PASS Study Progress Report	
Active substance	Tezepelumab
Study Code	H0005588
Version number	Version 1.0
Date	*29 April 2025*

TREATY: Tezepelumab Pregnancy Study

A Non-Interventional Multi-Database Post-Authorisation Study to Assess Pregnancy-Related Safety Data from Women with Severe Asthma Exposed to Tezepelumab

PASS INFORMATION

Title	A Non-Interventional Multi-Database Post-Authorisation Study to Assess Pregnancy-Related Safety Data from Women with Severe Asthma Exposed to Tezepelumab
Version identifier of the progress report	Version 1.0
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Active substance	Tezepelumab (R03DX11)
Medicinal product	TEZSPIRE
Product reference	H0005588
Procedure number	EMA/H/C/005588
Marketing authorisation holder(s)	ASTRAZENECA PHARMACEUTICALS LP, 1800 Concord Pike, Wilmington, Delaware 19803, United States of America.

Joint PASS	No
Research question and objectives	The aim of this report is to document the progress of the post-authorisation safety study on the risk of congenital malformations (CM), adverse pregnancy outcomes, and adverse birth outcomes in pregnancies and offspring of women who received tezepelumab for severe asthma during pregnancy and women who received other SOC treatments for severe asthma during pregnancy. Primary endpoint: Major CM. Secondary endpoints: • foetal death (composite of miscarriage, stillbirth, ectopic pregnancy), • minor CM, • individual adverse pregnancy outcomes (ectopic pregnancy, miscarriage, stillbirth, termination of pregnancy, pre-eclampsia), • individual birth outcomes (emergency c-section, preterm birth, small for gestational age, and low birth weight)
Countries of study	Denmark, France, Sweden, and United States of America
Author	*Lead Epidemiologist* PPD IQVIA PPD PPD PPD PPD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	ASTRAZENECA PHARMACEUTICALS LP, 1800 Concord Pike, Wilmington, Delaware 19803, United States of America.
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1. ABSTRACT

Title

A Non-Interventional Multi-Database Post-Authorisation Study to Assess Pregnancy-Related Safety Data from Women with Severe Asthma Exposed to Tezepelumab

Progress report version 1.0, 29 April 2025, PPD *(IQVIA)*

Rationale and background

TEZSPIRE® (tezepelumab) was approved by the Food and Drug Administration (FDA) in December 2021 and by the European Medicines Agency (EMA) in September 2022 for the treatment of severe asthma in adults and adolescents (12 years of age and older) who is not adequately controlled by a combination of high-dose corticosteroids (inhalation) plus another asthma medication. As severe asthma may affect women of childbearing potential, it is conceivable that tezepelumab exposure during pregnancy may occur. As part of the original marketing authorisation application to the EMA, AstraZeneca included a proposal within the European Union Risk Management Plan, to conduct a non-interventional multi-country PASS to assess pregnancy-related safety data from women with severe asthma exposed to tezepelumab. Consequently, a non-interventional PASS was designed to fill the evidence gap on the safety of tezepelumab exposure during pregnancy. The aim of this study is to describe the risk of congenital malformations (CM), adverse pregnancy outcomes, and adverse birth outcomes in pregnancies and offspring of women who received tezepelumab for severe asthma during pregnancy and women who received other standard of care (SOC) treatments for severe asthma during pregnancy. The study will utilise a non-interventional longitudinal population-based retrospective cohort design, using existing data from multiple data sources based on medical records. The data sources include national registries from Denmark, Sweden, France and claims data from Carelon Research in the United States of America (USA).

This progress report summarises the project activities since the endorsement of the protocol version 3.0 by the EMA on 25 January 2024 until the present date. These activities include setting up the independent SSC, start of data source contracting, and the development of the global study code list. This report also provides updated counts of patients with asthma related records, pregnancies, and general drug uptake.

Research question and objectives.

This report provides an update on the progress of the PASS on the risk of congenital malformations (CM), adverse pregnancy outcomes, and adverse birth outcomes in pregnancies and offspring of women who received tezepelumab for severe asthma during pregnancy and women who received other SOC treatments for severe asthma during pregnancy. The report does not address the research questions and study objectives themselves, but includes a status update on data source contracting, as well as quantitative assessment of annual counts on asthma

related hospital contacts, pregnancy counts, as well as uptake of tezepelumab and other selected biologics. Where available, pregnancy specific drug uptake is reported.

Setting

In protocol v3.0, data sources from four different countries were selected based on the feasibility assessment conducted between December 2022 and November 2023. All the selected data sources are unchanged, and the Danish Abortion registry has been added. The main start-up activities which included initiation and finalisation of the contracting process were completed for one data source, namely Healthcare Integrated Research Database (HIRD) from Carelon Research (the United States of America [USA]). Country level start-up activities for the remaining data sources will occur between Q3 2025 and Q2 2026.

Subjects and study size, including cohort attrition

Recorded uptake of tezepelumab during pregnancy was as expected for HIRD. Data are not provided for other data sources prior to contracting.

Variables

Patient counts requested from each data source for this report were based on codes used in the initial feasibility assessment. The global code lists v1.0 for the PASS have been developed in parallel.

Discussion

The required study activities are progressing as planned. We do not expect any delays in the timing of the first interim report due on 31 March 2028.

Marketing Authorisation Holder(s)

ASTRAZENECA PHARMACEUTICALS LP,
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2. LIST OF ABBREVIATIONS

Abbreviation	Explanation
ATC	Anatomical Therapeutic Chemical
ATIH	Technical Agency for Hospital Information
CM	Congenital malformation
DDD	Defined daily dose
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS	European Union Post-Authorisation Studies
FDA	Food and Drug Administration
HMA-EMA	The Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA);
HIRD	Healthcare Integrated Research Database
ICD-10	International Statistical Classification of Diseases, 10th Revision
ICD-10-CM	International Statistical Classification of Diseases, 10th Revision, Clinical Modification
IgE	Immunoglobin E
LBW	Low birth weight
MAH	Market Authorisation Holder
MCM	Major Congenital Malformation
mCM	Minor Congenital Malformation
N/A	Not applicable
PASS	Post-authorisation safety study
PDD	Prescribed daily dose
PRAC	Pharmacovigilance Risk Assessment Committee
QC	Quality control
SGA	Small for gestational age
SNDS	National Health Data System
SOC	Standard of care
SSC	Study Steering Committee
TBD	To be determined
TOPFA	Terminations of pregnancy for foetal anomalies
USA	United States of America
WHO	World Health Organisation

3. INVESTIGATORS

Responsible parties	Contact details
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Marketing Authorisation holder	ASTRAZENECA PHARMACEUTICALS LP, 1800 Concord Pike, Wilmington, Delaware 19803, United States of America.

4. OTHER RESPONSIBLE PARTIES

4.1 Study Steering Committee

A Study Steering Committee (SSC) composed of experts in respiratory diseases including severe asthma and retrospective database studies have been established to support both the TREATY[1] (current) and TRESPASS[2] (Cardiovascular endpoints) studies, with the addition of experts in perinatal outcomes for TREATY. An SSC Charter describing the SSC roles and responsibilities was developed. Introductory meetings have occurred, and an SSC Kick-Off Meeting will be held to provide an overview of the TREATY study, SSC structure, ways of working, and study timelines. The main SSC roles and responsibilities are:

- Provide independent, expert advice and recommendations for the study methodology (design, data collection, and analysis), clinical input, study conduct, and data interpretation.
- Review the Study Reports.

[1] EU PAS register number for TREATY - EUPAS1000000176
[2] EU PAS register number for TRESPASS - EUPAS1000000169

- Provide expertise/ guidance in the interpretation, suitability for inclusion and publication of study results.
- Attendance of SSC Meetings and approval of meeting minutes.

5. MILESTONES

Table 1 illustrates the market authorisation holder (MAH) proposed milestones incorporated in the Post-Authorisation Safety Study (PASS) protocol (version 3.0). The proposed milestones have not changed compared to the information provided in the endorsed protocol v3.0.

Table 1 Milestones

Milestone	Planned date	Actual date
Protocol submission v3.0	*N/A*	30 October 2023
PRAC approval of protocol v3.0	*N/A*	25 January 2024
Registration in the HMA-EMA Catalogue of real-world data studies[1]	11 May 2024	29 May 2024
Study progress report 1	30 May 2025	*29 April 2025*
Start of data collection	30 June 2027	*TBD*
Interim report 1	31 March 2028	*TBD*
Interim report 2	31 March 2031	*TBD*
End of data collection	31 March 2033	*TBD*
Final report of study results	31 March 2034	*TBD*

1 The HMA-EMA Catalogue of RWD studies has replaced the European Union electronic register of post-authorisation studies (EU PAS Register).
Abbreviations: HMA-EMA, Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA); N/A, Not applicable; PRAC, Pharmacovigilance Risk Assessment Committee.

6. RATIONALE AND BACKGROUND

TEZSPIRE® (tezepelumab) was approved by the Food and Drug Administration (FDA) in December 2021 and by the European Medicines Agency (EMA) in September 2022 for the treatment of severe asthma in adults and adolescents (12 years of age and older) who is not adequately controlled by a combination of high-dose corticosteroids (inhalation) plus another asthma medication. As severe asthma may affect women of childbearing potential, it is conceivable that tezepelumab exposure during pregnancy may occur. As part of the original marketing authorisation application to the EMA, AstraZeneca included a proposal within the European Union Risk Management Plan, to conduct a non-interventional multi-country PASS to assess pregnancy-related safety data from women with severe asthma exposed to tezepelumab. Consequently, a non-interventional PASS was designed to fill the evidence gap on the safety of tezepelumab exposure during pregnancy. The aim of this study is to describe the risk of congenital malformations (CM), adverse pregnancy outcomes, and adverse birth

outcomes in pregnancies and offspring of women who received tezepelumab for severe asthma during pregnancy and women who received other standard of care (SOC) treatments for severe asthma during pregnancy. The study will utilise a non-interventional longitudinal population-based retrospective cohort design, using existing data from multiple data sources based on medical records. The data sources include national registries from Denmark, Sweden, France and claims data from Carelon Research in the United States of America (USA).

This progress report summarises the project activities since the endorsement of the protocol version 3.0 by the EMA on 25 January 2024 until the present date. These activities include setting up the independent SSC, start of data source contracting, and the development of the global study code list. This report also provides updated counts of patients with asthma related records, pregnancies, and general drug uptake.

7. RESEARCH QUESTION AND OBJECTIVES

The purpose of this report is to provide an update on the progress of the PASS on the risk of CM, adverse pregnancy outcomes, and adverse birth outcomes in pregnancies and offspring of women who received tezepelumab for severe asthma during pregnancy and women who received other SOC treatments for severe asthma during pregnancy. The report does not address the research questions and study objectives themselves, but includes a status on data source contracting, as well as quantitative assessment of annual counts on asthma related hospital contacts, pregnancy counts, and uptake of tezepelumab and other selected biologics. Where available, pregnancy specific drug uptake is reported.

The report will provide updated counts since launch of tezepelumab on:

1) Annual number of patients[3] exposed to tezepelumab
2) Annual number of patients[3] exposed to other biologics indicated for severe asthma
3) Annual number of patients with asthma related contacts
4) Annual number of pregnancies

No modifications have been made to the study objectives and they remain as per study protocol v3.0.

8. AMENDMENTS AND UPDATES

There have been no major amendments since the endorsement of protocol v3.0.

[3] Or number of packs sold and/or reimbursed where patient counts were not available.

9. STATUS UPDATES

9.1 Setting

As per protocol v3.0, the study will use existing data from four different data sources in four countries: Denmark, France, Sweden, and the USA. In protocol v3.0 the following data sources were selected based on the feasibility assessment conducted between December 2022 and November 2023:

1. Danish national health and socio-economic registries - Denmark
2. National Health Data System (SNDS) - France
3. Swedish national health registries - Sweden
4. Healthcare Integrated Research Database (HIRD) from Carelon Research - USA

Since the approval of protocol v3.0, the Danish Registry of Legally Induced Abortions has been added to the list of data sets to cover all terminations in Denmark. The Danish setting of terminations has changed over time and is now managed by medical intervention over procedural intervention for more than 80% of terminations (1). This can be done by hospitals or specialist clinics and both private and public terminations will be captured in the Abortion registry mentioned above.

The status of the start-up activities for the study data sources are outlined in Table 2. At this stage, IQVIA has contracted Carelon Research (USA). In Denmark, Sweden, and France, country level start-up activities will occur between Q2 2025 and Q2 2026.

Table 2 Start-up activities status for the selected data sources

Data Source name	Status of data sources	Other actions/ comments
Danish national health and socio-economic registries (Denmark)	Data access application to start in Q2 2026	Local adaptation of code lists required
Swedish national health and socio-economic registries (Sweden)	Data access application to start in Q3 2025	Local adaptation of code lists required
SNDS (France)	Data access application to start on Q2 2025	Local adaptation of protocol required. Local adaptation of code lists required.
HIRD (USA)	Contracted with Carelon Research. Signed on the 22 August 2024	Study protocol v3.0 was reviewed by Carelon Research. Study Kick Off Meeting was held on the 23 October 2024

Abbreviations: HIRD, Healthcare Integrated Research Database; SNDS, National Health Data System; USA, United States of America; Q, Quarter

9.2 Subjects

Carelon Research have provided general counts for the prevalence of asthma among women of childbearing potential, as well as high-level population counts for the monitoring of uptake of tezepelumab and other selected biologics in HIRD. No data have been collected from other data sources (due to later European approval and data lag), however national statistics have been included to assess general uptake of relevant biologics, asthma prevalence and annual pregnancy counts (where available).

The study population of women with severe asthma during pregnancy require identification through a treatment and exacerbation algorithm as detailed in the protocol. As full data extraction and programming are not feasible prior to contracting, data application and extraction, this report is based on key counts provided by data source holders or through publicly available national statistics.

Patients with asthma related records (existing and new) each year from 2022 to 2024 were identified using the International Statistical Classification of Diseases, 10th Revision (ICD-10) diagnosis code J45 or J46 or national equivalent codes (Carelon Research used ICD-10 Clinical Modification [ICD-10-CM] equivalents). This was categorised by female sex, and 18 to 49 years of age where available. The number of pregnancies in each data source was also assessed and categorised into livebirths, stillbirths, miscarriages, ectopic pregnancies, and termination of pregnancy due to foetal anomalies, if available. Drug uptake was assessed for tezepelumab as well as other biologics used in the treatment of severe asthma including omalizumab, reslizumab, mepolizumab, benralizumab, or dupilumab (Anatomical Therapeutic Chemical [ATC] codes R03DX05, R03DX08, R03DX09, R03DX10, and D11AH05). Drug uptake was reported as number of patients, DDD or packs per year as available from each country.

9.2.1 Country specific asthma prevalence

Source population patient counts on asthma prevalence were requested from Carelon Research (USA) and based on publicly available reports and statistics for Denmark, Sweden, and France. Number of patients with a record of asthma each year (either new or existing) were requested and, where available, the numbers were provided for females aged 18-49 years. For Denmark and Sweden the age categories were not aligned with requested range (18-49) hence the 15-49 age range was provided instead. Counts of patients with severe asthma were not available prior to data extraction as this requires algorithmic derivation.

9.2.1.1.1 DENMARK

The Danish national registries cover the entire nation of 5.9 million people of which around 300,000 asthma patients each year have a contact with either primary care, hospital, or community care (2). National statistics were available for both cross-sectional care (primary care, community care and hospital care), as well as diagnosis specific records in the national

hospital data. Counts from both sources were categorised based on sex and age, however the requested age-range from 18 to 49 was not available, hence the range from 15-49 was provided instead (Table 3).

Approximately 31,000 people had a hospital record related to asthma each year (some overlap in patients is expected between years and total number of patients during period was not provided). Of these, approximately 5,500 patients were women of childbearing potential (female sex, aged 15-49).

Table 3 Annual asthma prevalence in Denmark

Denmark	**2022**	**2023**	**2024**	**2022-2024**
General asthma population (2)				
Asthma diagnosis (existing and new)	300,228	304,632	311,845 [a]	N/A
Female	161,341	164,120	167,988 [a]	N/A
15-49 years of age	82,967	83,733	84,857 [a]	N/A
Number of patients with an asthma specific hospital contact (3)				
Asthma diagnosis	J45: 30,990 J46: 510	J45: 31,189 J46: 523	Not yet available	
Female	J45: 16,872 J46: 317	J45: 17,053 J46: 315		
15-49 years of age	J45: 5,527 J46: 102	J45: 5,395 J46: 123		

[a)] Based on data until March 2024.

9.2.1.1.2 FRANCE

The SNDS covers 99% of the French population and include >66 million patients. Annual counts for in-patient and out-patient specific settings are presented in Table 4. Stratification by age and sex was not possible prior to data extraction.

Table 4 Annual asthma prevalence in France

France	**2022**	**2023**	**2024** [a]	**2022-2024**
Asthma diagnosis	In-patient: - J45: 51,041 - J46: 11,992 Out-patient: - J45: 147,080	In-patient: - J45: 56,635 - J46: 13,668 Out-patient: - J45: 149,050	In-patient: - J45: 51,339 - J46: 12,460 Out-patient: Not available	

[a] Data partially consolidated.

9.2.1.1.3 SWEDEN

The Swedish national registries cover the entire nation of >10 million people of which almost 4.5 million people had a record in the national registries each year. Counts were categorised based on sex and age, however the requested age-range from 18 to 49 was not available, hence the range from 15-49 was provided instead in Table 5. Approximately 75,000 people had a

hospital record related to asthma each year (some overlap expected between years and total during period was not provided). Of these, approximately 5,000 patients were women of childbearing potential (female sex, aged 15-49).

Table 5 Annual asthma prevalence in Sweden

Sweden	2022	2023	2024	2022-2024
Asthma diagnosis	J45: 74,744 J46: 689	J45: 77,875 J46: 710	Not yet available	
Female	J45: 33,735 J46: 424	J45: 35,193 J46: 445		
15-49 years of age	J45: 5,024 J46: 110	J45: 5,075 J46: 132		

9.2.1.1.4 USA – HIRD DATA FROM CARELON RESEARCH

Carelon Research's data source HIRD covers >31 million patients of which approximately 1.7 million patients had a record related to asthma between January 2022 and August 2024 as presented in Table 6. Of these, approximately 464,000 were women of childbearing potential (female sex, aged 18-49).

Table 6 Annual asthma prevalence in HIRD

HIRD	2022	2023	2024 [a]	2022-2024
Asthma diagnosis (existing and new)	935,431	954,508	727,480	1,735,368
Female	566,134	576,256	441,902	1,038,612
18 – 49 years of age	244,417	244,205	183,061	464,491

[a] Data from January to August 2024
Abbreviations: HIRD, Healthcare Integrated Research Database

9.2.2 Country specific annual number of pregnancies

General population counts for annual number of pregnancies were assessed from national statistics in Denmark, Sweden, and France. Carelon Research provided counts for pregnancies specific for the asthma population. Terminations of pregnancy for foetal anomalies (TOPFA) were not assessed in this report as this is not readily recorded and requires algorithmic programming of maternal antenatal care records in relation to termination.

9.2.2.1.1 DENMARK

Annual statistics were assessed from the Danish Health Data Authorities online statistics and included counts of annual deliveries including both live and stillbirths from the Medical Birth Register, terminations from the Abortion Register, and ectopic pregnancies and miscarriages from the National Hospital Patient Registry.

Table 7 Pregnancies in Denmark

Denmark	2022	2023	2024	2022-2024
Number of deliveries (livebirths)	58,670	57,870	Not yet available	
Number of deliveries (stillbirths)	220	205		
Number of miscarriages	2,307	2,135		
Number of terminations	14,935	15,260		
Number of ectopic pregnancies	854	845		

Source: https://www.esundhed.dk/Emner/Graviditet-foedsler-og-boern & https://www.esundhed.dk/Emner/Operationer-og-diagnoser/Landspatientregisteret-Avanceret-udtraek

9.2.2.1.2 FRANCE

Annual statistics were assessed from the ScanSanté platform providing annual hospital data from ATIH (Technical Agency for Hospital Information).

Table 8 Pregnancies in France

France	2022	2023	2024	2022-2024
Number of deliveries (livebirths)	612,730	571,496	481,185	1,665,411
Number of deliveries (stillbirths)	6,289	5,890	5,321	17,500
Number of miscarriages	33,015	31,607	26,779	91,401
Number of terminations	8,668	8,154	7,555	24,377
Number of ectopic pregnancies	15,526	15,658	15,632	46,816

Source: https://www.scansante.fr/applications/statistiques-activite-MCO-par-diagnostique-et-actes

9.2.2.1.3 SWEDEN

Annual statistics were assessed from the Swedish National Board of Health and Welfare's publicly available statistics database. Counts included annual deliveries including both live and stillbirths from the Medical Birth Register, terminations, ectopic pregnancies, and miscarriages from the National Hospital Patient Registry.

Table 9 Pregnancies in Sweden

Sweden	2022	2023	2024	2022-2024
Number of deliveries (livebirths)	104,346	98,331	Not yet available	
Number of deliveries (stillbirths)	343	286		
Number of miscarriages	9,530	9,102		
Number of terminations	11,660	11,765		
Number of ectopic pregnancies	1,791	1,789		

Source: https://sdb.socialstyrelsen.se/if_par/

9.2.2.1.4 USA – HIRD DATA FROM CARELON RESEARCH

Carelon Research identified 33,908 pregnancies in the data set from 2022 to August 2024. Of these, 300 pregnancies had more than one outcome of pregnancy recorded, and 2,984 did not have any of the specified codes for the pregnancy outcomes recorded. Table 10 details the 30,624 pregnancies with a recorded outcome. Among 25,113 pregnancies resulting in a live birth, six women were exposed to tezepelumab and of all pregnancies in women with asthma, 209 were exposed to other biologics.

Table 10 Pregnancies among women with asthma in HIRD from 2022 to August 2024

HIRD	2022	2023	2024	2022-2024
Number of deliveries (livebirths)	3,439	13,151	8,523	25,113
Number of deliveries (stillbirths)	16	34	23	73
Number of miscarriages	916	1,152	733	2,801
Number of terminations	508	758	507	1,773
Number of ectopic pregnancies	290	350	224	864
Total number of pregnancies with a recorded outcome	5,169	15,445	10,010	30,624

Abbreviations: HIRD, Healthcare Integrated Research Database

9.2.3 Assessment of annual uptake of tezepelumab and other biologics

For each year, the request included the number of patients with exposure to biologic drugs of interest (tezepelumab, omalizumab, reslizumab, mepolizumab, benralizumab, dupilumab). Data on biologics other than tezepelumab was requested to provide context for the interpretation of tezepelumab uptake. For Denmark, it was only possible to assess the number of defined daily doses (DDDs) and number of unique packs sold, while for France it was only possible to assess the number of packs that were dispensed and reimbursed. The available information differs between data sources, as detailed in Table 11.

Table 11 Available data for drug uptake in each data source

Country	Tezepelumab market launch	Measurement unit	Considered period
Denmark	April 2023	Number of DDDs (28 DDDs per administration) [a] + Number of packs per product including specific strength and pack size	May 2023-December 2024
Sweden	September 2022	Number of patients exposed	September 2022-December 2023
France	May 2023	Number of dispensed and reimbursed packs [b]	June 2023-December 2024
USA	December 2021	Number of patients exposed	January 2022-August 2024

[a] Tezepelumab is available in 210 mg per injection in the pre-filled syringes/pens, and the WHO DDD corresponds to 7.5 mg based on 210 mg every 4 weeks.

[b] Number of administrations per pack was not available. Tezepelumab is available in pack sizes of one pen or one pre-filled syringe. Mepolizumab is available in packs of three or one administration, and dupilumab are only available in two administrations per pack.

Abbreviations: DDD, defined daily dose; USA: United States of America; WHO, World Health Organisation

To interpret the available data, a conservative projection was performed to determine the approximate number of patients represented by DDDs and number of packs, respectively, as described in the following sections. Table 12 outline the available administration dosage as well as conversions of DDD to number of administrations and max number of administrations per person per year. Dosage of reslizumab is weight dependant, however the standard regime is administration every 4 weeks and the standard DDD as provided by world health organisation (WHO) was used for the conversion to DDD per administration (4). Dosage of omalizumab is weight and disease severity dependant and the administration schedule and dose are presented separately in Table 13. The standard DDD as provided by WHO was not aligned with the asthma label, hence Prescribed Daily Dose (PDD) based on the label was calculated per administration.

Table 12 Conversion table per biologic – DDDs/administration & administrations/year

Biologic	**Administration**	**Administration schedule** (every)	**DDD** (4) per administration (DDD/adm)	**Approximate number of administrations per year**
Tezepelumab (5)	Fixed: 210 mg Subcutaneous injection	4 weeks	7.5 mg/day = 28	52 weeks /4 = 13
Reslizumab (6)	Based on weight: ~ 200 mg Intravenous	4 weeks	7.1 mg/day = 28	52 weeks /4 = 13
Mepolizumab (7)	Fixed: 100 mg for ages ≥12 Subcutaneous injection	4 weeks	3.6 mg/day = 28	52 weeks /4 = 13
Benralizumab (8)	Fixed: 30 mg for ages ≥12 Subcutaneous injection	4 weeks for 3 doses, then 8 weeks	0.54 mg/day = 56	3 (every 4 weeks) + 5 (every 8 weeks) = 8 (first year) then 6
Dupilumab (9)	Fixed: 300 mg Subcutaneous injection Loading dose of 600 mg	2 weeks	21.4 mg/day = 14	52 weeks /2 = 26 + 1 (loading) 27 (first year) then 26

Abbreviations: adm, administration; DDD, defined daily dose

Table 13 Conversion table for Omalizumab - PDD/administration (adm) & adm/year

Biologic	**Administration**	**Prescribed Dose**	**PDD per administration**		**Approximate number of administrations per year**
			2-week regime	4-week regime	
Omalizumab (10)	Based on body weight and IgE levels Range: 150-375 mg Subcutaneous injection. DDD WHO: 16 mg/day	150 mg	10.7		Range 13 to 26: 52 weeks /4 = 13 52 weeks /2 = 26
		300 mg	21.4		
		225 mg		8	
		300 mg		10.7	
		375 mg		13.4	

Abbreviations: adm, administration, DDD, defined daily dose; IgE, Immunoglobin E; WHO, World Health Organisation; PDD, prescribed daily dose

Tezepelumab, reslizumab, and mepolizumab are all administrated every 4 weeks, whereas omalizumab could be administrated every 2 or 4 weeks, dupilumab every 2 weeks, and benralizumab every 8 weeks following three doses every 4 weeks.

9.2.3.1 Country specific uptake of tezepelumab

Data source holders were asked to provide data for the period from tezepelumab market launch to 31 December 2024 (or the most recent data available).

9.2.3.1.1 DENMARK

Tezepelumab was approved in Denmark by the Danish Medical Board on the 27th of April 2022. National drug sales statistics for Denmark are presented in Table 14. A total of 1,000 administrations (600 syringes and 400 pens) of tezepelumab were sold (in any setting) between May 2023 (launch 26th April 2023) and December 2023. For patients initiating tezepelumab in May 2023 at recommended dose (1 injection with 210 mg every 4 weeks) and being continuously treated until the end of the year, would require 8 injections. Assuming an even distribution of patients initiating treatment throughout the 8 months of tezepelumab availability in Denmark in 2023, an average of 4.5 administrations per patient would be expected. Based on this assumption, at least 222 patients would have received tezepelumab between May and December 2023. If all patients, initiated treatment in May and continued treatment, this would be at least 125 patients. Assuming patients initiating treatment in 2023 continued their treatment with tezepelumab 2,886 packs would be used by prevalent users (222 patients x 13 administrations). The remaining 514 packs would be used by new users. Assuming an even distribution of patients initiating treatment throughout the year in Denmark, an average of 7 administrations per patient would be expected. Based on these assumptions, at least 296 patients (222 prevalent and 74 new users) would be exposed to tezepelumab. If combining all available data for the entire period (20 months [86 weeks], from May 2023 to December 2024), with a total of 4,400 packs reimbursed during the entire period, the number of patients exposed would be 383 (based on an even distribution of patients initiating treatment throughout the 20 months, an average of 11.5 administrations per patients would be expected).

Table 14 Annual tezepelumab data in Denmark (11)

Denmark	2022	2023 [a]	2024	2022-2024
Number of DDDs	Tezepelumab not yet available	28,000	94,000	122,000
Number of packs		600 syringes 400 pens	600 syringes 2,800 pens	1,200 syringes 3,200 pens
Number of administrations (calculated)		1,000	3,400	4,400
Minimum number of patients (calculated)		~125	Not calculated	Not calculated
Average number of patients (calculated)		~222	~~296	383

[a] Data from May to December 2023.
Abbreviations: DDD, defined daily dose

9.2.3.1.2 FRANCE

Number of reimbursed packs of tezepelumab in France from June 2023 to November 2024 (both months included) is presented in Table 15. Each pack contains one administration. For patients initiating tezepelumab in June 2023 at recommended dose (1 injection with 210 mg every 4 weeks) and being continuously treated until the end of the year, would require 7 injections. Assuming an even distribution of patients initiating treatment throughout the 7 months tezepelumab availability in France, an average of four administrations per patient would be expected. Based on this assumption, at least 1,837 patients would have been exposed to tezepelumab between June and December 2023. If all patients initiated treatment in June and continued treatment, this would be at least 1,050 patients. In 2024, data were available for 11 months. Assuming patients initiating treatment in 2023 continued their treatment with tezepelumab 20,207 packs would be used by prevalent users (1,837 patients x 11 months). The remaining 11,060 packs would be used by new users. Assuming an even distribution of patients initiating treatment throughout the 11 months of data availability in France, an average of 6 administrations per patient would be expected. Based on these assumptions, at least 3,680 patients (1,837 prevalent and 1,843 new users) would be exposed to tezepelumab. If combining all available data for the entire period (18 months [78 weeks], from June 2023 to November 2024), with a total of 38,616 packs reimbursed during the entire period, the number of patients exposed would be 4,065 (based on an even distribution of patients initiating treatment throughout the 18 months, an average of 9.5 administrations per patients would be expected).

Table 15 Annual tezepelumab data in France

France	2022	2023 [a]	2024 [b]	2022-2024
Number of packs	Tezepelumab not yet available	7,349	31,267 (10,908 pens + 20,359 syringes)	38,616
Minimum number of patients (calculated)	Tezepelumab not yet available	~1,050	Not calculated	Not calculated
Average number of patients (calculated)	Tezepelumab not yet available	~1,837	~3,680	~4,065

[a] June to December 2023
[b] January to November 2024

9.2.3.1.3 SWEDEN

Tezepelumab was approved for reimbursement in Sweden by the Dental and Pharmaceutical Benefits Agency on the 24th March 2023. Number of patients exposed to tezepelumab in Sweden from March 2023 to end of 2023 was available through national statistics and were provided by sex and age categories as described in Table 16. Counts for uptake for 2024 were only available as monthly data (stratification by sex and age not possible) at the time of reporting. A monthly breakdown of overall number of patients exposed from March 2023 to December 2024 was illustrated in Figure 1. The age group included in the PASS was restricted

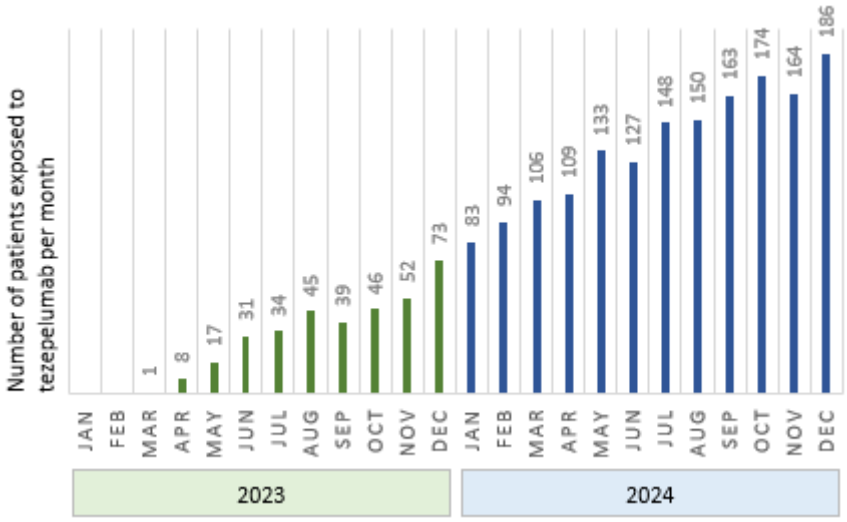
to women of childbearing potential defined as 18-49, however the age categories available in online statistics did not allow for this range, hence the 15-49 age range was provided instead.

Table 16 Annual tezepelumab data in Sweden

Sweden	2022	2023 [a]	2024	2022-2024
Number of patients	Tezepelumab not yet available	104	Not yet available	Not available
└Female		61		
└15-49 years of age		28		

[a] March to December 2023

Figure 1 Tezepelumab uptake in Sweden per month.



Source: https://sdb.socialstyrelsen.se/if_lak/val.aspx

As highlighted in Figure 1, 73 patients were exposed to tezepelumab in December 2023. The total number of patients exposed in 2023 was 104, indicating that not all patients initiating tezepelumab were adherent to treatment. The number of exposed patients increased to 186 by December 2024 (total number of patients exposed in 2024, not yet available).

9.2.3.1.4 USA – HIRD DATA THROUGH CARELON RESEARCH

Tezepelumab was approved by the FDA in December 2021, and aggregated patient counts in the HIRD dataset was provided by Carelon Research from January 2022 to August 2024. Number of patients were provided by sex, age, and uptake during pregnancy as presented in Table 17.

Table 17 Annual tezepelumab data in HIRD

USA (HIRD)	2022	2023	2024	2022-2024
Number of patients	672	1,601	2,011	2,800
└Female	470	1,132	1,417	1,960
└18-49 years of age	158	392	472	684

During pregnancy	0	<5	<5	6

Abbreviations: HIRD, Healthcare Integrated Research Database; USA, United States of America
Small number suppression rules were applied to counts 1-4, as well as additional suppression to prevent cross-calculations.

9.2.3.2 Estimated number of patients exposed to tezepelumab across data sources

Provided or calculated number of patients in each country were illustrated in Table 18.

Table 18 Estimated number of patients exposed to tezepelumab.

	2022	2023	2024	2022-2024
Denmark	Not yet available	~125-222	~296	~383
France	Not yet available	~1,050-1,837	~3,680	~4,065
Sweden	Not yet available	104	Not yet available	Not available
USA (HIRD)	672	1,601	2,011	2,800

~ indicates calculated number of patients exposed to tezepelumab.

9.2.3.3 Country specific uptake of selected biologics other than tezepelumab

Data source holders were asked to provide data for the period from 2022 to 2024 (or the most recent data available). Data from Denmark included both total number of DDDs as well as packs sold per year, while data from France was restricted to number of reimbursed packs per year. Using the treatment regime (number of days between administrations) and available pack sizes for each biologic, the estimated total number of administrations and minimum number of exposed patients (based on assumption of continuous use) were calculated for each biologic drug.

9.2.3.3.1 DENMARK

The calculated number of administrations per biologic are described in Table 19. A report on the use of biologics for asthma in the Nordics showed that only 15% of dupilumab was used for severe asthma as the main indication is atopic dermatitis (12).

Table 19 Calculated number of administrations of biologics in Denmark.

Denmark	2022	2023	2024	2022-2024
Omalizumab (4 weeks)[a]	~21,881	~24,927	~26,535	~73,343
Reslizumab (4 weeks)	~176	~126	~63	~365
Mepolizumab (4 weeks)	~6,052	~7,639	~9,226	~22,917
Benralizumab (8 weeks)	~1,290	~1,389	~1,389	~4,067
Dupilumab (2 weeks)	~25,000	~34,000	~41,800	~100,800

a Omalizumab can be administrated every 2 or 4 weeks. 2022 and 2023 counts would be 43,786 and 49,857 administrations, respectively, if given every 2 weeks.
~ indicates calculated number of administrations.

To calculate the minimum number of exposed patients each year, patients were assumed to receive treatment throughout each year (not accounting for patients initiating treatment or discontinuing treatment during each year). The calculated number of administrations (Table

19) were divided by the approximate number of administrations per year per biologic (Table 12) and presented in Table 20.

Table 20 Estimated minimum number of patients exposed to biologics in Denmark.

Denmark	2022	2023	2024	2022-2024
Omalizumab	~1,683	~1,917	~2,041	~5,642
Reslizumab	~14	~10	~5	~28
Mepolizumab	~466	~588	~710	~1,763
Benralizumab	~215	~231	~231	~678
Dupilumab [a]	~962 (~144)	~1,308 (~196)	~1,608 (~241)	~3,877 (~582)
Combined for severe asthma	~2,954	~3,531	~3,952	~10,437

[a] only 15% (2022: 144 of the 962, 2023: 196 of the 1,308, 2024: 241 of the 1,608, and 582 of the total 3,877) exposed patients were expected to be treated for severe asthma. The 15% were included in the combined for severe asthma estimation.
~ indicates calculated number of patients exposed.

9.2.3.3.2 FRANCE

For France the only information of number of reimbursed packs were provided. This information did not include pack size, however dupilumab is only marketed in pack sizes of 2 (28-day supply), whereas mepolizumab is marketed in pack sizes of 1 or 3 (28- or 84-day supply).

Table 21 Number of packs of biologics reimbursed each year in France.

France	2022	2023	2024	2022-2024
Omalizumab	567,126	598,071	565,759	1,730,956
Reslizumab	not available in France			
Mepolizumab	64,853	87,240	95,514	247,607
Benralizumab	36,024	39,421	32,000	107,445
Dupilumab	162,909	247,776	313,537	724,222

To calculate the minimum number of exposed patients each year, patients were assumed to receive treatment throughout each year (not accounting for patients initiating treatment or discontinuing treatment during each year). The provided number of reimbursed packs (Table 21) were divided by the approximate number of administrations per year per biologic (Table 12) and presented in Table 22. Dupilumab is sold in packs of two, hence number of administrations per year was divided by two. The minimum number of patients exposed to mepolizumab is likely underestimated as some packs would contain three instead of one administration.

Table 22 Estimated minimum number of patients exposed to biologics in France.

France	2022	2023	2024 [b]	2022-2024
Omalizumab	43,625	46,005	51,433	141,063
Reslizumab	not available in France			
Mepolizumab	4,989	6,711	8,683	20,383
Benralizumab	6,004	6,570	5,333	17,908
Dupilumab [a]	12,531 (~986)	19,060 (~2,859)	28,503 (~4,276)	60,095 (~8,120)
Combined for severe asthma	57,574	67,863	78,276	203,713

[a] using the Danish distribution of indication for dupilumab, only 15% (2022: 986 of the 12,531, 2023: 2,859 of the 19,060, and 2024: 4,276 of the 28,503) exposed patients were expected to be treated for severe asthma. The 15% were included in the combined for severe asthma estimation. ~ indicates calculated number of patients exposed.
[b] January to November 2024

9.2.3.3.3 SWEDEN

For Sweden, national statistics provided information on number of patients exposed to specific biologics as presented in Table 23.

Table 23 Number of patients exposed to biologics in Sweden

Sweden	2022	2023	2024	2022-2024
Omalizumab	3,004	3,579	Not yet available	
Reslizumab	NA	NA		
Mepolizumab	3,356	3,723		
Benralizumab	223	408		
Dupilumab [a]	2,240 (~336)	3,506 (~526)		
Combined for severe asthma	~6,919	~8,236		

[a] using the Danish distribution of indication for dupilumab, only 15% (2022: 336 of the 2,240, 2023: 526 of the 3,506) exposed patients were expected to be treated for severe asthma. The 15% were included in the combined for severe asthma estimation.
~ indicates calculated number of patients exposed.

9.2.3.3.4 USA – HIRD DATA FROM CARELON RESEARCH

Carelon Research provided information from the HIRD on the number of asthma patients exposed to specific biologics in general as presented in Table 24. Number of exposed pregnancies were presented separately in Table 25.

Table 24 Number of patients with asthma exposed to biologics in the HIRD from 2022 to August 2024.

HIRD	2022	2023	2024	2022-2024
Omalizumab	4,574	4,534	4,130	7,889
Reslizumab	65	49	47	86
Mepolizumab	2,291	2,513	2,317	4,055
Benralizumab	2,248	2,363	2,157	3,867
Dupilumab [a]	10,432	12,026	10,027	24,849
Any of above	18,986	20,934	18,298	38,938

[a] Carelon Research provided exposure counts for patients with at least one asthma diagnosis, so no adjustments were made to the counts of patients exposed to dupilumab.
Abbreviations: HIRD, Healthcare Integrated Research Database

Table 25 Number of pregnancies among patients with asthma exposed to biologics in the HIRD

HIRD	2022	2023	2024	2022-2024
Omalizumab	<5	24-27	16	44
Reslizumab	<5	<5	0	<5
Mepolizumab	<5	<5	<5	8
Benralizumab	<5	<5	<5	9
Dupilumab	23	78	46	147
Combined	30	111	68	209

Small number suppression rules were applied to counts 1-4, as well as additional suppression to prevent cross-calculations.
Abbreviations: HIRD, Healthcare Integrated Research Database

9.3 Variables

9.3.1 Code lists for the Pregnancy PASS

A comprehensive global code list (v1.0) has been developed. This code list was built upon exemplary code lists provided in the study protocol and further refined through literature review and clinical input. The ICD-10 and the World Health Organisation's (WHO) ATC classification systems were used for the definition of study variables. The code list includes definitions of primary outcome (Major CM [MCM]), secondary outcomes (foetal death, minor CM [mCM], individual adverse pregnancy outcomes [ectopic pregnancy, miscarriage, stillbirth, termination of pregnancy, and pre-eclampsia], individual birth outcomes [emergency caesarean section, preterm birth, small for gestational age, and low birth weight]), exposure (tezepelumab and severe asthma SOC drugs), participant's characteristics and potential confounders/risk factors, and variables required to apply the eligibility criteria in the study data sources (e.g., asthma diagnosis).

Based on the global code list, local code-list adaptations will be created for each data source, incorporating relevant changes in the ICD-10 and ATC coding systems, and adding procedure codes as needed.

9.4 Study size

The observed number of pregnancies exposed to tezepelumab (only provided for HIRD) were aligned with assumptions on uptake of tezepelumab made in the protocol sample size calculations. Number of exposed pregnancies was not available for the remaining data sources prior to contracting.

9.5 Quality control

The study will be conducted according to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, the International Society for Pharmacoepidemiology Good Pharmacoepidemiology Practice Guidelines and IQVIA standard operating procedures. At the study level, all aspects of the study, from protocol development to the reporting of the results, are and will be conducted within the framework of the IQVIA Quality Management System.

According to the policies and procedures above, a study Quality Control (QC) plan has been developed. This plan includes QC of the protocol, Statistical Analysis Plan, programming, data management and analysis, and study report including study results and conclusions.

Furthermore, the study QC plan states the following:

- Ownership for the execution of the individual QC steps should be established and the principle of the independence of QC should apply.
- IQVIA project management will ensure that individuals responsible for the execution of specific QC steps will have knowledge, capability, and experience which are adequate for the task.
- The result of the execution of the individual steps of the QC plan will be documented and will include required corrective actions, if any.
- The execution of any required corrective action will be documented.
- Datasets and analytic programmes will be stored according to IQVIA and data holder procedures, with access restricted to authorised study personnel at the respective entities.

Also, the study Project Manager will verify training compliance of IQVIA employees contributing to the study, as per IQVIA procedure.

The executed QC plan will be subjected to a final review and approval for sufficiency and completeness by the IQVIA project management team.

All appropriate documentation is filed within the Study Master File by IQVIA to be shared with AstraZeneca.

10. DISCUSSION

The ongoing study activities are progressing as planned. We do not expect any delays in the timing of the first interim report due on 31 March 2028.

11. OTHER INFORMATION

No additional information.

12. CONCLUSION

The study is progressing as expected and is on track to deliver the first interim report in 2028.

13. REFERENCES

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Appendix 1 List of stand-alone documents

None

Appendix 2 Additional information

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