Circassia Ltd

Clinical Study Protocol

Protocol Identifier: TH005

A Double-Blind, Randomised, Placebo-Controlled, Multi-Centre Field Study to Assess the Efficacy and Safety of HDM-SPIRE in Subjects with a History of House Dust Mite-Induced Rhinoconjunctivitis

PROTOCOL IDENTIFIER: TH005

Version: FINAL 4.0 (incorporating Protocol Amendment 3 and Replacing Protocol Version 3.0 dated 20 Aug 2014)

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EudraCT Number: 2014-001662-94

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This study will be conducted in compliance with:

- **This protocol**
- **ICH E6 GCP guidelines**
- **The applicable regulatory requirement(s)**
- **The principles of the Declaration of Helsinki**

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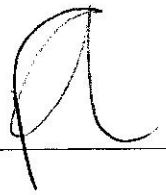

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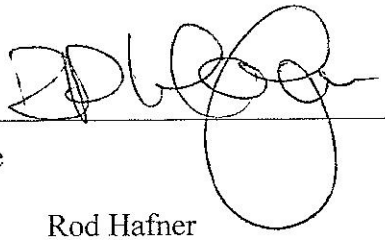

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I agree to conduct this study in accordance with:

- **This protocol**
- **ICH E6 GCP guidelines**
- **The applicable regulatory requirement(s)**
- **The principles of the Declaration of Helsinki**

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PROTOCOL SYNOPSIS

Protocol Identifier	TH005
Study Title	A Double-Blind, Randomised, Placebo-Controlled, Multi-Centre Field Study to Assess the Efficacy and Safety of HDM-SPIRE in Subjects with a History of House Dust Mite-Induced Rhinoconjunctivitis
Protocol Version	**FINAL 4.0**
Sponsor	Circassia Ltd
Phase	II
Indication	House dust mite (HDM)-induced rhinoconjunctivitis in subjects with clinically relevant symptoms.
Objectives	**Primary Objective:** • To evaluate the efficacy of HDM Synthetic Peptide Immuno-Regulatory Epitopes (HDM-SPIRE) in the reduction of symptoms and the use of allergy rescue medication associated with HDM allergy in subjects with clinically relevant symptoms. **Secondary Objectives:** • To evaluate the safety and tolerability of HDM-SPIRE. • To evaluate the effect of HDM-SPIRE on rhinoconjunctivitis specific quality of life. • To evaluate the effect of HDM-SPIRE on sleep quality.
Study Design	The study will be a randomised, double-blind, placebo-controlled, parallel group, multi-centre field assessment of 3 dose regimens of HDM-SPIRE administered at 4 weekly intervals for 28 weeks. Subjects will attend the investigative site for screening and administration of study medication and for periodic assessments of safety and efficacy. Subjects will also complete an electronic diary (eDiary) during four 3-week periods. These diaries will capture the primary efficacy variable data (symptom scores and medication use) as well as other patient reported data.
Sample Size	A total of approximately 660 subjects will be randomised into the study, with approximately 165 subjects in each of the 3 HDM-SPIRE treatment groups and 165 in the placebo group. A 10% drop-out rate is assumed with the expectation that ~150 subjects per group will complete the study. Randomisation will be stratified according to severity of rhinoconjunctivitis symptoms at baseline and the presence of asthma.
Study Population	Subjects aged 18-70 years with a documented history of moderate to severe HDM-induced rhinoconjunctivitis (without asthma or with controlled Step 1 or Step 2 asthma according to the Global Initiative for Asthma (GINA) Guidance).
Inclusion/Exclusion Criteria	**Inclusion Criteria** 1. Male or female, aged 18-70 years. 2. A reliable history consistent with moderate to severe rhinoconjunctivitis (sneezing, rhinorrhoea, itchy nose, nasal blockage and/or itchy eyes, red eyes, watering eyes and/or itchy ear/palate) on exposure to HDM for at least 1 year and which has required symptomatic treatment on at least one occasion during the last year. 3. Mean Total Rhinoconjunctivitis Symptom Score (TRSS) ≥10 from 4 nasal symptoms and 4 non-nasal symptoms over a consecutive 7 day period before

	the Screening Visit 1B/C. 4. Either *Dermatophagoides pteronyssinus* (Der p) or *Dermatophagoides farinae* (Der f) specific Immunoglobulin E (IgE) ≥0.35 kU/L measured by ImmunoCAP®. 5. Positive skin prick test (preferably using the ALK-Abello Allergen Extract test) to either Der p or Der f with a wheal diameter at least 5 mm (average of longest and orthogonal) larger than that produced by the negative control. The negative control must be <2 mm for the test to be valid. 6. Provide written informed consent. 7. Willing and able to comply with the study requirements. 8. If female and of childbearing potential, must practice a form of contraception with a failure rate of <1% when used correctly and produce a negative urine pregnancy test at the Screening Visit 1B/C. **Additional Inclusion Criteria at end of the Baseline Evaluation (BAE) Period** 9. Mean TRSS ≥12 from 4 nasal symptoms and 4 non-nasal symptoms during the BAE period (3 week period before randomisation). 10. Completed the eDiary during the BAE on at least 16 days (>75% of occasions) **Exclusion Criteria** 1. Diagnosis of asthma requiring Global Initiative for Asthma (GINA) Step 3 (www.ginasthma.org)or higher treatment. 2. If asthmatic, experienced a deterioration of asthma that resulted in emergency treatment or hospitalisation in the 12 months before randomisation, or experienced a life-threatening asthma attack (e.g. one requiring intubation and mechanical ventilation) at any time in the past. 3. Used any oral or parenteral corticosteroid at any time within 1 month prior to Screening Visit 1B/C. 4. Asthma requiring high-dose inhaled corticosteroids (ICS) or anti-IgE therapy within 6 months prior to Screening Visit 1B/C. 5. Forced expiratory volume in 1 second (FEV_1) <80% of predicted, or other evidence of partly controlled or uncontrolled asthma. 6. Clinically significant confounding symptoms of allergy to relevant local seasonal allergens (e.g. ragweed, mugwort, tree, grass or mould) and cannot complete the BAE and the final post-administration collection (PAC) period at 50-52 weeks (PAC3) outside the respective allergy seasons. 7. IgE ≥0.35 kU/L to other perennial allergens (e.g. animal dander, cockroach, mould) which cannot be avoided during the study or where sampling for these allergens demonstrates significant levels within the subject's home from dust and/or vacuum cleaner samples, analysed using Indoor biotechnologies Allergen Analysis Service. 8. Intends to be away for 7 days or more during the final PAC period at 50-52 weeks (PAC3), or whose lifestyle means that there is a high likelihood of them being away from home for more than 7 days during the PAC3 period. 9. Received an immunosuppressive treatment within 3 months prior to Visit 1B/C (except steroids for allergic and asthma symptoms). 10. Previous immunotherapy treatment with any HDM allergen product for more than 1 month within 5 years prior to screening.

	11. Receiving ongoing treatment with any specific immunotherapy at screening. 12. Administration of epinephrine is contraindicated (e.g. subjects with acute or chronic symptomatic coronary heart disease or severe hypertension). 13. Use of beta-blockers, alpha-adrenoceptor blockers or monoamine oxidase inhibitors within 14 days before the Screening Visit 1B/C. 14. History of significant recurrent acute sinusitis, defined as 2 episodes per year for the last 2 years, all of which required antibiotic treatment, or a history of chronic sinusitis, defined as sinus symptoms lasting greater than 12 weeks that include 2 or more major factors or 1 major factor and 2 minor factors. Major factors are defined as facial pain or pressure, nasal obstruction or blockage, nasal discharge or purulence or discoloured postnasal discharge, purulence in nasal cavity, or impaired or loss of smell. Minor factors are defined as headache, fever, halitosis, fatigue, dental pain, cough, and ear pain, pressure, or fullness. 15. Females who are pregnant, lactating or planning to become pregnant, or donate ova for *in vitro* fertilisation during the study period or within 30 days following the study period. Female subjects unwilling to employ appropriate contraceptive measures to ensure that pregnancy will not occur either during or for 30 days following the completion of study period. 16. Significant history of alcohol or drug abuse. 17. Previously been treated in this or another HDM-SPIRE (ToleroMune-HDM) study. 18. Any history of severe drug allergy, severe angioedema or anaphylactic reaction. 19. Received treatment with an investigational drug within 30 days prior to the study. 20. Are unable to communicate or to understand the requirements of the study, or exhibit any psychiatric disorder, which would impair communication between the subject and the Investigator thereby interfering with the informed consent procedure or the gathering of study data. 21. History or findings on physical examination of any significant disease or disorder (e.g. cardiovascular, pulmonary, gastrointestinal, liver, renal, neurological, immunopathological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment) which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, influence the results of the study or the subject's ability to participate in the study. 22. Dependent on the Investigator/site either for employment or education or are first degree relatives or partners of the Investigator/study staff. 23. Institutionalised because of a legal or regulatory order. 24. Active tuberculosis, auto-immune disorders, vaccination within 2 weeks before start of immunotherapy as well as subjects with hypersensitivity to excipients of HDM-SPIRE. **Additional Exclusion Criteria at end of BAE** 25. Used any oral or parenteral corticosteroid during the BAE period.
Investigational Product	HDM-SPIRE
Route of Administration	Intradermal injection (100 µL)

Treatment Regimen(s)	• 8 x placebo 4 weeks apart • 4 x 12 nmol HDM-SPIRE followed by 4 x placebo 4 weeks apart • 4 x 12 nmol HDM-SPIRE 4 weeks apart followed by a second course of 4 x 12 nmol HDM-SPIRE 4 weeks apart • 4 x 20 nmol HDM-SPIRE followed by 4 x placebo 4 weeks apart
Efficacy Parameters	The following efficacy parameters will be measured in the study: • Combined Score [CS] (TRSS/8 plus Rescue Medication Score [RMS]) • Rhinoconjunctivitis symptom scores (4 point categorical scale and visual analogue scale) • RMS • Nasal and non-nasal components of TRSS • Number of days subjects have no moderate or severe rhinoconjunctivitis symptoms score (RSS) symptoms without rescue medication usage • Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) • Asthma Control Test (ACT) in subjects with asthma • Home environment (exposure to allergen) • Pittsburgh Sleep Quality Index (PSQI) • Clinical Global Impression of Change in Rhinoconjunctivitis Symptoms
Safety Parameters	The safety and tolerability of HDM-SPIRE will be assessed by recording of: • Adverse Events (AEs) • Physical examination • Vital signs • Laboratory values (haematology, serum biochemistry, urine tests) • FEV_1 • Local reactions at the injection site
Pharmacokinetic Parameters	None
Statistical Analysis	A detailed Statistical Analysis Plan (including dictionaries for coding and software used) will be approved by the Sponsor prior to unblinding the study. If not otherwise specified, statistical significance is defined as $p<0.05$ and is 2-tailed when appropriate. Data will be summarised with respect to demographic and baseline characteristics, efficacy variables and safety variables. Summary statistics will include the mean, N, standard deviation, median, minimum and maximum values for continuous variables and frequencies and percentages for categorical variables. The primary efficacy variable will be the CS. This is derived from symptom scores and medication use recorded by subjects in an eDiary diary over a 3-week period on 4 occasions during the study. The primary endpoint for this study is the mean daily CS during the PAC3 period in HDM-SPIRE treated subjects compared with mean daily CS during the PAC3 in placebo treated subjects. The primary analysis will be the comparison between the HDM-SPIRE treatment groups and placebo for the Intent-to-Treat (ITT) population using Mixed Model Repeated Measurement analysis for the PAC1, PAC2 and PAC3 mean CS assessments per subject. The model will include treatment, period and pooled centre as main effects, gender, asthma status and Baseline Allergy Evaluation CS as covariate and treatment by period interaction. An unstructured covariance matrix will be used to assess within-subject dependence of the 3 observations of mean CS. A point estimate of the adjusted mean and two-sided 95% confidence interval for the

	difference in adjusted means between the active treatment groups and placebo will be calculated, with the treatment contrast corresponding to the mean CS of the PAC3 period. A hierarchical (step-down) approach will be used to control the overall type 1 error rate at 5%. Other endpoints will be analysed appropriately. Supportive analysis will include non-parametric methods, as appropriate. Safety data will be analysed descriptively. The primary safety endpoint will be a comparison of the number of adverse events, and subjects with adverse events, in the HDM-SPIRE groups compared to placebo.
Study Sites	To be determined.
Planned Study Dates **Start of clinical phase** **End of clinical phase**	 Q4 2014 Q4 2016
Duration of the Study	The duration of the study for each subject will be approximately 62 weeks.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ACT	Asthma Control Test
ANCOVA	Analysis of Covariance
ASS	Asthma Symptom Score
BAE	Baseline Allergy Evaluation
CRO	Clinical Research Organisation
CS	Combined Score
Der f	*Dermatophagoides farinae* allergen
Der p	*Dermatophagoides pteronyssinus* allergen
DSMC	Data Safety Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eDiary	Electronic Diary
EEC	Environmental Exposure Chamber
EU	Europe
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
FOCBP	Female of Child-bearing Potential
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HDM	House dust mite
HDM-SPIRE	House Dust Mite-SPIRE
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IRB	Institutional Review Board
IRT	Interactive response technology
ISO	International Standards Organisation
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measurements
PAC	Post-Administration Collection
pDiary	Paper Diary
PP	Per Protocol
PSQI	Pittsburgh Sleep Quality Index
QoL	Quality-of-Life
RMS	Rescue Medication Score
RQLQ	Rhinoconjunctivitis Quality-of-Life Questionnaire
RSS	Rhinoconjunctivitis symptom scores
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
SPIRE	Synthetic Peptide Immuno-Regulatory Epitopes
SUSAR	Suspected Unexpected Serious Adverse Reaction
TRSS	Total Rhinoconjunctivitis Symptom Score
UK	United Kingdom
USA	United States
VAS	Visual Analogue Scale
WBC	White Blood Cell
WFI	Water for Injection

1.0 INTRODUCTION

1.1 Allergy to House Dust Mites

House Dust Mites (HDM) are small translucent organisms belonging to the Arachnid class. They are found globally in mattresses or pillows of beds, sofas and carpets where they can reach a constant source of food (human skin scales) and where humidity is high enough to permit their survival. Throughout their lifetime of approximately 3 months, HDM produce around 2000 faecal pellets, each containing digestive enzymes and other proteins to which some people are allergic. The allergens found in the faecal pellets play a major part in the development of allergic asthma, rhinoconjunctivitis and eczema. There are two predominant 'allergenic' species of HDM, *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f) with *Euroglyphus maynei* also being a recognised indoor dust mite. The major allergenic proteins from these two species are very similar and there is a high degree of cross-reactivity of Immunoglobulin E (IgE) to proteins from both species.

Clinical manifestations of HDM allergy include rhinoconjunctivitis, asthma and eczema. Allergic rhinitis affects between 10% and 30% of all adults and up to 40% of children, 400 million people in the world. The Centers for Disease Control and Prevention report that in the United States of America, 30 to 60 million individuals are affected annually. In Europe, the European Community Respiratory Health Survey established the prevalence of allergic rhinitis as being from 4% to 32%. Epidemiological studies show that the prevalence of allergic rhinitis is increasing worldwide (World Allergy Organization White Book. 2011). In the third National Health and Nutrition Examination Surveys, 54.3% of the US population had positive skin prick test responses to one or more allergens; the prevalence for HDM was 27.4% (Arbes 2005). In a study on inner city children with asthma, aged from 5 to 11 years in the US, 62% of children had a positive skin prick test to HDM. This was as high as 84% in Dallas and 78% in Seattle (Gruchalla 2005). A study of 6 to 11 year olds in the UK showed that 37% were atopic and 68% of these had a positive HDM skin prick test (Linehan 2006). In Europe, the prevalence of HDM allergy varies according to geographical region but an increase in the prevalence of sensitisation to HDM is occurring across Europe correlating with the increase in allergic diseases.

The management of HDM-induced rhinoconjunctivitis, asthma and eczema includes allergen avoidance and medication. However, it can be difficult to avoid indoor allergens and there is no medication available that provides a definitive treatment for the symptoms of rhinoconjunctivitis, asthma or eczema.

1.2 House Dust Mite-SPIRE

HDM Synthetic Peptide Immuno-Regulatory Epitopes (HDM-SPIRE) is being developed for the treatment of HDM allergy. It has been designed on the basis of the selection of a set of seven peptides that on the one hand interact with T cells to induce tolerance but, on the other, are too short to cross-link IgE on mast cells and basophils, thereby greatly reducing the unwanted side effects of traditional immunotherapy using whole allergen extracts.

HDM-SPIRE has been investigated in two clinical trials, both conducted in Canada. These studies have recruited about 200 subjects (more than 150 exposed to relevant active doses) in total. A dose escalation study (Circassia TH001) evaluated 4 administrations of HDM-SPIRE (0.03-12 nmol) 4 weeks apart and demonstrated that all doses up to and including 12 nmol were well tolerated with no safety concerns identified. A second study (Circassia TH002), involving exposure to HDM allergen in an Environmental Exposure Chamber (EEC), found that a unit dose of 12 nmol HDM-SPIRE was effective in treating rhinoconjunctivitis symptoms and appeared to be more effective than lower doses (3 or 6 nmol unit doses). The study evaluated both 4 and 11 administration regimens of the 12 nmol unit dose and whereas the 4 administration regimen was significantly more effective than placebo, the 11 administration regimen did not appear to be (Table 1). *Post-hoc* analyses suggested that the lack of effect with 11 administrations may have been due to differential responses according to symptom severity at baseline, together with greater than expected data variability, and that while 11 administrations does not have any incremental benefit compared with four administrations, it also does not appear to have any detrimental effect.

All doses and regimens evaluated in this study were well tolerated and no safety concerns were raised.

Table 1 Study TH002: Summary of the Primary Efficacy Endpoint Analysis (ITT population)

						Difference between Active and Placebo		
Population	**n**	**Mean**	**SD**	**Median**	**LS Means**	**LS Means**	**95% CI**	**p-value**
Baseline TRSS								
Placebo	31	15.46	3.80	16.36				
HDM-SPIRE 4 x 12 nmol	33	16.21	5.03	15.64				
HDM-SPIRE 11 x 12 nmol	33	16.39	4.31	15.21				
HDM-SPIRE 11 x 3 nmol	15	15.47	3.67	15.29				
HDM-SPIRE 11 x 6 nmol	16	15.97	3.55	16.71				
Change from Baseline to EEC3 Challenge at 49-50 weeks								
Placebo	31	-3.04	4.53	-3.21	-2.969			
HDM-SPIRE 4 x 12 nmol	33	-5.82	4.37	-5.43	-5.879	-2.910	-5.396, -0.424	0.0223
HDM-SPIRE 11 x 12 nmol	33	-3.30	5.96	-2.86	-3.282	-0.313	-2.792, 2.167	0.8029
HDM-SPIRE 11 x 3 nmol	15	-3.17	5.92	-1.00	-3.656	-0.342	-3.569, 2.885	0.8328
HDM-SPIRE 11 x 6 nmol	16	-2.92	5.80	-2.61	-2.723	0.592	-2.593, 3.777	0.7112

Baseline is defined as the average of symptom scores at 1-4 hours on Days 2-3 at Baseline Challenge.
Environmental Exposure Chamber 3 (EEC3) Challenge is defined as the average of symptom scores at 1-4 h on Days 2-3 of EEC3 Challenge at 49-50 weeks.
SD – standard deviation; TRSS – Total Rhinoconjunctivitis Symptom Scores
Least Square Means (LSMeans), 95% confidence intervals (CI) and p-values are based on analysis of covariance (ANCOVA) with change from baseline as dependent variable, treatment as fixed effect and baseline and responder as covariate. P-values are from two-sided test at 5 %-level.
Note: Two separate ANCOVAs were performed, one for Placebo, 4 x 12 nmol and 11 x 12 nmol and another for Placebo, 11 x 3 nmol and 11 x 6 nmol.
Source: Table 10 in clinical study report TH002

As neither of the completed studies included subjects with asthma, a study is currently underway to evaluate the tolerability of HDM-SPIRE in subjects with Global Initiative for

Asthma (GINA) Step 1 or GINA Step 2 controlled asthma (Circassia TH004) and the results are expected to be available for evaluation prior to the start of dosing in this present study.

Further information on the safety and efficacy findings from the completed clinical studies, as well as a comprehensive summary of the non-clinical safety and biology data, may be found in the Investigator's Brochure.

1.3 Justification for Key Elements of the Study Design

1.3.1 Dose Selection

Three active dose regimes will be evaluated in this study. The doses have been selected on the basis of data from Study TH002 (see Section 1.2). In this study a unit dose of 12 nmol was found to be more effective than unit doses of 3 and 6 nmol whilst being equally well tolerated with no safety concerns. However, the data on the 12 nmol unit dose was not unequivocal in that subjects who received 4 administrations responded well, as did subjects in Phase 1 of the study who received 11 administrations of this dose. However, subjects in Phase 2 of the study who received 11 administrations of 12 nmol did not respond better than subjects who received placebo. *Post-hoc* analyses suggested that this lack of effect may have been due to differential responses according to symptom severity at baseline, together with greater than expected data variability, however it was not possible to refute conclusively the hypothesis that additional doses (over and above 4 doses) negated the beneficial effects of the 4 dose regimen.

The highest unit dose of HDM-SPIRE evaluated in any study is 12 nmol and in Study TH002 a regimen of four administrations of this dose was found to be effective. It is not known whether higher unit doses will be more effective and/or safe and well tolerated.

The rationale for each dose regimen of HDM-SPIRE in the TH005 study is, therefore, as follows:

Dose Group	Dose Regimen	Rationale
1	8 x placebo 4 weeks apart	Control group
2	4 x 12 nmol HDM-SPIRE followed by 4 x placebo 4 weeks apart	To confirm the efficacy of this dosing regimen that was observed in study TH002
3	4 x 12 nmol HDM-SPIRE 4 weeks apart followed by a second course of 4 x 12 nmol HDM-SPIRE 4 weeks apart	To determine whether a second course of 4 doses of HDM-SPIRE negates the efficacy of the first course, and To determine whether two courses of HDM-SPIRE are more effective than one course

4	4 x 20 nmol HDM-SPIRE followed by 4 x placebo 4 weeks apart	To determine whether a higher (than 12 nmol) unit dose has greater efficacy and equivalent safety/tolerability

1.3.2 Combined Score, components of Total Rhinoconjunctivitis Symptom Score and weighting of TRSS and Rescue Medication Score

The primary efficacy variable in this study will be the Combined Score (CS) which is derived by combining the total rhinoconjunctivitis symptom score (TRSS) and the rescue medication score (RMS). Eight symptoms are defined in the TRSS, 4 nasal symptoms: runny nose, sneezing, blocked nose, and itchy nose and 4 non-nasal symptoms: itchy eyes, watery eyes, red eyes and itchy ear/palate. Each TRSS symptom and RMS score will be rated in severity (0-3) as described in Section 6.2.1.2.1 and the TRSS will be divided by the number of symptoms (8) to provide an average score per symptom of 0-3. The RMS score is not additive and therefore the maximum RMS is 3 and the maximum CS is 6.

The primary efficacy endpoint will be a comparison of the CS during the Post Administration Collection (PAC) Period 3 (PAC3) in the HDM-SPIRE treatment groups compared with the mean CS in the placebo group during PAC3 (CS = TRSS [0-24]/8 + Rescue Medication Score (RMS) [0-3]).

Relevant regulatory guidance identifies that the scoring of rescue medications is related to the approximated relief of symptoms, as well as magnitude and duration of effect and to the kind of symptoms affected, and that the primary efficacy endpoint should reflect both symptom scores and rescue medication use (CHMP/EWP/18504/2006). A categorical scoring system consistent with ARIA Guidelines (2010) and published by Didier et al (Didier 2009) is included in this protocol. The use of rescue medications will be scored as detailed in Section 6.2.1.2.1.

The proposed equal weighting for nasal and non-nasal symptoms is consistent with the findings from Circassia studies TH002 and TH003. In both studies nasal and non-nasal symptoms contributed in approximately equal measure to the symptom score. Equal weighting of the symptom scores and rescue medication use scores to derive the CS is supported by the findings from a study by Clark and colleagues (Clark 2007) which showed that equal weighting had the highest precision and discriminatory power, and by the World Allergy Organization Taskforce Guidelines (Canonica 2007). The US Food and Drug Administration (FDA) has also recently adopted a combined score with equal weighting in its reviews of Oralair® grass sub-lingual immunotherapy.

2.0 OBJECTIVES

The purpose of the proposed study is to evaluate the efficacy, safety, tolerability and effect on quality of life of administration of a range of doses/regimens of HDM-SPIRE compared with placebo in HDM allergic subjects and thereby identify an appropriate dose and regimen to take forward into a confirmatory Phase 3 study.

2.1 Primary Objectives

To evaluate the efficacy of HDM-SPIRE in the reduction of symptoms and the use of allergy rescue medication associated with HDM allergy in subjects with clinically relevant symptoms.

2.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of HDM-SPIRE
- To evaluate the effect of HDM-SPIRE on rhinoconjunctivitis specific quality of life
- To evaluate the effect of HDM-SPIRE on sleep quality

3.0 STUDY DESIGN

3.1 Overall Study Design

The study will be a randomised, double-blind, placebo-controlled, parallel group, multi-centre field assessment of three dose regimens of HDM-SPIRE administered at 4 weekly intervals for 28 weeks.

Subjects will attend the investigative site for screening and administration of study drug and for periodic assessments of safety and efficacy (see Table 5). Subjects will also complete an electronic diary (eDiary) during four 3-week periods. These diaries will capture the primary efficacy variable data (symptom scores and medication use) as well as other subject reported data.

The study is designed to have Baseline Allergy Evaluation (BAE) for 3 weeks and collection of data for the primary efficacy endpoint, measured at 50-52 weeks after the initiation of treatment (PAC3), outside of any seasonal allergen pollen periods for which the subject has clinically significant symptoms. For each individual subject, the BAE must commence only after the relevant Autumn/Fall seasonal allergy pollen period is over, and it must complete at least 1 week before the anticipated start of the relevant next Spring seasonal allergy pollen period. The intermediate data collection times (PAC1 and PAC2 periods, collected at 18-20 and 37-39 weeks after the initiation of treatment respectively) may overlap seasonal allergy pollen periods. For each individual subject the PAC3 period will, ordinarily, occur only after the relevant Autumn/Fall seasonal allergy pollen period has ended and should finish at least one week before the relevant next Spring seasonal allergy pollen period commences.

Period 1, Consent, Screening and Baseline Allergy Evaluation: Rhinoconjunctivitis scores and allergy rescue medication usage will be collected. After consent has been obtained, screening will be conducted in a staged approach to minimise the number of investigations that a potentially ineligible subject undertakes. Firstly, a blood sample will be taken for measurement of IgE to Der f, Der p and relevant perennial allergens. This visit (visit 1A) may be performed during a seasonal allergen period and before the start of additional screening activities. Potential subjects with IgE above the required levels will complete, between visits 1A and visit 1B/C, a paper diary (pDiary) of symptoms for 1 week before additional screening activities are performed. Subjects found to be eligible based on these two steps will undergo screening up to a maximum of 8 weeks before randomisation which may consist of 1 or 2 visits to the clinic, at the Investigator's discretion. In exceptional circumstances, due to reasons beyond the control of the Investigator and/or subject (for example extreme weather), this 8 week period may be exceeded; however this requires documented approval by the Sponsor. Suitable subjects will record Baseline rhinoconjunctivitis symptom scores

(RSS) using a 4-point categorical scale and RMS for a 3-week period in an eDiary before randomisation. The completion of the p Diary over 7 days, allergy screening and the BAE period will take place outside of any and all relevant seasonal allergy periods for each individual subject.

Period 2, Study Medication Administration: Subjects meeting the inclusion/exclusion criteria will be randomised to either one of the 3 active treatment groups or the placebo group in equal proportions.

A total of 8 doses of HDM-SPIRE or placebo will be administered, one dose every 4 weeks (±2 days), for a total duration of 28 weeks as shown in Table 2.

Table 2 Dosing Schedule

Visit	**3A**	**3B**	**3C**	**3D**	**3E**	**3F**	**3G**	**3H**
Week (± 2 days)	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**
Treatment Groups								
Placebo	P	P	P	P	P	P	P	P
HDM-SPIRE 4 x 12 nmol	X	X	X	X	P	P	P	P
HDM-SPIRE 4 x 12 nmol, two courses	X	X	X	X	X	X	X	X
HDM-SPIRE 4 x 20 nmol	X	X	X	X	P	P	P	P

X = Active doses; P = Placebo doses

Period 3, Post-Administration Collection (PAC): The RSS and RMS for efficacy evaluation will be collected during Period 3. There will be 3 PAC periods: PAC1 (Weeks 18-20), PAC2 (Weeks 37-39) and PAC3 (Weeks 50-52). The primary efficacy evaluation period will be PAC3, commencing 50 weeks after randomisation and outside of any and all relevant seasonal allergy periods for the subject. The use of allergy rescue medication during the PAC periods will be according to a pre-specified Rescue Medication Plan (see Appendix 3). Data collected in the periods commencing at 18 weeks (PAC1) and 37 weeks (PAC2) after randomisation will be used for exploratory efficacy analyses.

At the Period 3 Follow-Up Visit 5, 52 weeks from first dosing, subjects will undergo a final safety assessment.

The duration of the study for each subject will be approximately 62 weeks.

3.2 Efficacy Endpoints

3.2.1 Primary Efficacy Variables

The primary efficacy variable will be the mean CS during the PAC3 period (Weeks 50-52 after randomisation) in the HDM-SPIRE treatment groups compared with the mean CS in the placebo group. Analysis of this endpoint is described in further detail in Section 7.5.3.1.1.

The CS is a composite measurement of symptoms as measured by the TRSS and RMS, as measured using a pre-defined rating system that takes into account the different potency of available rescue medication.

The TRSS comprises assessment of 8 symptoms that are given a score of between 0 and 3 giving a range of potential scores of 0 to 24.

Allergy rescue medications will be provided to subjects to be used according to a pre-specified Rescue Medication Plan (See Appendix 3). Subjects will be requested to use antihistamine eye drops as first line allergy rescue medication for troublesome ocular symptoms; with oral antihistamines and/or intranasal corticosteroids to be added or substituted if subjects have unacceptable nasal symptoms or ocular antihistamines do not provide adequate symptom relief (see Section 5.8.1). Oral corticosteroids may be prescribed at the Investigator's discretion. The use of allergy rescue medications will be scored based on Didier et al (Didier 2009) as follows:

- RMS = 0; no allergy rescue medication used per day
- RMS = 0.5; at least one dose of antihistamine eye drops used per day
- RMS = 1; at least one dose of oral antihistamine used per day
- RMS = 2; at least one dose of intranasal corticosteroid used per day
- RMS = 3; at least one dose of systemic corticosteroid used per day

The RMS score is not additive, and therefore the maximum RMS is 3. The TRSS (0-24) and the RMS (0-3) will be combined for analysis of the primary endpoint as follows:

CS = TRSS/8 + RMS

The maximum Combined Score is therefore 6.

3.2.2 Secondary Efficacy Variables

The secondary efficacy variables are

- Clinical Global Impression of Change in Rhinoconjunctivitis Symptoms for the HDM-SPIRE treatment groups compared with placebo at the end of study.
- Mean TRSS in the HDM-SPIRE treatment groups compared with placebo during the

PAC3 period.

- Mean component scores of the TRSS (nasal and non-nasal) in the HDM-SPIRE treatment groups compared with placebo during the PAC3 period.
- Mean RMS in the HDM-SPIRE treatment groups compared with placebo during the PAC3 period.
- Mean Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score in the HDM-SPIRE treatment groups compared with placebo at the end of the PAC3 period.
- Number of days subjects in the HDM-SPIRE treatment groups have no moderate or severe RSS symptoms without rescue medication usage compared with placebo during the PAC3 period.

3.2.3 Exploratory Endpoints

- Rhinoconjunctivitis symptom scores measured using a visual analogue scale (VAS) during the BAE and each PAC period
- Mean CS in the HDM-SPIRE treatment groups compared with placebo during PAC1 and PAC2 periods.
- Mean TRSS in the HDM-SPIRE treatment groups compared with placebo during PAC1 and PAC2 periods.
- Mean RMS in the HDM-SPIRE treatment groups compared with placebo during PAC1 and PAC2 periods.
- Mean component scores of the TRSS (nasal and non-nasal) in the HDM-SPIRE treatment groups compared with placebo during the PAC1 and PAC2 periods.
- Overall RQLQ score in the HDM-SPIRE treatment groups compared with placebo at the end of the PAC1 and PAC2 periods.
- Sleep quality measured using the Pittsburgh Sleep Quality Index (PSQI) for the HDM-SPIRE treatment groups compared with placebo at the end of each PAC and PAC period.

4.0 STUDY POPULATION

The study population will consist of subjects aged from 18 to 70 years, with a documented history of moderate to severe allergic rhinoconjunctivitis on exposure to HDM allergen for at least 1 year. This history is expected to include experiencing nasal and/or ocular symptoms on performing one or more of the following daily activities:

- Changing the bed linen
- Dusting
- Vacuum cleaning

Subjects must have required symptomatic treatment of their allergic rhinoconjunctivitis on at least one occasion during the last year. Asthmatic subjects will be permitted to participate provided that their symptoms are well controlled by GINA Step 1 or Step 2 therapy.

In both stages of the study, subjects will be stratified in each of the treatment groups according to presence or absence of asthma and by severity of their symptoms at baseline (TRSS <16, TRSS ≥16).

4.1 Number of Subjects

A total of approximately 660 subjects will be randomised into the study, with approximately 165 subjects in each of the three HDM-SPIRE treatment groups and 165 in the placebo group. A 10% drop-out rate is assumed with the expectation that ~150 subjects per group will complete the study. Randomisation will be stratified according to severity of rhinoconjunctivitis symptoms at baseline and the presence of asthma.

4.2 Inclusion Criteria

1. Male or female, aged 18-70 years.
2. A reliable history consistent with moderate to severe rhinoconjunctivitis (sneezing, rhinorrhoea, itchy nose, nasal blockage and/or itchy eyes, red eyes, watering eyes and/or itchy ear/palate) on exposure to HDM for at least 1 year and which has required symptomatic treatment on at least one occasion during the last year.
3. Mean TRSS ≥10 from 4 nasal and 4 non-nasal symptoms over a consecutive 7 day period before the Screening Visit 1B/C.
4. Either Der p or Der f specific IgE ≥0.35 kU/L measured by ImmunoCAP®.

5. Positive skin prick test (preferably using the ALK-Abello Allergen Extract test) to either Der p or Der f with a wheal diameter at least 5 mm (average of longest and orthogonal) larger than that produced by the negative control. The negative control must be <2 mm for the test to be valid.
6. Provide written informed consent.
7. Willing and able to comply with the study requirements.
8. If female of childbearing potential (FOCBP), must practice a form of contraception with a failure rate of <1% when used correctly and produce a negative urine pregnancy test at the Screening Visit 1B/C.

Additional Inclusion Criteria at End of BAE

9. Mean TRSS ≥12 from 4 nasal and 4 non-nasal symptoms during the BAE period (3-week period before randomisation).
10. Completed the eDiary during the BAE on at least 16 days (>75% of occasions).

4.3 Exclusion Criteria

1. Diagnosis of asthma requiring GINA Step 3 or higher treatment.
2. If asthmatic, experienced a deterioration of asthma that resulted in emergency treatment or hospitalisation in the 12 months before randomisation, or experienced a life-threatening asthma attack (e.g. one requiring intubation and mechanical ventilation) at any time in the past.
3. Used any oral or parenteral corticosteroids at any time within 1 month prior to Screening Visit 1B/C.
4. Asthma requiring high-dose inhaled corticosteroids (ICS) or anti-IgE therapy within 6 months prior to Screening Visit 1B/C.
5. Forced expiratory volume in 1 second (FEV_1) <80% of predicted, or other evidence of partly controlled or uncontrolled asthma.
6. Clinically significant confounding symptoms of allergy to relevant local seasonal allergens (e.g. ragweed, mugwort, tree, grass or mould) and cannot complete the BAE and the final PAC period at 50-52 weeks (PAC3) outside the respective allergy seasons.
7. IgE ≥0.35 kU/l to other perennial allergens (e.g. animal dander, cockroach, mould) which cannot be avoided during the study or where sampling for these allergens demonstrates significant levels within the subject's home from dust and/or vacuum cleaner samples, analysed using Indoor Biotechnologies Allergen Analysis Service.

8. Intends to be away for 7 days or more during the final PAC period at 50-52 weeks (PAC3), or whose lifestyle means that there is a high likelihood of them being away from home for more than 7 days during the PAC3 period.
9. Received an immunosuppressive treatment within 3 months prior to screening (except steroids for allergic and asthma symptoms).
10. Previous immunotherapy treatment with any HDM allergen for more than 1 month within 5 years prior to screening.
11. Receiving ongoing treatment with any specific immunotherapy at screening.
12. Administration of epinephrine is contraindicated (e.g. subjects with acute or chronic symptomatic coronary heart disease or severe hypertension).
13. Use of beta-blockers, alpha-adrenoceptor blockers or monoamine oxidase inhibitors within 14 days before the Screening Visit 1B/C.
14. History of significant recurrent acute sinusitis, defined as 2 episodes per year for the last 2 years, all of which required antibiotic treatment, or a history of chronic sinusitis, defined as sinus symptoms lasting greater than 12 weeks that include 2 or more major factors or 1 major factor and 2 minor factors. Major factors are defined as facial pain or pressure, nasal obstruction or blockage, nasal discharge or purulence or discoloured postnasal discharge, purulence in nasal cavity, or impaired or loss of smell. Minor factors are defined as headache, fever, halitosis, fatigue, dental pain, cough, and ear pain, pressure, or fullness.
15. Females who are pregnant, lactating or planning to become pregnant, or donate ova for *in vitro* fertilisation during the study period or within 30 days following the study period. Female subjects unwilling to employ appropriate contraceptive measures to ensure that pregnancy will not occur either during or for 30 days following the completion of study period.
16. Significant history of alcohol or drug abuse.
17. Previously been treated in this or another HDM-SPIRE (ToleroMune-HDM) study.
18. Any history of severe drug allergy, severe angioedema or anaphylactic reaction.
19. Received treatment with an investigational drug within 30 days prior to the study.
20. Are unable to communicate or to understand the requirements of the study, or exhibit any psychiatric disorder, which would impair communication between the subject and the Investigator thereby interfering with the informed consent procedure or the gathering of study data.

21. History or findings on physical examination of any significant disease or disorder (e.g. cardiovascular, pulmonary, gastrointestinal, liver, renal, neurological, immunopathological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment) which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, influence the results of the study or the subject's ability to participate in the study.
22. Dependent on the Investigator/site either for employment or education or are first degree relatives or partners of the Investigator/study staff.
23. Institutionalised because of a legal or regulatory order.
24. Active tuberculosis, auto-immune disorders, vaccination within 2 weeks before start of immunotherapy as well as subjects with hypersensitivity to excipients of HDM-SPIRE.

Additional Exclusion Criteria at end of BAE

25. Used any oral or parenteral corticosteroid during the BAE period.

4.4 Women of Childbearing Potential

A female is considered to be of childbearing potential (FOCBP) if she has experienced menarche and has not undergone successful sterilisation (e.g. hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal. A female is considered to be postmenopausal if amenorrheal for ≥2 consecutive years.

An effective method of birth control (one with a failure rate of <1% when used correctly) must be used by FOCBP during the course of the study, in a manner such that risk of failure is minimised.

A negative urine pregnancy test is required for all females at Screening Visit 1B/C and prior to each administration of study drug. A pregnancy test will also be conducted at the end of dosing assessment visit (Visit 3I) and at the Follow-Up Visit 5.

Female subjects should be instructed to contact the Investigator immediately if they suspect they might be pregnant.

4.5 Rescreening of Subjects

Rescreening of subjects is permitted in a limited number of circumstances for subjects who only failed to qualify for the study because of a criteria which is no longer applicable. The handling of the original and re-screen data for these subjects is described in Section 7.1.1.

Subjects who are rescreened will be given a new screening number and will be required to sign a new information sheet and consent form.

4.5.1 Subjects from cold climate sites

Subjects from cold climate sites (Northerly latitudes) whose second dust sample failed to meet the required criteria (see Section 6.2.1.2) but for which all other eligibility criteria were met, may be rescreened and enrolled once the mean average outdoor temperature at the site is above zero degrees Celsius.

Subjects will restart the study at Visit 1A but will only need to repeat certain screening assessments. The assessments to be repeated are shown in Section 6.1. For those assessments that are not repeated, the original data will be used and will need to be transcribed to the new eCRF.

4.5.2 Subjects with Previously Non-Qualifying Specific IgE Levels and/or Skin Prick Test

Versions 1.0 to 3.0, inclusive, of the protocol required subjects to have positive skin prick tests and specific IgE levels of ≥0.7 kU/L to both Der p and Der f. Version 4.0 of the protocol amends this to be a requirement for these assessments to be positive for either Der p or Der f and for a minimum IgE concentration of ≥0.35 kU/L. Subjects who previously failed to qualify for the study because of the original criteria but who now qualify based on the revised criteria may be rescreened and will restart the study at Visit 1A. The blood sample for specific IgE does not need to be repeated; the result from the previous Visit 1A can be entered into the eCRF. There is no time limit for this rescreening for this criteria.

4.6 Withdrawal of Subjects from the Study

The subjects will be informed that they have the right to withdraw from the study on their own accord at any time, for any reason and without having to state their reason and that this will not affect their future management and treatment. When a subject chooses to withdraw from the study, where possible, the Investigator will record a reason according to the following:

- Recovery/no longer experiencing symptoms of HDM allergic rhinoconjunctivitis.
- Lack of therapeutic response.
- Treatment related side effects.
- Unpleasant study procedures.
- Another disease or condition intervenes and prevents continuation in the study.
- External factors unrelated to the study.

The subject may also be withdrawn by the Investigator for the following reasons:

- Adverse events (AEs), which in the opinion of the Investigator compromises the subject's participation in the study.
- Non-compliance with study procedures.
- Lost to follow-up.
- Withdrawal of consent.
- Protocol violation.
- Termination of the study.
- Pregnancy prior to completion of administration of study medication.
- Deterioration in the subject's signs/symptoms and/or the subject develops a disease or condition prior to completion of administration of study medication that, in the opinion of the Investigator, would compromise the subject's safety in continuing in the study.
- Use of any of the prohibited therapies.

In addition to this list of general criteria for withdrawing subjects from the study dosing should immediately be discontinued (and not restarted) in the event of one or more of the following events:

- A grade 3 or 4 systemic allergic reaction (see Appendix 4)
- Two consecutive doses result in a grade 3 or 4 injection site reaction despite reduction of the dose (See Section 5.5.1)
- A serious adverse event that in the opinion of the Investigator is treatment related
- Medical necessity for a subject to use any of the contraindicated medications (see Section 5.8.5) during the treatment period.

Treatment discontinuation will not necessarily result in withdrawal of the subject from the study. For the subjects who withdraw from the study, all safety assessments scheduled for the Period 3 Follow-Up (Visit 5) (see Section 6.2.3.2) will be requested and observations will be recorded as far as is possible. Reasons for omission of tests will be documented. The date and reason(s), if provided, for withdrawal from the study will also be recorded in the electronic Case Report Form (eCRF).

If the subject withdraws due to an AE, all of the Period 3 Follow-Up (Visit 5) assessments will be requested and the event followed until resolution or care is transferred to the subject's primary care physician or a specialist.

Subjects who are withdrawn may be replaced.

4.7 Criteria for Stopping the Study

If, in the opinion of an Investigator, the clinical observations in the study suggest that it may be unwise to continue, the Investigator may terminate his or her involvement in the study after consultation with Circassia Ltd.

For the study as a whole, Circassia Ltd may terminate the study for safety or administrative reasons.

A Data Safety Monitoring Committee (DSMC) will be convened to provide independent oversight of the trial from a safety perspective (see Section 10.0). The DSMC may recommend stopping of the study for safety reasons and detailed guidance to the DSMC will be provided in the DSMC Charter.

4.8 End of the Study

The end of the study is when the last subject completes the Period 3 Follow-Up (Visit 5).

5.0 STUDY MEDICATION

5.1 Investigational Product

The investigational product for this study will be HDM-SPIRE, an equimolar mixture of seven peptides whose individual sequences are derived from Der p1, Der p2 and Der p7, supplied as a lyophilisate. Further details of the peptides are provided in the Investigator's Brochure for HDM-SPIRE. Two concentrations of HDM-SPIRE will be used in the study:

- A 120 µM product which will be used for administration of the 12 nmol doses
- A 200 µM product which will be used for administration of the 20 nmol dose

The blinded lyophilisate will be reconstituted with water for injection (WFI) as shown in Table 3.

The peptides have been synthesised by Bachem AG (Switzerland) and formulated, filled and finished by Patheon (Italy). All manufacturing processes have been performed according to current Good Manufacturing Practice.

Table 3 Reconstitution of Study Medication and Volume to be Administered

Study Medication	Volume of Water for Injection for Reconstitution	Volume Administered
Lyophilisate	300 µL	100 µL

5.2 Placebo

The placebo product is supplied as a lyophilisate with an appearance identical to that of the HDM-SPIRE product. When reconstituted it comprises the vehicle used (see Table 4) to formulate the HDM-SPIRE peptides and its appearance is identical to the reconstituted HDM-SPIRE lyophilisate. The injection volume will also be the same (100 µL).

Table 4 Nominal Composition of the Vehicle

Raw Material	Function	Nominal Concentration
L-Methionine	Antioxidant	5 mM
D-Trehalose dihydrate	Tonicity agent	260 mM
Hydrochloric acid Ammonia	pH adjustment	as needed to pH 4

5.3 Packaging and Labelling

Individual study packs containing blinded vials of lyophilisate of either HDM-SPIRE or placebo will be provided for each subject. Individual study medication vials and study packs will be labelled in accordance with local regulations and will include subject randomisation numbers. The outer packaging of each study pack will also be labelled in accordance with local regulations and will include a product description or identifier; a product lot number, storage conditions and expiry date; protocol details; sponsor name and address; and subject randomisation numbers.

5.4 Supply, Storage and Reconstitution

The Investigator has overall responsibility for all study medication issued to the Investigator's centre. The Investigator may delegate the management of the study medication to a Pharmacist or other qualified team member.

The randomised subject study packs will be shipped to the Investigator together with spares. Medication will be shipped under controlled conditions and a temperature logger will be included. The temperature logger must be returned following the instructions provided. The Investigator or designee will confirm receipt and disposition of the study medication in writing.

The study medication must be kept in an appropriate, limited access, secure storage area at 2 to 25°C until its use or return to Circassia Ltd or its designee for destruction. The temperature in the storage areas will be monitored and recorded daily (minimum and maximum temperature). Copies of temperature logs must be kept in the site study file.

Reconstitution should ideally be performed in an International Organisation for Standardization (ISO) Class 5 (or better), temperature-controlled area on a clean surface and with limited access. Only the required vial of lyophilisate for a single subject dose must be present in the preparation area during reconstitution to avoid any errors. Reconstitution will be achieved by injecting 300µL of sterile WFI into the study medication vial.

Warning: Study medication does not contain a preservative. Consequently, reconstitution more than a few hours prior to administration carries the risk of microbial contamination.

Following reconstitution, sufficient time (typically 3-5 minutes) should be allowed for any foaming of the solution to subside. The Investigator or designee should withdraw the necessary volume into the syringe to allow the administration of 100 µL; in practice this will be 180-250 µL to account for the dead volumes of the needle and syringe. This must not be

more than 6 hours after reconstitution is completed. If administration will not be performed within 1 hour after reconstitution, the reconstituted doses must be transferred to and kept at 5 ± 3ºC in injection vials until the point of administration.

Where an ISO Class 5 environment is not available, reconstitution should be performed in a temperature-controlled area on a clean surface and with limited access. In this situation the study medication must be administered within 1 hour of reconstitution.

Unused/excess solutions generated during the preparation of individual subject medication will be kept for accountability purposes. At the end of the study, upon written authorisation by Circassia Ltd, the Investigator will return unused study medication to Circassia Ltd or their designee for destruction. A copy of the completed Drug Accountability Record should be included in the shipment. The unused study medication will be destroyed and a certificate of destruction generated.

The study medication supplied for this study is intended for use only by subjects in this study.

5.5 Administration of the Study Medication

The reconstituted study medication will be administered by intradermal injection by the Investigator or designee into the flexor (volar) surface of the forearm. The dose to be administered is 100 µL.

5.5.1 Dose Reduction

In the event that a subject experiences a grade 3 or 4 injection site reaction (see Section 6.2.2.1) or a grade 2 systemic allergic reaction (See Appendix 4) the following dose reduction scheme should be followed:

- On first occurrence of a dose reduction trigger reaction the next dose should be reduced by half. This is achieved by administering a dose of 50 µL instead of 100 µL.
- If the reduced dose is well tolerated then the subsequent dose should be escalated back to 100 µL. If this is well tolerated then further doses should continue to be 100 µL.
- If however the full dose is again not well tolerated and a further trigger reaction occurs then the dose should again be reduced to 50 µL and remain at that dose for the remainder of the study.

- If two consecutive half doses are not well tolerated the subject should be withdrawn from the study.

5.5.2 Missed Dose

Dosing visits should be scheduled at intervals of 4 weeks from Visit 3A, with a window of ±2 days. In the event that a visit needs to be rescheduled it may be rearranged such that it falls no later than 7 days before or after the original 4 week interval from the prior dose. On successful completion of a rearranged dosing visit the next dose should then be scheduled as per the original schedule (± 2 days).

If it is not possible to reschedule within 3-5 weeks of the previous dose then it should be considered a missed dose and the next dose should be scheduled in accordance with the original schedule (± 2 days) provided that this does not result in an interval between any two doses of less than 3 or greater than 5 weeks.

5.6 Blinding

This is a double-blind study and the active treatments and placebo are identical in appearance both before and after reconstitution and administration. During the conduct of the study, the subject, Investigator/study staff, Circassia Ltd and the Clinical Research Organisation (CRO) staff directly involved in the clinical study will remain blind to the treatment group. Wherever possible, and considering the best interests of the study subject, once study medication has been administered, management of any subsequent AE should not be predicated upon knowledge of a subject's treatment assignment.

Where the Investigator believes that unblinding is required, they should document and explain the reasons for any unblinding of the study (e.g., due to a Serious Adverse Event (SAE)). The Investigator may discuss the decision to unblind with the Sponsor's medical monitor should time permit.

5.7 Randomisation

Subjects who successfully complete Period 1 Screening and continue to meet the study entry criteria at the end of the BAE, will be randomised to receive placebo or one of the HDM-SPIRE regimens. The Randomisation Schedule will be produced by a computer-generated algorithm by HMD Clinical.

Subjects will be randomised on an equal basis (i.e. 1:1:1:1) to placebo and each of the 3 HDM-SPIRE treatment groups.

Randomisation will be stratified according to the following criteria:

- Current history of asthma (present or absent)
- Mean TRSS during BAE (<16, ≥16)

Study medication packs will be assembled in accordance with the Randomisation Schedule. An interactive response technology (IRT) system will be used to allocate study medication packs to subjects, according to the randomisation and stratification schema. The Investigator or designee will also record the Subject Screening Number against the allocated randomised study pack on the Drug Accountability Record.

5.8 Concomitant Medication and Dietary Supplements

5.8.1 Rescue Medication

Subjects may, at any time during the study, take allergy medication. During the BAE and PAC periods subjects will be asked to use only allergy rescue medication provided to the subject in the Rescue Medication Package according to the defined Rescue Medication Plan (Appendix 3).

The following allergy rescue medications will be provided to subjects and their use will be documented in their eDiaries during the BAE and PAC periods:

- Antihistamine eye drops
- Oral antihistamines
- Intranasal corticosteroids

If a subject finds that he or she is not able to obtain a comfortable level of relief from symptoms with the allergy rescue medications provided during the BAE, the Investigator and subject may agree to use alternative allergy rescue medications in the same categories as above. Alternative allergy rescue medications will be scored on the same RMS scale as the equivalent category of allergy rescue medication from the Rescue Medication Package. The Investigator may also prescribe oral corticosteroids, if required and their use will be documented in the subjects' eDiaries during the PAC periods.

A subject who uses any other category of allergy medications than those included in the Rescue Medication Package during the BAE Period will not be randomised. Use of any other category of allergy medications during the PAC periods will be considered a protocol deviation.

Subjects will be instructed to record all allergy medications other than those provided in the Rescue Medication Package in the pDiary.

The recorded allergy rescue medication usage data in the eDiary will be transferred into the study database directly. No duplication of recording in eCRF is required.

All allergy rescue medications dispensed or prescribed to subjects as part of the Rescue Medication Package will be recorded in the eCRFs.

5.8.2 Treatment of Suspected Anaphylactic Reactions

Anaphylactic reactions may be life-threatening and any suspected anaphylactic reaction must be treated immediately.

All medications and medical equipment for the treatment of suspected anaphylactic reactions must be immediately available at the study centre.

Appendix 2 presents an example of algorithms for the management of suspected anaphylactic reactions (Resuscitation Council United Kingdom [UK], 2008 and Anaphylaxis Emergency Action Plan). The Investigator may follow their own national guidelines or Standard Operating Procedure (SOP) for treating suspected anaphylactic reactions, but a copy of the Guideline or SOP must be placed in the Investigator Site File and have been verified to be suitable by the CRO managing the study.

For all but the mildest cases of anaphylaxis, subjects should be hospitalised overnight or monitored for at least 12 hours.

All cases of anaphylaxis or suspected anaphylaxis must be recorded as an **AE of Special Interest** and should be reported in an expedited manner to the Sponsor in the same way as an SAE (See Section 6.4.2.1). The report must include a grading of the event using the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (See Appendix 4).

5.8.3 Asthma Medication

Subjects with asthma should be controlled and compliant with Treatment Step 1 or Step 2 (see GINA, Appendix 1). Treatment for asthma must have been stable (drug(s), dose, frequency) for at least 3 months prior to screening.

Short acting bronchodilator should not be used for a minimum of 4 hours before each spirometry assessment.

Full details of the subject's asthma medications will be entered into the eCRF. Use of short-acting inhaled ß$_2$ agonist and inhaled corticosteroid medications during the BAE Period and each PAC period will be recorded in the eDiary.

5.8.4 Other Medication

The Investigator should record the use of all concomitant medications, both prescribed and over-the-counter, into the eCRF and subject's medical records. This includes medications used on both a chronic and an as-needed basis. Subjects should be discouraged from starting any new medication, both prescribed and over-the-counter, without consulting the Investigator, unless the new medication is required for emergency use.

Hormonal contraceptives may be used by FOCBP. The peptides used in treatment are designed to induce immunological tolerance via binding to major histocompatibility complex Class II on antigen-presenting cells and are therefore not anticipated to interact with hormonal contraceptives.

5.8.5 Contraindicated Medication, Devices and Dietary Supplements

The following medications are not permitted during Periods 1 and 2 of the study. A minimum washout period of 14 days is required before Screening visit 1B/C.

- beta-blockers
- alpha-adrenoceptor blockers
- monoamine oxidase inhibitors

Subjects using any of the above during Period 1 will not be randomised and during Period 2 will be withdrawn from the study.

Subjects are prohibited from starting any other form of immunotherapy during the study.

6.0 STUDY CONDUCT

6.1 Schedule of Assessments

The study procedures, efficacy and safety assessments will be made as shown in **Table 5**.

Table 5 Schedule of Assessments

Study Periods	**Period 1**				**Period 2**		**Period 3**			
	Consent Visit	Screening	Baseline Allergy Evaluation		Dose Administration (every 4 wks ±2 days)[q]	End of Dosing Assessment	Post-Administration Collection			Follow-Up
							PAC1[a]	PAC2	PAC3	
Visit	**1A**	**1B/C**	**2A**	**2B**	**3A-3H**	**3I**	**4A-4B[b]**	**4C-4D[b]**	**4E-4F[b]**	**5**
Schedule (Week)		**-8 wks** (max)	**-3 wks**	**0**	**0-28 wks**	**32 wks** (±2days)	**18-20 wks** (±2 days)	**37-39 wks** (±2 days)	**50-52 wks** (±2 days)	**52 wks** (±5 days)
Duration		1-2 days	3 weeks			1 day	3 weeks	3 weeks	3 weeks	1 day
*Informed consent	X									
Inclusion / Exclusion Criteria		X		X						
Demography		X								
Medical history including allergy history		X								
Smoking history		X								
History of asthma		X								`
Physical examination		X				X				X
Urine dipstick		X				X				X
*Spirometry (FEV_1) [c]		X			X[d]	X	X[e]	X[e]	X[e]	
*Vital signs		X			X[d]	X	X	X	X	X
Skin prick testing[f]		X								
Issue dust collection pack	X								X[e]	
*Blood sample for haematology/biochemistry		X				X				X
Blood sample for specific IgE	X					X				X
Blood sample for Der p allergen analysis	X									
Biomarker sample[g] [OPTIONAL substudy]					X					X
Blood sample for tryptase					X[h]					
*Pregnancy test (FOCBP)		X			X[i]	X				X
Daily eDiary recording for 3wks: • RSS on a 4 point categorical scale • Asthma Symptom Score • Allergy rescue medication use			X				X	X	X	

Study Periods	**Period 1**				**Period 2**		**Period 3**			
	Consent Visit	Screening	Baseline Allergy Evaluation		Dose Administration (every 4 wks ±2 days)[q]	End of Dosing Assessment	Post-Administration Collection			Follow-Up
							PAC1[a]	PAC2	PAC3	
Visit	**1A**	**1B/C**	**2A**	**2B**	**3A-3H**	**3I**	**4A-4B[b]**	**4C-4D[b]**	**4E-4F[b]**	**5**
Schedule (Week)		**-8 wks** (max)	**-3 wks**	**0**	**0-28 wks**	**32 wks** (±2days)	**18-20 wks** (±2 days)	**37-39 wks** (±2 days)	**50-52 wks** (±2 days)	**52 wks** (±5 days)
Duration		1-2 days	3 weeks			1 day	3 weeks	3 weeks	3 weeks	1 day
For footnotes and abbreviations, please see end of table										
Visual analogue scales for allergy symptoms[j]			X				X	X	X	
Eligibility TRSS (from eDiary)				X						
HDM control measures[k]				X			X	X	X	
*pDiary[l] (dispense)	X	X	X	X	X	X	X	X	X	
*pDiary[l] (review/collect)		X	X	X	X	X	X	X	X	
Dispense rescue medication[m]			X				X	X	X	
ACT (asthmatics only)				X			X[e]	X[e]	X[e]	
RQLQ				X[n]			X[e]	X[e]	X[e]	
PSQI				X[n]			X[e]	X[e]	X[e]	
Clinical Global Impression of Change										X
Dosing					X					
Examination of injection site					X	X				
*Concomitant medication[o]		X	X	X	X	X	X	X	X	X
*Adverse Events[p]		X	X	X	X	X	X	X	X	X
For footnotes and abbreviations, please see end of table										

[a] Study Visit 4B will take place at the same time as dosing Visit 3F.
[b] Study visit will occur on the first and last day of the PAC (±2 days).
[c] Asthmatic subjects should not take their asthma medication for a minimum of 4 hours prior to spirometry.
[d] Pre-dose and 30 min post-dose.
[e] Measured on Visits 4B, 4D and 4F only. For dust collection - the kit will be issued on 4E and returned on 4F
[f] Skin prick testing to Der p, Der f and a battery of standard allergen extracts. (Antihistamines should not be taken three days prior to skin prick test)
[g] Biomarker samples will ONLY be collected from Canadian and US sites for this OPTIONAL sub- study – and only at Visit 3A and follow up.
[h] Measured only in the event of a suspected anaphylactic response, in which case blood sample taken approximately 1 hr and 3 hr after the suspected reaction and then repeated every 3 hr until discharge.
[i] Pre-dose.
[j] Visual Analogue Scales assessed once at the start of BAE visit 2A and at start of PAC periods.
[k] HDM control measures (e.g. humidity, regular washing, regular vacuuming and installation of mattress and pillow casings).
[l] Including RSS over 7 days at Visit 1 only, recording of AEs, recording of concomitant medications.
[m] Allergy rescue medication dispensed at the start of the BAE Period (Visit 2A) and the start of each PAC period (Visits 4A, 4C, 4E).
[n] After subject eligibility confirmed based on TRSS (from eDiary).
[o] Including all concomitant medications described in Sections 5.8.1-5.8.5.
[p] Investigator will ask non-leading questions.
[q] Visits may be rescheduled within $\pm$ 1 week of the scheduled date if required

*Rescreening assessments to be performed (See Section 4.5): informed consent, spirometry, vital signs, blood sample for haematology/biochemistry and pregnancy test (if applicable). A pDiary will also be issued. For concomitant medication and adverse events collect any new information since previous screening.

Abbreviations: AE = Adverse events; ACT = Asthma Control Test; BAE – baseline allergy evaluation Der f = *Dermatophagoides farinae* allergen; Der p -=*Dermatophagoides pteronyssinus* allergen; FEV_1 = forced expiratory volume in 1 second; FOCBP = female of child bearing potential; HDM = house dust mite; IgE = Immunoglobulin E; eDiary = electronic diary; PAC = Post-Administration Collection; pDiary = paper diary; PSQI = Pittsburgh Sleep Quality Questionnaire; RQLQ = Rhinoconjunctivitis Quality-of-Life Questionnaire; RMS = Rescue Medication Score; (T)RSS = (Total) Rhinoconjunctivitis Symptom Scores.

The schedule of assessments on dosing days (Visits 3A-3H) is stated in **Table 6**.

Table 6 Schedule of Assessments on Dosing Days

	Pre-dosing	TREATMENT	30 min Post-dosing
Urine pregnancy test for FOCBP	X		
FEV_1	X		X
Vital signs[a]	X[b]		X
Examination of injection site	X[c]		X
Adverse Events	X		X

[a] Vital signs to be measured after spirometry assessment.
[b] Short acting bronchodilators should not be used for a minimum of 4 hours before each spirometry assessment.
[c] At Visits 3B-3H, to include examination of the injection site where administration was made 4 weeks previously.

Note: FOCBP = Female of Child Bearing Potential; FEV_1= Forced Expiratory Volume in 1 second

6.2 Study Visit Procedures

6.2.1 Period 1: Screening and Baseline Allergy Evaluation

6.2.1.1 Visits 1A and 1B/C: Consent and Screening

At Visit 1A, prior to any study procedures starting, information about the study will be given to the subject both verbally and in writing, and written informed consent must be obtained from the subject. The study information sheet will explain the objectives of the study, its potential risks and benefits. If a subject agrees to participate, he/she will be asked to sign and date an Informed Consent Form (ICF).

After informed consent has been obtained the following procedures will take place at the Consent Visit (Visit 1A):

- A blood sample will be taken for IgE measurement of Der f, Der p and other perennial allergens by ImmunoCAP®.
- A blood sample will be taken for measurement of levels of IgE antibodies to a fixed panel of Der p allergens, using an immune-affinity based analysis technology such as ImmunoCAP®.
- Subjects will be issued with a dust collection pack for assessment of exposure in the home to perennial allergens. Subjects with evidence of exposure (in dust samples or via lifestyle) and sensitivity (positive IgE and skin prick test) to other perennial allergens (e.g. cockroach) will be excluded from further participation. Every reasonable effort should be made to collect dust samples but subjects in South Africa who do not have ready access to a vacuum cleaner will not be required to collect dust

samples and will be excluded if they have IgE ≥0.35 kU/L to any other perennial allergen.

- Subjects will be given a pDiary and asked to record their RSS for 4 nasal and 4 non-nasal symptoms on a scale of 0-3 each over the last 24 hours and concomitant medication use over a 7 day consecutive period. The timing of the completion of this diary card should be outside of any seasonal allergy periods to which the subject has clinically significant symptoms and completed for 1 week immediately before the start of formal Screening commences at Visit 1B/C. If more than 7 days are recorded then the last 7 days before Visit 1B/C will be used to assess their RSS symptoms.

The subject will return to the clinic after the diary has been completed and once the IgE and dust sample analysis results are available and provided their average TRSS meets Inclusion Criterion 3 and their Der p and Der f specific IgE meets Inclusion Criterion 4, the following procedures will take place at the Screening Visit (Visit 1B/C):

- The subject will be assessed for compliance with the inclusion and exclusion criteria.
- Demographic data (date of birth, gender, ethnicity, height and weight) will be obtained.
- A detailed medical history will be taken, including a detailed allergy history and a detailed history of asthma and details of exposure to HDM.
- A smoking history will be taken, including if the subject is a non-smoker, an ex-smoker or a current smoker and the number of cigarettes smoked each day.
- The subject will undergo a physical examination.
- The subject's FEV_1 will be measured using a spirometer. Short acting bronchodilators should not have been taken for a minimum of 4 hours before spirometry.
- Vital signs (sitting or semi-recumbent) will be measured.
- Skin prick testing with Der p, Der f, a battery of standard allergen extracts (e.g. mould, ragweed, grass, tree mix, animal danders, seasonal allergens appropriate for the local geography) and diluent control (performed on the flexor aspect of the forearm) after a suitable wash-out period (≥3 days) from last use of oral antihistamines. The orthogonal diameter will be measured at the mid-point of the longest axis and the average of the longest and the orthogonal diameter must be calculated. Pseudopodia will not be assessed. The negative control must be <2 mm for the test to be considered valid. If the negative control is ≥2 mm the test should be repeated on another day.
- Blood samples for routine haematology and biochemistry will be taken.
- A dipstick urinalysis will be performed on the subject's urine.

- Urine pregnancy test for FOCBP.
- Concomitant medications will be fully recorded.
- Recording of any AEs.
- Each subject will be provided with a pDiary to record AEs and concomitant medications.

Subjects who successfully complete Screening will undergo BAE.

6.2.1.2 Visits 2A and 2B: Baseline Allergy Evaluation

The Baseline Allergy Evaluation will take place during a 3-week period before randomisation and subjects will attend the clinic at the start and end of the BAE period, Visits 2A and 2B, respectively. The BAE must start after the end of the pollen period for all relevant seasonal allergens to which the subject has clinically significant symptoms and must complete at least 1 week before the anticipated start date of the Spring pollen season for any allergen to which the subject has clinically significant symptoms. The requirement to complete the BAE at least 1 week before the anticipated start date of the relevant Spring pollen season is intended to ensure the PAC3 period can also complete before the start date of the relevant Spring pollen season, 50-52 weeks after randomisation. This is illustrated schematically below.

For sites in the most Northerly latitudes with cold and dry winters the BAE should also generally take place before the onset of winter. Sites may be permitted to continue the BAE during winter months with the agreement of the Sponsor and where sampling of dust shows the presence of house dust mite allergen in the home at a suitable level.

Fall (Autumn) pollen season	**Winter period - no relevant pollen in air**	**Spring/ Summer/ Fall (Autumn) pollen season**	**Winter period - no relevant pollen in air**
Screening may occur	Baseline Allergy Evaluation occurs Must complete at least 1 week before anticipated start date of relevant spring allergen to which subject has clinically significant symptoms	PAC 1 and PAC 2 periods may occur during pollen periods	PAC3 period occurs Must complete at least 1 week before anticipated start date of relevant spring allergen to which subject has clinically significant symptoms

6.2.1.2.1 Visit 2A

The following procedures will take place at Visit 2A:

- Each subject will be provided with an eDiary to record RSS, Asthma Symptom Scores (ASS) and allergy rescue medication use.
- Recording of any changes to concomitant medication since last visit.
- Recording of any AEs.
- Dispense a pDiary to record AEs and concomitant medications.
- Subjects will be requested to discontinue their current allergy medication. Subjects will be trained on how to follow the study-specific Rescue Medication (Appendix 3) and will be asked to only use medications from the Rescue Medication Package for the duration of the BAE.
- Dispense allergy rescue medication.

The following information will be recorded in the eDiary on a daily basis first thing in the morning for a period of 3 weeks:

- RSS on a 4 point categorical scale
- Allergy rescue medication use
- ASS

If a subject's allergic rhinoconjunctivitis symptoms become unacceptable to them, they may take allergy rescue medications from the Rescue Medication Package provided in accordance with the Rescue Medication Plan (Appendix 3). Subjects will be instructed to inform the Investigator if they have taken any allergy medication other than those prescribed from the Rescue Medication Package. The Investigator must record these allergy medications as concomitant medications in the eCRF.

For each symptom, the subject will rate the severity over the last 24 hours as follows:

0 = absent
1 = mild, barely noticeable
2 = moderate, annoying/troublesome
3 = severe, very annoying/ very troublesome

RSS symptoms will be captured as follows:

Nasal Symptoms

- Runny nose
- Sneezing
- Blocked nose
- Itchy nose

Non nasal Symptoms

- Itchy eyes
- Watery eyes
- Red eyes
- Itchy ear/palate

The use of **rhinoconjunctivitis rescue medications** will be scored based on Didier et al (Didier 2009) as follows:

- RMS = 0; no rescue medication used per day;
- RMS = 0.5; at least one dose of antihistamine eye drops used per day;
- RMS = 1; at least one dose of oral antihistamine used per day;
- RMS = 2; at least one dose of intranasal corticosteroid used per day;
- RMS = 3; at least one dose of systemic corticosteroid used per day.

Where a subject finds that he or she is not able to obtain a suitable level of relief from symptoms with the provided allergy rescue medications, the Investigator and subject should discuss the use of alternative allergy rescue medications in the same categories as above. Alternative allergy rescue medications will be scored on the same RMS scale as the equivalent category of allergy rescue medication from the Rescue Medication Package.

Asthma Symptom Scores (ASS) will be captured as follows for all subjects using the same 4 point (0-3) grading scale described above:

Asthma Symptoms

- Cough
- Wheezing
- Shortness of breath

In addition, ASS will be captured as follows for subjects with asthma:

- **Limitations of activities**

  Over the last 24 hours, how limited have your activities been because of asthma?

  0: Not limited
  1: Very slightly limited
  2: Slightly limited
  3: Moderately limited or worse

- **Nocturnal symptoms or awakenings due to asthma**

  Overnight (last night) how has your asthma affected you?

  0: Not at all
  1: Hardly at all
  2: A few minutes disturbance

3: Several times or more

- **Need for short-acting inhaled β_2 agonist treatment**

  Over the last 24 hours, how many puffs of reliever medication (e.g. albuterol or salbutamol) have you used?

  0: None
  1: One
  2: Two
  3: Three or more

Study site personnel should contact subjects at the end of the first and second weeks of the BAE by telephone or text message to remind and encourage them to complete the eDiary on a daily basis.

VAS for allergy symptoms

In addition, at the start of the BAE period, subjects will record their RSS using a VAS. This assessment will be based on the subject's assessments of their symptoms over the preceding week. Subjects will be asked to rate their allergy symptoms on a visual scale where 0 = no symptoms and 10 = worst symptoms possible. This assessment will be recorded on the eDiary.

6.2.1.2.2 Visit 2B

Following completion of the Baseline Allergy Evaluation, subjects will attend the study centre for Visit 2B and will be eligible for randomisation provided they comply with Inclusion Criteria 9 and 10 and continue to comply with the Exclusion Criteria (particularly those related to asthma). The following procedures will take place at this visit:

- Recording of any change to concomitant medications, and any allergy medication other than those recorded in eDiary.
- Recording of any AEs.
- Completion of RQLQ.
- Completion of ACT (asthmatic subjects only).
- Completion of PSQI.
- Review pDiary and issue new pDiary

6.2.2 Period 2: Study Medication Administration (Visits 3A-3H) and End of Dosing Assessment (Visit 3I)

6.2.2.1 Visits 3A-3H: Study Medication Administration

Subjects will be randomised when they attend Visit 3A [note: Visit 3A should immediately follow completion of Visit 2B, or if this is not convenient may occur within 7 days of Visit 2B]. Study medication, HDM-SPIRE or placebo, will be administered at 8 visits (Visits 3A-3H) for each subject (see also Section 3.1). The 8 visits will take place at intervals of 4 weeks (±2 days). If the subject has a significant systemic or local illness that includes a fever (oral or aural temperature >38ºC), the dosing visit should be rescheduled for 5 days later; there is no need to reschedule dosing for subjects with an upper respiratory tract infection without any significant associated fever. If the subject's pre-dose FEV_1 is <70% of predicted the dosing visit should be rescheduled. Subjects will be permitted to leave the clinic after a minimum of 30 minutes based on the Investigator's assessment of their clinical condition. Intradermal injections of HDM-SPIRE or placebo (100 µL) will be made into the flexor (volar) surface of the forearm by the Investigator or designee. Standards for practical allergen-specific immunotherapy are described in Alvarez-Cuesta et al (Alvarez-Cuesta 2006).

Emergency treatment must be available and immediately accessible for treatment of suspected anaphylactic reactions (see Section 5.8.2 and Appendix 2)

The following procedures and assessments will take place at each of the study medication administration visits (Visits 3A-3H):

Pre-dose assessments:

- Recording of any AEs.
- Recording of any changes to concomitant medication since last visit.
- Urine pregnancy test (for females and which must be **negative** for the subject to continue in the study).
- Examination of the injection site from previous administration (not relevant for Visit 3A) with recording of any injection site reaction on the following scale (FDA Guidance for Industry 2007) (Table 7):

Table 7 Grading of Injection Site Reactions

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Pain	None	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	None	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/ Redness *	None	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/ Swelling**	None	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable. ** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

- Spirometry (FEV_1) [asthmatic subjects should not take their β agonist asthma medication for a minimum of 4 hours prior to spirometry]. FEV_1 must be ≥70% of predicted for a subject to be dosed.
- In the event that the FEV_1 is less than 70% of predicted the subject's asthma medication use should be reviewed and any appropriate adjustments made. The dosing visit should then be rescheduled within 5 days. A dosing visit may only be rescheduled once, after which time it becomes a missed visit.
- Vital signs (seated or semi-recumbent).
- Blood sample for biomarker analysis (OPTIONAL sub-study ONLY at Visit 3A – see Section 6.4.4.7)

Study medication administration:

- Intradermal injection of 100 µL of HDM-SPIRE or placebo.

Post-dose assessments:

- Spirometry (FEV_1) will be performed 30 minutes after injection. Asthmatic subjects should not take their asthma medication for a minimum of 4 hours prior to spirometry.
- Vital signs measured 30 minutes after injection (seated or semi-recumbent).
- Examination of the injection site between 30 minutes after injection, with findings recorded using the scale above.
- Blood sample for tryptase will be taken **only** in the event of a suspected anaphylactic response. The initial sample should be taken approximately 1 hour after the attack, with a further sample at approximately 3 hours and then repeated every 3 hours until the Investigator is satisfied that the subject may be discharged. **Note: blood sampling**

for tryptase must not delay initial resuscitation. Any subject that experiences a suspected anaphylactic reaction must also have a sample collected for assay of tryptase at the next dosing visit or the end of study visit.

- Recording of any AEs prior to discharge.
- Issue new pDiary prior to discharge and instruct subjects to record details of injection site reactions in the 7 days after each dose.

Post-treatment assessments made within ±5 minutes of the nominal times will not be regarded as a protocol deviation. Where more than one assessment is scheduled at a nominal time, the assessments will be conducted in the following order:

1. Vital signs
2. Spirometry (FEV_1)
3. Examination of injection site

Subjects will be asked to complete a pDiary from Visit 3A to Visit 3I of AEs and concomitant medications. The pDiary will be checked at all visits and information entered into the eCRF. The pDiary must then be retained in the Investigator Site File.

The Investigator will assess the need for any asthmatic subject to be provided with a salbutamol/albuterol inhaler and/or peak flow meter at Visit 3A before leaving the clinic.

6.2.2.2 Visit 3I: End of Dosing Assessment

An End of Dosing Assessment (Visit 3I) will take place 4 weeks (±2 days) after the subject received the last dose of study medication. Subjects who are withdrawn from the study prior to receiving the final dose for any reason will proceed directly to a Period 3 Follow-Up (Visit 5).

At Visit 3I the following procedures and assessments will take place:

- Targeted Physical Examination (guided by findings at screening and emerging AEs).
- Examination of the injection site from Visit 3H.
- Spirometry (FEV_1) [asthmatic subjects should not take their short acting bronchodilator for a minimum of 4 hours prior to spirometry].
- Vital Signs (seated or semi-recumbent).
- Clinical laboratory assessments including dipstick urinalysis and blood samples for clinical chemistry and haematology.
- Blood sample will be taken for Der p and Der f specific IgE by ImmunoCAP®.
- Urine pregnancy test (for FOCBP).
- Transfer information from pDiary to eCRF, i.e.:
    - Home environment changes (see Section 6.3.5).

- Concomitant Medications.
- AEs.

- Issue new pDiary.

6.2.3 Period 3: Post-Administration Collection (Visits 4A-4F) and Period 3 Follow-Up (Visit 5)

Investigators should ensure that subjects are contacted at least once per month by telephone or text message after Visit 3I to ensure subjects remain motivated to participate in the study and continue to complete their pDiary as well as to ensure the subject is available for their PAC2 and PAC3 periods.

6.2.3.1 Visits 4A-4F: Post-Administration Collection

Subjects will participate in three post-administration data collection (PAC) periods.

Each PAC will take place over a 3-week period and will consist of 1 clinic visit at the start of the PAC period to provide the eDiary and Rescue Medication Package to the subject and 1 visit at the end of each PAC period to collect the eDiary. Subjects will record symptom scores, rescue medication use and ASS (where relevant) daily (in the morning) in the eDiary in the intervening 3-week period.

Investigators should contact subjects at the end of the first and second week of each PAC period by telephone or text message to remind and encourage subjects to complete the eDiary on a daily basis.

Investigators must review completion of eDiary data through the web portal and immediately contact any subject who has not completed the eDiary during a PAC period and seek to encourage the subject to resume completing the eDiary as soon as possible.

The PAC periods are:

- PAC1: Weeks 18-20 (±2 days) Visits 4A and 4B will occur on the first and last day, respectively. Visit 4B will take place at the same time as the Dosing Visit 3F. PAC1 may occur during a pollen period to which the subject has clinically significant symptoms.
- PAC2: Weeks 37-39 (±2 days), Visits 4C and 4D will occur on the first and last day, respectively. PAC2 may occur during a pollen period to which the subject has clinically significant symptoms.
- PAC3: Weeks 50-52 (±2 days), Visits 4E and 4F will occur on the first and last day, respectively. The PAC3 period must start after the end of the pollen period for all relevant seasonal allergens to which the subject has clinically significant symptoms

and must complete at least 1 week before the anticipated start date of the Spring pollen season for any allergen to which the subject has clinically significant symptoms.

If a subject requires medication for allergy symptoms during a PAC period they may take allergy rescue medications from the Rescue Medication Package provided in accordance with the Rescue Medication Plan (Appendix 3).

At the start of each PAC (Visits 4A, 4C and 4E), the following assessments will be performed:

- Vital Signs (sitting or semi-recumbent)
- Recording of AEs.
- Recording any changes in concomitant medications since last visit.
- The subject must be retrained on how to follow the Rescue Medication Plan (Appendix 3).
- Allergy rescue medication will be dispensed.
- Subjects will be reminded to check with the Investigator before they start any new medications other than their allergy rescue medication.
- A new pDiary will be issued.
- At the end of the visit, subject will be provided with their eDiary to record the following information on a daily basis, first thing in the morning, for the next 3 weeks:
    - RSS using a 4 point categorical scale
    - ASS
    - Allergy rescue medication use

In addition, at the start of each PAC period, subjects will record their RSS using a VAS. This assessment will be based on the subject's assessments of their symptoms over the preceding week. Subjects will be asked to rate their allergy symptoms on a visual scale where 0 = no allergy symptom and 10 = my allergy symptom is the worst it could possibly be. This assessment will be recorded on the eDiary.

Note: Visit 4B at the end of PAC1 and the Dosing Visit 3F will take place at the same time and assessments that are duplicated at these two visits need to be made only once.

At the end of each PAC (Visits 4B, 4D and 4F), the following assessment will be performed:

- Vital Signs (sitting or semi-recumbent).
- Recording of AEs.

- Recording any changes in Concomitant Medication since the last visit, and any other allergy medication not recorded in the eDiary.
- Collect eDiary.
- Collect pDiary and transfer to eCRF:
    - Home environment changes (see Section 6.3.5).
    - Concomitant medications.
    - AEs.
- Issue new pDiary at Visits 4B and 4D.

In addition, at Visits 4B, 4D and 4F the subject will complete the following assessments:

- RQLQ (see Section 6.3.2).
- Spirometry (FEV_1) [asthmatic subjects should not take their asthma medication for a minimum of 4 hours prior to spirometry].
- ACT for asthmatic subjects.
- PSQI

6.2.3.2 Period 3 Follow-Up (Visit 5)

A Period 3 Follow-up (Visit 5) visit will be conducted either at the same time as Visit 4F or as a separate visit no later than 10 days after the PAC3 period is completed. The following procedures will be conducted:

- Vital signs (sitting or semi-recumbent).
- Targeted physical examination (guided by findings at screening and emerging AEs).
- Blood samples for routine haematology and biochemistry.
- Blood sample for Der p and Der f specific IgE.
- Blood sample for biomarker analysis (OPTIONAL sub-study – see Section 6.4.4.7)
- Blood sample for tryptase in any subject who has had a suspected anaphylactic response and is being withdrawn from the study.
- A dipstick urinalysis will be performed on the subject's urine.
- Urine pregnancy test (for FOCBP).
- Recording of any changes to concomitant medication since last visit.
- Recording of any AEs.
- Subjects will be asked to complete a Clinical Global Impression of Change in Rhinoconjunctivitis Symptoms.

6.3 Assessment of Efficacy

6.3.1 Measurement of RSS, ASS and Allergy Rescue Medication Use

Subjects will record their RSS using the 4 point categorical scale (reflective over last 24 hours), ASS and allergy rescue medication use on a daily basis, first thing in the morning, in an eDiary during the Baseline Allergy Evaluation, PAC1, PAC2 and PAC3.

Symptoms will be divided into nasal, non-nasal and asthma symptoms and rated for severity as described in Section 6.2.1.2.

Subjects will also record their RSS using the VAS (reflective over the past week) once at the beginning of the BAE and each PAC period.

6.3.2 Rhinoconjunctivitis Quality-of-Life Questionnaire

Subjects will complete the RQLQ at the end of the BAE and at the clinic visits at the end of PAC1, PAC2 and PAC3.

6.3.3 Asthma Control Test

The ACT will be completed by asthmatic subjects at the end of the BAE and at the clinic visits at the end of PAC1, PAC2 and PAC3.

6.3.4 Clinical Global Impression of Change in Rhinoconjunctivitis Symptoms

Subjects will complete a Clinical Global Impression of Change in Rhinoconjunctivitis Symptoms at the Period 3 Follow-up visit (Visit 5). Subjects will rate their overall allergy symptoms at the end of the study relative to Baseline on a 7 point scale as follows:

- Very much better (0)
- Moderately better (1)
- A little better (2)
- Unchanged (3)
- A little worse (4)
- Moderately worse (5)
- Very much worse (6)

6.3.5 Home Environment (Exposure to Allergen)

Subjects will be asked to record any changes to their home environment in the pDiary. This will include changes to HDM control measures, such as, humidity, regular washing, regular vacuuming, installation of mattress and pillow encasings and significant changes to their home furnishing (e.g. removal of carpets). The Investigator will transfer this information into the eCRF. At the start of the BAE and at the end of the final PAC period, subjects will provide dust samples from their homes for analysis to confirm domestic HDM exposure and to measure levels of other perennial allergens such as cockroach and moulds. (Subjects in South Africa who do not have ready access to a vacuum cleaner will not be required to collect dust samples).

6.3.6 Pittsburgh Sleep Quality Index

The PSQI will be completed by subjects at the end of the BAE and at the clinic visits at the end of PAC1, PAC2 and PAC3.

6.4 Assessment of Safety and Tolerability

6.4.1 Adverse Events

At each study visit, the Investigator will determine whether any AEs have occurred by asking non-leading questions. Adverse Event reporting begins from signed informed consent and ends at Visit 5.

An AE is any untoward medical occurrence. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease. An adverse drug reaction is defined as any noxious and unintended responses to a medicinal product related to any dose. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and the AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Treatment and placebo will be blinded in this study, so a causal relationship between treatment and an AE cannot be established before the data are unblinded.

All AEs must be fully recorded in the eCRF, from the time that a subject has provided signed informed consent to the time of their final study visit (although continued monitoring may be required for AEs ongoing at this visit).

When recording an AE, the following details should be given:

- Event observed (brief description using medical terminology);
- Start and stop dates and times;
- Severity (see below);

- Relationship to study medication (see below);
- Action taken (brief description);
- Outcome (see below);
- Serious (Yes/No).

An AE **does** include:

- Exacerbation of a pre-existing illness;
- Increase in frequency or severity of a pre-existing episodic condition;
- A condition detected or diagnosed after study start even though it may have been present prior to the start of the study.

An AE **does not** include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that led to the procedure is an AE.
- Pre-existing disease or conditions documented prior to the start of the study, which does not worsen.
- Elective surgery, social and/or convenience admissions previously arranged or anticipated before the start of the study and reported to the Investigator.
- Disease or disorder being studied or associated signs or symptoms provided these do not worsen/appear during treatment.
- Overdose of either study or concomitant medication without any signs or symptoms.
- Uncomplicated pregnancy

Adverse events will be recorded as they are reported, whether spontaneously volunteered by a subject or in response to questioning about well-being at each study visit. The subject will be questioned in a general way and no specific symptoms will be suggested. The questioning about AEs will cover the current visit and the period of time between the previous and current visit although subjects may report AEs occurring at any other time during the study. Follow-up of all AEs will continue until the overall clinical outcome is definitive. If any AEs have occurred, they will be recorded in the subject's medical record and transcribed to the eCRF. The Investigator must detail the symptom of the event, the onset of the event, the measures taken and the outcome, the date of disappearance or stabilisation. If known, the diagnosis should be recorded, in addition to the listing of individual signs and symptoms. The Investigator will assess each AE in terms of severity and relationship to study medication as indicated in the sections that follow.

Severity

Mild	Noticeable to the subject, but does not interfere with their usual activities. Usually does not require additional therapy, dose reduction or discontinuation of medicinal product.
Moderate	Interferes with usual activities, possibly requires additional therapy, but usually does not require discontinuation of medicinal product.
Severe	Incapacitating with inability to perform usual activities. May require medical intervention and treatment and may require discontinuation of medicinal product.

The Investigator will make a judgement regarding whether or not the AE was related to the study medication. The Investigator will evaluate any changes in laboratory values (including vital signs and 12-lead electrocardiogram and make a determination as to whether or not the change is clinically important and whether or not the changes were related to study medication. However, even if the Investigator feels there is no relationship to the study medication, the AEs MUST be recorded in the eCRF and the rationale for the judgement should be recorded in the medical notes.

Causality

Related:	Any event that follows a reasonable temporal sequence from administration of study treatment OR that follows a known response pattern to the investigational drug. (Any event that does not meet the criteria for unlikely or not related should be classified as related)
Unlikely to be related	Any event that does not follow a reasonable temporal sequence from administration of study treatment AND does not follow a known response pattern to the suspected drug.
Not related	Any event that starts before administration of study medication AND/OR for which there is a clear alternative explanation.

Outcome

For each event, the following outcomes are possible:

- Recovered;
- Recovered with sequelae;
- Ongoing;
- Death;

- Unknown (appropriate follow-up to determine the outcome of all AEs will be undertaken and therefore "Unknown" should only be used as a last resort).

Follow-Up of Adverse Events

If any AEs are present when a subject completes the study or if a subject is withdrawn from the study, the subject will be followed up by telephone in 3-7 days. If the AE has still not resolved, additional follow-up will be performed as appropriate. Every effort will be made by the Investigator or delegate to contact the subject until the AE has resolved or stabilised. This should be documented in the subject's medical records. All AEs must be followed until resolution, until the condition stabilises, until the subject dies or is lost to follow-up. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations that may be indicated, including (but not limited to) additional laboratory tests, histopathology or consultation with other health care professionals.

6.4.2 Serious Adverse Events

A SAE is any untoward medical occurrence that:

- Results in death;
- Is life-threatening (subject is at immediate risk of death in the judgement of the Principal Investigator at the time of the event);
- Results in persistent or significant disability or incapacity;
- Requires hospitalisation or prolongation of an existing hospitalisation;
- Is a congenital abnormality or birth defect;
- Is a medically significant event;

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also be considered to be SAEs.

6.4.2.1 Adverse events of Special Interest

Systemic Allergic Reaction (as defined by World Allergy Organization (WAO) Subcutaneous Immunotherapy Systemic Reaction Grading System, Appendix 4 [Cox et al., 2010]) are considered Adverse Events of Special Interest and should be reported expeditiously to the Sponsor in the same way as Serious Adverse Events.

If a systemic allergic reaction also meets any of the definitions of serious then it will also be

classified as a serious event and will be managed in the same way as any other serious event.

6.4.2.2 Life-Threatening Adverse Event

The term "life-threatening" in the definition of "serious" refers to an event in which the subject 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.

6.4.2.3 Hospitalisation

This is defined as the subject being hospitalised overnight. Any pre-planned or anticipated in-hospital visits should be documented in advance of the start of study medication administration and will be excluded from this category.

6.4.2.4 Subject Withdrawal

If the subject discontinues study medication administration due to a SAE and withdraws from the study, this should be reported using the SAE forms provided.

6.4.2.5 Unexpected Adverse Event

An unexpected AE is defined as an AE, the nature or severity of which is not consistent with the applicable product information (i.e., the Investigator's Brochure).

6.4.2.6 Reporting Serious Adverse Events/Expeditable Adverse Events

Investigators are obliged to notify, by fax, the contract Pharmacovigilance CRO, Icon plc (formerly Akos Ltd.), of all SAEs immediately (within 24 hours of the Investigator becoming aware of the event).

SERIOUS ADVERSE EVENTS MUST BE REPORTED BY PHONE, FAX OR EMAIL TO ICON IMMEDIATELY
(NO LATER THAN 24 HOURS OF THE INVESTIGATOR BEING NOTIFIED)
+44 1628 496300 (Phone for Rest of World)
+1 888 723 9952 (Phone for North America)
+44 1865 595595 (Fax for Rest of World)
+1 800 540 1863 (Fax for North America)
f2m-eastleigh-medical@iconplc.com (email)

The **minimum** information required on the SAE report is:

- Protocol number;
- Centre number or Investigator name;
- Subject number;
- An AE or outcome that can be identified as serious;
- A suspected investigational product;
- Investigator's or Co-Investigator's assessment of relationship to the investigational product;
- Name and signature of reporter.

Follow-up information must be actively sought and submitted as soon as it becomes available.

All serious, unexpected and related AEs (SUSARs) must also be reported to the reviewing Institutional Review Board (IRB)/Independent Ethics Committee (IEC) according to local and national requirements. Circassia Ltd will provide details to other Investigators of such AEs for this purpose.

Reports relating to the subject's subsequent medical course must be submitted to the Sponsor until the event has subsided or, in the case of permanent impairment, until it stabilises and the overall clinical outcome has been ascertained. The Investigator will also provide additional information, including a copy of the following documents (where applicable):

- Copies of all test results;
- Hospital discharge summary (as soon as it is available to the Investigator);
- Autopsy report (as soon as it is available to the Investigator).

SAEs that come to the attention of the Investigator at any time up until the end of the study (Visit 5) must be reported to the Sponsor in the same manner as a SAE occurring during the dosing period.

The Investigator will notify the IRB/IEC of all SAEs that occur during this study, if required by local or national laws and regulations.

The appropriate regulatory authority will be notified of all SUSARS within the required reporting timelines.

6.4.3 Reporting of Pregnancy

Subjects who become pregnant before the start of dosing (from consent to Visit 3A) must be withdrawn from study immediately after the pregnancy is confirmed. Subjects who become

pregnant during the dosing period must receive no further study treatment and the pregnancy must be reported using the same procedure as for SAEs (see Section 6.4.2). Subjects who become pregnant once dosing has completed may remain in the study and the pregnancy must be reported using the same procedure as for SAEs. Pregnancy will be recorded in the subject's medical files. A Pregnancy Notification Form must be completed and is reported using the same procedure as for the SAEs (see Section 6.4.2). The outcome of the pregnancy will be followed-up until term end, full or premature termination. A Pregnancy Outcome Form, to assess the health of the mother and any infants, will be completed and reported following the same procedure as the notification form.

6.4.4 Safety Evaluations

6.4.4.1 Demographic and Medical History

The demographic data and a complete medical history with an emphasis on allergy including rhinoconjunctivitis and asthma will be recorded at Screening (Visit 1B/C). This will include skin prick testing to HDM.

6.4.4.2 Physical Examination

A physical examination will be conducted at Screening (Visit 1B/C), at the End of Dosing Assessment (Visit 3I) and at the Period 3 Follow-Up (Visit 5). At Screening this will be a full examination comprising:

- Eye, ears, nose, throat, neck, including a check for nasal polyps;
- Respiratory system;
- Central and peripheral nervous system;
- Cardiovascular system;
- Gastrointestinal system (including the mouth);
- Musculoskeletal system;
- Skin;
- Lymph node palpation;
- Other systems if abnormality is suspected.

At visits 3I and 5 the physical examination will be a targeted exam, with organ systems examined if the medical history or AEs indicate a reason for examination.

6.4.4.3 Vital Signs

Blood pressure, pulse rate, respiratory rate and body temperature will be recorded at Screening (Visit 1B/C), prior to and 30 minutes after Study Medication Administration

(Visits 3A-3H), at the End of Dosing Assessment (Visit 3I), at each PAC visit and at Period 3 Follow-Up (Visit 5). Measurements will be made with the subjects rested and in the sitting or semi-recumbent position.

6.4.4.4 Laboratory Assessments

Blood samples using the Vacutainer® system for haematology and biochemistry tests and urine samples for urine dipstick tests will be obtained at Screening (Visit 1B/C), at the End of Dosing Assessment (Visit 3I) and at the Period 3 Follow-Up (Visit 5).

Blood samples for Der p, Der f and perennial allergen specific IgE will be obtained at Screening (Visit 1A) and will be measured by ImmunoCAP®. At the End of Dosing Assessment (Visit 3I) and at Period 3 Follow-Up (Visit 5) blood samples for Der p and Der f specific IgE, measured by ImmunoCAP®, will be obtained.

A blood sample will be taken at screening only for measurement of a fixed panel of Der p allergens using an immune-affinity based analysis technology such as ImmunoCAP®.

Urine samples for pregnancy tests will be collected from FOCBP and analysed immediately at Screening (Visit 1B/C), before dosing at Study Medication Administration Visits (Visits 3A-3H), at the End of Dosing Assessment (Visit 3I) and at Period 3 Follow-Up (Visit 5).

The following parameters will be measured:

Haematology:	haematocrit, haemoglobin, red blood cells, white blood cells (WBC), WBC differentials (neutrophils, eosinophils, basophils, lymphocytes, monocytes) and platelets.
Biochemistry:	sodium, potassium, chloride, urea, creatinine, calcium, phosphorus, total protein, albumin, uric acid, total bilirubin, glucose (random), lactate dehydrogenase, creatine phosphokinase, alanine transaminase, aspartate transaminase, gamma glutamyltransferase, and alkaline phosphatase ; Blood samples will be collected for assay of tryptase in the case of a suspected anaphylactic response [see Section 6.2.2]).
Urine dipstick:	pH, protein, ketones, blood and glucose.
Immunology:	Der p, Der f and relevant perennial allergen specific IgE (measured by ImmunoCAP®).

Additional tests may be performed if clinically warranted. Abnormal values should be followed up they have returned to normal or an adequate explanation has been established.

All laboratory test reports must be reviewed, signed and dated by the Investigator or delegated physician. Reports will then be filed with the subject's medical record. The Investigator will comment on all abnormal results and determine whether it is clinically significant. These assessments will be recorded in the eCRF.

Any clinically significant abnormal laboratory value constitutes an AE and must be recorded as an AE in the eCRF. For grading an abnormal value or result of a clinical or laboratory evaluation, Investigators are encouraged to consult National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. A value that increases by one grade from baseline or from the last post-baseline value that does not meet grading criteria should ordinarily be considered clinically relevant and hence reported as an adverse event. A CTCAE grade increase of one in clinical or laboratory evaluation will translate to 'mild' in the above grading, an increase of two will be 'moderate' and an increase of three or more will be 'severe'. For additional information and a printable version of the manual, consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

6.4.4.5 FEV_1

The FEV_1 will be measured at Screening (Visit 1B/C), prior to and 30 minutes after Study Medication Administration (Visits 3A-3H), at the End of Dosing Assessment (Visit 3I), and at the end of PAC1, PAC2 and PAC3 (Visits 4B, 4D and 4F). Asthmatic subjects should not use their asthma medication for a minimum of 4 hours prior to the spirometry assessment.

At each assessment FEV_1 will be measured according to the American Thoracic Society guidelines with the subject sitting and the highest reading will be recorded in the eCRF.

6.4.4.6 Injection Site Reactions

At each study medication administration (Visits 3A-3H), the injection site will be examined immediately prior to and 30 minutes after the administration of study drug for signs of reaction. Reactions should be graded on a 5 point (0-4) scale for each of the following parameters, as shown in Section 6.2.2.1: pain, tenderness, redness, swelling.

At Visits 3B-3H and at the End of Dosing Assessment (Visit 3I), this will include examination of the previous injection site.

6.4.4.7 OPTIONAL Biomarker Analysis

Blood samples for biomarker analysis will be obtained at Visit 3A and at Follow-Up (Visit 5). These samples will ONLY be taken from subjects at participating sites in Canada and US. Subjects will be required to sign a separate consent form to participate in this optional sub-study.

A blood sample (20 mL) will be collected and stored for future analysis. A biomarker analysis plan will be on file prior to the start of the biomarker analysis.

7.0 STATISTICAL CONSIDERATIONS

7.1 Data Management and Quality Assurance

All data in the study will be captured and maintained in a secure, validated electronic data capture (EDC) system. Study site staff will enter the data for each subject on an eCRF. The laboratory data and eDiary card data will be transferred electronically to Data Management and reconciled with the data entered at site. The subjects will enter their RSS, ASS and use of Rescue Medication directly into the study eDiary.

Additionally a pDiary Card will be used to aid the collection of AEs, concomitant medications and home environment changes. The Investigator will review the pDiary Card at each study visit and the data will be transcribed onto the eCRF.

The eCRF and eDiaries will contain automated edit checks to ensure the quality, integrity, accuracy and completeness of the data entered. The Study Monitor will periodically review the eCRF input and source document verify eCRF data. The medical monitor may examine eCRF and diary card data for preliminary medical review.

The eCRF data will be maintained in a validated study database with an audit trail of all changes that are made to the database, including the reason for the data change. Adverse events will be coded using a standard dictionary (Medical Dictionary for Regulatory Activities [MedDRA]), while concomitant medications will be categorised using the World Health Organisation drug dictionary.

Creation and validation of the EDC system and management of the data will be conducted in accordance with title 21 of the Code of Federal Regulations Part 11 and the US FDA Guidance for Industry on Computerised Systems used in Clinical Investigations. Methods used to ensure the quality and integrity of the data will be documented in the Data Management Plan, which will be approved by the Sponsor.

7.1.1 Rescreening Data

In a limited set of circumstances, subjects will be permitted to be rescreened for the study (See Section 4.5). All data from these subjects, both the original and repeat assessments, will be entered into the study database. For those parameters where repeat assessments are made, the repeat assessment will be used in data summaries. The original assessments will be listed only.

7.2 Sample Size

The study will recruit approximately 660 subjects (approximately 165 per group). Based on the data from observational study TH003, if a mean CS of 1.6 is observed for the placebo group, and a mean CS of 1.28 for the active group, the expected treatment difference of 0.32 will be a 20% improvement from placebo. The statistical model will include the baseline CS as a covariate, taking this into account a standard deviation of 0.986 is assumed, so that a sample of 150 patients will have 80% power to detect a statistically significant difference in treatment.

Other data sources result in sample size estimates that range from 103/group (based on the TRSS data from Study TH002) through to 200/group (based on symptom scores adjusted for medication use in a study of sublingual HDM immunotherapy [Bergmann et al, 2013]). These data support the assumptions from Study TH003 and indicate that a difference of 20% between placebo and active treatment will be observed with a sample size of 150 subjects per group. It is estimated that up to 10% of subjects may drop-out before PAC3 or have missing data during PAC3. Consequently, approximately 660 subjects in total will be randomised.

7.3 Interim Analysis

No interim analysis is planned for this study.

7.4 Analysis Populations

7.4.1 Intent-to-Treat Population

The population for the efficacy analyses will be the Intent-to-Treat (ITT) population consisting of all subjects who are randomised, who have received at least one dose of study medication. Subjects will be reported by the treatment they were randomised to. This is the primary population for the study, and all the primary and secondary efficacy analyses will be based on the ITT population.

7.4.2 Per Protocol Population

Subjects who are part of the ITT population, have no major protocol deviations likely to affect the integrity of the study and complete the entire study will constitute the Per Protocol (PP) population. The PP population will be evaluated for the primary endpoint to confirm results from the ITT population.

7.4.3 Safety Population

All subjects receiving at least 1 dose of study medication (HDM-SPIRE or placebo) and with at least one safety assessment will be included in the safety population. Subjects will be reported by the treatment they actually received. The safety population will be used for all of the safety endpoints.

7.5 Statistical Analysis

Further detail of the statistical analyses and data presentations to be used in reporting the study, including dictionaries used for coding and software used, will be provided in the Statistical Analysis Plan (SAP), which will be finalised prior to breaking the blind.

If not otherwise specified, statistical significance is defined as $p<0.05$ and is 2-sided.

Data will be summarised with respect to demographic and baseline characteristics, efficacy variables and safety variables. Summary statistics will include the mean, N, standard deviation (SD), median, minimum and maximum values for continuous variables and frequencies and percentages for categorical variables.

The primary efficacy analysis will utilize a Mixed Model Repeated Measures (MMRM) model. To assess the effect of missing data on the primary analysis, a sensitivity analysis using different imputation methods will be performed. The imputation method(s) to be applied will be defined in the SAP.

If any parametric analyses are found to be inappropriate and/or fail their assumptions then supportive analysis will include non-parametric methods, as appropriate.

7.5.1 Hypothesis Testing

The null (H_0) and alternative (H_1) hypotheses for the primary efficacy analysis are:

- H_0: there is no difference between the HDM-SPIRE treatment group(s) and the placebo group.
- H_1: there is a difference between the HDM-SPIRE treatment group(s) and the placebo group.

Such that:

H_0 $\mu_A = \mu_p$

H_1 $\mu_A \neq \mu_p$

where, μ_A is estimated by the mean daily CS during the PAC3 period in the HDM-SPIRE treatment group and μ_P by the mean daily CS during the PAC3 period in the placebo group.

7.5.2 Demographic and Baseline Characteristics

Data will be summarised with respect to demographic and baseline characteristics by study treatment group.

7.5.3 Efficacy Analysis

7.5.3.1 Primary Analysis

7.5.3.1.1 Combined Score (TRSS and RMS)

The primary endpoint for this study is the mean daily CS during the PAC3 period in HDM-SPIRE treated subjects compared with mean daily CS during the PAC3 period in placebo treated subjects. The CS is a composite measurement of symptoms as measured by the TRSS and RMS, as measured using a pre-defined rating system that takes into account the different potency of available rescue medication.

The TRSS comprises assessment of 8 symptoms (4 nasal and 4 non-nasal symptoms) that are given a score of between 0 (absent) and 3 (severe) giving a range of potential scores of 0 to 24. Subjects are asked to record the average intensity of their symptoms over the last 24 hours once each morning for 3 weeks in the baseline and PAC periods.

Subjects also record their use of any of the provided rescue medications in the previous 24 hours. These are assigned a score as follows:

- RMS = 0; no allergy rescue medication used per day
- RMS = 0.5; at least one dose of antihistamine eye drops used per day
- RMS = 1; at least one dose of oral antihistamine used per day
- RMS = 2; at least one dose of intranasal corticosteroid used per day
- RMS = 3; at least one dose of systemic corticosteroid used per day

The RMS score is not additive, and therefore the maximum RMS is 3.

The TRSS (0-24) and the RMS (0-3) will be combined for analysis of the primary endpoint as follows:

CS = TRSS/8 + RMS

The maximum Combined Score is therefore 6.

The primary analysis will be the comparison between the HDM-SPIRE treatment groups and placebo for the ITT population using MMRM analysis for the PAC1, PAC2 and PAC3 mean CS assessments per subject. The model will include treatment, period and pooled centre as main effects, gender, asthma status and Baseline Allergy Evaluations CS as covariate, and treatment by period interaction. An unstructured covariance matrix will be used to assess within-subject dependence of the 3 observations of mean CS. A point estimate of the adjusted mean and two-sided 95% confidence interval for the difference in adjusted means between the active treatment groups and placebo will be calculated, with the treatment contrast corresponding to the mean CS of the PAC3 period. The Baseline Allergy Evaluation CS is defined as the mean of daily CS during the BAE period, as defined in Section 6.2.1.2. A hierarchical (step-down) approach will be used to control the overall type 1 error rate at 5%.

For declaring statistical significance, a step-down approach (first 4 x 12 nmol versus placebo, then 4 x 20 nmol versus placebo and then 8 x 12 nmol versus placebo) will be used to control the overall type I error at 0.05. Thus:

- Step 1: If 4 x 12 nmol versus placebo is significantly different at the 0.05 significance level, move to Step 2. If there is no significance, no further statistical significance will be declared.
- Step 2: If 4 x 20 nmol versus placebo is significantly different at the 0.05 significance level, move to Step 3. If there is no significance, no further statistical significance will be declared.
- Step 3: If 8 x 12 nmol versus placebo is significantly different at the 0.05 significance level, declare statistical significance.

The above analysis will be performed using all available data on the assumption that the probability of missing observations is independent of unobserved measurements (missing at random). Therefore the missing values will not be imputed for the primary analysis.

A sensitivity analysis will be performed to check the robustness of the primary results, assuming a missing not at random process. A Patter-mixture model based on control-based imputation will be utilized for the sensitivity analysis.

Additional sensitivity analyses may be defined in the SAP as appropriate.

7.5.3.1.2 Supportive Analyses

The above analysis will be supported by a responder analysis identifying the number of subjects who show a reduction from baseline CS during PAC3 at each tenth percentile for the percentage change from baseline in CS for each HDM-SPIRE treatment and placebo. In terms of significant reductions in allergic rhinoconjunctivitis symptom scores in individual subjects, in general ≥20% reduction in baseline scores can be regarded as being clinically meaningful and this level, as well as a 10% reduction, will be particularly evaluated in a test of proportions analysis between the HDM-SPIRE treatment groups and placebo group. A waterfall plot of the clinical response showing change in CS from baseline to PAC3 for each individual subject will be plotted for the HDM-SPIRE treatment groups and the placebo group.

The effect of centre on the primary endpoint for the ITT population will be investigated via an MMRM with main effects and covariates as specified for the primary analysis together with a treatment-by-centre interaction. A significant treatment-by-centre interaction in this analysis will be explored further. The pooled centres will be defined in the SAP.

Sensitivity analysis of differing weightings of TRSS and RMS for CS and the contribution of oral corticosteroids to the RMS will be defined in the SAP.

If any of the model assumptions are not met, further supportive analysis will be defined in the SAP.

7.5.3.1.3 Handling Missing Data

The SAP will provide a detailed plan to account for other missing data as a result of blinded review(s) prior to breaking the study blind. Examples of reasons for missing data include missing score and sub-score data for a visit and/or missing data for whole visits as a result of subject drop-outs. However, some forms of missing data have been prospectively accounted for and are described below.

If any of the 8 individual RSS, namely sneezing, runny nose, blocked nose, itchy nose, itchy eyes, watery eyes, red eyes or itchy ear/palate for a given day is missing; the TRSS for that day will be considered missing. If either the TRSS or the RMS is missing for a particular day then the CS will also be considered missing. This will also apply to other symptoms score endpoints (e.g. Total nasal symptom score and Total non-nasal symptom score) that use the ITT population.

For each subject in the PAC3 period (Weeks 50-52) the mean of the daily non-missing CS during that period will be calculated.

7.5.3.2 Secondary Analysis

Secondary endpoints will be prioritised in order of importance as outlined below. If any of the model assumptions of analysis of covariance (ANCOVA) are not met for any of the secondary endpoints then more appropriate statistical method will be applied and explained in the CSR.

7.5.3.2.1 Rhinoconjunctivitis Symptom Scores – Categorical scores

The mean TRSS and the mean component scores of the TRSS (nasal and non-nasal) during the PAC3 period will be summarised by treatment group. The difference in the TRSS and the component scores of the TRSS between the HDM-SPIRE treatment groups and the placebo group will be calculated and treatment comparisons made using the same methodology as described for the primary efficacy analysis.

7.5.3.2.2 Rescue Medication Usage

The mean RMS during the PAC3 period will be summarised by treatment group. The difference in the RMS between the HDM-SPIRE treatment groups and the placebo group will be calculated and treatment comparisons made using the same methodology as described for the primary efficacy analysis.

7.5.3.2.3 Clinical Global Impression of Change in Rhinoconjunctivitis Symptoms

An evaluation of the number of subjects in each category of the Clinical Global Impression of Change in Rhinoconjunctivitis Symptoms will be presented. Global impression of Change will be analysed using the Cochran-Mantel-Haenszel test.

7.5.3.2.4 Proportion of Symptom-Free Days

The difference in proportion of Symptom-Free Days between HDM-SPIRE treatment groups compared with the placebo group will be calculated and treatment comparisons made using the same model as specified for the primary efficacy analysis.

7.5.3.2.5 Rhinoconjunctivitis Quality-of-Life Questionnaire

The mean RQLQ score and the RQLQ domains at the end of the PAC3 period will be summarised by treatment group. The difference in the RQLQ scores between the HDM-SPIRE treatment groups compared with the placebo group will be calculated and treatment comparisons made using an ANCOVA.

7.5.3.3 Exploratory Analysis

The PAC1 and PAC2 periods will be analysed by the same methods as for the PAC3 period. These analyses will be considered exploratory, since they may be confounded by seasonal allergies. Where appropriate, the same covariates will be included in the exploratory analysis statistical models as for the primary efficacy analysis.

7.5.3.3.1 Combined Score

The mean CS during the PAC1 and PAC2 periods will be summarised by treatment group. The difference between the HDM-SPIRE treatment groups and the placebo group will be calculated and treatment comparisons made using the same methodology as described for the primary efficacy analysis, except that the treatment contrast will be specified corresponding to the mean CS of the PAC1 and PAC2 periods respectively.

7.5.3.3.2 Rhinoconjunctivitis Symptom Scores – Categorical Scores

The mean component scores of the TRSS (nasal and non-nasal) and the mean TRSS during the PAC1 and PAC2 periods will be summarised by treatment group. The difference in component scores of the TRSS and the TRSS between the HDM-SPIRE treatment groups and the placebo group will be calculated and treatment comparisons made using the same methodology as described for the primary efficacy analysis, except that the treatment contrast will be specified corresponding to the mean CS of the PAC1 and PAC2 periods respectively.

7.5.3.3.3 Rhinoconjunctivitis Symptom Scores – VAS Scores

Rhinoconjunctivitis symptom scores recorded using the VAS will be summarised descriptively by treatment group.

7.5.3.3.4 Rescue Medication Usage

The mean RMS during the PAC1 and PAC2 periods will be summarised by treatment group. The difference in RMS between the HDM-SPIRE treatment group and the placebo group will be calculated and treatment comparisons made using the same methodology as described for the primary efficacy analysis, except that the treatment contrast will be specified corresponding to the mean CS of the PAC1 and PAC2 periods respectively.

7.5.3.3.5 Rhinoconjunctivitis Quality-of-Life Questionnaire

The overall RQLQ score and the RQLQ domains at the end of the PAC1 and PAC2 periods will be summarised by treatment group. The difference in the RQLQ scores between the HDM-SPIRE treatment groups and the placebo group will be calculated and treatment comparisons made using an ANCOVA.

7.5.3.3.6 Asthma

An evaluation of asthma control (ACT score) at the end of the BAE and each PAC period will be performed in asthmatic subjects.

7.5.3.3.7 Home Environment (Exposure to Allergen)

Exposure to allergen (extent and variability) at baseline and end of PAC3 based on home environment changes will be summarised by treatment group and listed.

7.5.3.3.8 Sleep

The overall and component scores of the PSQI at the end of the BAE and each PAC period will be summarised descriptively.

7.5.3.3.9 Concomitant Medication Use

An evaluation of the use of any concomitant medications associated with rhinoconjunctivitis or related conditions will be performed. This will not include the use of allergy rescue medications defined in the Rescue Medication Plan.

7.5.4 Safety Analysis

Safety will be evaluated by analysis of the following parameters:

- AEs;
- Physical examination;
- Clinical laboratory tests (including immunology);
- FEV_1;
- Vital signs;
- Local reactions at the injection site.

The primary safety endpoint will be a comparison of the number of adverse events, and subjects with adverse events, in the HDM-SPIRE groups compared to placebo.

For safety analysis, descriptive statistics such as N, mean, median, minimum, maximum and SD will be summarised by treatment group for continuous variables. Frequency distribution will be summarised for categorical variables. No formal inferential tests will be performed on safety data.

The number and percentage of subjects who experience AEs will be presented by treatment group. Based on the MedDRA Preferred Term, subjects who experience the same AE on multiple occasions will be summarised at the maximum severity and most conservative relationship to the study medication. If 2 or more AEs are reported as a single event, the

individual terms will be reported as separate AEs.

The total number of AEs will be summarised by MedDRA System Organ Class and Preferred Term for each treatment group. Descriptive statistics will be presented for differences between the HDM-SPIRE treatment groups and the placebo group, but no hypothesis testing is planned.

Any deaths, SAEs and AEs leading to discontinuation of study medication administration will also be summarised by treatment group.

Local reactions at the injection site will be summarised by type of reaction and visit for each treatment group.

Physical examinations data will be listed only.

Vital signs will be presented as descriptive statistics on absolute values and the change from baseline will be summarised for each treatment group by visit.

FEV_1 will be presented as descriptive statistics and the absolute change from baseline and percentage change from baseline will be summarised for each treatment group by visit.

Clinical laboratory data for individual subjects will be listed and any out of range values will be highlighted. Laboratory data will be summarised for each treatment group by visit as follows: summary of absolute values and change from baseline and analysis of shifts from baseline.

Values for total IgE at Screening and Period 3 Follow-Up (Visit 5) and values for Der p and Der f specific IgE at Screening, End of Dosing Assessment (Visit 3I) and Period 3 Follow-Up (Visit 5) will be presented separately. Changes in total IgE and Der p and Der f specific IgE will be compared descriptively between the HDM-SPIRE treatment groups and the placebo group. Values for tryptase (if analysed) will be listed separately.

8.0 INVESTIGATOR RESPONSIBILITIES

8.1 Investigator Performance

The Principal Investigator and each Investigator will ensure that the study described in this protocol will be carried out to the highest standards of medical and clinical research practice. Each Investigator will also ensure that all those involved in the conduct of the study, such as, Co-Investigators, Pharmacists and Research Nurses, are qualified by experience and training to participate in the study, are provided with copies of the protocol and all safety information before study start and are fully familiar with their role.

The study will be performed in full accordance with this protocol, the principals of the Declaration of Helsinki, International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP); and applicable local regulatory requirement(s).

8.2 Ethical Considerations

8.2.1 Ethics Committee Review and Approval

IRB/IEC approval for the study will be obtained prior to initiating the study at any study site. Documents reviewed by the IEC/IRB will include the protocol, ICF, subject information sheet, Investigator's Brochure, any materials used directly by subjects (diaries, rating scales etc.) and any advertisements that are intended to be used in the study. All the required study documents must be approved by the IRB/IEC prior to the consent of the first subject. A copy of the IRB/IEC written approvals must be submitted to Circassia Ltd before the study may start and Investigational Medicinal Product release. Written approval must be obtained from the IRB/IEC for all major changes to the protocol, except when necessary to eliminate apparent immediate hazard to the subject. In this case, the IRB/IEC should be notified as soon as possible and written approval obtained.

The study protocol will also be reviewed by the appropriate competent authority/authorities. The study will not proceed until the appropriate competent authority/authorities has/have granted a clinical study authorisation.

8.2.2 Written Informed Consent

Prior to enrolment, the study procedures and any known or likely risks will be explained to the subjects in lay language by the Investigator or designee. The study information sheet will explain the objectives of the study, its potential risks and benefits. The subject should have

adequate time to read the information sheet and to ask the Investigator any questions. The Investigator must be satisfied that the subject has understood the information provided before written consent is obtained. If there is any doubt as to whether the subject has understood the written and verbal information, the subject should not enter the study. If a subject agrees to participate, he/she will be asked to sign and date an ICF.

All subjects will receive a copy of the signed ICF, as well as the written information sheet about the study. The subjects will be assured that they can withdraw from the study at any time and for any reason. Written informed consent must be obtained before any study-related procedure is performed. Each subject's ICF must be signed and dated by both the Investigator or designee and the subject. All ICFs will be checked by the Study Monitor, but retained by the Investigator.

The original signed ICFs will be kept in the subject's medical notes and must be made available for inspection by the Study Monitor and/or the regulatory authority. A record should also be made in the medical records that the subject voluntarily agreed to participate in the study.

8.2.3 Information for Subject's General Practitioner/Primary Care Physician

If the subject consents, their general practitioner/primary care physician (and any specialist the subject might be treated by) will be notified of the subject's intended involvement in the study and will be asked whether or not there is any contraindication to the subject's participation.

8.3 Confidentiality

8.3.1 Subject Confidentiality

The Investigator shall reassure subjects that their identity will be kept confidential by third parties that conduct audits and inspections of the study centre and its documentation. A unique study number assigned to each subject at the start of the study will be used to identify the subject in the eCRF, on all study correspondence and in the study database. The Investigator will keep an identification code list and enrolment log, which will list the full name of each subject alongside the subject number assigned and the date enrolled. This log will remain in the Investigator's Site File at the study centre.

8.3.2 Sponsor Confidentiality

All information concerning the Circassia study medication and the operations of Circassia, such as patent applications, formulae, manufacturing processes, basic scientific data or formulation information, supplied to the Investigator by Circassia and not previously published in the open literature is considered confidential by Circassia and shall remain the sole property of the company. The Investigator agrees to use this information only in performing this study and will not use it for other purposes without the written consent of the company.

8.4 Study Documentation

8.4.1 Case Report Forms

Clinical data will be entered onto eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based EDC system must correspond to and be supported by source documentation maintained at the study centre. All eCRFs and records transmitted to the Sponsor must carry only coded identifiers such that personally identifying information is not transmitted. Access to the EDC system is available to authorised users via the study's Internet web site, where an assigned username and password are required for access.

Any changes made to data after collection will be made through the use of Data Clarification Forms. Data reported on the eCRFs, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. Electronic case report forms will be considered complete when all missing and/or incorrect data have been resolved. An audit trail of all changes that are made to the database, including the reason for the data change, will be created and maintained.

The assessments (RSS, RMS, ASS) captured in the eDiary will be used for efficacy analyses. Assessments captured in the pDiary (productivity, lost work/school days, additional doctor/clinic visit, home environment changes, recording of AEs, recording of concomitant medications) will be entered on the eCRF by the Investigator or designee. The pDiary cards must be retained in the Investigator Site File.

The Investigator will keep a copy of the eCRFs, the Investigator's Site File and source documents until notified otherwise by Circassia.

8.4.2 Investigator Site File

The Investigator Site File must be kept up to date and ready for inspection / audit at any time.

8.4.3 Study Drug Accountability Records

Detailed Drug Accountability Records must be generated and maintained for each shipment and subject.

The Investigator or their designee will be responsible for documenting the use of each pack of the study medication, including details of the study packs used for each subject, in the Drug Accountability Records. Periodically during the conduct of the study, Drug Accountability Records will be inspected by the Study Monitor.

All Drug Accountability Records and temperature logs must be maintained securely in the Pharmacy. At the end of the study the Pharmacy records must be transferred to the Investigator to archive within the Investigator Site File.

8.4.4 Record Retention

Study records and source documents need to be preserved for at least 15 years after the completion or discontinuation of the study or 2 years after the last approval of a marketing application in an ICH region, whichever is the longer time period. Records will be retained for longer time periods than specified above if required by any regulatory authority. No records must be destroyed without the prior permission of Circassia.

8.4.5 Source Documentation

The Investigator agrees to permit study-related monitoring, audits, IRB/IEC review and regulatory inspections of the study centre and any source documentation, by clinical research and audit personnel from the Sponsor or designee or representatives of regulatory authorities. Direct access to the subject's medical/clinical records (if applicable to the study) is necessary to verify and corroborate the data recorded on the eCRFs. This procedure is termed Source Document Verification. These third parties are obligated to maintain confidentiality of the subjects' identities.

8.5 Publication

Circassia intends to publish the results of this study, whether positive or negative, in line with the guidance in the Declaration of Helsinki (Part B, No 26). The Investigator and Circassia will normally prepare a manuscript together. To avoid disclosures that may affect the proprietary rights of the Sponsor, the Investigator agrees to allow Circassia the opportunity to review all manuscripts and abstracts 60 days prior to submission for publication. Circassia reserves the right to include the report of this study in any regulatory documentation or submission or in any informational materials.

8.6 Non-Protocol Research

No investigational research procedures pertaining to this study other than those outlined in this protocol may be undertaken on the subjects without the prior written permission of the subject, the Sponsor, the IRB/IEC and, when necessary, the appropriate competent authority.

9.0 SPONSOR RESPONSIBILITIES

9.1 General

Circassia agrees to adhere to the most current version of ICH E6 Guidelines on GCP. Circassia has a legal responsibility to report fully to regulatory authorities the results of this study.

9.2 No Fault Compensation and Indemnity

Circassia will provide "no-fault" compensation insurance against any injury incurred by a subject as a result of participation in the study. Circassia adheres to the ABPI "Clinical Trial Compensation Guidelines" (1991). The Investigators in this study will be indemnified as detailed in a separate document.

9.3 Monitoring

The study staff may not enter any subjects into the study prior to completion of a pre-study initiation meeting conducted by a representative of Circassia or designee.

Monitoring during the study will be undertaken at regular intervals by suitably qualified and appropriately trained personnel under contract to Circassia according to SOPs. The purpose of monitoring is to ensure:

- Compliance with the protocol;
- Adherence to regulatory and GCP obligations;
- Proper maintenance of all study documentation;
- The completeness and exactness of the data entered in the eCRFs;
- Accurate reporting of all AEs;
- Close liaison with the Investigator and study staff to clarify any problems that may arise during the study.

9.4 Confidentiality

Neither Circassia nor its designee(s) will keep any material on file referring to the study subject by their full name. The identity of the subject will be respected and maintained as confidential at all times.

9.5 Finance

Financial agreements between Circassia and the CRO managing the study and the CRO managing the study and the Investigator will be the subject of separate agreements.

9.6 Audit

Circassia may audit or appoint an independent auditor to conduct an audit of this study while it is running or after it has been completed. The study may also be inspected by a regulatory authority either while it is running or up to several years later.

10.0 DATA SAFETY MONITORING COMMITTEE

Circassia will appoint an independent Data Safety Monitoring Committee (DSMC) to conduct a review of the safety data. Full details of DSMC membership, responsibilities, statistical analyses and data presentations to be used in the safety review will be provided in a DSMC Charter which will be finalised prior to the first DSMC meeting. The Charter will include detailed guidance to the DSMC on the circumstances under which they should recommend temporary or permanent stopping of the trial.

11.0 WARNINGS, PRECAUTIONS AND CONTRA-INDICATIONS

As with any new drug, local or systemic allergic reactions, including anaphylaxis, may occur. Therefore medications for the treatment of anaphylactic reactions should be available for immediate use following administration of treatment (see Section 5.8.2). Subjects should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur.

It is possible that subjects may experience injection site reactions, including injection site pain, swelling, erythema and pruritus. Intradermal injection may also cause bruising or bleeding.

Blood sampling may result in bruising at the site of needle insertion and fainting.

Asthmatic reactions following administration of other SPIRE treatments (e.g. Cat-PAD) have been found to be uncommon and all have appeared to resolve with the use of short-acting β_2 agonists.

Concomitant use of beta-blockers, alpha-adrenoceptor blockers and monoamine oxidase inhibitors during Screening and Study Medication Administration is contraindicated and subjects using any of the above during these periods will be withdrawn from the study.

12.0 REFERENCES

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Circassia, TH003 Clinical Study Protocol – A Field Study to Observe Symptom Scores and Allergy Medication Usage in Subjects with a History of House Dust Mite-Induced Rhinoconjunctivitis. 2013.

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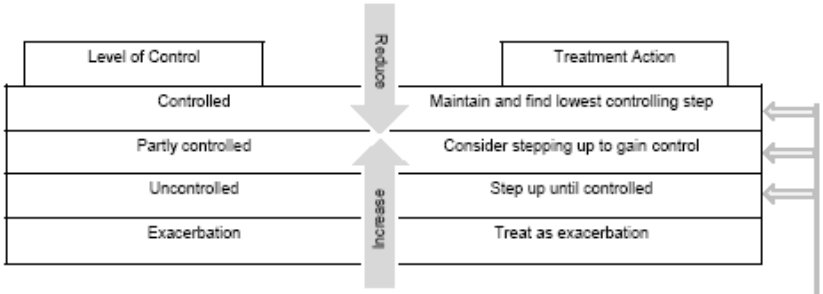
13.0 APPENDICES

APPENDIX 1 GINA Report 2012– Levels of Asthma Control (www.ginasthma.org)

Management approach based on control: Adults and children older than 5 years



Step 1	Step 2	Step 3	Step 4	Step 5
Asthma education Environmental control				
As needed rapid acting β_2- agonists	As needed rapid acting β_2- agonists			
Controller options ***	Select one	Select one	To step 3 treatment select one or more	To step 4 treatment add either
	Low-dose inhaled ICS*	Low dose ICF plus long-acting β_2 agonist	Medium or high-dose ICS plus long-acting β_2 agonist	Oral glucocorticosteroid (lowest dose)
	Leukotriene modifier**	Medium or high-dose ICS	Leukotriene modifier	Anti-IgE treatment
		Low-dose ICS plus leukotriene modifier	Sustained release theophylline	
		Low-dose ICS plus sustained release theophylline		

*ICS =inhaled glucocorticosteroids
**= Receptor antagonist or synthesis inhibitors
***= Preferred controller options are shown in shaded boxes

A. Assessment of current clinical control (preferably over 4 weeks)

Characteristic	Controlled (All of the following)	Partly Controlled (Any measure present)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	**Three or more features of partly controlled asthma*†**
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (Peak Expiratory Flow or FEV1)‡	Normal	< 80% predicted or personal best (if known)	

B. Assessment of Future Risk (risk of exacerbation, instability, rapid decline in lung function, side-effects)

Features that are associated with increased risk of AEs in the future include:

Poor clinical control, frequent exacerbations in the past year*, admission to critical care for asthma, low FEV_1, exposure to cigarette smoke, high dose medications.

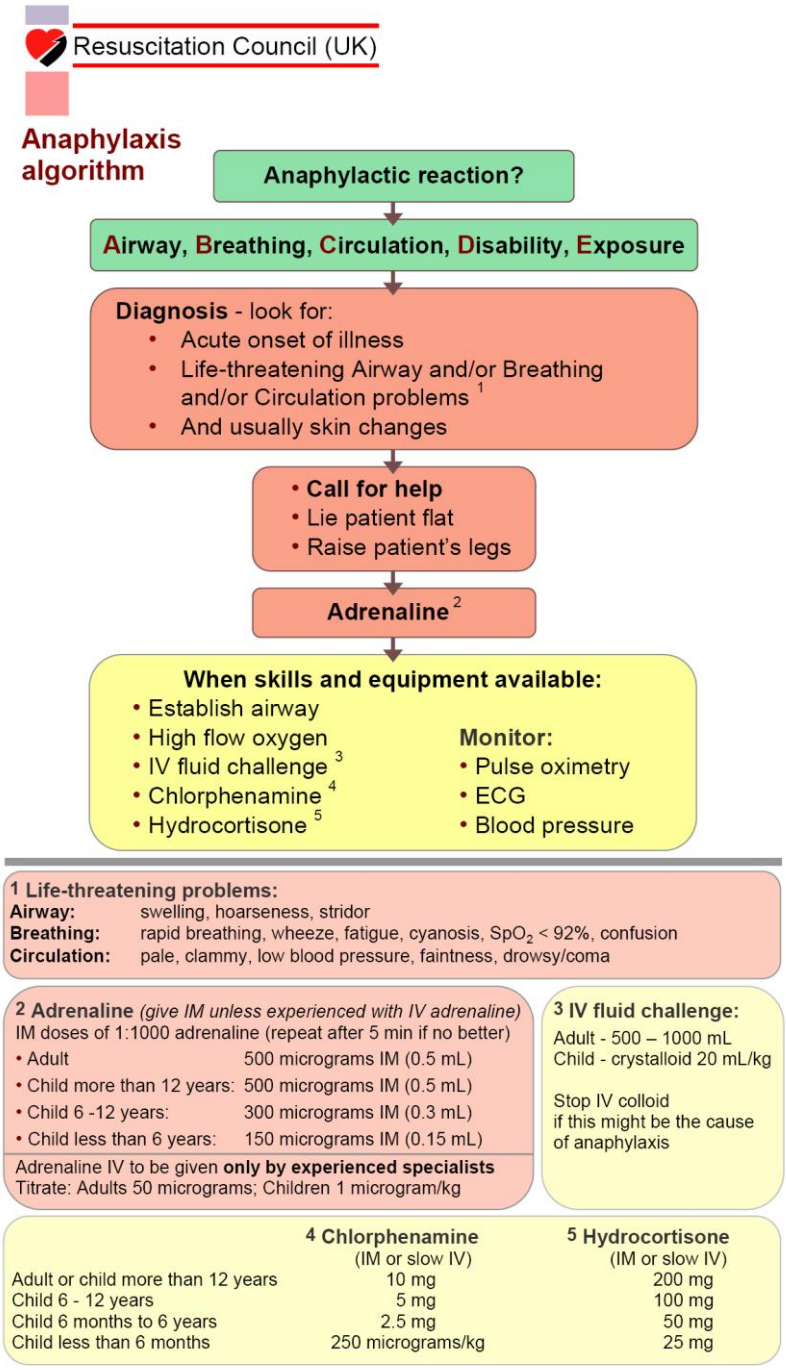
* *Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate.*

† *By definition, an exacerbation in any week makes that an uncontrolled asthma week.*

‡ *Without administration of bronchodilator*

Lung function is not a reliable test for children 5 years and younger.

APPENDIX 2 Anaphylaxis Algorithms



Appendix 3 Rescue Medication Package Description and Rescue Medication Plan

The "Rescue Medication Package" is a package of medications that you may use during the period you are scoring your symptoms on the eDiary to relieve any troublesome allergy symptoms that you may experience. The study doctor will give you the "Rescue Medication Package" and will explain **when** and **how** to use each type of medication. The Package will include the following allergy medications:

Rescue Medications for Allergy Symptoms (Rhinoconjunctivitis)		
Step	**Rescue Medication**	**Dosing Instruction**
1	Anti-Histamine Eye Drops	1 drop in each affected eye a maximum of twice a day
2	Anti-Histamine Tablets	Maximum of 1 tablet a day
3	Steroid Nasal Spray	Maximum of 2 sprays (usually just one) in each nostril a day
4	Steroid Tablets	Not included in the Rescue Medication Package but to be used as prescribed by the study doctor

Rescue Medication Plan

The Rescue Medication Package contains three medicines that are commonly used by doctors to treat allergy symptoms (rhinoconjunctivitis). You should wait until your allergy symptoms become troublesome **before** using any of the provided medication. The Rescue Medication Package medicines should be used as follows:

When your allergy symptoms are mainly ocular, such as itchy, watery, or red eyes.

If you mainly have ocular symptoms, wait until these become troublesome and then use the eye drops provided in the Rescue Medication Package. If you find your ocular symptoms do not improve or they are still troublesome half an hour after using an eye drop take one of the anti-histamine tablets from the Rescue Medication Package.

When you have nasal symptoms, such as runny nose, sneezing, blocked or itchy nose or when you have both nasal and non-nasal symptoms.

If you mainly have nasal symptoms, or nasal and non-nasal symptoms, treat them by taking one of the anti-histamine tablets from the Rescue Medication Package. If you find your nasal symptoms do not improve or they are still troublesome two hours after taking the tablet use the steroid nasal spray included in the Rescue Medication Package. If you find your ocular symptoms do not improve or they are still troublesome at two hours after using the tablet use your anti-histamine eye drops included in the Rescue Medication Package.

APPENDIX 4 World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/sign(s) of one organ system present[i] **Cutaneous** Generalized pruritus, urticaria, flushing or sensation of heat or warmth[ii] **or** Angioedema (not laryngeal, tongue or uvular) **or** **Upper respiratory** Rhinitis (e.g. sneezing, rhinorrhoea, nasal pruritus and/or nasal congestion) **or** Throat-clearing (itchy throat) **or** Cough perceived to come from the upper airway, not the lung, larynx, or trachea **or** **Conjunctival** Conjunctival erythema, pruritus or tearing **Other** Nausea, metallic taste, or headache	**Symptom(s)/sign(s) of more than one organ system present** **or** **Lower respiratory** Asthma: cough, wheezing, shortness of breath (e.g., less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) **or** **Gastrointestinal** Abdominal cramps, vomiting, or diarrhoea or **Other** Uterine cramps	**Lower respiratory** Asthma (e.g., 40% PEF or FEV1 drop, NOT responding to an inhaled bronchodilator) **or** **Upper respiratory** Laryngeal, uvula or tongue oedema with or without stridor	**Lower or Upper respiratory** Respiratory failure with or without loss of consciousness **or** **Cardiovascular** Hypotension with or without loss of consciousness	Death
Patients may also have a feeling of impending doom, especially in Grades 2, 3, or 4. Note: children with anaphylaxis seldom convey a sense of impending doom and their behaviour changes may be a sign of anaphylaxis, e.g., becoming very quiet or irritable and cranky.				

Scoring includes a suffix that denotes if and when epinephrine is or is not administered in relationship to symptom(s)/sign(s) of the systemic reaction: a, ≤5 minutes; b, >5 minutes to ≤10 minutes; c, >10 minutes to ≤20 minutes; d, >20 minutes; z, epinephrine not administered
The final grade of the reaction will not be determined until the event is over, regardless of the medication administered. The final report should include the first symptom(s)/sign(s) and the time of onset after the subcutaneous allergen immunotherapy injection[iii] and a suffix reflecting if and when epinephrine was or was not administered, **e.g., Grade 2a; rhinitis: 10 minutes.**
Final Report: Grade a-d, or z_____ **First symptom** _____ **Time of onset of first symptom** _____
Comments[iv]

i. Each Grade is based on organ system involved and severity. Organ systems are defined as: cutaneous, conjunctival, upper respiratory, lower respiratory, gastrointestinal, cardiovascular and other. A reaction from a single organ system such as cutaneous, conjunctival, or upper respiratory, but not asthma, gastrointestinal, or cardiovascular is classified as a Grade 1. Symptom(s)/sign(s) from more than one organ system or asthma, gastrointestinal, or cardiovascular are classified as Grades 2 or 3. Respiratory failure or hypotension, with or without loss of consciousness, defines Grade 4 and death Grade 5. The Grade is determined by the physician's clinical judgment.
ii. This constellation of symptoms may rapidly progress to a more severe reaction.
iii. Symptoms occurring within the first minutes after the injection may be a sign of severe anaphylaxis. Mild symptoms may progress rapidly to severe anaphylaxis and death.
iv. If signs or symptoms are not included in the Table or the differentiation between a systemic reaction and vasovagal (vasodepressor) reaction, which may occur with any medical intervention, is difficult, please include comment, as appropriate.

From: Cox L., Larenas-Linnemann D., Lockey R.F., Passalacqua G. (2010). Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol;**125**:569-74