CLINICAL STUDY PROTOCOL

Full Study Title: **P**reventing childhood **A**sthma using **P**rophylactic house dust mite **A**llergen immunotherapy

Short Study title / Acronym: PAPA

Product: ACARIZAX®

Development Phase: Phase IIb

Sponsor: University of Southampton

Version no: 2.1

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This protocol describes the PAPA trial and provides information about procedures for enrolling participants to the trial. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or modifications may be necessary. These will be circulated to investigators in the study, but centres enrolling participants for the first time are advised to contact the Trial Coordination centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Trial Coordination centre.

This trial will adhere to the principles outlined in The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS

AE	Adverse Event
AD	Atopic Dermatitis
ADL	Activities of Daily Living
AIT	Allergen Immunotherapy
ARW	Atopic Recurrent Wheeze
ATS	American Thoracic Society
CHI	Community Health Index
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
NCI-CTCAE	National Cancer Institute's - Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ERS	European Respiratory Society
EoE	Eosinophilic Oesophagitis
FDA	Food and Drug Administration
FeNO	Fractional Exhaled Nitric Oxide
GP	General Practitioner
HDM	House Dust Mite
HRA	Health Research Authority
IB	Investigator's Brochure
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IoW	Isle of Wight NHS Trust
ISAAC	International Study of Asthma and Allergies in Childhood
ISF	Investigator Site File
ITT	Intention to Treat
MHRA	Medicines and Healthcare Products Regulatory Agency

NHS	National Health Service
NIHR	National Institute for Health and Care Research
PIC	Participant Identification Centre
PI	Principal Investigator
PIS	Participant Information Sheet
POEM	Patient Orientated Eczema Measure
PPIE	Patient and Public Involvement and Engagement
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
RDN	Research Delivery Network
Rrs	Respiratory resistance
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SLIT	Sublingual Immunotherapy
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPT	Skin Prick Test
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCRS	Total Combined Rhinitis Score
TMG	Trial Management Group
TSC	Trial Steering Committee

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TRIAL SUMMARY

TITLE: Preventing childhood Asthma using Prophylactic house dust mite Allergen immunotherapy

OBJECTIVES: To establish efficacy and safety of house dust mite sublingual Immunotherapy (HDM-SLIT) by comparing Acarizax and placebo, when given sublingually for 3 years to high-risk infants aged between 5 to 12 months at enrolment in preventing the development of atopic recurrent wheeze.

PHASE: IIb

DESIGN: Randomised (1:1), double blind, placebo controlled, parallel arm, multi-site, 3-year treatment phase.

SAMPLE SIZE: 434

RECRUITMENT: 24 Months

KEY INCLUSION CRITERIA

(i) Parent/guardian must be able to understand and provide informed consent.
(ii) Aged 5 to 12 months of age at randomisation.
(iii) High risk of asthma (two or more of the three criteria);
   a. Single OR dual heredity for allergy (at least one biological mother, father or sibling affected by asthma or allergy, assessed through standardised questionnaires).
   b. Atopic dermatitis.
   c. Allergen sensitisation.

KEY EXCLUSION CRITERIA

(i) Evidence of sensitisation to HDM on skin prick test (SPT) ≥3 mm wheal diameter.
(ii) Prematurity (<37 weeks).
(iii) Faltering growth and/or need for oxygen for more than 5 days in the neonatal period or history of intubation or mechanical ventilation.
(iv) Other significant medical conditions including but not limited to eosinophilic esophagitis, seizures, major congenital anomalies, cardiac disorders requiring medical therapy, cystic fibrosis, chronic pulmonary diseases, bronchopulmonary dysplasia, significant developmental delay, cerebral palsy, immunodeficiency (primary or secondary), acute severe oral inflammation or oral ulceration (to be assessed by investigator at screening).
(v) Use of investigational drugs since birth.
(vi) Expecting to relocate out of country within 4 years of study initiation.
(vii) Deemed as unable to adhere to study activities by the investigator.
(viii) Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.
(ix) Has any clinically significant abnormal vital sign or laboratory value that in the opinion of the investigator would preclude participation in the trial.

TREATMENT/MAIN STUDY PROCEDURES (including treatment duration and follow-up)

Treatment Arm: Acarizax HDM-SLIT tablet (12SQ) once daily for 3 years

Control Arm: Placebo (identical) tablet once daily for 3 years

Study visits:

I. Screening Visit and Randomisation: Participants who fulfil all eligibility criteria will be randomised 1:1 to receive either HDM-SLIT or placebo tablet. The first dose will be

administered under direct supervision at the hospital where resuscitation equipment, oxygen and adrenaline are immediately available in the highly unlikely event of an allergic reaction. Participants will be observed in the department for 60 minutes, and if tolerated then one tablet, once daily will be administered at home for 3 years. Baseline assessments will include a Family Demographics and Medical History questionnaire, which will seek information on method of feeding and an Allergy and Environment questionnaire based on the standardised interview administered questionnaire, called International Study of Asthma and Allergy in Children (ISAAC) that has been previously validated for asthma and allergy assessment, which will seek information on environmental exposures (such as tobacco smoke or vaping, pets, mould/dampness). Physical examination, and collection of blood and nasal samples will also be conducted.

II. Telephone/virtual assessments: will occur every 6 weeks during the first year, then 3 monthly during years 2-3. These will include the Allergy and Environment questionnaire and seek self-reported adverse events and collect information on current medications.

III. Onsite visits: Annual visits at years 1 and 2 post-randomisation will include all the 6 weekly and 3 monthly assessments plus SPT to common allergens.

IV. Final visit, 3-years after randomisation (3½ to 4 years of age): will include all the annual visit procedures plus collection of blood and nasal samples, and oscillometry (applicable to site where oscillometry equipment is available), fractional exhaled nitric oxide (FeNO), and peak flow if they are able to cooperate and perform the procedures.

OUTCOME MEASURES

PRIMARY ENDPOINT

Atopic recurrent wheeze (ARW), assessed at the final year 3 visit and defined as:
A. *Recurrent wheeze (2 or more wheezing episodes) in the last 12 months of treatment AND
B. **Positive SPT and/or sIgE to one or more common allergens during the last 12 months

* A wheezing episode is defined as parental or documented report of an episode of wheezing or whistling in the chest that lasts at least 24 hours. Wheezing events separated by at least 5 consecutive days without wheezing shall be counted as separate episodes.
**The common allergens include HDM in duplicate (Dermatophagoides pteronyssinus and Dermatophagoides farinae), grass mix, tree mix, cat, dog, cow's milk, egg, peanut), as assessed both by; 1) SPT ≥3 mm wheal diameter, OR 2) sIgE ≥0.35 kU/litre.

SECONDARY ENDPOINT(S)

I. Allergic sensitisation and allergic disease

- Proportion of participants with ARW assessed at 3 years post-randomisation. With atopy defined as per the primary endpoint and wheeze defined as per the primary endpoint but excluding wheeze episodes occurring only in March to August (inclusive).
- Proportion of participants at 3 years post-randomisation with allergic sensitisation to HDM, as assessed by 1) SPT ≥ 3mm and/or 2) sIgE ≥0.35 kU/litre and recurrent wheeze during the last 12 months.

II. Allergic sensitisation

- Cumulative proportion of participants with sensitisation to one or more common allergens over the 3 years of study. The common allergens include HDM (D. pteronyssinus and D. farina), , grass pollen, tree pollen, , cat, dog, cow's milk, egg, peanut), as assessed both by; 1) SPT ≥3 mm and/or 2) sIgE ≥0.35 kU/litre.
- Cumulative proportion of participants with allergic sensitisation to HDM over the 3 years of study, as assessed by 1) SPT ≥ 3mm and/or 2) sIgE ≥0.35 kU/litre.

III. Allergic disease

- Proportion of participants with ARW at 1- and 2-years post-randomisation:

(a) Recurrent wheeze: defined as "two or more separate wheezing episodes in the last 12 months treatment period". A wheezing episode is defined as parental or documented report of an episode of wheezing or whistling in the chest that lasts at least 24 hours. Wheezing events separated by at least 5 consecutive days without wheezing shall be counted as separate episodes.

(b) Atopy: "Sensitisation to one or more common allergens in the last 12 months treatment period". The common allergens include HDM (D. pteronyssinus and D. farina), , grass pollen, tree pollen, , cat, dog, cow's milk, egg, peanut), as assessed by SPT ≥3 mm.

- Proportion of participants with allergic rhinitis in the 12 months before the final study visit at 3 years post-randomisation, as assessed by the Allergy and Environment questionnaire based on the standardised ISAAC questionnaire1, and evidence of allergic sensitisation to the relevant allergen.
- Proportion of participants with atopic dermatitis (AD) recorded using standard criteria in the 12 months before the final study visit at 3 years post-randomisation, using standardised criteria.2
- Proportion of participants with any recurrent wheeze assessed at 3 years post-randomisation (recurrent wheeze defined in 2.3 (a)).
- Impulse Oscillometry: Summaries of air flow measurements at the final visit at 3 years post-randomisation.3
- Proportion of participants with abnormal exhaled nitric oxide (FeNO) at the final visit at 3 years post-randomisation where a cutoff of < 20 parts per billion (ppb) will be considered normal, as per ATS guidelines.4
- Summaries of peak flow measurements at the final visit at 3 years post-randomisation.

IV. Safety
- Proportion of participants with any adverse events
- Proportion and incidence with clinically relevant asthma exacerbations over 3 years
- Proportion and incidence with clinically relevant anaphylactic reactions, anaphylaxis and/or systemic allergic reactions over 3 years
- Proportion and incidence treated with adrenaline/epinephrine over 3 years
- Proportion and incidence with severe oral swelling of the mouth and/or throat over 3 years
- Proportion and incidence with eosinophilic esophagitis over 3 years
- Proportion with an increase in proportion and incidence of HDM sensitisation over 3 years.

V. Tolerability
- Proportion of participants who stop treatment prior to planned 3 years of treatment of active HDM tablet compared with placebo
- Proportion of participants who stop treatment due to adverse events prior to planned 3 years of treatment of active HDM tablet compared with placebo
- Proportion of participant who took 60% of the treatment over 3 years as recorded in the MedSearchTM App.

VI. Mechanistic
- Functional IgG and IgA antibodies linked to the prevention of asthma
- Induction of regulatory T and B cell subsets that can produce immunomodulatory cytokines linked with the prevention of asthma

IMP(s)

House dust mite sublingual immunotherapy tablets (HDM-SLIT tablet; trade name: Acarizax)

FORMULATION, DOSE, ROUTE OF ADMINISTRATION
Active ingredients: Standardised allergen extract from the HDMs D. pteronyssinus and D. farinae
Dosage form: Sublingual lyophilisate
Dose/Strength: 12 SQ-HDM (30 µg of Der p/f 1 & 2)
Excipients: Gelatin (fish source), mannitol and sodium hydroxide

PLACEBO:
Tablet
Active ingredients: None
Dosage form: Sublingual lyophilisate
Excipient: Gelatin (fish source), mannitol and sodium hydroxide

1.1. Clinical Setting

The emergence of asthma and allergic disorders as a generational epidemic over the last 30 years has had a major health and socio-economic impact and thus represents a major challenge worldwide. Preventing asthma should be the highest priority, given that it is the most common chronic disease of childhood.5

Allergen Immunotherapy (AIT) is typically used for the treatment of allergic rhinoconjunctivitis and allergic asthma. AIT modulates the basic immunologic mechanism of the allergic disease and potentially has long-term, durable efficacy and disease-modifying effects.6 Repeated administration of high allergen loads has the potential to overcome sensitisation and drive the immune system into a tolerogenic state.7 House dust mite (HDM) allergen sensitisation is the most important risk factor for the development of asthma in children.8,9 We postulate that treatment of at-risk children with high doses of HDM will enhance the development of specific tolerance against this allergen, as well as having additional benefits beyond this allergen specific effect. Our rationale for this postulate stems from the evidence of a bystander/global effect of AIT beyond the targeted allergen, whereby T and B regulatory cells suppresses effector cell responses to other allergens and prevent development of new allergic sensitisation.10-13 We propose a novel use of AIT as a primary preventive strategy in infants who are not sensitised to HDM, to induce tolerance while the immune system is still in the post-natal developmental phase.14

Our current project is intended to provide definitive proof of efficacy that asthma can be prevented using an adequately powered, randomised controlled multicentre trial, in an ethnically diverse population. We propose to use HDM allergen as a monotherapy for primary prevention on the basis that there is very little evidence that AIT to multiple allergen mixture is effective in the treatment of asthma.[15]

1.2. Investigational Agent / Intervention Details

HDM-SLIT tablet Acarizax®) is a rapidly dissolving, freeze-dried, sublingual lyophilisate for oromucosal treatment, which contains a 1:1 mixture of two allergen extracts derived for the cultivated HDM, D. pteronyssinus and D. farinae. These species are included in SLIT tablet and subcutaneous immunotherapy administered for the treatment of allergic rhinitis and asthma in the paediatric and adult populations.

The dose of active therapy planned for this trial is 12 standardised quality units (SQ) (equivalent to 30 μg) daily. The SQ is an arbitrary biological unit and SQ is a method of standardization of biological potency, major allergen content and complexity of the allergen extract. Treatment involves once daily sublingual administration. The HDM-SLIT tablet has obtained marketing authorisation for treatment of asthma and/or rhinitis in 14 European countries, the United States, Canada, Japan, Australia, New Zealand, South Korea, Malaysia, Philippines, Hong Kong, and Thailand.

Recently, the 12 SQ HDM-SLIT tablet was approved by European medicinal Agency (EMA) for treatment of HMD allergic rhinitis with and without asthma in children 5 years and older and is under regulatory review in other regions of the world for the same age group.

Clinical studies: To date, the HDM-SLIT tablet has been investigated in 17 randomised, double-blind, placebo-controlled trials worldwide. These includes 2 paediatric phase I trials with doses up to 12 SQ-HDM (1 in children 5-14 years of age; 1 in adolescents 12-17 years of age), 2 paediatric Phase III trial in children 5-11 years of age and 1 paediatric phase III trial with the 6 SQ-HDM dose in children and adolescents 5-17 years of age. In addition, adolescent participants were included in 3 adult phase III trials.

A total of 3242 paediatric participants (<18 years) have been included in the completed clinical trials, 1262 of whom were treated with the 12 SQ-HDM dose. The majority of paediatric participants exposed to 12 SQ-HDM (n=1042) were <12 years of age. The efficacy and safety of treatment with the HDM-SLIT tablet in HDM allergic conditions have been investigated in 3 very similar phase III trials in adults/adolescents and in 2 paediatric phase III trial, as described in the following.

The 3 phase III trials MT-0616-18 were conducted in Europe, North America, and Japan to demonstrate efficacy in adults with HDM AR. Adolescent participants were included in the P001 and TO-203-3-2 trials. The 3 trials had a very similar design; all 3 were randomised, parallel-group, double-blind, placebo-controlled trials assessing primary efficacy based on average total combined rhinitis score (TCRS) during the last 8 weeks of approximately 1 year of daily treatment. Across trials, a consistent treatment benefit was demonstrated, with statistically significantly lower TCRS reported by participants on active treatment compared to placebo. Absolute TCRS differences from placebo were approximately 1 in all trials, corresponding to relative effect sizes between 17% and 22%. Similar numbers were seen for adolescent subpopulations. The HDM-SLIT tablet

(6 and 12 SQ-HDM doses) was generally well tolerated with a safety profile characterized by frequent but transient local allergic events (e.g. oral pruritus, throat irritation, mouth oedema and oral paraesthesia) that were typically assessed as mild or moderate in intensity. Severe allergic reactions were uncommon. No treatment-related serious adverse events (SAEs) were reported, one SAE of anaphylactic reaction occurred in a participant on placebo in the TO-203-3-2 trial. Stratified safety analyses showed no differences in the safety profile between participants <18 years of age and participants ≥18 years of age. Across the adolescent subpopulation, no severe oral swellings were reported and no adolescent participants were treated with adrenaline due to adverse events (AEs). A single event of anaphylactic reaction in an adolescent participant was reported: a participant in the 12 SQ-HDM group experienced moderate throat swelling after consuming a cookie; the event occurred 2 days after IMP discontinuation and was assessed as unrelated to treatment.19
The paediatric phase III trial TO-203-3-3 was a randomised, parallel-group, double-blind, placebo-controlled trial conducted in Japan to investigate the efficacy and safety of the HDM-SLIT tablet (dose 6 SQ-HDM) in children and adolescents (5 to 17 years) with moderate-to-severe HDM allergic rhinitis.20 458 participants were randomised to once daily treatment with 6 SQ-HDM or placebo for 1 year. The primary outcome was the average TCRS during the last 8 weeks of treatment. The primary efficacy analysis showed that TCRS was statistically significantly lower in the 6 SQ-HDM group compared to placebo. The absolute TCRS difference from placebo was 1.22 ($p<0.0001$), corresponding to a relative difference of 23%. The HDM-SLIT tablet (dose 6 SQ-HDM) was generally well tolerated. Most treatment-related AEs were mild or moderate in intensity and included predominantly the local application site AEs. No treatment-related SAEs were reported.

Recently, two trials have investigated 12 SQ-HDM in allergic asthma and allergic rhinitis. The paediatric asthma trial (MT-11) investigated the efficacy and safety of the HDM-SLIT tablet in children and adolescents (5-11 years of age) with HDM allergic asthma. MT-11 was a phase III, double-blind, parallel-group, placebo-controlled trial conducted in Europe and North America. The trial included 533 paediatric participants with HDM allergic asthma and a history of frequent exacerbations, who will be randomised to once daily treatment with 12 SQ-HDM or placebo for an intended treatment period of approximately 2 years. The primary outcome was the rate of protocol-defined clinically relevant asthma exacerbations assessed after at least 4 months of treatment. Treatment was well tolerated with no unexpected safety findings. The paediatric allergic rhinitis trial (MT-12) evaluated the efficacy and safety of the HDM-SLIT tablet in children 5-11 years of age. MT-12 was a phase III, double-blind, parallel-group, placebo-controlled trial conducted in Europe and North America. The trial included 1,460 participants with HDM allergic rhinitis randomised to 12 SQ-HDM or placebo for a treatment period of approximately 12 months. The primary outcome was the TCRS during the last 8 weeks of treatment and showed a 22% ($p<0.0001$) relative difference to placebo. Treatment was well tolerated with no unexpected safety findings.

1.3. Rationale for the study

1.1. Rationale for early intervention starting during infancy

There is considerable evidence that the risk of developing asthma is determined early in life.21 In infants with atopic heredity, there is evidence of delayed maturity at birth in both the Th2 (allergy-favouring) and Th1 (counterbalancing) response.22 The CD4+CD25high/CD127-/lo Treg population show reduced numbers and impaired function at birth which might contribute to the persistence of Th2 biased responses and the development of asthma.22 To counter the intrinsic Th2 bias in the developing immune system in at-risk infants and to overcome maturational deficiencies that may compromise induction of protective mucosal tolerance to allergens, strong and adequate immune stimulation with relevant allergens at a very young age is required. Thus, targeting young children is important as their allergen specific T-cell memory responses are at an early stage of development, are highly labile and, based on experimental findings, they should be maximally susceptible to repolarization from the allergy-driving Th2 phenotype towards either allergy-antagonistic Th1 immunity or tolerance.14 Thus, the window of opportunity is in the first year of life, before multiple aeroallergen sensitisation has taken hold – the scientific basis for our trial of HDM-SLIT therapy.

1.2. Rationale for selection of high-risk population

We focus on high-risk infant population as they stand to benefit most from the intervention. Early and multiple sensitisation increases the risk of asthma by 20-fold.[23] Those who develop early sensitisation to multiple allergens are at greatest risk for persistent asthma and severe exacerbations.[24-26] A combination of family history of allergy, AD and allergic sensitisation will provide the basis for high risk. Childhood asthma risk is up to 12 times with a biparental history of allergy.27 We wish to recruit infants with a ≥35% risk of ARW and asthma. Using data from large observational birth cohort studies in the UK and US (such as Cincinnati and the (Isle of Wight (IOW) cohort), we have devised the combination of risk factors criteria that will deliver this high-risk population. Table 1 shows that a combination of single (or dual) heredity, allergic sensitisation and/or AD would select infants with an estimated 30%-60% risk of ARW at 4 years (and asthma between 6 and 11 years).28-30 We will exclude infants who are already sensitised to HDM as this is a primary prevention study. We are therefore targeting a population that is at high risk of developing persistent asthma and yet amenable to the intervention.

Table 1: Risk of ARW and asthma in children with a family history of allergy, allergic sensitisation and AD (inclusion criteria)

IoW cohort (n=1,456)	**ARW at 4 years**	**Asthma at 10 years**
SH of allergy + AD	42.9% (21/49)	37.9% (36/95)
SH plus allergic sensitisation	58.3% (14/24)	48.9% (22/45)
AD plus allergic sensitisation	52.2% (12/23)	46.2% (18/39)
Avon Longitudinal Study of Parents and Children cohort (n=6,188)	**ARW at 5 years**	**Asthma at 11 years**
SH plus AD	43.1% (103/239)	38.6% (102/264)
Cincinati Childhood Allergy and Pollution Study cohort (n=762)	-	**Asthma at 6 years**
DH plus AD	N/A	30.2% (19/63)
Manchester Asthma and Allergy Study cohort (n=1163)	**ARW at 4 years**	**Asthma at 11 years**
Maternal allergy plus AD	30.7% (23/75)	46.4% (26 /56)
SH: one or both parents/sibling affected with asthma, AD or rhinitis DH: both parents or one parent and one sibling affected with allergic disease		

1.3. Rationale for the use of Acarizax (12 SQ)

The dose (12 SQ) has proven efficacy: A general principle of AIT is that efficacy is dose-and time-dependent.31 The dose response in allergen immunotherapy is well established.32 Higher dose AIT will show earlier onset of effect (4-8 weeks) and increase efficacy.31 Immunologic data from two trials one AR.18 and one in asthma.33 showed a clear dose-response with a statistically significant difference between 6 and 12 SQ-HDM. A subsequent study demonstrated a dose and time dependent response of HDM tablet on symptoms of allergic rhinitis.34 In another asthma trial evaluating 6 SQ, a dose-response correlation was observed and a dose below 6 SQ (=11ug) had no effect.[35] Hence, lower doses of SQ HDM show inconsistent clinical and immunologic effects.

The dose (12 SQ) is safe: HDM oral AIT is safe with only minor adverse effects in both children and adults when given to treat HDM allergic asthma and rhinitis who are sensitised.[36] The 12 SQ-HDM (30µg) dose of the HDM-SLIT tablet was selected based on data from the paediatric phase I trial and the subsequent phase III trials including adolescents,[19,37] Dosing of AIT is not age dependent as allergens are not metabolised by liver or kidneys and children are not at higher risk of AE than adults. Using the same dose

for adults and children is in line with clinical practice in AIT, as supported by treatment guidelines stating that the immune response in children and adolescents is not different from that of adults.[38] Thus, there are no lower doses approved or available for ALK SLIT-T treatment in Europe and North America. Safety of the HDM SLIT has been evaluated in 21 completed trials including more than 7500 participants. The safety profile of the HDM SLIT-T in paediatric participants was found to be similar to the safety profile observed for adult populations and doses up to 12 SQ-HDM are considered to have a safety profile allowing for further clinical development in children/adolescents (ODACTRA® Investigational Brochure). Food and Drug Administration (FDA) A and European Medicines Agency (EMA) reviewed the HDM SLIT-T evaluating dose-ranging Phase I-III trials and based on their review only the 12 SQ dose has been approved as the benefit-risk ratio favoured 12 SQ HDM SLIT-T over lower doses. We propose to administer HDM allergen to non-sensitised infants and hence the risk of adverse effects is negligible. We will therefore use 12 SQ-HDM to achieve optimal effect, now that the safety of this approach has been established.

Enrolled participants will not be sensitised to HDM: The data presented above is from previous studies where participants with HDM allergy were treated with Acarizax. This explains the mild, transient, local adverse effects seen with the therapy. The participants in this trial will not be allergic nor sensitised to house dust mite. Therefore, as in our proof-of-concept study (details below), we are not expecting to see these local adverse effects.

Acarizax tablet versus liquid formulation: In our preliminary study, we used liquid glycerinated allergen extract of HDM. Since then, HDM tablets (which dissolves quickly in the mouth) have been shown to be safe and effective in HDM allergic asthma and rhinitis and approved by FDA for human use.[33,39] We propose to use an HDM tablet as our intervention. The advantage of using the tablet formulation is accurate dosing using purified preparation with minimal contamination compared to the liquid extracts. Liquid formulation usually requires higher allergen content as the absorption kinetics are likely affected due to larger surface area compared to small area of tablet administration with increased bioavailability.
Given the quick dissolution (within 10 seconds), aspiration is not considered a risk. HDM SLIT tablet was demonstrated to be safe and effective in a small randomised controlled trial of 34, one to four years toddlers with allergic rhinitis.[40] There are other examples of approved rapidly dissolving tablets such as ondansetron (Zofran) given sublingually to infants from 1 month of age. Orapred is another orally disintegrating tablet where the label does not specify a lower age limit and post-approval pharmacovigilance have not reported serious events of aspiration even in infants down to 1 month of age.

1.4. Rationale for 3 years duration of immunotherapy

There is precedent for demonstrating the disease modifying effects of immunotherapy following 3 years of continuous treatment. Treatment duration of one year is likely too short considering potential carry over effects, later relapse and a risk of not capturing enough asthma events since they may occur infrequently, or the diagnosis may be uncertain. Two years of sublingual grass pollen immunotherapy was not significantly different than placebo in improving the nasal response to allergen challenge at 3 year follow-up.[41] Three year course of prophylactic AIT is in line with current recommendation for its use in established disease to ensure long-term effects.[41,42] Further, oral immunotherapy for food allergy for short durations are usually associated with desensitisation with benefit rapidly disappearing within a few months once the therapy has stopped.[43] Therefore, the planned treatment duration of this trial is 3 years.

1.5. Rationale for primary outcome of Atopic Recurrent Wheeze (ARW)

As this clinical trial is 6 years in duration, we use ARW at 4 years of age as a novel surrogate marker, which is highly predictive of asthma childhood asthma.[30,44,45] We analysed large population base cohorts and show that >75% children will develop asthma by age 7 to 11 years, if they have ARW between 3 to 5 years (**Table 3**). We have previously published scores that can be used to predict childhood asthma in wheezy 3-4 years old children.[30,44] Indeed, we have recently found that atopic wheeze at 4 years is highly predictive of persistent asthma up to age 26 years (sensitivity: 0.68, specificity 0.87, area under the curve: 0.80, 95% CI: 0.75-0.87). In the high-risk children recruited for this study, we estimate that even higher (~80-85%) children will develop asthma by age 6 to 10 years if they have ARW at 4 years. Hence, prevention of ARW at the end of treatment (3½ to 4 years of age) will be strongly indicative of prevention of childhood asthma.

If our study shows an effect on ARW, it is highly likely that funding would be secured to follow-up these children at 6-7 years for assessment of childhood asthma.

1.4. Risk / Benefit Assessment

Allergen immunotherapy is unique among the treatments for allergic disease in that it has the potential to modify disease and prevent the development of asthma. The advent of a rapid-dissolving tablet with high doses of HDM extract provides a novel vehicle as a natural preventative therapy for a disease that continues to represent a significant public health burden world-wide. Details regarding specific benefits and risks for participants participating in this clinical trial may be found in the Investigators Brochure (IB) and Informed Consent documents. The design of the trial complies with the EMA guideline for development of products for specific immunotherapy for treatment of allergic diseases.[38]

1.5. Proof of Concept Study

We conducted the first proof of concept randomised, placebo-controlled trial of HDM allergen immunotherapy (AIT) in infants to induce immune tolerance and thus prevent allergen sensitisation and childhood asthma.[46,47] We enrolled 111 high risk infants aged 5-9 months who were not sensitised to common allergens. HDM extract or placebo was administered orally twice daily for 1 year. We used liquid glycerinated allergen extract of HDM provided by ALK-Abello, consisting of D. pteronyssinus and D. farinae in equal parts ((6 SQ (11µg) major allergens (Der 1 and Der 2) in twice daily dosing. 6 SQ (11µg) was the maximal tolerated dose at that time and was used for treatment of HDM allergy in adults. Children were assessed at the end of one-year treatment, at 1.5 years (age 3 years) and 5 years (age 6 years) after treatment discontinuation. Reduction in allergic sensitisation was achieved at 18 months and asthma at 6 years (**Table 2**). Given that we propose to use ARW as a surrogate for childhood asthma (see primary outcome), we reanalyse our POC data with ARW at 3 years as the outcome. Six (11.8%) children in the placebo group had ARW compared to 2 (4.4%) in the active group. Notably, all 5 children with ARW at age 3, who were seen at age 6, developed definite or likely asthma.

The HDM extract was well tolerated with no child discontinuing the treatment because of adverse events. Multiple assessments (3 monthly during the 1-year trial period) and twice since the end of the trial (at 3 and 6-7 years of age) have not shown any adverse effects specifically related to the intervention. At all assessments there was no difference in adverse effects between intervention and placebo groups, and there were no systemic allergic reactions noted to the trial interventions, which were closely monitored by an independent data monitoring committee; the trial was conducted as a clinical trial for investigational medicinal product in accordance with, and following approval from, the UK Medicine and Healthcare Products Regulatory Agency (MHRA). There was a potential risk that infants could be sensitised by their exposure to HDM at this early age. We found lower allergic sensitisation (one of the aims of the study), in the intervention compared to placebo participants.

The feasibility of our study has been established by the preliminary study in terms of recruitment of a high-risk infant population and safety of the intervention.[7,47] We have learned much from this study including challenges of recruiting infants at high risk of allergy, administering high dose allergen at this early age, monitoring of adherence and ensuring high retention in a 5-year long trial. We have also learned how the design can be further improved in the definitive trial, which we address in the proposed trial. Briefly, these include stronger immune modulation (i.e. dose increased from 6 SQ to 12 SQ, duration of treatment from 1 to 3 years and use of orodispersible tablet instead of liquid extracts with

improved bioavailability. Further, this study is adequately powered with a larger sample size, (n= 434 compared to n= 111) with a higher risk of asthma in infants selected for prevention (additional criteria for high risk of atopic dermatitis (AD) and allergen sensitisation, in an ethnically diverse population. Once daily dosing (instead of twice daily in the preliminary study) should improve adherence further. Mechanistic studies are included to address the central question of tolerance induction using prophylactic immunotherapy.

2. OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

To establish efficacy and safety of HDM sublingual Immunotherapy (HDM-SLIT tablet) by comparing HDM-SLIT and placebo, when given sublingually for 3 years to high-risk infants aged between 5 to 12 months at enrolment in preventing the development of ARW.

2.2. Secondary Objective

Efficacy

To establish efficacy of HDM sublingual Immunotherapy (HDM-SLIT tablet) compared with placebo on the frequency and severity of: ARW at 1, 2 and 3-years post-treatment, allergic sensitisation to one or more allergens, HDM sensitisation, atopic dermatitis and allergic rhinitis.

To also establish efficacy of HDM sublingual Immunotherapy (HDM-SLIT tablet) compared with placebo on changes in lung function (oscillometry, FeNO and Peak Expiratory Flow).

Safety

- To establish safety and tolerability of HDM-SLIT tablet compared with placebo during the 3 years of treatment.

Mechanistic

- To assess whether house dust mite sublingual immunotherapy (HDM-SLIT) can generate functional IgG and IgA antibodies that are linked to the prevention of asthma.
- To assess whether HDM-SLIT is associated with the induction of regulatory T and B cell subsets that can produce immunomodulatory cytokines linked with the prevention of asthma.
- To assess and identify the underpinning molecular and epigenetic pathways associated with prevention of asthma by HDM SLIT using single-cell RNA-seq and ATAC-seq (multiome).

2.3. Primary Endpoint

Proportion of participants with ARW assessed at 3 years post-randomisation. Children will require both (a) recurrent wheeze during the last 12 months AND (b) atopy.

a. Recurrent wheeze: defined as "two or more separate wheezing episodes in the last 12 months treatment period". A wheezing episode is defined as parental or documented report of an episode of wheezing or whistling in the chest that lasts at least 24 hours. Wheezing events separated by at least 5 consecutive days without wheezing shall be counted as separate episodes.

Table 2: Allergic sensitisation and asthma reduction using House Dust Mite allergen immunotherapy

	HDM	Placebo	% Difference (CI)	P=
Allergic sensitisation				
18 months (n=104)	9.4%	25.5%	16.0 (1.7, 30.4)	0.03
3 years (n=94)	22.2%	34.0%	11.7 (-5.1%, 28.6)	0.12
6-7 years (n=84)	27.8%	45.5%	18.2 (-1.8, 35.1)	0.06
Definite Asthma				
MAPS (n=85)	2.9%	13.5%	10.6% (-1.8, 23.0)	0.11
MAPS + ITEC* (n=185)	2.9%	16.8%	13.8% (5.7, 22.0)	0.04
**The analysis was repeated with comparison between the MAPS Intervention group versus MAPS placebo and ITEC groups combined.*				

b. Atopy: "Sensitisation to one or more common allergens in the last 12 months treatment period". The common allergens include HDM (D. pteronyssinus and D. farina), cockroach, grass pollen, tree pollen, ragweed pollen, cat, dog, cow's milk, egg, peanut), as assessed both by; 1) SPT ≥3 mm, and 2) and/or sIgE ≥0.35 kU/litre.

2.4. Secondary Endpoints

2.4.1 Allergic sensitisation and allergic disease

- Proportion of participants with ARW assessed at 3 years post-randomisation. With atopy defined as per the primary endpoint and wheeze defined as per the primary endpoint but excluding wheeze episodes occurring only in March to August (inclusive).
- Proportion of participants at 3 years post-randomisation with allergic sensitisation to HDM, as assessed by 1) SPT ≥ 3mm and/or 2) sIgE ≥0.35 kU/litre and recurrent wheeze during the last 12 months.

2.4.2 Allergic sensitisation

- Cumulative proportion of participants with sensitisation to one or more common allergens over the 3 years of study. The common allergens include HDM (D. pteronyssinus and D. farina), , grass pollen, tree pollen, , cat, dog, cow's milk, egg, peanut), as assessed both by; 1) SPT ≥3 mm and/or 2) sIgE ≥0.35 kU/litre.

- Cumulative proportion of participants with allergic sensitisation to HDM over the 3 years of study, as assessed by 1) SPT ≥ 3mm and/or 2) sIgE ≥0.35 kU/litre.

2.4.3 Allergic disease

- Proportion of participants with ARW at 1- and 2-years post-randomisation:
  (a) Recurrent wheeze: defined as "two or more separate wheezing episodes in the last 12 months treatment period". A wheezing episode is defined as parental or documented report of an episode of wheezing or whistling in the chest that lasts at least 24 hours. Wheezing events separated by at least 5 consecutive days without wheezing shall be counted as separate episodes.
  (b) Atopy: "Sensitisation to one or more common allergens in the last 12 months treatment period". The common allergens include HDM (D. pteronyssinus and D. farina), , grass pollen, tree pollen, , cat, dog, cow's milk, egg, peanut), as assessed by SPT ≥3 mm.
- Proportion of participants with allergic rhinitis in the 12 months before the final study visit at 3 years post-randomisation, as assessed by the Allergy and Environment questionnaire based on the standardised ISAAC questionnaire1, and evidence of allergic sensitisation to the relevant allergen.
- Proportion of participants with atopic dermatitis (AD) recorded using standard criteria in the 12 months before the final study visit at 3 years post-randomisation, using standardised criteria.2
- Proportion of participants with any recurrent wheeze assessed at 3 years post-randomisation (recurrent wheeze defined in 2.3 (a)).
- Impulse Oscillometry: Summaries of air flow measurements at the final visit at 3 years post-randomisation.3
- Proportion of participants with abnormal exhaled nitric oxide (FeNO) at the final visit at 3 years post-randomisation where a cutoff of < 20 parts per billion (ppb) will be considered normal, as per ATS guidelines.4
- Summaries of peak flow measurements at the final visit at 3 years post-randomisation.

2.4.4 Safety

- Proportion of participants with any adverse events
- Proportion and incidence with clinically relevant asthma exacerbations over 3 years
- Proportion and incidence with clinically relevant anaphylactic reactions, anaphylaxis and/or systemic allergic reactions over 3 years
- Proportion and incidence treated with adrenaline/epinephrine over 3 years
- Proportion and incidence with severe oral swelling of the mouth and/or throat over 3 years
- Proportion and incidence with eosinophilic esophagitis over 3 years
- Proportion with an increase in proportion and incidence of HDM sensitisation over 3 years.

2.4.5 Tolerability

- Proportion of participants who stop treatment prior to planned 3 years of treatment of active HDM tablet compared with placebo
- Proportion of participants who stop treatment due to adverse events prior to planned 3 years of treatment of active HDM tablet compared with placebo
- Proportion of participant who took 60% of the treatment over 3 years as recorded in the MedSearchTM App.

2.4.6 Mechanistic

- Functional IgG and IgA antibodies linked to the prevention of asthma
- Induction of regulatory T and B cell subsets that can produce immunomodulatory cytokines linked with the prevention of asthma

2.5. Tertiary / Exploratory / Other endpoints

1) 48Molecular and epigenetic pathways associated with prevention of asthma by HDM SLIT using single-cell RNA-seq and ATAC-seq (multiome).
2) ARW severity as measured by a nine-level ordinal scale based on frequency of wheezing episodes and number of positive SPT at 3 years post-randomisation. Participants will be classified as:

   0 - 0 allergens on SPT and 0 wheeze,
   1 - 1 allergen on SPT and 0 wheeze,
   2 - ≥2 allergens on SPT and 0 wheeze,
   3 - 0 allergens on SPT and 1-2 wheeze,
   4 - 1 allergen on SPT and 1-2 wheeze,
   5 - ≥2 allergens on SPT and 1-2 wheeze,
   6 - 0 allergens and ≥3 wheeze,
   7 - 1 allergens on SPT and ≥3 wheeze,
   8 - ≥2 allergens on SPT and ≥3 wheeze.

3. STUDY DESIGN

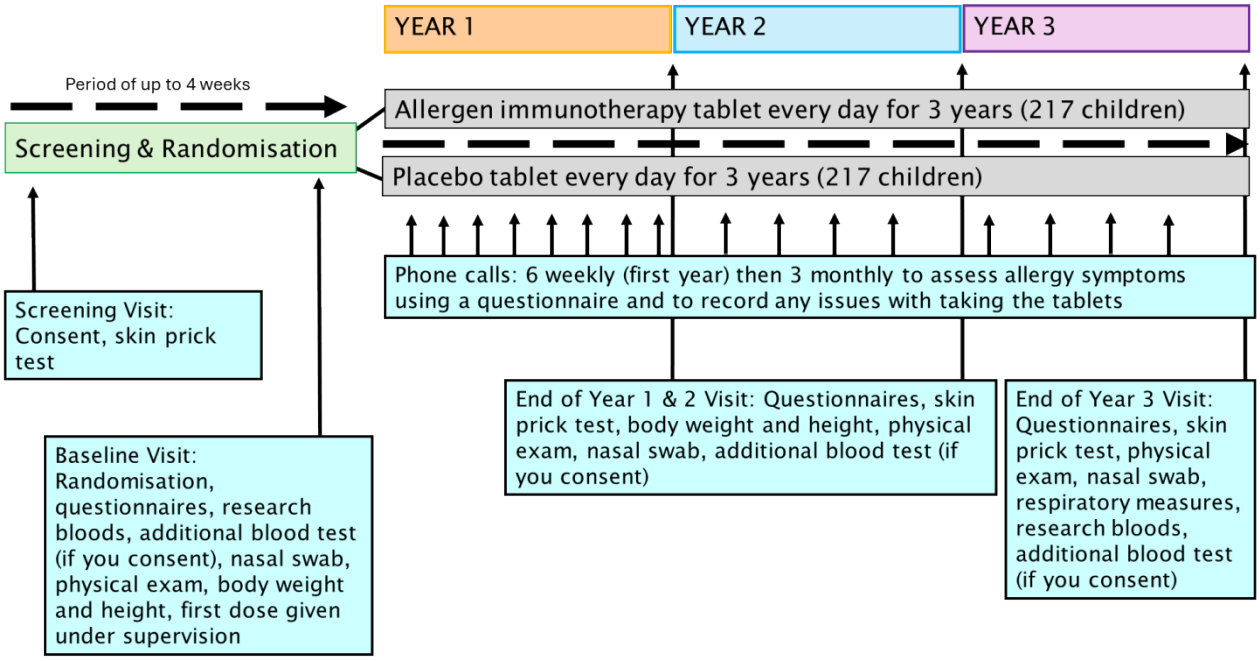
This is a randomised (1:1), double-blind, placebo-controlled, parallel arm, multi-site study with an internal pilot to evaluate feasibility of trial delivery. Participants will be randomised to one of HDM-SLIT or placebo treatment, as shown in Figure 1. HDM-SLIT (Acarizax) or placebo will be administered as a sublingual lyophilisate in a single dose of 12 SQ (30µg) once per day for 3 years.

Table 3: Treatment Regimens

Treatment Sequence	Number of participants	Treatment Period 1
1	217	Acarizax 12SQ (30µg)
2	217	Placebo
Total number of participants	434	

4. PARTICIPANT ENTRY

Figure 1. Study setting and population



To encourage retention and adherence, we will use an App (MedSearchTM) that has been developed as a health companion digital solution which will send notifications for their medications intake – in daily reminders. It will also be used for parents to raise any concerns regarding treatment. For those who do not own a smartphone and cannot access the app. In the case that any technically issues arise with the application, parents will be provided with a paper diary card to record daily administration in the interim. Parents/legal guardians should be instructed to return the completed diary cards using pre-paid envelopes ahead of their phone call appointments. The site team will measure adherence by performing accountability checks at the annual visits.

I. Inclusion criteria

Individuals who meet all the following criteria are eligible for enrolment as study participants:

1. Parent/guardian must be able to understand and provide informed consent.
2. Aged 5 to 12 months of age at randomisation
3. High risk of asthma (two or more of the three criteria);
   a. Single OR dual heredity for allergy (at least one biological mother, father or sibling affected by asthma, allergic rhinitis or atopic dermatitis, assessed through Allergy and Environment questionnaires).
   b. AD using standardised criteria.[2,49]

1) Allergen sensitisation; defined as positive SPT (≥3 mm wheal diameter) to at least one common allergen on SPT grass and tree pollen, cat, dog, peanut, milk, and egg).

Participants who fail to meet the criteria for enrolment in the trial may be reassessed for eligibility up to the age of 12 months (first birthday). Such participants may be enrolled at the time of reassessment if they meet all criteria for enrolment.

II. Exclusion criteria

Individuals who meet any of these criteria are not eligible for enrolment as study participants:

1) Evidence of sensitisation to HDM (Dermatophagoides Pteronyssinus and Dermatophagoides Farinae (SPT ≥3 mm).
2) Prematurity (<37 weeks/259 days of gestation).
3) Faltering growth and/or need for oxygen for more than 5 days in the neonatal period or history of intubation or mechanical ventilation.
4) Other significant medical conditions including but not limited to eosinophilic esophagitis, seizures, major congenital anomalies, cardiac disorders requiring medical therapy, cystic fibrosis, chronic pulmonary diseases, bronchopulmonary dysplasia, significant developmental delay, cerebral palsy, immunodeficiency (primary or secondary), acute severe oral inflammation or oral ulceration (to be assessed by investigator at screening).

Occurrence of screen fails as a result of significant medical conditions will be monitored via completion of screening logs and site retraining issued where applicable.

5) Use of investigational drugs since birth.
6) Expecting to relocate out of country within 4 years of study initiation.
7) Deemed as unable to adhere to study activities.
8) Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.
9) Has any clinically significant abnormal vital sign or laboratory value that in the opinion of the investigator would preclude participation in the trial.
10) Known history of allergy, hypersensitivity or intolerance to any of the excipients or active substances of the IMP (including D. pteronyssinus and/or D. farinae).
11) Personal relationship with trial staff who is directly involved with the conduct of the trial.
12) Those taking a beta-blocker.
13) Those currently taking allergen immunotherapy for any other indication.

5. PROCEDURES AND MEASUREMENTS

5.1. Identification and recruitment of participants

Recruitment Strategy:

Although a child must be at least 5 months of age at the time of randomisation, potential participants can be approached earlier than this. However, screening visit assessments can only start up to 4 weeks before they turn 5 months old.

Participants will be identified in three ways:

1) **GP practices:** The NIHR Research Delivery Network (RDN) and Scottish Primary Care Research Network (SPCRN) will be used to screen for eligible participants. The RDN will then send an expression of interest to GP practices. The GP practices will act as Participant Identification Centres (PICs) and send either a text message or Stage 1 PIS via email as an invitation to view more details about the study including a link to the study website for eligible participants. In Scotland, the SPCRN staff will identify eligible cases from GP records and send the study contact details via physical letter. The letter, text message or email from RDNs and SPCRNs will include a link or QR code to the study website which will provide a brief study summary and PIS with further information about the study.

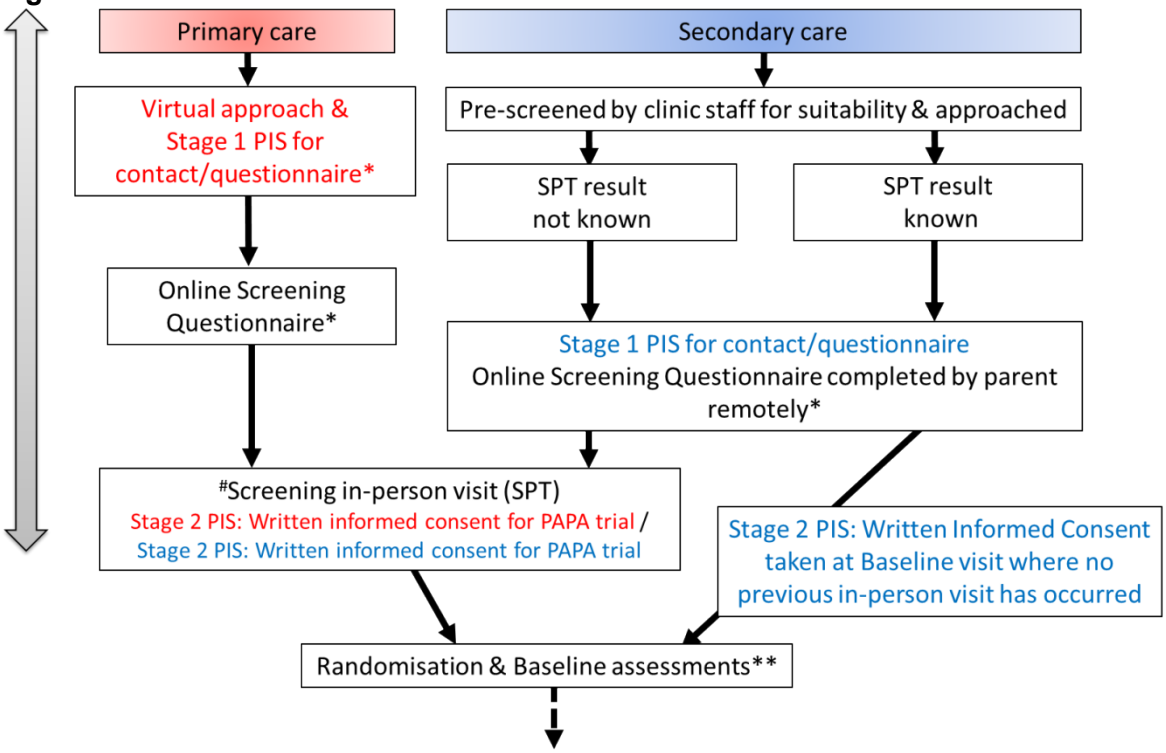
If parents/caregivers wish to proceed with the study, they will be asked to answer pre-screening questions on the eCRF which will determine basic eligibility. At this point they will see if their child is potentially eligible for the study.
If they would like to continue, the parent/caregiver will be asked to securely enter their contact details onto the website form and select their local study site where the visits will take place and a member of the study team will be in contact to answer questions and further determine eligibility of the potential participant.

If a potential participant is determined to not be eligible for the study based on the online pre-screening, there will be an option for the parent/caregiver to be contacted by the study site to further discuss why their child may not have been eligible.

2) **Secondary care:** Research sites throughout the UK who have expressed an interest in participating in the study will recruit eligible infants attending allergy and dermatology clinics, wards and any other secondary care pathways.

3) **Community:** We will also accept self-referrals direct to the study site (e.g. via trial website, universities, community centres, GP practices, baby/vaccine clinics, places of worship e.g. churches, mosques, temples, and other public places using posters, via local newspapers, social media and radio, videos, pop up events and research recruitment websites) which will provide contact details for the study team and links to the study website.

Figure 2: Recruitment Flow Chart



* Questionnaires may be completed at an in person visit where the parent would prefer this.

** randomisation can be done virtually up to 72hours prior to the baseline visit (only where written informed consent has been taken) if this is more practical for the study team and participant but should be done as close as possible to avoid drop-out
# The PIS can be shared (posted/emailed) to participants prior to the screening visit to allow for 24hrs decision time prior to the visit.

These methods of recruitment will ensure that a wide range of children are recruited, including those from underserved populations who may not attend a specialist clinic and those who are generally managed in primary care and not usually included in research.
All study research sites are led by national leaders in paediatric asthma clinical trials with a long-standing track record of recruiting and retaining the targeted population.
We expect half of the infants to be recruited from paediatric allergy and dermatology clinics where family history of allergy, AD and allergic sensitisation are prevalent (~50%) and parents keen to participate. Rest will be recruited from primary care and community.

Criteria to add sites: Recruitment will be closely monitored on a monthly basis including an internal pilot. Those sites not recruiting well will be provided with support. However, if they are unable to reach 50% of the target recruitment (5 children of 11 expected) in first 6 months of recruitment, we will consider adding, and diverting resources to, additional centre(s), unless there is a clear and credible plan to accelerate recruitment.

Ethnicity mix of the infant population to be recruited: We will aim to recruit participants from ethnic minorities (Black, Asian, and mixed race) representing the wider UK population ethnic mix. Most sites have significant proportion of ethnic minorities. We will focus on these sections of the society for enhanced recruitment efforts. By approaching populations with a higher proportion of ethnic minorities than the average UK population demography, we expect that the final study population will at least be representative of the overall UK population i.e. about 15% from the non-white race/ethnic background.

Retention: There are significant challenges in retaining participants for long term studies. However, we have had excellent success in previous studies, with a >90% retention rate in most of our longitudinal studies. We will utilise retention methods such as; telephone/App reminders, newsletters, informational sessions, and websites. This effort will be led by our PPI leads. We will also translate consent/recruitment/survey materials into local languages (Hindi/Urdu) to aid recruitment.

5.2. Recruitment Process

Summarised in Figure 2.

Participant Information Sheet

The Participant Information Sheet (PIS) for Stage 1 and 2 will be available on the study website but during the Screening visit this can be shared (paper or electronic form) with the parent/caregiver in parallel if requested. All participant information sheets are prepared in partnership with Asthma and Lung UK and the patient advisory groups. These will be available in different languages as appropriate and requested.

5.2.1. Stage 1

Stage 1 will involve collection of basic screening data via an online questionnaire and request the parent/caregiver's contact details to be contacted for further information. No sensitive data will be collected as part of the screening questionnaire. Participants are not considered enrolled in the trial at

this stage. If preferred, the parent/caregiver can attend an in-person Screening visit to complete the screening questionnaire, written consent and other screening assessments to determine eligibility.

5.2.2. Stage 2

If the online questionnaire suggests the child may be eligible for the PAPA trial, the team will approach the parent/caregiver to provide more information and discuss attending an in-person Screening visit.

The study team will explain the study and answer any questions the parent/caregiver might have. Parents/caregivers will be given an adequate amount of time to consider their child's participation in the study. The PIS may be posted or emailed to the parent/caregiver to assist in discussions. If there are no further questions and they do not request more time to consider, the parent/caregiver will attend an in-person Screening visit and provide written informed consent for the PAPA trial. Consent must be taken by a trained health care professional delegated by the Principal Investigator. At this point the participant is considered enrolled in the trial. The additional screening procedures will then be completed.

If all the required screening data is already known (the participant was approached via allergy and dermatology clinics and the information was already present in their medical record) no in person screening visit is required. Written informed consent will be taken at the Randomisation & Baseline visit but no data should be recorded in the trial database until consent is taken.

5.3. Screening and pre-randomisation evaluations

The purpose of the screening period is to confirm eligibility to continue in the study. For infants less than 5 months of age, screening visit assessments can only be conducted up to 4 weeks prior to them turning 5 months old. The following procedures, assessments, and laboratory measures will be conducted to determine participant eligibility:

Screening assessment

1. A screening questionnaire will be completed to assess allergic family history, presence of allergic manifestations (AD, wheeze) and exclusion criteria (pre-screening virtual visit).
2. Those who are eligible on questionnaire, would be asked to have skin prick test to evaluate presence of allergic sensitisation to common allergens HDM (D. pteronyssinus and D. farinae; 50/50), grass pollen, tree pollen, cat and dog, cow's milk, egg and peanut).
3. A positive test on SPT (≥3 mm wheal diameter) will be regarded as evidence of allergic sensitisation.
4. Once all the information is available from the screening visit, participants will be assessed for eligibility using inclusion and exclusion criteria described above, and randomised to active or placebo treatment via the web-based randomisation system up to 48 hours prior to the baseline visit. Note: The screening questionnaire can be completed online before the visit (at any age up to 12 months). Alternatively, all screening procedures including consent can be completed at the screening visit (up to 4 weeks before the minimum age requirement of 5 months). Randomisation and baseline visit can only take place once the participant is at least 5 months old (and at most 12 months old).

Data that is collected as part of standard of care (e.g. skin prick test prior to signing the consent form may be used as part of the trial screening to limit burden on participants.

5.4. Randomisation and Blinding

If the child is eligible for the study and at least 5 months of age, they will be randomised. Randomisation can occur up to 48 hours prior to the baseline visit (**Figure 2**), only where written informed consent has taken place and eligibility has been confirmed. Consenting and randomising

prior to the Baseline visit allows for low-risk study activities to proceed whilst the intervention is being dispensed in readiness for the Baseline visit. Dispensing the intervention ahead of the Baseline visit will minimise the time spent at the study centre and inconvenience for the child and their parent/ caregiver. Screening and Randomisation/Baseline visits can also be combined where applicable (**Figure 2**).

Allocation to treatment arms will be performed using an online system (OpenClinica) to ensure concealment. Allocation to treatment arms will be by minimisation and will include a 20% random element.65 The minimisation variables will be: sex (M/F), site, ethnicity (White, Black, Asian, mixed race), and low level HDM sensitisation (no sensitisation to HDM (SPT<0.5mm) or low level sensitisation to HDM (0.5≤ SPT≤2.9 mm a).

The study is double-blind where the caregivers, children, and clinical study team will be blinded to the assigned arms by use of a matching placebo tablet which will be indistinguishable from the active treatment. However, the trial statistician and senior statistician will be unblinded from the first DMC meeting that involves review of study data. The unblinded treatment allocation list will be held securely by the drug supply manufacturer.

5.4.1. Code-breaking/ Unblinding

Each participant will be assigned a unique trial ID and trial medication will be identified with a unique treatment code which is linked to the treatment allocation. The treatment code must not be broken except in medical emergencies when the appropriate management of the participant necessitates knowledge of the treatment, or in the event that expedited reporting to the Regulatory Authority and Ethics Committee of a Suspected Unexpected Serious Adverse Reaction (SUSAR) is required.

The trial electronic data capture (EDC) system will include an automated unblinding facility. In the event that emergency unblinding of an individual participant is required, authorised staff (as documented on the delegation log) will follow trial procedures to unblind the participant in question and proceed with expedited reporting, if required.

Unblinding must be approved by the study Chief Investigator (or delegate) unless an immediate life-threatening condition has developed and the Chief Investigator (or delegate) is not accessible. The site investigator will notify ICTU of the unblinding event on the next business day. The emergency unblinding will also be reported to the Data Monitoring Committee (DMC) and documented on the appropriate form as required by ICTU's Standard Operating Procedures (SOPs).

A full account of the event will be recorded, including the date and time of the unblinding, the reason for the decision to unblind, and the name of the individual who made the decision and the names of the Chief Investigator/ Medical Monitor and others who were notified. The reasons for unblinding of a participant's treatment will be included in the final study report.

Unblinding for statistical analysis and DMC reports: The integrity of trial blind should be maintained at all times, with the exception of the DMC who will have access to fully unblinded data. The trial statistician preparing the DMC report and senior statistician overseeing its preparation will also require access to fully unblinded data in order to prepare the report. Unblinding in these cases should take place in accordance with Imperial Clinical Trials Unit (ICTU) Standard Operating Procedures (SOP) and documented accordingly.

More details on randomisation and blinding will be provided in the study specific randomisation and blinding manual.

5.5. Study Visit Schedule and Study Assessments

All study visits are outlined in Table 4 and Figure 3.

Visit	Pre-screening[7]	Screening[8]	Baseline	Phone call	Annual Follow-up visit			*Ad hoc visit*	*IMP collection*
Time	**0-8 weeks prior to Baseline**		**Day 1**	**6-weekly / 3 monthly[1]**	**End of year 1**	**End of year 2**	**End of year 3**		
Window	**N/A**	**N/A**	**N/A**	**+/-15 days**	**+/- 30 days**	**+/- 30 days**	**+/- 30 days**		
Screening questionnaire	x	-	-	-	-	-	-		
Written informed consent	-	x	-	-	-	-	-		
Inclusion/ Exclusion	-	x	-	-	-	-	-		
Randomisation[5]	-	-	x	-	-	-	-		
Infant demographics	-	x							
Family Demographics and Medical History Questionnaire	-	-	x	-	-	-	-		
Allergy & Environment Questionnaire	-	-	x	x	x	x	x		
POEM Assessment[4]	-	-	x	-	x	x	x		
Physical examination	-	-	x	-	x	x	x		
SPT	-	x	-	-	x	x	x	x	
Oscillometry[10]	-	-	-	-	-	-	x		
Peak Flow	-	-	-	-	-	-	x		
Exhaled nitric oxide	-	-	-	-	-	-	x		
Research blood samples	-	-	x	-	-	-	x		
Additional research blood volume[6]	-	-	x	-	-	-	x		
Nasal swab samples	-	-	x	-	x	x	x		
Body weight and height	-	-	x	-	x	x	x		
Initial drug administration[2]	-	-	x	-	-	-	-		
Daily HDM/ Placebo tablets administration	-	-	Every day for 3 years						

Current medications	-		x	x	x	x	x	x	
Adverse events	-		x	x	x	x	x	x	
Medication adherence check	-	-	-	x	x	x	x		
Review of hospital medical records[3]	-	x	-	-	x	x	x	x	
Letter to GP	-	-	x	-	-	-	x		
IMP dispensing/collection[19]									x

SPT: Skin prick Test

[16] weekly in the first year and 3 monthly in years 2 and 3.

[2]Pre- and post-dose assessments (oral examination, heart rate, blood pressure, auscultation of chest) will be carried out. When the first dose is administered, the participant will be under medical supervision for at least 60 minutes after the tablet intake. Additionally, paediatric research nurses will call or text study participant's parents the following day, a week and 2 weeks after the first dose to ensure no adverse event has occurred.

[3]any relevant information that is not recorded through AEs or concomitant medication

[4]only those with the AD will have POEM assessment

[5]randomisation may occur up to 72 hours prior to the baseline visit and all eligible participants must be at least 5 months old at the time of randomisation.

[6]only centres taking part in this collection

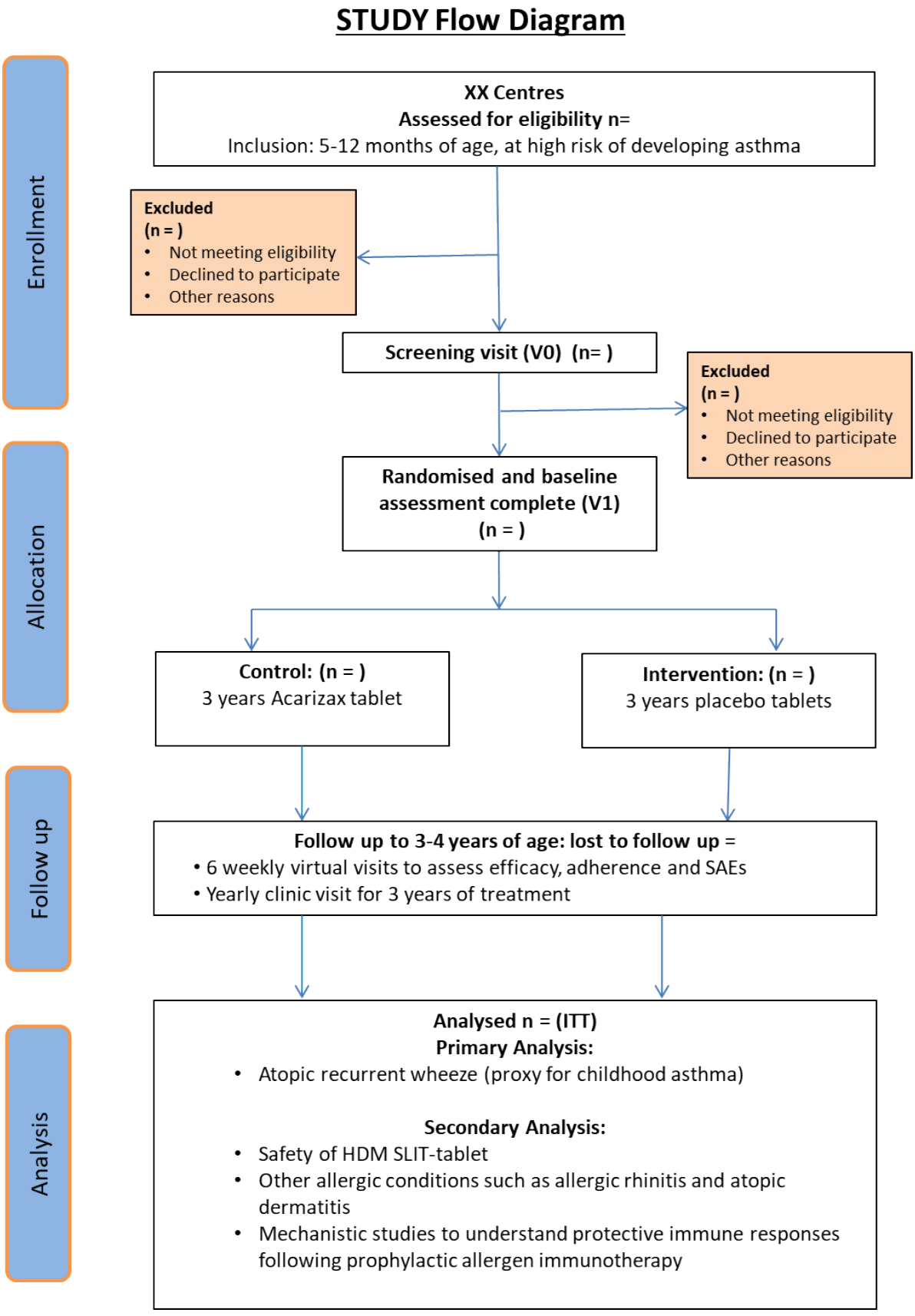
[7]if parents prefer an in person visit the pre-screening and screening visits can be combined.

[8]Screening visits can be combined with the baseline visit if applicable. Screening visit assessments for potential participants who are less than 5 months of age should be started no more than 4 weeks prior to them turning 5 months old. Where screening and baseline visits are combined, participants must be at least 5 months – 12 months old. If less than 5 months, participant has to come back for a separate baseline visit once they are at least 5 months old.

[9]dependent on IMP expiry dates, parents may be required to collect additional supplies from the site throughout the trial.

[10] Oscillometry will only be conducted at sites which have the equipment. Equipment used must conform to ATS/ERS standards.

Figure 3.


STUDY Flow Diagram
Enrollment
Allocation
Follow up
Analysis
XX Centres
Assessed for eligibility n=
Inclusion: 5-12 months of age, at high risk of developing asthma
Excluded
(n =)
• Not meeting eligibility
• Declined to participate
• Other reasons
Screening visit (V0) (n=)
Excluded
(n =)
• Not meeting eligibility
• Declined to participate
• Other reasons
Randomised and baseline assessment complete (V1) (n =)
Control: (n =)
3 years Acarizax tablet
Intervention: (n =)
3 years placebo tablets
Follow up to 3-4 years of age: lost to follow up =
• 6 weekly virtual visits to assess efficacy, adherence and SAEs
• Yearly clinic visit for 3 years of treatment
Analysed n = (ITT)
Primary Analysis:
• Atopic recurrent wheeze (proxy for childhood asthma)
Secondary Analysis:
• Safety of HDM SLIT-tablet
• Other allergic conditions such as allergic rhinitis and atopic dermatitis
• Mechanistic studies to understand protective immune responses following prophylactic allergen immunotherapy

5.6. Baseline visit

The following procedures and measurements will be conducted during the baseline visit:

1. Allergy & Environment questionnaire to assess allergic symptoms, environmental exposure, diet and other relevant information.
2. Family Demographics and Medical History questionnaire to obtain further information on any pre-existing health conditions.
3. Physical examination (oral examination, chest auscultation)
4. Body weight and height
5. POEM to assess extent and severity of AD in those where this diagnosis is made.
6. Nasal (swab) sample will be taken and stored for mechanistic studies.
7. Research blood sample.
8. Additional research blood sample volume will be taken from participants whose parent's consent at sites open to recruitment into mechanistic studies.

The first dose (HDM/placebo tablets) will be administered at the baseline visit followed by an observation period of 60 minutes. Pre- and post-dose assessments (oral examination, heart rate, blood pressure, auscultation of chest) will be made and infants will be discharged home only if these assessments show satisfactory outcomes.

Parents/ caregivers of the study participants will be provided with detailed instructions on how to use the intervention, what to look out for after doses, and what to do if they have any concerns. Parents will be given training and practical demonstration by paediatric research nurses on how to administer the tablet. Parents will also be provided with clear written instructions, which will explain how these tablets should be used once daily at home. The research team will also provide assistance to parents on how to use the MedSearchTM App in order to record adherence and raise concerns regarding daily dosing and ensure the notifications are working correctly. Please refer to the study specific procedures manual for more information. Wheeze recognition training will be provided to all parents at baseline using audio clips of wheezing and breathing sounds. These audio clips can be accessed by the parents on the study website at any stage during the course of the trial.

A standard letter will be sent to the GP if the participant is enrolled on to the study

Post-baseline visit monitoring

1. Paediatric research nurses will call or text study participant's parents/caregivers the following day, a week and 2 weeks after the first dose to ensure no adverse event has occurred. If there is any concern, they will be seen for an assessment at the Research Site.
2. Parents/caregivers will have access to a 24-hour telephone number manned by paediatric research nurses, research fellows and paediatric consultants who will give appropriate advice. If there is urgent or serious concern, parents/caregivers should follow their usual care pathways (GP, 111, 999 or A&E)
3. If there is any indication that a child may have developed sensitisation e.g. if they had a reproducible rash or swelling following administration of the tablet, they will be seen at the research site and skin prick tested.

5.6.1. Telephone contacts

Parents/ caregivers will be contacted over the phone 6 weekly in the first year and 3 monthly in years 2 and 3 to collect the following information:

1. Allergy and Environment questionnaire to assess allergic symptoms, environmental exposure, diet and other relevant information.
2. Adherence check will be carried out to assess compliance with the study medication during the three years of immunotherapy.
3. Information on any adverse events will be sought during the three years of immunotherapy.

5.7. Annual Follow-Up Visits

At the end of year 1, and 2, parents/caregivers will attend the annual follow-up visit. The following information will be collected during this visit:

1. Allergy and Environment questionnaire to assess allergic symptoms, environmental exposure, diet and other relevant information.
2. Review hospital medical records for anything not recorded through AEs and concomitant medication
3. Physical examination (chest auscultation) and POEM for those with evidence of AD.
4. Body weight and height
5. Skin prick test will be performed to evaluate presence of allergic sensitisation to common allergens: HDM (D. pteronyssinus and D. farinae; 50/50), grass pollen, tree pollen, cat, dog, cow's milk, egg and peanut).
6. Adherence check will be carried out to assess compliance with the study medication at all visits while the child is on IMP or placebo, during 3 years of treatment.
7. Information on any adverse effects will be sought throughout.
8. Parents will continue to have access to a 24-hour telephone number manned by paediatric research nurses, research fellows and paediatric consultants throughout the trial. If there is any concern, they will be seen immediately at any time of the day or night. If an adverse effect is reported over the phone but the concern is not immediate, child will be seen the following working day either at their home or in the research Centre.
9. If there is any indication that a child may have developed sensitisation e.g. if they had a reproducible rash or swelling following administration of the tablet, they will be seen at the research Centre and skin prick tested.

5.8. Year 3 Annual Follow-up Visit (at completion of allergen immunotherapy at age 3½ to 4 years)

1. All the procedures at annual visits 1 and 2 will be repeated at annual visit 3.
2. Child will be asked to perform lung function test (oscillometry – only at sites where equipment is available). We will also ask children to perform peak flow at the final visit.
3. Exhaled nitric oxide measurement will be performed.
4. Research Blood sample.

5. Additional research blood sample volume will be taken from participants whose parent's consent at sites open to recruitment into mechanistic studies.

5.9. Ad hoc/Unscheduled Visits

If there is any indication that a child may have developed sensitisation e.g. if they had a reproducible rash or swelling following administration of the tablet, they will be seen at the research site and skin prick tested.

If disease activity increases or other concerns arise between regularly scheduled visits, participants will be instructed to contact study personnel and may be asked to return to the study site for an "unscheduled" visit. This is primarily to ensure safety and to manage early manifestation of atopy such as wheeze.

5.10. Incidental findings

Any incidental findings discovered throughout the study will be referred back to the participant's GP.

5.11. Visit Windows

Study visits should take place within the time limits specified below: the designated visit windows for each scheduled visit are also indicated on the Table of Events (**Table 4**).

Visit window: +/- 15 days for 6 weekly and 3 monthly telephone calls, +/- 30 days for annual visits.

5.12. Description of Study Procedures and Measurements

Detailed SOPs will be developed for each of the study procedures, these will be outlined in the trial Manual of Operations.

5.12.1. Medical history

Note: only relevant conditions such as asthma and allergic diseases

5.12.2. **Demogra**phics

Age, gender, race and ethnicity will be collected.

5.12.3. Current Medications

Note: all medications

5.12.4. Medication Adherence Check

Residual and unused IMP and all empty packaging will be counted at each onsite visit. Parents/caregivers will be required to download an App (MedSearch™) on their cell phones which would aid monitoring of the compliance with the study medication.

5.12.5. Questionnaires

(i) [50-52]PAPA trial specific Family Demographics and Medical History questionnaire to obtain further information on any pre-existing health conditions[50].

(ii) PAPA trial specific Allergy and Environment questionnaire to assess allergic symptoms, environmental exposure, diet and other relevant information based on standardised ISAAC questionnaire and previous studies[49,51]

These questionnaires will be administered at all clinic visits and 6 weekly (first year)/3monthly (years 2 and 3) of the trial, with the addition or reduction of any supplementary asthma medications based on the symptom protocol and carefully tracked and monitored.

5.12.6. Physical Examination

Children will be examined by the PI or a designated member to detect the presence of wheeze (chest auscultation using a stethoscope) and/or AD on skin. For participants with AD or have developed AD, a standardised POEM assessment will be carried out.

5.12.7. Height and Body weight

Height and weight will be recorded.

5.12.8. Skin Prick Tests

Skin prick testing will be performed by experienced nurses/clinical trials assistants using standard technique. A panel of common allergens will be tested comprising house dust mite (D. pteronyssinus and D. farinae), grass pollen, tree pollen, cat, dog, cow's milk, egg, and peanut plus histamine and physiological saline to act as positive and negative controls, respectively. Allergen skin test reaction with a mean wheal diameter of at least 3 mm greater than the negative control will be regarded as positive and the participant defined as atopic.

5.12.9. Impulse Oscillomtery

The American Thoracic Society / European Respiratory Society guidelines will be followed.3 For sites with the equipment, Impulse oscillometry will be performed at the last visit (3½ to 4 years of age) using forced oscillometry technique (FOT), which is a simple, non-invasive technique performed during tidal breathing that is relatively easy to apply in preschool children. An external pressure wave is applied, usually at the mouth, and the resulting pressure–flow relationship is analysed in terms of respiratory impedance. It can identify airway obstruction and responses to bronchodilators. Results will be reported as the mean of the three to five measurements and a coefficient of variation will be calculated from the standard deviation to mean ratio. Respiratory resistance (Rrs) is considered a reasonable surrogate of airway resistance and this will be measured at 5 to 8 Hz. Pre- and post-bronchodilator values, measured using ATS standards, will be analysed. Quality control will be monitored and data will be read and interpreted by trained paediatric pulmonologist following ATS guidelines to ensure only reproducible high quality data are utilized in analysis.

5.12.10. Peak Flow

We will also ask children to perform peak flow readings to be assessed at the final visit.

5.12.11. Exhaled Nitric Oxide

Measurement of FeNO will be performed in all participants using standardised methodology.[4] We will do real-time measurements during each participant's final visit to the research site.

5.12.12. Laboratory Evaluations

Laboratory procedures are described in a separate laboratory manual that also details blood and nasal sampling and shipment procedures.

5.12.13. Research Blood Samples

A venous blood sample up to 15 ml will be obtained (where possible depending on the age of the child and feasibility) at baseline. A further up to 15ml sample will be taken at year 3. The blood sera from baseline and year 3 will be stored for later laboratory measurements of total and specific IgE and IgG at the central laboratory or the IMP provider ALK Abello laboratories in Copenhagen, Denmark.

In a subgroup of participating sites and where optional parental consent is given, up to an additional 10 ml volume of blood will be collected at baseline and year 3. These samples will be processed locally to isolate cells and plasma in separate tubes. These samples will be stored for later laboratory measurements for the mechanistic analyses, comprising of:

1) humoral response assessment (HDM-specific IgG1, IgG2, IgG4, IgA1 and IgA2)
2) cellular response assessment (T and B cells)
3) molecular response assessment.

Further details for all research blood samples are described in a laboratory manual. Local anaesthesia may be used in connection with blood sampling where required.

5.12.14. Nasal Samples

Nasal samples (swabs) will be taken from the child at the timepoints specified in the visit schedule. These samples will be frozen at -80°C and analysed at a later date. Details are described in a laboratory manual. Nasal samples will be collected and stored for mechanistic analyses. Levels of house dust mite (HDM)-specific IgG1, IgG2, IgA1 and IgA2 will be quantified in all study participants using enzyme-linked immunosorbent assays (ELISA) or proteomics via Proximity Extension Assay (PEA) technology. The functional activity of blocking antibodies will be assessed using the IgE-facilitated allergen binding (IgE-FAB) assay.

6. TREATMENTS

6.1. TREATMENT ARMS

The investigational medicinal product (IMP) for this trial is house dust mite sublingual immunotherapy (12 SQ-HDM-SLIT tablet), licensed in the US as ODACTRA®, in Japan as MITICURE® and in rest of the world as ACARIZAX® It will be compared to a matching placebo tablet. The trial medication supply will be provided as labelled (Qualified Person) QP-released IMP by ALK Abello.

6.2. INVESTIGATIONAL MEDICINAL PRODUCT DETAILS

The study drug and placebo have been manufactured to Good Manufacturing Practice by ALK-Abello, Denmark. The drug is approved for use in children 12 years of age for treatment of allergic rhinitis by the regulatory authority, the MHRA.

Formulation: The IMP provided in the trial is HDM-SLIT tablet or placebo. The placebo tablets are identical to the active tablet with respect to appearance, smell and taste.

Active treatment (HDM-SLIT Tablet)

- Active ingredients: Standardised allergen extract from the HDMs D. pteronyssinus and D. farinae
- Dosage form: Sublingual lyophilisate
- Dose/strength: 12 SQ-HDM
- Excipients: Gelatin (fish source), mannitol and sodium hydroxide

Placebo treatment

- Active ingredients: None
- Dosage form: Sublingual lyophilisate
- Excipients: Gelatin (fish source), mannitol and sodium hydroxide

The trial is being carried out under a Clinical Trial Authorisation (CTA). The drug is therefore only to be used by the named investigators, for the participants specified in this protocol, and within the trial.

An Investigator Brochure (IB) V 18.0 Dated 17 November 2024 will be used. Sites should refer to their Investigator Site File or ICTU for the current version.

6.3. LABELLING AND PACKAGING

- The IMP/ Placebo will be supplied in blister cards containing 10 tablets each. The blister cards will be packed in specific boxes containing a sufficient number of tablets to cover the treatment period between the dispensing visits and the end of trial visit.
- IMP/ placebo will be packaged and labelled according to EU Annex 13 and national requirements. The IMP/ placebo will be uniquely numbered with a study ID linked to the randomisation code.
- Packaging, labelling, and distribution will be outsourced to 3rd party manufacturer Sharp Clinical. Trial medication (HDM-SLIT / placebo) will be shipped to participating sites as labelled IMP in accordance with regulatory requirements (MHRA). Trial medication will be provided as an sublingual lyophilisate strength (SQ 12).
- The trial products provided by ALK (HDM-SLIT) are to be used only for this trial and not for any other purpose. Further information can be found in the IMP handling manual.

6.4. STORAGE AND DISPENSING

- IMP/-placebo must be stored in a secure, limited-access location separately from normal clinic stocks and according to label specifications (temperature range between 15-25°C). IMP/placebo returned by the participant must be stored separately from other medication, e.g. unused IMP/placebo that has not yet been dispensed.
- Site storage conditions for IMP must be monitored by the site staff for adherence to label specifications and reviewed by the Trial Monitor during monitoring visits.
- Temperature monitoring must be done using a calibrated, stationary and continuously recording system. As a minimum a calibrated min/max thermometer is required.
- Randomised participants are assigned a unique code from the study database which corresponds with IMP kits available at each participating site for dispensing.
- Further information can be found in the IMP handling manual.

6.5. DOSAGE, DURATION AND COMPLIANCE

- Dosage: Participants will receive a total daily dose of 12 SQ HDM-SLIT/placebo given sublingually, once daily. IMP/placebo will be provided as dissolvable tablets to be administered daily by the participants parent/caregiver.
- Duration: Trial treatment should begin on the day of randomisation or as close as possible to the date on which treatment is allocated/assigned at the investigator site, where the first IMP/placebo will be dispensed. Hereafter, IMP/placebo will be dispensed at the visits according to the agreed schedule.
- Method of administration: The HDM-SLIT/ placebo tablet should be taken with dry fingers from the blister unit immediately after opening the blister and placed under the tongue by the caregiver, where it will disperse. If possible, swallowing should be avoided for approximately 1 minute. Food and beverages should not be taken for 5 minutes after intake of IMP. The daily dose of IMP is 1 HDM-SLIT tablet, which should preferably be taken in the morning to observe for adverse events.
- Precautions in relation to first dosing: When the first dose is administered, the participant will be under medical supervision for at least 60 minutes after the tablet intake. Subsequent

dosing will be administered once daily to the participant, by a parent/caregiver, at approximately the same time each day.

- Monitoring of adherence: Parents/caregivers must be instructed to bring all residual and unused IMP and all empty packaging to the site at every visit. Compliance will be assessed at each in person visit by HDM-SLIT tablets/placebo tablets count using the packaging and/or tablets parents will bring with them. If IMP/placebo compliance is less than 80% or more than 100%, the investigator should discuss the reason and encourage the participant to comply with the protocol. Parents/caregivers will be required to download an App (MedSearch™) on their cell phones which would aid monitoring of the compliance with the study medication. The site staff should, in cooperation with the participant, aim at keeping the treatment compliance between 80-100%. Further information can be found in the IMP handling manual.

6.6. ACCOUNTABILITY

Site pharmacies will maintain accountability records for IMP/ Placebo which will be reviewed during site monitoring visits throughout the trial. Any un-used supply will be checked by the study Monitor and destroyed locally following receipt of approval from the Monitor. Further information can be found in the IMP handling manual

6.7. DRUG INTERACTIONS / PRECAUTIONS / CONTRAINDICATIONS

HDM oral AIT is safe with only minor adverse effects in both children and adults when given to treat HDM allergic asthma and rhinitis who are sensitised.[36] We propose to administer HDM allergen to non-sensitised infants and hence the risk of adverse effects is negligible.

No clinical trials have specifically investigated drug interactions, drug misuse and abuse, withdrawal and rebound, effects on ability to drive or operate machinery or impairment of mental ability, or use in pregnant or breastfeeding patients No drug interactions with the HDM SLIT tablet have been identified. Due to the limited systemic absorption and absence of hepatic or renal metabolism of the active ingredient, the potential for drug interactions with the HDM SLIT tablet is considered negligible . No cases of drug misuse or abuse of the HDM SLIT tablet have been reported during the clinical development programme. No significant cases of drug misuse have been reported post marketing. Drug misuse or abuse of the HDM SLIT tablet is not perceived as a risk due to the nature of the active ingredient. There are no indications of untoward effects following discontinuation of AIT. The available clinical data do not suggest a risk of AEs of clinical concern upon treatment re-initiation after treatment interruption. The available post marketing data showed no pattern between the duration of the treatment interruptions and reporting of serious allergic reactions and serious laryngo-pharyngeal reactions. Eosinophilic Esophagitis (EoE) is a chronic, inflammatory condition of the oesophagus which is most prevalent in atopic patients and may be triggered by sensitisation and subsequent exposure to food or aeroallergens. However, events of EoE are generally non serious and can be reversed with treatment interruption and appropriate treatment of the EoE. Based on data from clinical trials and reports from post marketing sources, the identified risks are altogether considered low (0.06%) and manageable and are expected to have a negligible impact on public health. The product information communicates measures to manage the identified risks (for further information on precautions and contraindications consult product labelling).

6.8. OVERDOSE OF IMP

Generally, overdose of the 12 SQ-HDM SLIT-tablet does not constitute a safety concern. Intake of a dose that is higher than or equal to 32 SQ-HDM constitutes a risk for an overdose leading to an adverse reaction in allergic patients. With regards to accidental overdose, this risk is considered negligible since participants are not HDM allergic and reaching 32 SQ-HDM would require taking at least three 12-SQ HDM SLIT-tablets at the same time. The risk of this happening by accident is considered

negligible due the packing of the SLIT-tablets in individual blister units. Accidental overdose is thus most likely to consist of taking two (rather than three) tablets within hours instead of a full 24-hour period apart.

6.9. DOSE INTERRUPTIONS & MODIFICATIONS FOR TOXICITY

There will be no dose modification for toxicity.

Treatment may be discontinued for up to 14 days for the following reasons:

(i) inflammatory conditions in the oral cavity, tooth loss

(ii) bleeding in the oral cavity

(iii) other reasons if deemed necessary by the investigator.

Interruptions should be kept to a minimum. If IMP is interrupted for more than 14 days in a row, the participant should contact the investigator before restarting the treatment. If IMP/placebo treatment is permanently discontinued, the participant is encouraged to continue in the trial for efficacy and safety assessments.

The ICTU should be notified in case of IMP/placebo discontinuation due to an AE.

6.10. STUDY DRUG ADMINISTRATION

The HDM-SLIT/ placebo tablet should be taken with dry fingers from the blister unit immediately after opening the blister and placed under the tongue by the parent/caregiver, where it will disperse. If possible, swallowing should be avoided for approximately 1 minute. Food and beverages should not be taken for 5 minutes after intake of IMP. The daily dose of IMP is 1 HDM-SLIT tablet/placebo, which should preferably be taken in the morning to observe for adverse events.

Precautions in relation to first dosing: When the first dose is administered, the participant will be under medical supervision for at least 60 minutes after the tablet intake. Subsequent dosing will be administered once daily to the participant, by a parent/caregiver, at approximately the same time each day.

6.11. PRE-MEDICATIONS / NON-IMP DETAILS

There are no protocol mandated medications aside from the IMP.

6.12. Permanent Discontinuation of Study Treatment and Withdrawal from Study

(i) Permanent discontinuation of study treatment

Participants may discontinue study treatment for the following reasons:

- The participant's parent/guardian elects to discontinue treatment.
- The Investigator no longer believes treatment is in the best interest of the participant.
- If the child becomes sensitised to HDM **AND** develops clinical allergy/anaphylaxis to the study medication.
- If the investigator considers that a participant's health will be compromised due to adverse events or concomitant illness that develop after entering the study.
- Funder/Sponsor terminated study.
- DMC/TSC terminated study.

The participants will continue to be followed up and attend visits even if treatment has been discontinued (unless consent for further assessment is withdrawn).

(ii) Withdrawal from Study

Withdrawal from the study refers to discontinuation of study treatment and study procedures and can occur for the following reasons:

- The participant dies
- Participant decision
- Investigator's decision
- Loss to follow-up

(iii) Procedures for Withdrawal from Study

Participation completion is defined as completion of the last visit. However, intention to treat analysis will require inclusion of all data available since randomisation until the last visit or contact with the participant. In the event that a participant discontinues study medication, follow-up of the participant will continue in accordance with the protocol visit schedule providing the participant and/or their parent/guardian does not withdraw consent from further visits or from the study completely. Reason for withdrawal must be recorded in the eCRF and medical records. If the participant does not agree for data and samples collected to be retained, the data/samples will be excluded from the analyses. Participants who have discontinued the trial intervention and/or have withdrawn from the trial will not be replaced, as the sample size allows for potential loss to follow-up.

7. PHARMACOVIGILANCE

7.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the trial medication, whether or not considered related to the IMP.

7.2. Adverse Reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions (ARs). The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

7.3. Unexpected Adverse Reaction

An AR, the nature or severity of which is not consistent with the applicable product information as set out in the Reference Safety Information (RSI) (in the investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).
When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the RSI section of the SmPC/IB which occur in a more severe form than anticipated are also considered to be unexpected.
Expectedness assessment will be performed by the Sponsor or person delegated by the Sponsor to assess expectedness. Site PI will be responsible for assessing expectedness.

7.4. Causality

The assignment of causality for adverse events should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigator. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.
In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

Definitions for assessment of causality:

Unrelated:	No evidence of any causal relationship
Unlikely:	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible:	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable:	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite:	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.5. Severity of Adverse Events

Mild:	Awareness of event but easily tolerated
Moderate:	Discomfort enough to cause some interference with usual activity
Severe:	Inability to carry out usual activity

7.6. Adverse Event recording

Collection Period: Adverse events will be collected from the time of randomisation until a participant completes study participation or until 30 days after the participant prematurely discontinues treatment (without withdrawing consent) or is withdrawn from the study.

Collecting Adverse Events: Adverse events may be discovered through any of these methods:

- Observing the participant.
- Interviewing the parent/caregiver during a study telephone or in-person visit using study-specific questionnaires.
- Receiving an unsolicited complaint or contact from the participant.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 7.1, Grading and Attribution of Adverse Events.

Outcome of AEs: The outcome of an AE is assessed by the investigator using the following definitions:

- Recovered: Fully recovered or the condition has returned to baseline
- Recovered with sequelae: As a result of the AE the participant suffered persistent disability/incapacity. If the sequelae meet an SAE criterion, the AE must be reported as an SAE
- Not recovered: The condition has not returned to baseline, however, symptoms may have improved
- Fatal: Event that results in death

- Unknown: The outcome is unknown. This term should only be used when no other definition is possible e.g. the participant is lost to follow-up

Recording Adverse Events: Throughout the study, the investigator will record adverse events and serious adverse events as described previously on the appropriate AE/SAE eCRF regardless of the relationship to study medication or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the participant prematurely discontinues treatment (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

Solicited Adverse Events: All adverse events of special interest will be treated as solicited adverse events and actively sought during the whole trial at regular intervals, through telephone and at visit questionnaires. These include clinically relevant asthma exacerbations, severe oral swelling of the mouth and/or throat, systemic allergic reactions or anaphylaxis, and eosinophilic esophagitis.

Symptoms suggestive of eosinophilic esophagitis (adverse events of special interest) will be actively sought. For eosinophilic esophagitis, parents/caregivers will be asked whether any of the following are present or has occurred since the last clinic visit:

- food impaction requiring medical intervention
- dysphagia/difficulty swallowing requiring the participant to drink large quantities of water to swallow food
- choking or gagging with meals
- persistent (8 weeks or more) dysphagia
- a sensation of food becoming lodged in the throat
- persistent (8 weeks or more) vomiting without evidence of infection
- persistent (8 weeks or more) early satiety
- unexplained weight loss in combination with other gastrointestinal symptoms

If a subject experiences any of the above symptoms as severe or persisting, the investigator must evaluate the subject and consider whether IMP treatment should be interrupted. If the IMP is interrupted and the symptom(s) resolves within 7 days, the diagnosis could be indicative of eosinophilia or another underlying condition and the investigator should consider whether to re-initiate IMP treatment. If the symptoms persist for at least 2 weeks after IMP treatment has been stopped, the investigator should refer the participant to a gastroenterologist to evaluate if there is a diagnosis of EoE or other underlying condition (e.g., abdominal angio-oedema or mast cell activation).

Recurrent AEs: If the same type of AE occurs with the same pattern (e.g. itching in the mouth for 5-10 minutes after intake of IMP) it is considered a recurrent AE. The AE form should be filled in with the start date, approximate daily duration in minutes and the description. Once the AE no longer, the AE form should be completed with a stop date. If the AE then re-appears on a subsequent day, a new AE form should be completed.

7.7. Abnormal Laboratory Test Results

All clinically important abnormal laboratory test results occurring during the study will be recorded as adverse events. The clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the clinical monitor, or until a diagnosis that explains them is made.

7.8. Serious Adverse Events (SAE)

(i) Definition of SAE

An SAE is defined as any event that

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission). *Insert any exceptions or different definitions.*

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a subject, or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

(ii) Definition of a Serious Adverse Reaction (SAR)

A SAR is defined as a SAE that is judged to be related to any dose of study drug administered to the participant.

(iii) Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAR that is NOT consistent with the applicable product information as set out in the Reference Safety Information (RSI) section of the Investigator Brochure (IB) or Summary of Product Characteristics (SPC).

(iv) Reporting of SAEs

Rapid reporting of all SAEs i.e. within 24 hours, occurring during the study must be performed as detailed in the study-specific Safety reporting instructions.
Active monitoring of participants after the end of the trial is not required but if the investigator becomes aware of safety information that appears to be drug related, involving a participant who participated in the study, even after an individual participant has completed the study, this should be reported to the Sponsor.

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Reporting of SAEs and review by the CI will be via the trial data collection system (CRF/eCRF).

Reporting of Serious Adverse Events (SAEs) to Sponsor (or delegate): Site teams will report all serious adverse events, regardless of relationship or expectedness within 24 hours of discovering the event. Further details can be found in the safety reporting manual.

For serious adverse events, all requested information on the AE/SAE eCRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE eCRF will be updated and submitted.

SAEs will be onward reported to the Sponsor within 24 hours of the ICTU trial team becoming aware of the event.

Reporting to IMP supplier (ALK): All SAEs will be reported to ALK via email within 15 calendar days of becoming aware of the event, 7 calendar days for fatal/life-threatening SAEs.

AEs excluded from safety reporting

Certain AEs occur commonly in this study population and will not be considered as unexpected events with potential for expedited safety reporting unless they meet seriousness criteria (SAE) and there is evidence to suggest a causal relationship to the HDM-SLIT. These events will be captured in the study database as study endpoints but will not be reported as Adverse Events:

- Wheeze/asthma and related events such as exacerbation
- Allergic rhinitis
- Atopic dermatitis occurrence and/or exacerbation

(v) Reporting of SUSARs

The sponsor (or delegate) shall report any suspected adverse reaction that is both serious and unexpected. The sponsor shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure;
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug;
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

SUSARs should be notified to the appropriate regulatory authority, the relevant REC and the Sponsor in accordance with regulatory requirements. Onwards reporting to the regulatory authorities has been delegated to ICTU by the University of Southampton.

SUSARs which are fatal or life-threatening will be reported not later than seven days after alerting the sponsor to the reaction. Any additional relevant information will be sent within eight days of the report. A SUSAR which is not fatal or life-threatening will be reported within 15 days of first knowledge by the sponsor. The sponsor will inform all investigators about SUSARs occurring on the study.

Follow up of participants who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised. SUSAR reports should be unblinded prior to submission if required by national regulatory requirements.

Reporting to IMP supplier (ALK): All SUSARs will be reported to ALK via email within 24 hours of becoming aware of the event.

7.9. Developmental Safety Update Reports

Developmental Safety Update Reports (DSUR) will be submitted to the Sponsor and Regulatory Authority in accordance with local / national regulatory requirements.

DSUR reports will be submitted annually via IRAS as the trial was submitted through combined review. There is no requirement in the UK to separately notify the REC. The MHRA will liaise with REC if deemed appropriate. DSURs will also be shared with the IMP manufacturer ALK.

ICTU will include in the annual study report to MHRA all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 7.8).
- Serious and unexpected adverse reaction (see Section 7.8).

7.10. Expedited Safety Reporting / Urgent Safety Measures

Any findings from studies that suggest a significant human risk: The sponsor (or delegate) shall report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or in vitro testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure or package insert or other aspects of the overall conduct of the study. In the UK, this will be reported under the 'Urgent Safety Measure' process.

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 7 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

8. STATISTICAL ANALYSES

8.1. Sample Size and power considerations

Data from large observational birth cohorts show that high-risk infants selected using our inclusion criteria will have an estimated 40% risk of ARW by age 3½ to 4 years. Other studies support our findings that, based on the risk profile, up to 50% of this population is expected to develop asthma.[53-59] Other studies support our findings that, based on the risk profile, up to 50% of this population is expected to develop asthma. We have observed a 67% relative risk reduction (RRR) in ARW (unpublished data from the POC study) and 80% RRR in childhood asthma in our POC study.60 However, we have powered the study on a conservative estimate that is of clinical relevance. Allowing for a 35% rate of ARW in our high-risk infant population, enrolling 185 per arm (total=370) will have 85% power, assuming a RRR of 40% (35% to 21%) with a two-sided Type I error rate of 0.05. We experienced a 5% loss to follow-up at one year in our POC study. Factoring in the extended follow-up in this study to 3 years, we estimate 15% loss to follow-up and thus aim to recruit 434 infants (217 per arm). Sample size calculated using Stata version 17.0 SE using power two proportions command

8.2. Planned recruitment rate

Please refer to Table 5.

8.3. Internal pilot

An internal pilot will take place to evaluate feasibility of trial delivery within the planned timeline and budget, prespecified criteria will be reviewed at 6 months and 12 months after recruitment start. We will use a traffic light system to inform progression from the internal pilot to the main trial. Thresholds are chosen to ensure deliverability of the trial and have been informed by our previous POC study. The initial 6-month analysis will focus on recruitment and retention. This will be overseen by the Trial Steering Committee (TSC) and recommendations regarding trial progress will be provided to the Trial Management Group. Criteria for review include:

1. Number of sites open to recruitment

2. Overall recruitment rate
3. Retention rates

Table 5: 6 months	Red – recommend do not progress to main trial	Amber – explore options to improve trial progress	Green – progress to main trial
# sites open	<4 sites	4 - 7 sites	≥8 sites
Recruitment rate	<60% = <28 participants (<1.2 participants/month/site	60-99.9% = 28 – 71* participants (1.2-1.7 participants/month/site)	100% = ≥72 participants (1.5 participants/month/site)
Retention (100%-withdrawal %)	<85%	85% - 99.9%	100%

*Upper bound allows for 1.7 participants/month/site at 7 sites i.e. target recruitment numbers achieved but at a reduced number of sites.

The later analysis at 12 months will focus on adherence to intervention and follow-up visits (we will also report recruitment to ensure on target to complete within 24 months). This will be overseen by the Data Monitoring Committee (DMC) who will be unblinded to data by treatment arm. Criteria will include:

Table 6: 12 months	Red – recommend do not progress to main trial	Amber – explore options to improve trial progress	Green – progress to main trial
# sites open	<8 sites	8-9 sites	≥10 sites
Recruitment rate	<60% = <115 participants (<1.2 participants/month/site	60-99.9% = 115 – 216* participants (1.2-2) participants/month/site)	100% = 217 participants (1.8 participants/month/site)
Adherence	<70% taking at least 60% of doses	70-99.9% taking at least 60% of doses	100% taking at least 60% of doses
Retention	<85%	85% - 99.9%	100%

*Upper bound allows for 2 participants/month/site at 9 sites i.e. target recruitment numbers achieved but at a reduced number of sites.

The DMC will also be responsible for review of all safety outcomes and ensure that data quality is high and safeguard the scientific credibility of the trial. The above criteria will only be advisory, and the DMC will be at liberty to make their own assessment and recommendation to the TSC.

8.4. Statistical analysis Plan

Participant flow and baseline characteristics

Participant baseline characteristics will be summarised by treatment arm and overall using suitable descriptive statistics. The flow of participants through the trial and trial results will be reported according to CONSORT.

Primary analysis and estimand

The primary analysis will use the intention-to-treat population including all participants who are eligible and undergo randomisation, and participants will be analysed according to the randomised

allocation. The primary estimand will estimate the treatment effect in those randomised to the HDM tablet regardless of the duration of treatment as we want to estimate treatment effect regardless of adherence in the real-world setting (treatment policy estimand). We will compare the proportion of infants who develop ARW by age 3½ to 4 years between arms by means of a generalised linear mixed model. The model will use a binomial distribution, with log link, with treatment arm as the discrete independent variable, adjusted for the minimisation variable site as a random intercept and other minimisation variables as fixed effects.61 We will also adjust for other covariates known to influence the risk of asthma this includes breast feeding for at least 6 months (not exclusive) and parental exposure to smoking/vaping, these will be included as fixed effects. If there are convergence issues with this model we will fit a Poisson regression model with robust standard errors. The intervention effect will be reported as a risk ratio with a 95% confidence interval, the primary hypothesis will be tested with a two-sided 0.05 significance level.[66,67]

Alongside this, in line with CONSORT recommendations to present both an absolute and relative measure of treatment effect we will fit a generalised linear mixed model with a binomial distribution and identity link function and the treatment effect will be reported as a risk difference with corresponding 95% confidence interval and p-values. Covariates will be included as above. If there are convergence issues we will instead fit a Poisson model with robust standard errors

Table 7: Primary estimand

Target population	Infants aged 5-12 months who are at high risk of developing asthma and meet all inclusion criteria and no exclusion criteria
Endpoint	Diagnosis of ARW at age 3½ to 4 years (measured at 3-year follow-up)
Treatment conditions	**Intervention:** HDM-SLIT orodispersible/dissolvable tablets containing *Dermatophagoides pteronyssinus* & *Dermatophagoides farinae*; 50:50, major allergens 1 and 2; total dose 30 µg, (ALK-Abello, Denmark), given sublingually, once daily, for 3 years **Control:** matching placebo
Summary measure	Risk ratio of ARW in the intervention arm relative to the placebo arm adjusted for minimisation variables and other prespecified covariates
Intercurrent events	
Treatment non-adherence	Treatment policy (use ARW outcome regardless of adherence to randomised treatment)
Receipt of rescue medication	Treatment policy (use ARW outcome regardless of whether any rescue medication such as inhaled or oral corticosteroids, inhaled bronchodilator and montelukast was received)

Missing data

Every effort will be taken to minimise missing data. To account for participants who have missing atopic recurrent wheeze we will impute missing outcomes using multiple imputation under the assumption of missing at random (MAR) in the primary analysis model. This assumes that the probability of being missing is not dependent on the values of unobserved data, conditional on the observed values of the variables included in the analysis model. Imputation under MAR using chained equations following the guidance of White et al. will be undertaken.[62]

Sensitivity analysis (to primary)

Multiple imputation makes a missing at random assumption, a sensitivity analysis will therefore be performed to explore a missing not at random assumption using controlled multiple imputation such as a reference based approach.

Supplementary analysis (to primary) (and estimands)

Supplementary estimands are defined to account for intercurrent events. We will use a principal stratum strategy to estimate the treatment effect in those that were able to tolerate treatment and adhered to the HDM tablets with a complier average causal effect (CACE) analysis using a two-stage least squares instrumental variable regression approach.63 A 'complier' will be defined as a parent that self-reported taking the tablets, supported by return of empty packaging, either completely or regularly (>60% of doses per year). We will also estimate the treatment effect in those who reported taking 1- and 2-years of treatment (completely or regularly). We will use a hypothetical strategy to account for receipt of rescue medication (including use of inhaled and oral steroids, inhaled short acting bronchodilator, montelukast) estimating the treatment effect if there had been no rescue medication used using an inverse probability weighting approach.[64]

Secondary outcomes

Analysis of secondary outcomes will follow the principles of the primary analysis.

A key secondary outcome is ARW severity as measured by a nine-level ordinal scale based on the number of allergens and wheeze episodes over three years. A mixed effects ordered logistic regression will be used to estimate the odds of ARW severity with site as a random effect and the same covariates as the primary analysis as fixed effects, using multiple imputation to ensure all randomised participants are included.

For continuous secondary outcomes, the mean difference between treatment groups will be estimated for final outcome measures of the follow-up using a mixed effects linear regression model including both participant and site as random effects and fixed effects for the same variables as the primary analysis with the inclusion of a treatment group by time interaction. The inclusion of measurements over time will allow all participants who contributed at least one post-baseline measurement to be included in the analysis model. No multiple imputation will be used as it is expected that a very high proportion will complete at least one post-baseline measurement.

Binary outcomes including ARW at one and two years, and allergic rhinitis and atopic dermatitis at the end of follow up will be analysed using a generalised linear mixed model with a binomial distribution and log link with site as a random effect and all of the same covariates as the primary analysis as fixed effects, using multiple imputation to ensure all randomised participants are included. To examine allergic sensitisation and HDM sensitisation status over time the proportions by arm will be plotted over time. In addition, a generalised linear mixed model with a binomial distribution and log link including participant and site as a random effect and time as fixed effects, along with covariates from the primary model will be fitted. This will allow us to examine differences over time and compare at each timepoint separately.

We will also re-examine the outcomes of allergic sensitisation to HDM, diagnosis of recurrent wheeze and atopic dermatitis in a time-to framework to examine change over time. Nelson-Aalen estimators will be calculated to plot cumulative probabilities and Cox proportional hazard models will be used as a time-to-event model (or a suitable alternative if assumptions are not met).

All secondary outcome models will include minimisation variables. No adjustment will be used for multiple testing on secondary outcomes, and all will be judged at the 5% significance threshold.

Subgroup analyses

Subgroup analyses will be performed for the following characteristics (as measured at baseline):

- Sex (M/F)
- Ethnicity (White, Black, Asian, mixed race)
- Low level of HDM sensitisation (Y/N)
- Breast feeding (Y/N)
- Exposure to smoking (Y/N)
- Exposure to vaping (Y/N)
- Allergic sensitisation (Y/N)

We will using the same model as the primary analysis with the inclusion of a treatment by covariate interaction. As the study is not powered to detect interaction effects these analyses will only be considered as hypothesis generating.

Harm outcomes

The safety population for the analysis of adverse events will comprise of all participants who received at least one dose of trial medication and analysis will be according to intervention received. Adverse events (AEs) will be recorded through reports from parents and carers during the 6-weekly phone follow-ups. All AEs will be tabulated by arm for the number of events and the number of participants with events at preferred term level. For system organ class level, where numbers permit, we will calculate the incidence rate ratio (IRR) with 95% confidence intervals using negative binomial regression to allow for over dispersion. The models will be adjusted for site as a fixed effect where the number of AEs permit this. Results will be presented in dot and volcano plots to aid assimilation and examine for signals of harm.

A full statistical analysis plan will be prepared.

Mechanistic outcomes

Mechanistic Analysis Plan will be prepared separately

9. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1. Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the 8th version revision of the 1964 Declaration of Helsinki.

9.2. Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 (R3) guidelines).

9.3. Research Ethics Committee (REC) Approval

9.3.1. Initial Approval

Prior to the shipment of IMP/ *Placebo* and the enrolment of participants, the REC must provide written approval of the conduct of the study at named trial locations, the protocol and any modifications, the

Participant Information Sheet and Consent Form, any other written information that will be provided to the participants, any advertisements that will be used and details of any participant compensation.

9.3.2. Approval of Modifications

Substantial modifications to the protocol and aforementioned documents must be submitted to the REC for approval as a modification. Modifications requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained. Minor modifications and Modifications of Important Details will not require REC approval prior to implementation.

Modifications that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Modification not considered substantial such as administrative changes will only be submitted to the regulatory authorities once another substantial Modification must be submitted or together with the end of trial notification unless national legislation requires otherwise.

The trial team, in collaboration with the Sponsor will assess whether a proposed Modification is substantial or non-substantial. For each proposed Modification , a revised version of the protocol will be prepared using tracked changes, a new version number assigned, and the revised document will be reviewed and approved by Protocol Development Group, NIHR and Sponsor prior to submission to the REC and Health Research Authority (HRA). The modified protocol will be sent to participating sites for local approval to be granted and the approved version will be shared with all staff involved in the trial.

9.3.3. End of Trial Notification

The REC will be informed about the end of the trial, within the required timelines.
For safety reporting and regulatory purposes, End of Trial will be when all study visits are complete, all data are captured on the database, and the study database is declared clean and hard-locked.
The end of trial notification will be submitted within 90 days of the end of trial definition being met.
In the event of a premature halt of the trial, the timeframe is 15 days, and the reasons should be clearly explained in the notification.
If the trial is prematurely terminated or suspended, the investigator should promptly inform the participants and ensure appropriate therapy and follow-up.

9.4. Regulatory Authority Approval

The study will be performed in compliance with UK regulatory requirements. Clinical Trial Authorisation from MHRA must be obtained prior to the start of the study. In addition, the Regulatory Authority must approve amendments prior to their implementation (as instructed by the Sponsor), receive SUSAR reports and annual safety updates, and be notified of the end of the trial.
Minor modifications and Modifications of Important Details will not require MHRA approval prior to implementation.

9.5. HRA approval

Health Research Authority (HRA) approval will be obtained prior to starting the study. Each trial location will confirm capacity and capability prior to commencing.

The HRA and all trial locations also need to be notified of substantial modifications to assess whether the modification affects the institutional approval for each trial locations. Minor modifications and Modifications of Important Details will not require HRA approval prior to implementation however trial locations will be notified.

9.6. Non-Compliance and Serious Breaches

The investigators and site staff will conduct the study in accordance with the protocol. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions (if needed) will be developed by the site PI and implemented promptly.

All protocol deviations and protocol violations will be reported via the eCRF/CRF and reviewed by the Chief Investigator and reported to the ICTU Head of QA on a monthly basis. Protocol violations will be reported to the Sponsor.
An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.
A serious breach is defined as:
A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

a. The safety or physical or mental integrity of the UK trial participants; or

b. The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the MHRA and REC within 7 days of becoming aware of the serious breach.

Minor Protocol Deviation - A minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

9.7. Insurance and Indemnity and Sponsor

University of Southampton will act as Sponsor for this study. It has civil liability insurance, which covers this study in the UK.

Delegated responsibilities will be assigned to the NHS trusts taking part in the trial.

9.8. Trial Registration

The study will be registered on the trial database ISRCTN in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

9.9. Informed Consent

The consent process will provide information about the study to a prospective participant's parent/guardian and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the study delegation log will review the consent and answer questions. The prospective participant's parent/guardian will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants' parents/guardians (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language, where parent/guardians comprehension of English is not sufficient. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing and it will be made clear to participants and their parents/guardians that they have the right to ask questions and/or withdraw at any time. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

Participants will be provided with a copy of the signed Participant Information Sheet/Informed Consent Form document. The original Informed Consent Form should be retained with the source documents.

9.10. Contact with General Practitioner

It is the investigator's responsibility to inform the participant's General Practitioner (where applicable) by letter that the participant is taking part in the study provided the participant agrees to this, and information to this effect is included in the Participant Information Sheet and Informed Consent. A copy of the letter should be filed in the Investigator Site File or participant health records.

9.11. Participant Confidentiality

The investigator must ensure that the participant's confidentiality is maintained. On the CRF or other documents submitted to the Sponsors, participants will be identified by a participant ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to participants' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and RECs.

Participants NHS or CHI (Scotland) number and date of birth will be collected with parent's consent to access NHS records for long term outcomes. This information will be stored securely in the EDC OpenClinica, with restricted access to only those where this is required for their role. Source data verification will be completed to ensure accurate collection of this data. Records generated up to 5 years after the participant has completed the trial may be accessed (funding dependant) to determine long term outcomes. This data will be shared by the PAPA trial team only with organisations such as NHS Digital (or subsequent organisations) to fulfil this purpose.

9.12. Data Protection and Participant Confidentiality

Investigators and staff will comply with the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Data will be handled in accordance with GDPR□aligned principles and the confidentiality requirements underpinning ICH GCP E6(R3), including appropriate controls on access, storage and secure transfer of identifiable information.

9.13. End of Trial

For safety reporting and regulatory purposes, End of Trial will be when all study visits are complete, all data are captured on the database and the study database is declared clean and hard-locked.

9.14. Study Documentation and Data Storage

The investigator must retain essential records until notified by the Sponsor, and for at least 25 years after study completion. Participant files and other source data (including copies of protocols, CRFs, original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

10. DATA MANAGEMENT

A Data Management Plan (DMP) summarising how data are handled from the first point of data entry through to final analysis, including data querying and cleaning procedures will be prepared during the study set-up phase.

10.1. Source Data

Source documents and source data are considered to be the original documentation where participant information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial. Source data identifiers will be completed for each participating site to document the type of source data in each case, these may be paper or electronic records as applicable in each case.

The site investigators and site staff will make all source data available to the University of Southampton (Sponsor) and their representatives, to the ICTU team as well as to relevant health authorities (MHRA). Authorised representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

10.2. Language

CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by participants must use vocabulary that is clearly understood and be in the language appropriate for the study site. Materials will be translated where appropriate.

10.3. Database

Trial data will be collected on an electronic case report form (eCRF). The principal means of data collection from participant visits will be Electronic Data Capture (EDC) via the internet using the OpenClinica database. Data is entered into the EDC system by trained and delegated site personnel. All data recorded in the eCRF will be signed off by the Investigator or his/her appropriate designee. All changes made following initial submission of data will have an electronic audit trail with a date. Specific instructions and further details will be outlined in the study specific eCRF manual.

10.4. Data Collection

Data to be collected and details of procedures for eCRF completion will be provided in the study specific eCRF manual.

10.5. Archiving

All trial documentation, including that held at trial locations and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study.

11. STUDY MANAGEMENT STRUCTURE

The trial will be sponsored by UoS. Professor Arshad, at UoS is the chief investigator. The Imperial Clinical Trials Unit (ICTU) will be involved with all aspects of the trial and responsible for oversight of operational aspects, trial design and statistics and data management, as well as Quality Assurance of these aspects.

11.1. Trial Steering Committee

A trial steering committee (TSC), consisting of an independent chair, independent experts including a statistician and at least two PPI representatives will be set up prior to the start of the study. The TSC will meet at the start of the project to agree their Terms of Reference and review the protocol. Thereafter they will meet approximately every six months. Details of membership, responsibilities and frequency of meetings will be defined in the TSC Charter. The TSC will be responsible for overseeing progress and conduct of the trial including the internal pilot.

11.2. Trial Management Group

A Trial Management Group (TMG) consisting of the co-chief investigators, co-applicants, senior statistician, operations manager, trial manager, collaborators and public representatives, will also be set up at the start of the grant with responsibility for day-to-day management of the study. The TMG will be chaired by Prof Arshad (chief investigator) and (in his absence) Prof. Graham Roberts (Co-chief investigator). TMG will meet regularly during the set-up phase of the trial and every three months thereafter.

11.3. Data Monitoring Committee

A fully independent Data Monitoring Committee (DMC) will be set up to monitor progress, participant safety, data quality and any ethical issues involved in this trial. The DMC will review trial progress, safety data and data quality / completeness. A separate DMC Charter based on the DAMOCLES charter template will be drawn up defining their responsibilities, frequency of meetings and reporting to the TSC.[65]

The statistician will analyse interim data for DMC meetings and act as data manager, in raising and resolving data queries with participating sites, via the ICTU Trial Manager. Closed DMC reports will include recruitment, randomisation balance and minimisation effectiveness, baseline characteristics, withdrawals, compliance, concomitant medications, efficacy, mediators, and adverse events. Open DMC and TSC reports will be provided without outcome or arm information.

Ad hoc DMC Reviews: In addition to the pre-scheduled data reviews and planned safety monitoring, the DMC may be called upon for ad hoc reviews. The DMC will review any event that potentially impacts safety at the request of the Chief Investigator or Sponsor (University of Southampton or delegate).

11.4. Early Discontinuation of the Study

The study may be prematurely terminated for the following reasons:

- If any of the listed events occurs, administration of trial medication will be temporarily discontinued until a thorough review of accumulated safety data is undertaken by DMC, the investigators, and/or ALK's representative. Trial termination criteria will be reviewed constantly by the investigators, the TSC, and the DMC.
  - Treatment- related death of an individual.
  - A treatment-related serious anaphylactic event in at least 2 participants.
  - Event/s which in the opinion of the DMC contraindicates further dosing of additional participants.
- Sponsor's decision.
- Regulatory Authority (MHRA) or Ethics Committee's decision.
- Funder's decision

The trial investigators will remain blinded as to the treatment allocation of the trial participant(s).

An internal pilot will take place after 6 and 12 months after recruitment has started. It will use traffic light system: if the red criteria are met there will be a discussion with the Trial Steering Committee about stopping the trial.

The DMC Charter will define procedures for early termination of the study due to safety, should this be required. In case of early discontinuation of the study, the follow-up visit assessments should be performed for each participant, if permitted and as far as possible.

In the event of resumption of the trial, we will first seek approvals from the regulatory bodies.

11.5. Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of 'low', 'medium' or 'high' to the trial. Risk assessment will be carried out by the ICTU Head of QA (or delegate) in collaboration with the Study Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study. The risk assessment will follow a proportionate and flexible model consistent with the amended UK CTR and ICH GCP E6 (R3).

11.6. Monitoring

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 (R3) guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

Monitoring procedures and requirements will be documented in a Monitoring Plan, developed in accordance with the risk assessment.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

11.7. Quality Control and Quality Assurance

Quality Control will be performed according to ICTU/Sponsor internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be participant to inspection and audit by regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research.

11.8. Peer review

The study has been extensively peer reviewed during the process of grant funding applications by both internal (University of Southampton) and external (NIHR) reviewers.

11.9. Public Involvement

Development of application

Patient and public involvement (PPI) has been at the centre of the trial design, starting in 2010 with the development of a proof-of-concept study. Multiple meetings with mothers of small children with allergies and asthma, including parents from Pakistani, Afghani and Indian backgrounds living in areas of Southampton with high socioeconomic deprivation, have been held. These conversations have shaped trial procedures, tested the feasibility of IMP administration, decided frequency of assessments and identified ideas to support adherence and recruitment. Multiple changes were made to the trial design as a result of PPI, including introduction of 6 weekly visits in the first year for additional reassurance and support for parents, and a new recruitment strategy. Parents were also clear that the opportunity to prevent likelihood of asthma developing in their children would be a strong motivation to take part in this trial.

Plans for involvement of people with lived experience

Our team is committed to meaningful PPI throughout this study. Our activities will focus on refining the study design, to ensure it is accessible and inclusive for families taking part, and supporting recruitment to, retention in and wider engagement with, the trial.

We will have 2 PPI coordinators, to ensure involvement across the hospital sites areas in South East, North East and North West England, East and West Midlands and Scotland. These leads will be based in key partners - Asthma + Lung UK and BEATAsthma. We will also work with local services including maternity units, breast feeding groups, infant nutrition support, and community dietitians.

We will build a core PPI group of parents and carers who have young children and family history of asthma and allergies. They will receive training and support to use their experiences to support the trial, with likely activities including:

- Assessing the acceptability and usability of treatment regimen and adherence reporting
- Reviewing public-facing materials, including Participant Information Sheet, to ensure they are clear and appropriate
- Developing effective plans to reach and engage potential trial participants
- Discussing how to address any recruitment barriers that may arise
- Supporting retention in the trial – shaping regular communications with families taking part and suggesting solutions to support adherence
- Communicating the results to members of the public and supporting implementation of intervention, if the trial has a positive outcome

We will also carry out additional involvement and engagement activities – such as workshops, focus groups and surveys – with underserved populations that are traditionally excluded from clinical trials and disproportionately affected by poor outcomes. This could include families with multiple allergies, from minority ethnic backgrounds, living in deprived areas and/or living with communication/learning needs.

Patient engagement and dissemination

An effective communication and dissemination strategy will be developed with the PPI group and partners, including Asthma + Lung UK, Natasha Allergy Research Foundation, BeatAsthma, British Society of Allergy and Clinical Immunology and Centre for Applied Respiratory Research Innovation and Impact (CARRii).

We will set up a study website that will include information on participation, progress, and results. This may include videos from trial team providing updates and parents of children with asthma explaining why they believe this trial is beneficial. At the end of the trial, we will also produce newsletter with the results that will be disseminated digitally with the option to opt out. Updates regarding recruitment, progress and results will also be posted on existing social media platforms, such as Asthma +Lung UK and Beat Asthma.

Timely feedback of research progress and findings to involve healthcare professionals and service users:

- Summary of trial progress followed by summary findings on the trial website.
- Regular study newsletters to all participating sites, followed by summary findings.
- Plain English summary of findings sent to all participants with the option to opt out and posted on Asthma + Lung UK website.
- YouTube explanation of findings, with links from Asthma + Lung UK site; versions in other languages for minority service users.
- We will organise a series of stakeholder meetings to involve patient, healthcare professional and health commissioning groups.

11.10. Publication and Dissemination policy

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study in connection with the development of the IMP/device and, therefore, may disclose it as required to other clinical investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

Any request by trial location investigators or other collaborators to access the study dataset must be formally reviewed by the TSC.

The results may be published or presented by the investigator(s), but the Funder and collaborator (ALK-Abello) will be given the opportunity to review and comment on any such results for up to 1 month before any presentations or publications are produced.

A Report summarising the study results will be prepared and submitted to the REC within 12 months of the end of study.

In line with the amended UK clinical trials regulations, trial results will be submitted to a public registry and provided to participants in an accessible format within 12 months of trial completion, unless a justified exemption applies.

Specifically;

- The trial will be registered with a clinical trial database
- The protocol and a methodology paper as well as the study results will be published in in peer-reviewed high impact factor journals
- Incorporation of findings in systematic reviews/meta-analyses of prevention of childhood wheeze/asthma (e.g. Cochrane)
- Results will be presented at national and international scientific meetings to both paediatric and adult allergy and general physicians
- We will work with the NIHR Dissemination Centre to promote wide dissemination of the study results to the general public. The trial PPIE group, Beat Asthma and Asthma+Lung UK would play a leading role with their experience of advocacy and interacting with social media and the press.

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13. REVISION HISTORY

Version	Date	Summary of changes
1.1	14/08/2025	First version
1.2	31/10/2025	Oscillometry only mandatory for sites that have equipment

1.3	18/12/2025	1) Extended randomisation window from 24 hours to 48 hours 2) Added contact details for new Trial Monitor 3) Minor updates e.g. typographical errors and clarifications
2.0	22/12/2025	1) Screening bloods removed 2) "Hospital clinics" recruitment strategy broadened to "secondary care"
2.1	24/03/2026	1)Trial Monitor updated 2)Extended randomisation window from 48 hours to 72 hours 3)Clarified that GP letters will be filed in ISF or participant health records 4)Clarified post-baseline visit monitoring 5)Clarified consent can be taken by trained healthcare professionals if delegated by the PI

SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory, on behalf of the Protocol Development Group, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Preventing childhood Asthma using Prophylactic house dust mite Allergen immunotherapy

Protocol Number: 89828

Signed: _____

Prof Hasan Arshad
Chief Investigator

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Preventing childhood Asthma using Prophylactic house dust mite Allergen immunotherapy

Protocol Number: 89828

Signed: _____

Linda Hammond
Head of Research Ethics and Governance
University of Southampton

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Preventing childhood Asthma using Prophylactic house dust mite Allergen immunotherapy

Protocol Number: 89828

Signed: _____

Dr Rachel Phillips
Senior Statistician
Imperial College London

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her trial location according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Preventing childhood Asthma using Prophylactic house dust mite Allergen immunotherapy

Protocol Number: 89828

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____