ADAPT:
Atopic Dermatitis Anti-IgE Paediatric Trial

The role of anti-IgE (omalizumab/Xolair) in the management of severe recalcitrant paediatric atopic eczema

PROTOCOL
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PROTOCOL TITLE:

The **A**topic **D**ermatitis **A**nti-IgE **P**aediatric **T**rial **(ADAPT)**: The role of anti-IgE (omalizumab/Xolair) in the management of severe recalcitrant paediatric atopic eczema

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Nomenclature

Anti-IgE	Omalizumab/Xolair
βhCG	β human chorionic gonadotrophin (pregnancy test)
BP	blood pressure
(C)DLQI	(Children's) Dermatology Life Quality Index
DMEC	Data Monitoring and Ethics Committee
EASI	Eczema Area and Severity Index
FBC	Full blood count
LFT	Liver function tests
m	months
PADQLQ	Paediatric Allergic Disease Quality of Life Questionnaire
POEM	Patient-oriented Eczema Measure
PO-SCORAD	Patient Orientated-SCORAD
Rx	treatment
SCORAD	SCORing Atopic Dermatitis (Eczema severity score)
TEWL	Transepidermal water loss
U&E	urea and electrolytes

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1. Background & Rationale

Our research aims to establish the role of anti-IgE therapy in children with severe eczema.

Significance:

Eczema is a chronic inflammatory skin disorder with a lifetime risk of up to 22% of children by the age of 12-14 years[1]. This results in an impact on the quality of life of the child as well as on the psychological status of their families[2]. There is a subgroup of children with severe recalcitrant eczema who remain symptomatic despite optimal topical therapy, and systemic therapy can have significant attendant side effects. In addition, children deficient in the enzyme thiopurine methyltransferase (TPMT) are more susceptible to the side effects of drugs like azathioprine. Studies suggest that whilst only 2% of eczema is severe, it is likely to persist in up to 91% of this subgroup[3;4]. These children are frequently treated with long-term systemic therapy, such as oral steroids, azathioprine, cyclosporin, with the attendant risk of severe side effects. Yet there are no good randomised controlled studies looking at the efficacy of these treatments. We aim to recruit children who have failed conventional topical therapies, who are most likely to comply with, and benefit from, injections of anti-IgE.

Background:

A complex interaction between genetics, environment and immunology define the pathophysiology of eczema. There is increasing in vitro and murine model evidence for the role of IgE in the immunopathogenesis in atopic eczema. A significant proportion of patients have elevated serum IgE levels and an atopic predisposition. Specific IgE may be critical in activating mast cells and dendritic cells, ultimately having an important role in antigen presentation and T cell activation, resulting in cutaneous inflammation. IgE-mediated histamine release from cutaneous mast cells may also aggravate eczema through the itch–scratch cycle[5]. IgE is likely to be of more relevance in paediatric disease than in adults, where eczema is thought to become less allergen driven and more "autoreactive". It may be that chronicity of disease into adulthood alters the relevance of different allergens, antigen and immune mediators in the pathogenesis of skin lesions and symptoms. By confining this study to a paediatric atopic population we therefore hope to target patients for whom IgE is more relevant[6]. This study will also provide the basis for storing samples used in future mechanistic work in this area. Omalizumab (Xolair®, Novartis) is the only commercially-available anti-IgE antibody. It binds to human IgE, limiting mast cell degranulation and inhibiting the release of inflammatory mediators. It has been approved by NICE for the treatment of asthma from the age of 6 years[7]. It is licensed for use from the age of 6 years of age, as safety data suggests that Xolair (omalizumab) is well tolerated in children in this age range[8]. Xolair (omalizumab) may be associated with type I allergic reactions. Serum sickness has rarely been seen with Xolair (omalizumab) and patients with severe asthma may rarely present with Churg-Strauss and hypereosinophilic syndrome. It may be associated with helminth infections and caution is advised in patients travelling to endemic areas. An FDA post marketing review (EXCELS) gave no indication that Xolair treatment is associated with an overall increased risk of malignancies.[9] Pooled analysis of trials by the manufacturers has not shown an imbalance in the rates of cardiovascular events and no imbalance in the rate of cerebrovascular events relative to published studies of asthma patients.

Manufacturer's dosing tables for anti-IgE are based upon the patient's weight and total IgE levels[10]. They have been derived to optimally lower IgE levels, the same mechanism thought to be of major importance in childhood eczema.

The available literature suggests that anti-IgE may be of benefit in the treatment of eczema from at least the age of 7 years. Lane reported on 3 children with eczema who showed a significant improvement, Belloni reported improvement in 6 of 11 adults, Vigo reported an improvement in 5 out of 7 children and adults and Sheinkopf reported improvements in all 21 teenagers and adults treated[11-14]. Reassuringly, none of these studies reported significant side effects from the therapy. However, none of these studies were randomised or placebo-controlled, and included a heterogenous mix of patients of different ages.

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and all of the applicable regulatory requirements. Regulatory approval has been sought from the Medicines and Healthcare products Regulatory Agency (MHRA). The King's Health Partners Clinical Trials Office (KHPCTO) will manage the sponsors responsibilities and Quality Assurance to ensure compliance with the Clinical Trial Regulations. Ethical approval is overseen by London Westminster NHS Research Ethics Committee (REC reference number: 11/LO/0123).

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2 Trial Objectives and Design

2.1. Trial Objectives

Our hypothesis is that anti-IgE will reduce the levels of IgE in children with severe eczema, thereby alleviating their symptoms.

Primary outcome measure:

1. ***Eczema severity:*** assessed by the validated eczema score, SCORAD (SCORing Atopic Dermatitis)[15] after 24 weeks of treatment.

Secondary outcome measures:

1. Treatment failure: patients who, after the 1st 12 weeks of treatment, have persistent severe eczema despite 2 courses of rescue therapy (0.5 to 1mg/kg/day of oral prednisolone for a week at a maximum dose of 40mg/day, followed by a week at 50% of this dose)

2. Alternative systemic therapy: patients in whom
a) alternative systemic therapy has been started as a result of treatment failure as defined above

OR

b) where alternative systemic therapy is being considered at 24 weeks in patients who have an objective SCORAD >40 and a (C)DLQI ≥10

3. Eczema quality of life: by questionnaire:
a) Patient-oriented Eczema Measure (POEM)
b)(Children's) Dermatology Life Quality Index ((C)DLQI).

4. Eczema severity: by SCORAD and EASI (**E**czema **A**rea and **S**everity **I**ndex) assessments, measurements of transepidermal water loss(TEWL) and medical photography.

5. Effect on co-existing allergic disease: by questionnaire (PADQLQ)

6. Adverse events*:* by history and investigations

7. Number of eczema exacerbations

8. Infective episodes of eczema

9 a) Change in free total IgE and allergen specific IgE: by collaboration with the in-house facilities at Novartis and
b) the change in reactivity to food and aeroallergens: by skin prick tests.

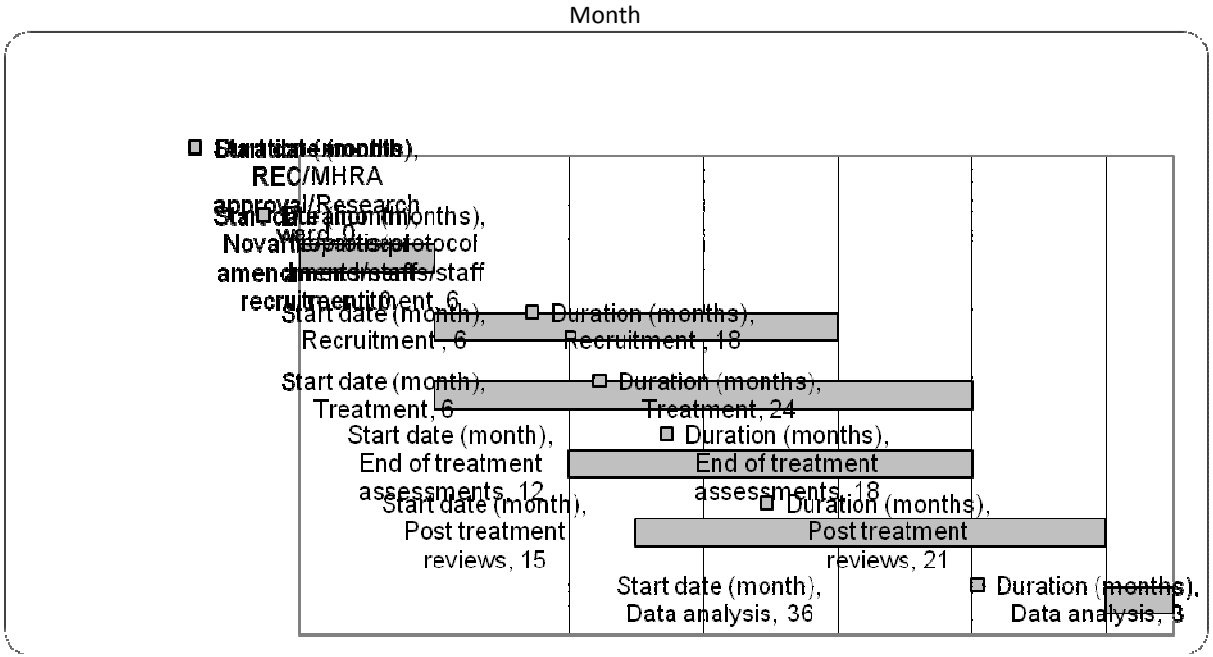
10. Mechanism of action of anti-IgE: this study will enable us to store the samples required to study the immunohistochemical changes and the immunomodulatory effects on allergen-specific T cells and FAP, . There will also be an option to store blood for genetic studies.

2.2 Trial Design

This will be a randomised double-blind placebo-controlled trial of anti-IgE therapy in children with severe eczema who have failed topical therapy. There will be an initial 78 week (18 month) period during which recruitment will occur (Fig. 1). 62 children will proceed with the trial if they have severe eczema defined as an objective SCORAD (a validated eczema severity score) of >40-83 (SCORAD range: 0-83, >40 indicates severe disease) at assessment.

Treatment phase: Each patient will be enrolled for 48 weeks. The children will be randomised to commence treatment with anti-IgE or placebo. They will undergo treatment for 24 weeks and continue to take their conventional treatments for eczema. At 24 weeks, assessments will be made of the primary outcome measure, their SCORAD, to determine their response to anti-IgE therapy.

Post treatment assessments: At the end of this 24 week treatment period, anti-IgE or placebo treatment will be discontinued. The children will be assessed and the doses of their other systemic eczema medications recorded. Further assessments at 36 and 48 weeks (post treatment reviews) will be performed.



TSC meetings will occur prior to recruitment, and then as determined by the TSC. The DMEC will meet at the onset and decisions about frequency of meetings, and the type, frequency and format of data reports will be established.

Fig. 1a: *Gantt chart*

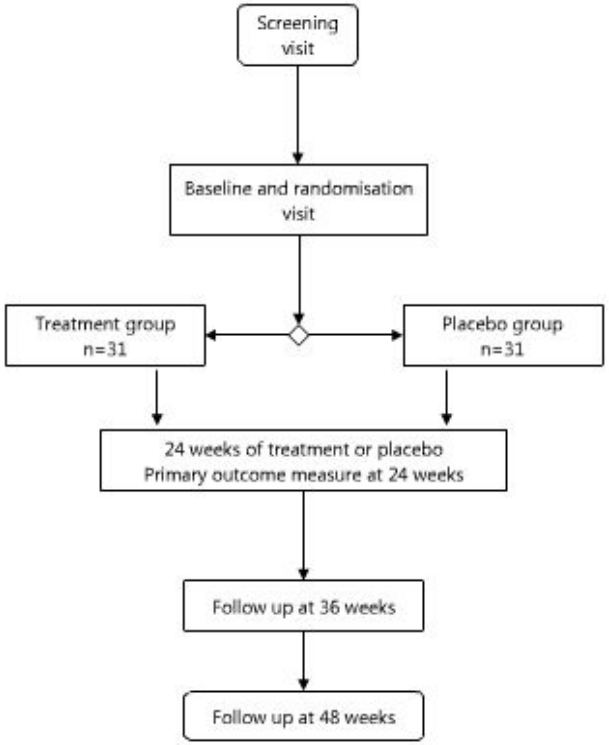


Fig. 1b: Study flow chart

2.3 Trial Flowchart

Week (All visits ± 5 days unless stated)		0	2*	4	6*	8	10*	12	14*	***16***	18*	20	22*	***24***		36 **(± 2 wks)**	48 **(± 2 wks)**	Ongoing
Visit	Screening Visit	Baseline and randomisation Visit (start Rx)																
Patient information and informed consent	X																	
Eczema history	X																	
Family history	X																	
Eczema impact	X													X			X	
Medical History and examination	X																	
Record of concomitant drugs	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Adverse event			X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Questionnaire - (C)DLQI	X	X		X		X		X		X		X		X		X	X	
Questionnaire-POEM	X	X		X		X		X		X		X		X		X	X	
Questionnaire-PADQLQ	X	X		X		X		X		X		X		X		X	X	
SCORAD	X	X		X		X		X		X		X		X		X	X	
EASI	X	X		X		X		X		X		X		X		X	X	
Height/weight	X	(X)												X		X	X	
BP/routine observations	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Skin prick tests	X													X				
Transepidermal water loss (TEWL) (optional)	X													X		X	X	
Bloods (FBC, eosinophils,U&E, LFT, Vitamin D, iron, bone	X													X				X

Week (All visits ± 5 days unless stated)		0	2*	4	6*	8	10*	12	14*	***16***	18*	20	22*	***24***		36 **(± 2 wks)**	48 **(± 2 wks)**	Ongoing
Visit	Screening Visit	Baseline and randomisation Visit (start Rx)																
profile, IgE)																		
Blood collection and storage for immunological studies	X													X				X
Blood for genetics studies	X																	X
Urinanalysis (glucose, protein, blood)	X													X		X	X	
Pregnancy test (βhCG)	X																	
Skin swabs	X																	
Skin biopsy (optional)		X												X			.	X
Skin biopsy (genetics studies)		X																X
Medical photography		X												X				
Eligibility criteria	X																	
Randomisation		X																
Anti-IgE or placebo injections (2 or 4 weekly)		X	X	X	X	X	X	X	X	X	X	X	X					
PO SCORAD																		X
Exacerbation/Infection																		X
Withdrawal																		X

Trial medication or placebo will be administered 2 or 4 weekly as described in section 3.2. The dose will be determined by the patient's weight and total IgE level. Thus some patients will not need to attend alternate injection visits (weeks 2, 6, 10, 14, 18, 22 marked*).

3 Trial Medication

3.1 Investigational Medicinal Product

Xolair (omalizumab):

Manufacturer: Novartis

Powder (to be made up with solvent) for solution for injection. Xolair is an off-white lyophilised powder. One vial contains 150 mg of omalizumab. After reconstitution the vial contains 125 mg/ml of omalizumab (150 mg in 1.2 ml).

Xolair 150mg powder (to be made up with solvent) for solution for injection is supplied by Novartis.

Placebo: This will be manufactured by Novartis to match the active drug.

Clinical Trials Labelling and QP Release

Novartis will provide the trial with bulk supplies of unlabelled active and placebo vials free of charge. Novartis will not, however, provide the solvent ampoules which contain 2 ml water for injections. Water for injections with marketing authorisation will be supplied by investigator site.

MODEPHARMA is responsible for arranging the IMP's labelling (according to Annex 13 guidelines) and final QP release for clinical trial use. The labelled and QP released medication will be shipped to the trial site following site initiation.

Please refer to the Summary of product Characteristics and Investigational Medicinal Product Dossier (IMPD) for more details about the active and placebo product.

Pharmacy staff at investigator site will be unblinded, as well as unblinded nurses who will be preparing the IMP. To minimise bias, unblinded nurses will not be involved in any further trial related activities. All other members of the research team will be blinded.

3.2 Dosing Regimen

Therapy in the treatment arm will comprise anti-IgE (Xolair/omalizumab) injections. The placebo arm will receive matching placebo injections supplied by the manufacturers of Xolair/omalizumab (Novartis).

The appropriate dose and dosing frequency of Xolair (omalizumab) is determined by baseline total IgE (range: 30 to 1 500 IU/ml), measured before the start of treatment, and body weight (kg). Prior to initial dosing, patients will have their IgE level determined by serum total IgE assay for their dose assignment. Based on these measurements, the dose of Xolair (omalizumab) will be calculated using the formula: 0.016 x weight (kg) x total IgE level (kU/l) or using the latest manufacturers dosing tables (according to the current Summary of Product Characteristics). 75 – 600 mg of Xolair (omalizumab) in 1 to 4 injections may be needed for each administration as shown in the tables. The dose of Xolair (omalizumab) stated on the table, closest to that child's

weight and IgE levels, will be administered. Thus, if the total IgE level is above the upper limit stated on the dosing table, the highest dose of Xolair (omalizumab) stated on the table closest to that child's weight will be administered (this is not a manufacturer's recommendation). The equivalent volume for placebo doses will be calculated in the same way. They will remain on this dose throughout the 24 weeks of treatment.

3.3 Drug Accountability

Study drugs will be dispensed by hospital pharmacy. Study drugs will be supplied only to subjects participating in the study.

The CI and delegates are responsible for ensuring that all study drugs at the site are inventoried and accounted for throughout the study. The dispensing of study drugs will be documented and accounted for. Patient specific inventories will be kept in the pharmacy as the completed worksheets for each patient. These will then be filed in the order that they are dispensed. Study drugs will be handled in strict accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. All IMPs must be stored at 2°C – 8°C in a refrigerator.

Used vials will not be retained for verification by the study monitor. Unused or expired study drugs not reconstituted into syringes will be available for verification by the Sponsor's site monitor.

Before proceeding to the disposal of any IMP, authorisation from the Sponsor will be sought. Once authorised, the disposal will be in accordance with the Local Pharmacy Standard Operating Procedure.

If IMP is reconstituted and subsequently not administered to the intended recipient, then the unused syringe is to be returned to pharmacy, logged and disposed according to local processes. Empty syringes will not be returned to the pharmacy but will be disposed of locally (i.e. on the ward) following injection according to local processes.

3.4 Subject Compliance.

Subject compliance with Xolair (omalizumab)/Placebo dosing will be monitored by nursing or medical staff in hospital at administration. Compliance with other aspects of this protocol such as taking of other eczema medications, attendance at trial visits and completion of trial related procedures such as questionnaires will be assessed at each visit. Participants that fail to comply with the required assessments may be discontinued from the trial.

3.5 Concomitant Medication

The participants will undergo Xolair (omalizumab)/Placebo treatment for 24 weeks and may continue to take their conventional treatments for eczema. Concomitant eczema medications would include topical treatments including any emollients, bath additives, topical steroids, topical calcineurin inhibitors, wet wraps, and systemic treatment including oral anti-pruritics/anti-histamines, oral/intravenous antibiotics, immunosuppressants and uv therapy.

During treatment with Xolair (omalizumab)/Placebo, the patients/parents will monitor the child's eczema at home and if there is a deterioration, they will score this at home using the Patient Orientated-SCORAD (PO-SCORAD) paper form (to be handed in at the following visit) or

online. If there is deterioration in their PO-SCORAD result, this would trigger the parents/ carers to contact the study team to discuss drug doses or a reassessment and modification of therapy. An exacerbation will be identified and managed, and any additional therapy will be recorded.

Any medication required for any ongoing illness (illnesses not listed in the exclusion criteria in section 4.2), birth contraception and any rescue medications will also be permitted and recorded. This may include inhalers and nebulisers, antihistamines, topical or oral steroids, wet wraps, montelukast, oxygen, nasal steroids, sodium cromoglycate nasal/eye drops or inhalers, anti-inflammatory or antibiotic eye drops, antibiotics, anti-pyretics, cough syrup and injected or inhaled adrenaline for symptoms of asthma, rhinoconjunctivitis, food allergy or intercurrent illness. Female patients who have attained menarche will undergo a pregnancy test at the baseline and randomisation visit. They will be counselled against pregnancy during the course of treatment, and will be advised to use contraceptive measures if appropriate.

All medications taken will be recorded as per section 5.1

4 Selection and Withdrawal of Subjects

4.1 Inclusion Criteria

1. Children between the ages of 4-19 years at the time of enrolment into the trial

2. Severe eczema with

i. an objective SCORAD (a validated eczema severity score) of over 40

ii. in a patient unresponsive to optimal topical therapy (potent topical steroids and topical calcineurin inhibitors) or systemic therapy

iii. in whom there is no impression of lack of compliance

iv. with a (C)DLQI score of ≥10

v. and in whom active infection has been ruled out and/or adequately treated

3. Raised SpIgE (>0.35 IU/ml)or SPT (>3mm)to at least 1 food allergen or 1 aeroallergen

AND/OR

4. Clinical impression that allergic exposures cause worsening eczema.

5. Total IgE level ≥300 kU/l.

6. Clinically proven IgE-mediated allergic disease including at least 1 of the following:

i) immediate hypersensitivity to a food as proven by raised specific IgE (SpIgE) or skin prick test (SPT) greater than the 95% positive predictive value or ≥8mm, or a positive double blind placebo controlled food challenge,

ii) allergic rhinoconjunctivitis as defined by sensitisation to a respiratory allergen and clinical history of rhinoconjunctivitis symptoms when exposed to the relevant allergen

iii) allergic asthma: a history of cough, wheeze, or shortness of breath that

(1) was responsive to therapy with bronchodilators on two or more occasions in the previous 24 months,

(2) required one visit to a physician in the previous 24 months, and

(3) occurred during the night, during early morning, or upon exercising in the intervals between exacerbations at any time in the previous 12 months and

(4) where allergic exacerbations can be clinically related to an allergen exposure WITH a corresponding positive SPT or SpIgE to allergen.

7. Written informed consent to participate.

4.2 Exclusion Criteria

The **exclusion** criteria are:

1. Children and/or families who are unable to comply with the regime of 2-4 weekly injections and clinic visits

2. Evidence of underlying immune compromise, autoimmune disease, immune complex mediated conditions.

3. Malignancy or a history of malignancy.

4. Known cardiovascular or ischaemic cerebrovascular abnormality.

5. Other serious or uncontrolled systemic disease.

6. Pregnancy or lactation.

7. Known history of hypersensitivity or anaphylaxis to anti-IgE injections or its constituents.

8. Insufficient understanding of the trial assessments**.**

9. Participation in a CTIMP in the previous 60 days or (if known) 4 half-lives of the relevant medication, whichever is the greater. In this case, entry may be delayed until the appropriate time.

10. Investigator feels that there is a good clinical reason why the child would be unsuitable to participate in the study.

4.3 Selection of Participants

Participants will be recruited from the Paediatric Allergy and dermatology clinics at St Thomas' Hospital and will be referred from secondary and tertiary colleagues. They may also be referred from Participant Identification Centres (PIC) or self-refer. Patients may wish to continue to have routine follow up at their local hospital and we will maintain two way communication with their local team.

4.4 Randomisation Procedure / Code Break

Participants will be allocated to treatment arm via an online dynamic algorithm which will be developed and hosted by the UKCRC registered King's College London CTU based at the Institute of Psychiatry. The use of the online system will ensure concealment of treatment allocation for clinicians who are recruiting participants. Randomisation procedure: Go to www.ctu.co.uk, select 'Randomisation Service-Advanced', then select 'ADAPT'. Usernames and passwords will all be assigned by the CTU.

Participants and any healthcare provider involved in trial assessments will be blinded to the group assignment. Code break will be provided by the pharmacy department at Guy's and St Thomas' NHS Foundation Trust. All patients will be provided with an emergency contact details card to be carried for the duration of the trial. Individual treatment codes will be supplied to the clinicians by pharmacy only if clinically indicated as per the local process.

4.5 Withdrawal of Subjects

Patients may withdraw from the study at any time if they so wish.

Children will be withdrawn by the study team if, in the judgment of the investigator, further participation in the trial would be deleterious to the participant's health. Reasons for withdrawal would include unacceptable adverse reactions or events thought likely to be related to treatment with Xolair (omalizumab).

Every effort will be made to follow-up patients in this category according to the usual trial schedule, with the exclusion of Xolair (omalizumab) or placebo injections. In other words, they will be invited back for a review at weeks 20, 24, 36, 48 if these have not already been completed. Home visits to complete the assessments may be performed. Unless a patient specifically requests, all trial data and samples until the date of withdrawal, will be retained for analysis.

4.6 Expected Duration of Trial.

Total duration of trial (including analysis): 169 weeks.

Clinical participation: up to 126 weeks.

Patients will be recruited during the first 78 weeks (18 months) of the study. Each patient will then undergo treatment/placebo injections for a total of 24 weeks. They will be reviewed at 24, 36 and 48 weeks. Each patient will therefore undergo 24 weeks of treatment or placebo injections, followed by 24 weeks of follow-up. The end of the trial will be defined as the last visit of the last patient. There will be 3 months for data analysis at the end.

5 Trial Procedures

5.1 By Visit (Home visits may be performed if deemed appropriate)

Screening visit:

Information leaflet and informed consent:

The patient/legal guardian and if appropriate, the child will have the opportunity to study the patient information leaflet prior to this visit. Review patient information leaflet and answer queries. Obtain informed consent.

Eczema history and impact, complete medical history and eligibility criteria:

- Any clinically significant diseases or medical procedures other than the disease under study, and any history which would exclude participation in the study as per the exclusion criteria
- Eczema: History of eczema course, current eczema treatment, previous courses of treatment and success/failure.
- History of asthma, rhinoconjunctivitis or food allergy.

Record of concomitant medications

Questionnaires*: The same questionnaires will be used for each patient throughout the study and are:*

1. (Children's) Dermatology Life Quality Index ((C)DLQI)

2. Patient-oriented Eczema Measure (POEM)

3. Paediatric Allergic Disease Quality of Life Questionnaire (PADQLQ)

Throughout the study, patients or parents/carers will be asked to perform a PO-SCORAD assessment at home on paper or online, if they suspect a deterioration in their/their child's eczema. Deterioration in PO-SCORAD score may suggest a deterioration in their eczema and will trigger the family to contact the study team for further advice.

Examination:

- Physical including SCORAD and EASI assessment, height, weight, blood pressure(BP) and routine observations.

Assessments:

- Skin prick testing to aeroallergens and to foods suspected of causing eczema or food allergic reactions.
- Urinanalysis (glucose, protein, blood, and in females patients who have reached menarche: βhCG pregnancy test)

Phlebotomy

Baseline FBC, eosinophils, U&E, LFT, IgE levels, vitamin D, iron levels, bone profile, storage for immunological studies, and if separate consent has been given, for genetics studies. 2ml/kg of blood will be collected, with a maximum of 50mls.

Skin swabs:

Skin swabs will be taken from active sites of eczema and the nose of the patient. Active infection will be treated as per routine practice.

Week 0: Baseline and randomisation visit

Record of concomitant medications

Questionnaires

Examination: Physical including height & weight (if not screened within the last 4 weeks or significant change suspected) , SCORAD and EASI assessment, BP.

Assessment

- Transepidermal water loss (optional)

A skin biopsy will be performed if separate consent is obtained

Medical photography

Randomisation

Injection of anti-IgE or placebo with routine observations including BP, for 2 hours

Week 2*, 4, 6*, 8, 10*, 12, 14*, 16, 18*, 20, 22*:

Visits are flexible within a period of ± 5 days (visit days will be counted from the date of the first dose regardless of the date of the previous visit).

(* Weeks 2, 6, 10, 14, 18, 22: If receiving a dose of anti-IgE requiring injections 2 weekly, participants will attend these visits. Other children, who are on lower doses and have 4 weekly injections, will not attend these visits)

Record of concomitant medications

Record of adverse events

Injection of anti-IgE or placebo with routine observations including blood pressure (BP) for 2 hours after the 1st 3 visits, and for 30 mins after each subsequent visit.

Weeks 4, 8, 12, 16, 20: In addition, participants will require:

Questionnaires (as before)

Examination:

- SCORAD and EASI assessment

  If a participant's eczema is stable (objective SCORAD or PO-SCORAD ≤25), then potent topical steroid therapy may be reduced by 1 day per week until the participant is on maintenance therapy (application of topical steroid therapy on 2 consecutive days per week), adjusted according to clinical response

Week 24 (review after 24 weeks of treatment):

Visits are flexible within a period of ± 5 days (visit days will be counted from the date of the first dose regardless of the date of the previous visit).

Eczema impact

Concomitant medications

Adverse events

Questionnaires (as above)

Examination:

- Physical including SCORAD and EASI assessment and BP.
- Height and weight

Assessments:

- Skin prick testing to aeroallergens and to foods suspected of causing eczema or food allergic reactions.
- Transepidermal water loss (optional)

Phlebotomy

FBC, eosinophils, U&E, LFT, IgE levels, vitamin D, iron levels, bone profile and storage for immunological studies. 2ml/kg of blood will be collected, with a maximum of 50mls.

Urinanalysis

Skin biopsy (optional)

Medical photography

Week 36 (12 weeks after treatment stopped) and 48 (24 weeks after treatment stopped):

Visits are flexible within a period of ± 14 days (visit days will be counted from the date of the first dose regardless of the date of the previous visit).

Eczema impact at week 48

Concomitant medications

Adverse events

Questionnaires (as before)

Examination:

- Physical including height, weight, SCORAD and EASI assessment.

Assessments:

- Urinanalysis

Transepidermal water loss (optional)

5.2 Early Withdrawal from the Trial

Every effort will be made to follow-up patients in this category according to the usual trial schedule, with the exclusion of Xolair (omalizumab) or placebo injections. In other words, they will be invited back for a review at weeks 20, 24, 36 and 48 if these have not already been completed. Home visits to complete the assessments may be performed.

5.3 Laboratory Tests

Blood taken into standard laboratory sample tubes (including EDTA, lithium heparin, clotted blood sample tubes, capillary tubes and sodium fluoride tubes), and will be sent to the in-house laboratory at Guys' and St Thomas' Hospitals NHS Foundation Trust for full blood count (FBC), eosinophils, urea and electrolytes (U&E), liver function tests (LFT), Vitamin D and iron levels, bone profile, estimation of total and specific IgE levels. Further blood will be collected in citrate tubes and transported to the Paediatric Allergy Laboratory, part of the Asthma, Allergy and Lung Biology Department at King's College London, which is based at Guy's Hospital. There the blood will be separated into plasma and cells and will be stored at -80°C in liquid nitrogen. Blood will also be stored for genetic studies.

Skin biopsies will be taken at baseline, and at 24 weeks. The sample will be divided vertically into two halves. One half will be placed in RNA*later* Solution and stored at 4°C overnight then moved to –20°C for use in semi-quantitative PCR or micro-array studies at a later date. The other half will be frozen in OCT compound and stored for use in immunohistochemistry and tissue phenotypic studies later. Skin biopsy samples will be stored in the Paediatric Allergy Laboratory as above.

Pregnancy testing will be performed on female patients who have reached menarche. This will be performed using urinary βHCG dipsticks on urine collected from the patient.

6 Assessment of Efficacy

6.1.1 Primary Efficacy Parameters and 6.1.2 Secondary Efficacy Parameters

See sections 2.1 and 6.2

6.2 Procedures for Assessing Efficacy Parameters

Primary efficacy parameters:

1. Eczema severity: will be determined by a reduction in the SCORAD in both groups, after 24 weeks of treatment with anti-IgE.

Secondary efficacy parameters:

1. Treatment failure:

Patients who, after the 1st 12 weeks of treatment, have persistent severe eczema despite 2 courses of rescue therapy (0.5 to 1mg/kg/day (to a maximum of 40mg/day) of oral prednisolone for a week at a maximum dose of 40mg/day, followed by a week at 50% of this dose)

2. Alternative systemic therapy: patients in whom

a) alternative systemic therapy has been started as a result of treatment failure as defined above, or

b) where alternative systemic therapy is being considered at 24 weeks in patients who have an objective SCORAD >40 and a DLQI ≥10

If after 2 courses of steroids, alternative systemic treatment is required, then methotrexate will be recommended, subject to physician and patient discretion.

3. Eczema quality of life: The following questionnaires will be administered before treatment commences, 4 weekly during the 24 weeks of treatment, and at the 36 and 48 week post treatment reviews:

Patient-oriented Eczema Measure (POEM)

(Children's) Dermatology Life Quality Index ((C)DLQI)

4. Eczema severity: SCORAD and EASI assessments will be used to examine eczema severity before and during treatment, and at 36 and 48 week post treatment reviews. Optional measurements of transepidermal water loss (TEWL) will also be performed according to standard departmental procedures at baseline, and at 24, 36 and 48 week (post treatment) reviews. Medical photography will also be used to record the condition of eczema at baseline and after 24 weeks of treatment.

5. Co-existing allergic disease: All children will complete a Paediatric Allergic Disease Quality of Life Questionnaire at baseline, during treatment and at the 36 and 48 week (post treatment) visits.

6. Adverse events/safety (see schedule under section 7.2): side effects of the trial drug will be monitored during the course of the study through frequency of AEs reported at visits.

7. Number of eczema exacerbations: We will record the rate and timing of exacerbations of eczema at each visit.

Exacerbations of eczema will be defined as follows:

- Clinician diagnosed exacerbation of eczema

OR

- Increase on SCORAD by 15 points from last recorded SCORAD
  WITH
- Patient perception of worsening eczema

Treatment will follow the following regimen:

- Exclusion and treatment of any infection with a 7 day course of flucloxacillin or erythromycin, modified if necessary once culture results are available.
- Daily use of potent topical steroids
- Patients not responding to a maximum of 2 weeks of consecutive daily potent topical steroids will start a week's rescue treatment with oral steroids (0.5-1mg/kg/day of oral prednisolone for a week at a maximum dose of 40mg/day, followed by a week at 50% of this dose). A 2 week course of oral steroid rescue treatment may be attempted a total of 2 times, after the 1st 12 weeks of treatment, before it is deemed a treatment failure, at which point alternative systemic therapy will be considered.

8. Infective episodes of eczema: We will record any infective exacerbations (defined as clinician diagnosed and treated infective episode of eczema, OR clinically apparent, culture positive infective exacerbations) at each visit.

9. Free total and allergen specific IgE and skin prick test reactivity: To determine the change in free total IgE and allergen specific IgE (in collaboration with the in-house facilities at Novartis) at screening and 24 weeks of treatment, and the change in skin prick test reactivity to food and aeroallergens at screening and 24 weeks.

10. Mechanism of action of anti-IgE: Blood samples will be taken and stored for immunological studies under a separate study protocol. 2ml/kg of blood will be collected at the screening visit at 24 weeks of treatment, with a maximum of 50mls at each of these visits. Blood will also be stored for genetics studies if separate consent has been given. Skin biopsies will also be collected at baseline and at 24 weeks of treatment if separate consent has been given. The procedure for a skin biopsy will follow local procedures. These samples will be stored with a view to performing immunohistochemical studies, microarrays and qPCR studies before and after treatment, to assess the effects of Xolair (omalizumab); and genetics studies.

7 Assessment of Safety

7.1 Specification, Timing and Recording of Safety Parameters.

Management of exacerbations and any additional therapy (eg.oral steroids or antibiotics) will be recorded.

All adverse events and side effects will be recorded in the CRF as per the Trial assessments, with the exception of abnormal blood results that are considered not clinically significant by the Investigator and will be managed as below.

Adverse events linked to the existing condition (atopic dermatitis) will be collected separately to help distinguish between expected events related to condition or side effects of concomitant medications.

7.2 Procedures for Recording and Reporting Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

> The summary of product characteristics (SmPC) for that product (for products with a marketing authorisation)

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

> Results in death;
> Is life-threatening;
> Required hospitalisation or prolongation of existing hospitalisation;
> Results in persistent or significant disability or incapacity;
> Consists of a congenital anomaly or birth defect.

Reporting Responsibilities

Guy's and St Thomas' NHS Foundation Trust and King's College London as co-sponsors have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHPCTO). All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately (and certainly no later than 24hrs) by the Investigator to the KHP-CTO who will review and report to the CI for Medical Review in accordance with the current Pharmacovigilance Policy.

Important Medical Events (IME) & Pregnancy:

- Events that may not be immediately life-threatening or result in death or hospitalisation

but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

- Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

The KHPCTO will report SUSARs (Suspected Unexpected Serious Adverse Reactions) and other SARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states in which the trial is taking place.

The Chief Investigator will report to the relevant ethics committees. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

The Chief Investigator will provide an annual report of all SARs (expected and unexpected), and SAEs which will be distributed to the Sponsor (KHPCTO), MHRA and the REC.

7.2.1 Adverse events that do not require reporting

All adverse events will be recorded.

The period for AE reporting will be from the first dose until the last visit (ie. 24 weeks after the final treatment/placebo dose).

7.3 Treatment Stopping Rules

The DMEC will review safety data on an ongoing basis and may stop enrolment or participation in the trial at any time if it concludes that there are significant safety concerns. The DMEC will decide on treatment stopping rules.

8 Statistics

Please see section 8.3 below.

8.1 Sample Size

Sample size power calculation for primary outcome: SCORAD at 24 weeks of treatment:

In order to determine the sample size, the following assumptions were made:

A 40% reduction in SCORAD in the treatment group (from 45 to 27), and a 10% reduction in the placebo group (45 to 40.5), equates to an absolute change in SCORAD of 13.5 points between the 2 groups (the assumed SD is 15, based upon a study by Hindley (Hindley D, Galloway G, Murray J, Gardener L. A randomised study of ''wet wraps'' versus conventional treatment for atopic eczema. Arch Dis Child 2006;91:164–168)).We would be able to detect this clinically meaningful difference of 33% relative reduction in SCORAD, using a significance level of 5% with 90% power, and including a 15% drop out rate. This would require 62 patients, 31 each in the treatment and placebo arms, which could be recruited at a single centre.

8.2 Randomisation

Participants will be randomised using an online randomisation system via the UKCRC registered King's College London CTU based at the Institute of Psychiatry. Participants will be allocated to treatment group using minimisation. This is to ensure that there will be minimal imbalance of total IgE (≤1500, >1500) and age (<10 or ≥10 years) between treatment groups.

8.3 Analysis

This will be according to the detailed statistical analysis plan approved by the Trial Steering Committee.

The primary analysis will be an intention to treat (ITT) analysis including all participants who were randomised regardless of treatment subsequently received. An analysis of covariance model will be used to obtain an estimate for the mean difference in SCORAD between the two treatment arms adjusted for baseline SCORAD and the randomisation stratification variables (total IgE and age). The estimated treatment effect will be reported with 95% confidence intervals and corresponding p value.

A sensitivity analysis adjusting for rescue medication will be undertaken using a model based approach based on methods suggested in White et al[16] & White et al[17]. Every effort will be made to obtain 6 month follow up data for all participants including those that have stopped treatment or withdrawn. Participants who have withdrawn will be assessed at 6 months, with the option of a home visit if necessary.. SCORAD values over time will be plotted by individual and the mean value for treatment group. A longitudinal analysis to assess change of SCORAD over time will be undertaken using a linear mixed model including baseline SCORAD, age and IgE as fixed effects for time points (8, 12, 16, 20, 24 weeks).

The dose and frequency of rescue treatment will be summarised by treatment group. Binary outcomes will be analysed using a logistic regression model. Secondary outcomes including Quality of Life (POEM and (C)DLQI), Co-existing allergic disease (PADQLQ) will be analysed using

analysis of covariance in a similar manner described above for the primary outcome. Adverse events will be tabulated by treatment arm.

The DMEC will be responsible for assessing safety and efficacy. They will be responsible for recommending to stop the trial at any time if there are significant safety issues or ethical issues regarding overwhelming evidence for benefit. Judgments made will be at their discretion and no formal statistical rules will be employed. A detailed statistical analysis plan will be developed for approval by the Trial Steering Committee and will be finalised before the first interim analysis is undertaken for the DMEC.

Reference List

(16) White I et al, Stats in medicine, 2003 ; 22; 1083-1096

(17) White I et al, Stats in Medicine, 2001; 20; 2995-3008

9. Trial Steering Committee

A proposed trial steering committee, to include at least 2 independent clinicians, 1 independent PPI (patient and public involvement) member, as well as Dr Susan Chan and Prof Gideon Lack, will be convened. The committee will meet at a time defined by the chair.

10. Data Monitoring and Ethics Committee

The proposed independent data monitoring and ethics committee, to include 2 independent clinicians and an independent statistician. The DMEC will meet at the onset and decisions about frequency of meetings, and the type, frequency and format of data reports will be established. The trial statistician will supply the necessary data to the Committee.

11 Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (ie patients' case sheets, blood test reports, X-ray reports, histology reports etc).

12 Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents and subsequent amendments has been submitted for review to the London-Westminster Research Ethics Committee (REC) (formerly St Thomas' Hospital and then South East London REC 2), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

Annual progress and safety reports and a final report at conclusion of the trial will be submitted to the KHPCTO (on behalf of the Sponsor), the REC and the MHRA within the timelines defined in the Regulations

13 Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained; by the King's Health Partners Clinical Trials Office Quality Team.

14 Data Handling

The eCRF will be designed and maintained by the King's Clinical Trials Unit using the InferMed MACRO system (Version 4.0), which is compliant with GCP and 21 CRF Part 11. Data will be collected on source data worksheets and stored in the patient's medical notes, and will be transcribed to the eCRF system. Usernames and passwords will be assigned by the Clinical Trials Unit and data experts from the system must be authorised by the Trial Statistician. At the end of the study, the eCRF system will be locked and data exported for final analysis. Access to the system is via www.ctu.co.uk (select MACRO EDC V4).

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to: Patient data will be anonymised. All anonymised data will be stored on a password protected computer.

All trial data will be stored and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the King's Health Partners Clinical Trials Office Archiving SOP.

15 Publication Policy and Finance

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

16 Financial Aspects

Funding to conduct the trial is provided by the National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme and Guy's and St Thomas' Charity.

17 Signatures

_____ _____

Chief Investigator
Dr Susan Chan

Date

_____ _____

Statistician

Dr Victoria Cornelius

Date