Circassia Ltd

Clinical Study Protocol

Protocol Identifier: CP007A

An Optional Prospective Follow-on Study to Evaluate the Continued Efficacy and Safety of Cat-PAD in Cat Allergic Subjects up to Five Years after the Administration of Treatment

PROTOCOL IDENTIFIER: CP007A

Version 5.0 Final (Incorporating Protocol Amendment 01, 02, 03 and 04 and replacing Version 4.0 dated 31 July 2014)

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EudraCT Number: 2013-004669-15

STUDY PERSONNEL

SPONSOR COMPANY	Circassia Ltd The Magdalen Centre The Oxford Science Park Oxford OX4 4GA +44 (0) 1865 598078 (‘Phone) +44 (0) 7092 987560 (Fax)
COORDINATING INVESTIGATOR	Joerg Kleine-Tebbe, MD Spandauer Damm 130 Berlin Germany +49 3030307126 (‘Phone) kleine-tebbe@allergie-experten.de (Email)
STUDY MONITOR	Roisin McGloughlin Quintiles (Irl) Ltd. Eastpoint Business Pk Dublin 3 Ireland +353 1 8391123 (‘Phone) roisin.mcgloughlin@quintiles.com (Email)
MEDICAL MONITOR	John Powell Circassia Ltd +44 (0) 1865 573737 (‘Phone)

EMERGENCY NUMBERS

SAE Reporting	**1 888 723 9952 ('Phone – USA and Canada)** **+44 1628 496 300 ('Phone - Rest of World)** **1 800 540 1863 (Fax – USA and Canada)** **+44 1865 595 595 (Fax - Rest of World)** **f2m-eastleigh-medical@iconplc.com (Email)**
Circassia Medical Representative	**+44 1865 573737 ('Phone)**
	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**

SIGNATURES

PROTOCOL PREPARED BY:

Signature

08 DEC 2014
Date dd mmm yyyy

Name: Katie Proctor

Job Title: Clinical Programme Manager

PROTOCOL APPROVED FOR USE IN CLINICAL STUDY BY:

Signature

08 DEC 2014
Date dd mmm yyyy

Name: John Powell

Job Title: Vice President, Medical Affairs

Signature

08 DEC 2014
Date dd mmm yyyy

Name: Steve Pawsey

Job Title: Chief Medical Officer

PRINCIPAL INVESTIGATOR'S AGREEMENT

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**

Signature Date dd mmm yyyy

Name:

Principal Investigator

PROTOCOL SYNOPSIS

Protocol Identifier	CP007A
Study Title	An Optional Prospective Follow-on Study to Evaluate the Continued Efficacy and Safety of Cat-PAD in Cat Allergic Subjects up to Five Years after the Administration of Treatment
Protocol Version	**5.0 Final**
Sponsor	Circassia Ltd
Phase	IIIb
Indication	Treatment of cat allergen induced rhinoconjunctivitis in subjects with clinically relevant symptoms.
Objectives	**Primary Objective:** • To evaluate the continued efficacy of Cat-PAD, the first in a new class of Synthetic Peptide Immuno-Regulatory Epitopes, for a total of up to five years after the administration of treatment, based on the reduction of symptoms and the use of allergy medication in subjects previously participating in CP007. **Secondary Objectives:** • To evaluate the continued safety and tolerability of Cat-PAD for up to five years after the administration of treatment. • To evaluate the effect of Cat-PAD on RQLQ for up to five years after the administration of treatment. • To evaluate the effect of Cat-PAD on the onset of asthma for up to five years after the administration of treatment. • To evaluate the effect of Cat-PAD on asthma progression in subjects previously enrolled in CP007 with GINA 1 asthma for up to five years after the administration of treatment. **Exploratory Objectives:** • To evaluate the effect of Cat-PAD on changes in asthma control in asthmatic subjects for up to five years after the administration of treatment. • To evaluate the effect of Cat-PAD on changes in sleep quality in adults using the PSQI for up to five years after the administration of treatment. • To evaluate the effect of Cat-PAD on changes in productivity using the WPAI:CIQ-AS for up to five years after the administration of treatment. • To evaluate the effect of Cat-PAD on symptomatology on unplanned exposure to a cat in normal daily life in subjects who no longer keep a cat for up to five years after the administration of treatment. • To evaluate the effect of Cat-PAD on health economic outcomes for up to five years after the administration of treatment.
Study Design	Subjects from participating sites who complete the final Post Administration Collection period (PAC3) in CP007 (a randomised, double-blind, superiority, multiple dose, placebo-controlled, parallel group, multi-centre, field study) will be invited to participate in CP007A. The CP007A Enrolment Visit may occur at or

	after the final Follow-Up Visit (Visit 5) in CP007. Subjects who wish to participate will be issued with a paper diary and digital pen (ePRO) to record the required patient reported outcomes data. This comprises annual and monthly evaluations. The annual assessment data will be recorded at the same time of year as the Baseline Allergy Evaluation visit in CP007. It will include scoring rhinoconjunctivitis symptoms and allergy medication use over a 3-week period, as well as single assessments of quality of life, sleep quality, asthma status and work/school interference. Additionally, on a monthly basis, subjects will record information regarding hospital/doctor visits; concomitant medication; illnesses/symptoms; asthma progression; and changes in home environment using the ePRO. Subjects will have up to four visits each year, two of which may be completed by telephone. At each visit, site staff will record any adverse events (AEs) and serious adverse events (SAEs), and at the on-site visits subjects will be provided with their next diary binder. One of the on-site visits will be scheduled just prior to the 3-week symptom and allergy medication use recording period. At this visit, subjects will be provided with an Allergy Medication Kit. For all on-site visits, where possible subjects will be instructed to complete the closest monthly assessment in the diary binder during the visit. Subjects will not be required to undergo any specific treatment or lab tests as a participant in this follow-up study. All physician visits and treatments / procedures will be administered per the physician's direction. Subjects will have a final End of Study Visit, which will coincide with the end of the final annual Allergy Evaluation Period assessment. The duration of data collection for this follow-up study will be up to 4 years for each subject.
Sample Size	Not Applicable
Study Population	Subjects who completed PAC3 in CP007 (a randomised, double-blind, superiority, multiple dose, placebo-controlled, parallel group, multi-centre, field study) will be invited to participate in this optional, prospective follow-on study. Subjects in countries where fewer than 10 subjects were randomised will not be invited to participate in this study.
Inclusion/Exclusion Criteria	**Inclusion Criteria** 1. Previously randomised into clinical study CP007 and completed PAC3. 2. Provide written informed consent or assent, as appropriate. (For subjects less than 18 years a Parent/Guardian will also be required to provide written informed consent). 3. Willing and able to comply with the study requirements. **Exclusion Criteria** 1. Started allergen immunotherapy since completing CP007. 2. Has been informed of the treatment received in study CP007. 3. Dependent on the Investigator/site either for employment or education or are first degree relatives or partners of the Investigator/study staff. 4. Subjects institutionalised due to a legal or regulatory order
Investigational Product	Not applicable - no additional investigational product will be administered

Route of Administration	Not applicable - no additional investigational product will be administered
Treatment Regimen(s)	Not applicable - no additional investigational product will be administered
Efficacy Parameters	The following efficacy parameters will be measured in the study: Monthly: • Hospital / Physician office visits • Number of lost work/ school days • Current status / change in home environment • Exposure to cat • Global assessment of symptoms on exposure to cat during normal life for those who no longer keep a cat • Asthma progression • Concomitant medications associated with rhinoconjunctivitis or related conditions Annually: • Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) • Pittsburgh Sleep Quality Index (PSQI) (if at least 18 years old at time of assessment period) • 6-Question Asthma Control Questionnaire (ACQ) (asthmatic subjects only) • Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific(WPAI:CIQ-AS) • Asthma progression • Change in geographic location • Total Rhinoconjunctivitis Symptom Score (TRSS) (for a three-week period) • Allergy medication usage (for a three-week period) • Asthma Symptom Score (for a three-week period) • Exposure to indoor cat (for a three-week period)
Safety Parameters	The safety and tolerability of Cat-PAD will be assessed by measurement/recording of: • AEs • SAEs
Pharmacokinetic Parameters	None
Statistical Analysis	A detailed Statistical Analysis Plan (SAP) (including dictionaries for coding and software used) will be developed and approved by the Sponsor prior to conducting any analyses. The nature of the formal statistical testing will be described and justified in the SAP, discussing any potential biases and challenges caused by the data collected and circumstances of the study. It is anticipated that the analyses will be similar to those performed for the CP007 study and that the statistical tests for each endpoint will use a Bonferroni-Holm adjustment for the two treatment comparisons (two courses of Cat-PAD versus placebo and one course of Cat-PAD versus placebo), thereby keeping the overall type I error rate at 0.05. The tests will be two sided. The first analysis of the data will be performed on the first year's data after all subjects have completed one year in this study. Additional analyses of the second,

	third and fourth year in the study will be performed after all subjects have completed each additional year in the study. At each of the statistical analyses performed after one, two, three and four years, there will be no adjustment to the significance level, apart from the Bonferroni-Holm correction (due to multiple treatment comparisons) stated above. Subject data will be pulled from CP007 and will be used as baseline data for CP007A. 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. Where appropriate confidence intervals will be used to explore the size and direction of any changes in variables or differences between groups. For the primary efficacy analysis, the data will be summarised and analysed using methods as for study CP007. The analysis will provide a comparison of the mean Combined Score (TRSS/8+Allergy Medication Score [AMS]) for each treatment group. The data will be analysed using covariates including pooled centre, age group (as randomised), gender, asthma status and baseline score. Additional informative subgroup descriptive analyses may also be performed. Other endpoints will be analysed appropriately to address the secondary objectives of the study, including non-parametric methods, where relevant. Safety data will be analysed descriptively.
Study Sites	Sites previously participating in clinical study CP007 will participate in this study with the exception of countries where fewer than 10 subjects were randomised.
Planned Study Dates **Start of clinical phase** **End of clinical phase**	 December 2013 June 2019
Duration of the Study	The duration of the study for each subject will be approximately 4 years.

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LIST OF ABBREVIATIONS

ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
ACQ	Asthma Control Questionnaire
AMS	Allergy Medication Score
ASS	Asthma Symptom Score
CFR	Code of Federal Regulations
CRF	Case Report Form
CS	Combined Score
EDC	Electronic Data Capture
ePRO	Digital Pen
Fel d 1	Cat (*Felis domesticus*) allergen 1
FOCBP	Female of Child-bearing Potential
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
IAF	Informed Assent Form
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
PAC	Post-Administration Collection
PAD	Peptide Antigen Desensitisation
PSQI	Pittsburgh Sleep Quality Index
RQLQ	Rhinoconjunctivitis Quality-of-Life Questionnaire
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMS	Short Message Service
TRSS	Total Rhinoconjunctivitis Symptom Score
USA	United States of America
WAO	World Allergy Organization
WHO	World Health Organization
WPAI:CIQ-AS	Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific

1.0 INTRODUCTION

Allergic rhinitis is a significant global public health concern, particularly in the economically developed world, affecting up to 30% of adults (Gupta *et al,* 2004) and up to 40% of children (ISAAC 1998). Allergy to cat dander is one of the most common forms of allergic disease in the United States of America (USA) and Europe, affecting 10%-15% of subjects with allergic rhinitis and/or asthma. Out of a population of 310 million people in the USA, approximately 62 million people suffer from allergies, with 26 million of these suffering from cat allergy (World Allergy Organization [WAO] 2011). Allergic rhinoconjunctivitis significantly reduces quality of life (Laforest *et al,* 2005). Using the well validated Short Form 36 Health Related Quality-of-Life questionnaire, it has been demonstrated that subjects with allergic rhinitis report more problems with social activities, difficulties with daily activities as a result of emotional problems and poorer mental wellbeing (Leynaert *et al,* 2000). In addition, it interferes with both attendance and performance at school and work (Blaiss 2004; Cockburn *et al,* 1999) and the prevalence of the condition is still rising (Maziak *et al,* 2003).

The prevalence of human allergy to pet dander is a growing problem of global public health importance, as the morbidity associated with allergic diseases disproportionately affects socio-economically disadvantaged populations, particularly children (Morris 2010). The animal-origin allergen Fel d 1 (*Felis domesticus* allergen 1), is present ubiquitously in the human environment, and is widely found in public buildings including schools, the work place, automobiles, airplanes and cinemas (Morris 2010). Cats are the dominant source of the allergen Fel d 1. Although several molecules in cat extracts are allergenic, the most important one is Fel d 1 with approximately 90% of individuals allergic to cats having elevated levels of specific immunoglobulin E to the protein. Levels of Fel d 1 are much higher in households with current cat residence. In homes where there has never been a resident cat, there is a direct correlation of indoor allergen level with the prevalence of cat ownership in the community at large. Fel d 1 is also detectible in many public places at levels capable of sensitising or exacerbating symptoms in susceptible individuals. This is especially relevant and problematic for children in schools (Morris 2010).

Existing treatment for cat-allergy induced allergic rhinoconjunctivitis is essentially symptomatic and consists of antihistamines given by mouth, intranasally or as eye drops, cromoglycate nasal sprays as well as topical corticosteroids. None of these treatments are disease-modifying and, unless taken regularly, offer poor protection. Immunotherapy, on the other hand, is directed toward the pathological basis of the disease and this form of treatment is used for cat allergy in some countries using whole allergen extract dander. However, there are few formal studies of its efficacy despite some reported short-term improvements in

bronchial hyperreactivity and other target organ sensitivities (Taylor *et al,* 1978; Ohman *et al,* 1984; Sundin *et al,* 1986; Alvarez-Cuesta *et al,* 1994; Varney *et al,* 1997). There are no long-term follow-up studies evaluating the continued benefit of immunotherapy for cat allergy on either allergic rhinoconjunctivitis symptoms or progression to asthma.

2.0 OBJECTIVES

The proposed study is designed to evaluate the continued efficacy and safety of Cat-PAD in cat allergic subjects for up to five years after the start of administration of treatment. This study is an optional follow-up study to a phase 3 double-blind placebo-controlled study; no further investigational product is being administered. The study's principal purpose is to continue to monitor subjects who have received investigational product as part of the CP007 study.

2.1 Primary Objective

To evaluate the continued efficacy of Cat-PAD, the first in a new class of Synthetic Peptide Immuno-Regulatory Epitopes, for a total of up to five years after the administration of treatment, based on the reduction of symptoms and the use of allergy medication in subjects previously participating in CP007.

2.2 Secondary Objectives

- To evaluate the continued safety and tolerability of Cat-PAD for up to five years after the administration of treatment.
- To evaluate the effect of Cat-PAD on Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ) for up to five years after the administration of treatment.
- To evaluate the effect of Cat-PAD on the onset of asthma for up to five years after the administration of treatment.
- To evaluate the effect of Cat-PAD on asthma progression in subjects previously enrolled in CP007 with GINA 1 asthma for up to five years after the administration of treatment.

2.3 Exploratory Objectives

- To evaluate the effect of Cat-PAD on changes in asthma control in asthmatic subjects for up to five years after the administration of treatment.
- To evaluate the effect of Cat-PAD on changes in sleep quality in adults using the Pittsburgh Sleep Quality Index (PSQI) for up to five years after the administration of treatment.
- To evaluate the effect of Cat-PAD on changes in productivity using the Work Productivity and Activity Impairment Questionnaire (WPAI:CIQ-AS) for up to five years after the administration of treatment.

- To evaluate the effect of Cat-PAD on symptomatology on unplanned exposure to a cat in normal daily life in subjects who no longer keep a cat for up to five years after the administration of treatment.
- To evaluate the effect of Cat-PAD on health economic outcomes for up to five years after the administration of treatment.

3.0 STUDY DESIGN

3.1 Overall Study Design

An optional prospective, follow-on study to a randomised, double-blind, superiority, multiple dose, placebo-controlled, parallel group, multi-centre, field study (CP007).

Subjects from participating sites who complete the final Post Administration Collection Period (PAC3) in CP007 will be invited to participate in CP007A. Where possible the Enrolment Visit will occur at the same time as the final Follow-Up Visit as scheduled in CP007. Subjects who consent to take part in this study and who meet all inclusion/exclusion criteria will be issued with paper diary binders and a digital pen (ePRO) to record the required patient reported outcomes data. This comprises annual and monthly evaluations. The annual assessment data will be recorded at the same time of year as the Baseline Allergy Evaluation Period (Visit 2A to Visit 2B) established in CP007. It will include scoring rhinoconjunctivitis symptoms and allergy medication use over a 3-week period, as well as single assessments of quality of life, sleep quality, asthma status and work/school interference. As with CP007, for this study, subjects will receive an Allergy Medication Kit containing approved allergy treatments prior to the start of this 3-week period. The kit will contain the same treatments provided to subjects in CP007.

Additionally, on a monthly basis, subjects will record information in their diary using the digital pen regarding hospital/doctor visits; concomitant medication use; illnesses/symptoms; asthma progression and changes in home environment. Subjects will be requested to upload data from the digital pen monthly via their home computer (internet) directly to a secure website or via a mobile 'phone; if a subject does not have access to a computer, a mobile 'phone will be provided to the subject for the duration of the study and for the sole purpose of uploading data and participating in the study.

Subjects will have up to four visits each year, two of which may be conducted by telephone. At each visit, site staff will record any adverse events (AEs) and serious adverse events (SAEs), and at the on-site visits subjects will be provided with their next diary binder. One of the on-site visits will be scheduled just prior to the annual 3-week symptom and allergy medication use recording period. At this visit, subjects will be provided with an Allergy Medication Kit. For all on-site visits, where possible subjects will be instructed to complete the closest monthly assessment in the diary binder during the visit. Subjects will not be required to undergo any specific treatment or lab tests at these visits.

Subjects will have a final End of Study Visit, which will coincide with the end of the final annual Allergy Evaluation Period assessment.

The duration of this follow-up study will be up to 4 years for each subject.

3.2 Endpoint

3.2.1 Primary Endpoint

- Mean Combined Score (CS) consisting of (TRSS/8 + Allergy Medication Score [AMS]).

The total rhinoconjunctivitis symptom score (TRSS) is the sum of the eight individual symptoms, each of which is scored from 0 to 3 resulting in a range of scores from 0-24. TRSS will be divided by the number of symptoms (8) to provide an average score range of 0-3.

Allergy medications will be provided to subjects to be used according to a pre-specified Allergy Medication Plan (See Appendix 1). Subjects will be requested to use antihistamine eye drops as first line allergy 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. Oral corticosteroids may be prescribed at the Investigator's discretion. The use of allergy medications will be scored based on Didier (Didier *et al,* 2009) as follows:

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

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

CS = TRSS/8 + AMS

3.2.2 Secondary Endpoints

- Mean TRSS
- Mean component scores of the TRSS (nasal and ocular)
- Mean AMS
- Mean RQLQ Score

- Concomitant medications associated with rhinoconjunctivitis or related conditions
- AEs

3.2.3 Exploratory Endpoints

- PSQI (if at least 18 years old at time of assessment period)
- 6-Question Asthma Control Questionnaire (ACQ) (excluding lung function) – for asthmatics only
- WPAI:CIQ-AS
- Global assessment of symptom severity on unplanned exposure to a cat in normal daily life in subjects who no longer keep a cat
- Health economic outcomes
- Hospital / Physician office visits
- Asthma progression

4.0 STUDY POPULATION

Only subjects completing the CP007 study will be allowed to enter this follow-up study. No other subjects will be enrolled in the study.

4.1 Number of Subjects

The population is limited to those in the CP007 study and the maximum number to be enrolled in this study will be 1400 subjects. Subjects in countries where fewer than 10 subjects were randomised in CP007 will not be invited to participate in this study.

4.2 Inclusion Criteria

1. Previously randomised into the clinical study CP007 and completed PAC3.
2. Provide written informed consent or assent, as appropriate. (For subjects less than 18 years a Parent/Guardian will also be required to provide written informed consent).
3. Willing and able to comply with the study requirements.

4.3 Exclusion Criteria

1. Started allergen immunotherapy since completing CP007.
2. Has been informed of the treatment received in study CP007.
3. Dependent on the Investigator/site either for employment or education or are first degree relatives or partners of the Investigator/study staff.
4. Subjects institutionalised due to a legal or regulatory order.

4.4 Females of Childbearing Potential

Females of Childbearing Potential (FOCBP) may participate in CP007A without taking any additional precautions to prevent pregnancy as there is no investigational product administration in this study.

4.5 Withdrawal of Subjects from the Study

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.

4.6 Criteria for Stopping the Study

Circassia Ltd may terminate the study for safety or administrative reasons.

4.7 End of the Study

The end of the study is when the last subject completes the end of study visit (following the last four year annual follow-up assessment).

5.0 STUDY MEDICATION

5.1 Investigational Product

No investigational product will be used in this follow-on study.

Subjects will have received one of the following three study drug regimens in study CP007:

- Single course of Cat-PAD (4 doses of Cat-PAD 6 nmol, 4 weeks apart, followed by 4 doses of placebo, 4 weeks apart)
- Two courses of Cat-PAD (8 doses of Cat-PAD 6 nmol, 4 weeks apart)
- Placebo (8 doses, 4 weeks apart)

5.2 Concomitant Medication and Dietary Supplements

5.2.1 Allergy Medication

In order to ensure consistency with results obtained from CP007, subjects will receive an Allergy Medication Kit prior to the start of the Allergy Evaluation Period to be used as needed. The Allergy Medication Kit will contain the same standardised therapies as those provided in CP007. Subjects will be asked to use only allergy medications provided in the Allergy Medication Kit according to the defined Allergy Medication Plan (Appendix 1) during the Allergy Evaluation period.

5.2.2 Treatment of Suspected Anaphylactic Reactions

Not applicable – subjects will not be deliberately exposed to additional allergen during the study beyond their normal daily exposure from e.g. living with a cat.

5.2.3 Other Medication

Subjects should record the use of all concomitant medications, both prescribed and over-the-counter, into the diary. This includes medications used on both a chronic and an as-needed basis. Hormonal contraceptives may be used by FOCBP.

5.3 Blinding

The subject will not know which treatment they received in CP007 and subjects will waive the right to be told their treatment in CP007 when they enrol in CP007A. If subjects wish to know the treatment they received in CP007 they will be withdrawn from study CP007A. New sequential subject numbers will be assigned to each subject from CP007 as they are enrolled in this study, this reassignment will occur within the electronic data capture (EDC) system to

ensure that all Circassia staff and Quintiles clinical staff directly involved in conduct of the study remain blind to the treatment received in CP007. The CP007 screening and randomisation numbers will not be presented in the CP007A documentation that is available to those who may introduce bias. In order to maintain blinding, once the CP007 study has been unblinded, Investigators and site staff will be kept blinded for any CP007 subjects that have enrolled into CP007A.

6.0 STUDY CONDUCT

6.1 Schedule of Assessments

Study assessments will occur as stated in Tables 1 and 2.

Table 1 Schedule of Assessments – Study Visits

Visit	Enrolment Visit (performed on site at or after Visit 5 of CP007)	Quarterly Visits[e]	Annual Visits[g]	End of Study / Early Termination Visit (performed on site upon study completion/subject withdrawal/ discontinuation)
Duration	1 day	1 day	1 day	1 day
Informed consent / assent[a]	X			
Inclusion / Exclusion Criteria[b]	X			
Adverse Events[c]		X	X	X
Subject collects patient diary binder	X	X	X	
Subject collects digital pen[d]	X			
Subject collects Allergy Medication Kit			X	
Subject completion of monthly assessment in subject diary		X[f]	X[f]	
Collection of digital pen (and mobile 'phone if applicable) from subject				X

[a] Consent/assent may be taken at the final PAC3 visit in CP007 (Visit 4F)
[b] Performed at or after Visit 5 of CP007
[c] Investigator will ask non-leading questions
[d] For subjects requiring a mobile 'phone for the study, a digital pen will be sent directly to the subject along with the mobile 'phone
[e] Three Quarterly Visits performed each year; up to 2 of these may be performed by telephone
[f] Where possible, subjects should complete the monthly assessment during all on-site Quarterly and Annual Visits (not required for 'phone-call visits)
[g] Annual Visit performed at site once per year prior to the Allergy Evaluation Period

Table 2 Schedule of Assessments – Evaluations (to be recorded in the subject diary)

Assessments	Monthly Evaluations	Annual Evaluation
Duration	1 day	3 weeks
Subject completion of monthly assessments in subject diary	X	X
Daily Diary recording for 3 weeks: • TRSS • ASS • Allergy medication use • Exposure to indoor cat		X
Diagnosis of Asthma[a]		X
Change in geographic location[b]		X
6-Question ACQ (for Asthmatics only)[b]		X
RQLQ[b]		X
PSQI (adults only)[b]		X
WPAI:CIQ-AS[b]		X
Hospital / Physician office visits	X	
Number of lost work / school days	X	
Current Status / Change in Home Environment	X	
Exposure to Cat	X	
Global assessment of symptoms to cat exposure[c]	X	
Asthma Progression	X	
Concomitant medication	X	
Illnesses / Symptoms	X	

[a] Completed at the start of annual Allergy Evaluation Period
[b] Completed at the end of annual Allergy Evaluation Period
[c] For subjects who no longer live in a house with an indoor cat

6.2 Study Procedures

6.2.1 Enrolment

Enrolment in to the study may occur at any time after a subject has completed study CP007, but ideally will take place at the final follow-up visit for CP007. Consent may also be taken at the final PAC3 visit (Visit 4F) in CP007.

Subjects will be provided with information about this follow-on study, both verbally and in writing, and written informed consent/assent will be obtained from the subject. Subjects will be provided with a study information sheet to explain the study objectives, as well as any potential risks and benefits. The subject will be given 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/assent 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.

Subjects agreeing to participate will be asked to sign and date an Informed Consent Form (ICF) or an Informed Assent Form (IAF). For adolescents, informed consent will be obtained from the legally-authorised representatives (e.g. parents/guardians) and informed assent will be obtained from the subject themselves. Any adolescent subjects who turn 18 years of age while in the follow-up portion of this study will be asked to sign a new informed consent form at the next on-site visit, which will include details of an additional questionnaire (PSQI) to be completed on an annual basis. The original signed ICF(s) and IAF(s) will be kept in the subject's medical file and a copy of the signed ICF(s)/IAF(s) will be given to the subject.

Once eligibility for the study is confirmed, subjects will be provided with their study materials, including the subject diary (to include three months of follow-up), digital pen, and if required, mobile telephone to support uploading of data. Site staff will provide training to subjects on how to use the digital pen and completion of the subject diary.

6.2.2 Monthly and annual assessments

Subjects will complete their subject diary on a monthly basis. Additionally, on an annual basis, subjects will participate in an Allergy Evaluation Period; a 3-week period where subjects will complete a number of questionnaires (to occur at the same time each year, coordinated with the Baseline Allergy Evaluation period [Visit 2A to Visit 2B] in CP007).

To support completion of data, email, SMS text messages and/or 'phone calls will be sent and/or made to subjects to remind them to complete both monthly assessments and the Allergy Evaluation Period assessments.

6.2.3 Quarterly / Annual Visits

Subjects will have up to four visits each year; three Quarterly Visits and one Annual Visit. The visits will be conducted at approximately three-monthly intervals. The Annual Visit must take place just prior to the Allergy Evaluation Period and must be conducted on-site. At least one of the three Quarterly Visits must be conducted on-site; the remaining visits can be conducted either on-site or via telephone. There will therefore be a minimum of two on-site visits per year.

During each visit (Quarterly and Annual), sites will record any AEs/SAEs and subjects will collect (or be sent) a new diary binder with the next set of monthly assessments to complete. For on-site visits, where possible, subjects will also be instructed to complete the closest monthly assessment in the subject diary during the visit. Subjects should complete the assessment by themselves without the influence of the site staff. For telephone visits, subjects will be reminded to complete their monthly assessment at home.

During the Annual Visits, subjects will be provided with an Allergy Medication Kit, further monthly diary binders and the diary binder pertaining to the Allergy Evaluation Period. In order to ensure consistency with results obtained from CP007, the Allergy Medication Kit will contain the same therapies as provided to subjects while participating in CP007. The medications are to be used on an 'as needed' basis in accordance with the Allergy Medication Plan (Appendix 1).

Subjects will not be required to undergo any other specific treatment or lab tests while participating in this follow-up study. All other physician visits and treatments / procedures will be administered per the physician's direction.

6.2.4 Study Completion

Subjects will be asked to return to site for a final End of Study Visit, which will coincide with the end of the final annual Allergy Evaluation Period assessment, anticipated to be after four years, or upon early discontinuation or subject withdrawal. During the visit, the date of study completion (date of visit) will be recorded, and, in the case of early discontinuation/subject withdrawal, the reason for discontinuation/withdrawal will also be recorded. The site will collect the digital pen (and mobile 'phone where applicable) from the subject. Subjects will also be asked to complete the Withdrawal/Discontinuation Page in the diary binder (either before or during the visit).

6.3 Assessment of Efficacy

Information to be collected for all study subjects will include the following:

6.3.1 Monthly

- Hospital / Physician office visits
- Lost work/ school days
- Change in home environment
- Exposure to cat
- Global assessment of symptoms to cat exposure (only for subjects no longer living with an indoor cat)
- Asthma progression
- Concomitant medications

6.3.2 Annually (for a three-week period)

- At the start of the 3-week allergy evaluation period:
    - Diagnosis of asthma
- Daily recording for 3 weeks:
    - TRSS
    - Asthma Symptom Score (ASS)
    - Allergy medication use
    - Exposure to indoor cat
- At the end of the 3-week allergy evaluation period:
    - Change in geographic location
    - 6-Question ACQ excluding lung function (for asthmatics only)
    - RQLQ
    - PSQI (if at least 18 years old at time of assessment period)
    - WPAI:CIQ-AS

For each rhinoconjunctivitis 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

Symptoms will be captured as follows:

Nasal Symptoms

- Runny nose
- Sneezing
- Blocked nose
- Itchy nose

Ocular Symptoms

- Itchy eyes
- Watery eyes
- Red eyes
- Sore eyes

ASS will be captured as follows for all subjects:

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

6.4 Assessment of Safety and Tolerability

6.4.1 Adverse Events

AE reporting begins from signed informed consent and ends when the subject completes the study or withdraws.

At each study visit, the Investigator will determine whether any AEs have occurred by asking non-leading questions and these will be recorded in the Case Report Form (CRF). Illnesses and symptoms information recorded by subjects in the diary binders will be used to aid recollection of events.

An AE is any untoward medical occurrence. An AE can therefore be any unfavourable and unintended sign, symptom or disease.

When recording an AE, the following details will be recorded:

- Event observed (brief description using medical terminology);
- Start and stop dates;
- 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 after signing informed consent 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 signing of informed consent, which does not worsen.
- Disease or disorder being studied or associated signs or symptoms provided these do not worsen/appear during follow-up.
- Overdose of 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 CRF. The Investigator must detail in the subject records 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.
Moderate	Interferes with usual activities, possibly requires additional therapy.
Severe	Incapacitating with inability to perform usual activities. May require medical intervention and treatment.

The Investigator will make a judgement regarding whether or not the AE was related to the study medication given in study CP007. However, even if the Investigator feels there is no relationship to the study medication, the AEs MUST still be recorded in the CRF 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 medication given in CP007 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 medication given in CP007 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 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 Serious Adverse Event (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 attending physician 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 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.

6.4.2.2 Hospitalisation

This is defined as the subject being hospitalised overnight. Any pre-planned or anticipated in-hospital visits at the time of signing informed consent should be documented and will be excluded from this category. Hospitalisation for social reasons, e.g. subjects admitted to hospital the night before a day surgical procedure due to their distance from the hospital, should not be reported as SAEs.

6.4.2.3 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 Cat-PAD Investigator's Brochure).

6.4.2.4 Reporting Serious Adverse Events/Expeditable Adverse Events

Investigators are obliged to notify Circassia's Pharmacovigilance vendor, ICON, of all SAEs as soon as possible and 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)

Email	f2m-eastleigh-medical@iconplc.com
Fax	USA and Canada: +1 800 540 1863 Rest of World: +44 1865 595 595
'Phone	USA and Canada: +1 888 723 9952 Rest of World: +44 1628 496 300

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 and unexpected AEs that are reasonably associated with the study medication given in study CP007 must also be reported to the reviewing Independent Ethics Committee/Institutional Review Board (IEC/IRB) by the Investigator. Circassia Ltd will provide details to other Investigators of such AEs for this purpose. Confirmation that these AEs have been submitted to the IEC/IRB must be forwarded to Circassia Ltd or designee.

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).

6.4.3 Reporting of Pregnancy

There is no requirement to report pregnancies in this study. However, any outcome of a pregnancy that meets the definition of a Serious Adverse Event will need to be reported (Section 6.4.2.4).

6.4.4 Safety Evaluations

Not applicable, AEs will be the only safety parameters evaluated in this follow-on study.

7.0 STATISTICAL CONSIDERATIONS

7.1 Data Management and Quality Assurance

Subjects will complete monthly evaluations in a paper diary using an ePRO pen. Investigators will record data onto CRFs at the Quarterly and Annual visits. All data in the study will be captured and maintained in a secure, validated EDC system. All subjects will be assigned a new subject ID upon entry in the study.

The diary and CRF data, once uploaded into the EDC system, will be checked to ensure the quality, integrity, accuracy and completeness of the data entered.

The diary and CRF 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 Organization (WHO) 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 (CFR) Part 11 and the Food and Drug Administration (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, Functional Specifications and Data Transfer Specifications, which will be approved by the Sponsor.

7.2 Sample Size

Subjects who were randomised in clinical study CP007 and completed PAC3 will be eligible for entry into this study, hence no formal sample size calculation has been performed.

A sample size of 266 evaluable subjects per arm will have at least 99% power to detect a 25% treatment difference in the mean CS during the PAC3 period between each of the Cat-PAD treatment groups and placebo. This is based on subjects in the placebo treatment group having a CS (0-6) of 2.10 which relates to a 25% Cat-PAD mean CS treatment difference of 0.525, with a common within-group standard deviation (SD) of 1.29 (i.e. the same assumptions as for CP007). Note: A treatment effect of 20% greater than placebo is considered clinically relevant because it exceeds the treatment effect of leukotriene receptor antagonists, antihistamines and intranasal corticosteroids (Wilson et al, 2004.) This power calculation is based on a Bonferroni-Holm adjusted alpha of 0.025 for the primary analysis given there will be two comparisons

(two courses of Cat-PAD versus placebo and one course of Cat-PAD versus placebo) with the tests assumed to be two sided.

It is recognised that some subjects will withdraw from the study before the end of the four year period but it will still have at least 80% power to detect a difference between active treatment and placebo with 130 subjects per arm.

7.3 Analysis Populations

7.3.1 Intent-to-Treat Population

The population for the primary analysis will be the Intent-to-Treat (ITT) population consisting of all subjects who are consented into the study. Subjects will be reported by the treatment they were randomised to in study CP007. This is the primary population for the study, and all the primary and secondary efficacy analyses will be based on the ITT population. Missing data will not be replaced meaning that all analyses will be performed on a Full Analysis Set.

7.3.2 Modified Intent to Treat Population

The modified Intent-to-Treat (mITT) population will consist of all subjects who are enrolled into the study and continue to live in a house with an indoor cat during the annual Allergy Evaluation period. The mITT population will be defined on an annual basis based on the subject's completion of the ePRO question as to whether the subject still lives in a house with an indoor cat. The mITT population may therefore change during the course of the study. The mITT population will be evaluated for all primary, secondary and exploratory endpoints with the exception of the global assessment of symptom severity on unplanned exposure to a cat in normal daily life in subjects who no longer keep a cat.

7.3.3 Safety Population

All subjects will be included in the safety population. Safety data will be listed and summarised by study medication actually received in CP007.

7.4 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 approved by Circassia prior to performing any analysis of the data.

The nature of the formal statistical testing will be described and justified in the SAP, discussing any potential biases and challenges caused by the data collected and circumstances of the study. It is anticipated that the analyses will be similar to those performed for the CP007 study. For the primary hypothesis testing versus placebo a Bonferroni-Holm procedure will be used to adjust alpha in order to compensate for multiplicity when comparing the two Cat-PAD treatment arms versus placebo, thereby keeping the overall type I error rate at 0.05. The Bonferroni-Holm procedure will assess each of the two treatment comparisons (two courses of Cat-PAD versus placebo and one course of Cat-PAD versus placebo), whereby the smallest p-value (of the two treatment comparisons) will be tested at the 0.05/2 (i.e. $p < 0.025$) alpha level. If this first comparison is statistically significant then the remaining treatment comparison p-value will be tested at the 0.05 alpha level. The tests will be two sided.

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

All data will be summarised to include the mean, N, SD, median, minimum and maximum values for continuous variables and frequencies and percentages for categorical variables.

The first analysis of the data will be performed on the first year's data after all subjects have completed one year in this study. Additional analyses of the second, third and fourth year in the study will be performed after all subjects have completed each additional year in the study. At each of the statistical analyses performed after one, two, three and four years, there will be no adjustment to the significance level, apart from the Bonferroni-Holm correction (due to multiple treatment comparisons) stated above, because analysis of the later years will only be performed if there was a positive outcome in the previous years, and this is, therefore, a hierarchical analysis.

7.4.1 Demographic and Baseline Characteristics

Subject data will be pulled from CP007 and will be used as baseline data for CP007A. Data will be summarised with respect to demographic and baseline characteristics by study treatment group.

7.4.2 Efficacy Analysis

In such a study it is expected that missing data will play an important role in the interpretation of any analysis or description of endpoints. Statistical methods will be used to explore the effects of and the nature of any missing information, including specifically the reasons for non-entry to or discontinuation from the study.

7.4.2.1 Primary Analysis

The primary efficacy variable for this study is the mean Combined Score (TRSS/8+AMS).

For the primary efficacy analysis, the data will be summarised and analysed using methods as for study CP007. The analysis will provide a comparison of the mean Combined Score (TRSS/8+AMS) for each treatment group. In addition, 95% Confidence intervals will be used to explore the size and direction of any differences between groups.

The statistical analysis will use covariates as used in CP007, including pooled centre, age group (as randomised), gender, asthma status and baseline score. Additional informative subgroup descriptive analyses may also be performed.

7.4.2.2 Secondary Analysis

Secondary endpoints will be statistically analysed appropriately to address the secondary objectives of the study, including non-parametric methods, where relevant.

7.4.2.2.1 Rhinoconjunctivitis Symptom Scores

The mean TRSS and the mean component scores of the TRSS (nasal and ocular) during the allergy evaluation periods will be analysed and summarised by treatment group.

7.4.2.2.2 Allergy Medication Usage

The mean AMS during the allergy evaluation period will be analysed and summarised by treatment group.

7.4.2.2.3 Concomitant Medication Use

An evaluation of the use of any concomitant medications associated with rhinoconjunctivitis or related conditions will be performed.

7.4.2.2.4 Rhinoconjunctivitis Quality-of-Life Questionnaire

The mean RQLQ score at the end of the allergy evaluation period will be analysed and summarised by treatment group.

7.4.2.2.5 Medical Visits

An evaluation of additional visits to doctors/clinics will be performed.

7.4.2.2.6 Asthma

An evaluation of asthma progression and the number of subjects developing asthma during the study will be performed in separate analyses.

7.4.2.3 Exploratory Analysis

Other endpoints will be analysed appropriately to address the exploratory objectives of the study, including non-parametric methods, where relevant.

7.4.2.3.1 Sleep

The overall and component scores of the PSQI will be summarised descriptively.

7.4.2.3.2 6-Question ACQ

The data for the 6-Question ACQ will be summarised.

7.4.2.3.1 Work Productivity and Activity Impairment Questionnaire

The overall and component scores of the WPAI:CIQ-AS will be summarised descriptively.

7.4.2.3.2 Global Assessment of Symptom Severity

An evaluation of the global assessment of symptom severity on unplanned exposure to a cat in normal daily life in subjects who no longer keep a cat will be performed.

7.4.2.3.3 Health Economic Outcomes

Health economic outcomes will be described and explored.

7.4.3 Safety Analysis

Safety will be evaluated by analysis of the following parameters:

- AEs;
- SAEs

For safety analysis, 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 each treatment group and the placebo group, but no hypothesis testing is planned.

Any deaths and SAEs and AEs will be summarised by CP007 treatment group.

8.0 INVESTIGATOR RESPONSIBILITIES

8.1 Investigator Performance

The Principal Investigator and each Investigator will ensure that each subject is consented.

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

8.2 Ethical Considerations

8.2.1 Ethics Committee Review and Approval

It is the responsibility of the Investigator or designee to submit the protocol, ICF/IAF, and subject information sheet, to an IRB/IEC for their review according to local regulation. 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. 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 regulatory authority/authorities. The study will not proceed until the appropriate regulatory 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. Subjects will also waive their right to the unblinding of study medication from CP007, as was previously stipulated in CP007. Any questions will be answered and subjects willing to participate, or their legally authorised representative, will provide written informed consent by reading and signing the ICF. Adolescent subjects will sign an IAF. Any adolescent subjects who turn 18 years of age while in this study will be asked to sign a new informed consent form at their next on-site visit. All subjects will receive a copy of the signed ICF(s), and if appropriate IAF(s), as well as written information sheets about the study. The subjects will be assured that they can withdraw from the study at any time and for any reason. Each subject's ICF/IAF must be signed and dated by both the Investigator or designee and the subject. The original signed ICF(s) and IAF(s) will kept in the patient's medical file and a copy of the signed ICF(s)/IAF(s) will be given to the subject.

8.2.3 Information for Subject's General Practitioner

If the subject consents, their general practitioner (and any specialist the subject might be treated by) will be notified of the subject's intended involvement in the study.

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 EDC system, on all study correspondence and in the study database.

8.4 Study Documentation

8.4.1 Case Report Forms

Data will be provided from electronically uploaded subject reported diaries and Investigator completed CRFs. Data will be periodically uploaded from the digital pen via secure web access from the site's/subject's home computer and the internet or via a mobile 'phone supplied specifically and for the sole purpose of uploading study data. Data on CRFs must correspond to and be supported by source documentation maintained at the study centre. All CRFs 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 CRFs, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. CRFs 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 database is fully 21CFRpart11 compliant and provides a secure environment for subject data.

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

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. The Investigators 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 regulatory 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 an 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 standard operating procedures. The monitoring will be conducted via on-site visits or remote monitoring. The purpose of the monitoring is to ensure:

- Compliance with the protocol;
- Adherence to regulatory and GCP obligations;
- Ensure filing of all study documents;
- The completeness of the data entered by sites and subjects;
- Accurate and timely reporting of AE(s) and SAEs
- 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 have access to 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.

The ePRO provider may hold personal information in a separate database, including name, address, email and mobile phone contact details. Only the ePRO provider will have access to this database. This information is required for:

- The potential dispatch of mobile 'phones for those subjects without internet access
- The release of email and/or mobile 'phone reminders and alerts.

Any collection or use of subject data will be in compliance with Data Protection requirements. Note, in Czech Republic, this personal information is not collected by the ePRO provider and only the site will hold this information.

The ePRO provider will ensure the databases are compliant with the clinical industry regulations and as such the confidentiality, integrity and accessibility of these systems are fully managed and controlled. Access to the data is provided only to specifically approved and authorised individuals for the duration of the study.

9.5 Finance

Financial agreements between Circassia, the Contract Research Organisation 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.

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11.0 APPENDICES

APPENDIX 1 Allergy Medication Plan

The "Allergy Medication Kit" is a package of medications that you may use during the period you are scoring your symptoms on the diary to relieve any troublesome allergy symptoms that you may experience. The kit will include the following allergy medications:

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

Allergy Medication Plan

The Allergy Medication Kit 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 Allergy Medication Kit medicines should be used as follows:

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

If you mainly have ocular symptoms, wait until these become troublesome and then use the eye drops provided in the Allergy Medication Kit. 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 Allergy Medication Kit.

When you have nasal symptoms, such as runny nose, sneezing, blocked or itchy nose or when you have both nasal and ocular (eye) symptoms.

If you mainly have nasal symptoms, or nasal and ocular symptoms, treat them by taking one of the anti-histamine tablets from the Allergy Medication Kit. 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 Allergy Medication Kit. 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 Allergy Medication Kit.