assessment in CRSwNP.

Clinical efficacy

Asthma

The efficacy of TEZSPIRE was evaluated in three randomised, double-blind, parallel group, placebo-controlled clinical trials (PATHWAY, NAVIGATOR and SOURCE) of 48 to 52 weeks in duration involving a total of 1761 patients aged 12 years and older. In all three trials, patients were enrolled without requiring a minimum baseline level of blood eosinophils or other inflammatory biomarkers (e.g. FeNO or IgE).
PATHWAY was a 52-week exacerbation trial which randomized a total of 550 patients (18 years of age and older) with severe, uncontrolled asthma to receive treatment with TEZSPIRE 70 mg SC Q4W, TEZSPIRE 210 mg SC Q4W, TEZSPIRE 280 mg SC Q2W or placebo. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment or 1 asthma exacerbation resulting in hospitalisation in the past 12 months.
NAVIGATOR was a 52-week exacerbation trial which randomized a total of 1061 patients (adults and adolescents 12 years of age and older) with severe, uncontrolled asthma to receive treatment with TEZSPIRE 210 mg SC Q4W or placebo. Patients were required to have a history of 2 or more asthma

exacerbations requiring oral or systemic corticosteroid treatment or resulting in hospitalisation in the past 12 months.

In both PATHWAY and NAVIGATOR, patients were required to have an Asthma Control Questionnaire 6 (ACQ-6) score of 1.5 or more at screening, and reduced lung function at baseline (pre-bronchodilator FEV_1 below 80% predicted in adults, and below 90% predicted in adolescents). Patients were required to have been on regular treatment with medium- or high-dose inhaled corticosteroids (ICS) and at least one additional asthma control therapy with or without oral corticosteroids (OCS). Patients continued background asthma therapy throughout the duration of the trials.

SOURCE was a 48-week OCS reduction trial which randomized a total of 150 asthma patients (18 years of age and older) who required treatment with daily OCS (7.5 mg to 30 mg per day) in addition to regular use of high-dose ICS and long-acting beta-agonist (LABA) with or without additional controller(s). Patients were required to have a history of at least one exacerbation in the past 12 months. After an up to 8-week OCS optimisation phase, patients received either tezepelumab 210 mg SC Q4W or placebo for a total of 48 weeks. Patients continued to receive their baseline background asthma medications during the study; however, their OCS dose was reduced every 4 weeks during the OCS reduction phase (Week 4 to 40), as long as asthma control was maintained. This was followed by an 8-week maintenance phase during which patients were to remain on the OCS dose achieved by Week 40.

The demographics and baseline characteristics of these 3 trials are provided in Table 2 below.

Table 2 Demographics and baseline characteristics of asthma trials

	PATHWAY n=550	NAVIGATOR n=1059	SOURCE n=150
Mean age (year) (SD)	52 (12)	50 (16)	53 (12)
Female (%)	66	64	63
White (%)	92	62	84
Black or African American (%)	3	6	1
Asian (%)	3	28	15
Hispanic or Latino (%)	1	15	16
Never smoked (%)	81	80	74
High-dose ICS use (%)	49	75	99
OCS use (%)	9	9	100
Mean number of exacerbations in previous year (SD)	2.4 (1.2)	2.8 (1.4)	2.0 (1.5)
Mean duration of asthma (years) (SD)	17 (12)	22 (16)	23 (15)
Mean baseline % predicted FEV_1 (SD)	60 (13)	63 (18)	54 (18)
Mean post-bronchodilator FEV_1 reversibility (%) (SD)	23 (20)	15 (15)	15 (15)
Mean baseline blood EOS count (cells/µL) (SD)	371 (353)	340 (403)	242 (180)
Positive allergic status (%)[a]	43	64	39
Mean FeNO (ppb) (SD)	35 (39)	44 (41)	41 (39)
Mean ACQ-6 (SD)	2.7 (0.8)	2.8 (0.8)	2.5 (1.1)

[a] Positive allergic status as defined by a positive serum IgE result specific to any perennial aeroallergen in the FEIA panel.
ACQ-6, Asthma Control Questionnaire 6; EOS, Eosinophils; FEIA, Fluorescent enzyme immunoassay; FeNO, Fractional exhaled nitric oxide; FEV_1, Forced expiratory volume in one second; ICS, Inhaled corticosteroid; IgE, Immunoglobulin E; OCS, Oral corticosteroid; ppb, Parts per billion; SD, Standard deviation.

The results summarised below are for the recommended tezepelumab 210 mg SC Q4W dosing regimen.

Exacerbations

The primary endpoint for PATHWAY and NAVIGATOR was the rate of clinically significant asthma exacerbations measured over 52 weeks. Clinically significant asthma exacerbations were defined as worsening of asthma requiring the use of or increase in oral or systemic corticosteroids for at least 3

days or a single depo-injection of corticosteroids, and/or emergency department visits requiring use of oral or systemic corticosteroids and/or hospitalisation.

In both PATHWAY and NAVIGATOR, patients receiving TEZSPIRE had significant reductions in the annualised rate of asthma exacerbations compared with placebo (Table 3). There were also fewer exacerbations requiring emergency room visits and/or hospitalisation in patients treated with TEZSPIRE compared with placebo. Additionally, a greater proportion of patients receiving TEZSPIRE did not experience an asthma exacerbation during the 52-week treatment compared with placebo.

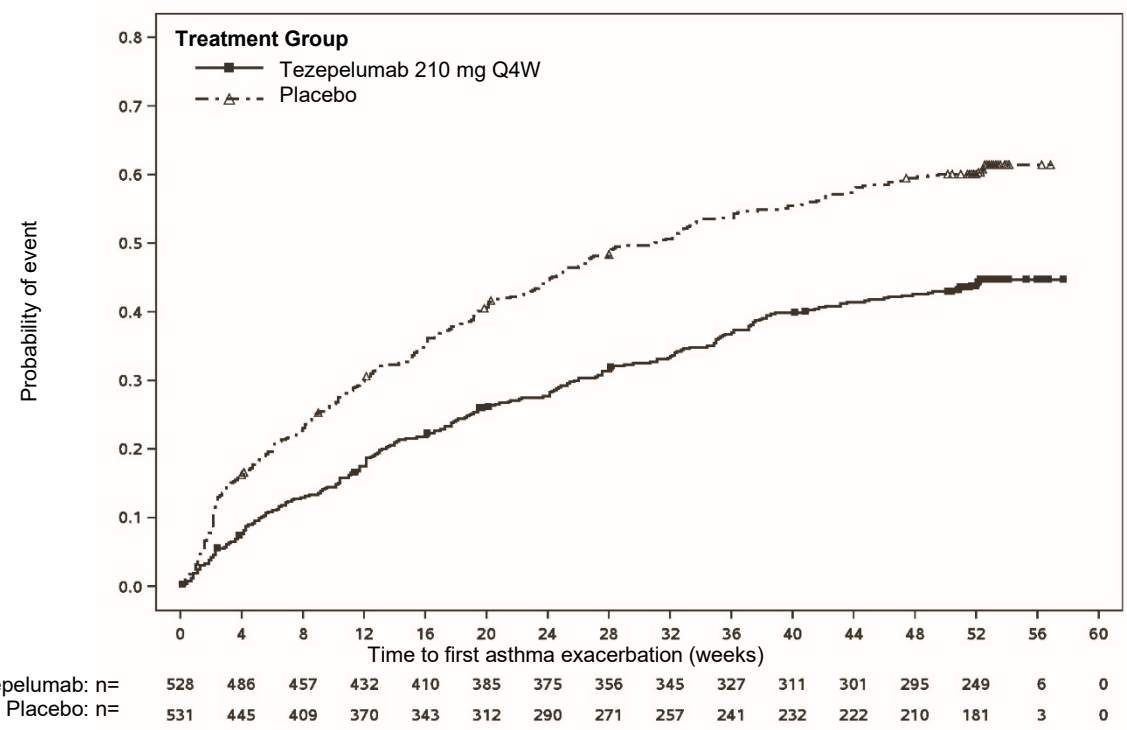
Table 3 Rate of clinically significant exacerbations over 52 weeks, PATHWAY and NAVIGATOR

	PATHWAY		**NAVIGATOR**	
	TEZSPIRE n=137	**Placebo n=138**	**TEZSPIRE n=528**	**Placebo n=531**
Annualised Asthma Exacerbation Rate				
Rate	0.20	0.72	0.93	2.10
Rate ratio (95% CI)	0.29 (0.16, 0.51)		0.44 (0.37, 0.53)	
p-value	<0.001		<0.001	

The rate of exacerbations requiring hospitalisation/emergency room visits for patients receiving TEZSPIRE compared with placebo were 0.03 versus 0.18 (rate ratio 0.15, 95% CI: 0.04, 0.58, p=0.005) for PATHWAY and 0.06 versus 0.28 (rate ratio 0.21, 95% CI: 0.12, 0.37, p<0.001) for NAVIGATOR. Similar results were seen in the reduction of the rate of exacerbations requiring hospitalisation alone (0.02 versus 0.14 [rate ratio 0.14, 95% CI: 0.03, 0.71, p=0.017]) for PATHWAY and 0.03 versus 0.19 (rate ratio 0.15, 95% CI: 0.07, 0.33, p<0.001) for NAVIGATOR.

The time to first exacerbation was longer for the patients receiving TEZSPIRE compared with placebo in NAVIGATOR (Figure 1). Similar results were seen in PATHWAY.

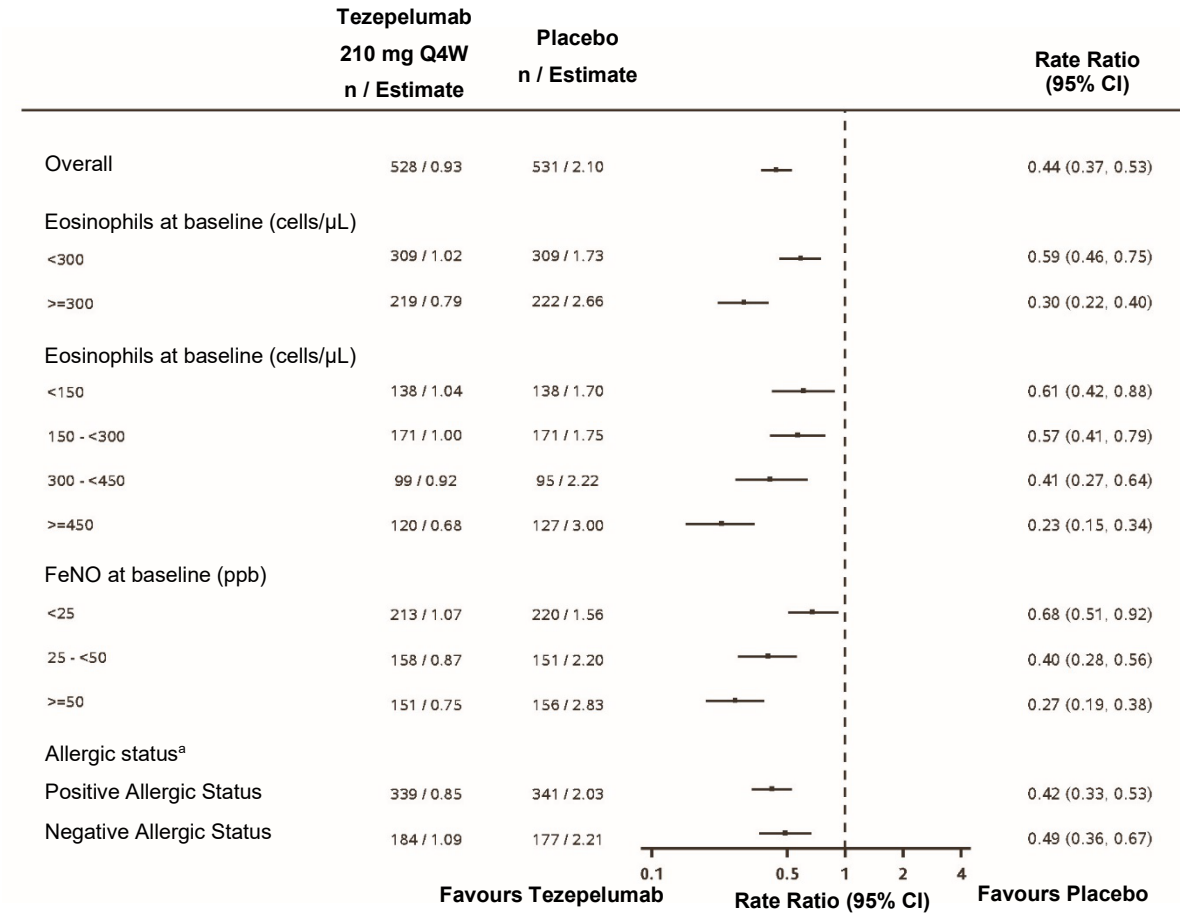
Figure 1 **Kaplan-Meier cumulative incidence curves for time to first exacerbation Through Week 52, NAVIGATOR**



Subgroup analysis

In NAVIGATOR, TEZSPIRE showed a reduction in the rate of asthma exacerbations both in the overall study population and in the subgroup of patients with baseline blood eosinophil counts <300 cells/µL.

Figure 2 **Annualised asthma exacerbation rate ratio over 52 weeks across different baseline biomarkers, NAVIGATOR**



[a]Allergic status as defined by a serum IgE result specific to any perennial aeroallergen in the FEIA panel

Lung function

Change from baseline in FEV_1 was assessed as a secondary endpoint in PATHWAY and NAVIGATOR. Compared with placebo, TEZSPIRE provided clinically meaningful improvements in the mean change from baseline in FEV_1 in both trials (Table 4).

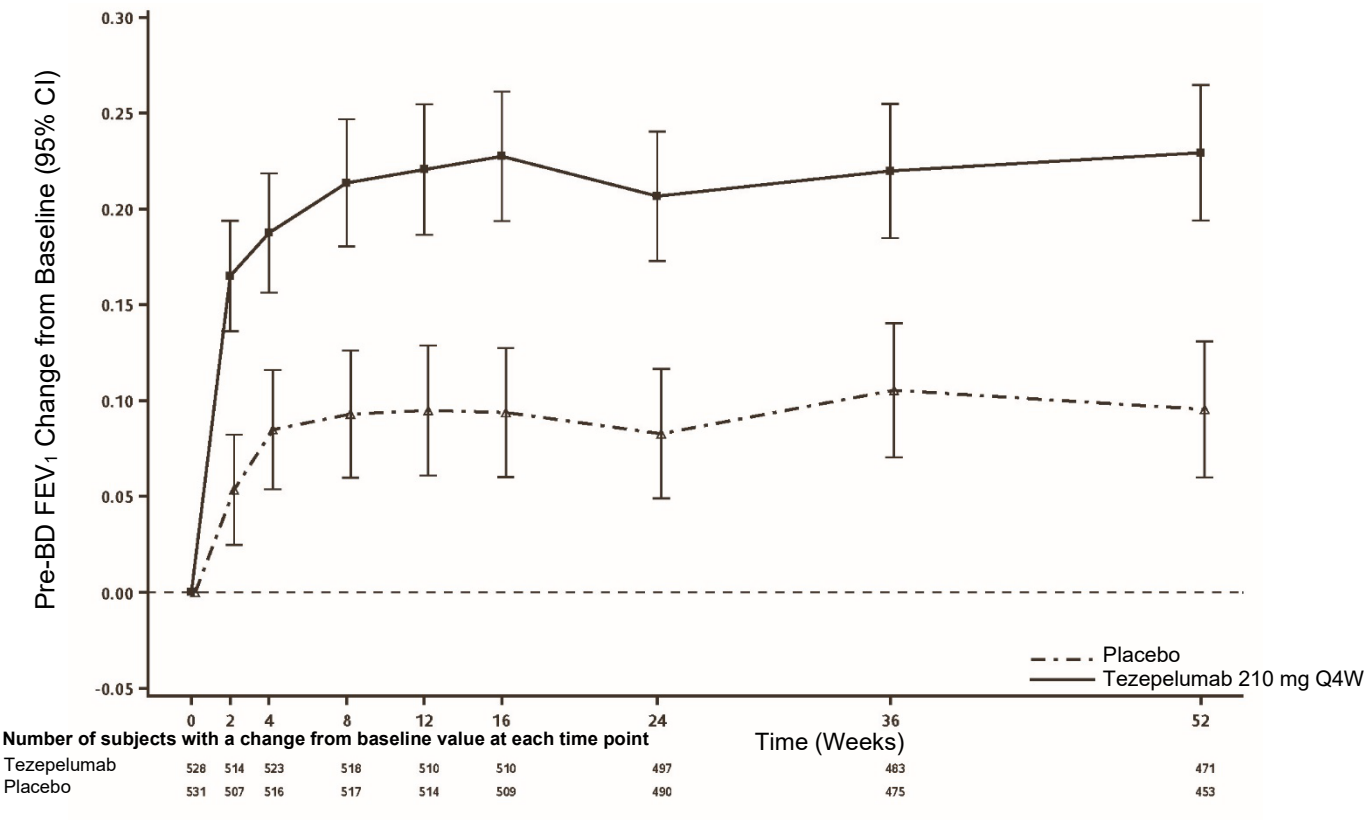
Table 4 **Mean change from baseline in pre-bronchodilator FEV_1 at week 52, PATHWAY and NAVIGATOR**

	PATHWAY		NAVIGATOR	
	TEZSPIRE N=133*	Placebo N=138*	TEZSPIRE N=527*	Placebo N=531*
LS Mean Change from Baseline (L)	0.08	-0.06	0.23	0.10
LS Mean Difference from Placebo (L) (95% CI)	0.13 (0.03, 0.23)		0.13 (0.08, 0.18)	
p-value	0.009†*		<0.001	

* Number of patients contributing to the full analysis (FA) with at least 1 change from baseline value
†* Nominal p-value
CI, Confidence interval; FEV1, Forced expiratory volume in one second; LS, Least square.

In NAVIGATOR, improvement in FEV_1 was seen as early as 2 weeks after initiation of treatment and was sustained through week 52 (Figure 3).

Figure 3 **Mean change (95% CI) from baseline in pre-bronchodilator FEV_1 (L) over time, NAVIGATOR**



Patient reported outcomes

Changes from baseline in Asthma Control Questionnaire 6 (ACQ-6) and Standardised Asthma Quality of Life Questionnaire for ages 12 and older [AQLQ(S)+12] were assessed as secondary endpoints in PATHWAY and NAVIGATOR. Results for NAVIGATOR are shown in Table 5. Improvements in ACQ-6 and AQLQ(S)+12 were seen as early as 2 weeks and 4 weeks after administration of TEZSPIRE, respectively, and sustained through Week 52 in both trials.

In both trials, more patients treated with TEZSPIRE compared to placebo had a clinically meaningful improvement in ACQ-6 and AQLQ(S)+12. Clinically meaningful improvement (responder rate) for ACQ-6 and AQLQ(S)+12 was defined as improvement in score of 0.5 at end of trial. In NAVIGATOR, the ACQ-6 responder rate for TEZSPIRE was 86% compared with 77% for placebo (odds ratio=1.99; 95% CI 1.43, 2.76) and the AQLQ(S)+12 responder rate for TEZSPIRE was 78% compared with 72% for placebo (odds ratio=1.36; 95% CI 1.02, 1.82). Similar findings were seen in PATHWAY.

Weekly mean Asthma Symptom Diary (ASD) scores were also assessed as a secondary endpoint in NAVIGATOR. Severity of wheezing, shortness of breath, cough, and chest tightness were assessed twice daily (morning and evening). Night-time awakening and activity were assessed on a daily basis. The total ASD score was calculated as the mean of 10 items. More patients treated with TEZSPIRE compared to placebo had a clinically meaningful improvement in the ASD score. Clinically meaningful improvement (responder rate) was defined as improvement in score of 0.5 or more at end of trial. The ASD responder rate for TEZSPIRE was 58% compared with 51 % for placebo (odds ratio=1.68; 95% CI 1.12, 2.53).

Table 5 Results of AQLQ(s)+12, ACQ-6 and ASD at week 52, NAVIGATOR

	N*	LS Mean Change from Baseline	Difference from Placebo (95% CI)	p-value
AQLQ(S)+12 total score				
TEZSPIRE	525	1.48	0.33 (0.20, 0.47)	<0.001
Placebo	526	1.14		
ACQ-6 score				
TEZSPIRE	527	-1.53	-0.33 (-0.46, -0.20)	<0.001
Placebo	531	-1.20		
ASD				
TEZSPIRE	525	-0.70	-0.11 (-0.19, -0.04)	0.004
Placebo	531	-0.59		

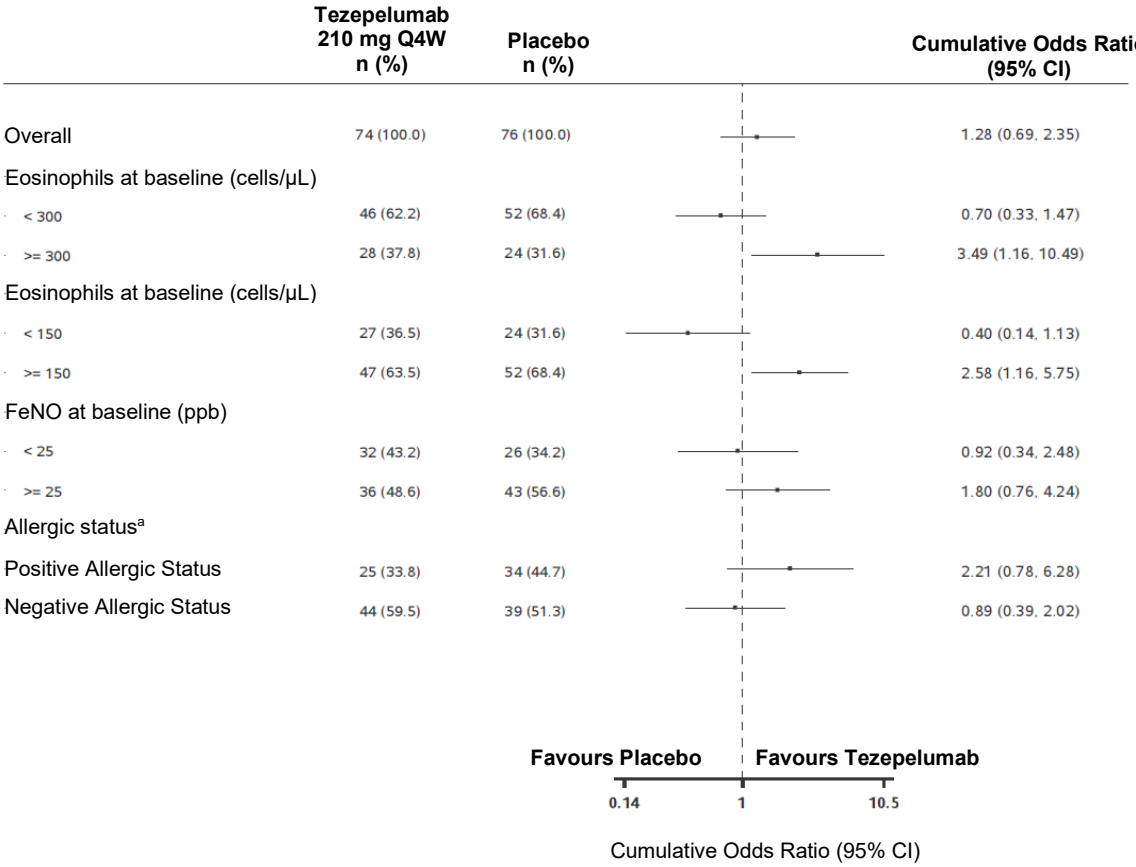
* Number of patients contributing to the full analysis (FA) with at least 1 change from baseline value

ACQ-6: Asthma Control Questionnaire 6; AQLQ(S)+12; Standardised Asthma Quality of Life Questionnaire for 12 years and older; ASD: Asthma Symptom Diary; CI: Confidence interval; LS: Least square.

Oral corticosteroid reduction

The effect of TEZSPIRE on reducing the use of maintenance OCS was evaluated in SOURCE. The primary endpoint was categorised percent reduction from baseline of the final OCS dose at week 48 (≥90% reduction, ≥75% to <90% reduction, ≥50% to <75% reduction, >0% to <50% reduction, and no change or any increase), while maintaining asthma control. Compared with placebo, numerically more patients receiving TEZSPIRE achieved a reduction from baseline in maintenance OCS dose without losing asthma control (cumulative odds ratio=1.28; 95% CI 0.69, 2.35), but the difference was not statistically significant.

Figure 4 Percentage reduction in final daily OCS dose at week 48 across different baseline biomarkers, SOURCE



[a]Allergic status as defined by a serum IgE result specific to any perennial aeroallergen in the FEIA panel

Secondary endpoints in SOURCE, including the annualised rate of asthma exacerbations, change from baseline in pre-bronchodilator FEV_1, ACQ-6 and AQLQ(S)+12, showed no statistically significant differences with TEZSPIRE compared to placebo.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

The efficacy of TEZSPIRE was evaluated in a randomised, double-blind, parallel group, multicentre, placebo-controlled trial (WAYPOINT) of 52 weeks treatment duration conducted in 408 patients aged 18 years and older on standard of care treatment for CRSwNP. Administration beyond 52 weeks was not investigated in CRSwNP.

This study included patients with symptomatic CRSwNP despite treatment with systemic corticosteroids within the past 12 months and/or any history of sino-nasal surgery, or contraindications/intolerance to either.

Patients received TEZSPIRE 210 mg or placebo s.c. Q4W for 52 weeks in addition to intranasal corticosteroid treatment for CRSwNP.

The demographics and baseline characteristics of WAYPOINT are provided in Table 6 below.

Table 6 Demographics and baseline characteristics of WAYPOINT

	WAYPOINT N=408[a]
Mean age (years) (SD)	50 (14)
Male (%)	65
Mean CRSwNP duration (years) (SD)	13 (10)
Patients with ≥ 1 prior surgery (%)	71
Patients with systemic corticosteriod use for CRSwNP in the previous year (%)	58
Mean total NPS[b] (SD), range 0-8	6.1 (1.2)
Mean bi-weekly NCS[b, c] (SD), range 0-3	2.6 (0.5)
Mean bi-weekly loss of smell[b, d] (SD), range 0-3	2.9 (0.4)
Mean SNOT-22 total score[b] (SD), range 0-110	69 (18)
Mean blood eosinophils (cells/µL) (SD)	358 (238)
Mean total IgE IU/mL (SD)	176 (285)
Asthma[e] (%)	61
NSAID-ERD/AERD (%)	17
Allergic rhinitis (%)	14

[a] Number of patients (N) =407 for mean total NPS; N=406 for mean bi-weekly NCS and mean bi-weekly loss of smell; N=404 for mean LMK sinus CT total score and mean blood eosinophils; N=389 for mean total IgE.

[b] Higher scores indicate greater disease severity or symptom severity.

[c] Evaluated as part of the Nasal Polyposis Symptom Diary (NPSD).

[d] Evaluated via difficulty with sense of smell score in the NPSD.

[e] Includes patients with asthma or AERD or NSAID-ERD. All but 3 patients with AERD or NSAID-ERD included in this subgroup also had a diagnosis of asthma reported.

AERD: Aspirin exacerbated respiratory disease; CRSwNP: Chronic rhinosinusitis with nasal polyps; CT: Computed tomography; IgE: Immunoglobulin E; IU: International units; LMK: Lund-Mackay; NCS: Nasal congestion score; NPS: Nasal polyp score; NSAID-ERD: Nonsteroidal anti-inflammatory drug exacerbated respiratory disease; SD: Standard deviation; SNOT-22: 22-item Sino-Nasal Outcome Test.

The co-primary efficacy endpoints were change from baseline in total nasal polyp score (NPS) evaluated by nasal endoscopy at week 52 as graded by independent blinded assessors, and change from baseline in bi-weekly mean nasal congestion score (NCS) evaluated as part of the Nasal Polyposis Symptom Diary (NPSD) at week 52. Total NPS was graded on a categorical scale (0-8).

Nasal congestion was rated daily by the patients on a 0 to 3 categorical severity scale. Unadjusted p-values are presented for WAYPOINT.

Statistically significant efficacy was observed in WAYPOINT with regard to improvement in total NPS and in bi-weekly mean NCS at week 52 (see Table 7).

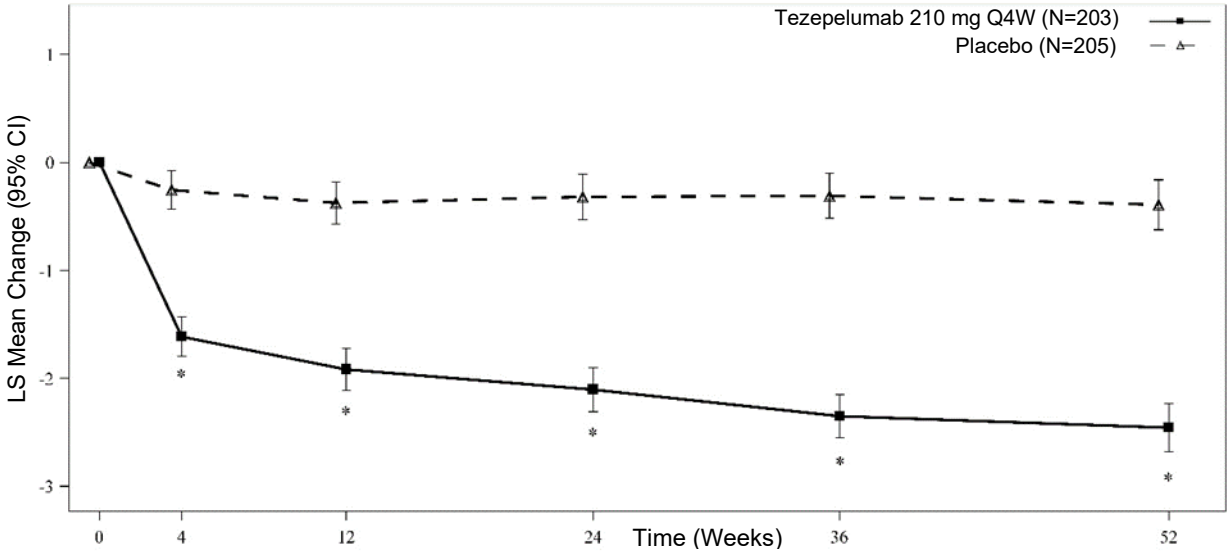
Table 7 Results of co-primary endpoints at week 52 in WAYPOINT

	TEZSPIRE (N=203)		**Placebo (N=205)**		**LS mean difference vs. placebo (95% CI)**
Scores	Baseline mean	LS mean change	Baseline mean	LS mean change	
NPS	6.1	-2.46	6.1	-0.38	-2.08 (-2.40, -1.76) p<0.0001[a]
NCS	2.59	-1.74	2.55	-0.70	-1.04 (-1.21, -0.87) p<0.0001[a]

[a] Unadjusted p-values are presented.

LS mean change, Least squared mean change from baseline; reduction in score indicates improvement; NCS, Nasal congestion score; NPS, Nasal polyp score

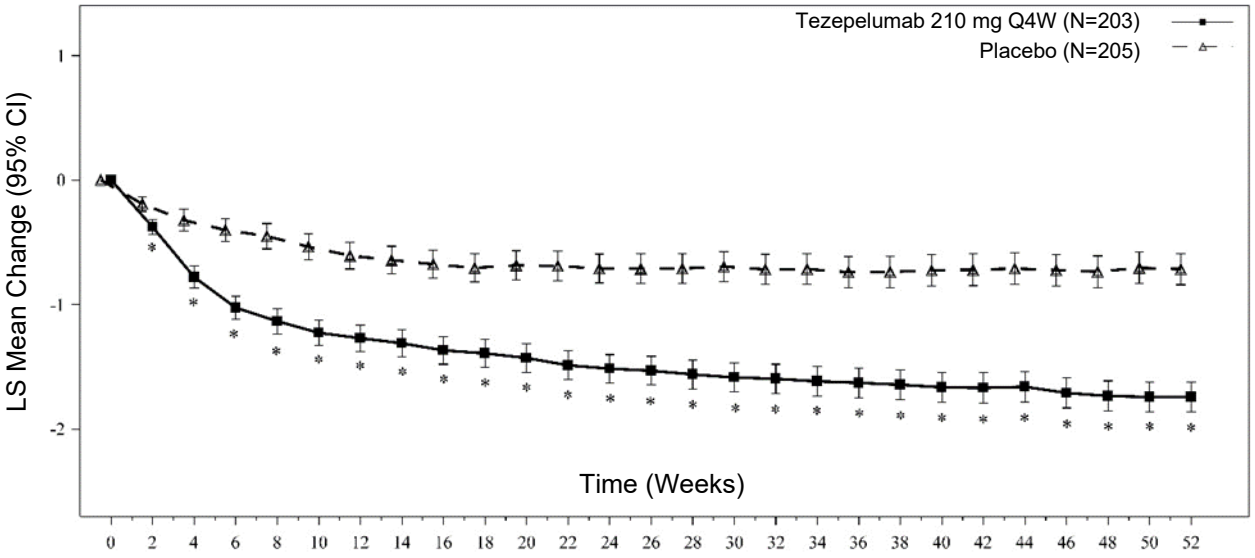
Figure 5 LS mean change from baseline in total nasal polyp score up to week 52



* Denotes unadjusted p<0.01 for tezepelumab 210 mg Q4W versus placebo treatment comparison.

At week 52, improvement over placebo in the primary endpoint of total NPS was consistent in patients with and without prior sino-nasal surgery and in patients with and without co-morbid asthma.

Figure 6 LS mean change from baseline in bi-weekly mean nasal congestion score up to week 52



* Denotes unadjusted p<0.01 for tezepelumab 210 mg Q4W versus placebo treatment comparison.

At week 52, improvement over placebo in the primary endpoint of NCS was consistent in patients with and without prior sino-nasal surgery and in patients with and without co-morbid asthma.
TEZSPIRE significantly improved the loss of smell compared to placebo. The LS mean difference for loss of smell (evaluated as bi-weekly mean NPSD difficulty with sense of smell score) at week 52 in the TEZSPIRE group versus placebo was -1.01 [95% CI: -1.18, -0.83; p<0.0001]. Significant improvement in loss of smell in patients treated with TEZSPIRE compared with those treated with placebo was seen as early as the first assessment at 2 weeks.
TEZSPIRE demonstrated a significant improvement in sino-nasal symptoms as measured by SNOT-22 score at 52 weeks (LS mean difference -27.44 [95% CI: -32.51, -22.37; p<0.0001]) versus placebo.
TEZSPIRE significantly reduced the proportion of patients with need for sino-nasal surgery or systemic corticosteroids by 92% compared to placebo over 52 weeks (Hazard Ratio: 0.08; 95% CI: 0.03, 0.176; p<0.0001).

Pharmacokinetics

The pharmacokinetics of tezepelumab is similar in patients with asthma and CRSwNP. Subcutaneous administration of 210 mg tezepelumab every 4 weeks in patients with CRSwNP resulted in exposures similar to those seen in patients with asthma.

Absorption

Following a single SC administration, the maximum serum concentration was reached in approximately 3 to 10 days. Based on population pharmacokinetic analysis, the estimated absolute

bioavailability was approximately 77%. There was no clinically relevant difference in bioavailability when administered to different injection sites (abdomen, thigh, or upper arm).

Distribution

Based on population pharmacokinetic analysis, central and peripheral volume of distribution of tezepelumab were 3.9 L and 2.2 L, respectively, for a 70 kg individual.

Metabolism

Specific metabolic studies have not been conducted. As tezepelumab is a human monoclonal antibody (IgG2λ), it is degraded by proteolytic enzymes.

Elimination

As a human monoclonal antibody, tezepelumab is eliminated by intracellular catabolism and there is no evidence of TSLP binding-mediated clearance. From population pharmacokinetic analysis, the estimated clearance (in the studied dose range of single dose of 2.1 to 420 mg subcutaneous and 210 and 700 mg intravenous doses) for tezepelumab was 0.17 L/d for a 70 kg individual. The elimination half-life was approximately 26 days.

Linearity

The pharmacokinetics of tezepelumab were dose-proportional following SC administration over a dose range of 2.1 mg to 420 mg.

Kinetics in specific patient groups

Age, gender, race

Based on population pharmacokinetic analysis, age (12-80), gender (M:F 44.0:46.0), and race (White: 77.3%; Asian, 13.3%; Black, 3.6%; Other, 5.8%) had no clinically meaningful effects on the pharmacokinetics of tezepelumab.

Body weight

Based on population pharmacokinetic analysis, higher body weight was associated with lower exposure. However, the effect of body weight on exposure had no meaningful impact on efficacy or safety.

Hepatic impairment

No formal clinical studies have been conducted to investigate the effect of hepatic impairment on tezepelumab. IgG monoclonal antibodies are not primarily cleared via hepatic pathway; change in hepatic function is not expected to influence tezepelumab clearance. Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (ALT, AST, and bilirubin) indicating normal liver function (1254 subjects), mild hepatic impairment (110 subjects) or moderate hepatic impairment (7 subjects) had no effect on tezepelumab clearance.

Renal impairment

No formal clinical studies have been conducted to investigate the effect of renal impairment on tezepelumab. Based on population pharmacokinetic analysis, tezepelumab clearance was similar in patients with mild renal impairment (creatinine clearance 60 to < 90 mL/min: 320 subjects), moderate renal impairment (creatinine clearance 30 to < 60 mL/min: 38 subjects) and those with normal renal function (creatinine clearance ≥ 90 mL/min: 1008 subjects). Tezepelumab has not been studied in patients with severe renal impairment (creatinine clearance < 30 mL/min); however, tezepelumab is not cleared renally.

Elderly patients

Based on population pharmacokinetic analysis, there was no clinically meaningful difference in the pharmacokinetics of tezepelumab between patients 65 years of age or older and younger patients. Of the 665 patients with asthma exposed to TEZSPIRE in the two placebo-controlled clinical studies of 52 weeks duration, a total of 119 patients were 65 years or older. Safety in this age group were similar to the overall study population.
Efficacy in this age group was similar to the overall study population in NAVIGATOR. PATHWAY did not include sufficient numbers of patients aged 65 and over to determine efficacy in this age group.

Preclinical data

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology and repeated dose toxicity studies in cynomolgus monkeys. In animals dosed with 300 mg/kg/week of SC tezepelumab (but not in animals dosed with 50 or 100 mg/kg/week), the immune response (IgG titer) to a T cell-dependent antigen was significantly reduced. The clinical relevance of this finding is unknown.

All preclinical studies were carried out at doses up to 300 mg/kg/week by either SC or IV administration, producing margins of greater than 100 times the maximum recommended human dose (MRHD) on a C_{max} and AUC at steady state basis.

Mutagenicity and carcinogenicity

Tezepelumab is a monoclonal antibody, as such genotoxicity and carcinogenicity studies have not been conducted.

Developmental toxicity

In a prenatal and postnatal development study conducted in cynomolgus monkeys, following IV administration of tezepelumab up to 300 mg/kg/week from early gestation through delivery, no adverse effects on maternal health, pregnancy outcome, embryo-foetal development, or neonatal growth and development up to 6.5 months of age were observed. Tezepelumab concentrations in milk were <1% of the serum concentrations. Comparison of maternal and infant serum ratios suggested

that the majority of tezepelumab transfer to the infant occurred *in utero* but transfer via milk cannot be excluded. No adverse effects on maternal health or neonatal health and development were observed.

Fertility

Effects on male and female fertility have not been directly evaluated in animal studies. Examination of surrogate fertility parameters (menstrual cycle, semen analysis, organ weights, and microscopic pathology) was performed in sexually mature male and female cynomolgus monkeys as part of a 6-month repeated dose toxicology study. There were no tezepelumab-related effects on these parameters at doses up to 300 mg/kg/week by SC administration.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

TEZSPIRE may be kept at room temperature (20°C-25°C) for a maximum of 30 days. After removal from the refrigerator, TEZSPIRE must be used within 30 days or discarded.

Special precautions for storage

Store in the refrigerator (2-8°C). For storage after removal from refrigeration, see “Shelf life after opening”.
Store in the original package in order to protect from light.
Do not freeze. Do not shake. Do not expose to heat.
Keep out of the reach of children.

Instructions for handling

This medicinal product is for single use only.
TEZSPIRE solution for injection is supplied in a sterile pre-filled syringe/pre-filled pen for individual use. Do not shake. Do not freeze. Protect from light.
Prior to administration, remove carton from refrigerator and allow TEZSPIRE to reach room temperature. This generally takes 60 minutes.
Visually inspect TEZSPIRE for particulate matter and discolouration prior to administration.
TEZSPIRE is clear to opalescent, colourless to yellowish. Do not use TEZSPIRE if liquid is cloudy, discoloured, or if it contains large particles or foreign particulate matter.

Additional information and instructions for the preparation and administration of TEZSPIRE using the pre-filled syringe/pre-filled pen are given in the package leaflet and ‘Instructions for Use’.

Authorisation number

68454, 69080 (Swissmedic)

Packs

TEZSPIRE pre-filled syringe: pack containing 1 single-use pre-filled syringe [B]
TEZSPIRE pre-filled pen: pack containing 1 single-use pre-filled pen [B]

Marketing authorisation holder

AstraZeneca AG, 6340 Baar

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