

1 SUMMARY/SYNOPSIS

Title of Study:	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.
Countries:	United Kingdom
Phase of development:	Phase I
Study Objectives:	
<p>PRIMARY</p> <ul style="list-style-type: none"> • 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. 	
<p>SECONDARY</p> <ul style="list-style-type: none"> • To assess the effects of ATX-GD-59 on TSHR antibody levels. • To assess the ratio of stimulatory vs inhibitory TSHR antibodies. • To assess the effect of ATX-GD-59 on free T3, free T4 and TSH serum levels. 	
<p>EXPLORATORY</p> <ul style="list-style-type: none"> • 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 (mRNA). 	
Methodology:	
<p>This will be an open label, ascending dose evaluation of the safety, tolerability 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.</p> <p>The first four subjects will be recruited sequentially with a minimum of 48 hours between the first dose of each subject. Individual subject safety data will be reviewed by the Investigator and the Sponsor or Sponsor's representative after the first dose of ATX-GD-59. Dosing of the remaining subjects will only commence once the first subject has received the second dose and there are no safety concerns identified.</p> <p>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 injection(s) of 800 µg injected on five further occasions. All doses are based on the total peptide.</p> <p>All doses will be administered by intradermal injection at intervals of 14 +/- 3 days.</p> <p>An estimated 33 subjects will be screened, with approximately 15 subjects receiving at least one dose of ATX-GD-59.</p>	
<p>Number of Subjects: Approximately 12 subjects to complete dosing and attend the Week 22 visit.</p>	

Inclusion criteria

1. A diagnosis of Graves' disease as assessed by a physician from clinical and laboratory findings and not receiving anti-thyroid therapy.
2. Quantifiable levels of TSHR antibodies.
3. Raised levels of free T3 and/or free T4 (not exceeding 15 pmol/L and 35 pmol/L respectively) including undetectable levels of thyroid stimulating hormone.
4. HLA-DRB1*15, HLA DRB1*03 and or HLA DRB1*04 positive.
5. Age 18 – 65 years inclusive at the time of informed consent.
6. The subject must be willing and able to give written informed consent and must be willing to comply with protocol assessments/procedures.
7. Male subjects must be sterile (biologically or surgically) or commit to the use of a reliable method of birth control for the duration of the study until at least 90 days after the last dose of ATX-GD-59.
8. Female subjects of child bearing potential must:
 - neither be pregnant nor breast-feeding, nor attempting to conceive, and
 - use a highly effective method of contraception as defined below, throughout the entire duration of the study and for at least 90 days after the last dose of ATX-GD-59.

A serum pregnancy test will be performed at the screening visit in women of child bearing potential. Thereafter urine pregnancy tests will be performed. A positive result will exclude the woman from the study immediately.

A highly effective method of contraception is defined as those which result in a low failure rate when used consistently and correctly such as implants, injectable, combined oral contraceptives, some Intrauterine Devices (IUDs), unless post-menopausal or surgically sterilized. Barrier forms of contraception are considered appropriate when used in combination with one of the above methods.

Exclusion criteria

1. Subjects who are pregnant or breastfeeding and/or subjects in the post-partum period.
2. A known history of, or hypersensitivity reactions that in the opinion of the investigator would exclude the subjects' participation in the study.
3. Treatment with any Anti-Thyroid Drugs e.g. carbimazole within the previous 3 months prior to Study Day 1.
4. Previous treatment with radioiodine or (partial or complete) thyroidectomy.
5. Signs of moderate or severe orbitopathy including optic nerve compression requiring steroids and/or a clinical activity score >3.
6. Large and compressive goitres causing localised symptoms such as difficulty swallowing or breathing.
7. Treatment with steroids (administered via the oral and/or parenteral routes) or adrenocorticotropic hormone with the exception of inhaled steroids within the three months prior to Study Day 1.
8. Symptoms and signs of thyroid storm such as confusion, pyrexia with no other cause than hyperthyroidism.
9. Significant cardiac disease and/or atrial fibrillation that would require urgent treatment of thyrotoxicosis.
10. Prior treatment with biological or peptide-based therapeutics including rituximab.
11. Prior use of disease related T cell vaccine or peptide-tolerising agent to treat Graves' disease.
12. Detectable levels of antibodies in plasma specific for any of the peptides within ATX-GD-59 at the screening visit.

13. A history of significant drug allergies.
14. The use of any investigational drug, or participation in any Clinical Trial within three months prior to Study Day 1.
15. Treatment with any cytokine or anti-cytokine therapy within three months prior to Study Day 1.
16. Inadequate liver function, defined by a total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) or alkaline phosphatase > 3 times the upper limit of the normal values at Screening visit.
17. Subject with any significant medical illness or psychiatric condition that in the opinion of the Investigator, would preclude participation in the study or impair the ability to give informed consent; any other clinically apparent autoimmune disease.
18. Clinically significant illness, as determined by the investigator, within 4 weeks prior to the first dose (Study Day 1) of ATX-GD-59.
19. Known history of active or chronic infectious disease or any disease which compromises immune function (e.g. HIV+, HTLV-1, Lyme disease, Latent or active TB, Hepatitis).
20. Major surgery in previous four weeks before screening visit.
21. Known osteoporosis or metabolic bone disease.

Withdrawal criteria

1. Subject experiences a serious or severe adverse event that prevents him/her from continuing.
2. Subject incurs a significant protocol violation that leads to an increased risk to the subject by continuing in the study.
3. Subject requests early discontinuation.
4. Investigator's or Sponsor's request (e.g. if it is considered that the subject's health is compromised by remaining in the study or the subject is not willing or able to comply with the protocol or study procedures).
5. Subject is lost to follow-up.
6. Subject requires treatments prohibited by the exclusion criteria or the protocol.
7. Subject demonstrates a robust and increasing positive response in the anti-drug anti-body assay accompanied by clinical signs of an adverse immune response to either peptide in ATX-GD-59. These may be unexplained chills, fever or flu like symptoms following treatment with ATX-GD-59.
8. Subject becomes pregnant.

Management of thyrotoxicosis during the study

- Symptomatic patients may be treated with propranolol (up to 160mg per day) adjusted to control tachycardia or other symptoms. If alternative beta-adrenergic receptor blockade is required, this must be agreed with the study medical monitor.
- If there is a contraindication to using a beta blocker (e.g., asthma) then rate limiting calcium channel blockers (e.g. Diltiazem MR 120 to 240mg daily) may be used instead. This must also be agreed with the study medical monitor.

Administration of Anti Thyroid Drug's during the study is indicated in the following instances:

- A subject has trigger levels of free T3 (>20pM) and/or free T4 (>45pM) on 2 consecutive scheduled or unscheduled visits.
- Continued weight loss >5kg from baseline (Study Day 1).
- Persistent tachycardia >120bpm.
- Significant cardiac event that would require urgent treatment of thyrotoxicosis.
- If the investigator or treating physician considers that it is appropriate to administer anti-thyroid drugs at any point during the study.

Duration of treatment:

The trial consists of a screening visit, a dosing period of 18 weeks, an efficacy assessment after 4 weeks (post final dose) and a follow-up period of 8 weeks.

Dose and mode of administration:

ATX-GD-59 is a lyophilised equimolar mixture of two peptides reconstituted at the clinic to provide one of two different concentrations, depending on dose, for injection prior to intradermal injection.

Dose Strengths: 4mg/ml and 0.5mg/ml total peptide content when reconstituted in water for injection and 0.9% saline respectively.

Safety monitoring and analysis:

Subjects will be observed in the clinic for at least two hours after administration of the study drug and vital signs will be recorded at 15 minute intervals for the first hour and 30 minute intervals for the second hour. If the subject is well (in the opinion of the Investigator), they will then be allowed to leave the clinic. A contact card with an emergency telephone number will be provided to each subject.

Subjects will be given diaries to take home to record injection site reactions for at least 24 hours after the study drug injection.

The first four subjects will be recruited sequentially with a minimum of 48 hours between the first dose of each subject. Individual subject safety data will be reviewed by the Investigator and the Sponsor or Sponsor's representative after the first dose of ATX-GD-59 and thereafter between the second (week 10) and third (week 12) 800 µg doses. Dosing of the remaining subjects will only commence once the first subject has received the second dose (week 2) 50 µg and there are no safety concerns identified.

For the first 5 subjects, the combined individual subject safety data will be reviewed by the Investigator and the Sponsor or Sponsor's representative after the second 800 µg dose (week 10) and prior to the third (week 12) 800µg dose.

The combined safety data for the first 5 subjects will be subject to interim review by a Data Monitoring Committee (DMC) after the last dose of 800 µg (week 18) has been administered.

The following will be presented to the DMC in a listing form:

- Summary vital signs.

- Summary ECG data- heart rate, PR interval, QRS width, QT interval and QTc interval.
- Clinical Laboratory data. Out of range values will be flagged in the data listings and a list of markedly abnormal values will be presented.
- Demographic data.
- Safety data, including all adverse events.

The DMC may request additional information as required.

Should safety concerns be identified, a decision may be taken to halt the trial. The DMC may convene at any point during the trial.

All adverse events will be coded using the MedDRA (Medical Dictionary for Regulatory Activities) drug dictionary. Adverse events will be listed and tabulated with simple analyses. Adverse events that occur intermittently will be reported as separate events.

Primary Objective

The primary endpoint of this study is a safety assessment to ensure, first of all, that the exposure to the study drug by the intradermal dose route will not harm a population affected by Graves' disease.

Safety endpoints, which will be evaluated on an ongoing basis **up to Week 22**, are:

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

Criteria for Evaluation of the Secondary Objectives:

- TSHR antibody levels.
- Ratio of stimulatory vs inhibitory TSHR antibodies.
- Free T3, free T4 and TSH serum levels.

Criteria for Evaluation of the Exploratory Objectives:

- TSHR induced PBMC T cell activity.
- T-cell cytokine signature.
- IL-10 pathway and associated genes (mRNA).

Statistical Considerations

A Statistical Analysis Plan (SAP) will be finalised prior to database lock describing details of analyses to be performed on all endpoints for the final analysis. Example tabulations and listings will also be included in this plan.

- All the data will be listed
- All relevant data will be summarised and tabulated in the most appropriate manner.

The statistical methods used will be appropriate to the objectives of the study and the nature of the data.

No formal sample size calculation has been performed. 12 evaluable subjects is considered a sufficient and adequate number of subjects to explore the defined safety aspects of the study and provide data about potential efficacy.

Study Population

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

All data listings will be based on the Study population.

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.

Per-Protocol Population (PP)

A per-protocol (PP) population 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 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 volume injected for the entire treatment phase, to be confirmed at the Data Review Meeting),
- Not taken prohibited medications during the treatment phase.
- Procedure done with consent
- Not received anti-thyroid drugs prior to week 22

Anti-thyroid drug Population

A third population, the anti-thyroid drug population, is defined as the per-protocol population plus those who had received anti-thyroid drugs during the ATX-GD-59 dosing and follow-up phase to week 22.

2 SUMMARY SCHEDULE OF EVENTS

Activity	Screen	Titration Period					Full dose Treatment Period					Follow-up		*ET /USV
		W -4	SD1	W 2	W 4	W 6	W 8	W 10	W 12	W 14	W 16	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. 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.

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

Estimation of Maximum Blood Volume (in mL) Collected Per Visit

Week Number	Screen	Titration Period					Full dose Treatment Period					Follow-up		*ET /USV	
		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	
Haematology & Chemistry Tests ¹	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Analysis and ratio of stimulatory vs inhibitory THSR antibodies	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
HLA Typing	6														
Anti-drug antibody test	5						5			5		5	5		5
Blood Sampling for specific T cell activity assay, additional Immunological Biomarkers	97	97										97	97		97
IL-10 pathway and associated genes (mRNA)	3	3										3	3		3
Total Volume of blood per visit (ml)	128	117	17	17	17	17	22	17	22	17	122	122	17	122	
Total Blood Volume = 652ml															

1. Serum pregnancy test at week -4 only.

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