A 52-Week, Open-Label, Multicentre Study to Evaluate the Safety of Tralokinumab in Japanese Adults and Adolescents with Asthma Inadequately Controlled on Inhaled Corticosteroid plus Long-Acting β2-Agonist

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Study Statistician

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Global Product Statistician

Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-Drug Antibodies
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AZ	AstraZeneca BD
	Bronchodilator
BMI	Body Mass Index
CI	Confidence Interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of Variation
DAE	Discontinuation of Investigational Product due to Adverse Event
DPP4	Dipeptidyl Peptidase-4
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
FAS	Full Analysis Set
FEV_1	Forced Expiratory Volume in 1 second
GGT	Gamma-Glutamyl Transpeptidase
ICS	Inhaled Corticosteroids
IP	Investigational Product
ITT	Intent-to-Treat
LABA	Long-Acting β2-Agonist
LLOQ	Lower Limit Of Quantification
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
nAb	Neutralizing Antibodies
NC	Not Calculable
NQ	Non-quantifiable
OAE	Other Significant Adverse Event
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcome
PT	Preferred Term
Q2W	Every 2 Weeks
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SOC	System Organ Class
TBL	Total Bilirubin
ULN	Upper Limit of Normal

AMENDMENT HISTORY

Date	Brief description of change
███████████	Updated to describe the analyses needed for the synopsis-format CSR.

1.   STUDY DETAILS

This is the statistical analysis plan (SAP) for study D2210C00029.

1.1   Study objectives

1.1.1   Primary objectives

Objective:	Outcome Measures:
To assess the safety and tolerability of tralokinumab.	- Adverse Events (AEs) and Serious Adverse Events (SAEs) - Laboratory variables - Physical examinations - Vital signs - ECG

1.1.2   Exploratory objectives

Exploratory Objectives:	Outcome Measures:
To collect data for the assessment of efficacy of tralokinumab	- Asthma Control Questionnaire-6 score (ACQ-6) - Forced expiratory volume in one second (FEV1) - Annual asthma exacerbation rate
To explore baseline level and change from baseline of biomarkers	- Periostin - Dipeptidyl peptidase-4 (DPP-4) - Other biomarkers that may be associated with upregulation of interleukin-13
To evaluate the pharmacokinetics and immunogenicity of tralokinumab	- Serum tralokinumab concentration - Incidence of positive assessments for anti-drug antibodies (ADA) and characterization of their neutralizing potential

Results from the exploratory analyses, if performed, may be reported separately from the Clinical Study Report (CSR).

1.2   Study design

This is an open-label study designed to evaluate the safety of a fixed 300 mg dose of tralokinumab administered subcutaneously (SC) in subjects with uncontrolled asthma receiving Inhaled Corticosteroids (ICS) (≥500 µg fluticasone propionate dry powder

formulation equivalents total daily dose) and a long-acting β2-agonist (LABA), and having a history of asthma exacerbations.

Subjects will receive tralokinumab 300 mg, every 2 weeks via subcutaneous injection at the study site, over a 52-week treatment period.

Approximately 26 subjects will enter treatment at approximately 4 sites in Japan with intention of 22 patients completing study.

After initial enrolment and confirmation of entry criteria, subjects will enter a run-in period of maximum 2 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Subjects who meet eligibility criteria will enter a 52-week treatment period. The first dose of tralokinumab will be administered at Week 0. Subsequent doses will be administered every 2 weeks up until Week 50 (for a total of 26 doses) with an end of treatment (EOT) visit occurring at Week 52. Subjects will be maintained on their currently prescribed ICS-LABA and any additional maintenance asthma controller medications, without change, from enrolment throughout the run-in and treatment period. All subjects will have site visits every 2 weeks.

Follow-up visits will be conducted at Weeks 56 and 66. The extended follow-up period is to ensure adequate determination of immunogenicity.

Figure 1   Study flow chart

Enrolment period Vhit I'''	Tr-eatment period Visit 2 27	EOT Visit 28	VisiLs 29 - 30 FU
Week · 2 · 0	WeckOSO	Week 52	Wed < S6 · 66

| EnrolmenJI Run-in | Tn.lokinumab300 mg.SC:: every2 weeks (.,...26) | End oftreat.mCl'llt | Follow up |

n1   [-?   -7
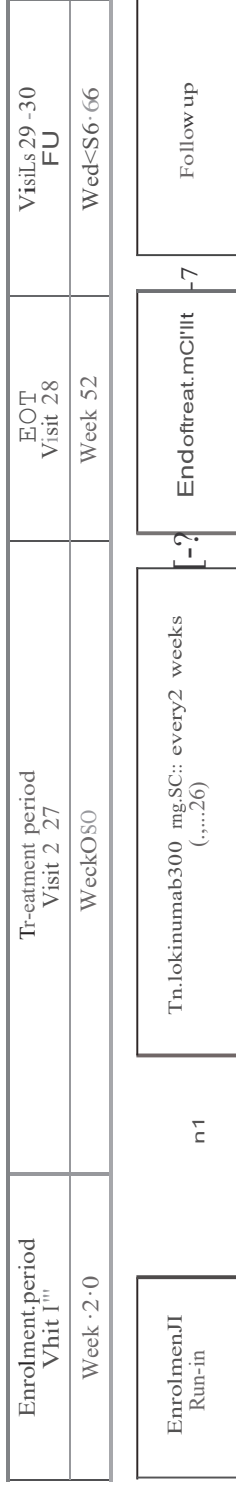
*the rtm-in period can be maximum 2 weeks in duration

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1.3   Number of subjects

No formal sample size calculation was conducted for this study. Approximately 22 Japanese patients who complete the planned 52-weeks treatment period are considered appropriate for collecting additional safety information of tralokinumab (300 mg SC Q2W) among Japanese patients. With an assumed drop-out rate of 15% during the 52-weeks treatment period, approximately 26 Japanese patients are needed to be dosed.

2.   ANALYSIS SETS

2.1   Definition of analysis sets

Subject disposition will be analyzed based on All patients analysis set, consisting of all subjects who are enrolled in the study.

Safety objectives will be analyzed based on the safety analysis set. Exploratory efficacy analyses will be performed using an intent-to-treat (ITT) approach based on the full analysis set. For consistency, demographic and baseline characteristics will be presented using the safety analysis set.

2.1.1   Efficacy analysis set

Fullanalysisset(FAS): All subjects receiving any investigational product (IP) will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. For subjects who withdraw consent or assent to participate in the study, all data will be included up to the date of their study termination.

2.1.2   Safety analysis set

Safetyanalysisset: All subjects who received at least one dose of investigational product will be included in the safety analysis set. All safety summaries and ADA analyses and summaries will be based on this analysis set.

2.1.3   PK analysis set

PKanalysisset: All subjects in FAS who received tralokinumab; including PK blood samples that are assumed not to be affected by factors such as protocol deviations (e.g., disallowed medication, or incorrect study medication received). All PK summaries will be based on this analysis set.

2.1.4   Patient reported outcome (PRO) analysis set

Not applicable.

2.2   Violations and deviations

Only important protocol deviations will be listed in the CSR. These are protocol deviations that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being and include:

- ✓   Subjects who do not meet the inclusion criteria

- ✓   Subjects who meet any of the exclusion criteria

- ✓   Subjects who use one or more disallowed medication (listed in Table 1, for any reason, unless otherwise specified) during the treatment period

Table 1   **Disallowed medications considered to be important protocol deviations**

Medication Details	Anatomical Therapeutic Chemical (ATC) code(s)	Preferred term[a] (if applicable)
Live Attenuated Vaccines[b]	J07BD , J07BF, J07BJ, J07BK, V04CF, J07AP, J06BB, J07BB J07BH J07BL	
Any immunomodulators or immunosuppressives	L04AX, L04AD, L01BA , L04AX	
Any marketed or investigational biologic treatment	R03DX, L04AC	OMALIZUMAB MEPOLIZUMAB RESLIZUMAB
Roflumilast (Daxas/ Daliresp)	R03DX	ROFLUMILAST
Oral or ophthalmic β- adrenergic antagonist[b]	S01ED, C07AA, C07AG	
Systemic corticosteroids[c]	H02AB	

[a]   Preferred term will be used in combination with the ATC codes to identify medications
[b]   Additional physicians review is required to identify these medications correctly. They will be programmatically isolated for review using the ATC codes.
[c]   Additional physicians review is required to identify these medications correctly. They will be programmatically isolated for review using the ATC codes and duration. Only medications with a duration of >= 30 days will be flagged for review,

- ✓   Subjects who developed discontinuation of IP criteria during the study but were not withdrawn from IP.

All important protocol deviations will be identified and documented prior to database lock.

Important deviations will be determined by reviewing a report from the Clinical Trial Management System which will be sent from the AstraZeneca (AZ) Study lead in Excel. Major deviations (deviations considered to be a major deviation from the protocol, but that are not deemed to impact the accuracy/reliability of the study data and do not significantly affect a subject's rights, safety, or well-being) will be reviewed jointly by study statistician and the AZ study physician manually and all important deviations will be flagged and added into the relevant dataset.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General Definitions

3.1.1 Definition of baseline

Baseline will be defined as the latest non-missing assessment prior to start of treatment if not specified otherwise.

For spirometry variables, the measurement recorded at the baseline visit (Visit 2) will be used as baseline. If the Visit 2 measurement is missing, the last non-missing value before Visit 2 will be used as baseline instead.

For post-bronchodilator (BD) FEV_1, the measurement after the first BD administration is the baseline.

The baseline for the PRO variable, ACQ-6 will be collected at Visit 2.

3.1.2 Absolute and percent change from baseline

Not applicable.

3.1.3 Reversibility

Not applicable.

3.1.4 Visit and period windows

Not applicable.

3.2 Calculation or derivation of efficacy variables

3.2.1 Exacerbation rate

Not applicable.

3.2.2 Forced expiratory volume in 1 second

Not applicable.

3.3 Calculation or derivation of patient reported outcome variables

Not applicable.

3.3.1 Asthma Control Questionnaire (ACQ-6)

Not applicable.

3.4 Calculation or derivation of safety variable(s)

The following safety data will be collected: vital signs, physical examination, 12-lead ECG, haematology, clinical chemistry, urinalysis, and reported AEs.

3.4.1 Adverse events

Adverse events experienced by the subjects will be collected throughout the entire study and will be coded by the AstraZeneca designee using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

AE data will be categorized according to their onset date into the following study periods:

- AEs occurring during run-in (onset date ≥ Visit 1 and before the first dose of study treatment)

- AEs occurring during study (onset date ≥ the first day of study treatment)

- AEs occurring during treatment (onset date ≥ the first day of study treatment and ≤ the last day of study treatment + 2 weeks)

- AEs occurring post-treatment (onset date > the last day of study treatment + 2 weeks)

The timing of AEs will be assigned to the period in which they first occurred. If an AE has a missing onset date, then unless the stop date of the AE indicates otherwise, this will be considered an on treatment event. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered an on treatment AE.

3.4.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or discontinuation of IP due to AEs (DAEs).

Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that led to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

3.4.3 Laboratory variables

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times detailed in the clinical study protocol (CSP), and will be assessed in a central laboratory. Laboratory data will be reported in SI units.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range).

All values (absolute and change) falling outside the reference ranges will be flagged.

Urinalysis data will be categorised as negative (0), trace or positive (+) at each time-point.

For the liver function tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT) and total bilirubin (TBL), the multiple of the AstraZeneca upper limit of normal (ULN) (not extended) range will be calculated for each data point.

Multiple = Value / ULN

i.e., if the ALT value was 72 IU/L (ULN 36) then the multiple would be 2.

Subjects who meet any of the following criteria at any point during the study will be flagged:

- AST $\geq$ 3x ULN

- ALT $\geq$ 3x ULN

- TBL $\geq$ 2xULN

3.4.4 ECGs

Twelve-lead ECG measurements will be recorded in accordance with the protocol, with the baseline visit being defined as Visit 1.

The outcome of the overall evaluation is to be recorded as normal/abnormal in the electronic case report form (eCRF), with any abnormalities being recorded as not clinically significant or clinically significant.

3.4.5 Physical examination

Complete and brief physical examinations will be performed at time points specified in the CSP. Only information on whether the assessment was performed or not will be recorded.

Any new finding(s), or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE.

3.4.6 Vital signs

Pre-dose vital signs (pulse, systolic blood pressure, diastolic blood pressure, respiration rate and body temperature) will be obtained in accordance with the schedule provided in the CSP.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

Body mass index (BMI) will be calculated from the height (in meters) and weight (in kilograms) as follows:

BMI = kg/m^2

The calculation is performed on the eCRF and this will be the value that is reported.

3.5 Calculations or derivation of Pharmacokinetic and Immunogenicity variables

Blood samples (processed to serum) for pharmacokinetic and immunogenicity assessments will be collected from all subjects at baseline prior to first IP administration at Visit 2, at multiple time points before IP administrations during the treatment period, and at selected time points in the follow-up phase of the study. Anti-drug antibodies assessments will be conducted utilizing a tiered approach (screen, confirm, titer). These validated methods are conducted using a bridging assay format and statistically determined floating screening assay cut point factor and confirmatory assay cut point. The minimal sample dilution is 1:13. Titer values are reported as the reciprocal of the highest dilution that yields a value above the cut point. Samples from pre-defined study time points that confirm positive for ADA will also be tested for neutralizing ADA/nAb activity. Both ADA and nAb will be summarized using descriptive statistics.

Pharmacokinetics and immunogenicity of tralokinumab:

Tralokinumab serum concentrations will be tabulated by time along with descriptive statistics. Population PK modelling may also be performed to better characterize the PK of tralokinumab, but will be reported separately from the CSR.

The incidence rate of ADA to tralokinumab will be reported. If possible and if relevant, the impact of ADA occurrence on the PK, pharmacodynamics and safety will be summarized in the CSR.

4. ANALYSIS METHODS

4.1 General principles

All possible data will be included unless otherwise specified.

Summary data will be presented in tabular format. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables for parametric data will be summarized by descriptive statistics including N, mean, standard deviation (SD), median, and range. All data will be listed. Data listings will be sorted by subject number.

Minimum and maximum values will be reported to the same degree of precision as the raw data unless otherwise stated. Mean, median, SD and confidence intervals (CIs) will be reported to one further degree of precision.

4.2 Analysis methods

4.2.1 Subject disposition, demography data and subjects characteristics

Subject disposition will be summarized using All patients analysis set.

The number of enrolled subjects will be summarized. The number and percentage of subjects will be presented by the following categories; received IP, didn't receive IP (and reason), completed treatment, discontinued treatment (and reason), completed study (subjects who completed IP and study, and subjects who discontinued IP but completed study assessments), and discontinued study (including reason).

The number and percentage of subjects, who discontinued IP, but remained in the study will be presented.

Demographic data, such as age, sex, race, and ethnicity, will be summarized for the safety analysis set.

4.2.2 Prior and Concomitant Medications

Not applicable.

4.2.3 Exposure

Extent of exposure to IP is defined as the number of days between the start and the end dates of study therapy plus the dosing frequency time:

Extent of exposure (days) = (Last dosing date + 2 weeks) – First dosing date + 1.

In addition, the total number of dosing occasions will be calculated per subject.

The extent of exposure to IP (days), the total number of dosing occasion, and the duration of follow-up (as defined in Section 3.2.1), will be summarised using the safety analysis set.

4.2.4 Compliance

Compliance is defined as:

Compliance (%) = (Total number of dosing occasions/total number of dosing occasions expected) x 100

The total number of dosing occasions expected per subject will be calculated based on the number of dosing occasions between the start of IP and the last dose of IP received (either at early discontinuation or at the end of the treatment period at week 50) will be summarized using the safety analysis set.

4.2.5 Analysis of efficacy

Not applicable.

4.2.6 Safety and tolerability

Safety variables will be summarized using the safety analysis set.

4.2.6.1   Adverse events (AEs)

AEs will be summarized separately for the study periods defined in Section 3.4.1. AEs occurring during the run-in period, or occurring post-treatment (as per the definition in Section 3.4.1) will be listed, but not summarized separately.

An overall summary table will be produced showing the number and percentage of subjects with at least 1 AE in any of the following categories: AEs, SAEs, deaths due to AE, deaths due to SAE, DAEs, and OAEs. OAEs will be defined following medical review of system organ classes/preferred terms.

AEs will be summarized by system organ class (SOC) and preferred term (PT) assigned to the event using MedDRA. For each PT, the number and percentage of subjects reporting at least one occurrence will be presented ie, for a subject multiple occurrences of an AE will only be counted once.

The following will also be summarised by SOC and PT:

- SAEs

- Severe Infections (as defined in the CSP)

Separate listings of subjects with AEs, SAEs, death due to AE, deaths due to SAE, DAEs, OAEs, or severe infections will be presented.

4.2.6.2   Laboratory data

Not applicable.

4.2.6.3   ECG

Not applicable.

4.2.6.4   Vital Signs

Not applicable.

4.2.6.5   Weight and BMI

Not applicable.

4.2.6.6   Analysis of Immunogenicity variables

All analyses of immunogenicity variables will be based on the safety analysis set.

ADA status (positive vs. negative), ADA titers, and neutralizing antibody status (positive vs. negative) at each visit will be summarized. The ADA status across the study for each subject (positive vs. negative) will also be classified and summarized. The association of ADA status across the study (positive vs. negative, ADA titers >= median titer vs. < median titer) with AEs/SAEs may be evaluated. The ADA-positive subjects across the study may also be divided into persistent positive versus transient positive. Persistently positive is defined as positive

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ADAs at >=2 post-baseline assessments (with >=16 weeks between the first and last positive result) or positive at the last post-baseline assessment. Otherwise, the subject will be considered as transient ADA positive.

However, if the number of ADA positive subjects in the safety analysis set is small, then the ADA variables may be listed only in the CSR.

4.2.7 Analysis of pharmacokinetics

All analyses of PK variables will be based on the PK analysis set.

Due to the limited sampling schedule, the PK assessment will be primarily based on the observed serum trough (predose) concentrations, C_{trough}.

For descriptive statistics of C_{trough}

- if, at a given time point, 50% or less of the concentrations are non-quantifiable (NQ), the geometric mean, coefficient of variation (CV), arithmetic mean and SD will be calculated by substituting the lower limit of quantification (LLOQ) divided by 2 for values which are NQ.

- if more than 50%, but not all, of the concentrations are NQ, the geometric mean, CV, arithmetic mean and SD will be reported as not calculable (NC)

- if all the concentrations are NQ, the geometric mean and arithmetic mean will be reported as NQ and the CV and SD as NC

- the median, minimum and maximum will also be reported.

The LLOQ of tralokinumab in serum will be 0.100 μg/mL.

4.2.8 Exploratory analysis

4.2.8.1 Lung Function

Not applicable.

4.2.8.2 Asthma exacerbation

Not applicable.

4.2.8.3 ACQ-6 defined asthma control

Not applicable.

4.2.8.4 Biomarkers

Not applicable.

5. INTERIM ANALYSES

Not applicable.

6. CHANGES OF ANALYSIS FROM PROTOCOL

SAP has been revised to describe the analyses needed for the synopsis-format CSR and the analyses not relevant to the synopsis-format CSR have been deleted. The interim analysis was deleted as communication with regulatory authorities were not planned.

7. REFERENCES

Not applicable.