Clinical Study Protocol	
Drug Substance	Tezepelumab
Study Code	D5180C00019
Version	3.0
Date	09 July 2020

A 52-Week, Open-Label, Multicentre Study to Evaluate the Safety of Tezepelumab in Japanese Adults and Adolescents with Inadequately Controlled Severe Asthma (NOZOMI)

Sponsor:

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Regulatory Agency Identifying Number(s): Not applicable

VERSION HISTORY

Version 3.0, 09 July 2020

Changes to the protocol are summarized below.

Section 1.1, SoA, Table 2 –Added footnote a "Spirometry should be tested only if allowed by local guidelines during the COVID-19 pandemic." due to COVID-19 pandemic. Under Table 2 added guidance on how to proceed with respect to Schedule of Activities during the COVID-19 pandemic to ensure the safety of the study subjects, to maintain compliance with GCP and to minimize risks to data integrity.

Section 1.2, Synopsis – Treatments and treatment duration - Added a note to refer to Appendix J for further guidance if subjects are unable to come to the site during the COVID-19 pandemic.

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 may be performed at the subject's home by a qualified HCP. This change is to reduce the risk to subjects of COVID-19 exposure with clinic visits.

Section 6.5, Table 7, Prohibited medications – For any immunomodulators or immunosuppressives, revised the text "(except for OCS used in the treatment of asthma/asthma exacerbations)" to "(except for OCS used in the maintenance treatment of asthma, asthma exacerbations in screening, and protocol defined asthma exacerbations on or after Visit 2)". This is to clarify the wording "except for OCS used in the treatment of asthma" is applicable for subjects on OCS maintenance treatment for asthma and "asthma exacerbation" is applicable if it was a protocol defined exacerbation occurring on or after Visit 2.

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 64".

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

Section 8.1.3.1, Asthma Control Questionnaire (ACQ-6) – Revised ACQ-6 score from "≤1.5" to "<1.5" to indicate partly controlled asthma and from ">1.5" to "≥1.5" to indicate uncontrolled asthma. This change aligns with the thresholds for partly controlled/uncontrolled asthma established by Juniper et al 2006.

Section 9.4.5, Safety analyses – Replaced "post-treatment" with "on-study", to clarify the periods of interest.

Section 9.4.6, Other analyses – Added "additional analyses assessing the impact of COVID-19 may be included in the SAP".

Appendix A 3 – 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 J" to accommodate the changes made in the protocol.

Appendix I, Table of Abbreviations – Added 1) COVID-19 and 2) HCP

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

Version 2.0, 12 April 2019

Changes to the protocol are summarized below.

Study Title, added "(NOZOMI)" at the end of study title. Study name was created.

CCI [redacted]

Section 1.2, Synopsis – Coordinating investigator – added *"*see Clinical Study Protocol Addendum". Coordinating investigator was decided.

Section 1.2, Synopsis – Study Period – changed *"*Estimated date of last patient completed: Q2 2021". To correct a typo error.

Section 1.2, Synopsis – Number of Subjects – Replaced the underlined words "The sample size of this study will be determined after the last Japanese subject randomization and confirmation of the number of randomized Japanese subjects in NAVIGATOR study (D5180C00007) to ensure that there are 100 total Japanese subjects who receive tezepelumab for 52 weeks." with "The actual number of Japanese subjects registered into the study will be determined after the confirmation of the number of randomized Japanese subjects in NAVIGATOR study (D5180C00007) to ensure that there are 100 total Japanese subjects who receive tezepelumab for 52 weeks.". To clarify the number of subjects.

Section 1.2, Synopsis – Statistical methods – added underlined words "An interim analysis will be performed when all subjects complete Visit 8 (24-week of treatment period) for marketing application submission purposes." To clarify purposes of interim analysis. *Section 5.1,* Inclusion Criteria #13 – Removed all. To align with the revised IB. *Section 5.3.5,* Contraception – Removed the wording "Nonsterilized males who are sexually active with a female partner of childbearing potential must use a male condom from the date of the first administration of IP through 16 weeks after receipt of the final dose of IP. Male subjects must not donate or bank sperm during this same time period.". To align with the revised IB. CCI [redacted] [redacted] *Section 8.4.2.2,* Paternal exposure – Removed wording "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 the revised IB. *Section 8.4.5,* Management of IP-related toxicities – Replaced "a local laboratory where applicable" with "central laboratory". Tryptase will be evaluate at central laboratory. CCI [redacted]
Version 1.0, 5 February 2019
Initial creation

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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1.1 Schedule of Activities (SoA)

Table 1 Study of Assessments - Screening

	Screening	Details in CSP section or Appendix
Visit	**1**	
Week	**-2 - 0**	
Visit window	**NA**	
Procedures		
Informed consent	X	A 3
Inclusion /exclusion criteria	X	5.1, 5.2
Demography	X	5.1
Patient Reported Outcome Assessments at Visit		
ACQ-6	X	8.1.3.1
Routine Safety Measurements		
Complete physical examination	X	8.2.3
Vital signs	X	8.2.4
Weight, Height	X	8.2.2
12-lead ECG	X	8.2.5
Adverse events (AEs/SAEs)	X	8.3
Medical and asthma history	X	5.1
Assessment of historical asthma exacerbations in the past 12 months	X	8.1.1
Concomitant medication	X	6.5
Laboratory Assessments		
Serum chemistry	X	8.2.1
Haematology	X	8.2.1
Urinalysis	X	8.2.1
Pregnancy or FSH test[a]	X	8.2.1.1
Serology (Hepatitis B, C; HIV-1; HIV-2)	X	8.2.6.1

[a] For WOCBP and adolescent females, serum β-hCG will be confirmed. FSH test done only in women < 50 years who have been amenorrheic for > 12 months to confirm postmenopausal status.

ACQ-6: Asthma Control Questionnaire-6, AE: Adverse Event, BD: Bronchodilator, β-hCG: β-human chorionic gonadotropin, CSP: Clinical Study Protocol, ECG: Electrocardiogram, CCI [redacted], FSH: Follicle Stimulating Hormone, CCI [redacted], HIV: Human Immunodeficiency Virus, SAE: Serious Adverse Event, WOCBP: Women of Childbearing Potential.

Table 2 Study of Assessments- Registration, treatment period, follow-up

	Registration	Treatment												EOT	IPD	FU 1	FU 2	UNS[i]	Details in CSP section or Appendix
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**					
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		**58**	**64**		
Day (visit window)	**0**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**		**±7**	**±7**		
Procedures																			
Inclusion /exclusion criteria	X																		5.1, 5.2
Lung Function Assessments																			
Spirometry [redacted]	X			X			X			X				X	X	X	X	X	8.1.2
Patient Reported Outcome Assessments at Visit																			
ACQ-6[b]	X			X			X			X				X	X	X	X		8.1.3.1
Routine Safety Measurements																			
Complete physical examination	X													X	X			X	8.2.3
Brief physical examination		X	X	X	X	X	X	X	X	X	X	X	X			X	X		8.2.3
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.4
Height[c]														X	X				8.2.2
Weight							X							X	X				8.2.2
12-lead ECG[d]	X						X							X	X		X		8.2.5
Adverse events (AEs/SAEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
Assessment of asthma exacerbation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Laboratory Assessments[e]																			
Serum Chemistry	X			X			X			X				X	X		X	X	8.2.1

Table 2 Study of Assessments- Registration, treatment period, follow-up

	Registration	Treatment												EOT	IPD	FU 1	FU 2	UNS[i]	Details in CSP section or Appendix
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**					
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		**58**	**64**		
Day (visit window)	**0**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**		**±7**	**±7**		
Haematology	X	X		X			X			X				X	X		X	X	8.2.1
Urinalysis	X			X			X			X				X	X		X	X	8.2.1
Urine pregnancy test, dipstick[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		8.2.1.1
Serum for immunogenicity[g]	X						X							X	X		X		8.5
CCI [redacted]	[redacted]						[redacted]							[redacted]	[redacted]		[redacted]		[redacted]
Blood sample for Gx (Optional)	X																		8.7
Study Treatment Administration																			
Registration	X																		6.1
Administration of IP[h]	X	X	X	X	X	X	X	X	X	X	X	X	X						6.2

[a] Spirometry should be tested only if allowed by local guidelines during the COVID pandemic.

[b] ACQ-6 should be completed at the beginning of site visits.

[c] Only to be measured for the adolescent subject.

[d] ECG must be collected prior to any blood draws, spirometry, BD administration and IP administration.

[e] All blood sampling should be done prior to IP administration.

[f] For WOCBP and adolescent females, urine pregnancy test (dipstick) will only be performed at each treatment visit, prior to IP administration. Positive urine test result must be confirmed with serum β-hCG.

CCI [redacted]

[h] IP should be administered after all other assessments have been completed to a scheduled visit.

[i] 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.

CCI, AE: Adverse Event, BD: Bronchodilator, β-hCG: β-human chorionic gonadotropin, CSP: Clinical Study Protocol, ECG: Electrocardiogram, EOT: End of Treatment, CCI, FSH: Follicle Stimulating Hormone, FU: Follow-up, CCI Gx: Genetic research, HIV: Human Immunodeficiency Virus, IP: Investigational Product, IPD: Investigational Product Discontinuation, CCI SAE: Serious Adverse Event, UNS: Unscheduled, WOCBP: Women of Childbearing Potential.

CHANGES REQUIRED DURING THE COVID-19 PANDEMIC

Please Note: Changes below should only be implemented during the COVID-19 pandemic.

During the COVID-19 pandemic, changes are being implemented in order to ensure the safety of study subjects, to maintain compliance with good clinical practices, and to minimize risks to data 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) 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.

- Remote visits (phone call and/or video conference) to replace on-site visits, if subjects cannot attend the visits at the study site, at an alternate site or have home visits. The rationale for this change is to ensure that assessments and collection of information continue for visits that cannot be done at the site, at an alternate site or at the subject's home. This will reduce the risk of subject exposure to COVID-19

- Re-consent will be obtained remotely and/or verbally if allowed by local and regional guidelines. 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.

For further details, please refer to Appendix J.

1.2 Synopsis

Principal investigator

The names and addresses of principal investigators are shown in Clinical Study Protocol Addendum.

Coordinating investigator, see Clinical Study Protocol Addendum.

For contact details of AstraZeneca personnel, see Clinical Study Protocol Addendum.

Protocol Title:

A 52-Week, Open-Label, Multicentre Study to Evaluate the Safety of Tezepelumab in Japanese Adults and Adolescents with Inadequately Controlled Severe Asthma

Short Title:

Tezepelumab Japan long-term safety study

Rationale:

This is a Japan long-term safety study to demonstrate the safety of tezepelumab in Japanese 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 (OCS).

The results from the previous Ph2b study (CD-RI-MEDI9929-1146) have been used to select the target population for Ph3 studies. It is expected that adolescent patients (12-17 years of age) in the target population will respond similarly to adults and are therefore included as part of the study population. Pharmacokinetic evaluations in adolescents with asthma confirm the same dose can be given to adolescents as to adults. Japanese patients with severe asthma are participating in the ongoing pivotal Ph3 study (NAVIGATOR study [D5180C00007]) to assess the efficacy and safety of tezepelumab in Japanese asthma subjects. The purpose of this open label long term safety study is to provide additional long-term safety data of tezepelumab to meet the regulatory requirement of one-year exposure to tezepelumab of 100 Japanese patients at the time of the Japan New Drug Application. The study will evaluate the safety of tezepelumab with regards to adverse events, as well as other safety parameters.

Objectives and Endpoints

Primary objective:	Endpoint/variable:
To evaluate the safety and tolerability of tezepelumab	Adverse events/Serious adverse events Vital signs Clinical chemistry/haematology/urinalysis parameters Electrocardiograms
Exploratory objectives:	**Endpoint/variable:**
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Overall design:

This is an open-label, single arm study designed to evaluate the safety of a 210 mg dose of tezepelumab administered subcutaneously every 4 weeks in Japanese adult and adolescent subjects with inadequately controlled severe asthma. Patients will have a history of at least one exacerbation in the past year and background asthma therapy of medium- or high dose ICS plus at least one additional asthma controller medication (long-acting β2 agonist, [LABA], leukotriene receptor antagonists [LTRA], long-acting muscarinic antagonists [LAMA], cromones, and theophylline) with or without maintenance OCS from screening and throughout the study including the follow-up period.

The study will consist of a screening period of 2 weeks, a treatment period of 52 weeks and a post-treatment follow-up period of 12 weeks.

After the informed consent is obtained, subjects will proceed to a screening period of 2 weeks maximum to allow adequate time for all of the eligibility criteria to be evaluated. Subjects who meet all the eligibility criteria will be registered to a treatment period. Subjects will be maintained on their currently prescribed ICS and at least one additional asthma controller medication at their dose they entered screening, without change, from screening throughout the treatment period.

Study Period:

Estimated date of first patient enrolled: Q2 2019

Estimated date of last patient completed: Q2 2021

Number of Subjects:

Approximately 66 Japanese subjects will be registered into the study and receive tezepelumab in order to reach 59 completed. The actual number of Japanese subjects registered into the study will be determined after the confirmation of the number of randomized Japanese subjects in NAVIGATOR study (D5180C00007) to ensure that there are 100 total Japanese subjects who receive tezepelumab for 52 weeks.

Treatments and treatment duration:

All subjects will receive tezepelumab 210 mg every 4 weeks via subcutaneous injection at the study site, over a 52-week treatment period.

Please note: If subjects are unable to come to the site during the COVID-19 pandemic, please refer to Appendix J for further guidance.

Statistical methods

No formal sample size calculation was conducted for this study. Approximately 66 Japanese patients are required to enter treatment period to obtain 59 patients who complete the planned 52-weeks treatment period assuming a drop-out rate of 10% during the 52-weeks treatment period.

All variables will be summarised descriptively. No hypothesis testing will be conducted for this study.

An interim analysis will be performed when all subjects complete Visit 8 (24-week of treatment period) for marketing application submission purposes.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design

<table>
<tr><td>Visit 1</td><td>Visit 2</td><td>Visit 3 to 14</td><td>Visit 15</td><td></td></tr>
<tr><td>Week
-2 to 0</td><td>Week
0</td><td>Week
4 to 48</td><td>Week
52</td><td>Week
58, 64</td></tr>
<tr><td>Screening</td><td colspan="2">Registration (Visit 2) & Treatment Period (Visit 2 to 14)</td><td>End of Treatment</td><td>Follow-up</td></tr>
<tr><td></td><td colspan="2">Tezepelumab 210 mg, SC every 4 weeks</td><td></td><td></td></tr>
</table>

SC: Subcutaneous

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 remodelling 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). According to a patient survey conducted by Ministry of Health, Labor and Welfare of Japan in 2014, the number of patients in Japan suffering from asthma was 1.31 million (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare 2014).

Approximately 5% to 10% of asthma patients have severe asthma, which may be inadequately controlled by ICS and LABA combinations together with additional controller therapies (Brightling et al 2008). These patients 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. Patients 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

This is a Japan long-term safety study to demonstrate the safety of tezepelumab in Japanese 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 ICS plus at least one additional asthma controller medication with or without OCS.

The results from the previous Ph2b study (CD-RI-MEDI9929-1146) have been used to select the target population for Ph3 studies. It is expected that adolescent patients (12-17 years of age) in the target population will respond similarly to adults and are therefore included as part of the study population. Pharmacokinetic evaluations in adolescents with asthma confirm the same dose can be given to adolescents as to adults. Japanese patients with severe asthma are participating in the ongoing pivotal Ph3 study (NAVIGATOR study [D5180C00007]) to assess the efficacy and safety of tezepelumab in Japanese asthma subjects. The purpose of this open label long term safety study is to provide additional long-term safety data of tezepelumab to meet the regulatory requirement of one-year exposure to tezepelumab of 100 Japanese patients at the time of the Japan New Drug Application. The study will evaluate the safety of tezepelumab with regards to adverse events, as well as other safety parameters.

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 2018, Xolair JP PI 2017). Three additional biologics, mepolizumab, reslizumab and benralizumab, have recently been approved for severe asthma with an eosinophilic phenotype (XOLAIR US PI 2018, Xolair JP PI 2017, CINQAIR US PI 2016, Fasenra US PI 2017, Fasenra JP PI 2018). Biologics targeting interleukin (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, Fasenra US PI 2017, Fasenra JP PI 2018). 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 cell type 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 G2λ (IgG2λ) 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 late asthmatic response (LAR) and early asthmatic response (EAR) to allergen challenge, as measured by the area under the curve (AUC) for the percent fall in FEV_1 and the maximum percent fall in FEV_1. Tezepelumab also attenuated the increase in fractional exhaled nitric oxide (FeNO) value on the post-allergen day compared with the pre-allergen day. Multiple doses of 700 mg intravenous (IV) tezepelumab demonstrated an acceptable safety profile in subjects with mild atopic asthma. No subjects developed ADA after receiving tezepelumab. Based upon these data, MedImmune/AZ have conducted a randomized, double-blind, placebo-controlled, dose range finding study in asthmatics who were inadequately controlled with medium or high dose ICS/ LABA with or without other controller medications.

Study CD-RI-MEDI9929-1146 was a Phase 2b multicenter, multinational, dose-ranging, double-blind, randomized, parallel-arm, placebo-controlled study to evaluate the effect of 3 dose levels of tezepelumab on the asthma exacerbation rate (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 subcutaneous (SC) tezepelumab (280 mg every 2 weeks [Q2W], 210 mg every 4 weeks [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 Good Clinical Practice (GCP) non-compliance, all data relating to 34 patients from this site were excluded and the Clinical Study Report (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 Intent-to-Treat (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 treatment-emergent adverse events (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 may include a clinically meaningful reduction in asthma exacerbations, and improvements in lung function and asthma control metrics.

Tezepelumab has been well tolerated with no safety concerns 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 defence against certain infections, there is no clear preclinical or clinical evidence supporting such a role, and no safety concerns 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.

3 OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Primary objective:	Endpoint/variable:
To evaluate the safety and tolerability of tezepelumab	Adverse events/Serious adverse events Vital signs Clinical chemistry/haematology/urinalysis parameters Electrocardiograms
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4 STUDY DESIGN

4.1 Overall design

For an overview of the study design see Figure 1, 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 efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

This is an open-label, single arm study designed to evaluate the safety of a 210 mg dose of tezepelumab administered subcutaneously every 4 weeks in Japanese adult and adolescent subjects with inadequately controlled severe asthma. Patients will have a history of at least one exacerbation in the past year and background asthma therapy of medium- or high dose ICS plus at least one additional asthma controller medication (LABA, LTRA, LAMA, cromones, and theophylline) with or without maintenance OCS from screening and throughout the study including the follow-up period.

The study will consist of a screening period of 2 weeks, a treatment period of 52 weeks and a post-treatment follow-up period of 12 weeks.

The investigator will obtain signed informed consent from the potential subject, or their legal representative, before any study specific procedures are performed (For subjects aged <20

years, in addition to the subject providing signed informed consent or assent, the subject's legally acceptable representative must also provide their informed consent.). And then the investigator will assign the potential subject a unique enrolment number via the Interactive Voice Response System (IVRS) / Interactive Web Response System (IWRS). Subjects will proceed to a screening period of 2 weeks maximum to allow adequate time for all of the eligibility criteria to be evaluated by the investigator. Subjects who meet all the eligibility criteria will be registered to a treatment period. Subjects will be maintained on their currently prescribed ICS and at least one additional asthma controller medication at their dose they entered screening, without change, from screening throughout the treatment period. During the treatment period, Investigational product (IP) will be administered subcutaneously every 4 weeks starting at Day 0 with the last dose at Week 48. IP will not be administered on Week 52. Subjects who discontinue IP during the study will be encouraged to undergo appropriate study visits/procedures for the full 52-week 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). Subjects who complete the 52-week study visit will complete a 12-week post treatment follow-up period for the assessment of safety and anti-drug antibodies.

4.2 Scientific rationale for study design

Pharmacokinetic evaluations in adolescents with asthma confirm the same dose can be given to adolescents as to adults. Japanese patients with severe asthma are participating in the ongoing pivotal Ph3 study (NAVIGATOR study [D5180C00007]) to assess the efficacy and safety of tezepelumab in Japanese asthma subjects. The purpose of this open label long term safety study is to provide additional long-term safety data of tezepelumab to meet the regulatory requirement of one-year exposure to tezepelumab of 100 Japanese patients at the time of the Japan New Drug Application. The study will evaluate the safety of tezepelumab with regards to adverse events, as well as other safety parameters.

4.3 Justification for dose

A 210 mg Q4W dosing regimen was selected for the Phase 3 studies based on efficacy data and an exposure-response analysis from the Phase 2b Study CD-RI-MEDI9929-1146 using population analysis methodology. The population PK model of tezepelumab was developed based on all available data from 5 Phase 1 studies (Study 20070620, Study 20080390, Study 2010118, Study D5180C00003, Study D5180C00002), and 2 Phase 2 studies (Study D5240C00001 and Study CD-RI-MEDI9929-1146). The exposure-response analysis was based on the Phase 2b Study CD-RI-MEDI9929-1146.

Analysis of data from the phase 2b study identified a statistically significant exposure-response against the primary efficacy endpoint of AAER and the pharmacodynamic (PD) endpoint of FeNO. These relationships indicate that the dose of 70 mg Q4W is a sub-optimally effective dose and the dose of 210 mg Q4W is optimally effective. In summary,

characterization of AAER data from Study CD-RI-MEDI9929-1146 indicate the 210 mg Q4W dose provides improved efficacy over the 70 mg Q4W dose, whereas the 280 mg Q2W dose did not further reduce AAER. Tezepelumab was well-tolerated at all investigated doses and the safety profile was well balanced between the tezepelumab and placebo groups with no evidence of a dose relationship to TEAEs in the adult population.

From the results of PK simulations, the mean exposure in the adolescent population as a whole was expected to be 1.67-fold higher in adolescents than in adults at the 210 mg Q4W dose. However, because of the fact that tezepelumab has been shown to be well-tolerated at the 280 mg Q2W dose (which resulted in approximately 2.7-fold higher exposure than at the 210 mg Q4W dose in adults), and considering the overall variability in the PK of tezepelumab (coefficient of variation [CV] approximately 45% to 50%), the adolescent exposures at the 210 mg SC dose are considered unlikely to pose a safety risk.

The dose of 210 mg SC Q4W has been selected for evaluation in both the adult and adolescent populations with a body weight of ≥40 kg.

The study is designed to dose subjects at Q4W with the last dose given at Week 48, a visit at Week 52, and a 12-week follow-up period.

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 eligibility 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 registered to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the eligibility criteria are screen failures, refer to section 5.4.

For procedures for withdrawal of incorrectly registered subjects see Section 7.3.

5.1 Inclusion criteria

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

(Subjects who have no written informed consent for genetic research [Gx] are eligible for the study without meeting inclusion criteria 2 provided that all 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 20 years of age or over. For subjects aged <20 years, in addition to the subject providing signed informed consent or assent, the subject's legally acceptable representative must also provide their informed consent.

2 Provision of written informed consent for Gx prior to collection of the optional sample for genetic analysis. Applicable to adult subjects only (20 years old or over).

The Informed Consent Form (ICF) process is described in Appendix A 3.

Age

3 Subjects must be 12 to 80 years of age inclusive at the time of signing the informed consent form.

Type of subject and disease characteristics

4 Documented physician-diagnosed asthma for at least 12 months prior to Visit 1.

5 Subjects who have received a physician-prescribed asthma controller medication with medium or high dose ICS as per Global Initiative for Asthma (GINA) guideline (GINA 2018) for subjects with ≥16 years of age and The Japanese Pediatric Guideline for the Treatment and Management of Asthma 2017 (Japanese Society of Pediatric Allergy and Clinical Immunology 2017) for subjects with <16 years of age for at least 12 months prior to Visit 1.

6 Documented treatment with a total daily dose of either medium or high dose ICS (≥ 500µg fluticasone propionate dry powder formulation equivalent total daily dose) for at least 3 months prior to Visit 1. The ICS can be contained within an ICS/LABA combination product.
Equivalent ICS doses are detailed in Appendix F

7 At least one additional maintenance asthma controller medication is required according to standard practice of care; e.g. LABA, LTRA, theophylline, LAMA, cromones etc. Use of additional asthma controller medications must be documented for at least 3 months prior to Visit 1.

8 Documented history of at least one asthma exacerbation events within 12 months prior to Visit 1. These can be as follows:

- An asthma exacerbation is defined as a worsening of asthma that required treatment with systemic corticosteroids for at least 3 consecutive days (a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids).
  OR
- An emergency room visit (defined as evaluation and treatment for <24 hours in an emergency room [ER] or urgent care center) that required systemic corticosteroids (as per above).
  OR
- An inpatient hospitalisation due to asthma (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours).

NOTE: For subjects receiving a stable maintenance dose of OCS, a temporary increase for at least 3 consecutive days over and above the stable existing maintenance dose qualifies as an exacerbation.

The below defines what is acceptable to document exacerbations in this program:

- Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a subject was hospitalized/treated with systemic steroids for an asthma exacerbation.
- Signed and dated notes from a referring physician, including information regarding diagnosis and treatment of an exacerbation with systemic steroids.
- Subjects can provide evidence of prescriptions for systemic steroids used during an exacerbation.
- A documented conversation that is recorded in a timely manner between the investigator/nurse and a subject who is already on an OCS action plan, detailing the diagnosis and treatment of an asthma exacerbation.
- A documented conversation between the treating/referral physician or nurse certifying that a subject was treated for an exacerbation with steroids at their clinic or under their supervision. The dates (month/year) of the exacerbations and verbal confirmation that appropriate prescriptions were provided is necessary. This option should be used only if reasonable attempts to procure subject records have been unsuccessful.

9 ACQ-6 score ≥1.5 at Visit 1. The subject who does not meet at Visit 1, but meet on the day of registration (Visit 2) is also eligible for the study.

Weight

10 Weight ≥40 kg at Visit 1.

Reproduction

11 Female patients who are not of child-bearing potential, or female subjects of childbearing potential with negative serum pregnancy test 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 registration 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.

12 Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception from time of signature of consent form, 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: a vasectomised sexual partner, female sterilization by tubal occlusion, any effective intrauterine device/system (IUD/IUS), and oral contraceptive.

Inclusion criteria at registration (Visit 2)

13 ACQ-6 score ≥1.5 on the day of registration if not met at Visit 1

14 Acceptable inhaler and spirometry techniques during the screening period as judged by the investigator(s).

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 cancer:

- Subjects who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible to participate in the study provided that curative therapy was completed at least 12 months prior to Visit 1.
- Subjects who have had other malignancies are eligible provided that curative therapy was completed at least 5 years prior to Visit 1.

4 History of a clinically significant infection, including upper respiratory tract infection (URTI) or lower respiratory tract infection (LRTI), requiring treatment with antibiotics or antiviral medications finalized <2 weeks before Visit 1 or during the screening period.

5 A helminth parasitic infection diagnosed within 6 months prior to Visit 1 that has not been treated with, or has failed to respond to, standard of care therapy.

6 Current smokers or subjects with smoking history ≥10 pack-years. Former smokers with smoking history of <10 pack years must have stopped for at least 6 months prior to Visit 1 to be eligible.

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

8 Tuberculosis requiring treatment within 12 months prior to Visit 1.

9 History of known immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at Visit 1, or the subject taking antiretroviral medications as determined by medical history and/or subject’s verbal report.

10 Major surgery within 8 weeks prior to Visit 1 or planned surgical procedures requiring general anaesthesia or in-patient status for >1 day during the conduct of the study.

Prior/concomitant therapy

11 Receipt of any marketed or investigational biologic agent within 4 months or 5 half-lives (whichever is longer) prior to Visit 1 or receipt of any investigational non-biologic agent within 30 days or 5 half-lives (whichever is longest) prior to Visit 1.

Note: Subjects on previous biologics treatment are allowed to register in the study treatment provided the appropriate washout period is fulfilled.

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

13 Receipt of immunoglobulin or blood products within 30 days prior to Visit 1.

14 Receipt of the Th2 cytokine inhibitor Suplatast tosilate within 15 days prior to Visit 1.

15 Receipt of live attenuated vaccines 30 days prior to the date of registration and during the study including the follow-up period.

16 Subjects that have been treated with bronchial thermoplasty in the last 24 months prior to Visit 1.

Prior/concurrent clinical study experience

17 Known history of sensitivity to any component of the IP formulation or a history of drug or other allergy that, in the opinion of the investigator or the Study Physician, contraindicates their participation

18 History of anaphylaxis or documented immune complex disease (Type III hypersensitivity reactions) following any biologic therapy.

19 Concurrent enrolment in another clinical study involving an IP.

20 Subject registered in the current study or randomized in previous Tezepelumab studies.

21 Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff and/or site staff), or subjects employed by or relatives of the employees of the site or sponsor.

Diagnostic assessments

22 Any clinically meaningful abnormal finding in physical examination, vital signs, electrocardiogram (ECG), haematology, clinical chemistry, or urinalysis during the screening period, 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.

23 Evidence of active liver disease, including jaundice or aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) > 2 times the upper limit of normal (ULN) at Visit 1.

24 Positive hepatitis B surface antigen, or hepatitis C virus antibody serology at screening, or a positive medical history for hepatitis B or C. Subjects with a history of hepatitis B vaccination without a history of hepatitis B are allowed to participate.

Other exclusions

25 Pregnant, breastfeeding, or lactating women.

A serum β-human chorionic gonadotropin (β-hCG) pregnancy test must be drawn for women of childbearing potential (WOCBP) (including adolescent females) at the screening visit. 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.

26 Unwillingness or inability to follow the study procedures, in the opinion of the investigator.

27 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.

Genetic Research exclusion criteria

28 Previous allogeneic bone marrow transplant.

29 Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

5.3 Lifestyle restrictions

The following restrictions apply while the patient is receiving study medication and for the specific times before and after.

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 center.

5.3.2 Alcohol and tobacco

Chronic alcohol or drug abuse within 12 months is restricted prior to Visit 1 and throughout the conduct of the study.

Current smokers or subjects with smoking history ≥10 pack-years at Visit 1 are not allowed. Former smokers with a smoking history of <10 pack years must have stopped for at least 6 months prior to Visit 1 to be eligible. Smoking is not allowed throughout the course of the study.

The use of e-cigarettes is also not allowed during the course of the study.

5.3.3 Activity

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

5.3.4 Blood donation

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.

5.3.5 Contraception

Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception from time of signature of consent form, and must 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. See inclusion criterion 12 in Section 5.1 for the details.

5.4 Screen failures

Screen failures are defined as subjects who signed the ICF to participate in the clinical study but are not subsequently entered in the treatment period. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

These subjects should have the reason for study withdrawal recorded as ‘Screen failures’ (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 registered subjects.

5.4.1 Re-screening

Re-screening is allowed only once under the following circumstances:

Subjects with respiratory infections requiring antibiotics or antiviral medication within 14 days prior to Visit 1 or during the screening period may be re-screened (exclusion criterion 4) 14 days after recovery, i.e., completion of the therapy.

If the reason for screen failure was transient (including but not limited to equipment failure, unforeseen personal events that mandate missed screening visits), subjects may potentially be re-screened. These cases should be discussed with the AstraZeneca study physician and documented in the Investigator Study File.

After signing a new ICF or assent form, subjects will be assigned the same enrolment code as for the initial screening via the IVRS/IWRS and performed Visit 1 assessments as listed in Table 1 (with the exception of testing for HIV1 and HIV2, hepatitis B and C, and FSH). Rescreening should be documented so that its effect on study results, if any, can be assessed.

Subjects who experience an asthma exacerbation during the screening period may remain in screening and proceed with study visits 14 days after they have completed their course of oral corticosteroids or returned to their maintenance dose of oral corticosteroids.

IMPORTANT! Re-screening for subjects who have screen-failed due to patient reported outcome (PRO) criteria (e.g. ACQ-6 score <1.5, did not meet minimum symptom requirement, or did not report adequate compliance with maintenance medications) is not allowed.

6 STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to tezepelumab.

6.1 Treatments administered

6.1.1 Investigational products

Table 4 Study Treatments

Study treatment name:	Tezepelumab (MEDI9929)
Dosage formulation:	110 mg/mL in 10 mM acetate, 3.0% (weight per volume [w/v]) L-proline, 0.01% (w/v) polysorbate 80, pH 5.2
Route of administration:	Subcutaneous
Dosing instructions:	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.

6.2 Preparation/handling/storage/accountability

IP will be supplied to the site in a kit with one vial of tezepelumab. 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 vial 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 study treatment.

Only subjects enrolled in the study may receive study treatment and only authorised 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 authorised 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 by a qualified HCP. Please refer to Appendix J 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 IVRS/IWRS. One vial of IP will be assigned by IVRS/IWRS 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 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 Standard Operating Procedures (SOP), the vial labels along with 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

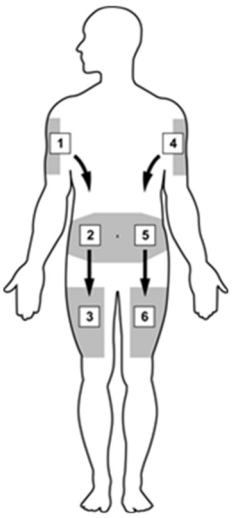
Dose	Number of vial(s) required	Syringe size required	Total volume administered
210 mg[a]	1	3 mL	1.9 mL

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

Dose Administration

IP will be administered by a qualified healthcare professional (e.g., the investigator 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 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 the Study Physician may compromise the safety of the subject in the study (e.g., viral illnesses).
- The subject, in the opinion of the investigator, is experiencing an acute or emerging asthma exacerbation.
- 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 AZ 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 Adverse Event (AE) eCRF page and an additional eCRF page with questions about the injection site reaction.

6.3 Measures to minimise bias: randomisation and blinding

This is an open-label, non-randomised study.

All subjects will be assigned to the study treatment using the IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

If a subject withdraws from the study, then his/her enrolment code cannot be reused. Withdrawn subjects will not be replaced

6.4 Treatment compliance

Any change from the dosing schedule or dose discontinuations should be recorded in 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 ICS asthma medications taken in the 12 months prior to Visit 1 must be recorded in the eCRF along with reason for treatment.

To satisfy inclusion criterion 6, a history of continuous treatment with medium or high dose ICS plus a second controller medication for at least 3 months prior to Visit 1 should be documented in source and recorded in the eCRF prior to the date of registration.

In order to satisfy inclusion criterion 7, a history of all asthma controller medications for the 3 months prior to Visit 1 until the end of the study should be documented in source and recorded in the eCRF. No changes are allowed to asthma background medications throughout the duration of the study except during the treatment of an asthma exacerbation.

All other medications taken for conditions other than asthma in the 3 months prior to Visit 1 must be recorded in the eCRF along with reason for treatment by the Investigator/authorized delegate at each visit (as shown in Table 1 and Table 2).

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.

As theophylline has a narrow therapeutic window, please note that subjects on maintenance treatment with theophylline should have blood concentration levels within therapeutic range and documented before Visit 1. If this is not documented before signing the informed consent, it can be obtained after informed consent has been given or as part of the Visit 1 procedures. The sample can be analysed at a local laboratory as applicable. Investigator can use their time and other factors that may impact the results. Investigator can use their clinical judgement

about the therapeutic range of theophylline levels on the basis of sampling time and other factors that may impact the results.

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

Table 6 Restricted medications

Medication/class of drug:	Usage:
Maintenance treatment with ICS and long-acting bronchodilators (including ICS/LABA combinations)	No changes in either dose or regimen are allowed from V1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP. The patients 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 spirometry at site. Once daily bronchodilators should be withheld for at least 24 hours prior to the scheduled spirometry at site. Subjects will not need a washout of their asthma medications for unscheduled visits due to asthma worsening.
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 spirometry and ECG at site with the exception of any unscheduled visits due to asthma worsening.

Table 6 Restricted medications

Medication/class of drug:	Usage:
Additional Maintenance Controllers	No changes in either dose or regimen are allowed from V1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP. Once daily LABA and LAMA should be withheld for at least 24 hours prior scheduled spirometry 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 spirometry at site with the exception of any unscheduled visits due to asthma worsening. LTRA should be withheld for at least 24 hours prior to scheduled spirometry at site with the exception of any unscheduled visits due to asthma worsening. Subjects on theophylline should have blood concentration levels within therapeutic range documented before proceeding in the study. Twice daily theophyllines should be withheld for at least 12 hours prior to scheduled spirometry 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 spirometry 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 study visit.
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:
Long-acting beta-agonists as a reliever (e.g. Symbicort Maintenance and Reliever Treatment)	Not allowed 15 days prior to Visit 1, during screening and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Suplatast tosilate (Th2 cytokine inhibitor)	Not allowed within 15 days prior to Visit 1, during screening and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Live Attenuated Vaccines	Not allowed 30 days prior to the date of registration, and during the study including the follow-up period.
Any immunomodulators or immunosuppressives (except for OCS used in the maintenance treatment of asthma/asthma exacerbations in screening, and protocol defined asthma exacerbations on or after Visit 2)	Not allowed 12 weeks prior to registration, during screening and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Immunoglobulin or blood products	Not allowed 30 days prior to Visit 1, during screening and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Any marketed (e.g. omalizumab, mepolizumab, reslizumab, benralizumab) or to be marketed or investigational biologic treatment	Not allowed 4 months or 5 half-lives (whichever is longer) prior to the date of Visit 1, throughout the entire, screening period, treatment period (even if the subject has discontinued IP) and until the follow up visit week 64.
Other investigational products (including investigational use of an approved drug)	Not allowed 30 days or 5 half-lives (whichever is longer) prior to Visit 1, during screening and throughout the IP treatment and until the follow up visit week 64.
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases	Not allowed 30 days prior to Visit 1, during screening and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Medications not currently licensed for use in the treatment of asthma, for example medications approved for Chronic Obstructive Pulmonary Disease and not part of current standard of care.	Not allowed 30 days prior to Visit 1, during screening and throughout the IP treatment and preferably 4 weeks after the last dose of IP.

6.5.1 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 eCRF.

6.5.2 Rescue medication

Short-acting β2-agonist (SABA) should be withheld for at least 6 hours prior to scheduled site visit spirometry and ECG at site with the exception of any unscheduled visits due to asthma worsening.

Rescue use of SABA administered via nebulization is discouraged, except as urgent treatment during an asthma exacerbation.

Rescue medication will not be provided by the sponsor.

6.5.3 Bronchial Thermoplasty

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

6.6 Dose modification

Not applicable

6.7 Treatment after the end of the study

Subjects who complete week 64 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 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 discontinue IP, without prejudice to further treatment
- Adverse Event considered to jeopardise the safety of a subject participating in the study by the investigator
- Pregnancy
- Severe non-compliance with the Clinical Study Protocol as judged by the investigator
- Development of any study specific criteria for discontinuation, 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
- Development of one or more of the following:
  - Confirmed ALT or AST increase of ≥8 × ULN
  - Confirmed ALT or AST increase of ≥5 × ULN for more than 2 weeks
  - Confirmed ALT or AST increase of ≥3 × ULN and total bilirubin of ≥2 × ULN
  - ALT or AST of ≥3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (≥5%)

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

7.1.1 Procedures for discontinuation of study treatment

Subjects are free to discontinue IP or withdraw from the study at any time without prejudice to further treatment. 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 discontinue IP should always be asked about the reason(s) and the presence of any adverse events. The reason for discontinuing treatment and the date of last IP administration should be recorded in the eCRF. Subjects permanently discontinuing IP administration should be given locally available standard of care therapy, at the discretion of the Investigator. However, treatment with marketed or investigational biologics is not allowed until Week 64 even if the subject has discontinued IP. Interaction studies between tezepelumab and other biologics indicated for the treatment of asthma have not been conducted. 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 center and complete the procedures described for the premature Investigational Product Discontinuation (IPD) visit at 4 weeks (+/-5 days) post last IP administration. Subjects who 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 as follows:

1 The subject should be encouraged to return for all regular clinic visits and perform all scheduled assessments until he/she completes a total of 52 weeks treatment period.

2 The subject will be offered follow-up on a monthly basis via telephone calls until the subject completes 52 weeks in the study. The subject should return for a follow-up visit 16 weeks (+/- 7 days) (refer to SoA, FU2 visit – Week 64) post last IP administration and for the end of treatment (EOT) visit at Week 52 (+/-5 days).

3 If the subject cannot or does not wish to comply with any of the options above, they will complete a follow-up visit at 16 weeks (+/- 7 days) (refer to SoA, FU2 visit – Week 64) post last IP administration. After this visit the Investigator will only contact the subject at 52 weeks post registration. No other study assessments will be performed prior to this contact.

If the last IP administration was after week 36 for options 1 or 2, the subject will return to the clinic for an EOT visit at Week 52 (+/- 5 days), and for option 3, the investigator will contact the subject at 52 weeks post registration. The subject for options 1, 2 and 3 will then return for a follow-up visit 16 weeks (+/- 7 days) post last IP administration (refer to SoA, FU2 visit – Week 64). If the last IP administration was at Week 36, the subject will follow EOT assessment rather than FU2 visit.

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 will be discontinued from the study.

If the subject chooses option 1, all assessments will be completed as per the SoA as indicated in Section 1.1. If the subject chooses 2 or 3, the key information to be collected during the telephone calls are AEs/SAEs, changes in concomitant medication, and asthma exacerbation information.

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

If a subject discontinues IP due to a study specific discontinuation criterion, this should always be recorded as ’Development of study specific withdrawal’ on the termination form in the eCRF.

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 any of the following attempts of contact are failed.
  - 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.

7.3 Withdrawal from the study

A subject may withdraw from the study (eg, withdraw consent), at any time (investigational product **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 (eg, telephone contact, a contact with a relative or treating physician, or information from medical records) as per Section 7.1.1.

A subject who withdraws consent will always be asked by the Investigator about the reason(s) and the presence of any AEs. 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, Table 2.

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.

If the subject only withdraws consent for the retention of blood samples for Gx, the subject will not be withdrawn from the study.

Withdrawal of consent from the study must be ascertained and documented by the Investigator and recorded in the eCRF.

7.3.1 Withdrawal due to recruitment completion

When the required number of subjects are registered in the study, ongoing subjects in screening will not be registered and will be withdrawn from the study. The reason of the withdrawal should be documented in the source and eCRF. As with screen failures, no further study related follow-up of these patients is required.

7.3.2 Discontinuation or suspension of the whole study program

If AstraZeneca decides to prematurely terminate or suspend the study, the Principal Investigator, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension. The Principal Investigator 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.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

The investigator will ensure that data are recorded on the eCRF. 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 eCRF. A copy of the completed eCRF will be archived at the study site. Additional data to assess the impact of COVID-19 pandemic will be collected.

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

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

The amount of blood collected from each subject over the duration of the study (excluding optional blood samples) will be approximately 115 mL including any extra assessments that may be required, and will not exceed 140 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

8.1.1 Assessment of asthma exacerbation

Subjects enrolled in the study should have had at least one exacerbation in the prior 12 months before Visit 1. The list below defines what is acceptable documentation for historical exacerbations:

- Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a subject was hospitalized/treated with systemic steroids for an asthma exacerbation.
- Signed and dated notes from a referring physician, including information regarding diagnosis and treatment of an exacerbation with systemic steroids.
- Evidence of prescriptions for systemic steroids used during an exacerbation.
- A documented conversation that is recorded in a timely manner between the investigator/nurse and a subject who is already on an OCS action plan, detailing the diagnosis and treatment of an asthma exacerbation.
- A documented conversation between the treating/referral physician or nurse certifying that a subject was treated for an exacerbation with steroids at their clinic or under their supervision. The dates (month/year) of the exacerbations and verbal confirmation that appropriate prescriptions were provided is necessary. This option should be used only if reasonable attempts to procure subject records have been unsuccessful.

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 center) 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 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, 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 Spirometry

8.1.2.1 General Requirements

Pulmonary function will be measured by spirometry at the study site using the site's own equipment. Spirometry will be performed by the Investigator or authorized delegate according to the respiratory function test guideline. (The Japanese Respiratory Society 2004).

Important!

- Subjects should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the center.
- Subjects should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the center.
- Subjects should withhold their usual maintenance therapies on the day(s) when lung function testing is being performed as below:
  - SABAs should be withheld at least 6 hours prior to scheduled spirometry at site.
  - Twice daily LABA or LAMA-containing therapies should be withheld for at least 12 hours prior to scheduled spirometry at site.
  - Once daily LABA or LAMA-containing therapies should be withheld for at least 24 hours prior to scheduled spirometry at site.
  - LTRA should be withheld for at least 24 hours prior to scheduled spirometry at site.
  - Twice daily theophyllines should be withheld for at least 12 hours prior to scheduled spirometry at site.
  - Once daily theophyllines for at least 24 hours prior to scheduled spirometry at site.

Note: If any of the above restriction are not met, the spirometry assessment should be rescheduled within the allowed visit window.

Time of day for scheduled site visit spirometry

Spirometry testing should be done according to the SoA. For adult subjects, spirometry testing must be initiated in the morning between 6:00 AM and 11:00 AM during the screening period and at registration visit (Visit 2). Spirometry testing can be initiated during the whole day for adolescent subjects.

All post- registration spirometry assessments should be performed within ± 1.5 hours of the time that the registration spirometry was performed. For example, if the registration spirometry was started at 8:00 AM, then all subsequent spirometry testing needs to be initiated between 6:30 AM and 9:30 AM.

Spirometry technique

Subjects should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Subjects should avoid eating a large meal for at least 2 hours prior to spirometry measurements at the site. All spirometry manoeuvres CCI should be performed with the subject seated in an upright position. If this is not comfortable for the subject, standing is permitted. The same position should be used by the subject for each forced expiratory manoeuvre from enrolment throughout the study. The head must not be tilted during manoeuvres and the thorax should be able to move freely; hence tight clothing should be loosened. A nose-clip should be used for the manoeuvre. Mouthpieces of the same dimension and shape should be used by the subject from enrolment throughout the study.

The spirometry manoeuvre consists of three phases, the first is the maximal inspiration, the second is a "blast" of exhalation (CCI) and the last is a continuation to complete exhalation. The subject should inhale rapidly and completely from functional residual capacity. It is important that the preceding inspiration is fast and that any pause at full inspiration be minimal (i.e. only for 1-2 seconds). The subject should be prompted to "blast", not just "blow", and they should be encouraged to fully exhale until the end of test criteria are met. If the patient feels dizzy, the manoeuvre should be stopped, since syncope could follow due to prolonged interruption of venous return to the thorax. Manoeuvres that do not meet the end of test criteria should not be used to satisfy the requirement of three acceptable manoeuvres. However early termination, by itself, is not a reason to eliminate all the results from such a manoeuvre from further consideration.

CCI

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each spirometry session. CCI

CCI [redacted]

Record keeping

A signed and dated copy of the pre- BD printout must be kept at study centre for source data verification. The printout must be marked with the study code, enrolment code, date and time of measurement, visit number. If a printout cannot be printed, the mean value of the measurements will be recorded in the subject's charts.

8.1.3 Patient reported outcome (PRO)

PRO paper form will be filled in by patient at the site under the supervision of the study staff. The study staff will transfer the responses into the eCRF.

8.1.3.1 Asthma Control Questionnaire-6 (ACQ-6)

The ACQ-6 captures asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing) and SABA use via subject-report.

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and <1.5 indicate partly controlled asthma, and a score ≥1.5 indicates uncontrolled asthma (Juniper et al 2006). CCI [redacted]

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 study 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.

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Table 8 Laboratory safety variables

Haematology (whole blood)	Clinical Chemistry (serum)
B-Haemoglobin	S-ALP
B-Leukocyte count	S-ALT
B-Leukocyte differential count (absolute count)	S-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-Occult blood	S-CRP
U-Protein	S-Gamma-glutamyl transferase (GGT)
U-Glucose	S-Glucose
U-Microscopy and culture as required *	S-Phosphorus
	S-Potassium
**Pregnancy test (Blood or urine) ** **	S-Sodium
S-β-hCG, FSH, U- hCG	S-Total cholesterol
	S-Uric acid

* Only when a positive dipstick result for any parameter is observed. Only the results to be reported as adverse events are recorded in AE section of the eCRF.

** See Section 8.2.1.1.

NB. In case a subject shows an AST **or** ALT ≥3×ULN together with total bilirubin ≥2×ULN please refer to Appendix E '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-hCG – the test done at enrolment (Visit 1) only, for WOCBP and adolescent females (analysed at a local laboratory or near to the Investigator site).
- FSH – the test done at enrolment (Visit 1) only, for female subjects to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 months. (analysed at a local laboratory or near to the Investigator site)
- Urine human Chorionic Gonadotropin (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. Positive urine test result must be confirmed with serum β-hCG.

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.

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, musculo-skeletal (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 the brief physical examination, 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, 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 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 (eg, television, cell phones).

Pulse rate will be obtained before blood pressure.

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 in degrees Celsius 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, spirometry, BD administration and IP administration. 12-lead ECG will be performed at a local laboratory or near to the Investigator site.

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 for re-evaluation.

It is highly recommended that the same machine is used for assessment throughout the subject’s participation in the study.

ECG data and evaluation will be recorded in the eCRF.

8.2.6 Other safety assessments

8.2.6.1 Serology

Hepatitis B surface antigen, hepatitis C antibody, HIV-1 and HIV-2 antibodies will be assessed at enrolment (Visit 1) only. All testing for these will be performed at a local laboratory or near to the Investigator site.

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

AEs, including SAEs will be collected from time of signature of ICF throughout the treatment period and the follow-up periods.

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 must 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 eCRF. 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 collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- 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 caused subject's withdrawal from study (yes or no)
- 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

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 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 eCRF. 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 summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values/vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for 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.

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 patient discontinues IP due to the sign or symptom
- The sign or symptom is new to the patient or not consistent with the patient's preexisting asthma history (defined as within 1 year of Visit 1) as judged by the Investigator.

Asthma exacerbation should be recorded as an AE or SAE only if it fulfils 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:

- Anaphylactic reactions
- Immune complex disease (Type III hypersensitivity reactions)
- Malignancy
- Helminth infections
- Severe infections which are defined as:
  - SAEs or
  - Requiring treatment with antiviral medications, intravenous antibiotics or medications for helminth parasitic infection or
  - Requiring a permanent discontinuation of study drug
- Injection site reactions
- Opportunistic infections
- Guillain Barre Syndrome

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 ≥ 3×ULN together with total bilirubin ≥ 2×ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

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 eCRF.

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 Patient 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.

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 will advise the Investigator/study site staff how to proceed.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca IP.

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 except for:

- If the pregnancy is discovered before the study subject has received any study drug.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, 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 abnormalities/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 abnormality) 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 1day 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 Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Appendix B) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report 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 abnormality) should be followed up and documented for conceptions occurring from the date of the first administration of IP until 16 weeks (5 half-lives) after the last administration of IP.

8.4.3 Overdose

A dose in excess of 280 mg administered within a 2-week period will be 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 eCRF and on the Overdose eCRF module.

An overdose without associated symptoms is only reported on the Overdose eCRF 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 Patient 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.

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 G.

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, if applicable) prior to IP administration. At Visits 2 and 3, subjects should be observed for a minimum of 2 hours after IP administration for the appearance of any acute drug reactions. For the remaining 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 central laboratory.

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.6 Pharmacodynamics

Pharmacodynamics is not evaluated in this study.

8.7 Genetics

CCI [redacted]

CCI

[redacted]

8.7.2 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples may be stored for a maximum of 15 years or as per local regulations from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organizations working with the DNA.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

No hypothesis testing will be conducted for this study.

9.2 Sample size determination

No formal sample size calculation was conducted for this study. Approximately 66 Japanese patients are required to enter treatment period to obtain 59 patients who complete the planned 52-weeks treatment period assuming a drop-out rate of 10% during the 52-weeks treatment period.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All subjects who sign the ICF
Assigned to Study treatment	All subjects registered to study treatment (irrespective of whether treatment is subsequently taken)
Safety Analysis Set	All subjects who received at least one dose of IP.
CCI [redacted]	[redacted]

Safety, efficacy and CCI presentations will be based on the safety analysis set. CCI [redacted]

9.4 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan (SAP) will be developed and finalised before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. 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 CSR.

Important protocol deviations will be defined at subject level prior to database lock and will be summarized. Subjects will not be excluded from analysis sets on the basis of any important protocol deviations. 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 to treatment period without fulfilling key entry criteria; subjects who received prohibited or restricted concomitant medications during IP treatment.

9.4.1 Subject disposition, demography and baseline characteristics

Frequency and percentages of subject disposition and reasons for discontinuation of IP will be presented. Subjects who prematurely discontinue the IP will be listed along with the reason for discontinuation. In addition, frequency and percentages of withdrawal from the study together with reasons will be presented.

Demographics and subject characteristics will be summarized using frequency and percentages (for categorical variables) and n, mean, standard deviation, minimum, median and maximum (for continuous variables) using the safety analysis set.

Relevant medical history/current medical conditions will be summarized by system organ class and preferred term of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary using frequency and percentage of subjects.

9.4.2 Prior and concomitant medication

Prior and concomitant medications, categorized according to the World Health Organization (WHO) Drug Reference List dictionary which employs the Anatomical Therapeutic Chemical (ATC) classification system, will be summarized as frequency and percentage of subjects reporting usage. Prior medications are defined as those which stopped before first dose of IP. Concomitant medications are defined as those which either started or continued after first dose of IP.

9.4.3 Definition of baseline

In general, the last measurement on or prior to the date of first dose of study treatment will serve as the baseline measurement. If there is no value on or prior to the date of first dose of study treatment, 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 time point during treatment period and the baseline value.

9.4.4 Efficacy analyses

All efficacy variables will be summarised using descriptive statistics. Where appropriate, change from baseline will also be summarised descriptively.

9.4.5 Safety analyses

Adverse events will be coded using the MedDRA version in force at database lock. The definition of on-treatment and on-study for adverse event analyses will be given in the SAP.

The number and percentage of subjects with on-treatment and on-study adverse events will be tabulated separately by preferred term and system organ class. An event that occurred one or more times during a period will contribute 1 observation to the numerator of the proportion. The denominator of the proportion will comprise all subjects in the safety population. On-treatment adverse events will also be summarized by intensity/severity and separately, by causality/relatedness (as determined by the investigator). Should a subject report the same preferred term/system organ class within multiple intensity/severity or causality/relatedness categories, the subject's worst occurrence (most severe/most related) will be tabulated. Serious AEs, AEs leading to discontinuation from IP, and commonly occurring AEs will be summarized in a generally similar manner. Adverse events, SAEs, AEs leading to death, and AEs leading to discontinuation of IP will be summarized as applicable. An overall summary of on-treatment AEs adjusted for subject exposure to treatment will be presented.

AESIs, as defined in Section 8.3.8 will also be summarized descriptively.

Laboratory data will be summarized by presenting shift tables using normal ranges (baseline 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.

Vital signs data will be summarized by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable vital signs abnormalities will be summarized. Abnormal ECGs as per Investigator's overall interpretation will be summarized.

9.4.6 Other analyses

CCI

[redacted]

9.5 Interim analyses

An interim analysis to summarise 6 months safety data will be performed when all subjects complete Visit 8 (24-week of treatment period) for submission.

The SAP will describe the planned interim analyses in greater detail.

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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 International Conference on Harmonisation (ICH) GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB) / Independent Ethics Committee (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.

The head of the study site 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 Code of Federal Regulations (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 authorised representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorised 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 authorised 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 authorised representative.

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Subjects who are rescreened are required to sign a new ICF.

CCI [redacted]

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 of subjects of COVID-19 exposure during clinic visits. For further details please refer to Appendix J.

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 authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

Any committee will not have.

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient 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://astrazenecaclinicaltrials.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 Case Report Form (CRF) unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or 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 authorised 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 Clinical Study Agreement and/or other documents.

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 unfavourable 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 abnormality 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, hospitalisation, 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.

- 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 a 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 a 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
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

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

- Errors related to or resulting from IVRS/IWRS - 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 AZ 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 at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre 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 AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

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 analysed, 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. 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
- **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 Genetics

D 1 Use/analysis of DNA

Genetic variation may impact a subject's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting subjects.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the subject´s DNA, i.e. the entire genome.

The results of genetic analyses may be reported in the CSR or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on Tezepelumab continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and: Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of consent for genetic research:

Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7 of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 2 (Registration). Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2 (Registration), it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the subject enrolment code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely withdrawal from the genetic aspect of the study at any time.

Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. In addition, Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can

only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual subject data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

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

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. 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 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 Total Bilirubin (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 Medicinal Product (IMP).

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

E 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, e.g., 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.

E 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

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 E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

E 4 Follow-up

E 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.

E 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 8.3.9)

- 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 Clinical Study Protocol process for SAE reporting.
- For subjects 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

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

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.
- Complete the three Liver CRF Modules as information becomes available

E 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 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 AZ 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 updated 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:

- Provides 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 Clinical Study Protocol 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 Clinical Study Protocol process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Laboratory tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended when using a central laboratory. For individual studies, the list may be reduced to a subset of tests after consultation with the Hepatic Safety Knowledge Group.

Some of the tests may also be considered for use with local laboratories that have respective testing capabilities. Any test results need to be recorded in the CRF.

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 IgM and 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

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 F Maintenance Therapy Equivalence Table

Estimated daily doses for inhaled corticosteroids[a]

Asthma Therapy	**Total Daily Dose (µg/day)**	
Inhaled Corticosteroid	**Medium**	**High**
Beclomethasone dipropionate (non HFA)	1000	>1000
Beclomethasone dipropionate (HFA)	400	>400
Ciclesonide	320	>320
Triamcinolone acetonide	2000	>2000
Flunisolide	2000	>2000
Fluticasone furoate (e.g. Arnuity® Ellipta®)	n.a.	200
Fluticasone propionate	500	>500
Fluticasone propionate HFA	440-500	>500
Budesonide	800	>800
Mometasone furoate	440	>440
Inhaled Corticosteroid in ICS/LABA combination[b]	**Medium**	**High**
Beclomethasone dipropionate (e.g. Fostair®)	400	>400
Fluticasone propionate HFA (e.g. Seretide®, Advair®)	500	>500
Fluticasone furoate (e.g. Relvar® Ellipta®, Breo® Ellipta®)	n.a.	184-200
Budesonide, if as delivered dose (e.g. Symbicort®)	640	>640
Mometasone Furoate (e.g. Dulera®)	400	>400

[a] The Japanese asthma pediatric guidelines will be followed for the Japanese adolescent subject (the medium to high dose for Japanese adolescent subjects 15 years or younger will be ≥ 200 µg/day of FP or other ICSs of equivalent dose).

[b] The ICS doses for the ICS/LABA combinations were derived from GINA 2018 and using prescribing information.

FP: Fluticasone Propionate, GINA: Global Initiative for Asthma, HFA: Hydrofluoroalkane, ICS: Inhaled Corticosteroid, LABA: Long-Acting β2-Agonist.

Appendix G Anaphylaxis: Signs and Symptoms, Management

G 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 Appendix G 2. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Appendix G 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.

G 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 peak expiratory flow [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.

G 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

G 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

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

(b) Establish and maintain airway.

(c) Administer oxygen.

(d) Establish venous access.

(e) Normal saline IV for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion.

(b) Consider H1 and H2 antihistamines.

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

(d) Consider systemic corticosteroids.

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

(f) Consider glucagon for subject taking b-blocker.

(g) Consider atropine for symptomatic bradycardia.

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

(i) 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.

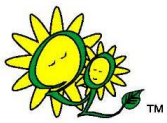
G 5 References

Johansson et al 2004
Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004May;113(5):832-6

Appendix H ACQ-6

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

ENGLISH FOR NORTH AMERICA VERSION
(QUESTIONS 1 – 6 ONLY: QUESTION 7 (FEV1) OMITTED)



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DECEMBER 2002

QUESTIONS 1 – 6 ONLY : MODIFIED JULY 2013 ENGLISH FOR NORTH AMERICA

ASTHMA CONTROL QUESTIONNAIRE© Page 1 of 2

Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been during the past week.

1.	On average, during the past week, how often were you **woken by your asthma** during the night?	0 Never 1 Hardly ever 2 A few times 3 Several times 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2.	On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3.	In general, during the past week, how **limited were you in your activities** because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited
4.	In general, during the past week, how much **shortness of breath** did you experience because of your asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal

QUESTIONS 1 – 6 ONLY : MODIFIED JULY 2013 ENGLISH FOR NORTH AMERICA

ASTHMA CONTROL QUESTIONNAIRE© Page 2 of 2

5. In general, during the past week, how much of the time did you **wheeze?**	0	Not at all
	1	Hardly any of the time
	2	A little of the time
	3	A moderate amount of the time
	4	A lot of the time
	5	Most of the time
	6	All the time
6. On average, during the past week, how many **puffs/inhalations of short-acting bronchodilator** (eg. Ventolin/Bricanyl) have you used each day? *(If you are not sure how to answer this question, please ask for help)*	0	None
	1	1 - 2 puffs/inhalations most days
	2	3 - 4 puffs/inhalations most days
	3	5 - 8 puffs/inhalations most days
	4	9 - 12 puffs/inhalations most days
	5	13 - 16 puffs/inhalations most days
	6	More than 16 puffs/inhalations most days

QUESTIONS 1 – 6 ONLY : MODIFIED JULY 2013 ENGLISH FOR NORTH AMERICA

Appendix I Abbreviations

Abbreviation or special term	Explanation
AAER	Annualized Asthma Exacerbation Rate
ACQ-6	Asthma Control Questionnaire-6
CCI	[redacted]
AE	Adverse Event
AER	Asthma Exacerbation Rate
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BD	Bronchodilator
β-hCG	Beta-Human Chorionic Gonadotropin
CFR	Code of Federal Regulations
CK	Creatinine Kinase
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form
CSGA	The Collaborative Study on the Genetics of Asthma
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of Variation
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic acid
EAR	Early Asthmatic Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
ER	Emergency Room
EU	European Union
FeNO	Fractional Exhaled Nitric Oxide
CCI	[redacted]
FSH	Follicle Stimulating Hormone
FU	Follow-Up
FVC	Forced Vital Capacity

Abbreviation or special term	Explanation
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
GMP	Good Manufacturing Practice
Gx	Genetic research
hCG	Human Chorionic Gonadotropin
HCP	Health Care Professional
HIV	Human Immunodeficiency Virus
HL	Hy's Law
IATA	International Airline Transportation Association
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG2λ	Immunoglobulin G2λ
IL	Interleukin
IMP	Investigational Medicinal Product
IP	Investigational Product
IPD	Investigational Product Discontinuation
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JRS	Japanese Respiratory Society
LABA	Long-Acting β2-Agonist
LAMA	Long-Acting Muscarinic Antagonists
LAR	Late Asthmatic Response
LRTI	Lower Respiratory Tract Infection
LTRA	Leukotriene Receptor Antagonists
mAb	Monoclonal Antibody

Abbreviation or special term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralizing Antibodies
OCS	Oral Corticosteroid(s)
PD	Pharmacodynamic
PEF	Peak Expiratory Flow
PHL	Potential Hy's Law
CCI	[redacted]
PNV	Predicted Normal Value
PRO	Patient Reported Outcome
Q2W	Every 2 Weeks
Q4W	Every 4 Weeks
SABA	Short-Acting β2-Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SoA	Schedule of Activities
SOP	Standard Operating Procedures
TBL	Total Bilirubin
TEAE	Treatment-emergent adverse event
Th2	T helper cell type 2
TSLP	Thymic Stromal Lymphopoietin
TSLPR	Thymic Stromal Lymphopoietin Receptor
ULN	Upper Limit of Normal
UNS	Unscheduled
URTI	Upper Respiratory Tract Infection
WBDC	Web Based Data Capture
WOCBP	Women of Childbearing Potential
w/v	Weight per Volume
WHO	World Health Organization

Appendix J Changes Related to COVID-19 Pandemic

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

J 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 (up to Visit 14) or without administration of IP for EOT Visit and FU1 Visit and FU2 Visit, provided this is acceptable within local regulation/guidance. Additional information related to the visit can be obtained remotely by phone call and/or video conference. This is to ensure safety of the study subjects and minimum disruption to IP administration that may occur during the COVID-19 pandemic.

Study assessments, where possible to be performed at home, should be conducted according to the SoA. At minimum, during home visit the qualified HCP is expected to:

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

Please refer to the separate IP Home (or Alternative Site) Administration Instructions for more information.

J 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 the subject's home, provided this is acceptable within local regulation/guidance.

Please refer to the separate IP Home (or Alternative Site) Administration Instructions for more information.

J 3 Remote Visits to Replace On-Site Visits (where applicable)

During the COVID-19 pandemic, on-site visits may be replaced by a remote visit (phone call and/or video conference) if subjects cannot attend the visits at the study site, at an alternate site or have home visits and 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 exacerbation while minimizing the risk to subjects of COVID-19 exposure.

J 4 End of Treatment Visit

If the EOT visit at Week 52 cannot be performed on-site, at an alternate site or at the subject's home, the EOT visit should be conducted as a remote visit.

J 5 Re-consenting 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.

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