STATISTICAL ANALYSIS PLAN

ATX-GD-59-001

SAFETY AND PROOF OF PRINCIPLE STUDY OF ATX-GD-59 IN MALE AND FEMALE SUBJECTS WITH GRAVES' DISEASE NOT CURRENTLY TREATED WITH ANTI-THYROID THERAPY: AN OPEN LABEL STUDY, WITH AN UPWARD TITRATION OVER FIVE DOSE LEVELS ADMINISTERED BY INTRADERMAL INJECTION.

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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OUTPUT TEMPLATES SIGNATURE PAGE

Table, Listing and Figure shells Final V1.0 (Dated 28FEB2018) for Protocol ATX-GD-59-001.

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1. LIST OF ABBREVIATIONS

AEs	Adverse Events
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ATC	Anatomic Therapeutic Class
AST	Aspartate Aminotransferase
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
CI	Confidence Interval
CTMS	Clinical Trial Management System
CS	Clinically Significant
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DHR	Data Handling Report
DMC	Data Monitoring Committee
DR	Data Review
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ET	Early Termination
FT3	Free Triiodothyronine
FT4	Free Thyroxine
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
ITT	Intention-to-treat
LLOD	Lower Limit of Detection
LLOQ	Lower Limit of Quantification

Max	Maximum
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mRNA	Messenger Ribonucleic Acid
NCS	Not Clinically Significant
PBMC	Peripheral Blood Mononuclear Cell
PP	Per-protocol
PPD	Purified protein derivative from Mycobacterium Tuberculosis
PR	Period that extends from the beginning of the P wave until the beginning of the QRS complex
PT	Preferred Term
Q1	25th Percentile
Q3	75th Percentile
QA	Quality Assurance
qPCR	quantitative Polymerase Chain Reaction
QRS	Onset of ventricular depolarisation
QT	Total duration of ventricular depolarisation
QTcB	Bazett's correction formula
r	Correlation coefficient
RBC	Red Blood Cell
RR	Heart Rate Variability
RQ	Relative Quantities
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure

SD	Standard Deviation
SD1	Study Day 1
SI	Système International
SOC	System Organ Class
SRR	Specimen-to-reference Ratio
STL	Statistical Team Lead
TBAb	Inhibitory TSHR Antibodies
TBII	TSHR-binding Inhibitory Immunoglobulin
TEAEs	Treatment-emergent Adverse Events
TESAE	Treatment-emergent Serious Adverse Events
TLF	Table, Listing and Figure
TSAb	Stimulatory TSHR Antibodies
TSH	Thyroid Stimulating Hormone
TSHR	Thyroid Stimulating Hormone Receptor
TT	Tetanus Toxoid
ULOQ	Upper Limit of Quantification
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol ATX-GD-59-001. It describes the data to be summarised and analysed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on the approved final protocol ATX-GD-59-001, dated 15JAN2016, including Amendment 1 dated 05APR2016, Amendment 2 dated 17MAY2016 and Amendment 3 dated 06JAN2017. In addition, it is based on the electronic case report form (eCRF) Version 5.0, dated 13APR2017.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective is to evaluate whether ATX-GD-59 administration every two weeks by intradermal injection is safe and well tolerated in male and female subjects with Graves' disease, not currently treated with anti-thyroid therapy.

Safety endpoints, that will be evaluated on an ongoing basis up to Week 22 (i.e., 28 days post last study medication dose), are:

- Injection site reactions as reported by the subjects in the diary card.
- Occurrence of treatment related Adverse Events (AEs), Serious Adverse Events (SAEs), and laboratory abnormalities compared to baseline.
- Results from the physical examination, and vital signs (reported on an ongoing basis and compared to baseline).
- Early withdrawal and reasons for early withdrawal from treatment and/or the study.

3.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To assess the effects of ATX-GD-59 on Thyroid Stimulating Hormone Receptor (TSHR) antibody levels.

- To assess the ratio of stimulatory TSHR antibodies (TSAb) versus Inhibitory TSHR antibodies (TBAb).
- To assess the effect of ATX-GD-59 on Free Triiodothyronine (FT3), Free Thyroxine (FT4) and Thyroid Stimulating Hormone (TSH) serum levels.

3.3. EXPLORATORY OBJECTIVES

The exploratory objectives of the study are as follows:

- To assess the effects of ATX-GD-59 on TSHR induced Peripheral Blood Mononuclear Cell (PBMC) T-cell activity.
- To assess the effects of ATX-GD-59 on the T-cell cytokine signature.
- To assess the effects of ATX-GD-59 IL-10 pathway and associated genes expression (Messenger Ribonucleic Acid [mRNA]).

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

This is a phase I, first in human, open-label within subject dose-escalating study to evaluate the safety and efficacy of ATX-GD-59 in approximately 12 evaluable subjects with Graves' disease who are HLA-DRB1*15, HLA-DRB1*03 and/or HLA-DRB1*04 positive and not currently treated with anti-thyroid therapy.

There will be an upward titration over five dose levels (injection(s) of 25, 50, 100, 400 and 800 µg) of ATX-GD-59, followed by a further five injections of the highest dose (expected to be 800 µg total peptide). All doses are based on the total peptide.

No control group will be utilized in this study and all subjects will receive the same dose-escalation schedule of ATX-GD-59.

All doses will be administered by intradermal injection to the anterior abdominal wall or thigh at intervals of 14 +/- 3 days.

4.2. SCHEDULE OF EVENTS

	Scree n	Titration Period					Full dose Treatment Period					Follow-up		*ET /USV
Activity	**W -4**	**SD1**	**W 2**	**W 4**	**W 6**	**W 8**	**W 10**	**W 12**	**W 14**	**W 16**	**W 18**	**W 22**	**W 30**	
Investigational Medicinal Product dose (µg)	0	25	50	100	400	800	800	800	800	800	800	0	0	0
Informed Consent prior to Screening (week-4)	●													
Demographics	●													
Inclusion/Exclusion Criteria	●	●												
Medical History[1]	●													
Family History of Autoimmune Disease	●													
Graves' disease History	●													
Physical Examination [2]	●	●	●	●	●	●	●	●	●	●	●	●		●
Vital signs[3,4]	●	●	●	●	●	●	●	●	●	●	●	●	●	●
12 lead ECG[3,4]	●	●	●	●	●	●	●	●	●	●	●	●		
Issue new diary/ diary review		●	●	●	●	●	●	●	●	●	●	●		●
Adverse Event Recording	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Injection site reaction assessment		●	●	●	●	●	●	●	●	●	●	●		●
Concomitant Medications/Procedures	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Haematology & Chemistry Tests[5]	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Analysis and ratio of stimulatory vs inhibitory THSR antibodies	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Urine/serum Pregnancy Test[6]	●	●		●		●		●		●		●	●	●
Urine Analysis	●	●	●	●	●	●	●	●	●	●	●	●	●	●
HLA Typing	●													
Anti-drug antibody test	●						●		●		●	●		●
Blood Sampling for specific T cell activity assay, additional Immunological Biomarkers[5] and IL-10 pathway and associated genes (mRNA).	●	●									●	●		●

1. Significant medical history as determined by the investigator to be recorded (including a history of autoimmune diseases).
2. Include height at week -4 only.
3. Respiration rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, oral body temperature, recorded after the subject has been sitting quietly for at least 5 minutes.
4. Electrocardiogram (ECG) and Vital signs will be measured pre and post dose.
5. Blood samples to be drawn prior to dosing.
6. Serum pregnancy test at week -4 only. Urine dipstick test for all subsequent visits.

* Early Termination (ET) is performed if the subject is withdrawn between Study Day 1 (SD1) and Week 22.
Unscheduled visit performed at any time during the study. Number of blood tests required to be agreed with the study medical monitor.

4.3. CHANGES TO ANALYSIS FROM PROTOCOL

4.3.1. POPULATIONS

The Per-protocol (PP) population requirements stated in the protocol (see section 20.4.2) included subjects required to receive the full treatment regimen (i.e., all doses received and at least 80% of protocol-specified total study drug volume injected for the entire treatment period). Compliance with respect to study drug volume (µL) injected will be replaced by compliance with respect to total study drug dose (µg) injected. Since the eCRF records changes from planned dose injected, not changes from planned dose volume injected and the direct calculation between study drug dose and volume, this change was implemented for consistency for reporting of study drug dosing data. Further the PP population will only be summarised separately, if it represents at least 50% of the total Intention-to-treat (ITT) population and is different from the ITT population by at least one subject.

The definition of the anti-thyroid drug population in the protocol (see section 20.4.3) is defined as the PP population plus those who had received anti-thyroid drugs during the ATX-GD-59 dosing and follow-up period to Week 22. Following a discussion with Apitope, the definition for the anti-thyroid drug population for analysis was updated to any ITT subject taking anti-thyroid drugs at any time post first dose of ATX-GD-59 up to and including the Week 22 visit. Further, this population will only be summarised separately, if it represents at least 50% of the total ITT population and is different from the ITT population by at least one subject.

4.3.2. BASELINE DEFINITION

The baseline for Vital Signs in the protocol (section 20.13) is defined as Screening (Week -4). Following a discussion with Apitope, the following baseline definition will be used instead “Baseline is defined as the last available (scheduled or unscheduled) assessment prior to the first administration of study drug”.

4.3.3. COMPLIANCE

Actual study drug volume (µL) injected, total study drug volume administered and percentage compliance with respect to volume injected will not be summarised or listed. This change from the protocol section 20.6 will be implemented since the eCRF records changes from planned dose injected, not changes from planned dose volume injected, and the latter can be directly derived from study drug dose administered, hence compliance can be determined based on study drug dose (µg) injected only.

4.3.4. EFFICACY ASSESSMENTS

The protocol (section 20.7) noted that the definition of responder to be used in the analysis would be defined in the SAP. A responder endpoint will however not be defined or used due to the small sample size and loss of information about magnitude of response due to the required dichotomisation needed and no published information on what is considered a clinically relevant cut-off between response and no response. Percentage change from baseline in addition to change from baseline at each time point for FT3, FT4 and TSH will be presented and summarised. Shifts to within and outside normal and abnormal range compared with baseline and incidence of markedly abnormal laboratory results will also be presented for the thyroid function tests.

4.3.5. ADVERSE EVENTS

Descriptive analysis of AEs will include frequency of events (AEs) in addition to incidence of subjects within each treatment period and dose level, to faciliate description of multiple reports of events of the same System Organ Class (SOC) or Preferred Term (PT).

The definition of post-treatment AEs stated in the protocol (section 20.9) was any AEs starting post treatment, commencing at Week 22. This was amended to AEs started or worsening after 28 days following last study drug treatment. This is to accommodate a variable Week 22 visit (window +/-3 days) and any ET visits where there is no Week 22 visit.

4.3.6. CONCOMITANT MEDICATIONS

Descriptive analysis of concomitant medications will include frequency of medications in addition to incidence of subjects within each treatment period, to faciliate description of multiple reports of medications of the same SOC or PT. The treatment period will also be sub-divided into the titration period and full treatment period.

4.3.7. PROCEDURES

Procedure period will also include 'prior' in order to identify in the listings and summarise any procedures occurring prior to first study drug administration. The treatment period will also be sub-divided into the titration period and full treatment period for listings and summaries.

4.3.8. SUMMARIES OF SAFETY AND EFFICACY ENDPOINTS

All study visits up to and including Week 30 will be presented in summaries of safety and efficacy endpoints which are summarised by scheduled visit. The protocol (sections 20.7 and 20.8) specifies that visits up to Week 22 will be summarised.

5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Interim safety analysis
- Final analysis

5.1. DATA MONITORING COMMITTEE

No analyses will be performed by IQVIA Biostatistics. IQVIA Data Management will produce the required listing output for the interim safety analysis review by the Data Review Committee (DMC) (see Data Monitoring Committee Plan, version 2.0, 10 February 2017).

5.2. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Apitope authorisation of this SAP, relevant set of the Table, Listing and Figure (TLF) shells, the final population assignments and database lock.

See Appendix 4: Population Assignment and Data Review (DR) Plan for details pertaining the requirements for the DR meeting and outputs to be produced.

5.3. STUDY POPULATION

The Study population corresponds to all enrolled subjects, i.e. all subjects eligible for enrolment into the study. All data listings will be based on the Study population. Screen failures (including the initial screen of re-screened subjects) will be included in the disposition, demographics and eligibility listings of all subjects (i.e., all subjects providing written informed consent), and the number of screen failures will be summarised in the Study Disposition table.

5.4. ANALYSIS POPULATIONS

5.4.1. INTENTION-TO-TREAT [ITT]/ SAFETY POPULATION

A primary ITT population will be defined for use in presenting baseline, efficacy and safety data. The ITT population corresponds to all subjects who received at least one administration of study drug at any time during the study, irrespective of compliance with eligibility and other protocol criteria.

The Safety population will be denoted as the 'ITT population' for the summarisation of safety endpoints.

5.4.2. PER-PROTOCOL [PP] POPULATION

A secondary PP population (i.e. the evaluable subjects) will be used to also consider all efficacy data, and is defined as all ITT subjects who complied with the protocol requirements. Subjects will need to have complied with the protocol (i.e. no major protocol deviations) up to and including the Week 22 visit, criteria to include (but not limited to):

- Met all inclusion and none of the exclusion criteria on study entry,
- Received the full treatment regimen (i.e. all doses received and at least 80% of protocol-specified total study drug dose (µg) injected for the entire treatment period, to be confirmed at the DR meeting),
- Not taken prohibited medications during the treatment period.
- Procedure done with consent.
- Not received anti-thyroid drugs prior to the Week 22 visit.

Efficacy parameters will be summarised for the PP population provided that it differs from the ITT population by at least one subject and is at least 50% of the ITT population.

Major protocol deviations determined programmatically, as well as the 'Protocol Deviations' log recorded in the IQVIA Clinical Trial Management System (CTMS) will be reviewed for determination of any further major deviations, to be included as reasons for exclusion from the PP population in the population assignment listing.

5.4.3. ANTI-THYROID DRUG POPULATION

A third analysis population, the anti-thyroid drug population, is defined as any ITT subject taking anti-thyroid drugs at any time post first dose of ATX-GD-59 to the Week 22 visit.

Efficacy parameters will be summarised for the anti-thyroid drug population provided that it differs from the ITT population by at least one subject and is at least 50% of the ITT population.

All data will be listed for subjects in the anti-thyroid drug population, however, only data up to the time point of dosing with anti-thyroid drugs will be included in summary tables of efficacy (TSHR antibodies and thyroid function tests for subjects in the anti-thyroid drug population). Additionally, visits post administration of anti-throid drugs in these subjects will be flagged in all by-visit listings of efficacy and safety data except diary card recordings of injection site reactions, and listings of exploratory efficacy parameter data (B set).

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to present start/ stop day of assessments and study events relative to the reference start date.

Reference start date is defined as the first administration date of study drug (Study Day 1).

- If the date of the assessment/event is on or after the reference start date then:

Study Day = (date of assessment/event – reference start date) + 1.

- If the date of the assessment/event is prior to the reference start date then:

Study Day = (date of assessment/event – reference start date).

In the situation where the assessment/event date is partial or missing, Study Day, and any corresponding durations will appear missing in the listings.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last available assessment (scheduled or unscheduled) prior to the first administration of study drug. In the case where the last non-missing measurement prior to first administration of study drug and the reference start date coincide, that measurement will be considered baseline.

Baseline and at each scheduled post-baseline visit as well as separately for multiple assessments within a visit, change from pre-dose to each post-dose assessment will also be evaluated.

6.3. POST-BASELINE

Unless otherwise specified, post-baseline is defined as any assessment (scheduled or unscheduled) obtained after the first study drug administration.

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries. In the case of a retest (same visit number assigned), the earliest available measurement for that visit will be used for by-visit summaries.

The Early termination (ET) visits will be reviewed at the DR meeting, and it will be determined for each ET visit, whether it will be included in summary tabulations in place of the scheduled visit (where the ET visit has occurred in place of the scheduled visit and is within the relevant visit window) or presented separately (where the ET visit is not in a scheduled visit window). All ET visits will be listed as ET visits in the data listings.

Listings will include scheduled, unscheduled, retest and ET assessment data.

6.5. WINDOWING CONVENTIONS

No visit windowing will be performed for this study, except for ET visits as specifically described in this SAP (see section 6.4).

6.6. STATISTICAL TESTS

No formal statistical testing will be carried out for the analyses of the data from this study. All data presentations will be descriptive only.

The default summary statistics for quantitative variables will be as follows:

- Number of subjects in each category (n)
- Mean
- Standard deviation (SD)
- Minimum
- 25th Percentile (Q1) (Efficacy outcomes)
- Median
- 75th Percentile (Q3) (Efficacy outcomes)
- Maximum
- Geometric Mean (Efficacy outcomes with exception of percentage change from baseline).
- 95% Confidence Interval (CI) based on geometric mean (Efficacy outcomes with exception of percentage change from baseline)
- Correlation coefficient (r) (Exploratory efficacy outcomes)
- P-value (Exploratory efficacy outcomes)

The default summary statistics for qualitative variables will be as follows:

- Number of subjects in each category (n).
- The percentages of subjects in each category (%) can be presented relative to either one of the following:

  - The total number of subjects in the relevant analysis population.
  - The total number of subjects in the relevant analysis population, with assessments available (observed cases).

If the original data has N decimal places, then the summary statistics should have the following decimal places:

- Minimum, maximum: N
- Mean, geometric mean, median, Q1, Q3 and 95% CI: N + 1
- SD: N + 2
- r: 3
- P-value: 4
- Fold change: 1

Frequencies and percentages (n and %):

- Percentage values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage.
- Percentages of subjects should be rounded to whole numbers. Percentages of events will be reported to one decimal place.

6.7. COMMON CALCULATIONS

6.7.1. CHANGE FROM BASELINE

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X (pre-dose or post-dose [if applicable]) – Baseline Value.

- For vital signs and 12-lead ECG findings, post-dose values at each post-baseline visit.

6.7.2. PERCENTAGE CHANGE FROM BASELINE

For FT3, FT4 and TSH, percentage (%) change from baseline will be calculated as:

- (Post-dose value - Baseline value)/Baseline value * 100

6.7.3. CHANGE FROM PRE-DOSE

For quantitative measurements, change from pre-dose will be calculated as:

- Test Value at Visit X, post dose – Pre-dose Value at Visit X

6.7.4. FOLD CHANGE FROM BASELINE

For quantitative measurements, fold change from basline will be calculated as:

- Exponential (natural log post baseline value – natural log baseline value)

6.7.5. TREATMENT PERIOD

Treatment period start for medications, procedures and AEs is defined as:

- First administration of study drug.

Titration period start for AEs, medications and procedures is defined as:

- First administration of study drug.

Full treatment period start for AEs, medications and procedures is defined as:

- First administration of full treatment period study drug (i.e., second dose of 800 µg).

Treatment period end for medications, procedures and AEs is defined as:

- Last administration of study drug date plus 28 days.
- For AEs onset dates/times are recorded, so the calculation of period starts/ends will take account of both dates and times.

6.7.6. POST-TREATMENT PERIOD

Post-treatment period start for medications, procedures and AEs is defined as:

- Last administration of study drug date plus 29 days. For AEs onset dates and times are recorded, so the calculation of period will take both onset dates and times into account.
- For AEs dates/times are recorded, so the calculation of period starts/ends will take account of both dates and times.

Any AE, medication or procedure with partially missing start date (and time for AEs) will be assigned on the basis of the information available and worst case principle. See Appendix 2: Partial Date Conventions for handling of partial dates for medications and procedures.

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

Not applicable, as no adjustment for covariates and factors will be done for this study.

7.2. MULTICENTRE STUDIES

Centre pooling will not be carried out for use in analyses for this study.

7.3. MISSING DATA

Missing efficacy data will not be imputed.

If a result/value is missing, change from pre-dose/baseline result will be presented as missing in the listing; hence no imputation for a missing change from pre-dose/baseline will be performed.

Any outlying data points will be included in the summary tables. Invalid data will be evaluated on a case by case basis at the DR meeting, and any exclusions from summary tables will be fully justified. Any

outlying/invalid data will be listed.

Any missing or partial dates/times will be imputed as described in this SAP. See Appendix 2: Partial Date Conventions for handling of partial dates for medications and procedures.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Not applicable, the study does not include any confirmatory objectives.

7.5. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for this study.

7.6. EXPLORATORY ANALYSIS

Selected secondary efficacy parameters will be further evaluated in exploratory analyses. In this non-comparative study, no formal hypothesis tests were determined in the protocol, hence the p-values presented will be interpreted in the descriptive sense only and are further described in section 14.2.2.

8. OUTPUT PRESENTATIONS

Appendix 1: Programming Conventions for Outputs, describes the conventions for presentation of data in outputs.

The TLF shells provided, together with this SAP describes the presentation of data for the final analysis for this study and therefore the format and content of the summary TLFs to be provided by IQVIA Biostatistics.

Note that verbatim terms and specifications (i.e., the reason a specific assessment was not performed, textual details and descriptions) contain verbatim text. Verbatim text will be reviewed for the presence of any spelling errors and processed according to data management procedures prior to database lock. Verbatim text will be presented in the listings 'as is' and no manual 'hard-coding' corrections of any remaining spelling errors will be made.

9. DISPOSITION AND WITHDRAWALS

Protocol deviations are recorded by the monitor in CTMS throughout the study. Disposition information is captured on the ET and End of Study eCRF.

All subjects who provide informed consent will be accounted for in this study.

The following summaries will be provided:

- Incidence of subjects enrolled, screen failures including the initial screen for re-screened subjects, treated, completed study treatment, early discontinuation of treatment, completed study, early withdrawal from study participation including the primary reasons for early discontinuation from treatment and withdrawal from study.

- Analysis populations.

The following data will be presented in by-subject listings:

- Study disposition details including last dose received (and whether titration or full treatment dose) prior to completion/early discontinuation from treatment or from the study (All subjects). Note screening failures will be flagged in the listing

- Protocol deviations. All protocol deviations recorded by the monitor in CTMS throughout the study (site-level and subject-level) (Study population).

- Study visits including protocol and actual study day, deviation, flagging of any outside protocol-specified windows as well as ET visit assignments to a scheduled visit (ITT population).

- Analysis population assignments including reason(s) for exclusion from the PP population. Note that all efficacy listings will also include analysis population membership flags. Major protocol deviations identified during the study by the monitor and protocol deviations determined during analysis and reporting of the study data will be included in the reason(s) for exclusion (Study population).

- Eligibility criteria, including inclusion and exclusion criteria exceptions and eligibility verification (All Subjects). Note screening failures will be flagged in the listing.

The following deviation will apply for the visit listing:

- Deviation = Protocol Study Day – Actual Study Day.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic, Autoimmune and other subject characteristics data will be recorded on the Demography and Medical History eCRFs.

The following summaries (descriptive statistics and frequency counts) will be presented for the ITT population:

- Demographic and Baseline characteristics at Screening (Age (years), Sex, Country, Ethnicity, Race, Height (cm), Weight (kg) and Body Mass Index (BMI) (kg/m^2). Age and BMI are pre-populated in the validated eCRF design, based on Year of birth (01 Jan for day and month) and height and weight entries in the eCRF).

- Autoimmune disease and other subject characteristics (Family History including incidence of autoimmune disease and Graves' disease or other diagnosis, thyroid function tests (summary statistics, and frequency counts of values relative to their normal range including markedly abnormal, below/above normal range and within normal range and Human Leukocyte Antigen (HLA) typing).

The following data will be presented in by-site/subject listings for all subjects:

- Demographics and Baseline characteristics at Screening. Note screening failures will be flagged in the listing

- Autoimmune disease and other subject characteristics, including family history of autoimmune disease, HLA typing and thyroid function tests at Screening. Note screening failures will be flagged in the listing.

11. MEDICAL HISTORY

Medical history (relevant medical history as determined by the investigator, including vaccination status, Human Immunodeficiency Virus (HIV) and Hepatitis status) of a subject is recorded on the Medical History eCRF during the screening visit.

All Medical History conditions (are) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1.

No partial date imputations for medical history start/stop dates will be performed and subsequently no study day calculated. If no stop date is reported it is assumed that the medical history condition is ongoing.

Medical history conditions will be listed for the Study population and summarised for the ITT population as:

- The number (n) and percentage (%) of subjects that received any Tetanus booster or BCG vaccine, with a history of HIV, Hepatitis B or Hepatitis C infection, as well as each of past and ongoing medical history conditions at Screening will be presented overall and by SOC and PT. If a medical history condition occurs more than once for a subject, the subject will only be counted once per MedDRA SOC or PT.

- A separate by-subject data listing will be produced for medical history conditions (past or ongoing) including the subject's vaccination status, as well as HIV and Hepatitis status.

12. MEDICATIONS AND PROCEDURES

Medications taken prior to and during the conduct of the study will be obtained from the Concomitant Medications eCRF and will be coded using World Health Organization Drug Dictionary (WHO-DD) Enhanced Version 01MAR2016E/WHO Herbal Dictionary.

Procedures performed during the conduct of the study will be obtained from the Concomitant Procedures eCRF and coded using the MedDRA coding dictionary, version 19.1.

Medications are allocated to a study period as follows:

- Prior medication: Any medication that started and stopped prior to first administration of study drug.
- Concomitant medications taken during the treatment period: Any medication that started or stopped on or after first administration of study drug up to and including 28 days after last administration of study drug, or is ongoing. Concomitant medications will be presented for titration period and full treatment period.
    - Titration period: Any medication that started or stopped on or after first administration of study drug up to first administration of full treatment period study drug, or is ongoing.
    - Full treatment period: Any medication that started or stopped on or after first administration of full treatment period study drug (i.e. 2nd 800 µg dose) up to and including 28 days after last administration of study drug, or is ongoing.
- Post-treatment medications: Any medication that started more than 28 days after last administration of study drug.

Procedures are allocated to a study period as follows

- Concomitant procedures taken during the treatment period: Any procedure that started or stopped on or after first administration of study drug, up to and including 28 days after last administration of study drug, or is ongoing. Procedures will be similarly broken down by titration and full treatment period as for medications.
- Post-treatment procedures: Any procedure that started more than 28 days after last administration of study drug.

Study periods for medications and procedures are mutually exclusive, therefore a medication or procedure can be only be assigned to one period, namely Prior, Concomitant or Post-treatment. Within concomitant medications and procedures the titration period and full treatment period are not mutually exclusive; hence a medication or procedure can be assigned to the titration period, full treatment period or both. Any medication ongoing during a treatment period will be included even if it started in an earlier period but has not ended before the start of the next period.

Note that the denominator for percentages of subjects is the total number of subjects in the ITT population with data available for the respective period. The denominator for percentages of events is the total number of events in the respective period.

See Appendix 2: Partial Date Conventions for handling of partial dates for medications/ procedures. In the case where it is not possible to define a medication/ procedure as prior, concomitant (titration period/full treatment period for medications), or post-treatment, the medication/ procedure will be classified by the worst case; i.e. titration period (concomitant) if it cannot be ruled out by the partial or missing date(s) recorded.

The following tables will be presented for the ITT population:

- The number (n) and percentage (%) of subjects with at least one medication and frequency of medications: Prior medication, concomitant medication taken during the treatment period, broken down by titration period and full treatment period, and overall and post-treatment medication taken more than 28 days after the last administration of study drug, will be presented overall and by Anatomic Therapeutic Class (ATC) Level 1 and within ATC Level 1 by ATC Level 3 and within ATC Level 3 and by WHO-DD Preferred Drug name. If medication occurred more than once for a subject within a period, the subject will only be counted once per ATC Level/Preferred drug name in that period.

- The number (n) and percentage (%) of subjects with at least one prior, concomitant (concomitant procedures occurring during the treatment period, broken down by titration period and full treatment period, and overall) and post-treatment procedures will be presented overall and by MedDRA SOC and within SOC by PT. If a procedure occurred more than once for a subject within a period, the subject will only be counted once per MedDRA SOC or PT in that period.

The following by-subject listings will be presented for the Study population:

- Prior, concomitant and post-treatment medications together with detail regarding indication, medication period as well as the relevant treatment period(s), as applicable.
- Prior, concomitant and post-treatment procedures together with detail regarding reason for procedure, procedure period as well as the relevant treatment period(s), as applicable.
- Contraception requirements and precautions taken.

13. STUDY DRUG EXPOSURE AND COMPLIANCE

Study drug administration details (planned and any deviations from planned), and administration times and site of administration details, as well as any injection related reactions are recorded for each dosing visit in the eCRF.

Study drug exposure and compliance will be summarised and listed for the ITT population.

Descriptive statistics will be provided for both study drug exposure and compliance for the dose amount (µg) per dose level, by visit, period (titration and full treatment) and overall. Number of doses injected will be presented per period (titration and full treatment) and overall. Planned volume (µL) will be listed.

The study drug dose amount (µg) over scheduled protocol visits, over the titration period, over the full treatment period and overall, for the entire treatment period will be listed and summarised. A summary of study drug exposure and compliance (%) indicating the actual dose (µg) injected as well as the number of doses over the scheduled protocol visits for the titration, full treatment periods and overall will be summarised and presented in a summary table.

The data is also to be presented in the following by-subject listings for the Study population:

- Study drug exposure and compliance (%) per site/subject per visit for the planned and actual dose number and dose (µg) as well as reason if deviating from the protocol, the injection site location and reaction indication will be listed. Note that since the eCRF records the actual dose only if different than planned dose, with reason if different, the actual dose will be populated where the record is 'blank' with the exception where the reason text indicates that the actual dose is less than planned but not known. In this case, study drug exposure and compliance for this dose level will not be calculated and presented as 'Unknown'. Sums across dose levels will not be calculated and will not form part of the summary statistics.
- Diary card dispensing, return and review details by visit.

The following derivations will apply:

- Number of doses compliance (%) will only be derived for the titration and full treatment periods, as well as 'Overall' for the study.

Number of dose compliance (%) = (Actual number of doses for the period / Protocol-specified number of doses for the period)*100

- Dose amount compliance (%) will be derived per visit, for the titration and full treatment periods, as well as 'Overall' for the study.

Dose amount compliance (%) = (Actual amount of drug injected / Protocol-specified drug amount)*100

Note that Dose Number 3 and 5 to 10 will include two intradermal injections; hence the compliance for dose number 3 and 5 to 10 will be derived based on the sum of the actual doses (µg) of the two intradermal injections. These doses will have a frequency count of one for the summary table.

Subjects will be assessed for exposure and compliance with respect to the dose and treatment period evaluated. Hence for a subject withdrawing after the first study drug dose, the subject will be included in exposure and compliance calculations for dose 1 , titration period and overall only, and will not contribute to calculations for subsequent dose levels.

14. EFFICACY OUTCOME

14.1. EFFICACY ENDPOINTS

The secondary objectives of the study relate to efficacy endpoints. Efficacy analyses will be performed for the ITT, PP and the anti-thyroid drug populations, if applicable. Separate summaries for the PP and anti-thyroid drug populations will only be done if the respective population is at least 50% of the total ITT population and at least one subject less than the ITT population.

TSHR-binding inhibitory immunoglobulin (TBII), TSAb and TBAb will be measured at the Molecular Thyroid Research Laboratory Department of Medicine facility, Mainz, Germany.

FT3, FT4 and TSH levels will be measured at the IQVIA Central Laboratory.

14.1.1. EFFICACY VARIABLES

The exploratory objectives of the study are as follows:

- TBII antibody levels.
- TSAb, TBAb and ratio of TSAb over TBAb.
- FT3, FT4 and TSH serum levels.

14.1.2. Missing Data Methods for Efficacy Variable(s)

No missing efficacy data will be imputed.

14.1.3. Presentation of Efficacy Variables

14.1.3.1. TSHR-binding inhibitory immunoglobulin (TBII)

TBII levels that are below the limit of quantitation (BLQ) will be treated as value for descriptive statistics/figures but presented as '< value', in listings. The BLQ levels will be confirmed by Apitope or the Molecular Thyroid Research Laboratory prior to database lock.

The following summaries will be provided for the TBII levels:

- Descriptive statistics (observed, change from baseline) will be presented for TBII levels at baseline and at each post-baseline visit for each analysis population as applicable.

The following figure will be presented for the ITT population:

- Line graph to present individual results for TBII levels on a linear scale over time. A horizontal dotted line will indicate the cut-off level of 1.75 IU/L.

TBII levels will be presented in by-subject listings for the Study population including absolute result and change from baseline. Levels above the cut-off level for TBII (1.75 IU/L) as well as levels that are not within the assay detection range of (0.3 to 40 IU/L) for TBII will be flagged. Assessments post administration of anti-thyroid drugs will also be flagged.

14.1.3.2. Stimulatory and inhibitory TSHR antibodies, and ratio of stimulatory to inhibitory TSHR antibodies

The following summaries will be provided for the TSAb, TBAb and ratio of stimulatory to inhibitory TSHR antibodies:

- Descriptive statistics (observed, change from baseline) will be presented for each antibody at baseline and at each post-baseline visit for each analysis population as applicable.

The following figures will be presented for the ITT population:

- Line graphs to present individual results for TSAb, TBAb and ratio of stimulatory to inhibitory TSHR antibodies (TSAb/TBAb) on a linear scale over time. For the TSAb and TBAb plots, a horizontal dotted line will indicate the cut-off level for TSAb and TBAb (140 % Specimen-to-reference ratio [SRR] and 34 % inhibition respectively).

- Scatter plot of the correlation of TSAb versus TBAb levels (all time points combined). Pre-treatment, titration, full treatment and post-treatment periods will be presented with different colours/symbols on the same graph.

TSAb, TBAb, and ratio of TSAb/TBAb will be presented in a by-subject listings for the Study population including observed results and change from baseline. Levels above the cut-off levels for TSAb (140 SRR%) and TBAb (34% inhibition) will be flagged. Assessments post administration of anti-thyroid drugs will also be flagged.

14.1.3.3. FT3, FT4 and TSH serum levels

TSH level results that are below the limit of quantitation (BLQ) will be treated as value for descriptive statistics but presented as '< value', in listings. The BLQ levels will be confirmed by Apitope ot the IQVIA Central Laboratory prior to database lock.

The following summaries will be provided for for the Thyroid function tests serum level data:

- Descriptive statistics (observed, change from baseline and percentage change from baseline) will be presented for each parameter at baseline and at each post-baseline visit for each analysis population as applicable.
- Shift from baseline to each scheduled protocol post-baseline visit for FT3, FT4 and TSH serum levels categorised according to normal reference range as low, normal and high, as well as a subcategory for markedly high. The high and markedly high categories are not mutually exclusive, thus the markedly high results will be included in the high category count. For the shift the percentage (%) of subjects in each category calculated relative to the total number of subjects in the relevant analysis population with assessments available at baseline and the relevant post-baseline visit per parameter.
- Incidence of markedly high results per time point of FT3 (>20 pmol/L) and FT4 (> 45 pmol/L) for the ITT population.

Only data up to the time point of dosing with anti-thyroid drugs will be included in summary tables and figures of efficacy for subjects in the anti-thyroid drug population.

The following figures will be presented for the ITT population:

- Line graph of geometric means ± 95% CI limits (geometric) for FT3 and FT4.
- Line graph of change from baseline and percentage change from baseline means ± SD for FT3 and FT4.
- Line graph of individual FT3 and FT4 results over time. Horizontal dotted lines will indicate the normal range lower and upper limits for each parameter.

- Scatter plots of each of change from baseline and percentage change from baseline versus baseline levels for FT3 and FT4 at Week 18, 22 and 30 will be presented with different colours/symbols on the same graph.

- Histograms of geometric means by timepoint, with a horizontal bar to indicate the normal range and vertical dotted line on the SD1 bar, to denote start of treatment, on the Week 10 bar to denote end of titration period and on the Week 22 bar to denote end of full treatment period for observed results for FT3 and FT4.

FT3, FT4 and TSH serum levels will be presented in a by-subject listings for the Study population including observed results, change from baseline, percentage change from baseline and fold change from baseline (see section 14.2.2.1). Results outside the normal range and above the markedly abnormal range (trigger values) for administration of anti-thyroid drug administration (FT3 > 20 pmol/L and/or FT4 > 45 pmol/L on 2 consecutive scheduled/unscheduled visits) will be flagged (i.e. worst case flag will be presented). Assessments post administration of anti-thyroid drugs will also be flagged.

Note that individual subjects with FT3, FT4 and TSH results outside of normal range and with clinical markedly abnormal laboratory results will also be listed with safety laboratory listings.

14.1.3.4. Anti-drug Antibodies

Anti-drug antibody data confirming positive or negative will be listed.

14.2. EXPLORATORY EFFICACY

KWS Biotest Ltd. is responsible for the assay methodology and providing the exploratory efficacy parameter data to IQVIA, for presentation in the Clinical Study Report (CSR) and for exploratory analyses. The presentation of these exploratory data within the CSR will be in the format of data listings of the assay data. Further exploratory summaries and graphical presentations will conducted separately after the finalisation of the TLFs and CSR for the study, by Apitope and will be reported in a separate report of the exploratory analyses.

Each listing will be provided as a separate output (flat file, MS/Word document) as well as a corresponding MS/Excel spreadsheet and SAS dataset.

14.2.1. ANALYSIS OF EXPLORATORY EFFICACY VARIABLES

14.2.1.1. TSHR induced Peripheral Blood Mononuclear Cell specific T cell activity (Flow Cytometry)

TSHR-induced PBMC Specific T-cell Activity (Flow Cytrometry) for both T-effector and T-regulatory assays will be presented in by-subject listings by assay day number (Day 6 and 8), parameter, visit (Screening, SD1, Week 18 and Week 22), and stimulus (negative control i.e., no antigen; test i.e., peptide and positive control i.e., influenza/ Tetanus toxoid (TT)/Purified protein derivative from Mycobacterium Tuberculosis (PPD)) for the Study population. Sample collection times/reasons not done and comments provided by the KWS Biotest Ltd in the data files will be listed. Poplulation flags and HLA typing status will also be included. Assessments post administration of anti-thyroid drugs will also be flagged. All flow cytometry results in % are to be presented to 3 significant figures and counts data as integers in this listing set.

A second set of listings of both the T-effector and T-regulatory results for each parameter expressed in percentages and counts separately will also be presented without flagging the values post administration of anti-thyroid drugs.

14.2.1.2. T-cell Cytokine Signature in Antigen-specific T-cells (Luminex Method)

The acceptable recovery range for standard curve points was set from 70 to 130%. The upper and lower limits of quantification (ULOQ/LLOQ) are defined as the highest and lowest standard curve points, respectively, that fall within this range.

The cytokine parameters (i.e., IL-2, IL-4, IL-6, IL-10, IL-13, IL-17A, GM-CSF, IFN-γ, TGF-β1) will be presented in by-subject listings per visit (for Screening, SD1, Week 18 and Week 22, assay day (Day 4, 6 and 8) and stimulus for the Study population. Poplulation flags and HLA typing status will also be included. Assessments post administration of anti-thyroid drugs will also be flagged and all cytokine results will be presented to 2 decimal places. Sample collection details and comments will be included in the listing.

A further listing presenting the same data, however, by cytokine and stimulus, with assay day nested within visit will also be presented without flagging the values post administration of anti-thyroid drugs.

14.2.1.3. Immunological Biomarkers: mRNA Pathway and Associated Genes

All values are relative quantities (RQ) compared with baseline (SD1 pre-dose) sample. The lower and upper error bars are the RQ minimum (Min) and maximum (Max), which are derived from the combined SD of triplicate PCR cycle (Ct) values for all four targets (i.e., the target gene and the three reference genes). A SD of (+/-) < 0.5 cycles is the limit applied, equating to an RQ Min of 70% and an RQ Max of 140% of the RQ value. LLOQ (concentration where the SD of 10 replicates is >0.5 cycles) and lower limit of detection (LLOD) (concentration that gives 95% positive quantitative Polymerase Chain Reaction (qPCRs) in 10 replicates) were empirically derived for each target using serial dilutions of template.

Target gene parameters (I,e., IL-10, TIGIT, TIM3, FoxP3, LAG3, cMAF, Nfil3, AHR, IL-21) will be presented in a by-subject listing for Screening, SD1, Week 18 and Week 22 (follow-up) for the Study population. Assay results wil be presented as quantities relative to SD1, and will be presented with lower and upper error bars, comments and sample collection details. Target genes where the measurements are below the LLQ and the SD is > 0.5 cycles, are flagged in the comments section as "<LLOQ" Assessments post administration of anti-thyroid drugs will also be flagged and all qPCR assay results will be presented to 2 decimal places in this listing.

14.2.2. FURTHER ANALYSIS OF EXPLORATORY EFFICACY VARIABLES

Selected secondary efficacy parameters will be further evaluated in two additional exploratory analyses. In this non-comparative study, no formal hypothesis tests were determined in the protocol, hence the p-values presented will be interpreted in the descriptive sense only and are further described below.

14.2.2.1. Baseline comparisons

Further exploratory descriptive analyses will be carried out for each analysis population to investigate the magnitude of change from baseline for TBII, TSAb, FT3 and FT4. The change from baseline for each parameter will be presented using both the parametric paired T-test and corresponding 95% CI and non-parametric Wilcoxon rank sum test. The p-values will be presented 2-sided and be interpreted in the descriptive sense only, as no formal hypothesis tests will be carried out.

For TBII and TSAb change from baseline will be presented for mean, SD and 95% CI, and for FT3 and FT4 fold change from baseline (see section 6.7.4) will be analysed using the natural logarithm of the raw data and presented using geometric mean, SD and 95% CI of the geometric mean fold change.

14.2.2.2. Correlation analysis

A correlation analysis will be carried out to investigate the relationships between the secondary efficacy parameters at Weeks 18 and 22 for FT3 and TBII, FT3 and TSAb, FT4 and TBII and FT4 and TSAb in the ITT and PP population.

Scatter plots of percentage change from baseline for each parameter versus the other at Weeks 18 and 22 will be presented with different colours and symbols on the same graph. Corresponding to each scatter plot, a non-parametric Spearman's Rank correlation coefficient to assess the extent to which the relationship between a pair of parameters are related by any monotonic function, without requiring knowledge of the joint probability distribution of the two parameters, and corresponding non-parametric Spearman's Rank correlation coefficient (permutation test) 2-sided p-value to describe the extent to which the correlation coefficient differs from zero, taking into account ties in the ranks, will be presented at each time point for each scatter plot as well in a corresponding summary table.

15. SAFETY OUTCOMES

All safety analysis will be based on the ITT population.

Only descriptive summaries of the safety data will be provided as detailed in the latest version of the TLF shell document. All available safety data will be presented in by-subject listings.

There will be no statistical comparisons done between the dose levels for safety data.

15.1. ADVERSE EVENTS

Adverse events are recorded on the AEs eCRF and coded using MedDRA central coding dictionary, version 19.1.

An AE is defined as any untoward medical occurrence in a subject administered study drug that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (i.e., an abnormal laboratory finding), symptom (i.e., rash, pain, discomfort, fever, dizziness, etc.), disease (i.e., peritonitis, bacteraemia, etc.) or outcome of death temporally associated with the use of study drug, whether or not considered causally related to the study drug.

For the purpose of the analysis, AEs are allocated to the study periods based on the start date (and time where available) of the AE as follows:

- Pre-treatment AE (Screening period): Any AE that started or worsened in severity on or after informed consent and prior to the first administration of study drug.
- Treatment-emergent adverse events (TEAEs): Any AE that started or worsened in severity on or after the first administration of study drug up to and including 28 days after the last administration of study drug.
- Non-TEAE commencing post-treatment: Any AE that started or worsened in severity more than 28 days after the last administration of study drug.
- Study periods for AEs are mutually exclusive; therefore it can only be assigned to one period, namely pre-treatment, TEAE or Non-TEAE.

AEs will be further identified as being either titration period or full treatment period AEs according to the definitions below:

- Titration period: Any AE that started or worsened in severity on or after the first administration of study drug up to the first full treatment period study drug (i.e., 2nd 800 µg dose) administration.

- Full treatment period: Any AE that started or worsened in severity on or after the first administration of full treatment period study drug (i.e., 2nd 800 µg dose) administration up to and including 28 days after last administration of study drug.

TEAEs are mutually exclusive for assignment to either the titration or full treatment periods. Note that the first dose at 800 µg is in the titraton period, and the full treatment period starts with the second dose of 800 µg.

Relationship, as indicated by the Investigator, is classed as 'not related', 'possibly related', 'probably related' or 'definitely related' (increasing severity of relationship). A drug-related AE is defined as an AE with a relationship to study drug of 'possibly related', 'probably related' or 'definitely related' or with a missing or unknown relationship to study drug. If a subject reports an AE more than once within that SOC and/or PT, the AE with the highest related assessment will be used in the corresponding summaries of relatedness.

Severity is classed as 'mild', 'moderate' or 'severe' (increasing severity). AEs with a missing severity will be classified as 'severe' (worst case). If a subject reports an AE more than once within that SOC and/or PT, the AE with the worst case severity will be used in the corresponding severity summaries.

See Appendix 2: Partial Date/Time Conventions for handling of partial dates/times for AEs. In cases where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case i.e. treatment emergent.

The following tables will be presented by dose level of study drug last received prior to onset of each individual subject's AE for the ITT population :

- An overview of the number and percentage (%) of subject and frequency of events will be provided for the following TEAEs per the dose levels per defined period (titration and full treatment periods) as well as overall:

  - TEAEs.
  - Drug related TEAEs.
  - Treatment-emergent serious adverse events (TESAEs).
  - Drug related TESAE.
  - TEAEs leading to death.
  - TEAEs leading to early study withdrawal.
  - TEAEs leading to dose interruption or suspension.

- Treatment emergent intradermal injection related reactions (Note such TEAEs will also be included in all other relevant categories, but broken out separately in addition).
- TEAEs by maximum severity.

- In addition to the overview of TEAEs, the following Incidence and frequency of TEAEs will be presented by SOC and PT. If an AE occurs more than once the subject will be counted once per MedDRA SOC and PT as relevant. Percentage of subjects in each category will be calculated relative to the total number of subjects in the ITT population for the respective dose level/period, implying all subjects who received the study drug administration or part thereof in the relevant period.

  - Incidence and Frequency of TEAEs.
  - Incidence and Frequency of TEAEs related to study drug.
  - Incidence and Frequency of TESAEs.
  - Incidence and Frequency of TEAEs leading to dose interruption, suspension or early study withdrawal.
  - Incidence and Frequency of Treatment emergent intradermal injection related reactions.
  - Incidence and Frequency of TEAEs by maximum severity.
  - Incidence and Frequency of Non-TEAEs commencing after 28 days post-treatment incorporating overview details (i.e., with the exception of dose interrupted/suspended).
  - Incidence and Frequency of Non-TESAEs commencing after 28 days post-treatment.
  - Incidence and Frequency of Non-TEAEs commencing after 28 days post-treatment, by maximum severity.

The denominator used for the calculation of percentage will be the number of subjects in the ITT population for the respective dose level/period for incidence calculations and the total number of events assigned to the dose level/period for frequency calculations.

- Listings of the following will be provided in section 14, Tables:

- Serious AEs leading to death: AEs leading to death are defined as AEs with an outcome recorded as ‘Death’ or serious event criteria recorded as ‘Death’ on the AEs eCRF.

- Serious AEs: A serious AE is defined as an AE with the result ‘Yes’ answered for the question ‘Serious event’ in the AEs eCRF.

- AEs leading to early study withdrawal: AEs leading to early study withdrawal are defined as AEs with action taken as ‘Subject withdrawn from study’ on the AEs eCRF.

- AEs leading to dose interruption or suspension: AEs will be captured on the AE and SAE eCRF where ‘Action taken with study treatment’ is indicated as ‘Study treatment permanently stopped’ or ‘Study treatment interrupted’.

The AEs data will also be presented in the following by-subject listings and include all AEs as reported from the signing of informed consent until the end of the study for the Study population:

- All AEs reported in the study together with all details, including flags for pre-treatment, TEAEs, Non-TEAEs. SAEs, injection site related and Graves' disease symptoms AEs and a flag for any subjects with no AEs reported.
- Pre-treatment AEs, TEAEs, non-TEAEs commencing post-treatment (other than Grave's disease and injection site reactions for each one), and Graves' disease symptoms and intradermal injection site related reactions will be listed separately.
- Intradermal injection related reactions will be captured on the AE and SAE eCRF where 'Is the event an intradermal injection related reaction? ' is indicated as 'Yes'. The site of last injection prior to the AE will be listed on the injection site reactions listing.
- Graves' disease symptoms will be captured where 'Causes of the event other than study drug' on the AE eCRF is indicated as 'Disease under study' and intradermal injection related reaction is not 'Yes'. Any with unknown cause will be listed as TEAEs and will not be listed as Graves' disease symptoms.

AE listings will include all details collected on the AE eCRF and additionally, time (days, hrs, mins) since last dose and a flag for period for TEAEs (titration, full treatment), last dose received prior to the AE and duration of the AE (calculated as resolution date – onset date of the AE + 1 day, and presented as Days).

15.1.1. Injection Site Reaction Diary Results

Injection site reactions captured on the diary card will be listed by subject and visit and include the AE number for reactions that are reported as AEs. Subjects were requested to complete the diary card for the first 3 days. If symptoms were still present after the 3 days, subjects would complete the diary until the symptoms had totally disappeared.

These data will be summarised as frequency counts for each grade of reaction parameter, by visit for the ITT population. In the event of more than one response per reaction parameter per visit per patient, only the most severe occurrence for each injection site reaction for each subject per visit will be counted.

15.2. Laboratory Evaluations

Blood samples for haematology, and biochemistry and urine samples for urinalysis will be collected and eCRF entries made for the collection date/time and reason for non-collection if applicable. The

Investigator is to review the laboratory report promptly, document this review, and record any clinically relevant changes occurring during the study on the Adverse Events eCRF.

Laboratory safety assessments will be assayed by Q2 Solutions Central Laboratory.

Results from the central laboratory will be included in the reporting of this study for Haematology, Biochemistry and Urinalysis. For a list of the clinical laboratory assessments to be included in the outputs together with their conversion factor to Système International (SI) units, refer to Appendix 3: Conversion Factors to Système International (SI) Units of this SAP.

Presentations will use SI units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULOQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the by-subject listings.

The following summaries will be provided for laboratory data for the ITT population:

- Descriptive statistics (observed and change from baseline) will be presented for quantitative measurements of Haematology, Biochemistry and Urinalysis laboratory results at baseline and the scheduled protocol post-baseline visits (excluding FT3, FT4 and TSH that will be summarised separately under efficacy).

- Frequency count for markedly abnormal results will be presented for quantitative measurements of Haematology, Biochemistry and Urinalysis laboratory results by visit and dose level (excluding FT3, FT4 and TSH that will be summarised separately under efficacy).

- Shift from baseline to each scheduled protocol post-baseline visit for quantitative measurements of Haematology and Biochemistry laboratory results categorised according to normal reference range as low, normal or high. Markedly low and markedly high results will be included in low and high counts respectively. For the shift the percentage (%) of subjects in each category calculated relative to the total number of subjects in the relevant analysis population with assessments available at baseline and the relevant post-baseline visit per laboratory parameter (excluding FT3, FT4 and TSH that will be summarised separately under efficacy).

- Listing of individual subjects with clinical laboratory results outside of normal range and markedly abnormal results, including their change from baseline (including FT3, FT4 and TSH). Only out of range results that are not also outside markedly abnormal ranges will be included in the normal range listing. Assessments post administration of anti-thyroid drugs will be flagged.

The following laboratory data will be presented in by-subject listings for the Study population:

- Serum and urine pregnancy test results.
- Reference ranges per laboratory parameter, sex and age range (including FT3, FT4 and TSH).
- Markedly abnormal ranges per laboratory parameter, sex, visit and age range (including FT3 and FT4).
- All clinical laboratory results including change from baseline values will be presented by site/subject, dose level and date/time of assessment, including scheduled, unscheduled and ET visits. Listings will include flags for outside of reference range, markedly abnormal results and will identify the values that are regarded as baseline values (excluding FT3, FT4 and TSH that will be listed separately under efficacy).
- Urinalysis results will be listed for continuous and categorical (e.g. positive/negative) data. Continuous data will be presented as above.
- Laboratory results for laboratory parameters not listed in the protocol will be listed only and will not appear in any summary tables.
- For all listings, all visits will be listed where protocol-specified tests are to be done. The accession number and reason if not done will also be listed. Assessments post administration of anti-thyroid drugs will be flagged.

15.2.1. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorised as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.
- Markedly Low: Below the lower limit of the laboratory markedly abnormal reference range.
- Markedly High: Above the upper limit of the laboratory markedly abnormal reference range.

15.3. VITAL SIGNS

Subjects will be observed in the clinic for at least two hours after administration of the study drug. Vital signs will be recorded at screening, and on each dosing day, pre-dose, then at 15 minute intervals for the first hour and 30 minute intervals for the second hour, and at Week 22 and 30 follow-up visits and at ET, after the subject has been sitting quietly for at least 5 minutes.

The following vital signs measurements will be reported for this study:

- Sitting SBP (mmHg)
- Sitting DBP (mmHg)
- Sitting Heart Rate (bpm)
- Oral Body Temperature (^{o}C)
- Respiratory Rate (breaths/min)
- Weight (kg) (Note BMI is calculated at Screening only).

The following summaries will be provided for the vital sign data for the ITT population:

- Descriptive statistics (observed, change from baseline and change from pre-dose to each post-dose time point for each parameter except weight) will be presented for each vital sign parameter at baseline, pre-dose and at each scheduled post-baseline visit.

The following vital signs listing will be presented for the Study population:

- Vital signs measurements (including change from baseline and change from pre-dose to each post-dose time point for each parameter except weight) by site, subject, date and time.
- Baseline values and trigger values will be flagged in the listings for the following:
  - Weight decrease from baseline by > 5 kg
  - Heart rate > 120 bpm
- Assessments post administration of anti-thyroid drugs will be flagged.

15.4. ELECTROCARDIOGRAM EVALUATIONS

12-lead ECG results obtained at the investigative site, and will be entered into the eCRF by site staff, at screening, pre-dose and post dose, Week 22 and at ET.

The following ECG parameters will be reported for this study:

- RR (heart rate variability) Interval (msec)
- PR (period that extends from the beginning of the P wave until the beginning of the QRS complex) Interval (msec)
- QRS (onset of ventricular depolarisation) Interval (msec)
- QT (total duration of ventricular depolarisation) Interval (msec)
- QTcB (Bazett's correction formula) Interval (msec)

Overall assessment of 12-lead as per Investigator's judgment of clinical significance:

- Normal
- Abnormal, Not Clinically Significant (NCS)
- Abnormal, Clinically Significant (CS)

The following summaries will be provided for the ECG interval data for the ITT population:

- Descriptive statistics (observed, change from baseline and change from pre-dose to each post-dose time point) will be presented for each ECG parameter at baseline and at each scheduled post-baseline visit.

The following ECG data will be presented in by-subject listings for the Study population:

- 12-Lead ECG interval assessment results, including change from baseline and change from pre-dose to each post-dose time point for each ECG parameter.
- 12-Lead ECG Interpretations (investigator's judgement).
- Assessments post administration of anti-thyroid drugs will be flagged.

15.5. PHYSICAL EXAMINATION

Physical examination assessments are as recorded on the Physical Examination eCRF.

Physical examination assessments will be listed for the Study population per body system by site/subject number, visits, date and time including any unscheduled assessments. Assessments post administration of anti-thyroid drugs will be flagged.

16. DATA NOT SUMMARIZED OR PRESENTED

In generall all eCRF data will be presented.

The other variables and/or domains not summarized or presented are:

Subject initials.

Investigator electronic signature in the eCRF.

17. REFERENCES

Safety and proof of principle study of ATX-GD-59 in male and female subjects with Graves ' disease not currently treated with anti-thyroid therapy: An Open label study, with an upward titration over five dose levels administered by Intradermal injection. Clinical study protocol: 17 May 2016**.**

ATX-GD-59-001 Study Protocol Version Amendment 3.0, dated 06JAN2017.

ATX-GD-59-001 Electronic Case Report Form Version 5.0, dated 13APR2017.

ATX-GD-59-001 Data Monitoring Committee Plan, Version 2.0, dated 10FEB2017.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

1. DATES & TIMES

Depending on data available, dates and times will take the form DDMMMYYYY HH:MM.

2. SPELLING FORMAT

English UK.

3. PRESENTATION OF VISITS

For outputs, visits will be represented as follows in the following order:

Long Name (default)
Screening
Baseline
Study Day 1
Week 2
Week 4
Week 6
Week 8
Week 12
Week 14
Week 16
Week 18
Week 22 (Follow-up)
Week 30 (Follow-up)
Early Termination
Unscheduled (chronologically)

4. LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Site
- Subject Number
- Dose Level
- Visit
- Date/Time

APPENDIX 2. PARTIAL DATE/TIME CONVENTIONS

Imputed date/times will NOT be presented in the listings.

If Date/Time is available the following derviations will be applied:

- Pre-treatment AE (Screening period): Any AE that started or worsened in severity on or after informed consent and prior to the first administration of study drug.

- TEAE: Any AE that started or worsened in severity on or after the first administration of study drug up to and including 28 days after the last administration of study drug.

  - Titration dose level received prior to AE: Assign any AE that started or worsened in severity on or after that dose level received up to the date/time of the next dose level administration for each dose level, up to the first administration of full treatment period study drug (i.e., 2nd 800 µg dose).

  - Full treatment dose level received prior to AE: Assign any AE that started or worsened in severity on or after the first full treatment dose (i.e., 2nd 800µg dose) up to and including 28 days after the last administration of study drug.

- Non-TEAE commencing post-treatment: Any AE that started or worsened in severity more than 28 days after the last administration of study drug.

1. ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

Start Date/Time	Stop Date	Action
Partial, but known components show that it cannot be on or after first dose of study drug administration date/time	Known/Partial/Missing/ Ongoing	Pre-treatment
*Partial, indicates to be on or after25 µg start date but before next dose level		Assumed TEAE and 25 µg (titration period)
*Partial, indicates to be on or after 50 µg start date but before next dose level		Assumed TEAE and 50 µg (titration period)
*Partial, indicates to be on or after 100 µg start date but before next dose level		Assumed TEAE and 100 µg (titration period)
*Partial, indicates to be on or after 400 µg start date but before next dose level		Assumed TEAE and 400 µg (titration period)
*Partial, indicates to be on or after 1st 800 µg start date but before next dose level		Assumed TEAE and 800 µg (titration period)
*Partial, indicates to be on or after 2nd 800 µg start date but before 28 days after last administration of study drug		Assumed TEAE and 800 µg (full treatment period)
Partial, but known components show that it started more than 28 days after last administration of study drug date (section 7.7.4)		Non-TEAE
Partial, could be on or after study drug start date	Known	If AE end date < first study drug administration start date, then Pre-treatment If AE end date >= first study drug administration start date, then assume TEAE (Reference * for assignment of specific dose and treatment period)
	Partial	Impute end date as latest possible date (i.e. last day of month if day unknown or 31st December if day and

Start Date/Time	Stop Date	Action
		month are unknown), then: If AE end date < first study drug administration start date, then Pre-treatment If AE end date >= first study drug administration start date, then assume TEAE (25 µg)
	Missing/Ongoing	Assumed TEAE and 25 µg
Missing	Known	If AE end date < first study drug administration start date, then Pre-treatment If AE end date >= first drug administration start date, then assume TEAE (25 µg/titration period)
	Partial	Impute AE end date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If AE end date < first study drug administration start date, then Pre-treatment If AE end date >= first study drug administration start date, then assume TEAE (25 µg)/titration period
	Missing /Ongoing	Assumed TEAE (25 µg)/titration period

2. ALGORITHM FOR PRIOR / CONCOMITANT /POST-TREATMENT MEDICATIONS AND PROCEDURES:

Start Date	End Date	Action
Known	Known	If medication/procedure end date < first drug administration start date, assign as prior If medication/procedure start date < first administration of full treatment period study drug (2nd 800 µg dose) and medication/procedure start or end date >= first drug administration, assign as titration period (Concomitant) If medication/procedure start date <= 28 days after last administration of study drug date and medication/procedure start or end date > first administration of full treatment period study drug (2nd 800 µg dose, assign as full treatment period (Concomitant) If medication/procedure start date > 28 days after last administration of study drug date, assign as post-treatment
	Partial	Impute medication/procedure end date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If medication/procedure end date < first study drug administration start date, assign as prior If medication/procedure start date < first administration of full treatment period study drug (2nd 800 µg dose) and medication/procedure start or end date >= first study drug administration, assign as titration period (Concomitant) If medication/procedure start date <= 28 days after last administration of study drug date and medication/procedure start or end date > first administration of full treatment period study drug (2nd 800 µg dose, assign as full treatment period (Concomitant) If medication/procedure start date > 28 days after last administration of study drug date (section 7.7.4), assign as post-treatment

Start Date	End Date	Action
Known	Missing/ Ongoing	If medication/procedure end date is missing/ongoing could never be assumed a prior medication Assign as titration period and full treatment period (Concomitant) unless, if medication/procedure start date >= first administration of full treatment period study drug (2nd 800 µg dose), assign as full treatment period (Concomitant) If medication/procedure start date > 28 days after last administration of study drug date (section 7.7.4), assign as post-treatment
Partial	Known	Impute medication/procedure start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If medication/procedure end date < first study drug administration start date, assign as prior If medication/procedure start date < first administration of full treatment period study drug (2nd 800 µg dose) and medication/procedure start or end date >= first drug administration, assign as titration period (Concomitant) If medication/procedure start date <= 28 days after last administration of study drug date and medication/procedure start or end date > first administration of full treatment period study drug (2nd 800 µg dose, assign as full treatment period (Concomitant). If medication/procedure end date >= first drug administration start date and medication/procedure start date > 28 days after last administration of study drug date (section 7.7.4), assign as post-treatment

Start Date	End Date	Action
Partial	Partial	Impute medication/procedure start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute medication/procedure end date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If medication/procedure end date < first drug administration start date, assign as prior If medication/procedure start date < first administration of full treatment period study drug (2nd 800 µg dose) and medication/procedure start or end date >= first study drug administration, assign as titration period (Concomitant) If medication/procedure start date <= 28 days after last administration of study drug date and medication/procedure start or end date > first administration of full treatment period study drug (2nd 800 µg dose, assign as full treatment period. (Concomitant) If medication/procedure end date >= first study drug administration start date and medication/procedure start date > 28 days after last administration of study drug date (section 7.7.4), assign as post-treatment
	Missing/ongoing	Impute medication/procedure start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then : If medication/procedure end date is missing could never be assumed a prior medication Assign as titration period and full treatment period (Concomitant) unless, if medication/procedure start date >= first administration of full treatment period study drug (2nd 800 µg dose), assign as full treatment period (Concomitant) If medication/procedure start date > 28 days after last administration of study drug date (section 7.7.4), assign as post-treatment
Missing	Known	If medication/procedure end date < first study drug administration start date, assign as prior If medication/procedure end date < full treatment period study drug (2nd 800 µg dose, assign as titration period (Concomitant) Else assign as titration period and full treatment period (Concomitant). Cannot be assigned as post-treatment

Start Date	End Date	Action
Missing	Partial	Impute medication/procedure end date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If medication/procedure end date < first study drug administration start date, assign as prior If medication/procedure end date < full treatment period study drug (2nd 800 µg dose, assign as titration period (Concomitant) Else assign as titration period and full treatment period (Concomitant). Cannot be assigned as post-treatment
	Missing/ongoing	Assign as titration period and full treatment period. (Concomitant)

APPENDIX 3. CONVERSION FACTORS TO SYSTÈME INTERNATIONAL UNITS

System	Panel	Parameter	Reported Unit	Conversion Factor	SI Unit
Haematology	Erythrocytes and Platelets	RBC Count	10^6/uL	1.0	10^12/L
		Haemoglobin	g/dL	10.0	g/L
		Haematocrit	%	0.01	V/V
		MCV	fL	1.0	fL
		MCHC	g/dL	1.0	g/dL
		Platelet count	10^3/uL	1.0	10^9/L
	Leukocytes	WBC Count	10^3/uL	1.0	10^9/L
		Neutrophils	10^3/uL	1.0	10^9/L
		Neutrophils (%)	%	1.0	%
		Lymphocytes	10^3/uL	1.0	10^9/L
		Lymphocytes (%)	%	1.0	%
		Monocytes	10^3/uL	1.0	10^9/L
		Monocytes (%)	%	1.0	%
		Eosinophils	10^3/uL	1.0	10^9/L
		Eosinophils (%)	%	1.0	%
		Basophils	10^3/uL	1.0	10^9/L
		Basophils (%)	%	1.0	%

System	Panel	Parameter	Reported Unit	Conversion Factor	SI Unit
Biochemistry	Liver Function	Total Bilirubin	mg/dL	17.1	umol/L
		AST	U/L	1.0	U/L
		ALT	U/L	1.0	U/L
		ALP	U/L	1.0	IU/L
	Electrolytes/ Minerals	Sodium	mEq/L	1.0	mmol/L
		Potassium	mEq/L	1.0	mmol/L
		Chloride	mEq/L	1.0	mmol/L
		Bicarbonate	mEq/L	1.0	mmol/L
		Calcium	mg/dL	0.25	mmol/L
		Phosphate	mg/dL	0.323	mmol/L
	Lipids/ Proteins	Serum Proteins	g/dL	10.0	g/L
	Other Chemistry	Urea	mg/dL	0.357	mmol/L
		Creatinine	mg/dL	88.4	umol/L
		Uric Acid	mg/dL	59.48	umol/L
Urinalysis		pH	(none)	1.0	(none)
		Specific Gravity	(none)	1.0	(none)
Thyroid Panel		FT3	pg/mL	1.54	pmol/L
		FT4	ng/dL	12.92	pmol/L
		TSH	uIU/mL	1.0	mIU/L

RBC = Red Blood Cell. WBC = White Blood Cell. MCV = Mean Corpuscular Volume. MCHC = Mean Corpuscular Haemoglobin Concentration. AST = Aspartate Aminotransferase. ALT = Alanine Aminotransferase. ALP = Alkaline Phosphatase. FT3 = Free Triiodothyronine. FT4 = Free Thyroxine. TSH = Thyroid Stimulating Hormone. SI = Système International.

APPENDIX 4. POPULATION ASSIGNMENT AND DATA REVIEW PLAN

1. INTRODUCTION

Prior to the final locking of the clinical study database of the ATX-GD-59-001 study, a DR is to be performed in order to meet the following objectives:

- Establish and finalise the analysis populations.
- Identify major protocol deviations programmatically and by means of the 'Protocol Deviations' log recorded in the IQVIA Clinical Trial Management System (CTMS).
- Discuss any data issues or outliers, not resolved and indicated as such in the data handling report (DHR), which might affect the analysis or require revision to the SAP.
- Evaluate visit deviations in terms of the protocol visit windowing, including mapping of ET visits to a scheduled visit, if applicable.

A clean snapshot of the clinical study database is to be considered as the source for the production of the DR meeting deliverables. The IQVIA BIOS and IQVIA Data Management DR deliverables will be produced based on the same clean snapshot provided by Data Management.

2. DELIVERABLES FROM IQVIA DATA MANAGEMENT

The final analysis will be performed following a pre-database lock DR meeting to determine population assignment and on a clean snapshot of the clinical study database with all data management procedures completed, including:

The following procedures need to be completed by IQVIA Data management:

- All outstanding data issues and queries resolved.
- All unresolved data issues that will remain present in the clinical study database are to be documented in the DHR, and provided to the IQVIA Statistical Team Lead (STL) and DR meeting attendees. This is a report containing a list of queries from both eCRF- and non-eCRF data that could not be resolved by sites following identification using edit checks/manual data reviews and are to remain present in the clinical study database at the DR.
- All coding of medications, procedures, medical history and AEs completed and authorised.

- SAEs reconciliation with the Safety Database completed.
- All reconciliation of external vendor data with the eCRF data completed successfully.
- The data review listings of all the data in the clean snapshot of pre-database lock datasets have been reviewed and no further data anomalies other than unresolvable data anomalies are present.

3. DELIVERABLES FROM IQVIA CLINICAL MONITORING/PROJECT MANAGEMENT

Any protocol deviations will be recorded in the CTMS and the Project Manager is to provide the 'Protocol Deviations' log, as a report from this system. In addition, clinical inspection reports and quality assurance (QA) site issues are to be provided, if applicable. These documents, if applicable, should be available at the time of the DR. It should be noted that if any Good Clinical Practice (GCP) issues are identified at specific sites, this information should be communicated to the IQVIA STL for documentation and discussion at the DR meeting.

4. DELIVERABLES FROM IQVIA BIOSTATISTICS

The following deliverables are to be provided by the IQVIA Biostatistics:

- Guidelines for the population assignment and DR Plan as Appendix to the SAP.
- MS/EXCEL dataset for the prior and concomitant medications (CRITERION [5]) as well as for the previous or concurrent prohibited medical conditions (CRITERION [6]), to IQVIA Medical Monitor (see Appendix 4 section 4.1.3.2 and 4.1.3.3)
- Specific DR listings (Protocol deviation [CTMS log], programmed deviations listing, population assignment and Visit windowing) (MS/WORD document and/or MS/EXCEL spreadsheet, as appropriate).
- Population assignment and major protocol deviations will be provided in an MS/EXCEL spreadsheet.
- Following the DR meeting the population assignment and major protocol deviations signature page for authorising.

4.1. IDENTIFICATION OF THE POPULATIONS AND MAJOR PROTOCOL DEVIATIONS

This section contains a detailed description of the criteria which are to be used in the definition of the populations and in the testing of subject validity for the various populations. The criteria to be used to define a valid course and potential protocol deviations are also defined in this section.

All potential protocol deviations are to be summarised in the MS/EXCEL spreadsheet. This MS/EXCEL spreadsheet is to provide a by-subject summary of each subject's validity together with all of his/her potential protocol deviations.

The following populations are defined for presentation of the safety and efficacy analysis:

4.1.1. STUDY POPULATION

The Study population corresponds to all enrolled subjects, i.e. all subjects eligible for enrolment into the study at the Screening visit.

Exclusion criteria from the study population:

4.1.1.1. Subjects who did not provide written informed consent prior to any specific study-related procedures.

CRITERION [1]: No Written Informed Consent.

FIXED CATEGORY: Inclusion and Exclusion Criteria.

DEVIATION STATUS: Major.

Note:

The criteria related to informed consent to be met by each subject to be assessed are:

Term/Description	Inclusion and Exclusion Criteria (as Recorded on the eCRF and Verified)
The subject must be willing and able to give written informed consent and must be willing to comply with protocol assessments/procedures.	Inclusion 6
Verify informed consent date collected on the eCRF to establish whether or not consent was provided prior to performing any study-related procedures and whether or not the subject was eligible for enrolment in the study in accordance with the clinical study protocol's specified inclusion and exclusion criteria.	Verify inclusion 6

4.1.2. INTENTION-TO-TREAT [ITT]/SAFETY POPULATION

An ITT population will be defined for use in presenting baseline, efficacy and safety data. The ITT population corresponds to all subjects who received at least one administration of study drug at any time+ during the study, irrespective of compliance with eligibility and other protocol criteria.

The ITT population set is regarded as primary for the safety analyses.

Exclusion criteria from the ITT population:

4.1.2.1. Subjects who did not receive a dose of study drug or part thereof.

CRITERION [2]: No Study Drug Administered.

FIXED CATEGORY: Treatment Schedule.

DEVIATION STATUS: Major.

4.1.3. PER-PROTOCOL [PP] POPULATION

The PP population to include all subjects considered valid for the ITT population with no identified major protocol deviations as reviewed and confirmed by Apitope prior to analysis.

Major protocol deviations are defined as any factor affecting the efficacy outcome or the treatment of the subject.

The PP population is further defined by the following valid course criteria (ICH-E9):

- Overall treatment compliance, i.e. subjects that did not receive the full treatment regimen.
- Eligible in accordance with the clinical study protocol's specified inclusion and exclusion criteria.
- Specifically criteria which could affect the efficacy outcome or the treatment of the subject:
    - Not taken prohibited medications during the treatment period.
    - Presence of prohibited medical conditions.
    - Not received anti-thyroid drugs prior to week 22.

Exclusion criterion from the PP population:

- All subjects excluded from the ITT population.
- Overall treatment non-compliance.

For each subject included in the PP population, the compliance with regards to the administration of the single dose of study drug is to be assessed as a binary outcome:

- Yes: All doses received and at least 80% of protocol-specified total study drug dose (µg) injected for the entire treatment period.
- No: Not all doses received or not at least 80% of protocol-specified total study drug dose (µg) injected for the entire treatment period

CRITERION [3]: Non-compliance with Study Drug Administration.

FIXED CATEGORY: Treatment Schedule.

DEVIATION STATUS: Major/Minor to be decided on a case-by-case basis at the DR meeting.

Notes:

Compliance of study drug administration is to be evaluated with regards to the number of injections and the amout of dose received. Each factor is formulated as a question with a binary response, either 'Yes' or 'No'.

The factors to be evaluated are as follows:

- All 10 doses received, that is 100% compliance to number of doses received. Major
- At least 80% of protocol-specified total study drug dose amount injected (Yes/No). Major.

Dose Compliance (%) = (Amount (µg) of drug injected / Protocol-specified drug amount (µg))*100

4.1.3.1. Met all Inclusion and none of the Exclusion Criterion

The inclusion criteria and exclusion criteria are presented in section 8 of the clinical study protocol. For each criterion, as appropriate, a response of 'Yes/No' is to be obtained at Screening. The aforementioned inclusion criteria and exclusion criteria responses are recorded in the eCRF.

CRITERION [4]: Eligibility Criteria Not Met.

FIXED CATEGORY: Inclusion and Exclusion Criteria.

DEVIATION STATUS: Major/Minor to be decided on a case-by-case basis at the DR meeting.

4.1.3.2. Subjects who used Prohibited Prior/Concomitant Medications (including anti-thyroid drugs before Week 22 visit)

CRITERION [5.1]: Use of Prohibited Prior/Concomitant Medications.

FIXED CATEGORY: Concomitant Medications.

DEVIATION STATUS: Major/Minor to be decided on a case-by-case basis (in collaboration with the IQVIA Medical Advisor) at the DR meeting.

CRITERION [5.2]: Received Anti-thyroid Drugs prior to Week 22.

FIXED CATEGORY: Concomitant Medications.

DEVIATION STATUS: Major deviation.

Note:

All prior/concomitant medications are to be reviewed on a by-subject basis by the IQVIA Medical Advisor in order to identify the use of the any prohibited prior/concomitant medication as specified in the protocol. The prohibited prior/concomitant medications identified by the IQVIA Medical Advisor are to be flagged in the DR listing as well as anti-thyroid drugs flagged programmatically for ease of review in inclusion in the summary excel document.

The duration (days) since the use of the prohibited prior/concomitant medication is calculated as follows:

- Duration (days) = (Start date of prior/concomitant medication – Date of first study drug administration) +1.

4.1.3.3. Subjects who have Previous or Concurrent Prohibited Medical Conditions

CRITERION [6]: Previous or Concurrent Prohibited Medical Conditions

FIXED CATEGORY: Medical History.

DEVIATION STATUS: Major/Minor to be decided on a case-by-case basis (in collaboration with the Medical Advisor) at the DR meeting.

Note:

All medical historys are to be reviewed on a by-subject basis by the IQVIA Medical Advisor in order to identify prohibited medical conditions. The prohibited medical conditions identified by the IQVIA Medical Advisor are to be flagged in the relevant MS/EXCEL doument and send back to the IQVIA STL for inclusion in the population and protocol deviation summary (MS/EXCEL document).

The effect of the possible deviation will be determined as Major/Minor during the DR meeting.

4.1.4. ANTI-THYROID DRUG POPULATION

The anti-thyroid drug population is defined as any ITT subject taking anti-thyroid drugs at any time post first dose of ATX-GD-59 up to the Week 22 visit.

Exclusion criterion from the anti-thyroid drug population:

- All subjects excluded from the ITT population.
- All subjects not taking anti-thyroid drugs at any time post first dose of ATX-GD-59 to the Week 22 visit.

CRITERION [7]: Did not Receive Anti-thyroid Drugs prior to Week 22.

FIXED CATEGORY: Concomitant Medications.

STATUS: Yes/No

4.2. SUBJECTS WHO DID NOT ADHERE TO THE VISIT SCHEDULE.

CRITERION [8]: Non-adherence to Visit Schedule.

FIXED CATEGORY: Assessment Schedule.

DEVIATION STATUS: Major/Minor to be decided on a case-by-case basis at the DR meeting.

Note:

Only scheduled visits adherence applicable to the the study is to be validated according to the relevant visit window below. Visits not in accordance with the table below are to be identified by means of a flag on the listing of study visits:

Visit	Protocol Study Day	Deviation if outside	Visit Window relative to date of first study drug administration
Screening visit (Week – 4:)	Day -28 to -1	+ 5 days	Week -4: Day -33 to Day -1
Study day 1 visit	1	Not applicable	
Dose titration period visits	Week 2: Day 14 Week 4: Day 28 Week 6: Day 42 Week 8: Day 56	± 3 days	Week 2: Day 11 to 17 Week 4: Day 25 to 31 Week 6: Day 39 to 45 Week 8: Day 53 to 59
Full dose Treatment visits	Week 10: Day 70 Week 12: Day 84 Week 14: Day 98 Week 16: Day 112 Week 18: Day 126	± 3 days	Week 10: Day 67 to 73 Week 12: Day 81 to 87 Week 14: Day 95 to 101 Week 16: Day 109 to 115 Week 18: Day 123 to 129
Follow-up visits (Week 22)	Week 22: Day 154	± 3 days,	Week 22: Day 151 to 157
Follow-up visits (Week 30)	Week 30: Day 210	± 7 days	Week 30: Day 203 to 217

Study day is calculated relative to the date of first administration of study drug and is only presented for subjects with a study drug administration date (see section 6.1).

The ET visit will be allocated to a scheduled visit according to the table above, where the ET visit has occurred in place of the scheduled visit and is within the relevant visit window. Any ET visits will be reviewed for allocation to a scheduled visit, at the DR meeting.

4.3. SUMMARY OF CRITERIA

Decode	Criterion	Fixed Category	Major/Minor
[1]	No Written Informed Consent Provided	Inclusion and Exclusion Criteria	Major
[2]	No Study Drug Administered	Treatment Schedule	Major
[3]	Non-compliance with Study Drug Administration	Treatment Schedule	Major/Minor
[4]	Eligibility Criteria Not Met	Inclusion and Exclusion Criteria	Major/Minor
[5.1]	Use of Prohibited Prior/Concomitant Medications	Concomitant Medications	Major/Minor
[5.2]	Received Anti-thyroid Drugs prior to Week 22	Concomitant Medications	Major
[6]	Previous or Concurrent Prohibited Medical Conditions	Medical History	Major/Minor
[7]	Did not Receive Anti-thyroid Drugs prior to Week 22	Concomitant Medications	Not applicable, flag only
[8]	Non-adherence to Visit Schedule	Assessment Schedule	Major/Minor

4.4. DISCUSSION OF DATA ISSUES

- Discuss any data issues or outliers, not resolved and indicated as such in the DHR, which might affect the analysis or require revision to the SAP.
- Confirmation of AE assignments to treatment periods/dose levels for AEs with partial/missing start/end dates/times and confirmation of medication/procedures assignments to treatment periods for medications/procedures with partial/missing start/end dates/times.