Clinical Study Protocol	
Drug Substance	Tezepelumab
Study Code	D5180C00018
Version	6.0
Date	12 Apr 2021

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)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

IND Number: 103031

EudraCT Number: 2018-002501-53

VERSION HISTORY

Version 6.0, 12 April 2021
CCI [redacted]
Section 6.3 (Measures to minimize bias: randomization and blinding): updated the reference to Parexel Informatics to Calyx, to reflect the company's name change. Section 6.5 (Concomitant Therapy): Updated Table 6 "Restricted Medication" was updated to add reference to section 6.5.5 (COVID-19 vaccine) and section 8.2.6 (regarding recommendations related to COVID-19 vaccinations). Section 6.5 (Concomitant Therapy): Clarification was added to Table 7 "Prohibited Medications" on biologics introduction following Week 116. Please note: biologics should only be introduced after Week 116, in the presence of evidence of asthma deterioration". Added section 6.5.5: (COVID-19 Vaccination) guidance on the time intervals between IP and COVID-19 vaccination. Section 7.1.1 (Procedures for discontinuation of study treatment): Clarification was added on biologics introduction following Week 116. The wording is as follows: text: "Biologics should only be introduced after Week 116, in the presence of evidence of asthma deterioration". Updated Section 8.2.1 (Table 8): footnote to 'Urine samples will be analyzed locally and sent to the central laboratory only for analysis when a positive dipstick result for U-Hb/Erythrocytes/Blood, U-Protein/Albumin or U-Glucose is observed.' to further clarify samples required to be sent for central laboratory. Added section 8.2.1.2 maintaining the blind to the subject's blood eosinophil, basophil and monocyte counts in cases of local laboratory usage: added guidance on maintaining blind in case local laboratory was used in the study.

Added section 8.2.6 (COVID-19 vaccination recommendation): added guidance for COVID-19 vaccination in the study 8.4.2.1 (Maternal Exposure), 8.4.2.2 (Paternal Exposure), Appendix B 2 (Definitions of Serious Adverse Event): revised wording related to congenital anomalies ('congenital anomaly' instead of 'congenital abnormality'). This change is implemented to address regulatory requirements.
CCI [redacted]
Appendix G (Abbreviations): added 'EUA: Emergency Use Authorization' as newly referenced in Section 8.2.6. Figure numbering has changed, due to the addition of one new figure (Figure 3, COVID-19 Vaccination between IP Dosing) to this CSP. Minor formatting updates and grammatically/spelling corrections implemented throughout the CSP.
Version 5.0, 02 June 2020
Section 1.1, SoA, Table 1:
CCI [redacted]
• Under Table 1 added note that guidance for sites who have subjects with pending roll-over to the DESTINATION study who cannot attend an on-site EOT visit in the predecessor study/Visit 1 in the DESTINATION study due to the COVID-19 pandemic is provided in Appendix H.
CCI [redacted]
• Updated Footnotes 'h' and 'q' to refer to Appendix H for guidance as during home IP administration, safety blood samples can be obtained post IP administration to allow additional time for processing of the safety samples at the site during the COVID-19 pandemic.
CCI [redacted]

Section 1.1, SoA, Table 2:

- Added Urine Pregnancy to visit 17 to ensure pregnancy state after completing IP treatment.

CCI [redacted]

Section 1.1, Added section 'CHANGES REQUIRED DURING THE COVID-19 PANDEMIC' to summarize changes that can be implemented during the COVID-19 pandemic to ensure the safety of subjects is maintained in accordance with GCP and to minimize risk to subjects during the COVI-19 pandemic, described in detail in Appendix H.

Section 1.2, Synopsis and 4.1, Overall Design - Added a note to refer to Appendix H for further guidance regarding the eligibility criteria for a subject that cannot complete an EOT on-site visit for the predecessor study due to the COVID-19 pandemic.

Section 5, Study Population - Added that 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 allowed to roll-over to the DESTINATION study by the end of the safety follow-up period of the predecessor study after confirmation of subject eligibility. Refer to Appendix H for further guidance.

Section 5.1, Inclusion Criteria #5 - added wording to clarify that outlines subjects with inadequate compliance with investigational product, assessed at the discretion of the sponsor, might not be randomized.

CCI [redacted]

Section 5.3.2 Alcohol, tobacco and other - Updated to clarify that restrictions are applicable throughout the course of the study, CCI [redacted]

Section 6.2, Preparation/handling/storage/accountability - Added a note to clarify that during the COVID-19 pandemic, if allowed by local/regional guidelines, IP preparation and administration can be performed at the subject's home by a qualified HCP to reduce the risk to subjects of COVID-19 exposure with clinic visits. In addition, wording related to the first 2 doses need to be on site as per Appendix H was added.

Section 6.5, Table 7, Prohibited medications - removed "investigational" from the biological treatment restriction as concurrent enrolment in another clinical study involving an IP is an exclusion criterion.

Section 6.5, Table 7, Prohibited medications - For other investigational products (including investigational use of an approved drug), revised the text "preferably 4 weeks after the last dose of IP" to "until the follow-up visit week 116."

Section 8, Study Assessments - Added "Additional data to assess the impact of the COVID-19 pandemic will be collected."

Section 8.2, Safety Assessments – Added reference to Appendix H for guidance on safety assessments during the COVID-19 pandemic.

CCI [redacted]

Section 8.2.1.1, Pregnancy Test - added "Additionally, the test has to be done at the Follow-up CCI [redacted] Visit 17 (Week 116) and the Follow-up CCI [redacted] even if the patient discontinued IP" based on the SoA. Also note "Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception from screening and must agree to continue using such precautions for 16 weeks after the final dose of IP (refer to Inclusion 3)" for clarity.

Section 9.4, Added "additional analyses assessing the impact of COVID-19 will be included in the SAP."

Appendix A3 - Added "During the COVID-19 pandemic, re-consent may be obtained remotely and/or verbally if local/regional guidelines allow in order to reduce the risk to subjects of COVID-19 exposure during clinic visits. For further details please refer to Appendix H" to accommodate the changes made in the protocol.

Appendix A6 - Updated link for the sponsor webpage for study information.

Appendix G, Table of Abbreviations - Added 1) COVID-19 ,2) HCP, 3) CCI [redacted] and 4) IRT. Removed 1) IVRS and 2) IWRS.

Appendix H - Added Appendix H to describe in more detail the changes made during the COVID-19 pandemic.

Minor formatting updates and grammatically/spelling corrections implemented throughout the CSP.

'Patient' replaced with 'Subject' throughout the protocol for consistency.

Version 4.0, 06 March 2020

Version History, Version 3.0, 10 January 2020 - Updates implemented to correct, clarify, and enhance completeness of revisions referenced.

Minor formatting updates and grammatically/spelling corrections implemented throughout the CSP.

Section 1.1. Schedule of Activities (SoA), Table 1 -

- *Corrected footnote applied to the 'IPD' visit in Table 1 to reference 'r', for 'Refer to section 8.1.2.2.' to address mis-assignment of footnote in the previous CSP version 3.0 amendment.*
- *Corrected footnote applied to the 'UNS' visit in Table 1 to reference 's', for 'At unscheduled visits for assessing an asthma exacerbation, the assessment/activity listed above is only the minimum needed to be performed. Other unscheduled visits may be initiated as needed, and assessments performed as per investigator's judgement' to address mis-assignment of footnote in previous CSP version 3.0 amendment.*

CCI [redacted]

- *Added assessment of 'Weight' at 'EOT visit' to correct omission in previous CSP version 3.0 amendment.*

CCI [redacted]

- *Removed footnote 't' from 'Complete Physical examination' to address mis-assignment of the footnote in previous CSP version 3.0 amendment.*

CCI [redacted]

- *Added assessment of the 'Urine pregnancy test, dipstick' at 'Visit 17' to correct omission in the previous CSP version 3.0 amendment.*

- *Removed assessment of the 'Serum Pregnancy Test' at the 'IPD visit' to address mis-assignment in the previous CSP version 3.0 amendment.*

- *Footnote 'j' text updated to include reference to 'follow-up Visit 17.' Revised text reads - "For WOCBP and adolescent females, urine pregnancy test (dipstick) will only be performed at treatment visits, prior to IP administration, at IPD, at EOT, and at follow-up Visit 17" as the urine pregnancy test (dipstick) is also done at certain visits without IP administration.*

Section 1.1. Schedule of Activities (SoA), Table 2 - added assessment of 'Weight' at 'EOT visit' to correct omission in previous CSP version 3.0 amendment.

Section 1.2., Synopsis, Overall design - added reference to week '110'' and '116' to the statement explaining the requirement for additional assessments for those subjects that sign CCI [redacted]

CCI [redacted]

Version 3.0, 10 January 2020

*The previously used phrase for the study 'the extension study' was replaced with 'Long Term Extension Study' or 'LTE' throughout the protocol to prevent confusion with newly introduced phrase '*CCI [redacted]

The terms 'discontinue'/'discontinuation' were qualified with the addition of 'premature'/ 'prematurely' to clarify instances where the cessation of IP treatment ahead of the end of treatment visit are described within the protocol.

Section 1.1. Schedule of Activities (SoA), Table 1:

- *The table 1 title was changed from "Schedule of Assessments" to more specific "Schedule of Assessments - for D5180C00007 and D5180C00009 subjects."*

CCI [redacted]

CCI

- *Footnote 'j' text updated to include additional visits "IPD" and "EOT". Revised text reads - "For WOCBP and adolescent females, urine pregnancy test (dipstick) will only be performed at treatment visits, prior to IP administration, at IPD and at EOT" as Urine pregnancy test (dipstick) is also done at certain visits without IP administration.*

- *Added footnote 't' applicable for assessment "Concomitant Medications" - "Consider stepping down of asthma background medications (starting from Visit 1) when asthma symptoms have been well controlled and lung function has been stable for 3 or more months. Refer to section 6.5.1 and Appendix F" to clarify that the asthma background medications can be reduced starting from Visit 1.*

CCI

CCI

Section 1.2., Synopsis, Objectives and Endpoints and Table 3 "Objectives and Endpoints"-

- *Primary objective - added "incidence" to the outcome measure for the primary endpoint to clarify that the primary outcome measure is the exposure adjusted incidence rate, i.e., number of subjects reporting events divided by person-time at risk.*

CCI

CCI [redacted]

Section 1.2., Study Period - estimated date of last subject completed changed to "Q2 2022"

Section 1.2., Synopsis, Treatments and treatment duration - added "Subjects that complete the treatment period in the LTE study will either complete a further 12 week follow-up period (assessments as listed in the schedule of assessments in Table 1) CCI [redacted]

Section 1.2., Synopsis, Independent Adjudication Committee and 8.4.7 Independent Adjudication Committee - updated to clarify that the Committee will assess MACE (major adverse cardiac events), malignancies and deaths until the completion of follow-up and/or the CCI [redacted]

Section 1.2., Synopsis, Statistical methods -

- *Clarified for the primary endpoint that exposure adjusted incidence rates will be presented (i.e., number of subjects reporting events divided by person-time at risk).*

CCI [redacted]

- *Clarified for the secondary objective of asthma exacerbations that the annualized exacerbation rate will be over 104 weeks.*

CCI [redacted]

Section 2.2. Background:

- *Added Dupilumab (DUPIXENT US PI 2018) as approved medication for severe asthma with an eosinophilic phenotype.*

- *In-text citation of the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) was corrected from '2017' to '2018' to align with the reference used in Appendix F.*

Section 4.1. Overall Design:

- *Added 'Subjects who prematurely discontinue IP or do not attend the EOT visit in one of the predecessor studies will not be eligible to participate in the Long Term Extension (LTE) study.*

- *Added the title "Randomization, Treatment and Follow-up for subjects that rolled over from D5180C00007 or D5180C00009" pertain to existing wording that explains Table 1 assessments. The section was reworded to clarify the follow-up for all subjects in Destination study.* CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI [redacted]

Section 6.3, Measures to minimize bias: randomization and blinding Ensuring blinding - added "Further details are provided in a separate Blinding Plan" for reference.

Section 6.3, Measures to minimise bias: randomisation and blinding, Ensuring blinding - added "until planned unblinding at primary database lock at Week 104" to "No other member of the extended study team at AstraZeneca, or any CRO handling data, will have access to the randomization scheme during the conduct of the study until planned unblinding at primary database lock" to accommodate a planned additional database lock once the last subject completes Week 104.

Section 6.3, Measures to minimise bias: randomisation and blinding; Methods for unblinding - added "Further details are provided in a separate Blinding Plan" for reference.

CCI [redacted]

Section 6.5., Table 6 Restricted medications, Inactive/killed vaccinations (e.g. inactive influenza) - restrictions updated to clarify that Inactive/killed vaccination is allowed within 5 days before or after any IP dosing visits.

Section 6.5., Table 7 Prohibited medications: Live Attenuated Vaccines - added Week 116 as the end of restrictions to "Not allowed during the study up to Week 116" to clarify that live attenuated vaccines are not allowed up to follow-up Week 116.

Section 6.5.1 Asthma Background Medications - added "starting from Visit 1 throughout the study" to "If the subject's symptoms are stable, as per investigator's judgement, attempts to reduce background asthma medications can be made every 3 months starting from Visit 1 throughout the study as per Appendix F1, Figure 4, if thought appropriate by the investigator" to clarify the reduction of asthma background medications can be started from Visit 1.

Section 6.7. Treatment after the end of the study - updated to clarify that subjects who complete follow-up at week 116 CCI [redacted] *should be given standard of care at the discretion of the investigator.*

Section 7.1.1 – Procedures for discontinuation of study treatment:

- *Follow-up Option 1 - updated from "The subject should be encouraged to return for all regular clinic visits and perform all scheduled assessments (excluding IP administration) until he/she completes their last visit at week 104." To "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)" to clarify that Option 1 is preferred.*

- *Follow-up Option 2 - updated from "The subject will be offered follow-up on a monthly basis via telephone calls. The subject should return for a follow-up visit 16 weeks (+/- 5 days) (refer to SoA, V17 – Week 116) post last IP administration and for the EOT visit at Week 104 (+/-5 days)." To "(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)" to clarify Option 2.*

- *Follow-up Option 3 - updated from "If the subject cannot or does not wish to comply with any of the options above, (or any component of them such as only telephone based visits, they will complete a 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 the subject at week 104. No other study assessments will be performed prior to this contact." to "(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" to clarify Option 3.*

- *Added "If the last IP administration was after week 88 for options 1 or 2, the subject will return to the clinic for an on-site EOT visit at Week 104 (+/- 5 days), and for option 3, the investigator will contact on phone the subject at 104 weeks post randomization. The subject for options 1, 2 and 3 will then return for an on-site follow-up visit 16 weeks (+/- 5 days) post last IP administration (refer to SoA, V17 – Week 116)." to further clarify follow-up options.*

- *Updated wording "discontinued from the study" to "withdrawal from the study" in "The EOT visit will be completed immediately in the case of subsequent early withdrawal from option 1 or 2. Subjects who do not wish to have any follow-up contacts should be considered to withdrawal from the study (refer to section 7.3)" for clarification and added reference to section.*

CCI [redacted]
Section 8.4.2. Pregnancy - added "Any cases of pregnancy during the treatment or follow-up CCI [redacted] *will be recorded in the specific eCRF module," to clarify that we collected the data about pregnancy in the specific eCRF module.*
CCI [redacted]

CCI [redacted]

Section 9.4 Statistical analyses:

- *Added text "There will be two DBLs in this study. The primary DBL will be conducted after last subject completes Week 104,* CCI [redacted] *All analyses of the primary and secondary objectives will be performed based on the primary DBL data." This provides clarity around timing of database locks and primary analysis evaluation.*

- *Added "primary" to database lock. To accommodate a planned additional database lock once the last subject completes treatment phase (week 104).*

- *Removed "Where applicable, the analyses will include all data from randomization in the predecessor studies until the end of extension study, including all available data post premature treatment discontinuation" for clarity.*

- *Added text "Further summaries may be provided using all data until the end of the* CCI [redacted] *and may also include the time period of Week 104* CCI [redacted]

CCI

- *Added text "In addition, important protocol deviations will be summarized overall (Week 0 to Week 104) and by time period (Week 0 to Week 52/48, Week 52/48 to Week 104) for the SAF and SAF-LTE analysis sets."*

Section 9.4.2. Safety analyses - clarified that the exposure adjusted incidence rate, i.e., number of subjects reporting events divided by person-time at risk will be reported. Added text to clarify that specific AEs will be summarized using exposure adjusted occurrence rates (i.e., number of events divided by person time at risk).

CCI

Section 10. References - updated for CINQAIR US PI 2016 and XOLAIR US PI 2003, added for NUCALA US PI 2015.

Appendix A1, Regulatory and ethical considerations - added "Regulatory Reporting Requirements for SAEs" in accordance with European Directive 2001/20/EC.

CCI

Appendix F1, Guidance to Step Down of Background medications - added "starting from Visit 1" to "Consider stepping down when asthma symptoms have been well controlled and lung function has been stable for 3 or more months, starting from Visit 1" to clarify that the attempt to step down background medication is permitted beginning at Visit 1.

Version 2.0, May 2019

Section 1.1, SoA- Table 1-Schedule of Assessments - added assessment of weight at EOT visit.

CCI

Section 4.2, Scientific rationale for study design - removed the word "initial" from the following sentence, "During the blinded treatment phase (Visits 1-15), half of the subjects…" to clarify that there is only one blinded treatment phase.

Section 5.1, Inclusion Criteria #3 - removed bullet; "Females of childbearing potential are defined as those who are no surgically sterile…", as WOCBP are further defined in later bullet "Women of childbearing potential are defined as…."

Section 5.1, Inclusion Criteria #3 - replaced 12 weeks with 16 weeks in 3 bullets, as this was contradictory to requirement of 16 weeks stated in first bullet point.

Section 5.1, Inclusion Criteria - removed inclusion criterion #4 - "Nonsterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from Day 1 through 16 weeks after receipt of the final dose of IP. In those countries where the above-mentioned method for contraception is not available a condom can be used alone. Male subjects must not donate or bank sperm during this same time period." Revised to align with revised IB version 4.2.

Section 5.2, Exclusion Criteria - removed exclusion criterion #5 - "Subjects who had a resection or treatment of in situ carcinoma of cervix during the predecessor study will be excluded from the study."

Section 5.3.2, Alcohol, tobacco and other - added "vaping products" restricted during the course of the study.

Section 6.2, preparation/handling/storage/accountability - added the word randomized to "only subjects enrolled/randomized in the study may receive study treatment."

Section 6.2, preparation/handling/storage/accountability - dose preparation steps - added that a 2 mL sterile syringe can be attached to a 21G 1 ½ inch sterile disposable needle during IP dose preparation and subsequently used for IP administration. This change allows for use of a 2 mL syringe in addition to 3 mL syringes because it meets the requirement for IP dose preparation and dosing.

Section 6.2, preparation/handling/storage/accountability - dose preparation steps - clarified that the vial labels along with the vials can be discarded immediately post IP preparation as per site's SOP.

Section 6.2, preparation/handling/storage/accountability - dose administration - removed wording "The subject, in the opinion of the investigator, is experiencing an acute or emerging asthma exacerbation" from the list of scenarios when IP should not be administered. An exacerbation per se is not a contraindication for IP administration. Reasons for administering IP are well covered by the remaining bullets.

Section 6.3, Measures to minimize bias: randomization and blinding - procedures for handling incorrectly enrolled or randomized subjects - revised text to clarify that if subject is prematurely discontinued from IP they should still follow the IP discontinuation procedures as defined in section 7.1.1.

Section 6.3, Measures to minimize bias: randomization and blinding - methods for unblinding - replaced "pharmacists" with "delegate(s)" to clarify that Investigator delegate(s) in addition to Investigator will be provided access to the unblinding of treatment. This change allows alignment with IXRS setup for this study.

CCI

[redacted]

Section 6.3, Measures to minimise bias: randomisation and blinding - ensuring blinding - clarified that no other members of the study team, other than those listed earlier within this section, will have access to the randomization list during the conduct of the study.

Section 6.5 - Table 7 - Prohibited medications - updated wording adding "adrenal insufficiency" now reads "Any immunomodulators or immunosuppressives (corticosteroids with systemic effects such as oral, parenteral, or intra-articular administration for reasons other than asthma are not allowed. However, corticosteroid treatment of adrenal insufficiency is allowed)."

Section 6.5 Table 5 - Restricted Medications table has been updated to include restrictions on use of immunomodulators and immunosuppressives.

Section 7.1, Discontinuation of study treatment - under "development of any study specific criteria for discontinuation, any malignancy" added the following statement "except subjects who develop basal cell carcinoma or localized squamous cell carcinoma of the skin, provided that the malignancy is excised and determined to have clean margins." This change allows subjects who have had excision of their lesions, which is considered curative, to continue study treatment.

Section 7.2, - Lost to Follow-up - updated to state "A subject is considered lost to follow-up when at least two of the following attempts."

Section 7.3.1, - The section "Discontinuation or suspension of entire study and site closure" was added. This was in order to provide information on Sponsor study termination, additional information about site closure and study completion.

CCI

Section 8.2.4, Vital Signs - revised text to specify that the pulse rate will be obtained before blood pressure only if the manual measurement technique is used. This is to reflect that when the automated device is used, the pulse and blood pressure measurements are taken simultaneously.

Section 8.2.4, Vital Signs - removed "in degrees Celsius" as the units of body temperature measurement. This is to accommodate the local guidelines as some regions may not measure in degrees Celsius.

Section 8.3.8, Adverse Events of Special Interest - added "systemic" in front of antiviral medications. The revised text reads: "Requiring treatment with systemic antiviral medications, intravenous antibiotics or medication for helminth parasitic infection." To clarify that infections treated with local antivirals are not considered as adverse events of special interest.

Section 8.3.8, Adverse Events of Special Interest - added "Adrenal Crisis" as an AESI.

Section 8.4.2.2, Paternal exposure - removed "Male subjects should refrain from fathering a child or donating sperm during the study and for 16 weeks (5 half-lives) following the last dose." To align with revised IB version 4.2.

Section 8.4.2.2, Paternal exposure - added "in the Pregnancy Report Form" to clarify where outcome of all pregnancies will be reported. This change aligns with eCRF design.

Section 8.4.2.2, Paternal exposure - added "Consent from the partner must be obtained before the Pregnancy Report Form is completed." To clarify that consent is being obtained from the pregnant partner prior to completing the pregnancy report form.

Appendix B5 - Important medical event or medical treatment - added "Examples of such events are" to clarify that the examples listed in this section can be considered as an important medical event or medical treatment.

Appendix D - Actions required in cases of increase in liver biochemistry and evaluation of Hy's law - The appendix has been updated including addition of section D6 in conjunction with sponsor's routine pharmacovigilance activities/processes. *Appendix E - Anaphylaxis: signs and symptoms, management - added a reference that was missing from the appendix.* *Appendix G - Abbreviations: the list of abbreviations were updated.*
Version 1.0, 20 August 2018
Initial Version

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1 Protocol Summary

1.1 Schedule of Activities (SoA)

Table 1 Schedule of Assessments - for D5180C00007 and D5180C00009 subjects

	Screening/ Randomization	Treatment													D5180C00007 (for subjects not participating in CCI CCI and D5180C00009			IPD[r]	UNS[s]	Details in CSP section
															EOT	Follow-up				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**			
Week	**D5180C00009 W48/ D5180C00007 W52**	**52** (Source Only)	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**110**	**116**			
Day (visit window)	**0**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**			
Procedures																				
Informed Consent	X																			Section 5.1 and 5.2
CCI																				
Inclusion /exclusion criteria	X																			Section 5.1 and 5.2
Demographics	X[a]																			Section 5.1
Medical and Asthma History	X[a]																			Section 5.1
Height[c]	X[b]														X					Section 8.2.2
Weight	X[b]														X					Section 8.2.2
CCI																				

	Screening/ Randomization	Treatment													D5180C00007 (for subjects not participating in CCI CCI and D5180C00009			IPD[r]	UNS[s]	Details in CSP section
															EOT	Follow-up				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**			
Week	**D5180C00009 W48/ D5180C00007 W52**	**52** (Source Only)	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**110**	**116**			
Day (visit window)	**0**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**			
Routine safety measurements																				
Complete Physical examination	X[b]														X					Section 8.2.3
Brief physical examination					X			X			X						X		X	Section 8.2.3
Vital signs	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.4
12-lead ECG[g]	X[b]														X		X			Section 8.2.5
Adverse events	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
Assessment of asthma exacerbation	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.1
Concomitant medication[t]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
Laboratory Assessments[h]																				
Serum Chemistry	X[b]				X			X							X			X	X	Section 8.2.1
Haematology (full)[i]	X[b]				X			X							X			X	X	Section 8.2.1
Urinalysis	X[b]				X			X							X			X		Section 8.2.1
Urine pregnancy test, dipstick[j]	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		Section 8.2.1.1
CCI [redacted]																				

	Screening/ Randomization	Treatment													D5180C00007 (for subjects not participating in CCI and D5180C00009			IPD[r]	UNS[s]	Details in CSP section
															EOT	Follow-up				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**			
Week	**D5180C00009 W48/ D5180C00007 W52**	**52** (Source Only)	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**110**	**116**			
Day (visit window)	**0**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**			
CCI																				
Serum Pregnancy Test[m]	X																			Section 8.2.1.1
CCI																				
Study treatment administration																				
Randomization	X																			Section 8.1
Administration of IP [q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X						Section 6.2

NOTE: Guidance for sites who have subjects with pending roll-over to the DESTINATION study who cannot attend an on-site EOT visit in the predecessor study/Visit 1 in the DESTINATION study due to the COVID-19 pandemic is provided in Appendix H.

[a] Medical and asthma history, demographics, AEs and concomitant medications will be linked to the predecessor study to create a complete and continuous record for the subject.

[b] Assessments done at the EOT visit of the predecessor study do not need to be repeated at Visit 1 of this study, as the data will be duplicated between study databases.

[c] Only to be measured for adolescent subjects.

[d] CCI

e CCI

f [redacted]

g ECG to be collected prior to any blood draws, CCI [redacted] administration and IP administration.

h All blood sampling should be done prior to IP administration. During the COVID-19 pandemic if the at home IP administration option is chosen, safety blood samples can be obtained post IP administration, please refer to Appendix H for further details.

i Eosinophils, basophil and monocyte counts will be redacted from all central laboratory reports throughout the study.

j For WOCBP and adolescent females, urine pregnancy test (dipstick) will only be performed at treatment visits, prior to IP administration, at IPD, at EOT and at follow-up Visit 17.

k CCI

l [redacted]

m Serum β-HCG will be taken with EOT labs from predecessor study for all WOCBP (including adolescent women), however subjects can be dosed at Visit 1 based on a negative urine pregnancy test.

n CCI

o [redacted]

p

q IP should be administered after all other assessments have been completed to a scheduled visit. During the COVID-19 pandemic if the at home IP administration option is chosen, safety blood samples can be obtained post IP administration, please refer to Appendix H for further details.

r Refer to section 7.1.

s At unscheduled visits for assessing an asthma exacerbation, the assessment/activity listed above is only the minimum needed to be performed. Other unscheduled visits may be initiated as needed, and assessments performed as per investigator's judgement.

t Consider stepping down of asthma background medications (starting from Visit 1) when asthma symptoms have been well controlled and lung function has been stable for 3 or more months. Refer to section 6.5.1 and Appendix F.

u CCI

[redacted]

w [redacted]

Table 2 CCI

CCI

CCI

[redacted]

CCI

[redacted]

CHANGES REQUIRED DURING THE COVID-19 PANDEMIC Please Note: Changes below should only be implemented during the COVID-19 pandemic. For further details, please refer to Appendix H.

During the COVID-19 pandemic, changes are being implemented to ensure the safety of trial subjects, to maintain compliance with good clinical practices, and to minimize risks to trial integrity. Where allowable by local Health Authorities, ethics committees and healthcare provider guidelines (e.g. hospital policies), these changes include:

- The option of home visits including home administration of Investigational Product (IP) must be performed by a qualified Health Care Professional (HCP). Additional information related to the visit can be obtained remotely by phone call and/or video conference. The rationale for this change is to minimize the risk of subjects missing scheduled IP administration and visit assessments due to inability/unwillingness to visit the site during the COVID-19 pandemic. During home visits, safety laboratory samples may be obtained post IP administration and during the 1-hour observation period. The rationale for this change is to allow processing of samples at the site according to the laboratory manual. Other samples should be collected prior to IP administration or not collected.

- The option of a visit at an alternative location including administration of IP and study assessments per the SoA, away from infection risk zones or closer to the subject's home. The rationale for this change is to minimize the risk of subjects missing scheduled IP administration and visit assessments due to inability/unwillingness to visit the site during the COVID-19 pandemic.

- Remote visits (phone call and/or video conference) to replace on-site visits, if subjects cannot attend the visits at the study site where necessary. The rationale for this change is to ensure continued assessments and collection of information for visits that cannot be done at the site during the COVID-19 pandemic.

CCI [redacted]

- Re-consent will be obtained verbally if allowed by local and regional guidelines. The signed COVID-19 Addendum to ICF should be obtained when possible. The rationale for

this change is to ensure that the subject agrees to the changes implemented during the COVID-19 pandemic while minimizing the risk to subjects of COVID-19 exposure.

- Subjects who are not able to attend an on-site EOT visit in the predecessor study due to the COVID-19 pandemic and are eligible for the DESTINATION study, are allowed to roll-over to the DESTINATION study by the end of safety follow-up of the predecessor study. The rationale for this change is to give subjects who did not complete an on-site EOT visit due to COVID-19 the possibility to participate in the study.

For further details, please refer to Appendix H.

1.2 Synopsis

International Co-ordinating Investigator

Dr. Andrew Menzies-Gow
Royal Brompton Hospital
Sydney Street
London, United Kingdom
SW3 6NP

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

Short Title: Tezepelumab Long Term Extension Study

Rationale:

The purpose of this Long Term Extension Study (LTE) is to evaluate the long-term safety and tolerability of tezepelumab versus placebo in adults and adolescents (12 years of age and older) with a history of asthma exacerbations and inadequately controlled severe asthma receiving medium or high dose inhaled corticosteroid (ICS) plus at least one additional asthma controller medication with or without oral corticosteroids. Subjects who complete either study D5180C00007 or D5180C00009 (referred to as "predecessor studies" for remainder of this document) on investigational product may be eligible to enroll into this study. CCI [redacted]

Objectives and Endpoints	
Primary objective:	**Outcome Measure:**
To evaluate the long-term safety and tolerability of tezepelumab in severe asthma subjects	Exposure adjusted incidence rates of AEs/SAEs over 104 weeks
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)

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Overall Design:

This is a multicentre, randomized, double-blind, placebo controlled, parallel group, phase 3 Long Term Extension (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 may be eligible to enroll into this study if they fulfil the inclusion/exclusion criteria. Those who prematurely discontinue IP during the predecessor studies will not be eligible for the LTE study.

CCI

[redacted]

The study will consist of a screening/randomization visit at the timepoint of the EOT Visit in the predecessor study for all subjects**.** A treatment period will follow whereby all subjects will continue on investigational product for an additional year, up to a total of 104 weeks (including predecessor study treatment period), followed by a post-treatment follow-up period of 12 weeks. Subjects who prematurely discontinue investigational product (IP) during the LTE study will be encouraged to undergo appropriate study visits/procedures for the full treatment period. CCI

[redacted]

Study Period:

Estimated date of first subject enrolled *Q1 2019*

Estimated date of last subject completed *Q2 2022*

Number of Subjects

Subjects who have continued to receive IP and attended the EOT visit in one of the predecessor studies may be eligible to enroll in the study. It is anticipated that approximately 975 subjects will enroll worldwide. This assumes that 90% of subjects in the predecessor studies complete dosing, and that 90% of those continue into the Long-Term Extension Study (i.e. approximately 860 subjects transitioning from D5180C00007 and approximately 115 subjects transitioning from D5180C00009).

Treatments and Treatment Duration:

The study will consist of a screening/randomization visit at the EOT Visit for the predecessor studies. If eligible, the first dose of IP will be administered at this visit. A treatment period will follow whereby all subjects will continue on treatment up to a total of 104 weeks (including predecessor study treatment period duration). All subjects will be re-randomized in the LTE study to maintain the blinding. Subjects previously randomized in one of the predecessor studies to the 210 mg tezepelumab Q4W SC arm, will be assigned and remain on 210 mg tezepelumab Q4W SC dosing in the LTE study. Subjects randomized to placebo arm in the predecessor studies will be re-randomized in a 1:1 ratio to either 210 mg tezepelumab or placebo, both administered Q4W SC. Given the randomization 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. During the treatment period, IP will be administered from day of randomization in the LTE study until week 100. No IP will be administered at week 104. Subjects that complete the treatment period in the LTE study will either complete a further 12-week follow-up period (assessments as listed in the schedule of assessments in Table 1) CCI [redacted]

Please NOTE: If a subject is unable to attend an onsite EOT visit in NAVIGATOR or SOURCE due to the COVID-19 pandemic please refer to Appendix H for further guidance on roll over and on-site participation into the DESTINATION study.

Independent Adjudication Committee

An independent adjudication committee will be constituted to provide an external independent assessment of blinded data during the study to confirm the diagnosis of: 1) MACE (Major Adverse Cardiac Events) (will be defined in the charter) and 2) investigator reported malignancies that occur from randomization until the end of the Follow-up [redacted]

This independent adjudication committee will also evaluate cases of ER or urgent care visits and hospitalizations that occur from randomization up to the end of the Follow-up [redacted] as well as all deaths from randomization until the end of the Follow-up [redacted] to evaluate whether any such event is due to a worsening of asthma. The committee will include specialists in pulmonology, cardiology, neurology and oncology and will operate in accordance with dedicated Adjudication Committee Charter/Manual of Operations.

Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be responsible for assessing safety aspects of adolescent involvement in the study. The DSMB will also review safety data for adults to provide context for the adolescent review. The DSMB will periodically review unblinded safety summary tables and listings and evaluate for subject safety and make appropriate recommendations. The committee will operate in accordance with a DSMB Charter.

Statistical Methods

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 any of the predecessor studies and meet all study eligibility criteria for the Long-Term Extension (LTE) study.

If a pooled analysis will be performed, assuming that 90% of the subjects complete the predecessor studies, and that 90% of those continue into the LTE study, 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 of [redacted] (in subjects randomized to tezepelumab) and [redacted] (in subjects randomized to placebo), total subject years of follow-up of approximately [redacted] for the "Randomized Placebo" and "Randomized Tezepelumab" treatment groups 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 "Randomized Placebo" and [redacted] for "Randomized 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

The primary objective of the study, which is to evaluate the long-term safety and tolerability of tezepelumab in severe asthma subjects, will be assessed through AEs (including AESIs) and SAEs. AEs, AESIs and SAEs will be summarized for the safety analysis set over the 104-week period using exposure adjusted incidence rates (i.e., number of subjects reporting events divided by person-time at risk) to account for the variability in follow-up. CCI [redacted]

The secondary objective of the study is to assess the long-term effect of 210 mg tezepelumab SC Q4W on asthma exacerbations with placebo. To assess this objective, the annualized asthma exacerbation rate over 104 weeks in the tezepelumab group will be compared to that seen in the placebo group using a negative binomial model including factors for treatment, region and history of exacerbations.

Additional supportive analysis of the primary and secondary endpoint will be performed based on different time periods and analysis sets. CCI [redacted]

1.3 Schema

The general study design is summarized in Figure 1.

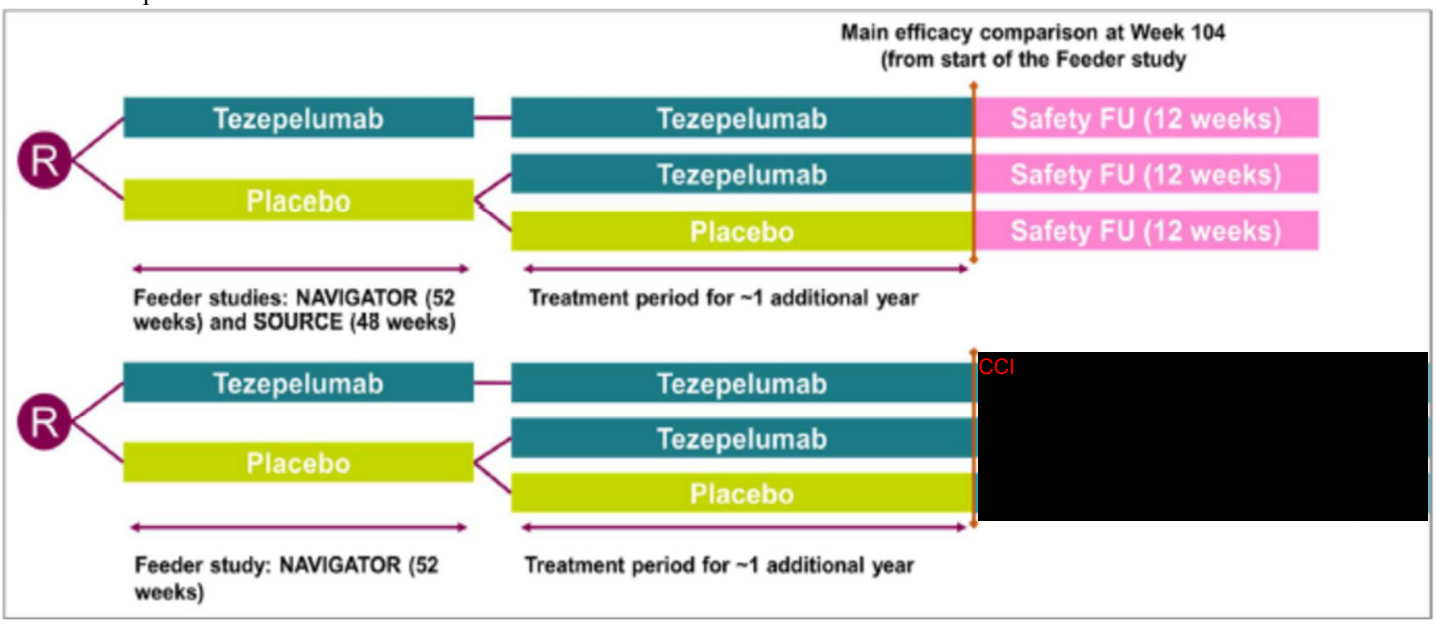
Figure 1 Study Design

<table>
<tr><td rowspan="2">Predecessor Studies</td><td colspan="5">LONG TERM EXTENDED (LTE) STUDY</td></tr>
<tr><td>Predecessor EOT/ V1</td><td>V2</td><td>V3 - V14</td><td>V15</td><td>V16, V17</td><td>CCI [redacted]</td></tr>
<tr><td>Week 0-48 (D5180C00007)</td><td>Week 52 Visit (D5180C00007)</td><td></td><td rowspan="2">Week

56-100</td><td rowspan="2">Week

104</td><td rowspan="2">Week

110, 116</td><td rowspan="2"></td></tr>
<tr><td>Week 0-44 (D5180C00009)</td><td>Week 48 Visit (D5180C00009)</td><td>Week 52 for D5180C00009 only</td></tr>
<tr><td>Treatment Phase</td><td>Screening/ Randomization</td><td colspan="2">Treatment Phase</td><td>End of Treatment</td><td colspan="2">Follow-up CCI [redacted]</td></tr>
</table>



V: Visit(s)

*All Subjects will be re-randomized in this study to maintain the blinding. Subjects randomized to tezepelumab in the predecessor studies will be assigned and remain on tezepelumab during the LTE study. Subjects randomized to placebo in the predecessor studies will be re-randomized to either tezepelumab or placebo (1:1). Given the randomization scheme of D5180C00007 or D5180C00009, this will produce a final subject distribution of 3:1 (tezepelumab:placebo) in the LTE study, assuming a similar number of subjects rollover from each arm in the predecessor studies.

2 Introduction

Asthma is a chronic inflammatory airway disorder caused by the interaction of genetic and environmental factors. It is characterized by widespread, variable, and reversible airflow obstruction, airway inflammation, excessive mucus production; and airway hyperresponsiveness that lead to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing (The Collaborative Study on the Genetics of Asthma (CSGA) 1997).

Progressive pathologic airway remodeling and scarring may occur in persistent asthma resulting in only partially reversible or irreversible airway obstruction (Pascual and Peters 2005).

The etiology of asthma is thought to be multi-factorial, influenced by both genetic and environmental mechanisms. The majority of cases arise when a person becomes hypersensitive to allergens. Despite the availability of multiple therapeutic options, asthma continues to be a major health problem. Worldwide, asthma currently affects approximately 300 million people; by 2020, asthma is expected to affect 400 million people (Partridge 2007). Each year in the US,

asthma accounts for an estimated 8.9 million outpatient visits, 1.9 million emergency room visits, 479,000 hospitalizations (DeFrances et al 2008), and 3400 deaths (Centers for Disease Control and Prevention 2017).

Approximately 5% to 10% of asthma subjects have severe asthma, which may be inadequately controlled by ICS and LABA combinations together with additional controller therapies (Brightling et al 2008). These subjects are at risk of asthma exacerbations (Tough et al 1998, Turner et al 1998) and have the greatest medical need among the asthmatic population today. Subjects with severe asthma represent the greatest economic cost (>50% of total asthma-related health care costs) (Antonicelli et al 2004, Serra Batlles et al 1998, Barnes and Kuitert 1996).

2.1 Study rationale

There are two Phase 3 studies currently ongoing.

The Navigator study (D5180C00007) is designed to evaluate the effect of tezepelumab on the AAER, lung function, asthma control, and safety in adult and adolescent subjects with uncontrolled severe asthma receiving medium or high-dose ICS plus at least one additional asthma controller medication with or without OCS. This will allow the benefit-risk profile of tezepelumab in the treatment of severe asthma to be further characterized and to enable a better understanding of how treatment with tezepelumab should be utilized in the management of severe asthma.

The Source study (D5180C00009) is designed to demonstrate the ability of tezepelumab versus placebo to enable reductions of the daily maintenance OCS use in adult asthmatic subjects who are also using high-dose ICS plus LABA with or without other asthma controller therapy, while maintaining asthma control.

Tezepelumab is a fully humanized immunoglobulin that binds to the TSLP and prevents it interaction with the TSLP receptor. TSLP has an upstream and central role in the initiation of the immune responses and is expected to have an impact on a broad range of cell types. In the predecessor studies the safety of tezepelumab dosing is being studied over a 52 week and 48 week treatment period in the D5180C00007 and D5180C00009 studies respectively. However, it is important to further understand the safety with continued dosing of tezepelumab for an additional year. The purpose of this Long-Term Extension (LTE) study is to continue to characterize the safety profile of tezepelumab administration in asthma subjects who have completed either of the 2 predecessor studies. CCI [redacted]

2.2 Background

Biologic therapies have been shown to reduce AAER in severe asthma subjects who are uncontrolled with medium to high dose ICS and additional asthma controller medications. Omalizumab provided benefit for a subgroup of subjects with proven reactivity to an aeroallergen and elevated serum immunoglobulin E (IgE) levels who remain inadequately controlled with ICS plus LABA (XOLAIR US PI 2003). Additional biologics, mepolizumab, reslizumab, benralizumab and dupilumab, have recently been approved for severe asthma with an eosinophilic phenotype (NUCALA US PI 2015; XOLAIR US PI 2003; CINQAIR US PI 2016; FASENRA US PI 2017; DUPIXENT US PI 2018). Biologics targeting IL-5 and IgE are now included in international treatment guidelines (GINA 2018) as an add-on treatment to subjects uncontrolled with ICS/LABA treatment. However, even when using currently available biologics, substantial proportions of subjects continue to experience exacerbations and may benefit from agents that target different molecular pathways (Wenzel 2016, Froidure et al, 2016, Swedin et al, 2017). Therefore, despite these additional therapeutic options, there is still a clear unmet medical need among subjects with severe asthma, independently of IgE status or eosinophil level, who are unable to gain complete asthma control using currently available therapies.

Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine that is produced in responses to proinflammatory stimuli (e.g. infectious, allergic and environmental stimuli) and trauma. TSLP has an upstream and central role in the initiation of immune responses, and can activate a broad range of cell types including eosinophils, mast cells, T cells, dendritic cells, type 2 innate lymphoid cells and basophils (Watson and Gauvreau, 2014). Classically, TSLP may be a critical component in the initiation and perpetuation of the T helper 2 (Th2) response and the resulting cascade of cytokines associated with Th2 driven asthma (Kaur and Brightling, 2012). Asthma is recognized as a heterogeneous disease. There are subsets of subjects that do not exhibit Th2-associated disease (Wenzel 2012), and there are emerging data that TSLP may also mediate non-allergic (non-T helper cell 2) inflammation (Tanaka et al, 2009, Ziegler et al, 2013).

Given that TSLP is an upstream and pleiotropic cytokine, the blockade of TSLP is therefore anticipated to have broad impact on the spectrum of inflammatory responses seen in asthma.

Tezepelumab is a fully human immunoglobulin G (IgG) 2λ monoclonal antibody (mAb) directed against TSLP. Tezepelumab binds to human TSLP and prevents its interaction with TSLP receptor (TSLPR). Owing to the central role of TSLP in initiating and maintaining a Th2 response, anti-TSLP therapy may provide an opportunity to treat the upstream underlying mechanisms of asthma by reversing the established inflammatory responses to asthma triggers.

Results of a completed inhaled allergen challenge study in 31 adult subjects with mild atopic asthma (Study 20101183) demonstrated that tezepelumab attenuated the LAR and EAR to allergen challenge, as measured by the AUC (Area Under the Curve) for the percent fall in FEV1 and the maximum percent fall in FEV1. Tezepelumab also attenuated the increase in FeNO value

on the post-allergen day compared with the pre-allergen day. Multiple doses of 700 mg IV tezepelumab demonstrated an acceptable safety profile in subjects with mild atopic asthma. No subjects developed anti-drug antibodies (ADA) after receiving tezepelumab. Based upon these data, MedImmune/AstraZeneca have conducted a randomized, double-blind, placebo-controlled, dose range finding study in asthmatics who were inadequately controlled with medium or high dose ICS/long-acting β2 agonist (LABA) with or without other controller medications.

Study CD-RI-MEDI9929-1146 was a Phase 2b multicentre, multinational, dose-ranging, double-blind, randomized, parallel-arm, placebo-controlled study to evaluate the effect of 3 dose levels of tezepelumab on the AER in adult subjects with inadequately controlled, severe asthma. Subjects were randomized in a 1:1:1:1 ratio to 1 of 3 dose levels of SC tezepelumab (280 mg Q2W, 210 mg Q4W, 70 mg Q4W) or placebo (Q2W) for 50 weeks. Anomalous data at a single site was identified following completion of this study and due to GCP non-compliance, all data relating to 34 subjects from this site were excluded and the CSR revised. Consequently, a total of 550 subjects received at least 1 dose of tezepelumab or placebo. Statistically significant annualized AER reductions of 62%, 71%, and 66% for the 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W tezepelumab groups, respectively, compared with placebo were observed in the ITT population ($p<0.001$).

After repeated SC administration, mean serum trough concentration increased over time and achieved steady-state by week 12. Tezepelumab exhibited linear pharmacokinetics (PK) across 3 doses. A low incidence of ADA was observed across all treatment subjects. 6 (4.3%) placebo subjects and 7 (1.7%) total tezepelumab subjects who had no detectable ADA at baseline had detectable ADA post-treatment; no subjects developed neutralizing ADA in the study. There was no impact of ADA on tezepelumab PK. The results of this study did not identify safety signals associated with tezepelumab for any dosing regimen. The overall incidence of TEAEs were similar between the placebo (65.9%) and the tezepelumab (66.0%) dose groups. A majority of subjects had TEAEs that were Grade 1(mild) or Grade 2 (moderate) in severity and not related to investigational product. TEAEs that resulted in permanent discontinuation of investigational product occurred in few subjects, and at a similar incidence between the tezepelumab (5 subjects [1.2%] overall) and placebo (1 subject [0.7%]) groups. Overall, tezepelumab was well-tolerated with an acceptable safety profile and no safety signals were identified.

2.3 Benefit/risk assessment

In order to evaluate the clinical benefit-risk balance for tezepelumab, preclinical and clinical data have been taken into consideration, as well as a review of the available information for monoclonal antibodies that are approved for and are in development for the treatment of severe asthma. Benefits for tezepelumab over placebo include a clinically meaningful reduction in asthma exacerbations, improvement in lung function and asthma control metrics.

Tezepelumab has been well tolerated with no safety signals identified in studies to date. No serious allergic reactions or anaphylactic reactions considered related to tezepelumab were reported in the Phase 2 program. Although TSLP suppression could theoretically have unanticipated immune-related side effects impairing host defense against certain infections, there is no clear preclinical or clinical evidence supporting such a role, and no safety signals related to infections have been detected in the tezepelumab program.

The benefit/risk assessment for tezepelumab in severe asthma based on the development through Phase 2 is favourable. The benefit / risk assessment will be further defined by results from the Phase 3 program.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of tezepelumab may be found in the Investigator's Brochure.

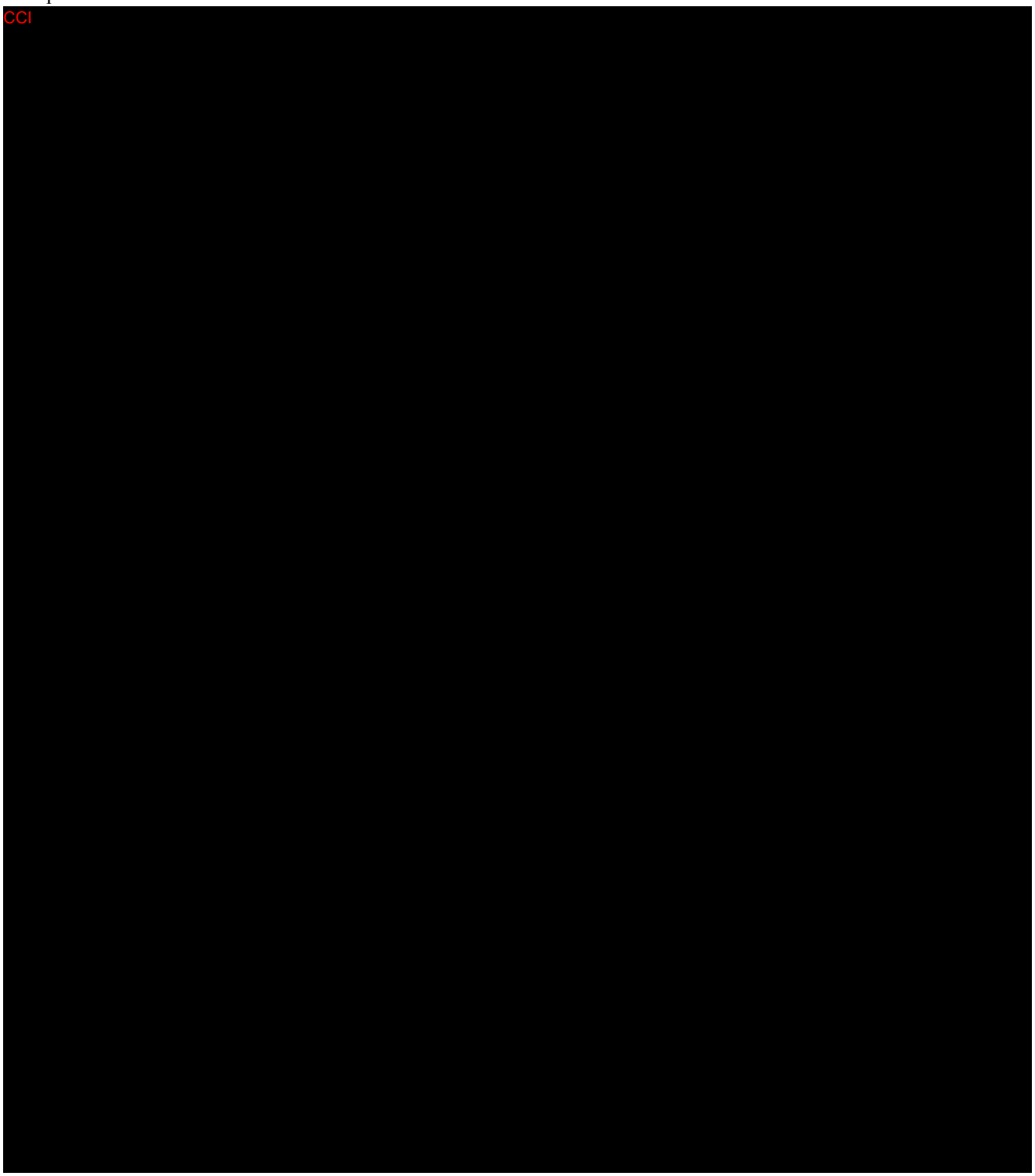
See Section 8.4.6 for information regarding the DSMB.

3 Objectives and Endpoints

Table 3 Objectives and Endpoints

Primary objective:	**Outcome Measure:**
To evaluate the long-term safety and tolerability of tezepelumab in severe asthma subjects	Exposure adjusted incidence rates of AEs/SAEs over 104 weeks
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)
CCI [redacted]	

CCI



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4 Study Design

4.1 Overall design

For an overview of the study design see Figure 1, in Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

For details on what is included in the safety and efficacy endpoints, see Section 3 Objectives and Endpoints.

This is a multicentre, randomized, double-blind, placebo-controlled, parallel group, long-term extension study to evaluate the safety and tolerability of 210 mg Q4W SC of tezepelumab in adults and adolescents with severe uncontrolled asthma. Subjects who have continued to receive investigational product and have attended the EOT visit in one of the predecessor studies may be eligible to enroll into this study if they fulfil the inclusion/exclusion criteria.

This study will be run at approximately 350 sites worldwide and will randomize approximately 975 subjects worldwide. All subjects will be re-randomized in this study to maintain the blinding. Subjects previously randomized to the 210 mg tezepelumab Q4W SC arm in either of the predecessor studies, will be assigned and remain on 210 mg tezepelumab Q4W SC dosing in the LTE study. Subjects randomized to placebo arm in the predecessor studies will be re-randomized in a 1:1 ratio to either 210 mg tezepelumab or placebo, both administered Q4W SC. Given the randomization scheme of subjects in the predecessor studies, this will give an overall subject distribution of 3:1 (tezepelumab:placebo).

Subjects who prematurely discontinue IP or do not attend the EOT visit in one of the predecessor studies will not be eligible to participate in the Long-Term Extension (LTE) study.

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 this study, subjects will be provided with the 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 this study prior to any study-specific procedures being performed.

Section 6.5 (Table 6 and Table 7) provides a list of medication restrictions and prohibitions to be followed throughout conduct of the clinical trial. See inclusion criteria Section 5.1.

On-Site Randomization, Treatment and Follow-up for subjects that rolled over from D5180C00007 or D5180C00009

Please NOTE: If a subject is unable to attend an onsite EOT visit in NAVIGATOR or SOURCE due to the COVID-19 pandemic please refer to Appendix H for further guidance on roll over and participation into the DESTINATION study.

The study will consist of a screening/randomization visit which will be the same day as the End of Treatment (EOT) visit from the predecessor studies D5180C00007 (Week 52) or D5180C00009 (Week 48). The first dose of IP will be administered the same day. During the screening/randomization visit, subjects must undergo all assessments per Table 1. Prior to randomization the subjects must meet all inclusion/exclusion criteria for LTE study. If a subject does not meet all inclusion criteria or meets any exclusion criteria as per 5.1 and section 5.2, the subject will be screen failed and would then complete the safety follow-up portion of the predecessor study. Further details are specified in section 5.4.

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. This is followed by a 12-week follow-up period which includes 2 follow-up visits (Visit 16 and Visit 17).

Subjects who prematurely discontinue IP during the LTE study will be encouraged to undergo all study visits/procedures for the full treatment period. Further information is provided in section 7.1.1. Any new treatments that are initiated will be recorded in the electronic case report form (eCRF).

4.2 Scientific rationale for study design

This is a global study designed to continue to investigate the safety and tolerability of tezepelumab versus placebo in severe asthma subjects receiving medium or high dose ICS plus at least one additional asthma controller medication, with or without chronic oral corticosteroids (OCS) and/or other asthma controllers for an additional year. The placebo-controlled study design will help to contextualize endpoints by providing a direct comparator. During the blinded treatment phase (Visits 1-15), half the subjects who were previously assigned to the placebo regimen during the predecessor study will be reassigned to receive tezepelumab, while those who received active drug during the predecessor study will continue on that same regimen. Subjects randomized to placebo in this study serve as comparators to support interpretability of the data collected for subjects randomized to tezepelumab. TSLP has an upstream and central role in the initiation of the immune responses and is expected to have an impact on a broad range of cell types. In the predecessor studies the safety of tezepelumab dosing is being studied over a 52

week and 48 week treatment period in the D5180C00007 and D5180C00009 studies respectively. However, it is important to further understand the safety with continued dosing of tezepelumab for an additional year.

4.2.1 CCI

CCI

4.3 Justification for dose

This is a Long-Term Extension study to gather more information on the safety and tolerability of 210 mg Tezepelumab Q4 weeks. Only subjects who have continued to receive investigational product and have attended the EOT visit in one of the predecessor studies may be eligible to enroll into this study if they fulfil the inclusion/exclusion criteria. Therefore, the dosage will remain the same as that which was given in the predecessor studies.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last subject undergoing the study.

A subject is considered to have completed the study when he/she has completed his/her last scheduled contact.

See Appendix A 6 for guidelines for the dissemination of study results.

5 Study Population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomized to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures and should therefore continue with the follow-up period as described in the protocol for the predecessor study, refer to Section 5.4.

In this protocol, “enrolled” subjects are defined as those who sign informed consent. “Randomized” subjects are defined as those who undergo randomization and receive a randomization number.

For procedures for withdrawal of incorrectly enrolled/randomized subjects see Section 7.3.

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. Refer to Appendix H for further guidance.

5.1 Inclusion criteria

Subjects are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1. Provision of signed and dated written informed consent form prior to any mandatory study specific procedures, sampling, and analyses for subjects who are at, or over the age of majority (as per local law). For subjects, less than the age of majority, in addition to the subject providing informed assent, the subject’s legal guardian must also provide their informed consent.

The ICF process is described in Appendix A 3.

Reproduction

2. Negative urine pregnancy test for female subjects of childbearing potential prior to administration of IP at visit 1.

3. Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception from screening and must agree to continue using such precautions for 16 weeks after the final dose of IP.

Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

Adolescent specific recommendations: If subject is female and has reached menarche or has reached Tanner stage 3 breast development (even if not having reached menarche), the subject will be considered a female of child bearing potential.

A highly effective method of contraception is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Highly effective forms of birth control include: true sexual abstinence, a vasectomised sexual partner, Implanon™, female sterilization by tubal occlusion, any effective intrauterine device/system (IUD/IUS), Depo-Provera™ injections, oral contraceptive, and Evra Patch ™ or Nuvaring™. WOCBP must agree to use highly effective method of birth control, as defined above, from enrolment (Visit 1), throughout the study duration and within 16 weeks after last dose of investigational product (IP), and have a negative urine pregnancy test result at Visit 1.

Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age specific requirements apply:

- Women <50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels in the postmenopausal range.
- Women ≥50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.

4. Inclusion criterion #4 removed with version 2.0 of the clinical study protocol.

5. **Inclusion criteria at randomization:** Female or male subjects who have not met investigational product discontinuation criteria and have attended the EOT visit in either study D5180C00007 or D5180C00009. Subjects with inadequate compliance with investigational product, assessed at the discretion of the sponsor, might not be randomized.

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[redacted]

5.2 Exclusion criteria

Medical conditions

1. Any clinically important pulmonary disease other than asthma (e.g., active lung infection, Chronic Obstructive Pulmonary Disease (COPD), bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or pulmonary or systemic diseases, other than asthma, that are associated with elevated peripheral eosinophil counts (e.g., allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).

2. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:

    - Affect the safety of the subject throughout the study
    - Influence the findings of the study or the interpretation
    - Impede the subject's ability to complete the entire duration of study

3. History of chronic alcohol or drug abuse within 12 months prior to Visit 1

4. Current malignancy or malignancy that developed during a predecessor study (subjects who had a basal cell carcinoma or a localized squamous cell carcinoma of the skin which was resected for cure will not be excluded)

5. Exclusion criterion #5 removed with version 2.0 of the clinical study protocol

6. Major surgery or planned surgical procedures requiring general anaesthesia or inpatient status for > 1 day during the conduct of the study, unless approved by the sponsor Study Physician

Prior/concomitant therapy

7. Treatment with the following medications within the last 12 weeks prior to randomization: Systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporine, etc.) except for OCS used in the treatment of asthma/asthma exacerbations

Prior/concurrent clinical study experience

8. Concurrent enrolment in another clinical study involving an IP

9. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

Diagnostic assessments

10. Any clinically meaningful abnormal finding in physical examination, vital signs, ECG, haematology, clinical chemistry, or urinalysis during the predecessor study, which in the opinion of the Investigator, may put the subject at risk because of his/her participation in the study, or may influence the results of the study, or the subject's ability to complete the entire duration of the study

Other exclusions

11. Pregnant, breastfeeding, or lactating women

    a. A serum β-HCG pregnancy test must be drawn for women of childbearing potential (including adolescent females) at the visit 1. If the results of the serum β-HCG cannot be obtained prior to dosing of the IP, a subject may be enrolled on the basis of a negative urine pregnancy test, though serum β-HCG must still be obtained. If either test is positive, the subject should be excluded. Since urine and serum tests may miss a pregnancy in the first days after conception, relevant

menstrual history and sexual history, including methods of contraception, should be considered. Any subject whose menstrual and/or sexual history suggests the possibility of early pregnancy should be excluded.

12. Subjects with important protocol deviations in either of the predecessor studies, assessed at the discretion of the sponsor

13. Judgment by the investigator that the subject should not participate in the study if the subject is unlikely to comply with study procedures, restrictions and requirements. Or unwillingness or inability to follow the study procedures by the subject, in the opinion of the investigator.

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5.3 Lifestyle restrictions

Subjects must abstain from donating blood and plasma from the time of informed consent, and for 16 weeks (5 half-lives) after last dose of IP.

5.3.1 Meals and dietary restrictions

Subjects should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the centre.

CCI [redacted]

5.3.2 Alcohol, tobacco and other

Chronic alcohol or drug abuse within 12 months is restricted throughout the conduct of the study CCI [redacted]

Smoking is not allowed throughout the course of the study CCI [redacted]

The use of e-cigarettes or vaping products is also not allowed during the course of the study CCI [redacted]

5.3.3 Activity

Subjects should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the centre.

5.4 Screen failures

Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

These subjects should have the reason for study withdrawal recorded as 'Screen Failure' (i.e., subject does not meet the required inclusion/exclusion criteria) in the eCRF. This reason for study withdrawal is only valid for screen failures, and not randomized subjects.

Re-screening is not allowed under any circumstances.

All subjects that are screen failed in this study, must go on to complete the follow-up period requirements as per the protocol of the predecessor study.

6 Study Treatments

Study treatment is defined as an IP (including placebo) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to tezepelumab or placebo.

6.1 Treatments administered

6.1.1 Investigational products

Table 4 Study Treatments

	Treatment 1	Treatment 2
Study treatment name:	Tezepelumab	Placebo
Dosage formulation:	CCI acetate, CCI L-proline, CCI polysorbate 80, pH 5.2	CCI sodium carboxy methyl cellulose in CCI acetate, CCI L-proline, CCI polysorbate 80, pH 5.0
Route of administration	Subcutaneous	Subcutaneous
Dosing instructions:	Refer to section 6.2	Refer to section 6.2
Packaging and labelling	Study treatment will be provided in 5cc vial. Each vial will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.	Study treatment will be provided in 5cc vial. Each vial will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.

6.2 Preparation/handling/storage/accountability

IP will be supplied to the site in a kit with one vial of either tezepelumab or placebo. Each kit has a unique number that is printed on all labels within the kit (i.e., the outer carton label and the label of each container within the carton).

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the IP.

Only subjects enrolled/randomized in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Please Note: During the COVID-19 pandemic, if allowed by local/regional guidelines, IP preparation and administration may be performed at the subject's home or at alternative site by a qualified HCP. Please refer to Appendix H for further details.

Dose Preparation

Each vial should be visually inspected prior to dose preparation. The IP will be provided to the study sites as a colorless to slightly yellow clear solution contained in a 5 mL single use glass vial to be stored at 2°C to 8°C until used. If defects are noted with the IP, the investigator and site monitor should be notified immediately. Preparation of IP must be performed by a qualified person (e.g., pharmacist or investigator) at the site.

The IP does not contain preservatives and any unused portion must be discarded. Preparation of the IP is to be performed aseptically. Total in-use storage time from needle puncture of the IP vial to start of administration should not exceed 4 hours at room temperature. If storage time exceeds this limit, a new dose must be prepared from new vials.

To prepare the subject's dose, the IP will be selected for administration according to the kit identification numbers assigned by the IRT. One vial of IP will be assigned by IRT for each dose.

Dose preparation steps:

1. Allow the vial to equilibrate at room temperature (about 30 minutes to 1 hour). Ensure that the vial is adequately protected from light during the warming process. Gently swirl the vial to ensure the contents are mixed to a clear, homogeneous solution. Do not shake.

2. To prepare IP for administration remove the tab portion of the vial cap and clean the stopper with 70% ethyl alcohol or equivalent.

3. Attach a 21G 1½-inch sterile disposable needle to a 2mL or 3mL sterile syringe.

4. Withdraw 1.9 mL of the IP from the vial.

5. Remove and discard the 21G 1½-inch sterile disposable needle from the syringe.

6. Attach a new 27G ½-inch sterile disposable needle to the same syringe in step 5.

7. Apply the appropriate label to the syringe.

The assigned vial should be used at one time to prepare the dose required at each visit. Unused product in opened and dispensed vials should not be used for subsequent dosing and should be stored for IP accountability. If the opened and dispensed vials must be discarded immediately after dose preparation as per site's SOP, the kit boxes must be retained for IP accountability.

The IP will be administered by one SC injection (see Table 5) and must be prepared using disposable plastic syringes and aseptic technique.

Table 5 Investigational Product Dose Preparation

Dose	Number of vial(s) required	Syringe size required	Total volume administered
210 mg[a]	1	2 or 3 mL	1.9 mL
Placebo	1	2 or 3 mL	1.9 mL

[a] Due to the gradations available on a 2 or 3 mL disposable plastic syringe, dose based on 1.9 mL administered volume is 209 mg.

Dose Administration

The first 2 IP doses must be administered on-site. For further details during the COVID-19 pandemic please refer to Appendix H.

IP will be administered by a qualified HCP (e.g. Pharmacist, or study nurse) at the site. The injection site must be recorded in the source documents at each treatment visit and in the eCRF. The person administering the dose will wipe the skin surface of the upper arm, anterior thigh or abdomen with alcohol and allow to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be inserted at a 90 degree angle approximately halfway into the SC tissue. The IP will be slowly injected (at least 5 second duration is recommended) into the SC tissue using gentle pressure. The area should not be massaged after injection. It is advised that the site of injection of IP be rotated such that the subject receives IP at a different anatomical site at each treatment visit. Injection site must be documented on the eCRF and in the source documents at each treatment visit. In cases when rotation of the injection site is not feasible and/or the subject prefers not to rotate injection sites, the reason for not rotating the injection site should be documented in the source documents. The suggested injection site rotation sequence is presented below in Figure 2.

Figure 2 Suggested Schema of Rotation of Injection Sites

Subjects should be observed for a minimum of 2 hours after administration of the first two IP administrations, in the DESTINATION Study for the appearance of any acute drug reactions. For the remaining doses, subjects will be observed for a minimum of 1 hour after IP administration for any such reaction.

If any of the following should occur, the IP should not be administered:

- The subject received allergen immunotherapy injection on the same day as scheduled IP administration.
- The subject has an intercurrent illness that in the opinion of the investigator and/or medical monitor may compromise the safety of the subject in the study (e.g., viral illnesses).
- The subject is febrile (≥ 38°C; ≥ 100.4°F) within 72 hours prior to IP administration.

The visit should be rescheduled within the allowed visit window and IP should be administered at that visit. If this is not possible the IP administration should be skipped. If a subject skips 2 consecutive IP administrations, the AstraZeneca Study Physician should be contacted to discuss further participation.

If the subject reports an injection site reaction, the investigator or qualified designee will complete the AE eCRF page.

6.3 Measures to minimise bias: randomisation and blinding

The Investigator(s) will:

1. Obtain signed informed consent or assent from the potential subject, or their guardian/legal representative, before any study specific procedures are performed.
2. Assign the potential subject a unique enrolment number (which begins with an CCI via the Interactive Response Technology (IRT).
3. Determine subject eligibility.
4. Assign the eligible subject unique randomization code via the Interactive Response Technology (IRT).

5. All subjects will be randomized in the LTE study to maintain the blinding. Subjects randomized to placebo in the predecessor studies will be randomized in a 1:1 ratio (tezepelumab:placebo) stratified by predecessor study. Subjects randomized to tezepelumab in the predecessor studies will be assigned and continue with tezepelumab in the LTE study. Randomization numbers will be grouped in blocks. If a subject withdraws from the study, then his/her enrolment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

Specific information concerning the use of the IRT will be provided in a separate manual.

Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be randomized or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the investigator regarding whether to continue or discontinue the subject from treatment. Study treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the subject and AstraZeneca Study Physician must ensure the decision is appropriately documented. Subjects that are discontinued from treatment should be followed up according to the options described in section 7.1.1.

In those cases where continuation of the study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented.

Methods for assigning treatment groups

All subjects will be centrally assigned to randomized study treatment using an interactive response technology (IRT). Randomization codes will be assigned strictly sequentially in each stratum as subjects become eligible for randomization. Randomization will be stratified by predecessor study.

All subjects will be re-randomized in this study, and will be assigned to treatment according to the following algorithm:
* Subjects previously randomized with blinded tezepelumab will be assigned and stay on blinded tezepelumab
* Subjects previously randomized to blinded placebo will be randomized 1:1 to blinded

tezepelumab or placebo.

The randomization list will be prepared by a computerized system provided by Calyx Clinical Research Solutions on behalf of AstraZeneca (AZRand).

Ensuring blinding

This study is a double-blind study in which tezepelumab and placebo are not visually distinct from each other. All packaging and labelling of IP will be done in such way as to ensure blinding for all sponsor and investigational site staff. Neither the subject nor any of the investigators or sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the subjects will be aware of the treatment received. Since tezepelumab and placebo are not visually distinct, IP will be handled by a qualified person (e.g., pharmacist or study nurse) at the site. Although the study will initially be completely double-blind (i.e., blind for subjects, Investigators/site staff, and Sponsor/designated CRO), at the conclusion of the Phase 3 Studies D5180C00007 or D5180C00009 treatment allocation for subjects may become known to the Sponsor staff and/or designated CRO. The blind will be maintained for the Investigator, investigational site staff, and for the subject. To prevent complete unblinding of this study, treatment-revealing information will not be shared with the study sites or subjects (subject-level listings, as well as other treatment-revealing information will be redacted from the Clinical Study Reports). Further details are provided in a separate Blinding Plan.

An AstraZeneca site monitor will perform IP accountability. In the event that the treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects or needs to be known to treat an individual subject for an AE, the sponsor must be notified immediately by the investigator and, if possible, before unblinding.

The following personnel will have access to the randomization list:

- Those carrying out the packaging and labelling of IP
- Those generating the randomization list
- Personnel at the IRT company
- Supply Chain Management department
- Patient Safety department at AstraZeneca
- CCI [redacted]
- Those involved in the reporting and reviewing the DSMB presentations

No other member of the extended study team at AstraZeneca, or any CRO handling data, will have access to the randomization scheme during the conduct of the study until planned unblinding at primary database lock at Week 104.

The information in the randomization list will be kept from other personnel involved in the conduct of the study and in a secure location until the end of the study. Further details are provided in a separate Blinding Plan.

Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) and delegate(s) at the study sites from the IRT. Routines for this will be described in the IRT user manual that will be provided to each site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomization. The Investigator should document and report the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented. Further details are provided in a separate Blinding Plan.

6.4 Treatment compliance

Any change from the dosing schedule or dose discontinuations should be recorded in the eCRF. The IP Storage Manager is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP. The date and time of all IP administrations, as well as any missed doses, should be recorded in the appropriate section of the eCRF.

6.5 Concomitant therapy

All subjects will be taking medium- or high-dose ICS and potentially at least one additional asthma controller medication (including LABA, Leukotriene modifiers, theophylline, cromones). Additionally, the subject may be taking OCS for the treatment of asthma.

During the study, subjects may use an inhaled short-acting bronchodilator as needed as a reliever or rescue medication due to worsening of asthma.

Maintenance regiment of allergen-specific immunotherapy is allowed but should not be administered on the same day as investigational product.

Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for those medications identified as "excluded" in Prohibited medications. See Table 7.

Maintenance asthma medication is not regarded as an IP but will be provided/reimbursed by AstraZeneca according to local regulations in order to maintain appropriate oversight and access to this concomitant therapy. Any marketed (e.g. omalizumab, mepolizumab, reslizumab, etc.) or to be marketed or investigational biologic treatment will not be provided/reimbursed by AstraZeneca.

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the subject is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

All concomitant medication should be documented in the source and recorded in the eCRF.

Table 6 Restricted Medications

Medication/class of drug:	Usage
Short-acting beta-agonists (SABA)	Regular scheduled use of SABA is not allowed from V1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP, PRN use is allowed if needed, however attention should be paid to the following restrictions. SABA should be withheld for at least 6 hours prior to scheduled CCI [redacted] at site with the exception of any unscheduled visits due to asthma worsening.
Maintenance treatment with ICS and long-acting bronchodilators (including ICS/LABA combinations)	The subject should be instructed not to take their usual asthma controller medication (i.e., LABA) prior to scheduled ECG assessment (please refer below for long-acting bronchodilator restrictions). Use of SABA should be avoided within 6 hours before ECG assessments. The medication restrictions are waived for the screening ECG at Visit 1. Twice daily bronchodilators should be withheld for at least 12 hours prior to the scheduled CCI [redacted] at site. Once daily bronchodilators should be withheld for at least 24 hours prior to the scheduled CCI [redacted] at site. Subjects will not need a washout of their asthma medications for unscheduled visits due to asthma worsening.

Medication/class of drug:	Usage
Additional Maintenance Controllers	Once daily LABA and LAMA should be withheld for at least 24 hours prior scheduled CCI [redacted] at site visits with the exception of any unscheduled visits due to asthma worsening. Twice daily LABA or LAMA containing therapies should be withheld for at least 12 hours prior to scheduled CCI [redacted] CCI [redacted] at site with the exception of any unscheduled visits due to asthma worsening. LTRA should be restricted for at least 24 hours prior to scheduled CCI [redacted] at site with the exception of any unscheduled visits due to asthma worsening. Twice daily theophyllines should be withheld for at least 12 hours prior to scheduled CCI [redacted] at site with the exception of any unscheduled visits due to asthma worsening. Once daily theophyllines should be withheld for at least 24 hours prior to scheduled CCI [redacted] at site with the exception of any unscheduled visits due to asthma worsening.
Short-acting anticholinergics (e.g. ipratropium)	These are not allowed as a rescue treatment for worsening asthma symptoms from V1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP. They may be used for managing an asthma exacerbation event.
Inactive/killed vaccinations (e.g. inactive influenza)	Allowed provided they are not administered within 5 days **before** or after any IP dosing visit.
COVID-19 vaccinations	Refer to section 6.5.5 and 8.2.6
Allergen Immunotherapy	Allowed, if on stable therapy for at least 2 months prior to date of Visit 1 with no anticipated change during the treatment period. These should not be administered on the same day as IP administration.

Table 7 Prohibited Medications

Prohibited medication/class of drug:	**Usage**
Live Attenuated Vaccines	Not allowed during the study up to Week 116.

Prohibited medication/class of drug:	Usage
Any immunomodulators or immunosuppressives (corticosteroids with systemic effects such as oral, parenteral, or intra-articular administration for reasons other than asthma are not allowed. However, corticosteroid treatment of adrenal insufficiency is allowed.)	Not allowed throughout the IP treatment period and preferably 4 weeks after the last dose of IP.
Immunoglobulin or blood products	Not allowed throughout the IP treatment period and preferably 4 weeks after the last dose of IP.
Any marketed (e.g. omalizumab, mepolizumab, reslizumab, etc.) or to be marketed biologic treatment	Not allowed throughout the IP treatment period (even if the subject has discontinued IP and continues with rest of the study visit till end of study) and until the week 116. **Please note:** Biologics should only be introduced after Week 116, in the presence of evidence of asthma deterioration.
Other investigational products (including investigational use of an approved drug)	Not allowed throughout the IP treatment period (even if the subject has discontinued IP and continues with rest of the study visit till end of study) CCI [redacted] CCI
Chronic use of oral corticosteroids in diseases other than asthma.	Not allowed throughout the IP treatment period and preferably 4 weeks after the last dose of IP.

6.5.1 Asthma Background Medication

If the subject's symptoms are stable, as per investigator's judgement, attempts to reduce background asthma medications can be made every 3 months starting from Visit 1 throughout the study as per Appendix F 1, Figure 4, if thought appropriate by the investigator.

In the event the subject experiences worsening of asthma symptoms due to the reduction of background asthma medications, guidance is provided in Appendix F 2, Figure 5 to step up the background asthma medications, as per investigator discretion, at 3 monthly intervals.

In the event a subject experience an exacerbation of asthma, this should be treated appropriately as per investigator discretion.

6.5.2 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

6.5.3 Rescue medication

SABA should be withheld for at least 6 hours prior to scheduled site visit [redacted] at site with the exception of any unscheduled visits due to asthma worsening.

Albuterol (US)/salbutamol (ex US) rescue medication will be provided by the sponsor and obtained locally. Rescue use of SABA administered via nebulization is discouraged, except as urgent treatment during an asthma exacerbation.

6.5.4 Bronchial Thermoplasty

Subjects should not be treated with bronchial thermoplasty during the study.

6.5.5 COVID-19 Vaccination

If COVID-19 vaccination is in the best interest of the subject it is recommended that for subjects in study treatment phase IP should not to be administered within 14 days before, or 28 days after a dose of vaccine. In case of subjects in follow up phase it is advised that vaccination should not occur within 14 days after the last IP dose. As those intervals might change, please discuss with the Study Physician. For details, refer to section 8.2.6.

6.6 Dose modification

N/A

6.7 Treatment after the end of the study

Subjects who complete follow-up at week 116 [redacted] should be given standard of care at the discretion of the investigator.

7 Discontinuation of treatment and subject Withdrawal

7.1 Discontinuation of study treatment

Subjects may be prematurely discontinued from investigational product (IP) in the following situations:
Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study

- Subject decision. The subject is at any time free to prematurely discontinue treatment, without prejudice to further treatment
- An adverse event considered to jeopardise the safety of a subject participating in the study

- Pregnancy
- Severe non-compliance with the Clinical Study Protocol
- Development of any study specific criteria for premature discontinuation of IP, including:
  - An anaphylactic reaction to the IP requiring administration of epinephrine
  - A helminth parasitic infestation requiring hospitalization
  - An asthma-related event requiring intubation
  - Any malignancy, except subjects who develop basal cell carcinoma or localized squamous cell carcinoma of the skin, provided that the malignancy is excised and determined to have clean margins.
- Development of one or more of the following:
  - Confirmed ALT or AST increase of ≥8 x ULN
  - Confirmed ALT or AST increase of ≥5 x ULN for more than 2 weeks
  - Confirmed ALT or AST increase of ≥3 x ULN and total bilirubin of ≥2 x ULN
  - ALT or AST of ≥3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (≥5%)

Before a decision to prematurely discontinue a subject from IP is instituted, the AstraZeneca Study Physician should be consulted regardless of the reason for discontinuation.

See the Schedule of Activities (SoA) for data to be collected at the time of premature treatment discontinuation and follow-up and for any further evaluations that need to be completed.

If a subject prematurely discontinues IP due to a study specific discontinuation criterion, this should always be recorded as 'Development of study specific withdrawal' on the Discontinuation of Investigation Product form in the eCRF.

7.1.1 Procedures for discontinuation of study treatment.

Subjects are free to prematurely discontinue IP or withdraw from the study at any time without prejudice to further treatment. Prematurely discontinuing study treatment is not the same as study withdrawal. Procedures to follow for study withdrawal are detailed below in section 7.3. If the subject decides to withdraw consent, then the reason for this must be recorded separately in the eCRF.

A subject that decides to prematurely discontinue IP should always be asked about the reason(s) and the presence of any adverse events. The reason for prematurely discontinuing treatment and the date of last IP administration should be recorded in the eCRF. Subjects prematurely discontinuing IP administration should be given locally available standard of care therapy, except for biologic treatments, at the discretion of the Investigator. Interaction studies between tezepelumab and other biologics indicated for the treatment of asthma have not been conducted. Treatment with marketed or investigational biologics is not allowed until Week 116 even if the subject has prematurely discontinued IP. Biologics should only be introduced after Week 116, in the presence of evidence of asthma deterioration. For additional information regarding pharmacokinetic and pharmacodynamic effects of tezepelumab reference should be made to the investigator brochure.

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:

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.

If the last IP administration was after week 88 for options 1 or 2, the subject will return to the clinic for an on-site EOT visit at Week 104 (+/- 5 days), and for option 3, the investigator will contact on phone the subject at 104 weeks post randomization. The subject for options 1, 2 and 3 will then return for an on-site follow-up visit 16 weeks (+/- 5 days) post last IP administration (refer to SoA, V17 – Week 116).

The EOT visit will be completed immediately in the case of subsequent early withdrawal from option 1 or 2. Subjects who do not wish to have any follow-up contacts should be considered to withdrawal from the study (refer to section 7.3).

If the subject chooses option 1, all assessments will be completed as indicated in the SoA (see Table 1). If the subject chooses 2 or 3, the key information to be collected during the telephone calls are AEs/SAEs, changes in concomitant medication, health care utilization and asthma exacerbation information.

Subjects who initially choose option 1 or 2 and subsequently cannot or do not wish to comply with the requirement of their option can continue with a less intensive option (i.e. subject initially choosing option 1 can continue with option 2 or 3, subject initially choosing option 2 can continue with option 3).

7.1.2 CCI

7.2 Lost to follow-up

A subject will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule.

- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject or next of kin by either repeated telephone calls, certified letter to the subject´s last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's medical record.

- Efforts to reach the subject should continue until the end of the study. Should the subject be unreachable at the end of the study, the subject should be considered to be lost to follow-up with unknown vital status at end of study and censored at latest follow-up contact.

A subject is considered lost to follow-up when at least two of the following attempts of contact are:

- 3 attempts of either phone calls, faxes or emails,

- having sent 1 registered letter/certified mail,

- one unsuccessful effort to check the status of the subject using publicly available sources, if allowed by local regulations.

7.3 Withdrawal from the study

A subject may withdraw from the study (e.g., withdraw consent), at any time (IP and assessments) at his/her own request, without prejudice to further treatment. A subject who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (e.g., telephone contacts, contacts with a relative or treating physician, or information from medical records) as per sections 7.1.1 and 7.3.2.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow-up subjects as medically indicated. A withdrawal visit is essential to collect as much data as possible for the subject as per EOT visit described in SoA, Section 1.1.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

CCI [redacted]

Withdrawal of consent from the study must be ascertained and documented by the Investigator and recorded in the eCRF as well as in the Informed Consent Form (ICF) or assent form.

7.3.1 Discontinuation or suspension of entire study and Site Closure

If AstraZeneca decides to prematurely terminate or suspend the study, the PI, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension. The PI will immediately notify the decision to the subjects and if relevant give appropriate medical treatment; take necessary measures and document these in the source notes.

The sponsor designee also reserves the right to close the study site at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

7.3.2 CCI [redacted]

CCI [redacted]

8 Study Assessments and Procedures

Study procedures and their timing are summarized in the Schedule of Activities (SoA).

The investigator will ensure that data are recorded on the electronic Case Report Forms. The Web Based Data Capture (WBDC) system will be used for data collection and query handling.

The investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site. Additional data will be collected to assess the impact of COVID-19.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or prematurely discontinue Study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities (SoA), is essential and required for study conduct.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (SoA).

The maximum amount of blood collected from each subject over the duration of the study will be approximately 100 mL, including any extra assessments that may be required, will not exceed 150 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. CCI [redacted]

8.1 Efficacy assessments

8.1.1 Assessment of asthma exacerbation

During the study, an asthma exacerbation will be defined 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 consecutive 3 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 emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as per the above).

- An in-patient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours) due to asthma.

The Investigator will have to justify the decision for defining the event as an exacerbation by recording all symptoms and signs in the eCRF.

The start of an exacerbation is defined as the start date of systemic corticosteroids or of a temporary increase in a stable OCS background dose, date of ER or urgent care visits requiring systemic corticosteroids, or date of hospital admission due to asthma, whichever occurs earlier.

The end date of an exacerbation is defined as the last date of systemic corticosteroids or of a temporary increase in a stable OCS background dose, date of ER or urgent care visit, or date of hospital discharge, whichever occurs later.

If less than 7 days have elapsed since the end date of an asthma exacerbation and the start date of a new asthma exacerbation, the second event will be considered a relapse of the prior asthma exacerbation.

All asthma exacerbations that occur during the treatment period and follow-up CCI must be recorded in the exacerbation eCRF. See section 8.3.7 for additional information on recording asthma exacerbations as an AE/SAE during the study.

8.1.2 CCI

8.1.2.1 CCI

CCI

CCI

[redacted]

8.1.2.2 CCI

CCI

8.1.3 CCI

CCI

8.1.4 CCI

CCI

CCI

8.1.4.1 CCI

CCI

8.1.4.2 CCI

CCI

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Clinical Safety Laboratory Assessments

See Table 8 for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

Table 8 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S-Alkaline phosphoatase (ALP)
B-Leukocyte count	S-Alanine transaminase (ALT)
B-Leukocyte differential count (absolute count)	S-Aspartate transaminase (AST)
B-Platelet count	S-Bilirubin, total
B-Hematocrit	S-Blood urea nitrogen
B-Mean Corpuscular Volume	S-Calcium, total
B-Red blood cell (RBC) count	S-Chloride
	S-Creatinine
Urinalysis (dipstick)	S-Creatinine kinase (CK)
U-Hb/Erythrocytes/Blood	S-CRP
U-Protein/Albumin	S-Gamma-glutamyl transpeptidase (GGT)
U-Glucose	S-Glucose
	S-Phosphorus
U-Microscopy and culture as required*	S-Potassium
	S-Sodium
	S-Total cholesterol
	S-Uric acid

*Urine samples will be analysed locally and sent to the central laboratory only for analysis when a positive dipstick result for U-Hb/Erythrocytes/Blood, U-Protein/Albumin or U-Glucose is observed.

NB. In case a subject shows an AST **or** ALT ≥3xULN together with total bilirubin ≥2xULN please refer to Appendix D Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law' for further instructions.

8.2.1.1 Pregnancy Test

The following tests are applicable to female subjects only and will be conducted in accordance with the schedule provided in section 1.1.

- Serum β-Human chorionic gonadotropin (β-HCG)- the test will be done at visit 1 only, for WOCBP and adolescent females (analysed at central laboratory) and should be added to the EOT visit for the predecessor study.
- Urine HCG – the test will be performed at the study site for WOCBP and adolescent females at each treatment visit before IP administration using a dipstick. Additionally, the test must be done at Follow-up[CCI] Visit 17 (Week 116) and Follow-up [CCI] even if subject discontinued IP. Positive urine test result must be confirmed with serum β-HCG.

Note: Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception from screening and must agree to continue using such precautions for 16 weeks after the final dose of IP (refer to Inclusion 3).

8.2.1.2 Maintaining the blind to the subject's blood eosinophil, basophil and monocyte counts in cases of local laboratory usage

The sponsor and site will be blinded to the eosinophil, basophil and monocyte counts from the central laboratory reports throughout the study. However when due to the global central laboratory kit shortage and/or other logistical factors limiting access to central laboratory, investigators could be unable to perform central lab assessments and in these situations they may use local laboratory for safety assessments.

To mitigate the risk of unblinding in case of a need to perform local safety laboratory assessments, the requested tests should be restricted to the relevant test(s) required. For example, if hemoglobin is desired, the investigator should avoid ordering a complete blood cell count with a differential count. In cases where the investigator requires an eosinophil, basophil, or monocyte count for managing safety issues, he/she may order these tests as per regular site practice. AstraZeneca should be notified of all such cases.

To maintain the blind in case of local laboratory results use, site staff who are directly involved in the subject's management should remain blinded to any blood eosinophil, basophil and monocyte counts results included as part of an outside laboratory report or electronic medical record. Similarly, eosinophil, basophil and monocyte counts results must be redacted from all communications with the sponsor.

8.2.2 Weight and Height

Weight and height will be measured in accordance with the SoA. The subject's weight will be recorded in kilograms, and height will be recorded in centimeters. Weight and height measurements will be performed in light clothing and with shoes off. Reasonable attempts should be made to use the same equipment at each visit to measure height and weight.

8.2.3 Physical examinations

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems. Brief physical examination will also be performed and include an assessment of the general appearance, abdomen, cardiovascular and respiratory system. For both the complete and brief physical examinations, only information on whether the assessment was performed or not will be recorded.

Physical examination (complete and brief) will be performed at timelines as specified in the SoA. Investigators should pay special attention to clinical signs related to previous serious illnesses, as new or worsening abnormalities may qualify as adverse events, see Section 8.3.7 for details.

8.2.4 Vital signs

Vital signs (i.e. pulse, blood pressure, respiration rate and body temperature) will be obtained in accordance with the Schedule of Activities (SoA).

Vital signs will be taken prior to blood drawing, IP administration, and, if possible, usual asthma controller medication.

Blood pressure and pulse measurements will be assessed in sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).

Pulse rate will be obtained before blood pressure, if the manual measurement technique is used.

Respiration rate will be obtained after subject has been resting for at least 5 minutes, by counting number of breaths (i.e., how many times the chest rises) for one minute.

Body temperature will be measured prior to IP administration, in accordance with local standards.

8.2.5 Electrocardiograms

A 12-lead ECG will be taken in supine position, prior to blood draw, CCI administration and IP administration.

The investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. In case of discrepancy between the investigator's interpretation and that provided by the ECG machine (if applicable), the investigator's interpretation will take precedence and should be noted on the printout and recorded in the eCRF. A copy of the ECG will be produced and quality checked and kept in case of further need to re-evaluation.

ECG data and evaluation will be recorded in the eCRF.

8.2.6 COVID-19 vaccination recommendations

COVID-19 vaccines are either nucleic acid vaccines (which can include DNA plasmid and mRNA), recombinant vector vaccines (non-replicating viral vectors) or inactivated virus vaccines. DNA plasmid and mRNA vaccines are considered an inactivated vaccine. Recombinant vector candidates potentially may be in a new category. Based on available publications on mRNA and virus vector anti-SARS CoV-2 vaccines, the immune response is developed rapidly after vaccine administration. For vaccines that are currently approved under emergency use authorization (EUA) or approved in the future, please refer to relevant health authority websites for further guidance.

Please note: Any live attenuated vaccine is prohibited during study conduct (see Table 7).

Given the limited long term safety data of COVID-19 vaccines and the potential to confound the interpretation of safety results in the study, the following COVID-19 vaccination guidance provided in Table 9 should be followed based on the study period.

Table 9 COVID-19 Vaccination Guidance

Study Period	Vaccine usage
Subject in treatment phase	If COVID-19 vaccination is in the best interest of the subject and the subject is vaccinated during the study, IP dosing can continue. However, it is recommended that IP not be administered within 14 days before or 28 days after a dose of vaccine. As these intervals might change, please consult with the AstraZeneca Study Physician for the most current recommended time interval, prior to any vaccine dose. If a subject receives a COVID-19 vaccine less than 14 days from the last IP dose, the next IP administration should be rescheduled or skipped to ensure the next IP dose is at least 28 days after the vaccine administration.

Study Period	Vaccine usage
	COVID-19 vaccination schedule should follow country specific health authority guidelines. Vaccination against COVID-19 should be planned in advance to ensure the IP dosing/COVID-19 vaccination intervals are maintained . Study visits should still be conducted within the protocol-specified time window, even if a subject receives a COVID-19 vaccine dose. However, if IP is not administered at a study visit because of COVID-19 vaccination restrictions, the other site visit assessments should be still be performed according to the Schedule of Activities (SoA). At every study visit during the treatment period, the investigator must ask if the subject has received or is planning to receive a COVID-19 vaccination. This is to ensure that the required time interval for IP dosing (mentioned above) is maintained. If it is anticipated that a subject will miss two consecutive IP administrations, the AstraZeneca Study Physician should be contacted to discuss further subject participation in the study. The reason for skipping IP administration should be recorded with the prefix “COVID-19” in medical records.
Subject in follow-up [redacted]	If COVID-19 vaccination is in the best interest of the subject, COVID-19 vaccination could be administered. Subject should follow schedule of assessments; no special adjustments are needed to the SoA. It is advised that subject wait for 14 days after the last IP dose. As these intervals might change, please discuss with Study Physician for the most current recommended time interval prior to any vaccine dose

The suggested IP dosing/COVID-19 intervals is summarized in Figure 3.

Figure 3 COVID-19 Vaccination Between IP Dosing

Reporting of COVID-19 Vaccination in eCRF

COVID-19 vaccine details including vaccine's name/manufacturer, route of administration, and vaccination date should be entered into the eCRF CM module.

If a subject has experienced an AE/SAE associated with COVID-19 vaccination, the investigator should record this in the source documentation and determine whether the IP should be continued, skipped or permanently discontinued in accordance with section 7.1.

8.3 Collection of adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

Adverse Events (new and ongoing from predecessor study) will be collected from time of signature of consent form throughout the treatment period and including the follow-up CCI [redacted] period.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAE/non-serious AEs/AEs of special interest will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- AE intensity (mild, moderate, severe)
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE

- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication(s)

8.3.5 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or care provider or reported in response to the open question from the study site staff: *'Have you/the child had any health problems since the previous visit/you were last asked?'* or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to predecessor study baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil

any of the SAE criteria or are the reason for premature discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g. anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see sections 8.3.9 and 8.3.10.

When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. Asthma symptoms or signs, such as wheeze, cough, chest tightness, dyspnea, breathlessness and phlegm, will be recorded as AEs only when:

- The sign or symptom is serious according to definitions, see Appendix B
- The subject prematurely discontinues IP due to the sign or symptom
- The sign or symptom is new to the subject or not consistent with the subject's preexisting asthma history (defined as within 1 year of Visit 1 in predecessor study), as judged by the Investigator.

Asthma exacerbation should be recorded as an AE or SAE only if it fulfills any of the above criteria.

8.3.8 Adverse Events of Special Interest

An adverse event of special interest (AESI) is an event of scientific and medical interest towards improving the understanding of the IP. An AESI may be serious or non-serious. For this study, AESIs include:

1. Anaphylactic reactions
2. Immune complex disease (Type III hypersensitivity reactions)
3. Malignancy
4. Helminth infections
5. Severe infections which are defined as:

- SAEs or
- Requiring treatment with systemic antiviral medications, intravenous antibiotics or medications for helminth parasitic infection or
- Requiring a premature and permanent discontinuation of study drug

6. Injection site reactions
7. Opportunistic infections
8. Guillain-Barre Syndrome
9. Adrenal crisis

8.3.9 Hy's Law

Cases where a subject shows elevation in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN needs to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.10 Disease-under study (DUS)

Asthma symptoms or signs, such as, wheeze, cough, chest tightness, dyspnoea, breathlessness and phlegm, will be recorded as AEs when:

- the sign or symptom is serious according to definitions, see Appendix B
- the subject prematurely discontinues IP due to the sign or symptom, and/or
- the sign or symptom is new to the subject or not consistent with the subject's pre-existing asthma history as judged by the Investigator

Asthma exacerbations should not be recorded as AEs, unless it fulfils any of the above criteria.

All asthma exacerbations should be recorded in the EXACATE module as per Section 8.1.1.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Subject Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative(s).

If the WBDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative(s) will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy. Any cases of pregnancy during the treatment or follow-up CCI CCI period will be recorded in the specific eCRF module.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomalies) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Subject Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

8.4.2.2 Paternal exposure

Pregnancy of the subject's partners will not be considered an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) should be followed up and documented in the pregnancy report form for conceptions occurring from the date of the first administration of IP until 16 weeks (5 half-lives) after the last administration of IP. Consent from the partner must be obtained before the pregnancy report form is completed.

8.4.3 Overdose

A dose in excess of 280 mg SC administered within a 2-week period is considered an overdose.

There is currently no specific treatment in the event of overdose of IP and possible symptoms of an overdose are not established.

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Subject Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.4.5 Management of IP-related toxicities

Appropriate drugs, such as epinephrine, H1 and H2 antihistamines, and corticosteroids, as well as medical equipment to treat acute anaphylactic reactions, must be immediately available when IP is being administered. Study site personnel must be trained to recognize and treat anaphylaxis (Lieberman et al. 2010). Details on anaphylaxis management are provided in Appendix E.

Anaphylaxis will be defined as a serious reaction that is rapid in onset and may cause death (Sampson et al. 2006). Anaphylaxis typically manifest as 1 of 3 clinical scenarios:

1. The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and at least one of the following: a) respiratory compromise; or b) reduced blood pressure or symptoms of end-organ dysfunction

2. Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms and/or persistent gastrointestinal symptoms

3. Reduced blood pressure after exposure.

Subjects will have had a pre-assessment (i.e., vital signs and lung function) prior to IP administration. For visits involving IP administration, subjects will be observed for a minimum of 1 hour after IP administration for any such reaction.

If an anaphylactic reaction occurs, a blood sample will be drawn from the subject as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge for analysis of serum tryptase. The sample will be tested at the local lab or central lab where applicable.

8.4.6 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) is an independent expert advisory group commissioned and charged with the responsibility of assessing safety aspects of adolescent involvement in the study. The DSMB will also review safety data for adults to provide context for the adolescent review. The DSMB will evaluate cumulative safety and other clinical trial data at regular intervals and making appropriate recommendations based on the available data. The DSMB will function independently of all other individuals associated with the conduct of the studies, including the study sponsor, AstraZeneca. The committee will operate in accordance with a DSMB Charter.

The DSMB will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing if and as required. 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.

8.4.7 Independent Adjudication Committee

An independent adjudication committee will be constituted to provide an external independent assessment of blinded data during the study to confirm the diagnosis of MACE events and investigator reported malignancies that occur from randomization until the end of Follow-up or CCI period.

This independent adjudication committee will also evaluate cases of ER or urgent care visits and hospitalizations that occur from randomization up to the end of the Follow-up CCI as well as all deaths from randomization until the end of Follow-up CCI to evaluate whether any such event is due to a worsening of asthma. The committee will include specialists in accordance with the Adjudication Committee Charter/Manual of Operations.

8.5 CCI

8.5.1 CCI

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8.9 CCI

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9 Statistical Considerations

9.1 Statistical hypotheses

No statistical hypotheses will be formally tested in this study.

9.2 Sample size determination

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 any 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 study, 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 of CCI (in subjects randomized to tezepelumab) and CCI (in subjects randomized to placebo), total subject years of follow-up of approximately CCI for the "Randomized Placebo" and "Randomized Tezepelumab" treatment groups (as defined in Figure 4 below) are expected in the pooled dataset. Given this exposure, the 95% CIs for an adverse event for which the observed incidence rate is CCI for "Randomized Placebo" and CCI for "Randomized 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.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Safety analysis set	All subjects who were randomized and received at least 1 dose of investigational product 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 the LTE study. Subjects will be assigned according to their randomized 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
Full analysis set	All subjects who were randomized and received at least 1 dose of investigational product 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 the LTE study. Subjects will be assigned according to their randomized treatment

In addition, to the populations defined above, a subset (safety analysis set-long term extension: "SAF-LTE", full analysis set-long term extension: "FAS-LTE") of each population will be defined which includes only subjects who enrolled and received at least 1 dose of IP in the LTE study. As these are based on subjects who complete the predecessor study, it may be subject to selection bias especially for measures of asthma control, where less severe subjects may be more likely to complete the predecessor study and enroll into the LTE study; these populations will be

used for supportive analyses only. The number of subjects discontinuing IP and patterns of discontinuations will be considered when interpreting the data.

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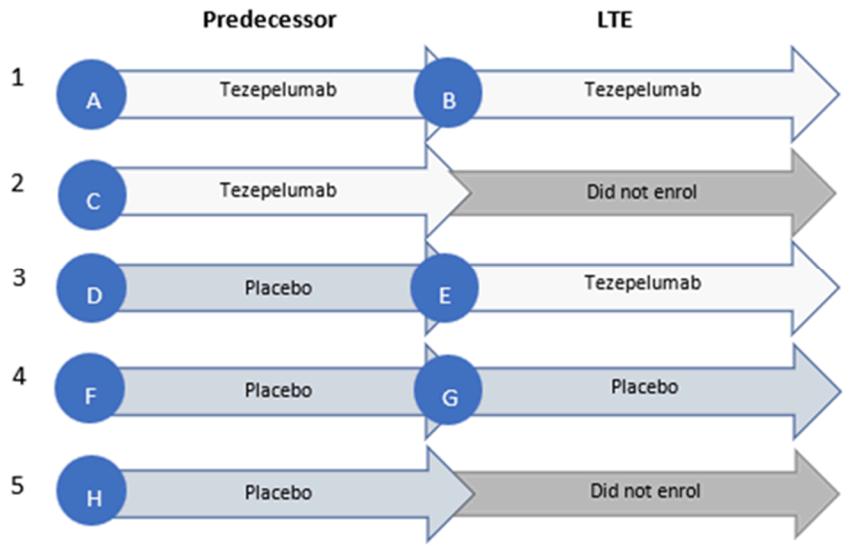
9.3.1 Treatment groups

The are 5 possible groupings across the predecessor and Long-Term Extension (LTE) studies as shown in Figure 4 below.

Figure 4 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 randomization is applicable for the efficacy analysis:

Primary:

- **Randomized Tezepelumab:** All subjects originally randomized to tezepelumab in the predecessor studies. Will include all data from first dose/randomization in the predecessor studies to end of the LTE study. (A, B and C above).
- **Randomized Placebo:** All subjects originally randomized to placebo in the predecessor studies. Will include all data from first dose/randomization in

predecessor studies up until switch to tezepelumab, and all data from first dose/randomization in the predecessor studies to end of the LTE study for subjects randomized to placebo in the predecessor studies and the LTE study. (D, F, G and H above).

Supportive:

- **Tezepelumab Predecessor+Tezepelumab LTE:** All subjects originally randomized to tezepelumab in the predecessor studies and re-randomized to tezepelumab in the LTE study. Will include all data from first dose/randomization in the predecessor study to end of the LTE study for only subjects enrolled into the LTE study. (A and B above).

- **Placebo Predecessor+Placebo LTE:** All subjects randomized to placebo in the predecessor studies, and later re-randomized 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 above).

Supportive (for exposure summaries and rare events):

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

Additional (for the assessment of durability of benefit):

- **Tezepelumab Predecessor+Tezepelumab LTE:** as defined above.

- **Placebo Predecessor+Placebo LTE:** as defined above.

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

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- CCI [redacted]

- CCI [redacted]
- CCI [redacted]

9.4 Statistical analyses

There will be two DBLs in this study. The primary DBL will be conducted after the last subject completes Week 104, and the final DBL will be conducted once all subjects have completed the last follow-up visit CCI [redacted] All analyses of the primary and secondary objectives will be performed based on the primary DBL data.

Analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will be developed and finalized before primary database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Additional analyses assessing the impact of COVID-19 will also be included in the SAP. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the clinical study report.

Unless otherwise specified, all presentations will be split by predecessor study, and data will not be pooled across the 2 predecessor studies. In addition, where relevant, presentations may be split by time period (i.e. Week 0 to Week 52/48, Week 52/48 to Week 104,). CCI [redacted]

An overall summary of subject disposition will be presented for the safety analysis set using the relevant treatment groups. The summary will present the number and percentage subjects who completed and prematurely discontinued IP and study from enrolment in the predecessor studies until end of the LTE study. CCI [redacted] The number and percentage of subjects completing the predecessor studies but not enrolling into the LTE study will also be presented.

Demographics and key subject characteristics at predecessor study entry will be summarized for the safety and SAF-LTE analysis sets by relevant treatment groups.

Relevant medical history/current medical conditions at predecessor study entry will be summarized for the safety and SAF-LTE analysis sets by relevant treatment group and preferred term of the MedDRA dictionary.

Important protocol deviations during the LTE study will be defined at subject level prior to unblinding and will be summarized for the SAF-LTE analysis set. In addition, important protocol deviations will be summarized overall (Week 0 to Week 104) and by time period (Week 0 to Week 52/48, Week 52/48 to Week 104) for the SAF and SAF-LTE analysis sets. The definitions of each category of important protocol deviation will be fully specified in the SAP, and will include (but may not be limited to): subjects who entered the LTE study without fulfilling key entry criteria; subjects who received prohibited or restricted concomitant medications during IP treatment in the LTE study, subjects who received the incorrect study treatment or study dose at any time during the LTE study.

9.4.1 Definition of baseline and change from baseline

In general, the last measurement on or prior to the date of randomization in the predecessor study will serve as the baseline measurement for efficacy endpoints. The last measurement on or prior to the first dose of predecessor study treatment will serve as the baseline measurement for safety endpoints. If there is no value prior to randomization (or the first dose of study treatment for safety endpoints), then the baseline value will not be imputed, and will be set to missing.

Further details regarding baseline definitions will be provided in the SAP.

Change from baseline is defined as the absolute difference between the measurement at the relevant post-randomization time point and the baseline value.

9.4.2 Safety analyses

All safety analyses will be performed on the safety analysis set. Key safety analyses will be repeated using the SAF-LTE analysis set.

The primary objective of the study to evaluate the long-term safety and tolerability of tezepelumab in severe asthma subjects will be assessed through on-treatment AEs (including AESIs, as defined in Section 8.3.8) and SAEs. AEs, AESIs and SAEs will be summarized using exposure adjusted incidence rates (i.e., number of subjects reporting events divided by person-time at risk) to account for the variability in follow-up. CCI [redacted] The definition of on-treatment AEs and post-treatment AEs will be defined in the SAP.

The treatment groups for addressing the primary objective will be “Randomized Tezepelumab” and “Randomized Placebo” using the safety analysis set. Supportive analysis of key safety data will be presented for the “Tezepelumab Predecessor+Tezepelumab LTE” and “Placebo Predecessor+Placebo LTE” treatment groups using the SAF-LTE analysis set. Summaries for these 4 treatment groups will be provided overall (Week 0 to Week 104) and by time period

(Week 0 to Week 52/48, Week 52/48 to Week 104). An additional summary of key safety data will be provided for the "Placebo Predecessor+Tezepelumab LTE" treatment group for the SAF-LTE analysis set by time period (Week 0 to Week 52/48, Week 52/48 to Week 104) only. CCI The "All Tezepelumab" treatment group may additionally be used to report AESIs (rare events) for the safety analysis set. In addition, AESIs may be assessed using the pooled data across the 2 studies.

Laboratory data will be summarized by presenting shift tables using normal ranges (baseline in predecessor study to most extreme post-baseline value) and by presenting summary statistics of observed and change from baseline values (means, medians, quartiles, ranges). The incidence of clinically notable laboratory abnormalities will be summarized.

Further details on additional analyses and presentation of safety data will be provided in the SAP.

9.4.3 Efficacy analyses

All efficacy analyses will be performed primarily on the Full analysis set. Key efficacy analyses may be repeated using the FAS-LTE analysis set.

The secondary objective of the study is 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. To assess this objective, the annualized asthma exacerbation rate in the tezepelumab group will be compared to that seen in the placebo group in the hypothetical scenario that other biologic treatments are not available. This approach assumes that the response after start of another biologic is different from the response for subjects who complete their randomized treatment, therefore only data collected up until the initiation of the other biologic treatment will be included in the analysis. A different approach may be considered depending on the number and pattern of drop-outs. Further details will be provided in the SAP.

The annualized asthma exacerbation rate in the tezepelumab group will be compared to that seen in the placebo group using a negative binomial model. The response variable in the model will be the number of asthma exacerbations experienced from baseline in the predecessor study until Week 104, covariates and factors included in the model will include at least treatment group, history of exacerbations and stratifying variables (as in the predecessor studies). The logarithm of the subject's corresponding time at risk for exacerbation during the predecessor and LTE studies 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. Marginal annual asthma exacerbation rates will also be presented, over the entire treatment period (i.e. across both the predecessor and LTE studies).

The treatment groups for addressing the secondary objective will be "Randomized Tezepelumab" and "Randomized Placebo" using the full analysis set. A supportive analysis will be performed using the "Tezepelumab Predecessor+Tezepelumab LTE" and "Placebo Predecessor+Placebo LTE" treatment groups based on the FAS-LTE analysis set. Asthma exacerbation rates overall (Week 0 to Week 104) and by time period (Week 0 to Week 52/48, Week 52/48 to Week 104) will be presented for the "Randomized Tezepelumab" and "Randomised Placebo" treatment groups, as well as the "Tezepelumab Predecessor+Tezepelumab LTE" and "Placebo Predecessor+Placebo LTE" treatment groups. Any further supportive analyses of the secondary objective, such as assessing different treatment groups, will be specified in the SAP.

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9.4.4.1 CCI

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9.5 Interim analyses

Interim analyses may be performed at appropriate timepoints during the study, according to regulatory and other requirements. Further details of interim analyses will be provided in the SAP.

9.5.1 Data Safety Monitoring Board (DSMB)

A data safety monitoring board will be utilized for this study, more details are provided in Section 8.4.6.

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11 Supporting Documentation and Operational Considerations

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will

review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

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During the COVID-19 pandemic.

During the COVID-19 pandemic, re-consenting of subjects must follow local/regional guidelines with regard to informed consent. It is critical that where the written COVID-19 addendum to ICF cannot be obtained, and local/regional guidance allows, the subject's verbal consent via phone or teleconference is obtained before conducting any subject related changes implemented during the COVID-19 pandemic. Confirmation of subject's re-consent needs to be documented in the source documents. Refer to Appendix H.

A 4 Data protection

Each subject will be assigned a unique identifier by the sponsor. Any subject records or data sets transferred to the sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Subject Safety. Issues identified will be

addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on *http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov* as will the summary of the *main* study results when they are available. The clinical trial and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data quality assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data can be found in the Source Data Agreement.

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the subject or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life threatening

‘Life-threatening’ means that the subject was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the subject’s death. ‘Life-threatening’ does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

B 4 Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used. Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

B 6 Intensity rating scale:

1. mild (awareness of sign or symptom, but easily tolerated)
2. moderate (discomfort sufficient to cause interference with normal activities)
3. severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related.'

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT errors)
- Wrong drug administered to participant (excluding IRT errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator keeps full traceability of collected biological samples from the subjects while in storage at the cent until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological sample(s) is an integral part of the study, then the subject is withdrawn from further study participation.

The Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories (https://www.iata.org/whatwedo/cargo/dgr/Documents/infectious-substance-classification-DGR56-en.pdf). For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient
- temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/infectious-substance-classification-DGR56-en.pdf.)
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**

- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's law (PHL) cases and cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 7.1 of the Clinical Study Protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated TBL from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the investigational product.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 ×ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

D 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Central laboratories being used:

When a subject meet any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (and also to the AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the subject meets PHL criteria (see Appendix D 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the subject meets PHL criteria (see Appendix D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

D 4 Follow-up

D 4.1 Potential Hy's Law criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

D 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

Determine whether PHL criteria were met at any study visit prior to starting Study treatment (See Section 8.4)

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting
- For subject that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change in the subject's condition

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.
- Complete the three Liver CRF Modules as information becomes available

D 5 Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date of PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below. Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, update the previously submitted Potential Hy's law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
    - The 'Medically Important' serious criterion should be used if no other serious criteria apply
    - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of 'Potential Hy's Law, (report term now 'Hy's law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Laboratory tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgement. If required, additional assistance on which tests could be used to evaluate other potential causes of liver dysfunction consult with the Hepatic Safety Knowledge Group. Any test results need to be recorded in the eCRF. **Hy's Law lab kit for central laboratories.**

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgG, anti-HCV HCV RNA* IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)**
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

* HCV RNA is only tested when IgG anti-HCV is positive or inconclusive

** Carbohydrate deficient transferrin (CD-transferrin) is not available in China. Study teams should amend this list accordingly

References

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'

Appendix E Anaphylaxis: signs and symptoms, management

E 1 Introduction

As with any antibody, allergic reactions to dose administration are possible. The World Health Organization has categorized anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic [IgE-mediated and non-IgE-mediated (eg, IgG and immune complex mediated) and nonimmunologic (Johansson et al, 2004). The clinical criteria for defining anaphylaxis for this study are listed in section E 2. A guide to the signs and symptoms and management of acute anaphylaxis is provided in section E 3. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc., and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognize and treat anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs, a blood sample will be drawn from the subject as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge for analysis of serum tryptase.

E 2 Clinical Criteria for Defining Anaphylaxis and Immune Complex Disease

Anaphylaxis

In adults, anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING

   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

   (b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):

   (a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).

   (b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

(c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).

(d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

3. Reduced BP after exposure to known allergen for that subject (minutes to several hours): Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that subject's baseline.

Immune Complex Disease

Immune complex disease or Hypersensitivity Type III is evoked by the deposition of antigen-antibody or antigen-antibody-complement complexes on cell surfaces, with subsequent involvement of breakdown products of complement, platelets, and polymorphonuclear leukocytes, and development of vasculitis; serum sickness and nephritis is common.

E 3 Signs and Symptoms and Management of Acute Anaphylaxis

Anaphylaxis is an acute and potentially lethal multi-system allergic reaction in which some or all of the following signs and symptoms occur:

- Diffuse erythema
- Pruritus
- Urticaria and/or angioedema
- Bronchospasm
- Laryngeal edema
- Hypotension
- Cardiac arrhythmias
- Feeling of impending doom
- Unconsciousness
- Shock

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles

- Rhinorrhea
- Change in voice
- Metallic taste
- Nausea, vomiting, diarrhea, abdominal cramps and bloating
- Lightheadedness
- Headache
- Uterine cramps
- Generalized warmth

E 4 Management of Acute Anaphylaxis

Immediate intervention

1. Assessment of airway, breathing, circulation, and adequacy of mentation
2. Administer epinephrine intramuscularly every 5-15 minutes, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms such as respiratory distress, hypotension, shock and unconsciousness.

Possibly appropriate, subsequent measures depending on response to epinephrine

(e) Place subject in recumbent position and elevate lower extremities.

(f) Establish and maintain airway.

(g) Administer oxygen.

(h) Establish venous access.

(i) Normal saline IV for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate

(j) Consider epinephrine infusion.

(k) Consider H1 and H2 antihistamines.

(l) Consider nebulized β2 agonist [eg, albuterol (salbutamol)] for bronchospasm resistant to epinephrine.

(m) Consider systemic corticosteroids.

(n) Consider vasopressor (e.g. dopamine).

(o) Consider glucagon for subject taking β-blocker.

(p) Consider atropine for symptomatic bradycardia.

(q) Consider transportation to an emergency department or an intensive care facility.

(r) For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary.

Adapted from: Kemp SF, Lockey RF, Simons FE; World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy. 2008; 63(8):1061-70.

Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC. A revised nomenclature for allergy for global use: report of the nomenclature review committee of world allergy organization. J Allergy Clin Immunol. 2004;113:832–6.

Appendix F Guidance for Changes to Background Asthma Medication adapted from GINA 2018

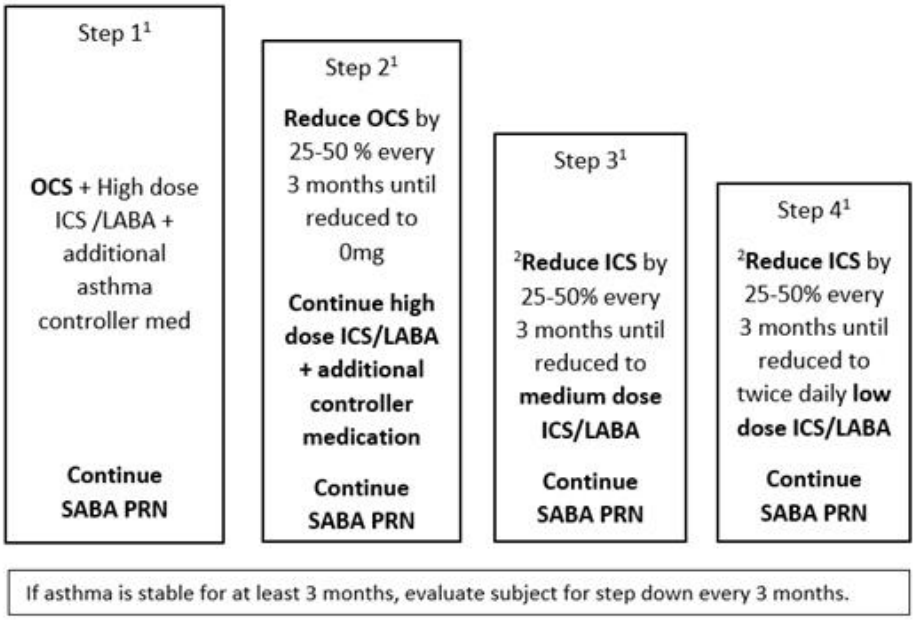
F 1 Guidance to Step Down of Background Medication

- Consider stepping down when asthma symptoms have been well controlled and lung function has been stable for 3 or more months, starting from Visit 1. If the subject has risk factors for exacerbations or fixed airflow limitation, do not step down without close supervision.

- Approach each step as a therapeutic trial. Engage the subject in the process; document their asthma status (symptom control, lung function and risk factors); provide clearinstructions; and ensure the subject has sufficient medication to resume their previous dose if necessary; monitor symptoms; and schedule a follow-up visit.

- Stepping down ICS doses by 25-50% at 3-month intervals is feasible and safe for most subjects.

Figure 5 Step Down of Background Medication



[1] The additional asthma controller medications or their dose can be increased or decreased as per PI's discretion.

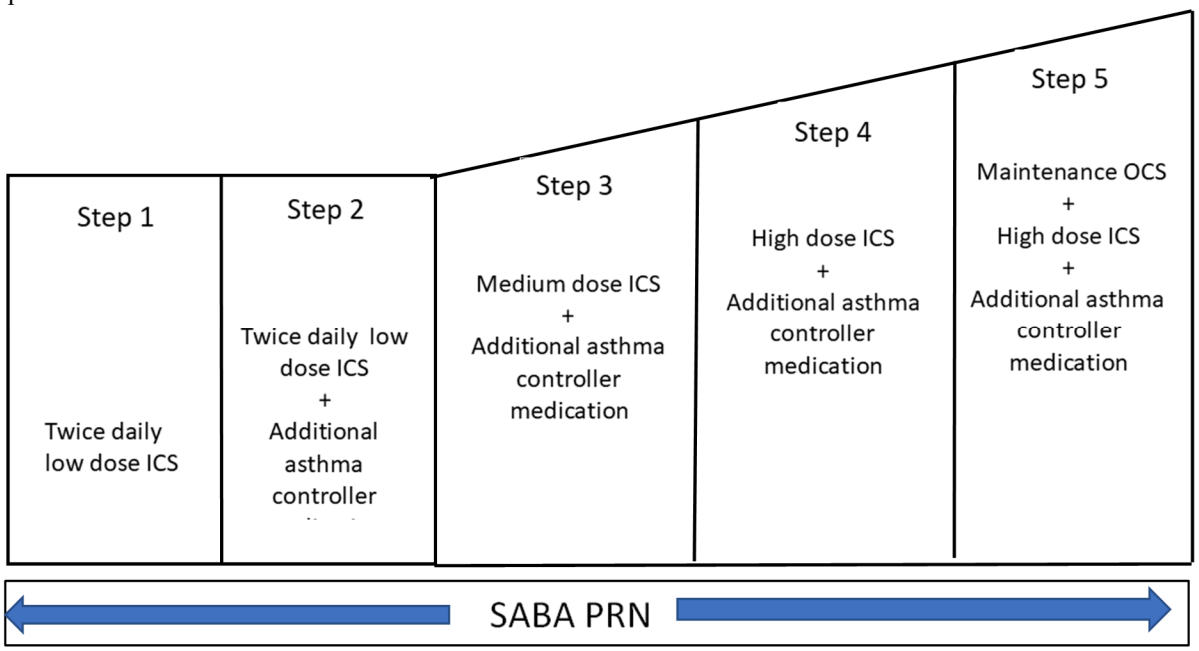
[2] If the subject is not on a combination ICS/LABA and is on a separate ICS and another additional asthma controller medication, reduce only the dose of ICS and continue the same dose of additional asthma controller medications.

F 2 Guidance to Step Up of Background Medication

- If the subject's symptoms are worsening after step down of asthma background medication as per Figure 5, they can be up titrated as per Figure 6 below, at the Investigator's discretion.

Figure 6 Step Up of Asthma Background Medication

*If a subject experiences an asthma exacerbation, this should be treated appropriately as per investigator discretion.


Step 1
Twice daily low dose ICS
Step 2
Twice daily low dose ICS
+
Additional asthma controller
Step 3
Medium dose ICS
+
Additional asthma controller medication
Step 4
High dose ICS
+
Additional asthma controller medication
Step 5
Maintenance OCS
+
High dose ICS
+
Additional asthma controller medication
SABA PRN

Appendix G Abbreviations

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AAER	Annualized Asthma Exacerbation Rate
CCI	
ADA	Anti-Drug Antibodies
AE	Adverse Event
AERR	Asthma Exacerbation Reduction Rate
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ATS	American Thoracic Society
ASD	Asthma Symptom Diary
AST	Aspartate Aminotransferase
BD	Bronchodilator
β-HCG	Beta-Human Chorionic Gonadotropin
BUN	Blood Urea Nitrogen
CO_2	Carbon Dioxide
CompEx	Composite Endpoint for Exacerbations
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DSMB	Data and Safety Monitoring Board
DUS	Disease under Study
EAR	Early Asthmatic Response

Abbreviation or special term	Explanation
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ER	Emergency Room
EOT	End of Treatment
ePRO	Electronic Subject Reported Outcome device
EU	European Union
EUA	Emergency Use Authorization
FEIA	Fluorescent Enzyme Immunoassay
CCI	
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FSH	Follicle-Stimulating Hormone
FU	Follow-up
CCI	
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
HCP	Health Care Provider
IATA	International Air Transport Association
ICH	International Conference on Harmonization
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
ICF	Informed Consent Form
ICS	Inhaled Corticosteroids
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
IL-13	Interleukin-13

Abbreviation or special term	Explanation
IP	Investigational Product
IPD	Investigational Product Discontinuation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Study File
ITT	Intent-to-Treat
IUO	Investigational Use Only
LABA	Long-Acting β2-Agonist
LAMA	Long-Acting Muscarinic Antagonists
LAR	Late Asthmatic Response
LIMS	Laboratory Information Management System
LRTI	Low Respiratory Tract Infection
LTE	Long Term Extension
LTRA	Leukotriene Receptor Antagonists
LSLV	Last Subject Last Visit
MAb	Monoclonal Antibody
MACE	Major Adverse Cardiac Events
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MCID	Minimum Clinically Important Difference
nAB	Neutralizing Antibodies
OCS	Oral Corticosteroids
OAE	Other Significant Adverse Event
PD	Pharmacodynamic
PGx	Genetic research
PGI-S	Subject Global Impression of Severity
PI	Principal Investigator
CCI	
PNV	Predicted Normal Value
CCI	
PT	Preferred Term

Abbreviation or special term	Explanation
Q4W	Every 4 Weeks
SABA	Short-Acting β2-Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
CCI	
SOA	Schedule of Assessment
SOC	System Organ Class
SDV	Source Data Verification
Th2	T Helper 2 Cells
TLC	Total Lung Capacity
TSLP	Thymic Stromal Lymphopoietin
TSLPR	Thymic Stromal Derived Lymphopoietin Receptor
ULN	Upper Limit of Normal
UNS	Unscheduled
WBDC	Web Based Data Capture
WOCBP	Women of Childbearing Potential

Appendix H Changes to the protocol related to the COVID-19 Pandemic

Please Note: Changes below should only be implemented during the COVID-19 pandemic and if allowable by local/regional guidelines.

H 1 Home Visits to Replace On-Site Visits (where applicable)

Due to local travel restrictions and/or site restrictions, subjects may not wish to or may not be able to go to the study site for study visits and related procedures. If an on-site visit is not possible, it is recommended to have a home visit with home administration of IP by a qualified HCP, provided this is acceptable within local regulation/guidance. This is to ensure safety of the trial subjects and minimum disruption to IP administration that may occur during the COVID-19 pandemic.

NOTE: The first 2 IP administrations in DESTINATION must be done on site.

Where possible study assessments should be conducted according to the SoA.

At minimum, during home visit the qualified HCP is expected to:

- Collect adverse events
- Review concomitant medications
- Collection information on asthma exacerbation and healthcare resources utilization
- Perform a physical examination
- Collect vital signs
- Conduct urine pregnancy test (dipstick), prior to IP administration, if applicable
- If possible, collect blood and urine sample according to the SoA
- Administer IP
- Observe the subject for one hour after IP administration for the signs or symptoms of any acute drug reactions
- Document the visit

Laboratory assessments during home visit

If safety blood samples are being collected, they may be obtained post IP administration and during the 1-hour observation period to allow additional time for processing of the safety samples at the site according to the laboratory manual.

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H 2 Visits at an Alternate Location (where applicable)

Study visits including administration of IP and study assessments according to the SoA can take place at an alternative location away from infection risk zones, or closer to subjects' homes, provided this is acceptable within local regulation/guidance.

H 3 Phone Call Visit to Replace On-Site Visit (where applicable)

During the COVID-19 pandemic, on-site visits may be replaced by a remote visit (phone call and/or video conference) if allowed by local/regional guidelines. Having a phone call and/or a video conference with the subject will allow conduct of study procedures including reporting of adverse events, concomitant medication, information on asthma control/exacerbation and healthcare resource utilization.

H 4 Subject Rollover Process

For NAVIGATOR subjects pending roll over

If on-site Randomization and IP administration in the DESTINATION study is not possible by the end of the NAVIGATOR Safety Follow-Up (Visit 19), a subject will not roll-over to DESTINATION.

Subjects aimed to roll over to the DESTINATION study will continue participation in the NAVIGATOR study Safety Follow-Up (Visit 18 and Visit 19, 12 weeks) until the on-site DESTINATION randomization and IP administration can be conducted.

- If the subject is able to attend an on-site Visit 18 of the NAVIGATOR study, they can be randomized into the DESTINATION study at this visit. During this visit the informed consent form, eligibility check, unscheduled safety labs, serum pregnancy test (if applicable) and randomization must be completed along with assessments as per Visit 3 in

DESTINATION Table 1. If Visit 4 cannot be conducted on-site this can be conducted as a phone visit without IP administration. Please note the Home visit with IP administration alternative cannot be used until the first 2 IP doses are administered during an on-site visit.

- If the subject is able to attend an on-site Visit 19 of the NAVIGATOR study, they can be randomized into the DESTINATION study at this visit. During this visit the informed consent form, eligibility check, serum pregnancy test (if applicable) and randomization must be completed along with assessments as per Visit 5 in DESTINATION Table 1. Visit 3 and Visit 4 will be skipped. If Visit 6 cannot be conducted on-site this can be conducted as phone visit without IP administration. Please note the Home visit with IP administration alternative cannot be used until the first 2 IP doses are administered during an on-site visit.

For SOURCE subjects pending roll over

If on-site Randomization and IP administration in the DESTINATION study is not possible by the end of the SOURCE Safety Follow-Up (Visit 20), a subject will not roll-over to the DESTINATION study.

Subjects aimed to roll over to the DESTINATION study will continue participation in the SOURCE study Safety Follow-Up (Visit 19 and Visit 20, 12 weeks) until the on-site DESTINATION randomization and IP administration can be conducted.

- If the subject is able to attend an on-site Visit 19 of the SOURCE study, they can be randomized into the DESTINATION study at this visit. During this visit the informed consent form, eligibility check, unscheduled safety labs, serum pregnancy test (if applicable) and randomization must be completed along with assessments as per Visit 2 in DESTINATION Table 1. If Visit 3 cannot be conducted on-site this can be conducted as a phone visit without IP administration. Please note the Home visit with IP administration alternative cannot be used until the first 2 IP doses are administered during an on-site visit.
- If the subject is able to attend an on-site Visit 20 of the SOURCE study, they can be randomized into the DESTINATION study at this visit. During this visit the informed consent form, eligibility check, unscheduled safety labs, serum pregnancy test (if applicable) and randomization must be completed along with assessments as per Visit 4 in DESTINATION Table 1. Visit 2 and Visit 3 will be skipped. If Visit 5 cannot be conducted on-site this can be conducted as a phone visit without IP administration. Please note the Home visit with IP administration alternative cannot be used until the first 2 IP doses are administered during an on-site visit.

H 5 CCI [redacted]

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H 6 Reconsenting of Subjects During The COVID-19 Pandemic

If a subject is unable to travel to the site due to the COVID-19 pandemic, it is necessary to obtain re-consent remotely and/or verbally for the implementation of the new urgent changes in the study during the COVID-19 pandemic. This will minimize the risk to the subject of COVID-19 exposure with clinic visits. Applicable local guidelines and regulations on re-consenting process should be followed.

SIGNATURE PAGE

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Document Name: d5180c00018-csp-v6		
Document Title:	D5180C00018 Clinical Study Protocol version 6	
Document ID:	Doc ID-003834571	
Version Label:	8.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
15-Apr-2021 18:15 UTC	PPD	Author Approval
15-Apr-2021 12:28 UTC	PPD	Content Approval
15-Apr-2021 07:57 UTC	PPD	Content Approval
14-Apr-2021 16:48 UTC	PPD	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.