Statistical Analysis Plan	
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A Multicentre, Double-blind, Randomized, Placebo Controlled, Parallel Group, Phase 3, Safety Extension Study to Evaluate the Safety and Tolerability of Tezepelumab in Adults and Adolescents with Severe Uncontrolled Asthma (DESTINATION)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
CCI	[redacted]
AE	Adverse Event
AESI	Adverse Events of Special Interest
AAER	Annualized asthma exacerbation rate
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AZ	AstraZeneca
BD	Bronchodilator
BMI	Body Mass Index
COVID-19	Coronavirus Disease 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DAE	Adverse Event Leading to Discontinuation of Investigational Product
DRMI	Dropout Reason-based Multiple Imputation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
ER	Emergency Room
FAS	Full Analysis Set
FEF25-75%	Forced Expiratory Flow over 25-75% of the vital capacity

Abbreviation or special term	Explanation
FeNO	Fractional Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
FWER	Familywise Error rate
GCP	Good Clinical Practice
HRU	Healthcare Resource Utilisation
ICF	Informed Consent Form
ICS	Inhaled Corticosteroids
IgE	Immunoglobulin E
IP	Investigational Product
IPD	Investigational Product Discontinuation
ITT	Intent-to-Treat
IXRS	Interactive Voice/Web Response System
L	Litre
LABA	Long-Acting Beta Agonist
LLOQ	Lower Limit of Quantification
LLT	Lower Level Term
LTE	Long Term Extension
MACE	Major Adverse Cardiac Events
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random
N/A	Not Applicable
CCI	
NB	Negative Binomial
NC	Not Calculable
NQ	Non-quantifiable
OCS	Oral Corticosteroids
PD	Protocol Deviation
CCI	

Abbreviation or special term	Explanation
PT	Preferred Term
Q4W	Every 4 Weeks
QTc	Corrected QT Interval
SABA	Short-Acting Beta Agonist
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
CCI	
SMQ	Standardized MedDRA Query
SoA	Schedule of Assessments
TBL	Total Bilirubin
UC	Urgent Care
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
WHO	World Health Organisation

AMENDMENT HISTORY

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
N/A	30-Jul-19	Initially Approved SAP	Yes (v2)	Initial SAP. In line with CSP version 2.0 (23 May 2019).
Data presentations	28-Oct-20	Throughout SAP: Updated the phrase “extension study” to “LTE study”	Yes (v5)	To be consistent with CSP.
Data presentations	28-Oct-20	Throughout SAP: Updated the phrase “another biologic” to “another biologic that impacts asthma control”	Yes (v5)	To clarify the interest is only biologic that impacts asthma control, not any biologics other than tezepelumab.
Study objectives	28-Oct-20	CCI	Yes (v5)	CCI
Study objectives	28-Oct-20		Yes (v5)	
Study objectives	28-Oct-20		Yes (v5)	

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		CCI		
Derivation of primary or secondary endpoints	28-Oct-20	Sections 1.1, 3.3.2.5, 4.6.2.5: Removed "Urgent Care" from definition of secondary and supportive analyses.	No	Provide clarification that only emergency room visit data is collected in the eCRF.
Study design	28-Oct-20	Section 1.2: • CCI • Updated text for the 3 follow-up options at the IPD visit for subjects who prematurely discontinue IP	Yes (v5)	To be consistent with the CSP
Analysis sets	28-Oct-20	CCI	N/A	CCI
Analysis sets	28-Oct-20		Yes (v5)	
Analysis sets	28-Oct-20		Yes (v5)	
Analysis sets	28-Oct-20	Section 2.2: Clarified that not fulfilling key eligibility criteria will be considered important PDs	N/A	To be consistent with Protocol Deviation plan.
Data presentations	28-Oct-20	Section 2.2: Moved the description of analysis of IPDs to Section 4.3 for better flow; In Section 4.3, update IPD summary to be on LTE period only using SAF-LTE analysis set.	N/A	Better flow and simplify analyses.
Derivation of primary or secondary endpoints	28-Oct-20	Section 3.1.2: Baseline definition clarified regarding the use of unscheduled visits in the baseline derivation and to ensure consistent approach taken for using last available measurement prior to randomisation or dosing.	N/A	To remove redundant text and simplify section.
Data presentations	28-Oct-20	Section 3.1.5 updated "Post-treatment" period to "Post-treatment/Follow-up" period.	Yes (v5)	To be consistent with programming reporting requirements.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Data presentations	28-Oct-20	Section 3.1.5 Updated text to clarify how the predecessor period and LTE period should be defined due to all possible delay scenarios between the predecessor EOT visit and the first dose of IP in LTE study.	Yes (v5)	To cover all possible delay scenarios, including the delays that are due to COVID-19.
		Section 3.1.5 Updated text to clarify the difference between LTE period and LTE study; removed the time window from the titles of predecessor period and LTE period to avoid confusion.	N/A	To provide additional clarification on LTE period vs LTE study.
Data presentations	28-Oct-20	CCI	Yes (v5)	CCI
Data presentations	28-Oct-20	Section 3.1.6: Clarified that any listings produced will include all data recorded.	N/A	Provide additional clarification.
Data presentations	28-Oct-20	CCI	N/A	CCI
Data presentations	28-Oct-20		N/A	
Data presentations	28-Oct-20	Section 3.1.8: Changed age categories from adults (>65), adults (≥18 to ≤65) to adults (≥65), adults (≥18 to <65)	N/A	In line with AZ standards.
Data presentations	28-Oct-20	Section 3.1.8: Added new subgroups for perennial and seasonal specific IgE status (FEIA); Updated text for definition of baseline (any) IgE status (FEIA) subgroup; Updated subgroup of OCS at study entry to OCS at baseline. Added new subgroups for nasal polyps at study entry, and nasal polyps in the 2 years before randomisation.	N/A	To be consistent with predecessor studies.
Data presentations	28-Oct-20	Section 3.2.6: calculation of change from baseline in ECG variables removed from section	N/A	No continuous ECG measurements are collected.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Data presentations	28-Oct-20	Section 3.1.9: Time to premature study withdrawal for subjects ongoing at primary DBL will be censored at last contact date rather than at Week 104.	N/A	To provide additional information of progress of ongoing subjects.
Data presentations	28-Oct-20	Section 3.2.2: Treatment-emergent text replaced with “during on-treatment period”.	N/A	To be consistent with reporting periods.
Data presentations	28-Oct-20	Section 3.2.2: Updated texts to clearly define exposure adjusted incidence rate and exposure adjusted occurrence rate.	N/A	To provide clarity.
Primary or secondary endpoints	28-Oct-20	Section 3.3.1.1: Added reference to the definition in the CSP.	Yes (v5)	To provide clarification that the definition of an exacerbation is from the CSP.
Derivation of primary or secondary endpoints	28-Oct-20	CCI	N/A	CCI
CCI	28-Oct-20		N/A	
Data presentations	28-Oct-20		N/A	
Data presentations	28-Oct-20		N/A	
Other	28-Oct-20		No	
Data presentations	28-Oct-20		Yes (v5)	

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		CCI [redacted]		
Data presentations	28-Oct-20	Section 4.2: Kaplan-Meier plots of time to last dose of IP and premature withdrawal will also be produced for the SAF-LTE analysis set.	N/A	To be consistent with Table 9.
Data presentations	28-Oct-20	Section 4.3: Added text noting that baseline total daily dose to be displayed will be the categories low/medium/high.	N/A	To provide additional clarification.
Data presentations	28-Oct-20	Section 4.3: Added text regarding disallowed medications.	Yes (v5)	To provide additional clarification.
Statistical analysis methods	28-Oct-20	Section 4.4: Extent of exposure to IP and compliance summaries will only be provided by time period for the FAS-LTE analysis set.	N/A	To be consistent with Table 9.
Statistical analysis methods	28-Oct-20	Section 4.5.1: • Summaries of AEs by causality and maximum intensity will be produced by preferred term and not system organ class. • Updated the text to clarify AESI data will be presented for the SAF analysis set. • Added text to summarise AESI data using exposure adjusted occurrence rates	N/A	To be consistent with AZ reporting standards and predecessor studies.
Statistical analysis methods	28-Oct-20	Section 4.5.1.1: Subgroup summaries will be provided only for study D5180C00007and will also be produced for SAF-LTE analysis set. Overall summary of AEs and AEs by SOC and PT will also be provided by subgroup for the SAF analysis set.	N/A	To be consistent with Table 10.
Statistical analysis methods	28-Oct-20	Section 4.5.2: • Laboratory data will be summarised over time for the on-study period instead of the on-treatment period. • Removed figure of mean changes from baseline. • All summaries and figures will report laboratory data in SI units. • Shift tables will not display missing values.	N/A	To be consistent with predecessor studies.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Statistical analysis methods	28-Oct-20	Section 4.5.3: • Vital signs will be summarised over time for the on-study period instead of the on-treatment period. • Shift tables will not display missing values.	N/A	To be consistent with predecessor studies.
Statistical analysis methods	28-Oct-20	Section 4.5.4: summaries of change from baseline in ECG variables removed from section	N/A	No continuous ECG measurements are collected.
Statistical analysis methods	28-Oct-20	Section 4.6.1: Changed study discontinuation to study withdrawal.	N/A	To be consistent within SAP.
Statistical analysis methods	28-Oct-20	Section 4.6.1: Definition of hypothetical policy estimand includes all data in the planned treatment period until initiation of another biologic that impacts asthma control.	N/A	To provide additional clarification.
Statistical analysis methods	28-Oct-20	Section 4.6.1 and 4.6.2.1: Noted that death may also be a source of missing information for the main analysis.	N/A	To provide additional clarification.
Statistical analysis methods	28-Oct-20	Section 4.6.1.1: Text added to imputation of missing data for secondary endpoint.	N/A	To provide additional clarification.
Statistical analysis methods	28-Oct-20	CCI [redacted]	N/A	CCI [redacted]
Statistical analysis methods	28-Oct-20		N/A	
Statistical analysis methods	28-Oct-20		N/A	
Data presentations	28-Oct-20		N/A	
Data presentations	28-Oct-20		N/A	
Data presentations	28-Oct-20		N/A	

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Data presentations	28-Oct-20	CCI [redacted]	N/A	CCI [redacted]
Other	28-Oct-20	Reference to DBL updated to primary DBL in the following sections: Section 3.1.9, Section 4.3, Section 4.6.1.1, Section 8.1.	Yes (v5)	To accommodate a planned additional database lock once the last subject completes treatment phase (week 104).
Protocol amendment	28-Oct-20	CCI [redacted]	Yes (v5)	CCI [redacted]
Date presentations	28-Oct-20	Section 6: Updated text to reflect the final change from analyses in CSP.	Yes (v5)	To reflect the latest changes in CSP v5
Data presentations	28-Oct-20	Section 8.1.2: Immune complex disease will be identified based on PT of "Type III immune complex mediated reaction" and not "hypersensitivity".	N/A	To be consistent with predecessor studies.
Data presentations	28-Oct-20	Section 8.4: Updated Table 9 and Table 10 to be in line with texts	Yes (v5)	To be consistent between SAP text and tables.
Protocol amendment	28-Oct-20	Added Section 8.5 to describe additional reporting needed to assess the impact of the COVID-19 pandemic.	Yes (v5)	New analyses due to protocol amendment
Data presentations	09-Dec-20	Section 2.2: updated IPD texts to be consistent with protocol deviation plan v5.0: • Removed category of "did not adhere to protocol-required procedure". • Clarified that IPD Code 10.9 receiving wrong IP kit number and Code 10.22 IP dose in excess of 700 mg administered within a 2-week period will only be identified after the unblinding of LTE study.	N/A	To be consistent with protocol deviation plan v5.0.
Data presentations	09-Dec-20	Section 3.1.6: updated Visit Windows to cover different schedules for various endpoints (e.g., CCI [redacted] urinalysis) after having CCI [redacted] period, and cover the FU visits from predecessor studies	Yes (v5)	To be consistent with the CSP.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Data presentations	09-Dec-20	Section 3.1.8: Added a new rule for safety/efficacy subgroup analyses: if any of the subgroups has fewer than 10 subjects in one or both treatment arms, the corresponding safety and efficacy subgroup analyses will not be conducted.	N/A	To be consistent with predecessor studies
Data presentations	09-Dec-20	Section 3.2.1: Updated the text to clarify that if the last date of predecessor period is the same date as the first date of LTE period, that date will be counted in both periods for the extent of exposure. However, it will be only counted once for the overall extent of exposure.	N/A	To provide additional clarity.
Data presentations	09-Dec-20	Section 3.3.1.1: Updated the derivation algorithms for time at risk for exacerbation endpoint, to account for subjects who changed treatment after entering LTE study.	N/A	To provide additional clarity.
Data presentations	09-Dec-20	CCI [redacted]	N/A	CCI [redacted]
Data presentations	09-Dec-20	Section 4.2: Updated the descriptions • Removed the first paragraph about general disposition/demographic summaries because it was redundant and not accurately reflecting the following planned analyses • Moved the category of "subjects who enrolled into LTE but had a delay due TO COVID-19" from disposition predecessor period table to disposition LTE period table. • Removed SAF-LTE analysis set for KM plots • Updated the age subgroup variable from 2 levels (≥12 to <18, ≥18) to 3 levels (≥12 to <18, ≥18 to <65, ≥65	N/A	To provide additional clarity, to be consistent with predecessor study, and to remove some unnecessary analyses.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Data presentations	09-Dec-20	Section 4.5.2: removed the "separately for predecessor period and LTE period" text for the by-visit summary table of lab data, because it is by-visit summary already.	N/A	To provide additional clarity.
Data presentations	09-Dec-20	Section 4.5.3: removed the "separately for predecessor period and LTE period" text for the by-visit summary table of vital signs data, because it is by-visit summary already.	N/A	To provide additional clarity.
Data presentations	09-Dec-20	Section 4.6.1: added section 4.6.1.3 to describe the AAER subgroup analyses for D5180C00007 subjects only.	N/A	To be consistent with Section 3.1.8 and Section 8.4
Data presentations	09-Dec-20	Section 4.6.1: Removed additional sensitivity or supportive analyses: • Removed on-treatment period analysis for D5180C00007 subjects.	N/A	To remove unnecessary analyses.
Data presentations	09-Dec-20	CCI [redacted]	N/A	CCI [redacted]
Data presentations	09-Dec-20		N/A	
Data presentations	09-Dec-20		N/A	

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Data presentations	09-Dec-20	CCI [redacted]	N/A	CCI [redacted]
Data presentations	09-Dec-20		N/A	
Data presentations	09-Dec-20		N/A	
Data presentations	09-Dec-20	Appendix 8.1: Added hypersensitivity reactions as a new AESI category	N/A	To be consistent with Integrated Summary of Safety reporting.
Data presentations	09-Dec-20	Appendix 8.5: • Updated the analysis set from SAF to SAF-LTE for COVID-19 related PD summaries. • Updated the definition of exacerbation time at risk for pre-pandemic analysis to account from subjects who changed treatment after entering LTE study.	N/A	To be consistent with main SAP.
Other	18-Feb-21	Section 3.1.5.1: Removed 'Visit 1' from time period definitions for the Predecessor and LTE periods to provide flexibility for those who have delayed roll-overs due to COVID-19 and other circumstances	N/A	To provide additional clarity
Data presentations	01-Mar-21	CCI [redacted]	N/A	CCI [redacted]
Protocol amendment	01-Apr-21		Yes (v6)	
Other	01-Oct-21	Section 1.2: Changed instances of 'the LTE study' to 'DESTINATION'	N/A	To provide additional clarity and align with 4MSU report
Data presentations	01-Oct-21	Section 2.1: removed the modified SAF and modified FAS analysis sets	N/A	To reduce the number of outputs and streamline those that are key to the interpretation of data from DESTINATION.
Data presentations	01-Oct-21	Section 2.1.1: removed the Teze+No LTE and Pbo+No LTE analysis sets	N/A	To reduce the number of outputs and streamline those that are key to the

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
				interpretation of data from DESTINATION.
Other	01-Oct-21	Section 3.1.5: • Updated text to clarify the difference between the LTE study and the LTE period • CCI [redacted]	N/A	To provide additional clarity
Other	01-Oct-21	Section 3.1.6: Listed all outcomes collected in Visit Window 1 and Visit Window 2	N/A	To provide additional clarity
Data presentations	01-Oct-21	Section 3.1.8: Added an '*' to the following subgroups to indicate they will be included in the subgroup analysis of AAER: • Baseline eosinophils group: <150 µL, ≥150/µL • ICS dose at study entry: low, medium, high (also specified that this is defined in Appendix 8.3, not the CSP) • OCS at baseline: present, absent	N/A	To be consistent with important subgroup analyses identified in the predecessor studies
Data presentations	01-Oct-21	Section 3.1.9: Added text describing how data will be censored for subjects who switch from placebo in the predecessor period to tezepelumab in the LTE period will be handled for Kaplan-Meier analyses for time to last dose of IP	N/A	To provide additional clarity
Other	01-Oct-21	Section 3.2.2: Clarified that the same version of MedDRA will be used for the primary and final database locks	N/A	To provide additional clarity
Data presentations	01-Oct-21	CCI [redacted]	N/A	CCI [redacted]
Other	01-Oct-21		N/A	
Statistical analysis methods	01-Oct-21		N/A	
Statistical analysis methods	01-Oct-21		N/A	

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Data presentations	01-Oct-21	Section 4.2: • Removed the number randomised and not randomised from predecessor period subject disposition analysis • Removed Modified SAF and SAF analysis set containing those subjects who did not enrol into the LTE period • Added that randomisation and disposition information will be listed	N/A	To remove unnecessary analyses, align with analyses presented in Sections 2.1 and 2.1.1, and add in necessary listings (respectively)
Data presentations	01-Oct-21	Section 4.3: Removed maintenance medication analysis for those subjects who did not enrol into the LTE period	N/A	To align with analyses presented in Section 2.1.1
Data presentations	01-Oct-21	Section 4.3: Added that the Placebo Predecessor+Tezepelumab LTE group will be included in summaries of prior and post-treatment medications	N/A	To provide transparency for all treatment groups
Statistical analysis methods	01-Oct-21	Section 4.4: • Added that the total number of dosing occasions will also be summarised for the SAF-LTE analysis set for the Tezepelumab Predecessor+ Tezepelumab LTE and Placebo Predecessor+Placebo LTE treatment groups • Added that IP administration will be listed	N/A	To provide a comprehensive analysis
Data presentations	01-Oct-21	Section 4.5.1: • Added that AEs for the Placebo Predecessor+Tezepelumab LTE group will be summarised for the predecessor and LTE periods • Added that AEs and pregnancy information will be listed for the SAF-LTE analysis set • Specified that DAEs, DAEs casually related to IP, SAEs leading to discontinuation of IP, each AESI category separately, most common AEs, and AESIs of injection site	N/A	To provide additional clarity

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		reactions will be summarised for the on-treatment period only		
Data presentations	01-Oct-2021	Section 4.5.1: Removed Modified SAF and SAF analysis set containing those subjects who did not enrol into the LTE period	N/A	To align with analyses presented in Section 2.1.1
Data presentations	01-Oct-21	Section 4.5.1.1: Removed subgroups analyses of each AESI category separately and adjudicated AEs	N/A	To remove unnecessary analyses
Statistical analysis methods	01-Oct-21	Sections 4.5.2, 4.5.3, and 4.5.4: Changed analyses of shift tables from the on-study period to the on-treatment period	N/A	To streamline production of outputs that are key to main CSR
Data presentations	01-Oct-21	Sections 4.5.2, 4.5.3, 4.5.4, and 4.6.1: Added that laboratory data, vital signs, 12-lead ECG, and asthma exacerbations (respectively) will be listed	N/A	To provide additional clarity
Data presentation	01-Oct-21	Sections 4.6.1.1 and 4.6.2.1: Removed Modified FAS and FAS analysis set containing those subjects who did not enrol into the LTE period	N/A	To align with analyses presented in Section 2.1.1
Statistical analysis methods	01-Oct-21	CCI [redacted]	N/A	CCI [redacted]
Statistical analysis methods	01-Oct-21	[redacted]	N/A	[redacted]
Statistical analysis methods	01-Oct-21	[redacted]	N/A	[redacted]
Statistical analysis methods	01-Oct-21	[redacted]	N/A	[redacted]
Other	01-Oct-21	[redacted]	N/A	[redacted]
Statistical analysis methods	01-Oct-21	[redacted]	N/A	[redacted]

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Statistical analysis methods	01-Oct-21	CCI [redacted]	N/A	CCI [redacted]
Data presentations	01-Oct-21		N/A	
Statistical analysis methods	01-Oct-21		N/A	
Data presentations	01-Oct-21		N/A	
Data presentations	01-Oct-21		N/A	
Data presentation	01-Oct-21		N/A	
Other	01-Oct-21	Section 6: Removed 2nd and 3rd bullet points describing the addition of analyses for the Modified SAF, Modified FAS, and reference to those subjects who did not enrol into the LTE period	N/A	To align with analyses presented in Section 2.1.1
Other	01-Oct-21	Appendix 8: • Section 8.1: Added common 5-line paragraph that Sections 8.1.1, 8.1.4, 8.1.8, and 8.1.9 shared • Sections 8.1.1, 8.1.4, 8.1.8, and 8.1.9: Removed common 5-line paragraph	N/A	To avoid repetition
Data presentations	01-Oct-2021	Appendix 8.4: updated tables to be in line with all new changes in the text.	N/A	To be consistent with main SAP
Data presentations	01-Oct-21	Appendix 8.5: Specified that analyses will be performed during the LTE period on the SAF-LTE analysis set	N/A	To provide additional clarity
Other	01-Oct-21	All instances of 'Tezepelumab' updated to 'tezepelumab'	N/A	To be consistent throughout the document.

1 STUDY DETAILS

This statistical analysis plan (SAP) for study D5180C00018 outlines the statistical analyses specified in the latest version of the Clinical Study Protocol (CSP) in more detail; any changes to what is specified in the CSP will be described in Section 6.

1.1 Study objectives

For the outcome measures below, "Analysed separately by predecessor study" means that the predecessor study data and LTE study data will be combined but will be analysed separately for subjects originally enrolled in D5180C00007 from those originally enrolled in D5180C00009.

Table 1 Objectives and Endpoints

Primary objective:	**Outcome Measure:**
To evaluate the long-term safety and tolerability of tezepelumab in severe asthma subjects	Exposure adjusted rates of AEs/SAEs over 104 weeks *Analysed separately by predecessor study*
Secondary objective:	**Outcome Measure:**
To assess the long-term effect of 210 mg tezepelumab SC Q4W on asthma exacerbations in adult and adolescent subjects with severe uncontrolled asthma compared with placebo	Annualized asthma exacerbation rate (AAER) over 104 weeks (Baseline is week 0 in predecessor study) *Analysed separately by predecessor study*
CCI	[redacted]

CCI

[redacted]

CCI

1.2 Study design

This is a multicentre, randomised, double-blind, placebo controlled, parallel group, phase 3 LTE study designed to evaluate the safety and tolerability of 210 mg Q4W (SC) of tezepelumab in adults and adolescents with severe, uncontrolled asthma on medium to high-dose ICS and at least one additional asthma controller with or without OCS. Subjects who have continued to receive investigational product and have attended the End of Treatment (EOT) visit in one of the predecessor studies, week 52 in study D5180C00007 or week 48 in study D5180C00009, on investigational product (IP) may be eligible to enrol into this study if they fulfil the inclusion/exclusion criteria.

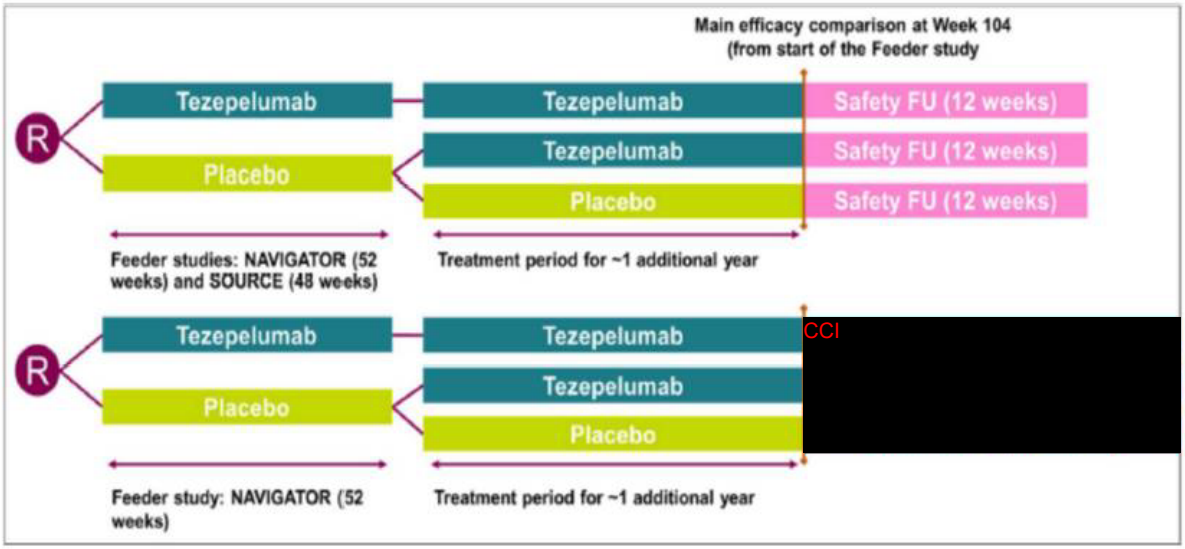
The aim of this study is to evaluate the safety and efficacy over 104 weeks. Data from the predecessor studies will be integrated with the data from DESTINATION but will be reported separately for subjects enrolled in D5180C00007 from those enrolled in D5180C0009 unless otherwise stated explicitly. CCI

CCI [redacted]

This study will be run at approximately 350 sites worldwide and will randomise approximately 975 subjects worldwide. All subjects will be re-randomised in this study to maintain the blinding. Subjects previously randomised to the 210 mg tezepelumab Q4W SC arm in either of the predecessor studies, will be assigned to remain on 210 mg tezepelumab Q4W SC dosing in DESTINATION. Subjects randomised to placebo arm in the predecessor studies will be re-randomised in a 1:1 ratio to either 210 mg tezepelumab or placebo, both administered Q4W SC. Given the randomisation scheme of subjects in the predecessor studies, this will give an overall subject distribution of 3:1 (tezepelumab:placebo), assuming a similar number of subjects rollover from each arm in the predecessor studies. See Figure 1 below for the general study design.

Figure 1 Study Design

Predecessor Studies	LONG TERM EXTENDED (LTE) STUDY					
	Predecessor EOT/ V1	V2	V3 - V14	V15	V16, V17	CCI [redacted]
Week 0-48 (D5180C00007)	Week 52 Visit (D5180C00007)		Week 56-100	Week 104	Week 110, 116	
Week 0-44 (D5180C00009)	Week 48 Visit (D5180C00009)	Week 52 for D5180C00009 only				
Treatment Phase	Screening/ Randomization	Treatment Phase		End of Treatment	Follow-up CCI [redacted]	



V: Visits

Subjects who discontinue IP, do not attend the EOT visit in one of the predecessor studies or do not meet the entry requirements for DESTINATION will not be eligible to participate in DESTINATION.

Subjects who are not able to attend an on-site EOT visit in the predecessor study/Visit 1 in the DESTINATION study due to the COVID-19 pandemic, are still allowed to roll-over to the DESTINATION study by the end of the safety follow-up of the predecessor study after confirmation of subject eligibility.

In order to provide sufficient time for subjects to consider participation in this study, and to ensure an uninterrupted dosing regimen, as subjects transition between the predecessor study and DESTINATION, subjects will be provided with the Informed Consent Form (ICF) at/after the visit at which they receive their last dose of IP in the predecessor study and will be asked to sign the ICF at Visit 1 of the LTE study prior to any study-specific procedures being performed.

Section 6.5 of the CSP provides a list of medication restrictions and prohibitions to be followed throughout conduct of the clinical trial.

The study will consist of a screening/randomisation visit which will be the same day as the EOT visit from the predecessor studies D5180C00007 (Week 52) or D5180C00009 (Week 48). The first dose of IP will be administered the same day in most cases unless some delays (for example, due to COVID-19). A treatment period duration of 52 weeks for subjects who previously completed study D5180C00007 or 56 weeks for subjects who previously completed the D5180C00009 will follow. The last dose of IP will be administered at Week 100. EOT visit will be conducted at Week 104. IP will not be administered at Week 104. Subjects that complete the treatment period in DESTINATION will either complete a 12 week follow up period which includes 2 follow-up visits CCI [redacted]

During the screening/randomisation visit, subjects must undergo all assessments as detailed in Table 1 of the CSP.

Prior to randomisation, the subjects must meet all inclusion/exclusion criteria for DESTINATION. If a subject does not meet all inclusion criteria or meets any exclusion criteria as per section 5.1 and section 5.2 of the CSP, the subject will be screen failed and would then complete the safety follow-up portion of the predecessor study. Further details are specified in the CSP section 5.4.

All subjects who prematurely discontinue IP should return to the study centre and complete the procedures described for the premature IP Discontinuation visit (IPD) at 4 weeks (+/-5 days) post last IP administration. Subjects who prematurely discontinue treatment should be encouraged to return for all regularly scheduled visits for safety and efficacy assessments. At

the IPD visit the subject will be given three options as to how they will be followed (further information is provided in the CSP section 7.1.1):

1. Ideally the subject should continue all regular clinic visits and perform all scheduled assessments (excluding IP administration) until the scheduled EOT visit at week 104 (+/-5 days).

2. (If the subject cannot comply or does not wish to comply with option 1 above), the subject will be offered follow-up on a monthly basis via telephone calls. The subject should return for an on-site follow up visit 16 weeks (+/- 5 days) (refer to SoA, V17 – Week 116) post last IP administration and for the on-site EOT visit at Week 104 (+/-5 days).
3. (If the subject cannot or does not wish to comply with option 1 or option 2), they will complete an on-site follow-up visit at 16 weeks (+/-5 days) (refer to SoA, Visit 17 – week 116) post last IP administration. After this visit the Investigator will only contact by phone the subject at week 104 (+/-5 days). No other study assessments will be performed prior to this contact.

CCI [redacted]

During the initial part of the study, subjects, Investigators/site staff and the Sponsor/designated CRO will be blinded to treatment. At the planned unblinding of the predecessor studies D5180C00007 or D5180C00009, the blind for DESTINATION will be maintained for the subjects, Investigators/site staff or any CRO handling data. However, the individual treatment allocation for subjects in DESTINATION may become known to the Sponsor. The Sponsor has designated that there will be 3 separate teams for DESTINATION; an AZ Core Blinded team, AZ Partially blinded team, and an AZ Extended Blinded team (see D5180C00018 Blinding Plan for further details).

To prevent complete unblinding of this study, treatment-revealing information will not be shared with the subjects, Investigators/site staff and CRO, and the AZ Core Blinded study team. The only exception to this is information regarding any deaths reported during the predecessor studies.

1.3 Number of subjects

The sample size is not based on statistical considerations but will be determined by the number of subjects who complete the double-blind treatment period on investigation product in either of the predecessor studies (D5180C00007 or D5180C00009) and meet all study eligibility criteria for the LTE study.

If a pooled analysis will be performed, then assuming that 90% of the subjects complete the predecessor studies, and that 90% of those continue into the LTE, approximately 975 subjects (860 from D5180C00007 and 115 from D5180C00009) are anticipated to enter the LTE study. Furthermore, assuming annual dropout rates during the LTE study of CCI [redacted] (in subjects randomised to tezepelumab) and CCI [redacted] (in subjects randomised to placebo), total subject years

of follow up of approximately [redacted] for the "Randomised Placebo" and "Randomised Tezepelumab" treatment groups (as defined in Figure 2 below) are expected in the pooled dataset. Given this exposure, the 95% CIs for an adverse event for which the observed incidence rate is [redacted] for "Randomised Placebo" and [redacted] for "Randomised Tezepelumab" using the Rothman-Greenland Method. Confidence intervals based on the data from the individual predecessor studies (non-pooled data) will be wider than described above. Unless otherwise specified, all presentations will be split by predecessor study, and data will not be pooled across the 2 predecessor studies.

2 ANALYSIS SETS

2.1 Definition of analysis sets

For purposes of analysis, the following populations are defined below in Table 2.

Note that subjects included in the SAF and SAF-LTE analysis sets will be assigned to the treatment they are randomised to in the predecessor and LTE studies. In the case of discrepancies between the randomised and actual treatment, where a subject randomised to placebo, receives at least one dose of tezepelumab then all data from the date of the incorrect treatment within that time period (predecessor study, LTE study) will be excluded from the analysis and will be listed separately.

This is a different approach from the reporting of the individual predecessor studies, where treatment is based on the treatment subjects received in the case of any discrepancies between randomised and actual treatment. The reason for the difference in approaches is to avoid adding further complexity to the treatment groups as defined in Section 2.1.2.

Table 2 Analysis sets

Population	Description
Safety analysis set (SAF)	All subjects who were randomised and received at least 1 dose of IP in any of the predecessor studies, irrespective of their protocol adherence and continued participation in any of the studies, and regardless of their enrolment into this LTE study. Subjects will be assigned according to their randomised treatment. However, if a subject randomised to placebo receives an incorrect treatment, all data after the date the incorrect treatment was received within that time period (predecessor study, LTE study) will be excluded from the analysis, and listed separately. If a subject randomised to tezepelumab receives an incorrect treatment, it will still be regarded as a tezepelumab subject and no data will be excluded after the dose of placebo. Other incorrect dosing, if any, will be handled case-by-case.

Population	Description
SAF-LTE	Subjects who were randomised and received at least 1 dose of IP in the LTE study. Subjects will be assigned according to their randomised treatment. However, if a subject randomised to placebo receives an incorrect treatment, all data after the date the incorrect treatment was received within that time period (predecessor study, LTE study) will be excluded from the analysis, and listed separately. If a subject randomised to tezepelumab receives an incorrect treatment, it will still be regarded as a tezepelumab subject and no data will be excluded after the dose of placebo. Other incorrect dosing, if any, will be handled case-by-case.
Full analysis set (FAS)	All subjects who were randomised and received at least 1 dose of IP in any of the predecessor studies, irrespective of their protocol adherence and continued participation in any of the studies, and regardless of their enrolment into this LTE study. Subjects will be assigned according to their randomised treatment.
FAS-LTE	Subjects who were randomised and received at least 1 dose of IP in the LTE study. Subjects will be assigned according to their randomised treatment.
CCI [redacted]	[redacted]

The SAF is the primary population for the reporting of the safety data. The FAS is the primary population for the reporting of efficacy data. The SAF-LTE, FAS-LTE will be used for supportive analyses only.

The main summaries of demographics and baseline characteristics will be based on the SAF and SAF-LTE analysis sets, but additional summaries may be provided as detailed in Section 4.2.

CCI

In addition to the analysis sets defined above, LTE analysis set will be defined as all subjects who signed the informed consent for the LTE study. This analysis set will be used for reporting the disposition data during the LTE period.

2.1.1 Handling of other issues which may impact analysis sets

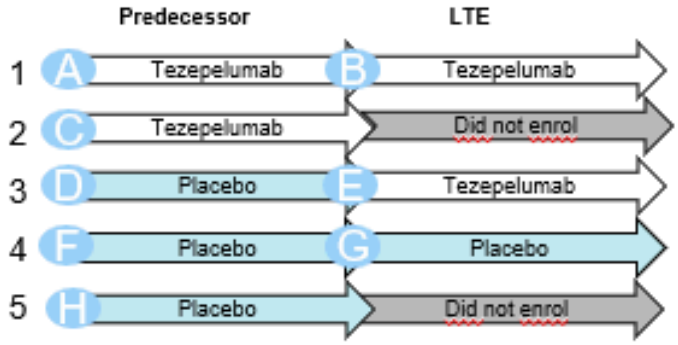
In a similar manner to the approach taken in the predecessor studies, if it is found that any subject has been randomised on more than one occasion (contrary to the protocol) under different subject numbers, either at the same site or at different sites, then data corresponding to the first subject participation will be used in the analyses. Data associated with the second (and any subsequent) participation of the same subject will be listed and discussed in the CSR. All data associated with duplicate randomisations will be reviewed, and decisions regarding the analysis and reporting of these data will be documented, prior to unblinding at the primary database lock for the predecessor studies and also the LTE study.

The above analysis set definitions assume the integrity of data captured from all participating sites in the trial. If it is deemed necessary to exclude subjects from analysis sets due to suspected fraud/other serious non-compliance at a particular site, or to perform sensitivity analyses with subjects from such a site removed for the same reason, this will be documented in this SAP (amended if necessary) where this is possible prior to database lock. Otherwise, it will be fully described in the CSR. The SAP will not be updated for this after database lock.

2.1.2 Treatment groups

There are 5 possible groupings across the predecessor and LTE studies as shown in Figure 2 below.

Figure 2 Treatment groupings

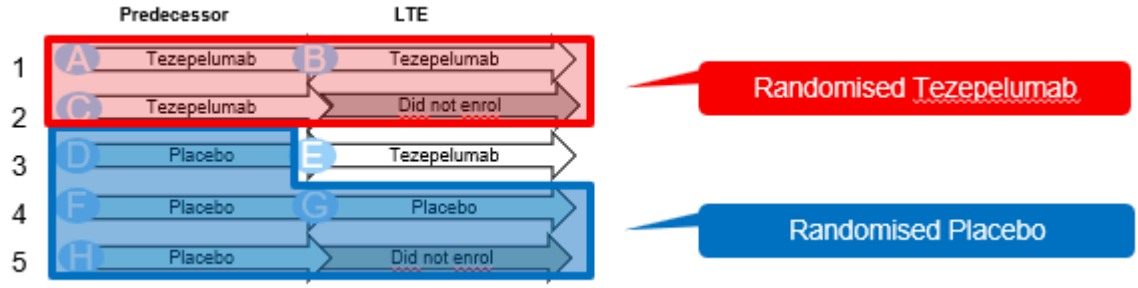


Note: Groups 2 and 5 reflect subjects in the predecessor studies who do not enrol in the LTE study.

The following treatment groups for analyses will be considered, where time from first dose is applicable for the safety analysis, and time from randomisation is applicable for the efficacy analysis:

Primary (based on the SAF and FAS analysis sets):

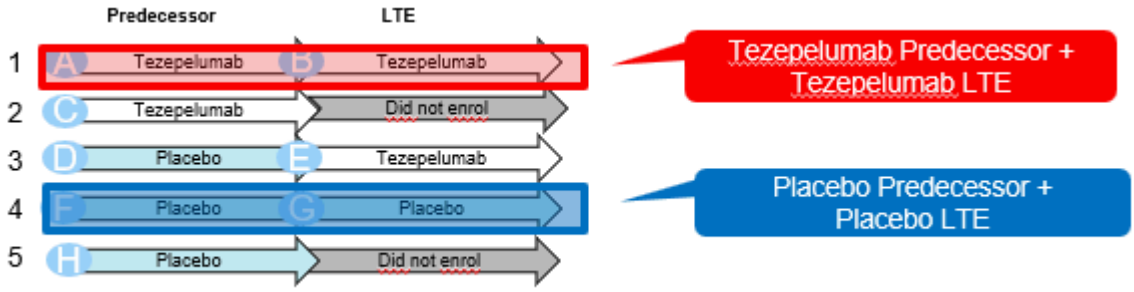
- **Randomised Tezepelumab (Rand Teze):** All subjects originally randomised to tezepelumab in the predecessor studies. Will include all data from first dose/randomisation in the predecessor studies to end of the LTE study. (A, B and C)
- **Randomised Placebo (Rand Pbo):** All subjects originally randomised to placebo in the predecessor studies. Will include all data from first dose/randomisation in predecessor studies up until switch to tezepelumab, and all data from first dose/randomisation in the predecessor studies to end of the LTE study for subjects randomised to placebo in the predecessor studies and the LTE study. (D, F, G and H)



Supportive (based on the SAF-LTE and FAS-LTE analysis sets):

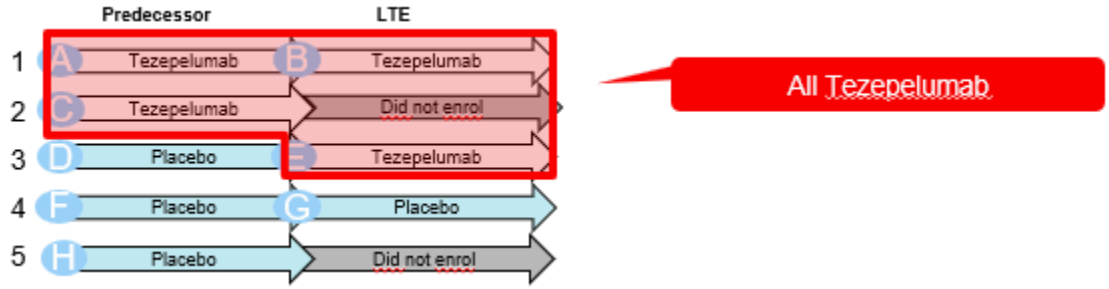
- **Tezepelumab Predecessor+Tezepelumab LTE (Teze+Teze):** All subjects originally randomised to tezepelumab in the predecessor studies and re-randomised to tezepelumab in the LTE study. Will include all data from first dose/randomisation in the predecessor study to end of the LTE study for only subjects enrolled into the LTE study. (A and B)
- **Placebo Predecessor+Placebo LTE (Pbo+Pbo):** All subjects randomised to placebo in the predecessor studies, and later re-randomised to placebo in the LTE study. Will

include all data from first dose in predecessor studies until end of the LTE study for only subjects enrolled into the LTE study. (F and G)



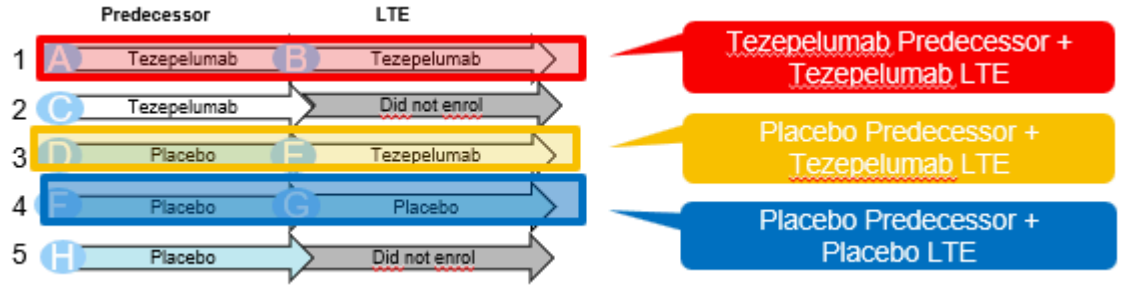
Supportive (for exposure summaries and rare events based on the SAF analysis set):

- **All Tezepelumab (All Teze)**: All subjects randomised to tezepelumab in the predecessor studies and subjects randomised to tezepelumab in the LTE study. It will include all data from time of first dose/randomisation to tezepelumab. (A, B, C and E)



Additional (for the assessment of durability of benefit based on the SAF-LTE and FAS-LTE analysis sets):

- **Tezepelumab Predecessor+Tezepelumab LTE (Teze+Teze):** as defined above
- **Placebo Predecessor+Placebo LTE (Pbo+Pbo):** as defined above
- **Placebo Predecessor+Tezepelumab LTE (Pbo+Teze):** All subjects originally randomised to placebo in the predecessor studies and re-randomised to tezepelumab in the LTE study. Will include all data from first dose/randomisation in the predecessor studies to end of the LTE study for only subjects enrolled into the LTE study. (D and E)



CCI

[redacted]

2.2 Violations and deviations

Important protocol deviations (PDs) will be listed and tabulated in the Clinical Study Report (CSR) only for randomised subjects. These are defined as PDs which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a subject's rights, safety, or well-being. Important PDs in this study will be grouped under one of the following categories (refer to Protocol Deviation Plan):

- Did not fulfil key eligibility criteria
- Developed discontinuation criteria during the LTE study but continued IP
- Received prohibited concomitant medication during the LTE study

- Did not comply with restrictions during the study
- IP management issues

All important PDs, except Code 10.9 receiving wrong IP kit number and Code 10.22 IP dose in excess of 700 mg administered within a 2-week period, will be identified and documented by the study team prior to unblinding of the LTE study. As far as possible, the occurrence of important PDs will be monitored (blinded) during the study, with the emphasis on their future prevention.

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[redacted]

The study PD Plan outlines the management of PDs and includes the proposed specific categories of PDs in this study. Any PDs which are not defined as important or COVID-19 related will not be reported and discussed in the CSR.

3 PRIMARY AND SECONDARY VARIABLES

For the definition of primary and secondary variables, unless stated otherwise, all references to Day 1 and date of first dose of IP, refer to the respective day in the predecessor studies. The date of last dose of IP refers to the last dose during the LTE study for subjects who enrol in the LTE study (and received IP in the LTE study) and the last dose of IP in the predecessor studies for subjects not continuing into the LTE study.

3.1.1 Data integration

Data from the predecessor studies will be integrated with the data from the LTE study. However, data will be reported separately for subjects initially enrolled in D5180C00007 from those initially in enrolled in D5180C00009, unless otherwise stated.

Subjects are assigned new enrolment codes (ecodes) in the LTE study from those assigned in the predecessor studies. The new ecodes will not overlap with those used in the predecessor studies. The SUTRA eCRF module in the database for the LTE study provides the decode link to allow subjects data across the studies to be integrated.

Ongoing AEs, concomitant medications and exacerbations will be recorded in both the predecessor study database and the LTE study database. If possible, they will be combined into one record for the purpose of analysis, based on the worst case (e.g., an ongoing AE recorded as mild in the predecessor study and recorded as moderate in the LTE study will be reported as one AE of moderate intensity).

Throughout this document reference to a particular week is in relation to Week 0 from the predecessor study (e.g., for study D5180C00007, Week 12 refers to 12 weeks after randomisation in the predecessor study; Week 64 refers to 12 weeks after enrolment into the LTE study).

3.1.2 Definition of baseline

The main objectives of the study are to look at the safety and efficacy over 104 weeks, therefore the baseline definition is as defined in Section 3.1.1 of the SAPs of the predecessor studies and detailed below.

In general, the last non-missing measurement on or prior to the date of randomisation in the predecessor studies will serve as the baseline measurement for efficacy variables. If there is no value on or prior to the date of randomisation, then the baseline value will not be imputed, and will be set to missing.

In general, the last non-missing measurement prior to first dose of study treatment in the predecessor studies will serve as the baseline measurement for safety variables. If there is no value prior to first dose of study treatment, then the baseline value will not be imputed, and will be set to missing.

Where unscheduled/repeat assessments are relevant and exist for any subject at a particular visit they will also be considered in the baseline definitions, provided they remain prior to the date of randomisation (efficacy) or the date of first dose of study treatment (safety) in the predecessor studies.

For safety variables (vital signs, weight/BMI, haematology, clinical chemistry, urinalysis, 12-lead ECG), baseline will be defined as the latest non-missing assessment prior to first dose in the predecessor studies. If no time is recorded for an assessment, and the assessment takes place at the randomisation visit, this will be assumed to be a pre-dose assessment.

3.1.3 Absolute change from baseline

Absolute change from baseline is defined as *(post-baseline value - baseline value)*.

If either the post-baseline value or the baseline value is missing, then the absolute change from baseline will also be missing.

Unless otherwise specified, “change from baseline” is assumed to be the absolute change from baseline.

3.1.4 Reversibility

Percentage reversibility is defined as follows, for pre-BD and post-BD measurements taken on the same date:

$$\%Reversibility = [(Post\text{-}BD\ FEV_1 - Pre\text{-}BD\ FEV_1)/Pre\text{-}BD\ FEV_1] \times 100\%$$

The FEV_1 post-BD measurement in the reversibility derivation is the measurement after up to 4 SABA inhalations.

3.1.5 Study periods

The following study periods are defined for analysis purposes:

Enrolment / Run-in period: starting on the date of the first study procedure and for D5180C00007, ending one day prior to randomisation in D5180C00007 (for randomised subjects), and for D5180C00009, ending one day prior to the start of the optimization period (Visit 2) (for randomised subjects) or on the date of the last study procedure (for screening failures). If any subject is re-screened in the predecessor studies, the latest available screening will be used for this purpose.

Optimization period (for D5180C00009 only): starting on the date of the first visit in the optimisation period (Visit 2) in the predecessor study and ending one day prior to randomisation in D5180C00009 (for randomised subjects). If any subject is re-screened, the latest available screening will be used for this purpose.

Planned treatment period (on-treatment and off-treatment): starting on the date of randomisation in the predecessor study (efficacy) / date of first dose of IP (safety) and ending on the minimum (date of the Week 104 visit, date of study withdrawal, day prior to start date of another biologic that impacts asthma control should this occur) for subjects enrolling into the LTE study, or ending on the minimum (date of the Week 52/48 visit, date of study withdrawal) otherwise.

On-treatment period: starting on the date of randomisation in the predecessor study (efficacy) / date of first dose of IP (safety) and ending on the minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal, day prior to start date of another biologic that impacts asthma control should this occur).

Post-treatment/Follow-up period: starting one day after the end date of the on-treatment period and ending on the study completion or withdrawal date (this will be the later date if a subject completes the predecessor study and enrols in the LTE study).

On-study period (planned treatment and follow-up): starting on the date of randomisation in the predecessor studies (efficacy) / date of first dose of IP (safety) and ending on the study completion or withdrawal date (this will be the later date if a subject completes the predecessor study and enrols in the LTE study).

CCI [redacted]

3.1.5.1 Time periods

In addition to the study periods defined above in Section 3.1.5, a predecessor period, LTE period, and CCI [redacted] period will be defined as subsets of the study periods. Data collected at EOT Week 52/48 visit in the predecessor studies will be regarded as during the predecessor period even if this data is recorded on the same day as the randomisation/first dose of IP during the LTE study. Note due to the difference in predecessor study durations, the predecessor period for data from D5180C00007 will be approximately 52 weeks and will be approximately 48 weeks for data from D5180C00009. Similarly, the LTE period will be approximately 52 weeks for D5180C00007 and approximately 56 weeks for D5180C00009.

CCI [redacted]

CCI [redacted] Subjects from D5180C00009 will only enter approximately 12 weeks of FU period.

For most cases, the predecessor EOT visit, the enrolment visit of the LTE study, and the first dose of the LTE study occur on the same day. However, if subjects had a delay between the predecessor EOT visit and the first dose of IP in the LTE study, the predecessor period definitions below include all data up to the day of the first dose of IP in the LTE study. Likewise, the LTE period definitions below will start from the day of first dose of IP in the LTE study. If a subject had the enrolment visit of the LTE study but received no dose of IP afterwards, it was only counted in the predecessor periods.

Predecessor period:

- **Planned treatment period:** starting on the date of randomisation in the predecessor study (efficacy) / date of first dose of IP (safety) and ending on the enrolment visit in LTE study for subjects enrolling into the LTE study or ending on the minimum (date of the EOT visit in the predecessor study, date of study withdrawal in the predecessor study, day prior to start date of another biologic that impacts asthma control should this occur) for subjects not enrolling into the LTE study.
- **On-treatment period:** starting on the date of randomisation in the predecessor study (efficacy) / date of first dose of IP (safety) and ending on the enrolment visit in LTE study for subjects enrolling into the LTE study or the minimum (date of last dose of IP in the predecessor study + 33 days, date of death, date of study withdrawal, day prior to start date of another biologic that impacts asthma control should this occur) for subjects not enrolling into the LTE study.
- **On-study period:** starting on the date of randomisation in the predecessor studies (efficacy) / date of first dose of IP (safety) and ending on the enrolment visit in LTE study for subjects enrolling into the LTE study or ending on the study completion or withdrawal date in the predecessor study for those subjects not enrolling into the LTE study.

LTE period:

Note: LTE period is different from LTE study. LTE period includes the 12-week safety follow-up (for those who do not enrol into the CCI [redacted] *period) but does not include* CCI [redacted] *period; whereas the LTE study (DESTINATION) includes* CCI [redacted] *period.*

- **Planned treatment period:** starting on the day of the enrolment visit in the LTE study and ending on the date of the planned treatment period as defined above in Section 3.1.5.
- **On-treatment period:** starting on the day of the enrolment visit in the LTE study and ending on the date of the on-treatment period as defined above in Section 3.1.5.
- **On-study period:** for subjects who do not enter the CCI [redacted] period, defined as starting on the day of the enrolment visit in the LTE study and ending on the date of the on-study period as defined above in Section 3.1.5. This end date will be the study completion date (Week 116) or early withdrawal date. For subjects who enter the

CCI period, defined as starting on the day of enrolment visit in the LTE study and ending on the Week 104 date.

EOT visit of the predecessor studies is on the same date of the enrolment visit of the LTE study unless some delays. Data collected at EOT visit of the predecessor studies prior to the first dose of IP in the LTE study will be included in the predecessor period.

CCI

3.1.6 Visit windows

All summaries and analyses, both efficacy and safety, which are presented by time point (e.g., "Week 104") will use study period (Predecessor, LTE, CCI and a visit window to classify the data record, which is derived from the assessment date relative to the reference start date. This approach allows appropriate classification of visits which may have occurred significantly earlier or later than the protocol assessment schedule, as well as the use of data captured at visits which have no fixed timing (notably the IPD visit), and the handling of data captured at visits for which the database label is incorrect and unresolvable.

Nominal database visit numbers will not be used in any summary or analysis by visit.

For safety variables, the reference start date is the date of first dose of IP in the predecessor study, and relative day is therefore defined as:

(Date of assessment – Date of first dose of IP) + 1.

For efficacy variables, the reference start date is the date of randomisation in the predecessor study, and relative day is therefore defined as:

(Date of assessment – Date of randomisation) + 1.

Any data collected at unscheduled or repeat visits will be listed and will be included in baseline definitions (see Section 3.1.2), and in any definitions of maximum value, minimum value or last value within the relevant study period.

Data collected at unscheduled or repeat visits will also be included in visit windows, and therefore may be included in summaries or analyses by visit or used in any sensitivity analyses which involve imputation of data from subjects with non-missing values to subjects with missing values. In the case of a missing value at a scheduled visit, which is then followed by a non-missing value at an unscheduled or repeat assessment within the same visit window, the non-missing value at the unscheduled/repeat assessment will replace the missing value at the scheduled visit.

If a subject has more than one non-missing value within the same visit window, the following rules will apply:

- The non-missing value closest to the target day will be selected for analysis at that visit.
- If two non-missing values are the same distance from the target day, the earlier of the two values will be selected for analysis at that visit.
- If two non-missing values are recorded on the same day and have a different assessment time associated with both of them, the value with the earliest assessment time will be selected for analysis at that visit.
- If two non-missing values (for continuous variables) are recorded on the same day and have no assessment time associated with at least one of them, or the same assessment time associated with both of them, the average of the two values will be selected for analysis at that visit. For categorical variables in this situation, the worst case will be used.

If a subject has no value within a particular visit window, then the subject will have a missing value at that visit in summaries and analysis.

The same visit window definitions below will be used regardless of whether the planned treatment period or the on-treatment period is used for analysis (see Section 3.1.5). In practice, each data record in the planned treatment period will be first identified, and then further flagged according to whether it is on-treatment or off-treatment. This flag will be used to select all eligible records for subsequent visit windowing, according to whether the derived visits are to be used in a planned treatment period or an on-treatment period analysis. It should be noted that, if treatment was discontinued within a particular visit window, the rules above for handling multiple values within the same visit window could select a different record according to whether a planned treatment period analysis or an on-treatment period analysis is needed.

Table 3 summarises the visit windows to be used in analyses as follows:

- "Visit Window 1" will be used only for variables which are captured at every clinic visit in the LTE period (vital signs, CCI AEs, assessment of asthma exacerbation, concomitant medication, and urine pregnancy test) CCI [redacted]
- "Visit Window 2" will be used for all variables (e.g., CCI urinalysis) except those specified for Visit Windows 1 and 3. CCI [redacted]

- "Visit Window 3" will be used for weight, height (adolescents in Study D5180C00007 only), CCI [redacted]

Table 3 Visit windows

Time Point	Target Day	Visit Window 1		Visit Window 2		Visit Window 3	
		D5180 C00007	D5180 C00009	D5180 C00007	D5180 C00009	D5180 C00007	D5180 C00009
Baseline (Week 0)	1	See Section 3.1.2 for baseline definitions					
Week 2	15	2-21	N/A	2-21	N/A	-	
Week 4	29	22-42	2-42	22-42	2-42	N/A	2-56 CCI [redacted]
Week 8	57	43-70		43-70		-	
Week 12	85	71-98		71-98		-	
Week 16	113	99-126		99-126		-	
Week 20	141	127-154		127-154		-	
Week 24	169	155-182		155-182		141-196	
Week 28	197	183-210		183-210		-	
Week 32	225	211-238		211-238		-	
Week 36	253	239-266		239-266		-	
Week 40	281	267-294		267-294		-	
Week 44	309	295-322		295-322		-	
Week 48	337	323-350		323-350		N/A	309-364
Week 52	365	351-378		351-378		337-392	N/A
Follow-up Week 54 [a]	379	N/A	351-399	N/A	351-399	N/A	
Week 56	393	379-406		-		-	
Follow-up Week 58 [a]	407	386-427	N/A	386-427	N/A	N/A	
Follow-up Week 60 [a]	421	N/A	400-441	N/A	400-441	N/A	
Week 60	421	407-434		-		-	

Time Point	Target Day	Visit Window 1		Visit Window 2		Visit Window 3	
		D5180 C00007	D5180 C00009	D5180 C00007	D5180 C00009	D5180 C00007	D5180 C00009
Follow-up Week 64 [a]	449	428-469	N/A	428-469	N/A	N/A	
Week 64	449	435-462		379-490		-	
Week 68	477	463-490		-		-	
Week 72	505	491-518		-		-	
Week 76	533	519-546		491-574		393-630	365-630
Week 80	561	547-574		-		-	
Week 84	589	575-602		-		-	
Week 88	617	603-630		575-672		-	
Week 92	645	631-658		-		-	
Week 96	673	659-686		-		-	
Week 100	701	687-714		-		-	
EOT Week 104	729	715-749		673-770		631-812	
Follow-up Week 110	771	750-791		-		-	
Follow-up Week 116	813	792-833		771-896		-	
CCI [redacted]							

[a] Only applicable for subjects who do not enrol into the LTE study.

Time Point	Target Day	Visit Window 2	
		CCI [redacted]	Urinalysis
EOT Week 104	729		673-854
Follow-up Week 110	771		-

Follow-up Week 116	813	CCI	-
CCI			

In all cases above, no time points will be presented in summary tables or included in statistical analysis which do not correspond to the time points scheduled in the protocol for the variable in question. Listings of data will include all scheduled and unscheduled visits.

3.1.7 Prior and concomitant medications

Medications taken by any subject at any time during the study will be coded using the ATC classification system within the WHO Drug Dictionary.

Medications will be categorised for analysis according to their onset and end dates as follows, where first dose of IP refers to first dose of IP in the predecessor studies:

- Prior medications:
  - end date ≤ date of first dose of IP
- Concomitant medications during on-treatment period:
  - end date > date of first dose of IP in the predecessor study and start date ≤ minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal), or
  - end date ongoing and start date ≤ minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal)
- Concomitant medications during post-treatment period:
  - start date > date of last dose of IP + 33 days.

Essentially the above says that:

- Prior and concomitant medications are mutually exclusive.
- Concomitant medications on-treatment and post-treatment are also mutually exclusive (here, the word “concomitant” means concomitant with study procedures, irrespective of whether IP was still being taken). Specifically, a concomitant medication which started on-treatment and ended post-treatment will only be considered on-treatment.

In addition, concomitant medications will be categorised by predecessor period and LTE period as follows:

- Concomitant medications during on-treatment predecessor period:
  - end date > date of first dose of IP in the predecessor study and start date ≤ minimum (date of last dose of IP in the predecessor study + 33 days, date of death, date of study withdrawal, date of enrolment into the LTE study*), or

  - end date ongoing and start date ≤ minimum (date of last dose of IP in the predecessor study + 33 days, date of death, date of study withdrawal, date of enrolment into the LTE study*)
- Concomitant medications during on-treatment LTE period:
  - end date > date of enrolment in the LTE study* and start date ≤ minimum (date of last dose of IP in the LTE study + 33 days, date of death, date of study withdrawal), or
  - end date ongoing and start date ≤ minimum (date of last dose of IP in the LTE study + 33 days, date of death, date of study withdrawal)

** For subjects in the Placebo Predecessor+Tezepelumab LTE treatment group who do not receive their first dose of IP in the LTE study on the date of enrolment into the LTE study, replace the date of enrolment into the LTE study with the date of first dose of IP in the LTE study in the derivations above.*

If the medication record has a completely missing onset date, the subject will be assumed to have been on the medication on the date of the first study procedure. If the medication record has a partially missing onset date (month/year or year only) which is the same as that for the end of IP treatment, it will be assumed to have started on-treatment. If the medication record has a partially missing onset date (month/year or year only) which is the same as that for the start of IP treatment, it will be assumed to have started before treatment.

If the medication record has a completely missing end date, the subject will be assumed to have been on the medication on the date of study completion or withdrawal. If the medication record has a partially missing end date (month/year or year only) which is the same as that for start of IP treatment, it will be assumed to have ended on-treatment. If the medication record has a partially missing end date (month/year or year only) which is the same as that for end of IP treatment, it will be assumed to have ended post-treatment.

3.1.8 Definition of subgroups

The following subgroups are defined for the purposes of efficacy and safety subgroup analyses and/or demographic and baseline summaries where baseline will be defined as specified in Section 3.1.2. Efficacy and safety subgroup analyses will only be conducted on summary data from subjects with D5180C00007 as predecessor study; variables to be analysed by subgroup are marked with *. If any of the subgroups has fewer than 10 subjects in one or both treatment arms, the corresponding safety and efficacy subgroup analyses will not be conducted. CCI [redacted]

For D5180C00007:

- *Baseline eosinophils group: <300/µL, ≥300/µL
- Baseline eosinophils group: <150/µL, 150-<300/µL, 300-<450/µL, ≥450/µL
- *Baseline eosinophils group: <150/µL, ≥150/µL (only for analyses of AAER)

- *Baseline clinic visit FeNO group: <25ppb, ≥25ppb
- Baseline clinic visit FeNO group: <25ppb, 25-<50ppb, ≥50ppb
- Baseline (Any) specific IgE status (FEIA): Any FEIA positive, All FEIA negative, Unknown FEIA
  - "Any FEIA positive" requires 1 or more specific IgE panels using fluorescent enzyme immunoassay (FEIA) to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 12 panels to be available.
  - "All FEIA negative" requires all 12 specific IgE panels to be negative. If there are fewer than 12 panels with data available and none of these is positive, then IgE status is considered "Unknown FEIA".
  - Positive is defined as a value ≥0.35 kU/mL.
- * Baseline perennial specific IgE status (FEIA): Any perennial FEIA positive, All perennial FEIA negative, Unknown perennial FEIA
  - "Any perennial FEIA positive" requires 1 or more specific IgE (FEIA) panels to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 8 panels to be available.
  - "All perennial FEIA negative" requires all 8 specific IgE panels to be negative. If there are fewer than 8 panels with data available and none of these is positive, then IgE status is considered "Unknown perennial FEIA".
  - Positive is defined as a value ≥0.35 kU/L. The 8 panels include: American Cockroach, Cat Dander, D. farina, D. pteronyssinus, Dog Dander, German Cockroach, Mould Mix, Oriental Cockroach.
- Baseline seasonal specific IgE status (FEIA): Any seasonal FEIA positive, All seasonal FEIA negative, Unknown seasonal FEIA
  - "Any seasonal FEIA positive" requires 1 or more specific IgE (FEIA) panels to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 4 panels to be available.
  - "All seasonal FEIA negative" requires all 4 specific IgE panels to be negative. If there are fewer than 4 panels with data available and none of these is positive, then IgE status is considered "Unknown seasonal FEIA".
  - Positive is defined as a value ≥0.35 kU/L. The 4 panels include: Grass Mix Pollen, Silver Birch Pollen, Weed Mix Pollen, Japanese Cedar.
- *ICS dose at study entry: low, medium, high (as defined in Appendix 8.3 – only for analyses of AAER)
- *OCS at baseline: present, absent. Note OCS at baseline will be defined as OCS administered at baseline for disease under study (only for analyses of AAER)
- Age category used for stratification: adults (≥18) and adolescents (≥12 to <18)
- *Age category: adults (≥65), adults (≥18 to <65) and adolescents (≥12 to <18)
- Gender: Male, Female
- Race: White, Black or African American, Asian, Other
- *Exacerbations in the year before study: ≤2 exacerbations, >2 exacerbations

- Baseline body mass index (BMI): <18.5 kg/m^2, 18.5-<25.0 kg/m^2, 25.0-<30.0 kg/m^2, ≥30.0 kg/m^2
- Geographical region: Asia Pacific [incl. Japan, South Korea, Taiwan and Vietnam], North America [incl. Canada and USA], South America [incl. Argentina and Brazil], Central/Eastern Europe [incl. Russia and Ukraine], Western Europe plus Australia [incl. Austria, France, Germany, UK and Australia], Rest of World [incl. Israel, Saudi Arabia and South Africa]. Note all subjects from Japan who were in study C00007 were not enrolled into the LTE study.
- Country
- Baseline CRSwNP status: Yes, No
  - Chronic rhinosinusitis with nasal polyps at baseline will be defined by the presence of the following on the Respiratory Disease History eCRF page for a particular subject: Nasal polyps plus at least one of (Diagnosis of rhinitis; Diagnosis of chronic sinusitis).
- Nasal polyps status at study entry: Yes, No
  - Nasal polyps at baseline will be defined by the presence of nasal polyps on the Respiratory Disease History eCRF page for a particular subject.
- *Nasal polyps in the 2 years before randomisation status: Yes, No

  Nasal polyps in the 2 years before randomisation will be defined by the presence of nasal polyps on the Respiratory Disease History eCRF page for a particular subject, with no associated stop date on the Medical History eCRF or an associated stop date less than, or equal to 24 months before randomisation.

For D5180C00009:

- Baseline eosinophils group: <300/µL, ≥300/µL
- Baseline eosinophils group: <150/µL, ≥150/µL
- Baseline eosinophils group: <150/µL, ≥ 150/µL to < 300/µL, ≥ 300/µL to <450/µL, ≥ 450/µL
- Baseline clinic visit FeNO group: < 25ppb, ≥ 25ppb
- Baseline clinic visit FeNO group: <25ppb, 25-<50ppb, ≥50ppb
- Baseline (Any) specific IgE status (FEIA): defined the same as D5180C00007
- Baseline perennial specific IgE status (FEIA): defined the same as D5180C00007
- Baseline seasonal specific IgE status (FEIA): defined the same as D5180C00007
- OCS dose at randomisation: (≤10 mg versus >10 mg prednisone or prednisolone)
- Age category: adults (≥65) and adults (≥18 to <65)
- Gender: Male/Female
- Race: White, Black or African American, Asian, Other
- Baseline body mass index (BMI): <18.5 kg/m^2, 18.5-<25.0 kg/m^2, 25.0-<30.0 kg/m^2, >= 30.0 kg/m^2

- Geographical region: Western Europe and North America (incl. Germany and USA); Central/Eastern Europe (incl. Poland, Turkey and Ukraine); Rest of World (incl. Argentina and South Korea).
- Country

3.1.9 Disposition

The following definitions will be used for time to event variables in Kaplan-Meier disposition plots:

Time to last dose of IP

Time to last dose of IP will be defined as follows:

Time to last dose (days) = [Date of last dose of IP from eCRF – date of first dose of IP in the predecessor studies] + 1.

Date of last dose of IP will be the date of last dose taken from the "Discontinuation of Investigational Product" eCRF page for all subjects; those who prematurely discontinue IP as well as those who complete IP dosing as per protocol. For subjects who are not enrolled in the LTE study or do not receive IP during the LTE study, the date of last dose of IP will be taken from the predecessor study eCRF.

Subjects on placebo in a predecessor study, enrolled in LTE study, and randomised to receive tezepelumab in the LTE study will be censored on the date of last dose of IP taken from the predecessor study eCRF.

Time to premature study withdrawal

Time to premature study withdrawal will be defined as follows:

Time to premature study withdrawal (days) = [study withdrawal date from eCRF – date of randomisation in the predecessor studies] + 1.

Study withdrawal date will be the completion or discontinuation date from the "Disposition" eCRF page, where any subject status other than "Completed" has been entered. For subjects enrolling into the LTE study, this will be the Disposition eCRF from the LTE study (as all subjects enrolling in the LTE study will have completed the predecessor study).

Subjects who did not prematurely withdraw from study will be censored at one of the following dates:

- For subjects not enrolling into the LTE study, completion or discontinuation date from the "Disposition" eCRF page from the predecessor study, where subject status of "Completed" has been entered.

- For subjects enrolling into the LTE study, completion or discontinuation date from the "Disposition" eCRF page from the LTE study, where subject status of "Completed" has been entered.

At primary DBL, ongoing subjects will be censored at their last contact date.

3.2 Derivation of safety variables

3.2.1 Exposure to IP and treatment compliance

Extent of exposure to IP is defined as the number of days between the date of first dose of IP in the predecessor study and the date of last dose of IP inclusive plus the number of days allowance for the dosing interval that is:

Extent of exposure (days) = [minimum (date of last dose of IP + 33 days; date of death; date of study withdrawal) – date of first dose of IP in the predecessor study] + 1

The extent of exposure will be calculated separately for exposure to tezepelumab and exposure to placebo, so in the above calculation, the extent of exposure to placebo will be based on the first and last dose of placebo, reflecting that the last dose of placebo may be in the predecessor study despite the subject continuing to be dosed in the LTE study. Similarly, the extent of exposure to tezepelumab for the All Tezepelumab treatment group will be based on the first and last dose of tezepelumab, reflecting that the first dose of tezepelumab will be during the LTE study for some subjects.

The above calculation does not consider any gaps in exposure caused by the subject missing one or more intermediate scheduled 4-weekly doses. Such cases will be identified in the CSR if they occur but will not explicitly be accounted for in any analysis.

Extent of exposure will also be calculated separately for the predecessor and LTE period, using only dates from the corresponding period as defined for the on-treatment period in Section 3.1.5.1. If the last date of predecessor period is on the same date as the first date of LTE period, then the date will be counted in both periods. However, it will be only counted once for the overall extent of exposure using the formula above.

The total subject-years exposure for a treatment group will be derived as the sum of the individual subject extents of exposure (days) for that treatment group and divided by 365.25.

Treatment compliance will be calculated as follows:

Treatment compliance (%) = [(Total number of actual dosing occasions/total number of expected dosing occasions)] x *100%*

In order to allow for subjects who discontinue IP early in the compliance calculation, the number of expected dosing occasions will be calculated as the number of scheduled dosing visits up to and including the last available dosing visit for that subject.

Treatment compliance will also be calculated separately for the predecessor and LTE periods.

3.2.2 Adverse events – general

Adverse events (AEs) experienced by any subject at any time during the entire study will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of the primary database lock. This version of MedDRA will also be used during the final database lock.

AEs will be categorised for analysis according to their onset date into the following study periods for the SAF and SAF-LTE analysis sets:

- AEs occurring during screening/run-in period: date of Visit 1 in the predecessor study ≤ AE onset date < date of first dose of IP in the predecessor study
- AEs occurring during on-treatment period: date of first dose of IP ≤ AE onset date ≤ minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal)
- AEs occurring during post-treatment/follow-up period (for subjects still being followed up then): date of last dose of IP + 33 days < AE onset date ≤ study completion or withdrawal date
- AEs occurring during on-study period: date of first dose of IP ≤ AE onset date ≤ study completion or withdrawal date.

In addition, AEs will be further categorised for analysis for the on-treatment and on-study periods by the predecessor and LTE time periods as defined in Section 3.1.5.1.

If the AE has a completely missing (and unresolvable) onset date, then the AE will be assumed to have occurred during the on-treatment period, unless the end date indicates unambiguously that the AE resolved before treatment started. If the AE has a partially missing (and unresolvable) onset date, then the AE will also be assumed to have occurred during the on-treatment period, unless either the end date indicates unambiguously that the AE resolved before treatment started, or the partial onset date is in the month/year prior to start of treatment.

For each treatment group, exposure adjusted incidence rates will be defined as the number of subjects reporting adverse events divided by total exposure duration for that treatment group.

For individual subjects, exposure duration (days) for each time period is derived using the start date and end date defined for the on-treatment and on-study period in Section 3.1.5.1. The total exposure duration (years) for a treatment group will be derived as the sum of the individual subject exposure duration (days) for that treatment group and divided by 365.25.

In all incident rate summaries of AEs, multiple occurrences of the same event for a particular subject will not be counted as separate events. A subject will either be considered to have no events of the type being summarised, or one or more occurrences of that event.

Furthermore, for specific AEs, exposure adjusted occurrence rates will be defined as the number of events divided by total exposure duration for that treatment group, as described above.

3.2.3 Adverse events of special interest

The protocol specifies Adverse Events of Special Interest (AESIs) as those which merit special attention in this trial, and for which derivation details (for those derived from the eCRF), or a statement when the derivation needs to be referenced externally to the SAP (for those derived from MedDRA dictionary terms), are given in Appendix 8.1.

3.2.4 Laboratory variables

Clinical chemistry, haematology and urinalysis will be performed by a central laboratory according to the schedule and the variable specifications described in the CSP. Urine samples will be analysed locally and sent for analysis at the central laboratory only if a positive dipstick result for any parameter is observed.

Changes from baseline in continuous laboratory variables will be calculated at relevant visits as specified in Section 3.1.2 and Section 3.1.3.

In all analyses of continuous laboratory variables, any value recorded only as below Lower Limit of Quantification (LLOQ) will be set to the LLOQ and included in the analysis. Any value recorded only as above Upper Limit of Quantification (ULOQ) will be set to the ULOQ and included in the analysis.

Absolute values will be compared to the relevant normal reference range, as provided by the central laboratory, and classified as low (below range), normal (within range or on the limits) or high (above range). All values falling outside the normal reference ranges will be flagged. These classifications will also be used for shift tables.

For the purposes of shift tables, baseline will be defined as specified in Section 3.1.2. Minimum, maximum and last values calculated across all visits in the relevant study period will use all available values including those from unscheduled and repeat visits, and irrespective of whether the values have been selected for use in summaries using visit windows (see Section 3.1.6).

Liver function tests will also be evaluated as multiples of the upper limit of the normal reference range (ULN). Subjects who meet any of the following criteria at any time during the study will be flagged:

- AST $\geq$ 3 x ULN
- ALT $\geq$ 3 x ULN
- TBL $\geq$ 2 x ULN

Other multiples of ULN will also be used in the display of liver function tests.

3.2.5 Vital signs

Changes from baseline in vital signs (pulse rate, systolic blood pressure (BP), diastolic BP, respiratory rate, body temperature, body weight, body mass index (BMI)) will be calculated at relevant visits as specified in Section 3.1.2 and Section 3.1.3.

BMI is calculated as:

BMI = Weight (kg) / [Height (m)]^2.

Absolute values and changes from baseline (where applicable) will be compared to the relevant reference range tabulated below, and classified as low (below range), normal (within range or on the limits) or high (above range). All values falling outside the reference ranges will be flagged.

Table 4 Vital signs reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit	Change from Baseline Criteria
Diastolic BP (sitting)	mmHg	60	100	±15
Systolic BP (sitting)	mmHg	90	160	±30
Pulse rate (sitting)	beats/min	50	100	±20
Respiratory rate	breaths/min	8	20	
Body temperature	Celsius	36.0	37.5	
Weight	kg	40	150	

3.2.6 12-lead ECG

The outcome of the overall evaluation (normal, abnormal or borderline) will be taken directly from the eCRF, as will the assessment of clinical significance.

3.2.7 Physical examination

Only physical examination results judged as a new clinically meaningful finding or a clinically meaningful aggravation of an existing finding by the investigator will be captured, and these will be reported as AEs.

3.2.8 Medical history

If a partial diagnosis date is available only, the following rules will be used to impute a complete date (e.g. for derivation of time since diagnosis):

If both the month and the year are available, the first of the recorded month will be imputed, unless the date of birth is within the same month and year (where date of birth is available, which will not be the case in all countries). In this case, the date of birth will be imputed instead.

If only the year is available, 1st January will be imputed, unless the date of birth is within that same year (where date of birth is available). In this case, the date of birth will be imputed instead.

3.3 Derivation of efficacy variables

3.3.1 Secondary endpoint (first efficacy endpoint)

3.3.1.1 Annualised asthma exacerbation rate over 104 weeks

An asthma exacerbation (recorded on the exacerbation eCRF page) is defined in the CSP as a worsening of asthma that leads to any of the following:

- A temporary bolus/burst of systemic corticosteroids (or a temporary increase in stable OCS background dose) for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids
- An emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an ER or UC centre) due to asthma that required systemic corticosteroids (as per above)
- An inpatient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma.

The start of an exacerbation is defined in the CSP as the start date of systemic corticosteroids, ER or UC visits requiring systemic corticosteroids, or hospital admissions due to asthma, whichever occurs earlier. The end date is defined in the CSP as the last day of systemic corticosteroids or ER/UC/hospital discharge, whichever occurs later.

Two or more exacerbations with the same start date and end date will be counted as one exacerbation for the purposes of calculating the number and duration of exacerbations for a subject. In the case that one or more exacerbations are recorded as starting or ending during another exacerbation, these will be counted as one exacerbation, using the earliest exacerbation start date and the latest exacerbation stop date to calculate duration.

Additional systemic corticosteroid treatments, ER or UC visits requiring use of systemic corticosteroids, or inpatient hospitalisation due to asthma occurring during an exacerbation will not be regarded as a new exacerbation. To be counted as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled. If the end date of the first exacerbation and the start date of the second exacerbation are less than 7 days apart, then these will be counted as one exacerbation.

For planned treatment analyses, the overall time at risk will be defined as follows:

Time at risk (days) = [earliest (X; date of last exacerbation assessment status from the eCRF; date of death; day prior to start date of another biologic that impacts asthma control) – date of randomisation in the predecessor study] + 1.

where X is defined as

- *If subjects do not enrol into LTE and had EOT visit in predecessor studies, then date of EOT visit at Week 52 (or 48 in D5180C00009);*
- *If subjects do not enrol into LTE and no EOT visit in predecessor studies, then randomisation date + 364 days (or 336 days in D5180C00009) + 5 days;*
- *If subjects enrol into LTE and are randomised to remain on the same treatment, and had EOT visit in LTE study, then date of EOT visit at Week 104;*
- *If subjects enrol into LTE and are randomised to remain on the same treatment, and no EOT visit in LTE study, then randomisation date in the predecessor study + 728 days + 5 days;*

If subjects enrol into LTE with treatment cross-over, the time at risk needs to be calculated separately by period.

- For the predecessor period, *time at risk (days) = [earliest (end date of predecessor period, date of last exacerbation assessment status from the eCRF; date of death; day prior to start date of another biologic that impacts asthma control) – date of randomisation in the predecessor study] + 1.*
- For the LTE period with LTE EOT visit, *time at risk (days) = [earliest (date of EOT visit at Week 104, date of last exacerbation assessment status from the eCRF; date of death; day prior to start date of another biologic that impacts asthma control) – start date of LTE period] +1.*
- For the LTE period without LTE EOT visit*, time at risk (days) = [earliest (randomisation date in the predecessor study + 728 days + 5 days, date of last exacerbation assessment status from the eCRF; date of death; day prior to start date of another biologic that impacts asthma control) – start date of LTE period] +1.*

The number of days the subject experiences a protocol defined exacerbation, including the subsequent 7 days (when a further exacerbation would not be considered as a second exacerbation), will be subtracted from the time at risk defined above. For example, if a subject has a single exacerbation which lasts 4 days then 7 + 4 =11 days will be subtracted from the time at risk.

It should be noted that the date of last assessment of exacerbation status from the eCRF might be later than the last available visit during the planned treatment period, in the case that the

subject remained in the study with incomplete follow-up options after early discontinuation of IP.

For the primary analysis (planned treatment), exacerbations that occur after a subject has discontinued IP but before the end of the time at risk will still be accounted when deriving the total number of exacerbations. Likewise, the time at risk will reflect the time at risk regardless of whether the subject is still on IP or not.

Any exacerbations that starts within the time at risk but ends after this time point will be included in analyses with the end date adjusted to be no later than the time at risk. Any exacerbation that starts after this time will not be included in analyses.

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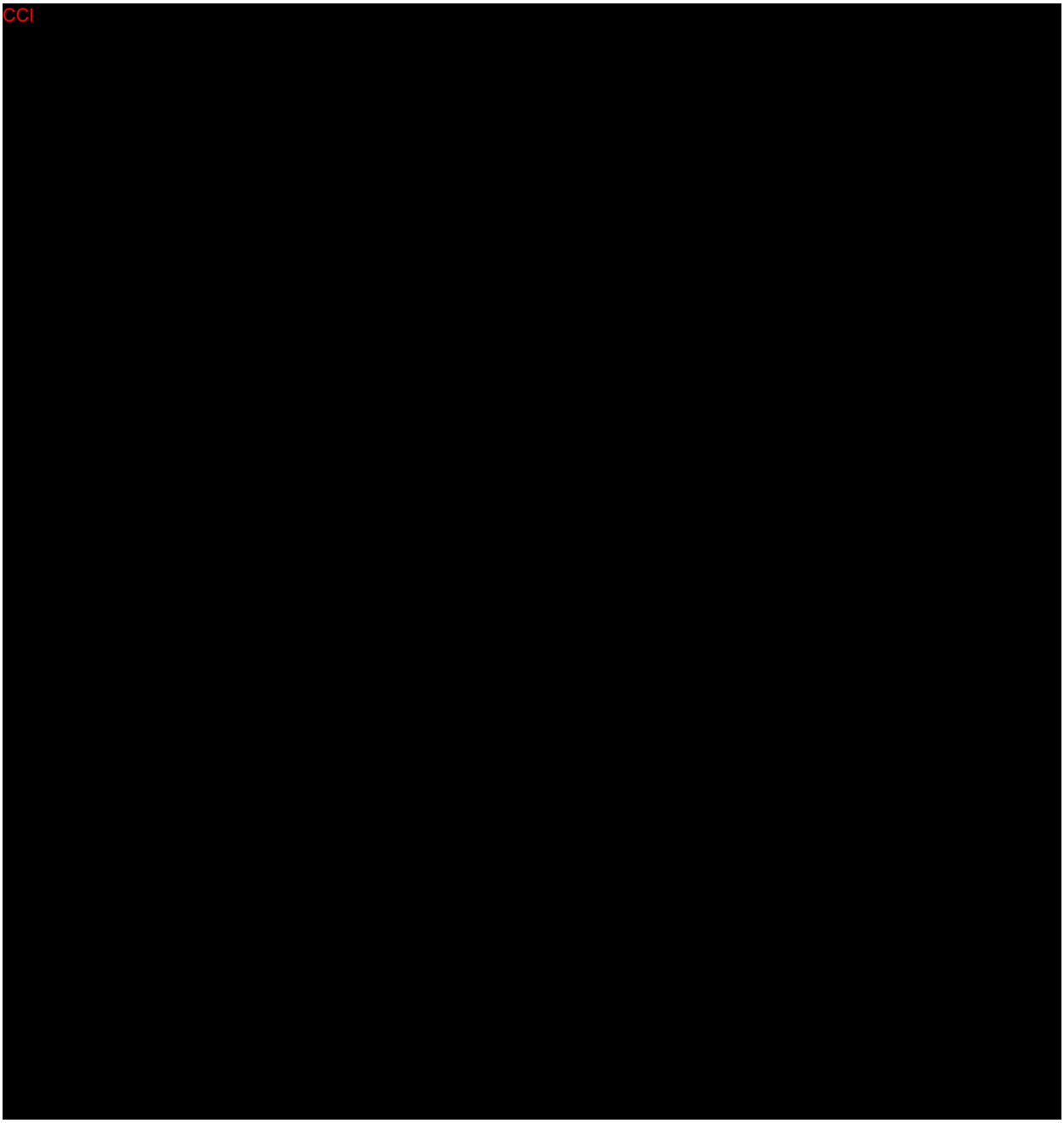

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3.4 CCI

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4 ANALYSIS METHODS

Unless otherwise specified, all presentations will be split by predecessor study, and data will not be pooled across the 2 predecessor studies. Table 9 and Table 10 in Appendix 8.4 provides information on the data to be summarised by analysis sets and treatment groups. CCI [redacted] Additional reporting to assess the impact of the COVID-19 pandemic are provided in Appendix 8.5.

4.1 General principles

4.1.1 Statistical Hypotheses

No statistical hypotheses will be formally tested in this study.

4.2 Subject disposition, demography and baseline characteristics

Subject disposition will be summarised using the SAF analysis set for the predecessor period and using the LTE analysis set for the LTE period.

For the predecessor period, the number and percentage of subjects within each treatment group (Randomised Tezepelumab and Randomised Placebo) will be presented by the following categories; received IP, did not receive IP (and reason), completed treatment, discontinued treatment (and reason), completed study (including subjects who completed IP and study, and subjects who discontinued IP but completed study assessments), discontinued study (including reason), and subjects who did not enrol into the LTE study.

For the LTE period, the number of subjects enrolled into the LTE study will be summarised, and the number and percentage of subjects within each treatment group (Tezepelumab Predecessor+Tezepelumab LTE, Placebo Predecessor+Placebo LTE and Placebo Predecessor+Tezepelumab LTE) will be presented by the following categories; randomised, not randomised (and reason), received IP, did not receive IP (and reason), completed treatment, discontinued treatment (and reason), completed study (including subjects who completed IP and study, and subjects who discontinued IP but completed study assessments), discontinued study (including reason), and subjects who enrolled into LTE but had a delay due to COVID-19. Randomisation information will also be listed.

The number and percentage of subjects who discontinued IP, but remained in the study, will be presented by treatment group and option of follow up (Section 1.2) for the SAF-LTE analysis set for the LTE period only. Subject disposition will also be presented in listings. A separate listing will be produced for: those who discontinue IP, those who discontinue the study, and those who complete the study.

Kaplan-Meier plots will be produced summarising separately the time (in days) to last dose of IP and premature withdrawal from the study for the SAF analysis set. Subjects without the premature event will be censored as described in Section 3.1.9. The number of subjects discontinuing IP and prematurely withdrawing from the study will be monitored as the study

progresses. Additional summaries of this data including investigation of the reasons for discontinuations by treatment group may also be provided.

Demographic data, and baseline characteristics will be summarised using the following analysis sets and treatment groups. For subjects receiving placebo in the predecessor studies and tezepelumab in the LTE study, the data collected at the baseline of the predecessor studies will be included.

- SAF (Randomised Tezepelumab and Randomised Placebo)
- SAF-LTE (Tezepelumab Predecessor+Tezepelumab LTE, Placebo Predecessor+Placebo LTE and Placebo Predecessor+Tezepelumab LTE)
- SAF (All Tezepelumab)

Demographic data, such as age, gender, and race, will be summarised by analysis set and treatment groups as described above. All subgroups as defined in Section 3.1.8 will be summarised by treatment group for the SAF and SAF-LTE analysis sets. In addition, for study D5180C00007, demographic data will also be summarised by adults (≥65), adults (≥18 to <65) and adolescents (≥12 to <18) separately for the SAF-LTE analysis set. Subjects will be categorised by age based on their age at screening in the predecessor study (e.g., an adolescent subject who turns 18 during the predecessor or LTE periods will be regarded as an adolescent for both periods).

Various baseline characteristics will also be summarised by analysis set and treatment groups as described above. These include medical, surgical and respiratory disease histories, weight, height and BMI, smoking status, history of allergy, CCI [redacted] asthma duration, age at onset of asthma, asthma medications, the number of asthma exacerbations in the previous 12 months, CCI [redacted] In addition, for study D5180C00007, baseline characteristics data will also be summarised by adults (≥65), adults (≥18 to <65) and adolescents (≥12 to <18) separately for the SAF-LTE analysis set.

Medical and surgical histories will be summarised by MedDRA Preferred Term (PT) within the System Organ Class (SOC) level of MedDRA for the SAF and SAF-LTE analysis sets.

Important PDs reported over the 104-week planned treatment period will be summarised using the SAF-LTE analysis set for the Tezepelumab Predecessor+Tezepelumab LTE, Placebo Predecessor+Placebo LTE, and Placebo Predecessor+Tezepelumab LTE treatment groups by period (Predecessor and LTE).

The number and percentage of subjects in each of the analysis sets defined in Section 2.1 will be summarised by the primary and supportive treatment groups (as defined in Section 2.1.2) separately.

4.3 Prior and concomitant medications

Unless stated otherwise, for all the summaries described in this section, summaries using the SAF analysis set will present the Randomised Tezepelumab and Randomised Placebo treatment groups; summaries using the SAF-LTE analysis set will present the Tezepelumab Predecessor+Tezepelumab LTE and Placebo Predecessor+Placebo LTE treatment groups. In addition, any summaries split by predecessor period and LTE period for the SAF-LTE analysis set will also include the Placebo Predecessor+Tezepelumab LTE treatment group.

The number and percentage of subjects receiving each medication (by ATC classification system codes and generic name) will be presented by treatment for the SAF and SAF-LTE analysis sets. Separate tables will be presented for all medications received during each of the following periods as defined in Section 3.1.7: Prior, Concomitant (on-treatment), Concomitant (post-treatment) for the SAF and SAF-LTE analysis sets. Summaries of Concomitant (on-treatment) medications during the predecessor period and LTE period will also be provided by the SAF and SAF-LTE analysis sets. Summaries of Prior and Concomitant (post-treatment) for the SAF-LTE analysis set will also include the Placebo Predecessor+Tezepelumab LTE treatment group.

Tables for maintenance medications (started prior to and ongoing after the first day of IP) will be produced displaying the baseline total daily dose categories (low/medium/high) of ICS medications for the SAF and SAF-LTE analysis sets. The number of subjects using other maintenance asthma medications at baseline will also be summarised for the SAF and SAF-LTE analysis sets.

In addition, the total number of days of systemic corticosteroid treatment associated with asthma exacerbations per subject from the first day of IP up to Week 104 will also be summarised for the SAF and SAF-LTE, and also split by predecessor and LTE periods.

For study D5180C00007, summary statistics will be produced of total daily OCS dose converted to a prednisone equivalent irrespective of reason/condition treated (for subjects taking OCS at baseline). Conversion factors to be applied for this purpose are given in Appendix 8.2.

For study D5180C00009, a summary of the OCS medication at study entry and baseline total daily dose will be produced for the SAF and SAF-LTE analysis sets. In addition, a summary of the OCS total dose at study entry to optimized baseline OCS dose will be produced for the SAF and SAF-LTE analysis sets.

Separate tables will be presented for subjects who took disallowed concomitant medications for the SAF and SAF-LTE analysis sets, and also split by predecessor and LTE period for disallowed concomitant medications taken during the on-treatment period. Summaries of prior and post-treatment disallowed medications for the SAF-LTE analysis set will also include the Placebo Predecessor+Tezepelumab LTE treatment group.

Disallowed medications will include medications defined as prohibited according to Section 6.5 of each study CSP. Disallowed medications include prohibited and restricted drugs;

restricted drugs are considered a disallowed medication depending on timing of use, or if there are changes in dose and regimen during the study as defined in the CSP. They will be defined following a physician review (prior to planned unblinding of each study) of the unique combinations of ATC code classifications and generic terms captured.

Medications will be classified using the same version of the WHO Drug Dictionary that was used at the time of primary database lock for the predecessor studies.

Percentages will be calculated relative to the number of subjects in the SAF and SAF-LTE analysis sets as appropriate.

Data from subjects who discontinued IP, regardless of level of follow up chosen will, where possible and relevant, be included in the appropriate medication summaries.

Potential prior biologics use will be summarised separately, similarly to above. In addition, biologics introduced during the post-treatment period will be summarised for the SAF and SAF-LTE analysis sets. Summaries of prior and post-treatment biologics for the SAF-LTE analysis set will also include the Placebo Predecessor+Tezepelumab LTE treatment group. Any biologics that are taken during the on-treatment period will be summarised as part of the disallowed medications but may also be reported separately.

4.4 Exposure and compliance

Exposure and treatment compliance derivation details are defined in Section 3.2.1.

Extent of exposure to IP and compliance will be summarised by treatment group for the SAF analysis set for the Randomised Tezepelumab and Randomised Placebo treatment groups; and for the SAF-LTE analysis set for the Tezepelumab Predecessor+Tezepelumab LTE and Placebo Predecessor+Placebo LTE treatment groups. Summaries will also be presented by predecessor period and LTE period separately for the SAF-LTE analysis set and will also include the Placebo Predecessor+Tezepelumab LTE treatment group.

A further summary of extent of exposure to IP will be presented for the SAF analysis set using the All Tezepelumab treatment group. This summary will be presented separately for subjects enrolled in D5180C00007 from those enrolled into D5180C00009. A further summary of extent of exposure to IP will be provided based on the combined data from both predecessor studies.

The total number of dosing occasions will be summarised by treatment group for the SAF analysis set for the Randomised Tezepelumab and Randomised Placebo treatment groups as well as the All Tezepelumab treatment group; and for the SAF-LTE analysis set for the Tezepelumab Predecessor+ Tezepelumab LTE and Placebo Predecessor+Placebo LTE treatment groups.

The date and time of IP administrations, and all missed doses will be listed using the SAF analysis set. An additional listing detailing the various batches of administered IP will also be provided.

4.5 Safety and tolerability

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4.5.1 Adverse events

AEs will be summarised separately for the on-treatment and on-study periods as defined in Section 3.2.2 unless stated otherwise. All AE summaries will be presented by analysis set and treatment groups as follows:

- SAF (Randomised Tezepelumab and Randomised Placebo), overall only
- SAF-LTE (Tezepelumab Predecessor+Tezepelumab LTE and Placebo Predecessor+Placebo LTE), overall and by time period
- SAF-LTE (Placebo Predecessor+Tezepelumab LTE), predecessor and LTE periods

All AEs will be listed for the SAF-LTE analysis set. AEs occurring during the screening/run-in period or occurring post-treatment will be highlighted with an asterisk in the listing, but not summarised separately. In addition, for subjects with a delay between the predecessor study EOT visit and LTE study Visit 1, a listing of AEs starting more than 33 days after the last dose of IP in the predecessor study but prior to Visit 1 in the LTE study will be provided. A further listing of AEs occurring between the LTE study Visit 1 and the date of first dose in the LTE study will be provided for those subjects who do not receive their first dose of IP in the LTE study at Visit 1 of the LTE study. Information related to the outcome of any pregnancies will also be listed for the SAF-LTE analysis set.

For each of the summaries below, the following will be included:

- Number and percentage of subjects reporting at least one AE.
- Exposure adjusted incidence rates (as defined in Section 3.2.2) per 100 subject-years

An overall summary table will be produced showing the following categories: any AEs, serious adverse events (SAEs), AEs with a fatal outcome, and AEs leading to discontinuation of IP (DAEs).

All AEs will be summarised by system organ class (SOC) and preferred term (PT) assigned to the event using the MedDRA dictionary. For each PT, for the number of subjects reporting at least one occurrence of the event, subjects with multiple occurrences of the same PT will only be counted once for the calculation of incidence rates.

Similar summaries by SOC and PT will also be presented for:

- SAEs
- Fatal AEs
- DAEs - on-treatment period only

- DAEs causally related to IP – on-treatment period only
- SAEs leading to discontinuation of IP – on-treatment period only
- Each AESI category separately – on-treatment period only
- The most common AEs (defined as those occurring in ≥3% of subjects in either treatment group) – by PT only for on-treatment period only

All AEs (by PT) will be summarised additionally by causality and maximum intensity. For summaries based on the number of subjects reporting at least one occurrence of the event, if a subject reports multiple occurrences within each PT, the maximum intensity will be taken as the highest recorded (the order being mild, moderate and severe) respectively.

In addition, each AESI category will be summarised by causality.

The AESI of injection site reactions will be further summarised for the on-treatment period by:

- Site of injection (arm, thigh, abdominal wall)
- Total number of doses administered (1, 2, …, 26), irrespective of timing of the injection site reaction event.

Events confirmed by the independent adjudication committee (major adverse cardiac events (MACE) and malignancies) will be summarised by treatment. All events submitted for adjudication will also be listed for the SAF-LTE analysis set.

Further AE summaries will also be provided for overall summary of AEs, AEs by SOC and PT, SAEs, DAEs and each AESI category separately, for the on-treatment data. These summaries will be provided overall for the SAF (All Tezepelumab) analysis set.

Furthermore, AESI summaries described above will be repeated using exposure adjusted occurrence rates defined in Section 3.2.2.

4.5.1.1 Subgroup analyses

The following AE summaries will also be provided by subgroups as defined in Section 3.1.8 for the on-treatment period for the SAF and SAF-LTE analysis sets for study D5180C000007 as predecessor only:

- SAEs
- DAEs

In addition, the overall summary of AEs as well as the summary of AEs by SOC and PT for the on-treatment period will also be provided by subgroups for the SAF analysis set and study D5180C00007 only.

4.5.2 Laboratory data

All continuous laboratory variables will be summarised by absolute value at each visit by treatment group, together with the corresponding changes from baseline. These summaries will be produced for the on-study period, as defined in Section 3.1.5, for the SAF analysis set for the Randomised Tezepelumab and Randomised Placebo treatment groups, as well as for the SAF-LTE analysis set for the Tezepelumab Predecessor+Tezepelumab LTE and Placebo Predecessor+Placebo LTE treatment groups. Summaries for the SAF-LTE analysis set for the Placebo Predecessor+Tezepelumab LTE treatment group will also be provided. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD.

Central laboratory normal reference ranges will be used for the identification of individual clinically important abnormalities. A shift table will be produced for each laboratory variable to display low, normal and high. The shift tables will present baseline and maximum/minimum/last post-baseline values for each variable.

Shift plots showing each individual subject's laboratory value at baseline and at maximum/minimum/last value post-baseline will be produced for each continuous laboratory variable. If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at other time points, then shift plots of these data may be produced. The diagonal line of no change, and horizontal and vertical reference lines indicating the limits of the normal reference ranges, will also be displayed on the shift plots.

Both shift tables and shift plots will be produced using all data for the on-treatment period, as defined Section 3.1.5, for the SAF analysis set for the Randomised Tezepelumab and Randomised Placebo treatment groups, as well as for the SAF-LTE analysis set for the Tezepelumab Predecessor+Tezepelumab LTE and Placebo Predecessor+Placebo LTE treatment groups.

The frequencies of clinically noteworthy values (using normal reference ranges) occurring during the study will also be given.

In order to identify potential Hy's Law cases, maximum post-baseline TBL will be plotted separately against both maximum post-baseline ALT and AST, expressed as multiples of ULN. These plots will be produced on a log scale, with reference lines included at 2xULN for TBL, and at 3xULN for both ALT and AST. These plots will be produced using all data for the on-study period, for the SAF analysis set for the Randomised Tezepelumab and Randomised Placebo treatment groups, as well as for the SAF-LTE analysis set for the Tezepelumab Predecessor+Tezepelumab LTE and Placebo Predecessor+Placebo LTE treatment groups. The plots will also be produced separately for the predecessor period and LTE period for the SAF and SAF-LTE analysis sets, where the SAF-LTE analysis set will also include the Placebo Predecessor+Tezepelumab LTE treatment group.

For all subjects who meet the biochemical criteria for Hy's Law (potential Hy's Law cases), the relevant laboratory variables will be tabulated showing all visits for these subjects.

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For urinalysis data, a shift table will be generated to present changes from baseline to maximum/last value post-baseline. All data for the on-treatment period will be used and will be presented for the SAF analysis set for the Randomised Tezepelumab and Randomised Placebo treatment groups, as well as for the SAF-LTE analysis set for the Tezepelumab Predecessor+Tezepelumab LTE and Placebo Predecessor+Placebo LTE treatment groups.

All summaries and figures will report laboratory data in SI units. Any data outside the central laboratory normal reference ranges will be explicitly noted on the listings that are produced for haematology, chemistry and urinalysis parameters for the SAF-LTE analysis set.

4.5.3 Vital signs

All vital signs variables will be summarised by absolute value at each visit by treatment group, together with the corresponding changes from baseline. This will also include weight, BMI and height (for study D5180C00007 adolescents only). These summaries will be produced for the on-study period, as defined in Section 3.1.5, for the SAF analysis set for the Randomised Tezepelumab and Randomised Placebo treatment groups, as well as for the SAF-LTE analysis set for the Tezepelumab Predecessor+Tezepelumab LTE and Placebo Predecessor+Placebo LTE treatment groups. Summaries for the SAF-LTE analysis set for the Placebo Predecessor+Tezepelumab LTE treatment group will also be provided. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD.

AZ-defined reference ranges (see Section 3.2.5) will be used for the identification of individual abnormalities. A shift table will be produced for each vital sign variable to display low, normal and high values. The shift tables will present baseline and maximum/minimum/last post-baseline values for each variable.

Shift plots showing each individual subject's vital signs value at baseline and at maximum/minimum/last value post-baseline will be produced for each continuous vital sign variable.

Both shift tables and shift plots will be produced using all data for the on-treatment period, as defined in Section 3.1.5, for the SAF analysis set for the Randomised Tezepelumab and Randomised Placebo treatment groups, as well as for the SAF-LTE analysis set for the Tezepelumab Predecessor+Tezepelumab LTE and Placebo Predecessor+Placebo LTE treatment groups.

Subjects who have changes from baseline outside the pre-defined AZ clinically important change criteria in Section 3.2.5 will be summarised. All data for the on-study period will be used, for the SAF analysis set for the Randomised Tezepelumab and Randomised Placebo treatment groups, as well as for the SAF-LTE analysis set for the Tezepelumab Predecessor+Tezepelumab LTE and Placebo Predecessor+Placebo LTE treatment groups. All recorded vital signs data will be listed.

4.5.4 12-lead ECG

The investigator's assessment of the 12-lead ECG (normal or abnormal) will be listed for all subjects, along with detailing whether any abnormalities were clinically significant or not for the SAF-LTE analysis set.

A shift table will be produced to display the investigator assessment of normal, abnormal – not clinically significant, abnormal – clinically significant and not done between baseline and end of treatment. For this purpose, borderline (also recorded on the eCRF) will be grouped with normal. This table will be produced for the SAF analysis set for the Randomised Tezepelumab and Randomised Placebo treatment groups, as well as for the SAF-LTE analysis set for the Tezepelumab Predecessor+Tezepelumab LTE and Placebo Predecessor+Placebo LTE treatment groups.

4.5.5 Physical examination

No separate summaries of physical examination findings will be produced since there are no physical examination results reported outside of AE reporting.

4.6 Efficacy

4.6.1 Secondary endpoint (first efficacy endpoint)

The primary analysis of the secondary endpoint (AAER over 104 weeks) will quantify the effect of the initially randomised treatment, regardless of the treatments that subjects actually received, or whether the subjects received other controller therapy/rescue medications post IP discontinuation based on the hypothetical scenario that other biologic treatments are not available. This approach assumes that the response after start of another biologic that impacts asthma control is different from the response for subjects who complete their randomised treatment. A hypothetical strategy will be used which will include all available data after treatment discontinuation in the planned treatment period but only up until the initiation of another biologic that impacts asthma control treatment. Subjects will be encouraged to continue to undergo applicable study related visits/procedures for the full 104-week period even after premature discontinuation of IP. Consequently, subjects lost to follow-up, subjects who die, subjects who withdraw their consent, those who do not enrol into the LTE study, and those who start another biologic that impacts asthma control will be the sources of missing information for the primary analysis. Missing data from premature study withdrawal will be modelled based on what was observed during the study using direct likelihood approaches, which is a valid approach under the assumption that data are missing at random (MAR).

AAER in the tezepelumab group will be compared to that seen in the placebo group using a negative binomial model. This model will be used to estimate the treatment effect and 95% confidence intervals. Analysis will be performed for the FAS comparing the Randomised Tezepelumab treatment group with the Randomised Placebo treatment group.

The response variable in the model will be the number of asthma exacerbations experienced by a subject over the 104-week planned treatment period (or shorter duration if not followed up for the full 104 weeks). Treatment, region and history of exacerbations (<=2 or >2 in

previous 12 months) will be included as factors in this model. For study D5180C00007, age at screening (adolescents or adults) will also be included in the model. The logarithm of the time at risk (in years) for exacerbation will be used as an offset variable in the model, to adjust for subjects having different follow-up times during which the events occur. Time during an exacerbation and the 7 days following an exacerbation in which a new exacerbation cannot occur, will not be included in the calculation of time at risk for exacerbation. For all further endpoint derivation details, see Section 3.3.1.1.

Descriptive summaries of the asthma exacerbations will also be presented. Unadjusted exacerbation rates will be summarised using an approach weighted by subject's time at risk (i.e., the total number of exacerbations for each treatment divided by the total time at risk for that treatment). Asthma exacerbation information will also be listed for the FAS-LTE analysis set. Subjects with a delay between the predecessor study EOT visit and the enrolment visit in the LTE study will be highlighted with an asterisk in the exacerbation listings.

Adjusted (model-based) exacerbation rates will be presented using the marginal rates approach described in Bartlett, 2018.

The following sensitivity analyses may be conducted.

Controlled imputation

To examine the sensitivity of the results of the primary analysis to departures from the underlying assumptions about missing data, controlled multiple imputation analyses may be performed which allow for different underlying assumptions to be used.

An underlying negative binomial stochastic process for the number of exacerbations will be assumed and post-study withdrawal counts will be imputed conditional upon the observed number of events prior to the withdrawal under both missing at random (MAR) and missing not at random (MNAR)/dropout reason-based multiple imputation (DRMI) assumptions respectively:

MAR: Missing counts in each arm will be imputed assuming the estimated event rate within that treatment group.

MNAR/DRMI: Missing counts will be imputed differently depending on the reason for dropout;

Missing counts for subjects in the tezepelumab arm at the time of the dropout who dropped out for a treatment-related reason will be imputed based on the estimated event rate in the placebo arm (the "copy reference" approach), whereas the remaining subjects who dropped out will be imputed assuming MAR.

Error! Reference source not found. Table 6 Treatment arms for imputation of tezepelumab subjects under DRMIsummarises how tezepelumab subjects withdrawing from study will be handled in the DRMI analyses described above. The rules in the table will be

applied irrespective of the length of time between discontinuing IP and withdrawing from the study (noting that the treatment policy strategy is used for these sensitivity analyses

Table 6 Treatment arms for imputation of tezepelumab subjects under DRMI

Reason for withdrawing from study	Reason for discontinuing IP	DRMI
Death		Placebo
Site terminated by sponsor		Tezepelumab
Study terminated by sponsor		Tezepelumab
Loss to follow-up Withdrawal by subject Withdrawal by parent/guardian Other	Death	Placebo
	Adverse event	Placebo
	Development of study-specific discontinuation criteria	Placebo
	Severe non-compliance to protocol	Placebo
	Subject lost to follow-up	Placebo by default (pending blinded review of any further information)
	Subject decision	Placebo by default (pending blinded review of any further information)
	Other	Placebo by default (pending blinded review of any further information)

A blinded review of subjects who discontinued IP for reasons of "Subject lost to follow-up", "Subject decision" or "Other" will be performed prior to unblinding at the primary database lock. A listing of these subjects and the assumptions made under DRMI will be documented. If any recorded comments (on either of the "Discontinuation of Investigational Product" or "Disposition" eCRF pages) indicate clearly that the reason for study withdrawal was not related to treatment, then the "Placebo" default for DRMI in the above table may be changed for that subject.

The methodology used for sensitivity analysis is described in more detail in Keene et al., 2014. The steps for carrying out multiple imputation are outlined below.

Step 1: Fitting a negative binomial model to the observed data

A negative binomial regression model will be fitted to the observed exacerbation data with treatment group, region, age and history of exacerbations included as covariates. The logarithm of the time at risk (in years) for exacerbation will be used as an offset variable in the model.

Step 2: Drawing samples from the posterior distribution

The negative binomial distribution is conventionally defined as the probability distribution of the number of successes Y before k failures are seen in a series of independent Bernoulli trials with probability p of success and (1-p) of failure.

The posterior distribution for parameter k and coefficients β will be created as a product of non-informative prior and the likelihood from the model in Step 1. A uniform prior distribution will be assumed for the regression coefficients. A Gamma (10^{-4}, 10^{-4}) will be assumed for 1/k.

With the use of Markov Chain Monte Carlo (MCMC) method, 100 samples of k and β will be drawn from their posterior distribution. Convergence of the MCMC algorithm will be assessed.

A random seed of 991511 will be used. The first 2000 iterations will be discarded to allow for convergence to a stationary distribution and to remove the effect of the starting values ("burn-in"). A gap of 100 iterations will be used between imputations to ensure independence between imputations ("thinning").

Step 3: Imputing missing data

For a subject who withdrew from the study early, let Y_1 denote the number of events prior to withdrawal (over time t_1), and let Y_2 denote the number of unobserved events after withdrawal until the end of the study's planned treatment period (over time t_2). For a subject who completes the planned treatment period, Y_1 denotes the number of events prior to completion (over time t_1). Using the formula in Keene et al., 2014, the unobserved events Y_2 will be imputed from a negative binomial distribution with parameters k^* and p^*, where:

$k^* = k + Y_1$

$p^* = (k + \varphi_1) / (k + \varphi_1 + \varphi_2)$

φ_1 is the expected number of events prior to withdrawal

φ_2 is the expected number of events after withdrawal

Thus, Y_1+Y_2 gives the number of exacerbations (observed and imputed) over the planned treatment period, $t_1+ t_2$. A random seed of 112358 will be used for the imputation.

The parameters φ_1 and φ_2 will be derived for each set of β and k parameters sampled in Step 2 under 2 different missing data scenarios, MAR and DRMI.

Step 4: Multiple imputation algorithm

For each scenario detailed in Step 3, the algorithm for implementing multiple imputation is:

Select the first set of parameters $(\hat{\beta}, \hat{k})$ from Step 2

Impute Y_2 for each subject who discontinued from the study early, using the method outlined in Step 3

Calculate $Y_3 = Y_1 + Y_2$ for all subjects, where $Y_2 = 0$ for subjects who completed the study and $Y_2 \geq 0$ for subjects who discontinued from the study early.

A negative binomial regression model will be fitted using Y_3 as the response variable with treatment group, region, age and history of exacerbations included as covariates. For subjects completing the planned treatment period, the offset will be the logarithm of the time at risk (in years) for exacerbation. For subjects with an imputed number of exacerbations after withdrawal, the offset will be the logarithm of the study's planned treatment period excluding the time during an observed observation and the 7 days following an observed exacerbation.

Using the model from (iv) calculate treatment differences for the comparisons of interest

Select the next set of parameters $(\hat{\beta}, \hat{k})$ from Step 2 and repeat (ii) through to (v) a further 99 times.

Using Rubin's formulae, summarise the sets of treatment differences in (v) to give an overall treatment difference for the comparisons of interest with 95% confidence limits. The number of events and total time at risk will be derived by taking the arithmetic mean of these values across the sets of data.

Back-transform the estimates and 95% confidence limits to give a rate ratio and corresponding limits

4.6.1.1 Supportive analysis

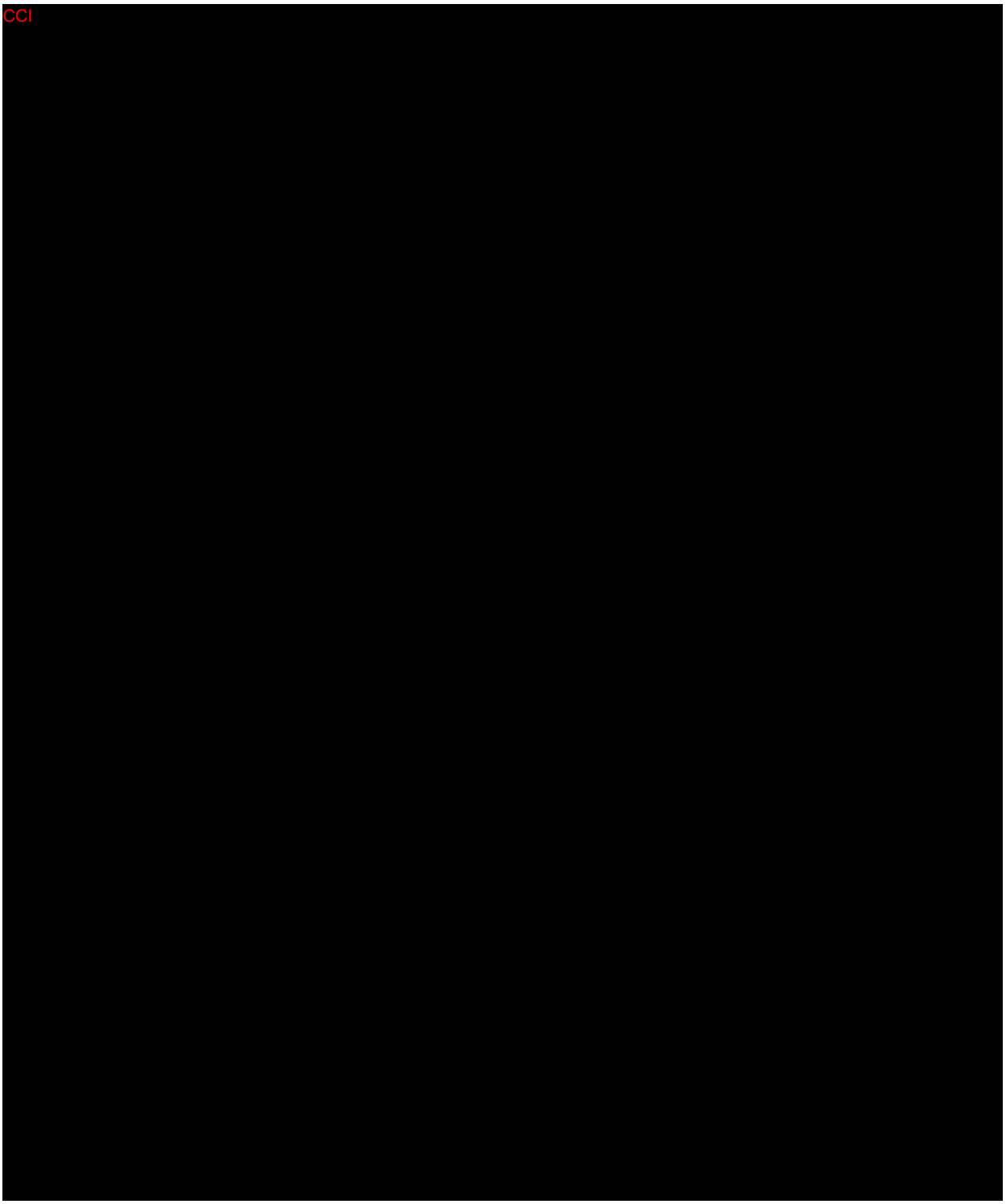
The analysis described above in Section 4.6.1 will be repeated based on the FAS-LTE comparing Tezepelumab Predecessor+Tezepelumab LTE with Placebo Predecessor+Placebo LTE. Descriptive statistics of the asthma exacerbations will be provided overall (Week 0 to Week 104).

4.6.1.2 Durability of benefit during the treatment period

Durability of benefit will be explored for the FAS-LTE analysis set. Exacerbations rates will be presented for the predecessor period and LTE period separately for the Tezepelumab Predecessor+Tezepelumab LTE and Placebo Predecessor+Placebo LTE treatment groups, as well as the Placebo Predecessor+Tezepelumab LTE treatment group. Time at risk during the predecessor and LTE period should be used accordingly.

4.6.1.3 Subgroup analyses

The AAER negative binomial model will also be provided by subgroups as defined in Section 3.1.8 for the planned-treatment period for the FAS analysis sets for study D5180C000007 only. A model similar to the one described in Section 4.1.6 will be used with the addition of a covariate for the interaction term between treatment and subgroup.



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5 INTERIM ANALYSES

No interim analyses are planned in this trial.

An independent Data and Safety Monitoring Board (DSMB) will safeguard the interests of adolescent subjects by assessing the safety of the intervention. The DSMB will review safety data on a regular basis as set out in a DSMB charter. The data for review will be outlined in a DSMB charter. The DSMB will have access to individual treatment codes and will be able to merge these with the collected study data whilst the study is ongoing. For reference, the DSMB will also have access to study data from adults.

The personnel involved in the clinical study at AstraZeneca will remain blinded to these analyses and will have no knowledge of the results presented to the DSMB.

6 CHANGES OF ANALYSIS FROM PROTOCOL

- A new analysis set “LTE analysis set” has been added to the SAP to show the full disposition of subjects from the predecessor studies, and to allow for the possibility that subjects may be enrolled or randomised in the LTE study but do not take IP in the LTE study.

CCI

7 REFERENCES

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8 APPENDIX

8.1 Adverse events of special interest

For adverse events of special interest (AESIs) summarised in sections 8.1.1, 8.1.4, 8.1.8, and 8.1.9, AESIs and related definitions based on MedDRA terms are not included in this SAP to facilitate their maintenance (e.g., management of MedDRA version changes), and for convenience in using them directly in SAS programming. These detailed definitions will be finalised by the study team prior to the primary database lock and provided together with the study datasets at the time of submission.

8.1.1 Anaphylactic reactions

Potential anaphylactic reactions will be defined on the basis of Sampson's criteria (see Sampson et al., 2006). These will be identified using a modified Standardized MedDRA Query (SMQ), with additional constraints on the timing of the AE onset date relative to the timing of the injection.

Confirmed anaphylactic reactions will be those defined following medical review of the preferred terms identified as potential anaphylactic reactions, as well as any relevant supporting data.

8.1.2 Immune complex disease (Type III hypersensitivity reactions)

Immune complex disease will be defined using a single PT of "Type III immune complex mediated reaction". Since this will already be covered by the general AE reporting by SOC/PT, separate summary tables will not be needed for this AESI.

8.1.3 Hypersensitivity reactions

Hypersensitivity reactions will be defined on the basis of an SMQ: Hypersensitivity (narrow). All hypersensitivity reactions (serious plus non-serious) as well as serious hypersensitivity reactions will be summarised.

8.1.4 Malignancy

Malignancy will be defined on the basis of an SMQ: Malignant or Unspecified Tumors Non-haematological malignant tumours; (narrow), Haematological tumours of unspecified malignancy; (narrow), Non-haematological tumours of unspecified malignancy; (narrow), Haematological malignant tumours; (narrow).

8.1.5 Helminth infections

Helminth infection will use an investigator-driven definition, i.e., will be directly determined from what is entered on the eCRF.

A subject will be considered to have this AESI if the subject has at least one preferred term where the dedicated Helminth Infection eCRF page was also completed for that event (linked by AE number), with AE onset date during the relevant study period for analysis.

8.1.6 Severe infections (as defined in the protocol)

Severe infections will use an investigator-driven definition, i.e. will be directly determined from what is entered on the eCRF.

A subject will be considered to have this AESI if the subject has at least one preferred term with AE onset date during the relevant study period for analysis, which satisfies the following:

"AE Category" on Adverse Events eCRF page marked as "Severe Infection", and one or more of the following:

- AE is serious ("Serious" on Adverse Events eCRF page marked as "Yes"), or
- AE required treatment with systemic antiviral medications, intravenous antibiotics or medications for Helminth parasitic infection, or
- AE resulted in permanent discontinuation of study drug ("Action taken, investigational product" on Adverse Events eCRF page marked as "Drug permanently discontinued").

8.1.7 Injection site reactions

Injection site reactions will use an investigator-driven definition, i.e. will be directly determined from what is entered on the eCRF.

A subject will be considered to have this AESI if the subject has at least one preferred term with AE onset date during the relevant study period for analysis, which has "AE category" on the Adverse Events eCRF page marked as "Injection Site Reaction".

8.1.8 Opportunistic infections

Opportunistic infections will be defined using a pre-specified list of preferred terms (AZ defined SMQ).

8.1.9 Guillain-Barre syndrome

Guillain-Barre syndrome will be defined using an SMQ: Guillain-Barre (narrow).

8.1.10 Adrenal crisis (D5180C00009 only)

Adrenal crisis will be defined using a pre-specified list of high level and lower level MedDRA terms.

8.2 OCS conversion factors for prednisone equivalents

Total daily OCS dose will be converted to a prednisone equivalent using the following table:

Table 7 Estimated OCS dose therapy equivalence

Oral Corticosteroid	Approximate equivalence dose
Prednisone	10 mg
Prednisolone	10 mg
Cortisone	50 mg
Hydrocortisone	40 mg
Methylprednisolone	8 mg
Triamcinolone	8 mg
Betamethasone	1.2 mg
Dexamethasone	1.5 mg
Deflazacort	12 mg

For example, to convert a cortisone total daily dose to a prednisone equivalent total daily dose, a multiplication factor of 0.2 = 10/50 should be used.

8.3 Maintenance Therapy Equivalence Table

Table 8 Estimated daily doses for inhaled corticosteroids

Asthma Therapy	Total Daily Dose (µg/day)		
Inhaled Corticosteroid	**Low**	**Medium**	**High**
Beclomethasone dipropionate (CFC)*	200-500	>500-1000	>1000
Beclomethasone dipropionate (HFA)	100-200	>200-400	>400
Budesonide (DPI)	200-400	>400-800	>800
Ciclesonide (HFA)	80-160	>160-320	>320
Fluticasone furoate (DPI)	100	n.a.	200

Asthma Therapy	**Total Daily Dose (µg/day)**		
Inhaled Corticosteroid	**Low**	**Medium**	**High**
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (HFA)	100-250	>250-500	>500
Mometasone furoate	110-220	>220-440	>440
Triamcinolone acetonide	400-1000	>1000-2000	>2000

CFC: Chlorofluorocarbon propellant; DPI: dry powder inhaler; HFA: hydrofluroalkane propellant.

* Included for comparison with older literature. From GINA 2018

8.4 Summary of data to be presented

Table 9 Disposition, demographics and baseline characteristics

Analysis sets		SAF		SAF-LTE		LTE	CCI
Treatment groups		(Rand Teze/ Rand Pbo)	(All Teze)	(Teze+Teze/ Pbo+Pbo)	(Pbo+Teze)	(Teze+Teze/ Pbo+Pbo/ Pbo+Teze)	
Study	**Data**	**Overall**	**Overall**	**Overall**	**Overall**	**Overall**	
Disposition, demographics and baseline characteristics (Section 4.2, 4.7.1)							
Both	Disposition	✓ PreD				✓ LTE	
Both	Demographics	✓	✓	✓	✓		
C00007	Demographics by age group (≥12 to <18, ≥18 to <65, ≥65)			✓	✓		
Both	Baseline characteristics	✓	✓	✓	✓		
C00007	Baseline characteristics by age group (≥12 to <18, ≥18 to <65, ≥65)			✓	✓		
Both	Time to last dose/withdrawal from study	✓					

✓PreD = Predecessor period only;
✓LTE = LTE period only;
CCI
C00007 = D5180C00007;
Rand Teze = Randomised Tezepelumab;
Rand Pbo = Randomised Placebo;
Teze+Teze = Tezepelumab Predecessor+Tezepelumab LTE;
Pbo+Teze = Placebo Predecessor+ Tezepelumab LTE;
Pbo+Pbo = Placebo Predecessor+Placebo LTE;
All Teze = All Tezepelumab;

Table 10 Important PDs, medications, safety and tolerability, and efficacy

Analysis sets		SAF/FAS		SAF-LTE/FAS-LTE			CCI
Treatment groups		(Rand Teze/ Rand Pbo)	(All Teze)	(Teze+Teze/ Pbo+Pbo)		(Pbo+Teze)	
Study	Data	Overall	Overall	Overall	By period (PreD, LTE)	By period (PreD, LTE)	
Important protocol deviations (Section 4.2, 4.7.1)							
Both	Important PDs				✓	✓	
Prior and concomitant medications (Section 4.3)							
Both	Prior	✓		✓		✓Overall	
Both	Concomitant (on-treatment)	✓		✓	✓	✓	
Both	Concomitant (post-treatment)	✓		✓		✓Overall	
Both	Maintenance medications	✓		✓			
Both	Days of systemic corticosteroids	✓		✓	✓	✓	
C00007	Total daily OCS dose	✓		✓	✓	✓	
C00009	OCS medication at study entry/baseline	✓		✓			
C00009	OCS baseline to optimised dose	✓		✓			
Both	Disallowed Medications (prior)	✓		✓		✓Overall	
Both	Disallowed Medications (on-treatment)	✓		✓	✓	✓	
Both	Disallowed Medications (post-treatment)	✓		✓		✓Overall	
Both	Biologics (prior)	✓		✓		✓Overall	
Both	Biologics (post-treatment)	✓		✓		✓ Overall	
Exposure and compliance (Section 4.4)							

Analysis sets		SAF/FAS		SAF-LTE/FAS-LTE			CCI
Treatment groups		(Rand Teze/ Rand Pbo)	(All Teze)	(Teze+Teze/ Pbo+Pbo)		(Pbo+Teze)	
Study	Data	Overall	Overall	Overall	By period (PreD, LTE)	By period (PreD, LTE)	
Both	Exposure	✓	✓+C	✓	✓	✓	
Both	Compliance	✓		✓	✓	✓	
Both	Total number of dosing occasions	✓	✓	✓			
SAFETY and TOLERABILITY							
Adverse events (Section 4.5.1, 4.7.2)							
Both	Overall summary	✓+SG	✓On-Trt	✓	✓	✓	
Both	AEs by SOC/PT	✓+SG	✓On-Trt	✓	✓	✓	
Both	AEs by PT and causality	✓		✓	✓	✓	
Both	AEs by PT and max intensity	✓		✓	✓	✓	
Both	SAEs by SOC/PT	✓+SG	✓On-Trt	✓+SG	✓+SG	✓	
Both	Fatal AEs by SOC/PT	✓		✓	✓	✓	
Both	DAEs by SOC/PT	✓+SG	✓On-Trt	✓+SG	✓+SG	✓	
Both	DAEs causally related to IP by SOC/PT	✓		✓	✓	✓	
Both	SAEs leading to discontinuation by SOC/PT	✓		✓	✓	✓	
Both	Each AESI category by SOC/PT	✓	✓On-Trt	✓	✓	✓	
Both	Each AESI category by PT and causality	✓		✓	✓	✓	

Analysis sets		SAF/FAS		SAF-LTE/FAS-LTE			CCI
Treatment groups		(Rand Teze/ Rand Pbo)	(All Teze)	(Teze+Teze/ Pbo+Pbo)		(Pbo+Teze)	
Study	Data	Overall	Overall	Overall	By period (PreD, LTE)	By period (PreD, LTE)	
Both	Further summaries of AESI of injection site reactions	✓		✓	✓	✓	
Both	Most common AEs by PT only	✓		✓	✓	✓	
Both	Adjudicated AEs	✓		✓	✓	✓	
Both	AESIs - exposure adjusted occurrence rate	✓	✓On-Trt	✓	✓	✓	
Laboratory data (Section 4.5.2, 4.7.2)							
Both	Haematology/Clinical chemistry - summaries over time	✓By period (PreD, LTE)				✓	
Both	Haematology/Clinical chemistry - shift tables and shift plots	✓		✓			
Both	Hy's law	✓		✓			
Both	Urinalysis - shift tables	✓		✓			
Vital Signs (Section 4.5.3, 4.7.2)							
Both	Vital signs - summaries over time	✓By period (PreD, LTE)			✓	✓	
Both	Vital signs - shift tables and shift plots	✓		✓			
ECG (Section 4.5.4)							
Both	ECG - shift tables	✓		✓			
EFFICACY							
Exacerbations (Section 4.6.1, 4.6.2.5, and 4.7.3.2)							

Analysis sets		SAF/FAS		SAF-LTE/FAS-LTE			CCI
Treatment groups		(Rand Teze/ Rand Pbo)	(All Teze)	(Teze+Teze/ Pbo+Pbo)		(Pbo+Teze)	
Study	Data	Overall	Overall	Overall	By period (PreD, LTE)	By period (PreD, LTE)	
Both	AAER	✓+SG		✓			
Both	Multiple Imputation	✓					
Both	Exacerbation rates (descriptive only)	✓		✓	✓	✓	

CCI

Analysis sets		SAF/FAS		SAF-LTE/FAS-LTE			CCI
Treatment groups		(Rand Teze/ Rand Pbo)	(All Teze)	(Teze+Teze/ Pbo+Pbo)		(Pbo+Teze)	
Study	Data	Overall	Overall	Overall	By period (PreD, LTE)	By period (PreD, LTE)	
CCI							

Analysis sets		SAF/FAS		SAF-LTE/FAS-LTE			CCI
Treatment groups		(Rand Teze/ Rand Pbo)	(All Teze)	(Teze+Teze/ Pbo+Pbo)		(Pbo+Teze)	
Study	Data	Overall	Overall	Overall	By period (PreD, LTE)	By period (PreD, LTE)	
CCI							

Analysis sets		SAF/FAS		SAF-LTE/FAS-LTE			CCI
Treatment groups		(Rand Teze/ Rand Pbo)	(All Teze)	(Teze+Teze/ Pbo+Pbo)		(Pbo+Teze)	
Study	Data	Overall	Overall	Overall	By period (PreD, LTE)	By period (PreD, LTE)	
CCI							

+C = Also produced for combined data from D5180C00007 and D5180C00009;
+SG = Also produced for subgroups for D5180C00007 only (on-treatment period only for safety data, planned treatment period only for efficacy data);
FAS and FAS-LTE were only applicable for efficacy analyses; Otherwise, SAF and SAF-LTE were applied;
CCI
✓On-Trt = On-treatment period only;
✓LTE = LTE period only;
CCI
C00007 = D5180C00007;
C00009 = D5180C00009;
Rand Teze = Randomised Tezepelumab;
Rand Pbo = Randomised Placebo;
Teze+Teze = Tezepelumab Predecessor+Tezepelumab LTE;
Pbo+Teze = Placebo Predecessor+ Tezepelumab LTE;
Pbo+Pbo = Placebo Predecessor+Placebo LTE;
All Teze = All Tezepelumab;

8.5 Additional reporting to assess the impact of the COVID-19 pandemic

In order to assess the impact of the COVID-19 pandemic on the planned analyses, further additional summaries and analyses will be conducted. These are described below, with the section of the main SAP in which they relate to. The start date of the COVID-19 pandemic is defined as 11th March 2020; the date the World Health Organisation (WHO) declared it a pandemic. We assume the pandemic is ongoing by the time the study ends. Unless stated otherwise, data will be presented pre-pandemic, and during-pandemic. Data recorded before the pandemic start date will be *pre-pandemic;* data recorded on or after the start date will be *during-pandemic*. If deemed necessary, additional analyses for post-pandemic may be added at a later time after the pandemic ends.

Section 2.2 Violations and Deviations

All COVID-19 related IPDs will be grouped as described in Section **2.2** and summarised together with all non-COVID-19 related IPDs as described in Section 4.2 on SAF-LTE analysis set. A listing of all COVID-19 related protocol deviations (important and non-important PDs) will be provided on SAF-LTE analysis set.

An additional summary will be provided of IPDs related to COVID-19, and IPDs excluding COVID-19 related IPDs separately by treatment group (Tezepelumab Predecessor+Tezepelumab LTE, Placebo Predecessor+Placebo LTE, and Placebo Predecessor+Tezepelumab LTE) on SAF-LTE analysis set.

Section 4.2 Subject disposition, demography and baseline characteristics

The number of subjects randomised prior to the COVID-19 pandemic, and number of subjects ongoing in the study, as well as ongoing in the planned treatment period during the COVID-19 pandemic will be summarised by treatment group. The total duration of follow-up for subjects during the study will be summarised, together with the duration of follow-up during the COVID-19 pandemic. The proportion of time on study during the pandemic will also be provided by treatment group.

The number and percentage of subjects with at least one missed scheduled visit or changed format of scheduled visit will be summarised by treatment group during the LTE period. Changed format of scheduled visit will be grouped into “On-site, partial visit”, “Remote visit (Phone or Video)”, “Other”. The number of subjects discontinuing IP or withdrawing from the study due to COVID-19 will also be summarised by treatment group. All of the above analyses will be summarised by treatment group (Tezepelumab Predecessor+Tezepelumab LTE, Placebo Predecessor+Placebo LTE, Placebo Predecessor+Tezepelumab LTE), on the SAF-LTE analysis set during the LTE period.

A listing of all subjects in SAF-LTE analysis set impacted by COVID-19 will be produced with details of changed or missed visits and change of location of IP administration or missed IP administration.

Section 4.4 Exposure and compliance

The number of subjects with delayed roll-over from the predecessor studies into the LTE period due to COVID-19, the number of subjects with missed IP doses due to COVID-19, including consecutive missed doses, will be summarised by treatment group. In addition, the number of IP doses administered by location (home, other) will be summarised by treatment group. All of these new analyses will be summarised by treatment group (Tezepelumab Predecessor+Tezepelumab LTE, Placebo Predecessor+Placebo LTE, Placebo Predecessor+Tezepelumab LTE) on SAF-LTE analysis set during the LTE period.

Section 4.5.1 Adverse events

All AE-related analyses described below will be based on SAF-LTE analysis set using the on-treatment period.

The overall AE summary table (AEs in any category reported) will be summarised by pre-pandemic and during-pandemic. Categories will include: any AEs, SAEs, AEs with a fatal outcome, DAEs, and COVID-19 AEs (as defined based on the COVID-19 MedDRA terms).

Summary statistics of AEs and SAEs by SOC and PT using exposure adjusted incidence rates will be provided by pre-pandemic and during-pandemic. COVID-19 related AEs by SOC and PT will also be provided during the pandemic.

In addition, if there are more than 10 subjects reporting COVID-19 AEs during the LTE period, then the AE listing will be repeated including only these subjects, with details of all AEs reported by these subjects.

For the adjudication AE summary tables, the number of subjects reported AEs that were adjudicated to be related to COVID-19 will be included. The adjudication listing will show the adjudicated relationship to COVID-19 (related, not related, undetermined, and not applicable). Not applicable will be used for adjudication AEs with an onset date prior to 01 January 2020.

Section 4.6.1 Secondary endpoint (first efficacy endpoint - AAER)

Supplementary analysis

A supplementary analysis of the secondary endpoint (AAER) will be performed based on the hypothetical scenario that the COVID-19 pandemic did not occur. This approach assumes that the response for subjects whose participation during the planned treatment period was impacted by the COVID-19 pandemic is different from those subjects who were not impacted. Only the pre-pandemic data will be used.

The analysis will be performed for the Randomised Tezepelumab and Randomised Placebo treatment groups in the FAS using the same methods described in Section 4.6.1.

For pre-pandemic, the time at risk for this analysis will be defined as follows:

> *Time at risk (days) = [earliest (X; day prior to the start date of another biologic that impacts asthma control; date of last exacerbation assessment status during planned treatment; 10th March 2020) – date of randomisation at predecessor study] + 1*

where *X* is defined in Section 3.3.1.1.

The number of days the subject experiences a protocol defined exacerbation, including the subsequent 7 days (when a further exacerbation would not be considered as a second exacerbation), will be subtracted from the time at risk defined above for the analysis.

Sensitivity analysis

To evaluate the impact of the pandemic on the overall AAER, a sensitivity analysis will be performed using the pre-pandemic and during-pandemic data separately. For subjects who don't enrol in the LTE study, only limited data are collected during-pandemic. Therefore, this analysis will be performed for the Tezepelumab Predecessor+Tezepelumab LTE and Placebo Predecessor+Placebo LTE treatment groups in the FAS-LTE. The same methods described in Section 4.6.1 will be used.

The pre-pandemic time at risk is defined above. Similarly, for during-pandemic,
Time at risk (days) = earliest (X; day prior to the start date of another biologic that impacts asthma control; date of last exacerbation assessment status during planned treatment) – 11th March 2020] +1

If *earliest (X; day prior to the start date of another biologic that impacts asthma control; date of last exacerbation assessment status during planned treatment) < 11th March 2020,* no data are available during-pandemic and the subject will not be included in the during-pandemic analysis.

The number of days the subject experiences a protocol defined exacerbation, including the subsequent 7 days (when a further exacerbation would not be considered as a second exacerbation), will be subtracted from the time at risk defined above for the analysis.

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