Randomised controlled trial of plasma cell depletion for severe Graves' disease

Newcastle University
Institute of Health & Society

Statistical Analysis Plan for Graves- PCD

13th October 2022

SAP Version number: 1.0

This statistical analysis plan is based on protocol version 3.0 [30/09/2021]

Sponsor: The Newcastle upon Tyne Hospitals NHS Foundation Trust

Funded by: Medical Research Council

Funder ID: MR/V005898/1

EudraCT Number: 2020-005635-78

ISRCTN: 81162400

NHS REC Reference: 21/LO/0449

IRAS ID Number: 1003652

Trial Statistician: Mike Cole, PHSI, Newcastle University

Signature: M. Cole **Date:** *13/10/2022*

Reviewed and Approved by:

Signature: *statistical* **Date: 13/10/2022**

Signature: *clinical* **Date: 13/10/2022**

Revision history

Version	Date	Changes made	Justification for change	Timing of change
1.0	13/10/2022	First version	First version of SAP to provide details of interim analysis. Details of primary analysis will be included in subsequent versions of this SAP	

Glossary of abbreviations

ABBREVIATION	DEFINITION
AE	Adverse Event
AR	Adverse Reaction
ATPO	Antibodies to thyroid peroxidase
BMI	Body Mass Index
BTF	British Thyroid Foundation
CA	Competent Authority
CAS	Clinical Activity Score
CDMS	Clinical data management system
CI	Chief Investigator
COPD	Chronic obstructive pulmonary disease
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMC	Data Monitoring Committee
DPFS	Developmental Pathway Funding Scheme
DR	Dose-response
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EoT	End of trial
EudraCT	European Clinical Trials Database
FACS	Fluorescence Activated Cell Sorting
FBC	Full Blood Count
FEV	Forced Expiratory Volume
FSH	Follicle stimulating hormone
FT3	Serum free tri-iodothyronine
FT4	Serum free thyroxine
GCP	Good Clinical Practice
GOQoL	Graves' Ophthalmopathy Quality of Life Questionnaire
GP	General Practitioner
HBsAG	Hepatitis B surface antigen

HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
hr	Hour
HRA	Health Research Authority
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IRR	Infusion related reactions
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
ITT	Intention to treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
kg	Kilogram
LFT	Liver Function Test
LPLV	Last Patient Last Visit
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
mg	Milligram
ml	Millilitre
mRNA	Messenger ribonucleic acids
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
NIMP	Non-investigational medicinal product
NUTH	The Newcastle upon Tyne Hospitals NHS Foundation Trust
PBMC	Peripheral blood mononuclear cell
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PP	Per-protocol
PR	Percentage reduction
PTU	Propylthiouracil
QA	Quality Assurance

R&D	Research & Development
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SAR	Serious Adverse Reaction
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SI	Statutory Instruments
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TBII	Thyrotropin-binding Inhibitory Immunoglobulin
TED	Thyroid Eye Disease
Tg	Thyroglobulin
TgAB	Thyroglobulin antibodies
ThyPRO	Thyroid Patient Reported Outcome
TMG	Trial Management Group
TRAb	TSH receptor antibodies
TSC	Trial Steering Committee
TSH	Thyroid Stimulating hormone
TMF	Trial Master File
U & E	Urea & Electrolytes
USM	Urgent Safety Measure
USS	Ultrasound Scan
WHO	World Health Organisation

Table of Contents

1 INTRODUCTION

1.1 Background and rationale

Graves' disease (autoimmune hyperthyroidism) affects around 3% of women and 0·5% of men over a lifetime, and most commonly presents in the 4th and 5th decades of life, with a disproportionate burden of ill-health falling on working-age women. Typical symptoms include weight loss, palpitations, breathlessness, sweating, heat intolerance, tremor, insomnia, loss of concentration and irritability. Around 40% of patients develop an inflammatory eye condition, Thyroid Eye Disease (TED) which can cause facial disfigurement as well as functional visual problems and loss of sight. Rarely, a specific skin complication, Thyroid Dermopathy (aka Pretibial Myxoedema) may occur leading to a brawny thickening of the skin on the lower legs and feet. These latter 2 problems produce particularly distressing symptoms for a relatively young and active patient group.

The usual treatments for the hyperthyroidism of Graves' disease are either antithyroid drugs (carbimazole), radio-active iodine or surgical thyroidectomy. Antithyroid drugs lead to remission in only around 50% of people. Around 10% of patients have severe Graves' disease, defined by severe thyrotoxicosis (serum FT4 ≥50pmol/l or FT3 ≥15pmol), failure of medical control of hyperthyroidism, large goitre, inflammatory thyroid eye disease or thyroid dermopathy. They are characterised by high concentrations of the directly pathogenic TSH-receptor stimulating antibodies (TRAb), and 80% of them relapse following conventional medical therapy with antithyroid drugs. Quality of life in thyroid eye disease patients is poor, worse than for diabetes, and similar to patients with inflammatory bowel disease. Current treatments for these patients give unsatisfactory outcomes and are expensive, typically involving multiple episodes of eye surgery and/or surgical thyroidectomy. This study will determine proof of concept that the plasma cell depleting antibody daratumumab can ameliorate severe Graves' disease, using TRAb concentrations and circulating thyroid hormone levels along with clinical disease severity/activity scores as outcome measures.

Severe Graves' disease is caused by high titres of directly pathogenic TRAb, which are secreted from terminally differentiated B lymphocytes known as plasma cells. Failure of medical control and/or early relapse following conventional antithyroid drugs reflects persistence of these long-lived, TRAb-secreting plasma cells in the secondary lymphoid tissues and bone marrow. Both benign and malignant plasma cells express high levels of the cell-surface glycoprotein CD38. Daratumumab, a monoclonal antibody that binds to CD38 was recently licenced for the plasma cell malignancy, myeloma, has the potential to deplete plasma cells and produce a rapid reduction in TRAb levels, which may alter the natural history of severe Graves' disease. This trial aims to establish proof of concept that daratumumab has efficacy in severe Graves' disease patients and will provide important data to inform a choice of dosing regimen.

Daratumumab is licenced for use in myeloma at a dose of 16mg/kg, but the optimal dose in patients with Graves' disease is currently unknown. In contrast to patients with myeloma, those with Graves' disease have several orders of magnitude fewer plasma cells and it is therefore expected that lower doses of drug will be active in this patient group with benign disease. In addition, patients with Graves' disease will be younger (median age of presentation is 40 years) and in better overall health (bearing in mind study exclusion criteria) than patients with

myeloma who had to have refractory disease to several previous treatments to enter the early-phase trials of daratumumab. Dose-finding trials in myeloma patients showed no difference in adverse event rates between doses of 8mg/kg and 16mg/kg, and no dose-limiting toxicity up to 24mg/kg. Therefore, in order to define a signal for efficacy this study will use 9mg/kg as the top dose in stage 1, with reducing concentrations (3mg/kg, 1mg/kg and 0.5mg/kg) along with placebo to determine the dose response in stage 1.

1.2 Trial Objectives and outcome measures

1.2.1 Primary objective

- To determine if daratumumab modulates the humoral immune response in Graves' disease patients

1.2.2 Secondary objectives

- To determine how fast daratumumab modulates the humoral immune response in Graves' disease patients
- To determine the optimal dose (or dose range) of daratumumab for Graves' disease patients
- To determine if daratumumab reduces thyroid hormone levels
- To determine if daratumumab changes the time course of serum TSH
- To determine if daratumumab changes thyroid size
- To determine if daratumumab changes other thyroid autoantibodies
- To determine if daratumumab improves thyroid eye disease
- To determine if daratumumab improves thyroid symptom related QoL
- To determine if daratumumab is safe in this patient group

1.2.3 Exploratory objectives

- To determine if daratumumab changes lymphocyte/plasma cell transcriptomic markers
- To determine if daratumumab changes the lymphocyte subsets

1.2.4 Primary outcome measure

- Change in serum TRAb antibodies from baseline to 12 weeks compared to change in placebo group

1.2.5 Secondary outcome measures

- Change in serum TRAb antibodies from baseline to 2, 4, 6, 12 and 24 weeks
- Dose-response curve for daratumumab against change in serum TRAb antibodies from baseline to 6 and 12 weeks
- Change in serum FT3 and FT4 from baseline to 2, 4, 6, 12 and 24 weeks
- Change in serum TSH from baseline to 2, 4, 6, 12 and 24 weeks
- Change in thyroid volume from baseline to 24 weeks measured by ultrasound
- Change in serum ATPO and thyroglobulin antibodies from baseline to 6, 12 and 24 weeks
- Change in CAS, composite eye index and GOQoL score from baseline to 6, 12 and 24 weeks

- Change in ThyPRO39 score from baseline to 6, 12 and 24 weeks
- Change in serum immunoglobulins, specific antibodies including (SARS-CoV2) and blood count parameters from baseline to 6, 12 and 24 weeks.
- Adverse Reactions to 24 weeks

1.2.6 Exploratory objectives / outcome measures

- Analysis of blood plasma cell markers and mRNA signature
- Change in lymphocyte subsets (by FACS) from baseline to 6, 12 and 24 weeks

2 STUDY METHODS

2.1 Trial design

Graves-PCD is an adaptive, 2-stage randomised phase IIa clinical trial that will recruit 30 patients with severe Graves' disease from NHS secondary care. It is a single blinded trial in which participants will be blind to allocation.

Stage 1 is a dose-response study using 4 doses of daratumumab (9mg/kg, 3mg/kg, 1mg/kg, 0.5mg/kg) and a colourless, volume-matched placebo infusion in approximately 15 patients (i.e. five groups of n=3, randomised in a 1:1:1:1:1 ratio).

Following Stage 1, an interim analysis will be performed in order to select an optimal dose(s) of daratumumab for Stage 2. ***The dose selection will be based on an analysis of the reduction in TRAb antibody concentration and safety assessed at 12 weeks.***

In Stage 2, the remaining patients will be randomised between placebo and one or two chosen doses of daratumumab depending on results of the interim analysis.

The target recruitment rate is 2 participants per month. Recruitment will continue using Stage 1 dose allocations during the 12 weeks follow up of Stage 1 participants and during the interim analysis. Recruitment to Stage 2 will then take place over a further 7 months. Patients in both stages of the trial will be followed for 24 weeks, with the primary endpoint being measured at week 12.

2.2 Trial setting and patient population

This is a single centre trial which will be undertaken at the Newcastle upon Tyne Hospitals NHS Foundation Trust (NUTH) site. Patients will be recruited during attendance at NHS specialist thyroid/ TED clinics. Participants will also be identified through local neighbouring trusts acting as participant identification centres (PICs) and by self-referral through adverts.

If after IMP dosing, avoidable individual travel is not recommended due to local or national restrictions, then visits 6 to 8 may be performed by phone, followed by a home visit for collecting a blood sample to ascertain safety and outcome measures. In these circumstances, treatment of newly recruited participants will also be temporarily halted, but treatment of participants who have already received the first dose of daratumumab/placebo would continue.

2.3 Inclusion Criteria

1. Patients ≥18yrs old

2. Recent-onset Graves' disease (within 12 months) (defined as date of first thyroid function test showing hyperthyroidism (FT4 and TSH))

3. TRAb antibody concentrations above 10U/L (on Roche or Brahms TBII assays)

4. One or more of:

    - Pre-treatment severe hyperthyroidism (FT4 ≥50 pmol/L; or FT3 ≥15 pmol/l)
    - Persisting hyperthyroidism despite more than 12 weeks of antithyroid drug therapy (defined as FT3 above the upper limit of the reference range following 12 weeks of carbimazole treatment at a dose of 40mg or more daily (or equivalent dose of PTU))
    - Inflammatory thyroid eye disease (defined as clinical activity score, CAS≥3), or thyroid dermopathy
    - Large (visible) goitre (WHO grade III)

5. For women of child-bearing potential, willing to use a highly effective contraceptive method during their participation in the trial. Highly effective methods of contraception include:

    - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
    - progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
    - intrauterine device (IUD)
    - intrauterine hormone-releasing system (IUS)
    - vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
    - bilateral tubal occlusion
    - sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Abstinence is acceptable only as true abstinence: when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception).

6. Able to understand and speak sufficient English to complete trial procedures

7. Willing and able to provide informed consent prior to any trial procedures taking place

2.4 Exclusion Criteria

1. Previous thyroidectomy, or radioiodine treatment within 2 years
2. Pregnant or breastfeeding, or with a plan for pregnancy within 6 months
3. Previous shingles, known untreated cervical dysplasia, hepatitis B & C or HIV infection
4. Anaemia (Hb ≤ 100g/l), thrombocytopenia (≤75 $x10^9$/L) or neutropenia (≤1.0 $x10^9$/L)
5. Known chronic obstructive pulmonary disease (COPD) (defined as a forced expiratory volume [FEV] in 1 second <60% of predicted normal), persistent asthma, or a history of asthma within the last 2 years (intermittent asthma without hospitalisation is allowed)
6. Any significant physical or mental health condition that impacts the safety of the intervention, the interpretation of thyroid function or the ability of a participant to attend for intervention and safety monitoring, e.g. major cardiorespiratory disease, renal or hepatic failure, pancreatitis, cancer undergoing active treatment (excluding non-melanoma skin cancer), untreated chronic infection including TB, psychosis, depression impairing Activities of Daily Living
7. Current use of immunosuppressive therapy for thyroid eye disease or other conditions (within 3 months)
8. Current or previous participation in a CTIMP research study within 4 months
9. Hypersensitivity or anaphylactic reaction to previous monoclonal antibody treatments or methylprednisolone
10. Inability, in the opinion of the investigator, to be able to complete the clinical trial visits or procedures.

2.5 Randomisation and blinding

Stage 1: Trial participants will be randomly allocated to receive one of four different doses of daratumumab (9, 3, 1, 0.5mg/Kg) or matched placebo. Participants will be randomised in a ratio of 1:1:1:1:1 to the 4 daratumumab regimens or placebo intervention.

Stage 2: Participants will be randomly allocated to receive daratumumab (the one or two doses available at Stage 2 as determined by the interim analysis), or matched placebo. Participants will be randomised in a ratio of 1:1:1 to the 2 chosen daratumumab regimens or placebo intervention. If the interim analysis recommends only one daratumumab regimen, then patients will be randomised 1:1 between daratumumab and placebo.

Allocation sequences for both Stages will be computer-generated, using a random permuted block design; blocks might vary in size. Block sizes will not be disclosed, to ensure concealment. Randomisation will be performed by delegated and trained members of the research team using the Sealed Envelope system and should take place as close as practically possible to the baseline visit but with sufficient time to allow for prescription and medication ordering and dispensing. The allocation will be documented in the participant medical records and will be the same for each participant for both of their trial treatment visits.

The trial is single-blinded. Participants will be unaware of their allocated treatment group. The CI/PI and delegated clinicians as well as the TMG will be unblinded to the treatment allocation.

2.6 Sample size and power

The trial has been powered on change in TRAb antibody concentration. Daratumumab can selectively deplete antibody-secreting plasma cells to undetectable circulating numbers and so, a 50% or larger reduction in TRAb antibody concentration within 12 weeks of daratumumab administration is biologically plausible and would be a clinically important effect.

Data from an observational study in milder Graves' disease showed a mean change in TRAb concentration of 2% over 6 weeks, with an SD of 15%. Here, we assume a larger SD of 25% (to account for the outcome in this trial being measured at 12 weeks as opposed to 6 weeks).

The logarithm of the percentage reduction in TRAb is assumed normally distributed with SD 0.5 (based on untransformed values of 25% SD and 50% mean, i.e. CV is 0.5).

Simulations are performed using 4 different dose-response relationships:

1. plateau effect corresponds to 80% mean reduction in TRAb, 3mg/kg ED50
2. plateau effect corresponds to 60% reduction, 1mg/kg ED50
3. plateau effect corresponds to 60% reduction, 3mg/kg ED50
4. 5% mean reduction regardless of dose - null scenario.

All simulations assume an Emax dose-response and a 5% mean reduction in placebo treated participants. The ED50 is the dose that gives 50% of the difference in effect between placebo and plateau

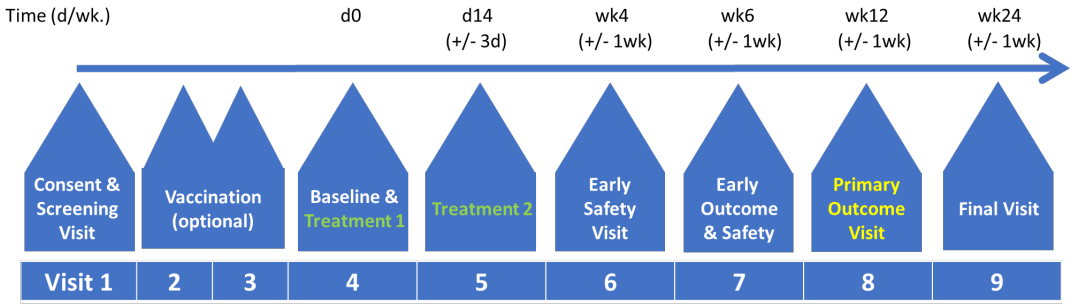
The power/type I error rate of the trial for each scenario is in the table below:

Scenario	**Probability to conclude dose-response (10000 replicates)**
1 – plateau of 80%, 3mg/kg ED50	>99%
2 – plateau of 60%, 1 mg/kg ED50	92%
3 – plateau of 60%, 3mg/kg ED50	83%
4 – null scenario	3.2%

For Scenario 2, a trial with 27 participants will have more than 90% power (one-sided a=0.05) to conclude there is a dose response relationship. In order to allow for an assumed 10% drop out, we will plan to recruit 30 participants.

Details of the interim analysis and criteria for premature termination of the trial are given in section 4.0. Simulations used in the power calculations follow this analysis plan with one exception; if the estimated plateau effect (the maximum effect possible as the dose becomes very large) lies between a 25%-50% reduction, then we have assumed, conservatively, that the trial will continue with doses of 3mg/kg, 9mg/kg plus placebo rather than doses of 9mg/kg, 12 or 16mg/Kg, and placebo as specified in section 4.3.3.

2.7 Study Diagram/Flowchart

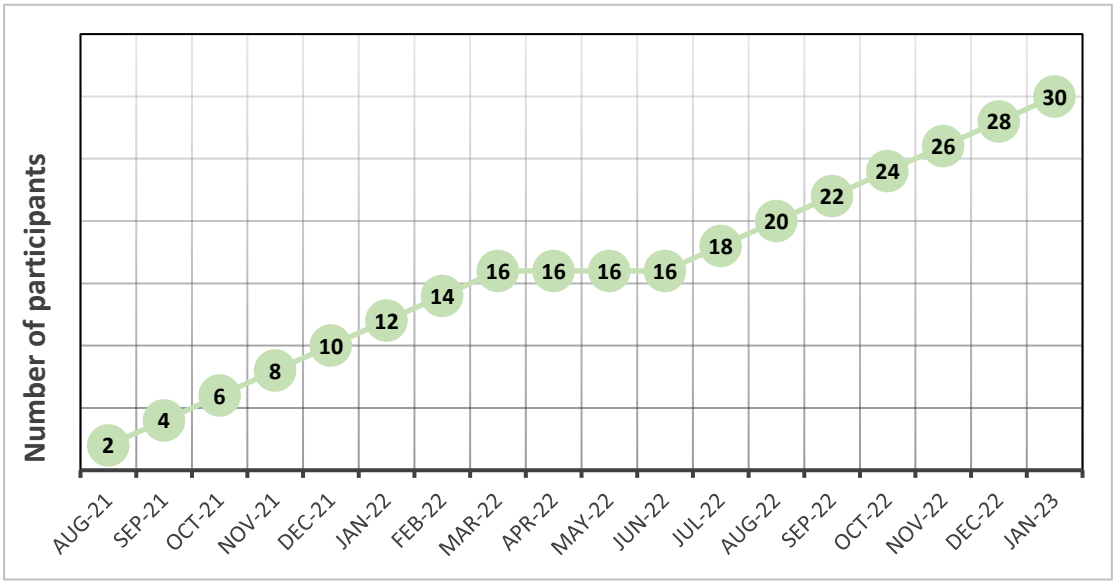


Study milestones

2.8 Trial timelines

Duration of funding / grant	Duration: 36 months. From: February 2021, To: 30th January 2024
Date of ethical favourable opinion	8/7/2021
Date of MHRA approval	21/7/2021
Date of HRA approval	21/7/2021
Date first site open to recruitment	29/9/2021
Date first participant randomised	14/10/2021
Planned end of recruitment	January 2023
Last participant recruited	NA
Planned time of formal interim analysis	11/2022
Planned time of primary analysis	8/2023 to 1/2024

2.9 Target accrual



Target accrual based on recruiting 2 participants per month with an anticipated three month pause for interim dose selection analysis.

3 DATA COLLECTION AND OUTCOME MEASURES

3.1 Trial assessments

Refer to protocol section ***7. Trial Procedures*** for full details of all trial assessments.

3.1.1 Primary outcome

Change in serum TRAb antibodies from baseline to 12 weeks compared to change in placebo group. Blood samples for the primary outcome measure are taken at Visit 4 (Baseline) and Visit 8 (Primary outcome visit). Extra TRAb samples are taken and stored until data lock at these visits.

If the baseline sample is not available, TRAb at the screening visit can be used for the primary outcome provided ***the visit occurs within 28 days of the baseline visit***.

3.1.2 Secondary outcomes

Important assessments related to secondary outcomes are:

- Serum TRAb antibodies assessed at baseline and at weeks 2, 4, 6, 12 and 24.
- Serum TSH, FT3 and FT4 assessed at baseline and at weeks 2, 4, 6, 12 and 24.
- Thyroid volume assessed at baseline and 24 weeks.
- Serum ATPO and thyroglobulin antibodies assessed at baseline and at weeks 6, 12 and 24 weeks.
- Clinical Activity Score (CAS), composite eye index and GOQoL score assessed at baseline and weeks 6, 12 and 24.
- ThyPRO39 score assessed at baseline and weeks 6, 12 and 24 weeks.

3.2 Definition and calculation of outcome measures

3.2.1 Primary outcome

The primary outcome measure is an individual's change in serum TRAb antibody level from baseline to 12 weeks. TRAb antibody levels will be high at baseline (inclusion criteria requires TRAb concentrations above 10U/L) thus change will tend to be a reduction in TRAb levels.

Define $\text{TRAb}^t = \text{TRAb concentration at week t}$. The percentage reduction (PR) in TRAb at week *t* is given by:

$$PR_t = 100 * \frac{[\text{TRAb}^0 - \text{TRAb}^t]}{\text{TRAb}^0}$$

The primary outcome is therefore PR_{12}

where,

TRAb^0 = TRAb at *Visit 4, day 0*
TRAb^{12} = TRAb at *Visit 8, week 12*

If TRAb^0 is unavailable, TRAb at the screening visit can be used for the primary outcome ***provided the visit occurs within 28 days of the baseline visit***.

3.2.2 Secondary outcomes

Change in serum TRAb antibodies from baseline to 2, 4, 6, 12 and 24 weeks is defined in a similar way to the primary outcome, i.e. percentage reduction in TRAb from baseline.

To be completed after interim analysis in SAP v2.0

3.2.3 Dose of IMP received (mg/kg)

The prescribed dose of IMP (mg) is administered as an infusion made up of 1L saline plus a volume of IMP (ml) determined using the Dose Banding Tables in Appendix 3 of Graves-PCD Protocol v3.0, dated 30 September 2021. The volume of IMP (ml) added is dependent on randomised group (mg/kg) and patient weight (kg). IMP is supplied as daratumumab 20mg/ml vials.

If 100% of the prescribed infusion volume is successfully administered, as is usually the case, then

IMP received (mg/kg) $= \left[\frac{\text{banded dose (mg)}}{\text{patient weight (kg)}}\right]$.

If, however, less than 100% is administered, then

IMP received (mg/kg) $= \left[\frac{\text{percentage of infusion volume administered}}{100}\right] \times \left[\frac{\text{banded dose (mg)}}{\text{patient weight (kg)}}\right]$

where,

percentage of infusion volume administered $= \frac{100 \text{ x } [\text{approximate infusion administered (ml)}]}{[1000+\text{prescribed IMP volume (ml)}]}$

and

prescribed IMP volume (ml) = banded dose (mg) / 20 (mg/ml).

4 STATISTICAL CONSIDERATIONS

4.1 Timing of analyses

The final analysis will take place after the last recruited participant has attended their 24-week follow-up visit, data queries have been resolved, and the database has been locked. Final analysis is expected to take place between 8/2023 and 1/2024.

4.2 Analysis populations

Intention-to-treat (ITT) population	Participants analysed according to randomisation allocation following the intention-to-treat principle.
Per-protocol (PP) population	Participants analysed according to whether 75% or more of the full allocated doses of daratumumab or placebo were received.
Dose-response (DR) population	Participants analysed according to the amount of daratumumab received, according to the agreed optimal dose(s) from the interim analysis.
Safety population (SP)	All recruited participants who received any study treatment, regardless of whether it was the protocol specified treatment.

4.3 Interim analyses, data monitoring and stopping guidelines

The trial will be monitored by an external DMC that will meet at the start of the trial, for the interim analysis and annually throughout the recruitment and follow-up period of the trial, and on ad hoc basis if required.

The trial includes an interim analysis of the dose-response after 15 participants (n≅3 per allocation) have provided 12-week follow-up data. The interim analysis will consider both efficacy and safety of the daratumumab doses in stage 1. The recommended dose from the stage 1 interim analysis will be presented to the DMC for approval.

During the period of the trial where stage 1 participants are followed-up for 12-week outcome data, it is anticipated that recruited participants may continue to be allocated according to stage 1 allocation until the interim analysis is conducted, and its results are implemented.

No formal statistical stopping rules will be used.

4.3.1 Dose-response modelling

The analysis population will be the ***Dose-response (DR) population*** (participants analysed according to the amount of daratumumab received).

In order to assess efficacy, a three-parameter Emax model will be fitted to the percentage change in TRAb concentration, defined in 3.2.1. Analysis of the percentage reduction in TRAb will be performed on a log transformed variable δ_t, where

$$\delta_t = -\log_e\left[1 - \frac{PR_t}{100}\right] = \log_e \mathrm{TRAb}^0 - \log_e \mathrm{TRAb}^t \quad (1)$$

i.e. the change from baseline to time *t* in $\log_e$TRAb. Normally distributed data and homoscedastic variance will be assumed.

The Emax model to be fitted is:

$$\delta_t = E_0 + E_{max}\left(\frac{dose}{ED_{50}+dose}\right) \quad (2)$$

where,

dose is the estimated amount of IMP (mg/kg) received by the patient - as defined in section 3.2.3., E_{max} is the asymptotic maximum response attributable to the drug, E_0 is the response when *dose* is 0, and ED_{50} is the *dose* giving response $E_0 + \frac{1}{2}E_{max}$.

The asymptotic plateau on the response scale (i.e. change in $\log_e$ TRAb) is given by

$$E_0 + E_{max} \quad (3)$$

and the dose *D* which gives a response δ_t is given by

$$D = \frac{(\delta_t - E_0)ED_{50}}{E_{max} - (\delta_t - E_0)} \quad (4)$$

Given estimates of E_0, ED_{50} and E_{max} from model (1) the following additional estimates may be obtained:

A. the plateau effect, in terms of PR, by substituting $E_0 + E_{max}$ for δ_t in equation (1)

$$100(1 - exp[-(E_0 + E_{max})])$$

B. the dose that gives 90% of the plateau effect, by substituting $\delta_t = 0.9(E_0 + E_{max})$ into equation (4), and

C. the dose that gives a mean reduction of 50%, by substituting

$$\delta_t = -\log_e\left[1 - \frac{50}{100}\right] = -\log_e(0.5)$$

into equation (4).

It is feasible that TRAb concentrations at week 12, and at other times points, might be below the limit of quantification of the assay. If this situation arises, such values will be replaced by $LOQ/\sqrt{2}$ where LOQ is the limit of quantification of the assay. The use of $\mathrm{LOQ}/\sqrt{2}$ is based on the assumption that data below the LOQ follows a triangular distribution with median $\mathrm{LOQ}/\sqrt{2}$ (i.e. values drop linearly to zero density at zero concentration).

Dose-response modelling will be performed using:

i. change in TRAb from baseline to 12 weeks, and
ii. change in TRAb from baseline to 6 weeks.

4.3.2 Model-based interim analysis dosing decisions

Model-based stopping criteria and Stage 2 dose recommendations are based on the change in TRAb from baseline to 12 weeks.

1. If the estimated plateau effect (i.e. the maximum percentage reduction in TRAb as the dose of daratumumab increases, A. in 4.3.1) corresponds to >50.0% reduction at 12 weeks, the trial will continue with placebo and the doses B. and C. defined in 4.3.1. Dose B is the dose expected to yield 90% of the estimated maximum TRAb reduction, and C is the dose expected to yield a 50% reduction in TRAb.

If either of the doses B. or C. are close to a stage 1 dose, consideration will be given to proceeding to stage 2 with the approximate stage 1 dose rather than the exact dose defined in 4.3.1.

2. If the estimated plateau effect (A. in 4.3.1) corresponds to <25.0% reduction in TRAb at 12 weeks, the trial will terminate early for lack of promising dose-response unless the DMC agree

that there has been an unequivocal improvement in serum thyroid hormone measurements in the active IMP vs placebo groups.

3. If the estimated plateau effect (A. in 4.3.1) corresponds to between a 25%-50% reduction in TRAb at 12 weeks, i.e. 25.0% ≤ plateau effect ≤ 50.0%, the trial will continue with placebo plus doses of 9mg/kg and a higher daratumumab dose (e.g. 12 or 16mg/Kg) as determined by safety data.

4.3.3 Dosing decisions, other considerations

In addition to the efficacy analysis detailed 4.3.1, the DMC will be provided with line listings of all grade 3 or higher AEs with corresponding dose allocations. This safety information will be taken into consideration in deciding stage 2 dose(s). For instance, if more than one IMP-related severe adverse reaction is observed at higher doses (9 or 3mg/kg), then lower doses will be selected for stage 2 of the trial provided there is evidence for efficacy. The DMC will be guided by the principle that in the absence of any observed dose-related safety signals the dose(s) will be selected for stage 2 according to the three rules stated in 4.3.2.

4.3.4 Contents of interim analysis report

4.3.4.1 Dose response modelling results

Dose-response (DR) population

1. Summary of individual IMP dosing and TRAb results – see ***Table 1*** below
2. Line listing of TRAb results by participant – appendix
3. Plot of TRAb levels versus visit, by individual – highlighting randomised group
4. Plot of percentage reduction in TRAb from baseline versus visit, by individual – highlighting randomised group
5. Summary statistics for percentage reduction in TRAb from baseline to week 6 and 12 by randomised group (mean, median, SD, min, max)
6. Summary statistics for change in $\log_e$TRAb from baseline to week 6 and 12 by randomised group (mean, median, SD, min, max)
7. Plot of change in $\log_e$TRAb from baseline to week 12 versus dose of IMP received (mg/kg) with fitted Emax model
8. Plot of percentage reduction in TRAb from baseline to week 12 versus dose of IMP received (mg/kg) with fitted Emax model
9. Parameter estimates from Emax model (week 12): E_0, ED_{50} and E_{max}
10. The plateau effect, in terms of percentage reduction (week 12)
11. The plateau effect, in terms of change in $\log_e$ TRAb (week 12)
12. The dose that gives 90% of the plateau effect (week 12)
13. The dose that gives a mean reduction of 50% (week 12)
14. Items 7 – 13 repeated for week 6 outcome data
15. Recommended doses for stage 2 based on week 12 results

Table 1 Summary of individual IMP dosing and TRAb results

Patient number	Randomised group	Dose of IMP received (mg/kg)	TRAB (U/L) at Baseline	TRAB (U/L) at week 6	TRAB (U/L) at week 12	PR in TRAb at week 6	PR in TRAb at week 12

4.3.4.2 Individual participant details

The DMC will be provided with the following information, by participant and at available visits (see table below), to provide context to the analysis and to inform the dosing decision. Participant details will be listed by their randomised group. Abnormal blood values will be highlighted – see Appendix section 9.1 for normal ranges.

1. Demographics (gender at birth, age at randomisation)
2. Thyroid disease at diagnosis (age, FT4, FT3, TSH, TRAb)
3. Randomised group
4. TSH (mU/L), FT4 (pmol/L), FT3 (pmol/L), TRAb (U/L)
5. Full blood count (FBC) [haemoglobin (g/L), platelets (10^9L), white cell (10^9L) , neutrophils (10^9L), lymphocytes (10^9L)]
6. Liver function tests (LFT) [ALT (U/L), bilirubin (µmol/L), alkaline phosphatase (IU/L)]
7. U&E test results
8. IgGAM [IgA, IgG, IgM (g/L)]
9. Treatment received - IMP [Randomised dose (mg/kg), prescribed dose (mg/kg), dose received (mg/kg)]
10. Thyroid concomitant medications
11. Non-thyroid concomitant medications
12. Adverse events – grade 3 or higher

Availability of blood results

Parameter	Baseline/ Treatment 1	Treatment 2 (Week 2)	Safety Visit (Week 4)	Early outcome visit (Week 6)	Primary outcome visit (Week 12)
TSH, FT4, FT, TRAb	Yes	Yes	Yes	Yes	Yes
FBC	Yes	Yes	Yes	Yes	Yes
LFTs and U&E	Yes	Yes	Yes	Yes	**No**
IgGAM	Yes	**No**	**No**	Yes	Yes

***Table2*.** Dummy table for Safety bloods (e.g. FBC, LFTs, IgGAMs and U&Es)
Values above the normal range shown in red, those below the normal range shown in blue

Participant ID	Randomised group	Visit	Haemoglobin (g/L)	Platelets (10^9/L)	Total White Cell (10^9/L)	Lymphocytes (10^9/L)	Neutrophils (10^9/L)
01-006	Placebo	Visit 4 - Baseline & Treatment 1	123	123	4	2	2
01-006	Placebo	Visit 5 - Treatment 2	123	111	1413	1911	2
01-006	Placebo	Visit 6 - Early Safety Visit	123	115	5011	149	2
01-006	Placebo	Visit 7 - Early Outcome & Safety Visit	123	123	415	13	2
01-006	Placebo	Visit 8 - Primary Outcome Visit	123	100	325	3	2
01-003	1mg/Kg	Visit 4 - Baseline & Treatment 1	121	134	1210	249	1
01-003	1mg/Kg	Visit 5 - Treatment 2	200	215	2	1	1
01-003	1mg/Kg	Visit 6 - Early Safety Visit	121	163	18	1	7
01-003	1mg/Kg	Visit 7 - Early Outcome & Safety Visit	134	222	923	122	21
01-003	1mg/Kg	Visit 8 - Primary Outcome Visit	142	76	817	124	13
01-004	9mg/Kg	Visit 4 - Baseline & Treatment 1	123	541	22	11	11
01-004	9mg/Kg	Visit 5 - Treatment 2	132	231	85	122	3
01-004	9mg/Kg	Visit 6 - Early Safety Visit	142	132	18	7	12
01-004	9mg/Kg	Visit 7 - Early Outcome & Safety Visit	111	124	7	12	1
01-004	9mg/Kg	Visit 8 - Primary Outcome Visit	121	143	710	183	7

4.4 **Analysis Methods**

4.4.1 Analysis of primary outcome

To be completed after interim analysis in SAP v2.0

4.4.2 Analysis of secondary outcomes

To be completed after interim analysis in SAP v2.0

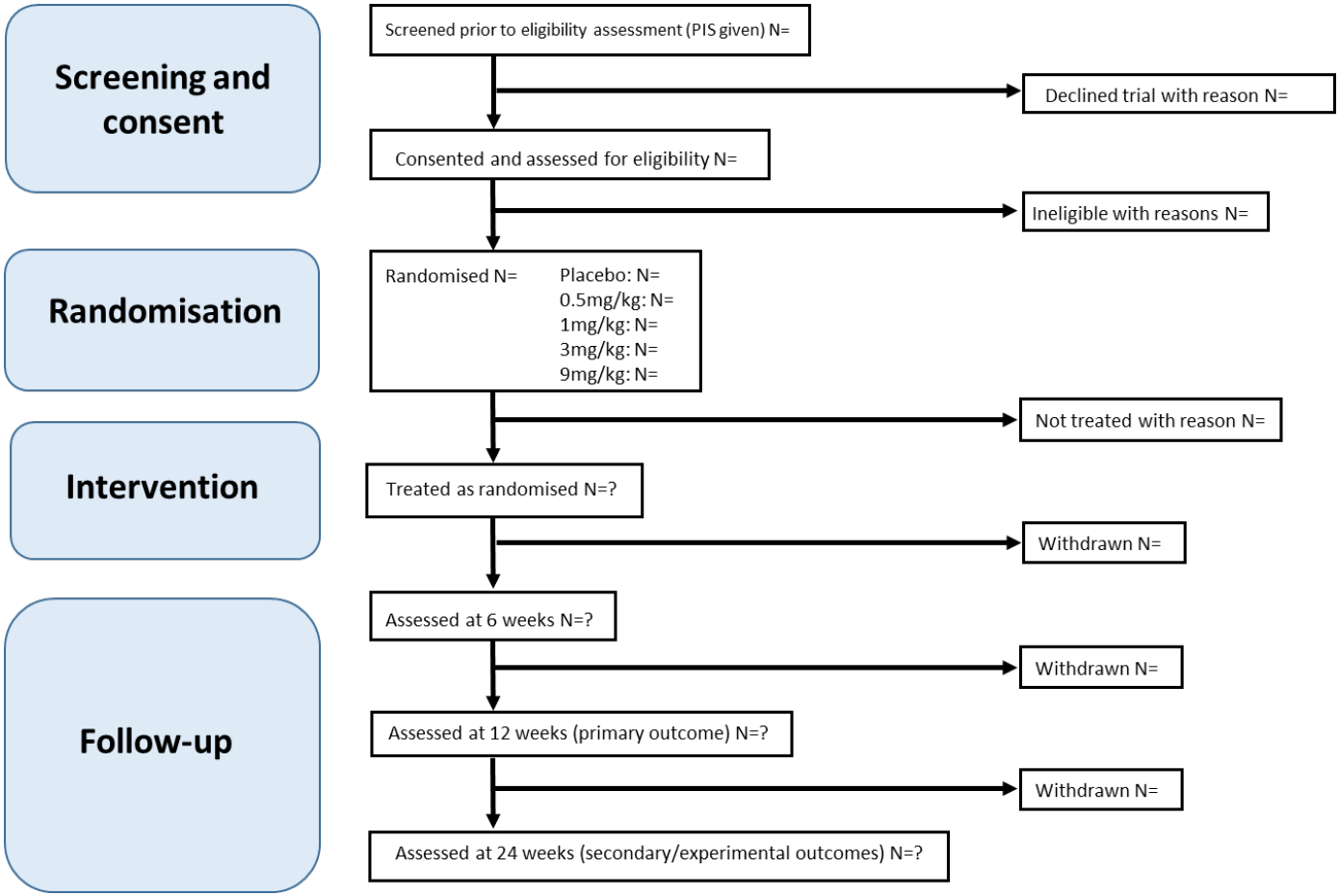
5 TRIAL POPULATION

5.1 Patient flow through trial

Patient flow through the trial will be presented using a CONSORT diagram. Information will be provided on numbers and reasons (where appropriate) for: patients invited but not interested; consented patients not being eligible; randomised patients subsequently found to be ineligible; patients deviating from treatment as randomised; patients not evaluable for the primary endpoint; patients withdrawing from the trial; patients withdrawing consent and all protocol violations.

The number of ineligible patients and reasons for ineligibility will be reported.

5.2 CONSORT flow diagram



5.3 Recruitment

Observed recruitment will be presented graphically over time.

5.4 Baseline characteristics

Intention-to-treat (ITT) population

Demographic, clinical and baseline characteristics at recruitment will be summarised descriptively. For categorical variables, the frequency and percentage in each group will be reported and for continuous variables the mean, standard deviation (SD) and/or median, IQR and range will be reported.

Reported characteristics at Baseline will include:

- Age (years), Gender (Male/Female)
- Smoking and vaping status
- Current thyroid disease (FT4, FT3, TSH, TRAb at diagnosis)
- Treatment given for Current thyroid disease
- Height (cm), Weight (kg), Pulse (bpm), BMI SD score
- Goitre size (neither palpable nor visible; palpable only, not visible; palpable and visible; large goitre and hence easily seen at a distance)
- Blood Count: Haemoglobin (g/L), Platelets (10^9/l), Neutrophils (10^9/l), Lymphocytes 10^9/l), White Blood Cells (cell/µl or (10^9/l))
- Liver function: ALT (U/L), Bilirubin (µmol/L), Alkaline Phosphatase (IU/L)
- Blood Sampling - IgGAM: IgA, IgG, IgM (g/L)
- Blood sampling - ATPO & TgAb: TPOAb (kU/L), TgAb (IU/ml)
- Thyroid function: TSH (mU/L), FT3 (pmol/L), FT4 (pmol/L), TRAb (U/L)
- Thyroid eye disease (Yes or No)

5.5 **Treatment received**

5.5.1 Daratumumab

Intention-to-treat (ITT) population

To be completed after interim analysis in SAP v2.0

5.5.2 ATD

Intention-to-treat (ITT) population

To be completed after interim analysis in SAP v2.0

5.6 **Follow-Up**

To be completed after interim analysis in SAP v2.0

5.7 **Protocol deviations**

To be completed after interim analysis in SAP v2.0

6 SAFETY

To be completed after interim analysis in SAP v2.0

6.1 Adverse events

To be completed after interim analysis in SAP v2.0

6.2 Serious adverse events

To be completed after interim analysis in SAP v2.0

6.3 Other safety measures

To be completed after interim analysis in SAP v2.0

7 STATISTICAL SOFTWARE

Dose-response modelling will be performed using the ***DoseFinding*** package (Bjoern Bornkamp, 2019) in R Statistical Software (v3.6.0; R Core Team, 2019). All other statistical analysis will be performed in Stata V16 (StatCorp, 2020). Statistical analyses will be carried out by the Trial Statistician at the Biostatistics Research Group, PHSI, Newcastle University. All programs will be stored in the School Statistics folder on the PHSI server. A paper master copy of all analysis reports will be stored securely in the statistical section of the trial master file.

8 REFERENCES

(R Core Team, 2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Bjoern Bornkamp (2019). DoseFinding: Planning and Analyzing Dose Finding Experiments. R package version 0.9-17. https://CRAN.R-project.org/package=DoseFinding

9 APPENDIX

9.1 Indicative normal ranges pertinent to Stage 1 interim analysis

Parameter	**Normal range**	**Units**
TSH	0.3 – 4.5	mU/L
FT4	10 – 22	pmol/L
FT3	3.1 – 6.8	pmol/L
TRAb	<1.8	U/L
Haemoglobin	115 – 180	g/L
Platelets	150 – 450	10^9L
Neutrophils	2 – 7	10^9L
Lymphocytes	1.5 – 7	10^9L
White Blood Cells	4 – 11	10^9L
ALT	0 – 40	U/L
Bilirubin	0 – 20	µmol/L
Alkaline phosphatase	20 - 130	IU/L
IgA	0.8 – 3	g/L
IgG	6 – 16	g/L
IgM	0.4 – 2.5	g/L
TPO	<35	kU/L
TgAb	<20	IU/ml
Tetanus	0 – 40	IU/ml
Pneumococcus	0 – 100	mg/L