Date: 24 August 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

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
Marketing Authorisation Holder: AstraZeneca AG
Marketing Authorisation No.: 68454
Decision and decision date: approved on 13 June 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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Table of contents

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AQLQ(S)+12	Asthma Quality of Life Questionnaire (Standardised) for 12 years and older
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
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
CEX-UHPLC	Cation exchange ultra-high performance liquid chromatography
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed plasma/serum concentration of drug
CRCL	Creatinine clearance
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ePPND	Enhanced pre-/postnatal development
ERA	Environmental risk assessment
FDA	U.S. Food and Drug Administration
FEV1	Forced expiratory volume in one second
Gfr	Glomerular filtration rate
GLP	Good Laboratory Practice
HPLC	High performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroids
Ig	Immunoglobulin
INN	International nonproprietary name
IL	Interleukin
IL-7Rα	Interleukin-7 receptor alpha
ITT	Intention-to-treat
IV	Intravenous
JP	Japanese Pharmacopoeia
KLH	Keyhole limpet haemocyanin
LABA	Long-acting β2 agonist
LAMA	Long-acting muscarinic antagonists
LoQ	List of Questions
LTRA	Leukotriene receptor antagonists
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
OCS	Oral corticosteroids
PBPK	Physiology based pharmacokinetic
PD	Pharmacodynamics
PFS-SA	Prefilled syringe subassembly
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan (EMA)

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PK	Pharmacokinetics
PopPK	Population pharmacokinetic
PSP	Pediatric Study Plan (US-FDA)
rCE-SDS	Capillary electrophoresis sodium dodecyl sulfate under reducing conditions
RMP	Risk Management Plan
SAE	Serious adverse event
SC	Subcutaneous
SE-UHPLC	Size exclusion ultra-high performance liquid chromatography
SwissPAR	Swiss Public Assessment Report
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)
TSLP	Thymic stromal lymphopoietin
TSLPR	TSLP receptor
Vc	Central volume of distribution
Vp	Peripheral volume of distribution
USP	United States Pharmacopeia

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance tezepelumab of the medicinal product mentioned above.

Fast-track authorisation procedure (FTP)
The applicant requested a fast-track authorisation procedure in accordance with Article 7 of the TPO.

2.2 Indication and Dosage

2.2.1 Requested Indication

TRADE NAME is indicated as an adjunct to maintenance therapy in adults with severe asthma (see "Properties/effects").

2.2.2 Approved Indication

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".

2.2.3 Requested Dosage

Summary of the applied standard dosage:

The recommended dose is 210 mg of TRADE NAME given by subcutaneous injection every 4 weeks. A decision on continuation of therapy should be made at least once a year based on the patient's degree of asthma control.

2.2.4 Approved Dosage

(See appendix)

2.3 Regulatory History (Milestones)

Application	15 July 2021
Formal control completed	19 July 2021
List of Questions (LoQ)	14 September 2021
Answers to LoQ	2 December 2021
Predecision	19 January 2022
Answers to Predecision	17 March 2022
2nd Predecision	22 April 2022
Answers to Predecision	24 May 2022
Final Decision	13 June 2022
Decision	approval

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3 Medical Context

The term “asthma” applies to a group of chronic inflammatory respiratory diseases attributable to various pathogenic mechanisms that may manifest as different phenotypes. One subgroup of asthma diseases is known as type 2 inflammation. This subgroup is characterised by increased stimulation of T-helper type 2 lymphocytes, which may manifest as eosinophilia, increased nitrogen monoxide (FeNO) exhalation and/or concomitant atopic disease.
Mild and moderate forms generally respond well to inhaled corticosteroids (ICS) on their own or to a combination of ICS and long-acting Beta2 sympathomimetics (LABA). Severe forms may be ICS-refractory. In cases of type 2 inflammation, the relevant guidelines recommend add-on therapy with anti-IgE (omalizumab), anti-IL5/5R (mepolizumab, benralizumab or reslizumab) or anti-IL-4R (dupilumab).
If type 2 inflammation cannot be detected, the relevant guidelines primarily suggest attempting add-on therapy with off-label macrolides or inhaled muscarinic agents.
Tezepelumab is a human monoclonal antibody (IgG2 lambda) that blocks the cytokine thymic stromal lymphopoietin (TSLP). The applicant claims that TSLP plays a role in persisting respiratory tract inflammation, regardless of whether the inflammation is type 2.

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4 Quality Aspects

4.1 Drug Substance

Tezepelumab is a human monoclonal antibody of the immunoglobulin G2 (IgG2) subclass directed against human thymic stromal lymphopoietin (TSLP). Human thymic stromal lymphopoietin is an epithelial cell derived cytokine produced in response to pro-inflammatory stimuli that drives allergic inflammatory. TSLP signals through a heterodimeric receptor consisting of the Interleukin-7 receptor alpha (IL-7Rα) chain and TSLP receptor (TSLPR) forming the TSLPR complex. Tezepelumab specifically binds to TSLP and prevents its interaction with the TSLP receptor (TSLPR). Tezepelumab exerts its mechanism of action as a full antagonist to the soluble target TSLP, therefore effector function activity is not part of the mode of action.
The tezepelumab drug substance is produced from a mammalian cell line (Chinese Hamster Ovary, CHO) in a production bioreactor. The cell broth is harvested and subsequently purified by several chromatographic steps. The drug substance is finally frozen for storage.
The fermentation and purification processes were each validated on four batches. Production was consistent and impurities were efficiently reduced.

Changes were implemented during the development of the tezepelumab drug substance process, including changes to production and scale, site, drug substance concentration and drug substance composition. However, all processes used the same manufacturing cell line and the analytical comparability studies, which also considered clinical and commercial drug substance batches, demonstrated comparability between process changes. Characterisation and stability data were evaluated for this assessment release.

The physicochemical and biological properties of the drug substance and its impurities were characterised using state-of-the-art methods.

The specifications for release include relevant tests and limits, e.g. for appearance, identity and purity [e.g. size exclusion ultra-high performance liquid chromatography (SE-UHPLC), cation exchange ultra-high performance liquid chromatography (CEX-UHPLC), capillary electrophoresis sodium dodecyl sulfate under reducing conditions (rCE-SDS) and a receptor-ligand binding bioassay]. Specifications are based on clinical data and batch analysis (release and stability data) and are in conformance with current compendial or regulatory guidelines. A few tests are conducted as in-process controls (IPCs).

Batch analysis data for development, clinical, and process validation batches were provided. All batch release data comply with the drug product specifications that were valid at the time of batch release. All specific analytical methods are described and were fully validated.

The drug substance is frozen for storage. No significant changes were observed during storage under the proposed storage conditions.

4.2 Drug Product

The drug product is supplied in a prefilled syringe as a sterile, single-dose, preservative-free solution intended for subcutaneous injection and containing 210 mg deliverable drug product. The tezepelumab drug product is formulated with an acetate buffer with L-proline, and polysorbate 80. All excipients used comply with the requirements of the European Pharmacopoeia.
The syringe contains a 1.91 mL deliverable volume of 110 mg/mL tezepelumab. A plastic plunger rod is attached to the prefilled syringe. The syringe subassembly is inserted into an automatic needle guard with extended finger flange.

In connection with changes in active substance production, changes were also introduced for the drug product, e.g. protein concentration, drug product composition, primary container, and drug product site

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change. However, a comparability assessment was performed, and the comparability acceptance criteria or specification limits in place were met.

The tezepelumab drug product manufacturing process for 110 mg/mL prefilled syringe subassembly (PFS-SA), includes formulation buffer preparation, drug substance thaw, drug product formulation, bioburden reduction filtration, filtered formulated drug product hold, sterile filtration and aseptic filling, syringe plunger placement, inspection, and storage.
The validation of the drug product manufacturing process was validated using three consecutive commercial-size batches of tezepelumab.
The assembly process for the finger flange and automatic needle guard has been qualified.

The release and stability specifications include relevant tests and limits, e.g. for appearance, identity, pH, deliverable volume, purity tests (e.g. SE-UHPLC, CEX-UHPLC, rCE-SDS), protein concentration, a receptor-ligand binding bioassay, subvisible particles, osmolality, sterility and bacterial endotoxins. All specific methods are described and validated.

Batch analysis data for development, clinical, and process validation batches were provided. All batch release data comply with the drug product specifications that were valid at the time of batch release.

The PFS-SA primary container closure consists of a 2.25 mL type I glass syringe with a staked stainless steel needle protected by an elastomeric needle shield and a laminated elastomeric plunger-stopper. All components are Ph. Eur., USP, and JP compliant.
The accessorised prefilled syringe (APFS) fulfils the requirements of the EU medical devices regulation.

All drug product shelf-life acceptance criteria are fulfilled if the product is stored under the proposed long-term storage conditions of 2 – 8°C. A shelf-life of 36 months has been accepted.

4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf-life of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk for adventitious agents is minimised.

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5 Nonclinical Aspects

5.1 Pharmacology

During *in vitro* assays tezepelumab demonstrated a high affinity for thymic stromal lymphopoietin (TSLP) from humans (K_D 15.8 pM) and cynomolgus monkeys (K_D 32.3 pM). Tezepelumab did not bind to TSLP from mouse, rat, or rabbit, which is consistent with the low sequence homology (43-55% homology to human TSLP). In cell-based assays, tezepelumab showed potent antagonist activity against human or cynomolgus monkey TSLP-dependent pathways, with K_I or IC_{50} values in pM range. These studies support the proposed mechanism of action of tezepelumab and the use of cynomolgus monkeys as a pharmacologically relevant species for safety assessment.
Nonclinical *in vivo* pharmacology studies were conducted in mice using a surrogate anti-mouse TSLP IgG2a antibody (M702). In the ovalbumin-induced asthma model, intranasal administration of M702 led to decreased total and ovalbumin-specific serum IgE levels, whereas intravenous (IV) administration had no effect on this parameter. This could be related to the lower M702 concentrations in bronchoalveolar fluid following IV treatment as compared to intranasal administration. Notably, none of the treatments improved the lung inflammation score. In a study with repeated TSLP intranasal challenge in female mice, weekly intraperitoneal treatment with 50 mg/kg M702 inhibited TSLP-related lung inflammation. In a mouse model of contact hypersensitivity that bears some similarities to human type 2 inflammation, IV and intraperitoneal treatment with M702 during sensitisation and/or challenge led to a reduction of ear swelling and cell number in draining lymph nodes. Overall, inhibition of TSLP was associated with anti-inflammatory effects in the *in vivo* studies, although efficacy in the asthma model was low, particularly with the IV administration route. Since clinical efficacy studies exist for the requested indication and administration route (SC), additional nonclinical data are not required.
Studies of secondary pharmacodynamics were not conducted and are not required given the highly targeted nature of tezepelumab. The binding affinity of tezepelumab to C1q or Fcγ-receptors was not investigated. However, as tezepelumab is an IgG2 antibody, the risk of triggering Fc-related effects is considered to be low.
Safety pharmacology parameters were assessed in a single-dose IV study and in repeated-dose toxicity studies in cynomolgus monkeys. No effects on cardiovascular, respiratory and central nervous system function were observed in these studies at exposure levels up to multiple greater than clinical exposure levels.

5.2 Pharmacokinetics

The pharmacokinetics (PK) of tezepelumab were investigated in cynomolgus monkeys following single and repeated SC and IV administration. The PK parameters are typical of monoclonal antibodies and similar to the PK in humans. The increase in serum exposure was approximately proportional to dose and was comparable in males and females. T_{max} after single SC administration was 3-4 days post-dosing, and bioavailability was approximately 73%. Mean terminal half-life ($t_{1/2}$) after single SC and IV administration was 10-14 days, *i.e.* lower than $t_{1/2}$ in humans (25.5 days). Clearance was quite low (3.7-6.0 mL/day/kg), and volume of distribution was similar to plasma volume, indicating limited extravascular distribution. Accumulation ratios upon repeated weekly administration of up to 300 mg/kg (SC or IV) were ≤ 3.2.
Based on analyses of infant serum and milk, tezepelumab crosses the placental barrier and is excreted in milk. Therefore, use during pregnancy and lactation should be avoided, even though no adverse effects were observed in the enhanced pre/postnatal development (ePPND) study. This is addressed in the information for healthcare professionals.
In line with ICH S6(R1), distribution, metabolism, and excretion were not investigated.
In the toxicity studies with repeated dose administration, binding ADAs developed in several animals during the treatment and/or recovery periods. Exposure and bioactivity analyses in serum indicate that the presence of ADAs did not interfere with the validity of the studies. In the pivotal 6-month study, none of the animals tested positive for neutralising antibodies.

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5.3 Toxicology

The species selected for safety assessment (cynomolgus monkey) and the toxicology study programme for tezepelumab are in line with ICH S6(R1). The vehicle/formulation used in the studies differed from the clinical formulation. Since clinical safety data are available for the proposed formulation, additional nonclinical data are not required. The route of administration in the single-dose, ePPND, and local tolerance studies was IV injection. In the repeated-dose toxicity studies, tezepelumab was administered via IV or SC injection, which permitted an assessment of local effects with the proposed clinical administration route (SC). The dosing frequency in studies with repeated administration was once weekly, *i.e.* more than that proposed for clinical use. This accounts for the shorter serum $t_{1/2}$ in monkeys. The maximum duration of the repeated-dose studies of six months supports the proposed long-term use.

No local or systemic adverse effects related to tezepelumab were observed in the single-dose and repeated-dose studies at doses up to 300 mg/kg. Exposure at the 300 mg/kg/week SC dose (NOAEL) in the pivotal 6-month study was 134 times the clinical $AUC_{0\text{-}28d}$ (based on exposure in patients with 70 kg body weight). Findings related to tezepelumab treatment included reversible decreases in serum cholesterol and lower anti-KLH (keyhole limpet haemocyanin) IgG titres in animals at 300 mg/kg SC. The lower response to the T-cell dependent antigen was not considered adverse since no changes related to infection were observed in the study. The assessment of haematology, immunophenotyping, organ weights, and histopathology did not identify any other effects on the immune system.

In the 6-month study, one female in the 50 mg/kg IV dose group was euthanised because of poor clinical condition. This was attributed to ADA-related circulating immune complexes and was not directly related to tezepelumab. Since development of ADAs in monkeys is not predictive of immunogenicity in human, the formation of immune complexes is not considered relevant to an assessment of safety in humans.

In accordance with ICH S6(R1), genotoxicity and carcinogenicity studies were not conducted. The carcinogenic potential of tezepelumab was addressed in a risk assessment based on bibliographic data. The weight of evidence generally indicates a low risk of carcinogenicity, but the possibility that inhibition of TSLP could potentially promote tumours under certain conditions cannot be excluded. A respective warning note is included in the information for healthcare professionals and malignancy is considered an important potential risk (RMP).

In accordance with ICH S6(R1), the potential impact of tezepelumab on male and female fertility was assessed by evaluating the reproductive organs, sperm parameters, and menstrual cycles of sexually mature animals in the 6-month study. There were no tezepelumab-related findings.

In the ePPND study, pregnant cynomolgus monkeys received up to 300 mg/kg by IV injection once weekly from gestation day 20 through parturition. This involved an exposure of 169 times the clinical $AUC_{0\text{-}28d}$. No tezepelumab-related effects on fetal/infant survival, growth, and development were noted in the 6.5-month observation period. Assessments of the infants' immune system (immune response to KLH, immunophenotyping, haematology, and histopathology of lymphoid tissues) did not reveal any tezepelumab-related changes.

The requested indication included paediatric patients from 12 years of age. The nonclinical studies do not give rise to specific safety concerns with regard to the use of tezepelumab in adolescents. The 1–3-month repeated-dose toxicity studies were conducted in pre-pubertal/pubertal cynomolgus monkeys (3-5 years old), *i.e.* the studies covered the 12-18 year-old patient population.

Local tolerance following SC administration was assessed in the toxicity studies in monkeys. SC injection of 300 mg/kg caused an increased incidence in reversible minimal to slight perivascular infiltrates in the dermis and/or subcutis at the injection site.

The results of the evaluation of immune system parameters in the repeated-dose toxicity and ePPND study indicate a low risk of immunotoxicity and additional studies are not required.

A tissue cross-reactivity study detected no tezepelumab-specific staining in panels of normal human and cynomolgus monkey tissues. The lack of staining could be related to the low TSLP expression in healthy tissues.

The summary of the key findings from the nonclinical studies in the RMP is acceptable.

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Since tezepelumab is a protein, its use in patients presents no environmental risk.

5.4 Nonclinical Conclusions

The submitted pharmacology studies showed that tezepelumab has a high binding affinity for human TSLP and potently inhibits TSLP-related signalling. An adequate set of toxicity studies in a pharmacologically relevant animal species identified no safety concerns. From a nonclinical view, the application is approvable.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The PK of tezepelumab have been studied in healthy subjects and asthma patients following IV and SC administration in a dose range of 210–700 mg IV and 2.1–420 mg SC.

ADME

Absorption
Following SC administration, tezepelumab reached maximum concentrations after 3-10 days. A PopPK analysis estimated the absolute bioavailability at 76.8%.

Pharmacokinetics after multiple doses
Tezepelumab concentrations reached steady state by around 12 weeks after SC administration of the therapeutic dose of 210 mg Q4W and the mean accumulation ratio was 1.58.

Distribution
A PopPK analysis estimated the typical central and peripheral volumes of distribution (Vc and Vp) at 3.9 L, and 2.2 L respectively.

Metabolism and excretion
Given the biological nature of Tezepelumab, its metabolism has not been studied.

The terminal half-life after SC and IV administration ranged from 19.9 to 25.7 days across all studied dose levels. There was no apparent difference between SC and IV administration and terminal half-life did not appear to be dose-dependent. The PopPK analysis estimated typical clearance (CL) at 0.17 L/day, resulting in a half-life of 25.5 days.

Dose proportionality
The PK of tezepelumab were linear in the investigated dose range and no signs of target-mediated disposition were observed.

Special Populations / Intrinsic Factors

The effects of demographic covariates on the PK of tezepelumab were assessed in the PopPK analysis and the following statistically significant covariates were identified: Body weight on CL, Vc, intercompartmental clearance (Q), 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 on the PK of tezepelumab.
Of these, body weight had the most pronounced effects on tezepelumab exposure. Compared with a typical subject with a body weight of 70 kg, subjects with a body weight of 49 kg were expected to have 43.2 %, 41.8%, and 46.1% higher AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$ respectively, while subjects with a body weight of 114 kg were expected to have 38.8%, 38.0%, and 40.5% lower AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$ respectively.

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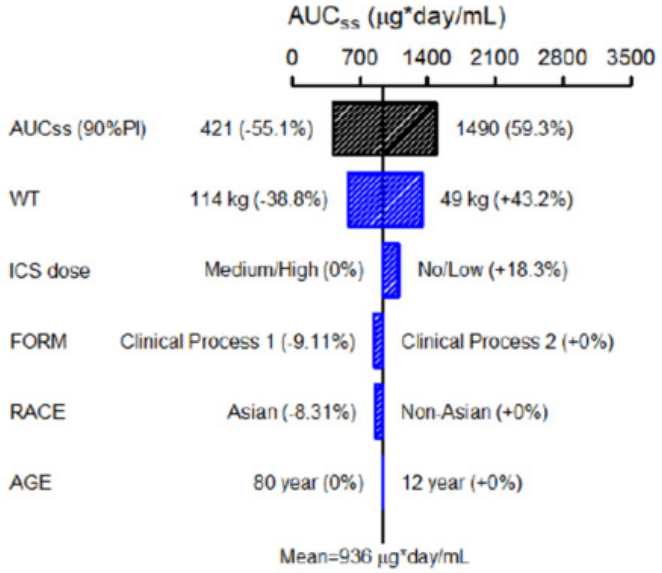
The effects of ICS, formulation, race and age were limited and not expected to be clinically relevant.



Effects of significant covariates on tezepelumab exposure (AUC_{SS}). Source: applicant`s documentation

No significant covariate effects were detected for other covariates, including sex, CRCL (> 30 ml/min), GFR, renal function categories, hepatic function measures (AST, ALT and total bilirubin levels) and disease status (healthy subjects versus asthma patients), and no dose adjustments based on any factors are required from a PK perspective.

Interactions

No dedicated interaction studies were submitted. The direct DDI potential of tezepelumab with drug-metabolising enzymes and drug transporters is considered low owing to the biological nature of the molecule. However, antibodies that modulate cytokine levels may modify the metabolism of drugs that are substrates for P450 enzymes by virtue of their effects on the regulation pathways of P450 enzymes.

Pharmacodynamics

Mechanism of action and primary pharmacology
Tezepelumab is an anti-thymic stromal lymphopoietin (TSLP), human monoclonal antibody immunoglobulin G2λ that binds to human TSLP and prevents its interaction with the heterodimeric TSLP receptor.

Secondary pharmacology (safety)
Given its biological nature, tezepelumab is not expected to affect the QT interval . An exploratory assessment of potential QT effects was conducted as part of a single ascending dose study and indicated no risk of QT prolongation for tezepelumab.

6.2 Dose Finding and Dose Recommendation

Dose-finding was based primarily on the results of the PATHWAY trial. This randomised, double-blind, parallel-group trial compared the following add-on therapies in groups of 138 patients aged 18 to 75 over a period of 52 weeks: Placebo versus 70 mg tezepelumab SC every four weeks; placebo versus 210 mg tezepelumab SC every four weeks; and placebo versus 280 mg tezepelumab SC every two weeks.
The patients had severe asthma that could not be adequately controlled with ICS-LABA (equivalent to ≥250 mcg fluticasone propionate). Patients were also stratified by eosinophil count (≥250 vs <250 cells per µL), ICS dose (> vs ≤ 500µg fluticasone) and location (non-Japanese vs Japanese).

The key endpoints were the calculated annualised rate of asthma exacerbations, and $\Delta FEV1_{\text{baseline week 52}}$.
A statistically significant benefit compared to placebo was found in all tezepelumab arms. The numerical differences between the different doses were minor. The requested dose (210 mg tezepelumab SC every four weeks) performed best in numerical terms.
The differences in exacerbation rates were similar to those in the overall population for all doses in all strata. The trial did not show that the 210 mg dose had any compelling benefits over the 70 mg dose. The non-weight-dependent dose of 210 mg may therefore be unnecessarily high. In terms of tolerability and safety, there were no consistent differences between the treatment arms; however, assay sensitivity of the study was limited. The dose-related and numerically slight increase in the drop-out rate hints at the possibility of dose-dependent safety issues.
In view of the results of the dose-finding studies, uncertainties remain as regards the optimal dose of tezepelumab for treating patients with severe asthma, even though the phase 3 trials have demonstrated the efficacy and safety of tezepelumab at a dosage of 210 mg.

6.3 Efficacy

Proof of efficacy was based primarily on two trials – NAVIGATOR and SOURCE – involving approximately 1,210 asthma patients aged 12 or over.

NAVIGATOR was a 52-week 1:1 parallel-group trial comparing placebo versus 210mg tezepelumab SC every four weeks in approximately 1,000 patients as add-on therapy to at least medium-dose ICS and at least one controller medication (LABA with/without LTRA/LAMA in the majority of cases).
The patients had asthma that was not fully controlled despite full-scale inhaled treatment and had suffered a minimum of two at least moderately severe exacerbations in the preceding twelve months.
The primary endpoint was the annualised rate of asthma exacerbations over the 52-week treatment period; $\Delta FEV1_{\text{baseline-week 52}}$ in the overall population was an important secondary endpoint. Other hierarchically controlled endpoints included quality of life (AQLQ(S)+12) and asthma control (ACQ-6).
There were significant differences between tezepelumab and placebo – in tezepelumab's favour – at these endpoints. The rate ratio for the annualised rate of asthma exacerbations over the 52-week treatment period was 0.29 [0.16–0.51] in PATHWAY and 0.44 [0.37–0.53] in NAVIGATOR. The difference in least square means compared to placebo for the change in FEV1 between week 52 and baseline was 0.13 [0.03–0.23] in PATHWAY and 0.13 [0.08–0.18] in NAVIGATOR. Tezepelumab was consistently found to be beneficial across all eosinophilia subgroups, except for adolescents, patients taking OCS, and underweight patients.

SOURCE was a 48-week 1:1 parallel-group comparison of tezepelumab in the requested dose versus placebo in approximately 150 patients as add-on therapy to high-dose ICS, at least one controller medication and oral corticosteroids (OCS; equivalent to 7.5-30mg prednisone). During the run-in phase, the OCS dose was adjusted for optimal clinical asthma control. During the treatment phase, once double-blind treatment had been in progress for four weeks, investigators attempted to gradually reduce the OCS dose with no loss of clinical control of the asthma.
The primary endpoint was the percentage reduction in OCS dosage at 48 weeks while not losing asthma control. The secondary endpoint was the reduction in annualised exacerbation rates (the two endpoints are interdependent).
A smaller number of patients who were administered tezepelumab completed their treatment compared to patients who were administered placebo (64/74 versus 71/76). In both endpoints, the differences in tezepelumab's favour in the overall population were only numerical. While a reduction in maintenance OCS therapy was numerically more frequent on tezepelumab than on placebo, the value was not large enough to be statistically significant (cumulative odds ratio 1.28 [95% CI: 0.69–2.35]).
There was no statistically significant difference between tezepelumab and placebo in terms of reduction in annualised exacerbation rates.

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The subgroups showed a heterogeneous picture. While benefits of tezepelumab treatment were demonstrated in eosinophilic forms of asthma, there tended to be disadvantages in patients with an $OCS_{baseline}$ >10mg, patients over 65, and patients with a BMI (body mass index) >30kg/m^2 .

6.4 Safety

A total of 1,326 asthma patients received at least one dose of tezepelumab; 787 of these received tezepelumab for at least 48 weeks and up to a maximum of 60 weeks. It is difficult to make a valid comparison of the patients in the various studies due to the varying severity of their asthma and the fact that some were taking systemic corticosteroids as co-medication.
The primary placebo-controlled safety pool consisted of around 650 asthma patients per arm, the majority of whom could not be adequately controlled with full-scale inhaled therapy, but could not be treated with oral corticosteroids either. The average observation period was just under one year. There was virtually no difference in the incidence of adverse reactions in both arms (placebo versus 210mg tezepelumab SC every four weeks); severe adverse reactions – particularly asthma-related reactions – were more common in patients on placebo (87/669 versus 57/665). The most common adverse reactions were pharyngitis, skin rash, joint pain, and local reactions at the site of injection. The investigator concluded a causal relation between tezepelumab and the following severe adverse reactions: one malignant melanoma in situ, one Guillain-Barré syndrome, migraine, myositis, and infections of the upper airways. In addition, a slight disparity was found in regard of focal infections (3 vs. 2), and malignancies [6 (0.9%) vs. 5 (0.7%)]. Additional long-term studies were still in progress when authorisation was granted.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

The pharmacokinetic / pharmacodynamic properties of tezepelumab were documented appropriately.

The documentation submitted demonstrated that treatment with tezepelumab is beneficial in certain (sub)populations. The NAVIGATOR trial demonstrated statistically significant and clinically relevant benefits for tezepelumab compared to placebo in the overall population of around 500 patients per arm. While there were no statistically significant differences in the overall population in SOURCE, the results of the trial suggested a clinical benefit for certain subgroups, particularly patients with eosinophilic forms of asthma. It is not yet possible to conclusively determine which patients could benefit optimally from treatment. There are several uncertainties in regard of safety, as well as concerns about the (at least theoretical) long-term risks. Thymic stromal lymphopoietin (TSLP) inhibition is a novel mechanism of action that has been investigated relatively little. Relevant literature describes TSLP as having promoting and inhibiting roles in inflammation-related tissue damage and the development of malignancies, which leaves the possibility that systemic TSLP inhibition could have undesirable long-term effects. In light of this, the presented safety documentation is limited in both its scope and observation period (1,104 patients exposed to therapeutic dosages for ≥20 weeks, 787 exposed for ≥48–60 weeks). Furthermore, identifying safety signals was further hampered by the fact that analyses were broken down into several subpopulations. Therefore further long term safety data will be collected post-marketing.
While the submitted safety data do not suggest that tezepelumab has any conclusive and detrimental disadvantage compared to placebo, a slight disparity in terms of neoplasia has been described. Such events are rare and require a sufficiently long observation period so that they can be appropriately monitored.
A slight disparity in terms of focal infections leaves open the possibility of impaired immune response to infections, especially as patients with parasitic worm infections, a history of clinically significant infections and worm infections or recent vaccination with a live vaccine were excluded from the trials. In this context, the lack of data on the effects of tezepelumab treatment on vaccination response represents a serious omission in the documentation. For this reason, it is not possible to recommend the use of attenuated live vaccines during or immediately before tezepelumab treatment. To evaluate

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the effect of TSLP inhibition on post-vaccination immune response, the Marketing Authorisation Holder is requested to submit the definitive results of the ongoing VECTOR trial.

Overall, the documented benefits of tezepelumab as add-on therapy for full inhalation-based maintenance therapy in adult asthma patients are offset primarily by hypothetical long-term risks that could include an increase in malignancies and/or impaired immune response to infections as a result of TSLP inhibition (as with other immunomodulators), but which may not yet have been recorded owing to the shortness of the observation period. As stated in the RMP, Swissmedic is closely monitoring these risks.
Overall, the assessment of the risk-benefit ratio of tezepelumab in the treatment of adult patients with uncontrolled severe asthma and no long-term OCS therapy is positive. As a condition, the final reports from the ongoing DESTINATION long-term extension study and the VECTOR vaccination study must be submitted to Swissmedic on completion to augment the current efficacy and safety data.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to 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 reference document, which is valid and relevant 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. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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

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

Indications/Uses

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”.

Dosage/Administration

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

Usual dosage

Adults

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.

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

The safety and efficacy of TEZSPIRE in children and adolescents under 18 years of age have not been established. Only limited data are available (see “Properties/Effects”).

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 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. 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.

Vaccinations

No data is available on response to vaccinations in patients receiving treatment with TEZSPIRE. Based on current evidence, it cannot be evaluated whether TEZSPIRE inhibits the immune response to neo-antigens and/or booster antigens. Prior to initiation of TEZSPIRE therapy, it is recommended to bring the patient’s vaccination status up to date.
The use of live attenuated vaccines is not recommended during or immediately before TEZSPIRE therapy. 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”.
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

In clinical studies in patients with severe asthma, the most commonly reported adverse reaction during treatment were arthralgia and pharyngitis.

Adverse Drug Reactions

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.

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	Pharyngitis[a]	Common
Skin and subcutaneous tissue disorders	Rash[b]	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Common
General disorders and administration site conditions	Injection site reaction	Common

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

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

Description of specific adverse reactions

Injection site reactions

In the 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 the asthma inflammatory cascade and plays a role in the initiation and persistence of airway inflammation in asthma. TSLP regulates immunity at the airway barrier surface 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). In asthma, 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

In NAVIGATOR, administration of tezepelumab 210 mg SC Q4W (n=528) reduced inflammatory biomarkers and cytokines from baseline compared with placebo (n=531) 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 52 weeks of treatment. Similar effects were seen in PATHWAY.
A 28-week Phase 2 randomised, double-blind, placebo-controlled, parallel-group mechanistic study evaluated the effect of tezepelumab 210 mg SC Q4W on airway inflammation in adults (n=116) with inadequately controlled moderate to severe asthma. Tezepelumab reduced submucosal eosinophil counts by 89% (end of treatment to baseline ratio 0.11 [90% CI 0.06, 0.21]) compared with a 25% reduction with placebo (0.75 [90% CI 0.41, 1.38]). Reduction was consistent regardless of baseline subgroup levels of blood eosinophils, FeNO, serum IL-5, serum IL-13 and allergic status (determined by a perennial aeroallergen specific IgE).

Immunogenicity

In NAVIGATOR, anti-drug antibodies (ADA) were detected 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.

Clinical efficacy

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.

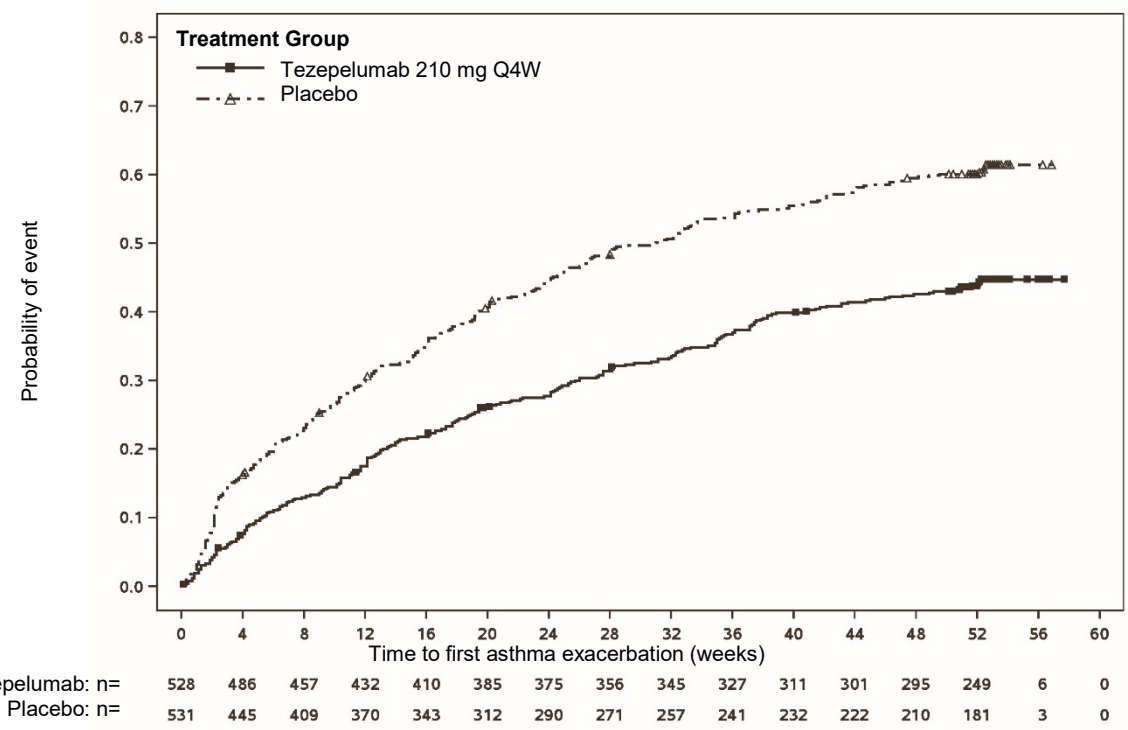
Table 3 Rate of Clinically Significant Exacerbations Over 52 Weeks, Trial 1 and Trial 2

	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.

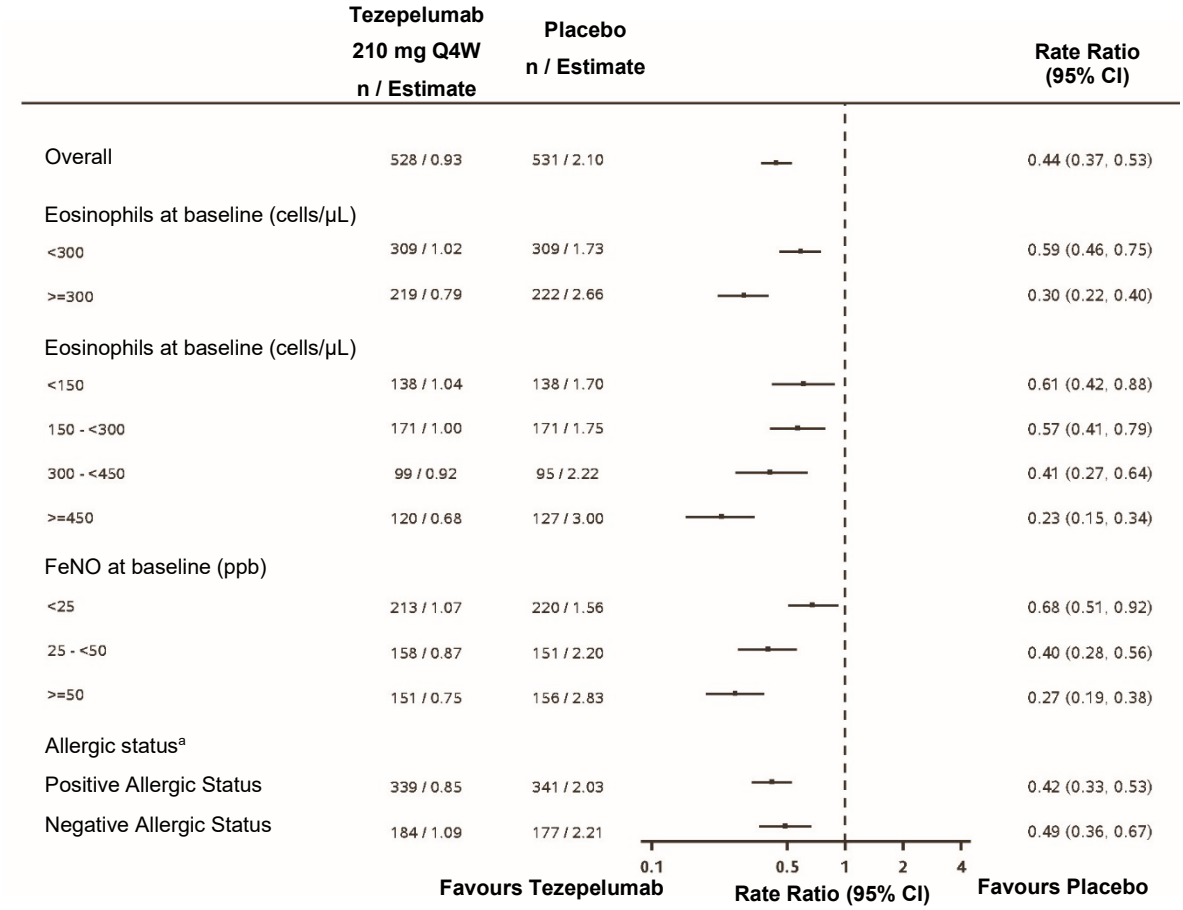
Figure 1 **Kaplan-Meier Cumulative Incidence Curves for Time to First Exacerbation Through Week 52, Trial 2**



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).

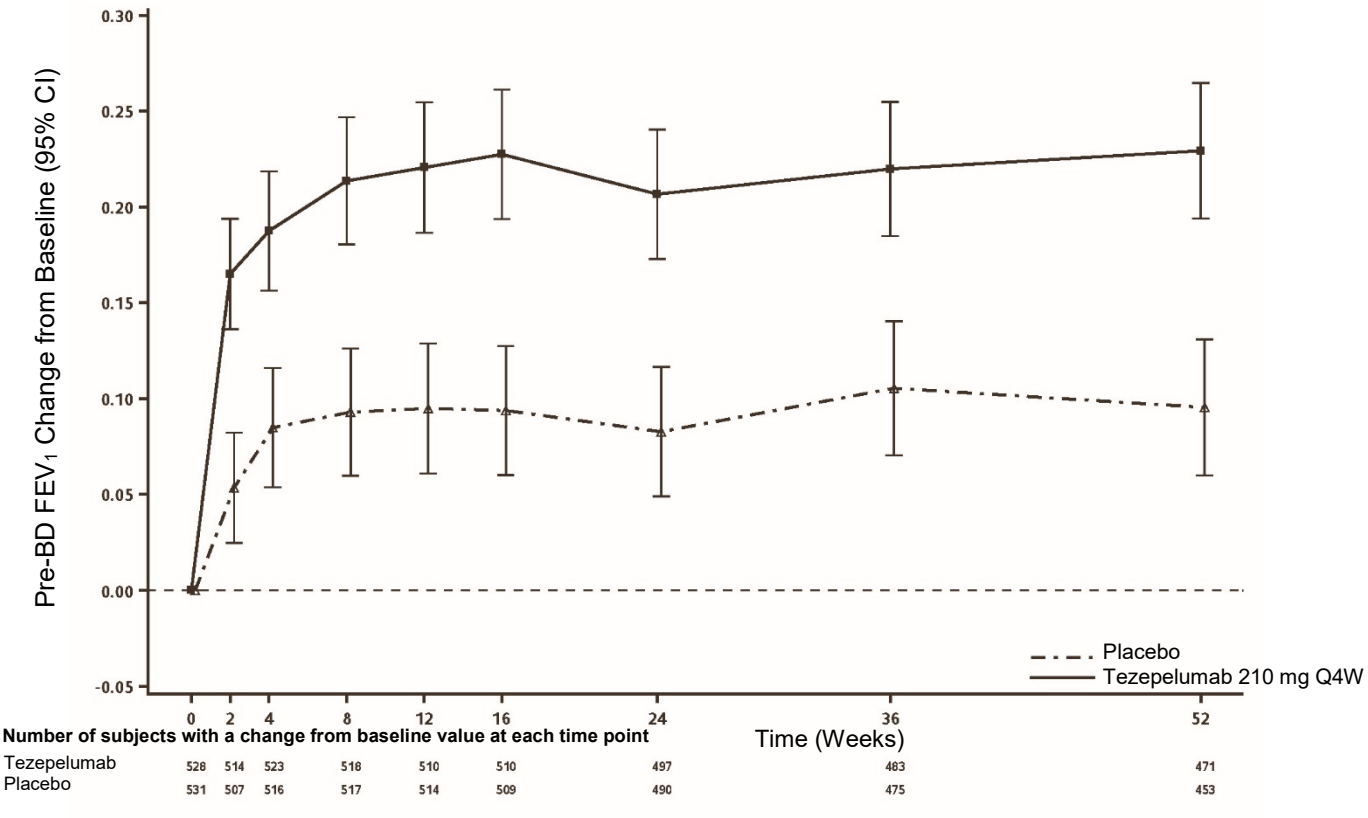
Table 4 Mean Change from Baseline in Pre-Bronchodilator FEV_1 at Week 52, PATHWAY and NAVIGATOR

	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		

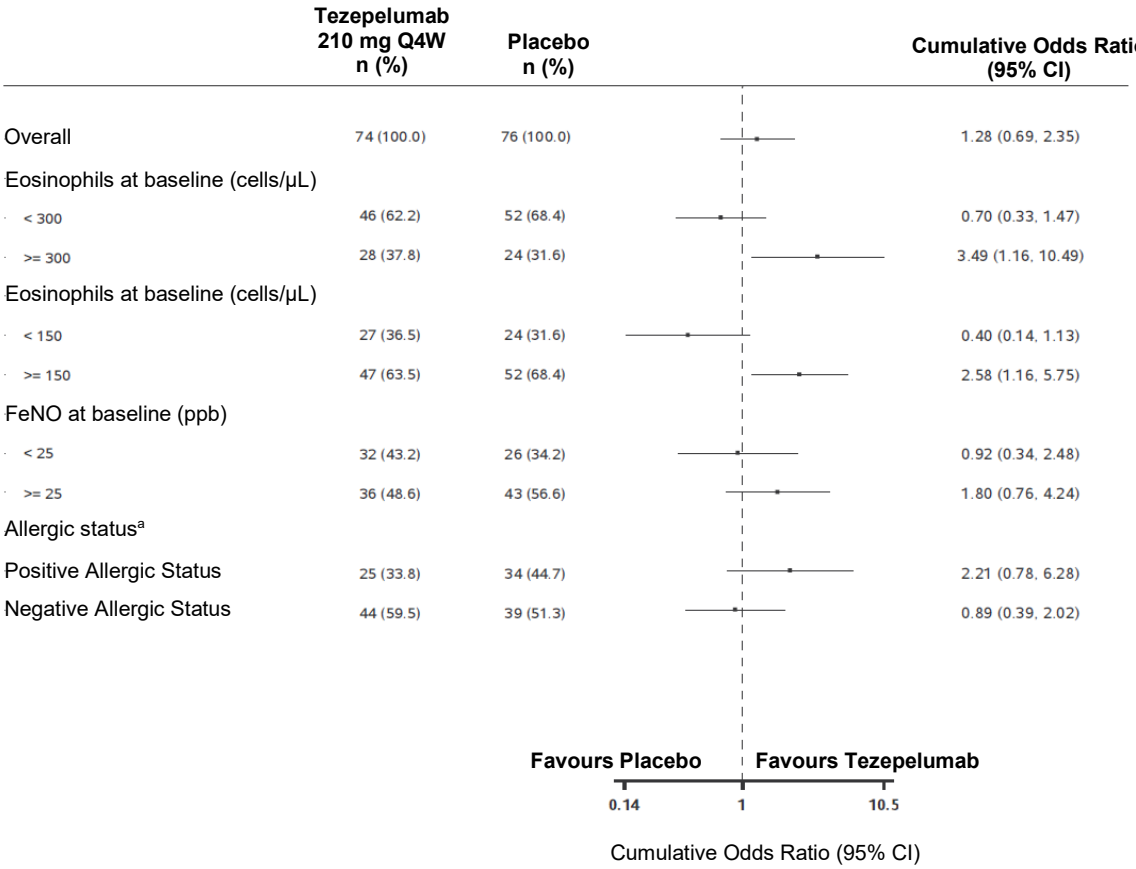
* Number of patients contributing to the full analysis (FA) with at least 1 change from baseline value

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.

Pharmacokinetics

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 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 light yellow. 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 are given in the package leaflet and ‘Instructions for Use’.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

68454 (Swissmedic)

Packs

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

Marketing authorisation holder

AstraZeneca AG, 6340 Baar

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