Topical rVA576 for treatment of atopic keratoconjunctivitis: a randomised placebo controlled double masked parallel trial (TRACKER)

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SPONSOR:	Akari Therapeutics Plc
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Complement activity (CH50, drug levels, anti-drug antibodies):

CH50 The Doctors Laboratory The Halo Building 1 Mabledon Place London, W1CH 9AX UK	Unbound rVA576 and Anti-Drug antibody SYNLAB pharma institute AG Sternenfeldstrasse 14 4127 Birsfelden, Switzerland

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LIST OF ABBREVIATIONS

Abbreviation	Definition/Term
AD	Atopic Dermatitis
ADA	Anti-drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
AKC	Atopic keratoconjunctivitis
ANOVA	Analysis of Variance
ARDS	Adult Respiratory Distress Syndrome
BP	Blood Pressure
BUT	Break Up Time
CIP	Conjunctival Impression Cytology
CRF	Case Report Form
CRO	Contract Research Organisation
CSLM	Confocal Scanning Laser Microscopy
CK	Creatinine Kinase
CT	Computerised Tomography
DLT	Dose Limiting Toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ED	Effective Dose
EIC	Experimental Immune Conjunctivitis
EMA	European Medicines Agency
ELISA	Enzyme-Linked Immunosorbent Assay
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HED	Human Equivalent Dose
HRP	Horseradish Peroxidase
ICH	International Committee on Harmonisation
IRB	Institutional Review Board (or equivalent, e.g. Ethics Committee)
IMP	Investigational Medicinal Product
ITT	Intention to Treat
i.v.	Intravenous
KS	Keratoconjunctivitis sicca
LLOQ	Lower Limit of Quantification
LPS	Lipopolysaccharide
MAC	Membrane Attack Complex
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary of Regulatory Activities

Abbreviation	Definition/Term
MHRA	Medicines and Healthcare Regulatory Agency
MTD	Maximum Tolerated Dose
MMP	Mucous membrane pemphigoid
MMP-9	Matrix metalloprotease 9
MW	Molecular Weight
NOAEL	No Observable Adverse Event Level
OD	Oculus Dexter (Right Eye)
OmCI	*Ornithodoros moubata* Complement Inhibitor
OS	Oculus Sinister (Left Eye)
OVA	Ovalbumin
PAC	Perennial allergic conjunctivitis
PAD	Pharmacologically Active Dose
PBS	Phosphate Buffered Saline
PI	Principal Investigator
PNH	Paroxysmal Nocturnal Haemoglobinuria
POM	Prescription Only Medicine
PP	Per Protocol
p.r.n	*pro re nata* (as necessary)
QA	Quality Assurance
QC	Quality Control
SAC	Seasonal allergic conjunctivitis
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SJS	Stevens Johnson Syndrome
SS	Sjögren's Syndrome
s.c.	Subcutaneous
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBUT	Tear film break up time
TCA	Terminal Complement Activity
TEAE	Treatment Emergent Adverse Events
TMF	Trial Master File
ULN	Upper Limit of Normal
VKC	Vernal keratoconjunctivitis

PROTOCOL SIGNATURE PAGE

Protocol Title:	Topical rVA576 for treatment of atopic keratoconjunctivitis: a randomised placebo controlled double masked parallel trial (TRACKER) AK701

Authorized Sponsor Representative Signature:

Signature: _____ Date: _____

Dr Wynne H Weston-Davies MB FRCS
Akari Therapeutics Plc,
75 Wimpole Street
London
W1G 9RT
UK

Principal Investigators Signatures:
I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it as well as per the principles of Good Clinical Practice, applicable laws and regulations and the Declaration of Helsinki.

Signature: _____ Date: _____

1 PROTOCOL SYNOPSIS

Protocol Title:	Topical rVA576 for treatment of atopic keratoconjunctivitis: a randomised placebo controlled double masked parallel trial (TRACKER)
Protocol Number:	AK701
Sponsor:	Akari Therapeutics Plc 75 Wimpole Street London W1G 9RT UK
Investigational Product(s):	rVA576 (2.5 mg/mL) eye drops solution or placebo. For Ophthalmic use.
Phase of Development:	I/II
Indication:	Moderate to severe atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC),and severe allergic conjunctivitis (seasonal (SAC) or perennial (PAC))
Study Center(s):	Sites in United Kingdom and Spain
Objectives:	**Primary Objectives:** Safety and tolerability of topical rVA576 for AKC, VKC and severe allergic conjunctivitis (SAC or PAC)
	Secondary Objective: Efficacy of topical rVA576 for the treatment of patients with AKC, VKC, and severe allergic conjunctivitis (SAC or PAC)
Study Design:	Randomised, double masked, placebo controlled parallel group comparison with open label sentinel group. **Part 1:** The first 3 patients selected for the study will be treated with active drug in open-label manner at intervals of 1 week and will have weekly clinic visits until Day 14, after which the visit will be every two weeks. When the first 3 patients have completed two weeks of treatment and the safety and tolerability data has been reviewed by the PI and an independent clinician, provided the data is favourable the randomisation process will begin (Part 2). The first 3 patients will continue treatment for a total of 8 weeks and will be assessed through-out the trial by the Principal Investigator according to the Schedule of Events **Part 2**: Sixteen patients will be randomised 1:1. between active and placebo and patients allocated to either group will receive the appropriate product throughout the trial. All randomised patients will be seen and assessed at bi-weekly intervals until the end of the study by a masked observer who will not know to which product, active or placebo the patients have been randomised. Unmasking for individual patients may be ordered by:

	1. The PI 2. Any medically qualified person having temporary or long-term clinical responsibility for the well-being of the patient At the conclusion of the trial all patients will, if they wish, be informed as to the nature of the treatment they received.
Planned Number of Subjects:	up to 19
Subject Population:	Patients with moderate to severe AKC, VKC, or severe allergic conjunctivitis(seasonal (SAC) or perennial (PAC))
Criteria for Inclusion and Exclusion:	**Inclusion Criteria:** 1. Aged 18 and above 2. Diagnosis of moderate to severe AKC, VKC, or severe allergic conjunctivitis (seasonal or perennial). Defined as: • **AKC, VKC** - a composite symptom/sign score from one eye of ≥ 18 out of 33 (see Clinical Scoring Section 17.1) • **Severe allergic conjunctivitis (SAC or PAC)** - a composite symptom/sign score from one eye of ≥ 15 out of 27 (see Clinical Scoring Section 17.1) 3. Will have had received some topical therapy during the last 3 months without improvement but will not currently be receiving systemic immunotherapy. Topical therapy may be topical calcineurin inhibitors, antihistamines or corticosteroids alone or in combination. Lubricants or artificial tears will not a count as topical therapy for these purposes. 4. Will have had at least 7 days without topical ocular corticosteroids prior to entry 5. Willing to give informed consent 6. Willing to use highly effective contraceptive precautions for the duration of the study and for 90 days after the last dose of IMP 7. Willing to avoid prohibited medications for duration of study (see list of prohibited medications)

Exclusion Criteria:

1. Eye surface disease other than AKC, VKC or severe allergic conjunctivitis (SAC or PAC)
2. Contact lens use during the study
3. Complete or partial tarsorrhaphy. If such a procedure becomes necessary during the course of the trial patients may remain in the trial providing that at least 50% of the eye surface remains visible to slit lamp examination
4. Ankyloblepharon of any degree at entry to the trial
5. Known or suspected ocular malignancy
6. Active ocular infection at entry to the trial. Patients with eye surface bacterial, viral, fungal or protozoal infection may enter the trial after elimination of the infection as confirmed by eye swabs
7. Known or suspected uveitis
8. Participation in any other clinical trial within 1 month of enrolment
9. Use of any of the following prohibited medications:
    - Eculizumab
    - Any other investigational complement inhibitor whether systemic or topical (e.g. RA101495)
    - Montelukast
    - Zafirlukast
    - Pranlukast
    - Zileuton
    - Hypericum perforatum (St John's wort)
10. Corneal perforation
11. Uncontrolled glaucoma (increase in dose of glaucoma medication or surgical intervention for glaucoma within 3 months prior to entry)
12. Pregnancy (females)
13. Breast feeding (females)
14. Known allergy to ticks or severe reaction to arthropod venom (e.g. bee or wasp venom)
15. Use of topical ocular steroids within 7 days of the Screening visit
16. Failure to satisfy the PI of suitability to participate for any other reason

Treatment Regimen:	Part 1: Sterile eye drops 0.25% w/v (2.5 mg/mL), solution in 6mL glass vials containing 1mL solution. Eye dropper pipettes will also be supplied. Part 2: Sterile rVA576 0.25% w/v (2.5 mg/mL) or placebo solution in 6 mL glass vials containing 1 mL. Eye dropper pipettes will also be supplied. The product should be administered as one drop to each eye every 12 hours (i.e. twice daily) for a total of 56 Days. Background therapy: Patients should continue on whatever topical therapy they are on at the time of screening (ciclosporin or antihistamines) but this should remain stable during the trial. Lubricants and artificial tears may be used *ad libitum* but should not be administered for 15 minutes before or after the trial medication. In the event of worsening of signs or symptoms that, in the clinician's opinion is so severe as to necessitate a change of medication, ciclosporin and/or antihistamines may be introduced or increased in dose/frequency and this will be considered as a treatment failure for purposes of efficacy analysis. Topical corticosteroids may be added following introduction or increase in ciclosporin/antihistamine therapy if considered necessary. Should not be on topical ocular steroids at start of the trial but may be used as rescue therapy during the trial if necessary (see above)
Duration of Treatment:	56 Days each for active and placebo dosing plus 7 (±2) days between screening and entry and 28 (±2) days between final trial visit and follow up visit. Total trial duration 6-12 months.
Endpoints:	**Primary Endpoint:** Incidence of ocular treatment emergent adverse events during the treatment period (adverse events which have occurred during the 56 days following randomisation (Part 2 of the study only) will be considered in the analysis of the primary safety outcome). Secondary Endpoints will include: • Post-instillation comfort, as graded on patient diary cards at the following intervals Days 1-14, Day 15-28, Day 29-42 and Day 43-56 • Visual acuity by Early Treatment Diabetic Retinopathy Study (ETDRS) charts comparison from Day 1 to Day 56 • Change from Day 1 in composite clinical scores at Day 14, 28, 42 and 56 • Number and percentage of patients with MMP-9 positive levels at Days 1, 28 and 56 • Change from Day 1 in Tear film break up time (TBUT) at Day 14, 28, 42 and 56

Statistical Methods:	The two parts of the study will be reported separately. Data from patients included in Part 1 will only be listed, while the following text applies for data from patients included in Part 2: Safety analyses will be performed using the Safety Analysis Set, and efficacy analyses will be performed using the Full Analysis Set. Ocular adverse events which have occurred during the treatment period will be considered in the analysis of the primary safety outcome. The difference between the two treatments in the proportion of patients experiencing any ocular treatment-emergent AEs will be reported with its associated 95% confidence interval.

SUBSTANTIAL AMENDMENT 1

Summary of Changes and Justification – Version 2.0 – Version 3.0

Change 1: Title

Previous text:

Topical rVA576 for treatment of atopic keratoconjunctivitis: a randomised placebo single masked parallel trial (TRACKER)

Current text:

Topical rVA576 for treatment of atopic keratoconjunctivitis: a randomised placebo **controlled double** masked parallel trial (TRACKER)

Justification: The design of the study has been changed to improve the scientific validity of the study and to protect the trial integrity by complete blinding.

Change 2: Synopsis: study design

Previous text:

Randomised, single masked, placebo controlled parallel group comparison with open label sentinel group.

Part 1: … When the first 3 patients have completed two weeks of treatment and the safety and tolerability data has been reviewed by the PI and Medical director, provided the data is favourable the randomisation process will begin (Part 2).

Part 2: Sixteen patients will be randomised 1:1. Active and placebo drug product will be labelled X and Y, or *vice versa*, in a randomised fashion and patients allocated to either group will receive the appropriate product throughout the trial.

All randomised patients will be seen and assessed at bi weekly intervals until the end of the study by a masked observer who will not know to which group, X or Y, the patients have been randomised. Even if the masked observer becomes aware of the group assignment they will continue to be masked. Unmasking of the nature of X and Y will not take place until after database lock. The PI will be aware of which patients have been allocated to X or Y but will remain unaware of the treatment being received unless the trial or patient is to be unmasked for safety reasons. Unmasking may be ordered by:

1. The PI
2. Any medically qualified person having temporary or long-term clinical responsibility for the well-being of the patient

Should unmasking take place during the trial, although the PI will become aware of the nature of X and Y, the masked observer and the trial patients will, to the greatest extent possible, remain unaware of the identities of X and Y in order to maintain the integrity of the trial.

Current text:

Randomised, ~~single~~ **double** masked, placebo controlled parallel group comparison with open label sentinel group.

Part 1: When the first 3 patients have completed two weeks of treatment and the safety and tolerability data has been reviewed by the PI and ~~Medical director~~ **an independent clinician**, provided the data is favourable the randomisation process will begin (Part 2).
Part 2: Sixteen patients will be randomised 1:1 ~~Active and placebo drug product will be labelled X and Y, or *vice versa*, in a randomised fashion~~ **between active and placebo** and patients allocated to either group will receive the appropriate product throughout the trial.
All randomised patients will be seen and assessed at bi-weekly intervals until the end of the study by a masked observer who will not know to which ~~group X or Y~~ **product, active or placebo** the patients have been randomised. ~~Even if the masked observer becomes aware of the group assignment they will continue to be masked. Unmasking of the nature of X and Y will not take place until after database lock. The PI will be aware of which patients have been allocated to X or Y but will remain unaware of the treatment being received unless the trial or patient is to be unmasked for safety reasons.~~ Unmasking **for individual patients** may be ordered by:

1. The PI
2. Any medically qualified person having temporary or long-term clinical responsibility for the well-being of the patient

~~Should unmasking take place during the trial, although the PI will become aware of the nature of X and Y, the masked observer and the trial patients will, to the greatest extent possible, remain unaware of the identities of X and Y in order to maintain the integrity of the trial.~~

Justification:
The design of the study has been changed to improve the scientific validity of the study and to protect the trial integrity by complete blinding.

Change 3 Section 4.4 Contraception
Previous text:

Patients who are or become sexually active during the course of the study must use, with their partner, two approved methods of highly effective contraception from the time of signing the Informed Consent Form (ICF) until 90 days after the last dose of rVA576.

Two or more of the following methods are acceptable and must include at least one barrier method:

- …
- Barrier methods must be used in conjunction with another method.

Alternatively, true abstinence is acceptable when consistent with the patient's preferred and usual lifestyle. If a patient is usually not sexually active but becomes active during the course of the study, they and their partner should use two of the contraceptive methods listed above. Any female patient who becomes pregnant during the course of the trial will be withdrawn from the trial unless she consents to a termination of the pregnancy.

Current Text:
All trial participants (male and female) of childbearing potential must use, with their partner, **a combination of** ~~two~~ **an** approved method~~s~~ of highly effective contraception **with at**

least one barrier method of contraception from the time of signing the Informed Consent Form (ICF) until 90 days after the last dose of rVA576.

The following methods of highly effective contraception are acceptable and must be combined with at least one of the barrier method of contraception

- …
- Barrier methods must be used in conjunction with a ~~another method~~ **highly effective method of contraception listed above**

Alternatively, true abstinence is acceptable when consistent with the patient's preferred and usual lifestyle. ~~If a patient is usually not sexually active but becomes active during the course of the study, they and their partner should use two of the contraceptive methods listed above.~~ Any female patient who becomes pregnant during the course of the trial will be withdrawn from the trial ~~unless she consents to a termination of the pregnancy~~.

Justification: To address the MHRA concerns on contraceptive measurements.

Change 4 section 4.4.1 Exposure of Partners During the Study

Previous text:

There is a risk of drug exposure through ejaculate (which also applies to vasectomised males) which might be harmful to the sexual partners, including pregnant partners of male patients. Barrier contraception should be used throughout the study and for 90 days after the last day of IMP administration.

New text:

There is a risk of drug exposure through ejaculate (which also applies to vasectomised males) which might be harmful to the sexual partners, including pregnant partners of male patients. ~~Barrier contraception~~ **A combination of an approved method of highly effective contraception with at least one barrier method of contraception** should be used throughout the study and for 90 days after the last day of IMP administration.

Justification: To address the MHRA concerns on contraceptive measurements.

Change 5 section 6.1 Trial Design

Previous text:

Part 1: …When the third of the first 3 patients has completed their first 2 weeks treatment, the PI will review the safety, tolerability and ease of application for each patient before deciding to proceed to the randomised, single-masked comparative phase of the study (Part 2).

Part 2: A randomised, single-masked, placebo-controlled trial of topical rVA576 or placebo eye drops in moderate to severe AKC. The part 2 trial population will comprise 16 patients who meet the inclusion and exclusion criteria (Section 4.1 and Section 4.2). In this part, the fully masked sub-investigator will see all patients to assess safety and conduct the clinical examinations used for the composite clinical scores.

Current text:

Part 1: When the third of the first 3 patients has completed their first 2 weeks treatment, the PI will review the safety, tolerability and ease of application for each patient before deciding to proceed to the randomised, ~~single~~ **double** masked comparative phase of the study (Part 2).

Part 2: A randomised, ~~single~~ **double**-masked, placebo controlled trial of topical rVA576 or placebo eye drops in moderate to severe AKC. The part 2 trial population will comprise 16 patients who meet **all** the inclusion and **none of the** exclusion criteria (Section 4.1 and Section 4.2). ~~In this part, the fully masked sub-investigator will see all patients to assess safety and conduct the clinical examinations used for the composite clinical scores.~~

Justification:
The design of the study has been changed to improve the scientific validity of the study and to protect the trial integrity by complete blinding.

Change 6- Figure 6
Previous text: single masked
Current text: double masked
Justification:
The design of the study has been changed to improve the scientific validity of the study and to protect the trial integrity by complete blinding.

Change 7-Section 6.3 Dosing Scheme
Previous text:
The patients will be randomised to receive either rVA576 active or placebo in single masked fashion.

Current text:
The patients will be randomised to receive either rVA576 active or placebo in ~~single~~ **double** masked fashion.

Justification:
The design of the study has been changed to improve the scientific validity of the study and to protect the trial integrity by complete blinding.

Change 8 section 7.4: Method of Assigning Subjects to Treatments and Masking
Previous text:
After the initial 3 open label patients (Part 1), subsequent patients entering this clinical trial will be randomised in permuted blocks to either treatment X or Y (i.e. in each block of patients the actual order of X or Y will vary randomly).

This master data set will be output from the system to generate an unmasked treatment sequence. The unmasked treatment sequence will be further manipulated to remove any unmasking information, thus creating a masked treatment allocation list which will be provided to the dispensing pharmacist.

At the Screening visit, the investigator, or other site personnel under the direction of the investigator, should access the eCRF to register the subject, obtain the subject identification number. Upon confirmation of a subject's eligibility at the randomisation visit, the investigator, or designee, will contact the Pharmacist to register the subject as randomized and obtain the assigned medication letter to be dispensed to this subject. This information will be recorded in the patient notes and transcribed eCRF.

An X/Y randomisation where X is active and Y placebo (or vice versa) will be used in this study. It is accepted that this is less rigorous than a patient by patient randomisation and that there is a risk of the study becoming unmasked if, for instance, the mask has to be broken for

an individual patient but that is acceptable to the Sponsor given that there is no absolute requirement for the study to be either comparative or masked. X/Y randomisation allows an early indication of a separation, either of safety or efficacy, between the two groups whilst the trial is still in progress even though the actual nature of X and Y is still masked.

Current text:
After the initial 3 open label patients (Part 1), subsequent patients entering this clinical trial will be randomised ~~in permuted blocks to either treatment X or Y (i.e. in each block of patients the actual order of X or Y will vary randomly)~~ **in a 1:1 fashion.**

~~This master data set will be output from the system to generate an unmasked treatment sequence. The unmasked treatment sequence will be further manipulated to remove any unmasking information, thus creating a masked treatment allocation list which will be provided to the dispensing pharmacist.~~

At the Screening visit, the investigator, or other site personnel under the direction of the investigator, should access the eCRF to register the subject, obtain the subject identification number. Upon confirmation of a subject's eligibility at the randomisation visit, the investigator, or designee, will contact the Pharmacist to register the subject as randomized and obtain the ~~assigned medication letter~~ **next sequence number** to be dispensed to this subject. This information will be recorded in the patient notes and transcribed eCRF.

~~An X/Y randomisation where X is active and Y placebo (or vice versa) will be used in this study. It is accepted that this is less rigorous than a patient by patient randomisation and that there is a risk of the study becoming unmasked if, for instance, the mask has to be broken for an individual patient but that is acceptable to the Sponsor given that there is no absolute requirement for the study to be either comparative or masked. X/Y randomisation allows an early indication of a separation, either of safety or efficacy, between the two groups whilst the trial is still in progress even though the actual nature of X and Y is still masked.~~

Justification:
The design of the study has been changed to improve the scientific validity of the study and to protect the trial integrity by complete blinding.

Change 9 Section 6.4.1 Emergency Unmasking for Safety Reasons
Current text:
In the unlikely event of an emergency where, in the opinion of the investigator, discontinuation of study treatment for an individual patient is not sufficient and the study treatment must be unmasked in order to evaluate further course of action, the investigator should contact the sponsor or designee's Medical Monitor in the first instance to discuss the unmasking and to confirm that unmasking of the subject is necessary and directly impacts the subject's immediate medical management.

The investigator will consult the randomisation codes held by the CRO, the trial pharmacist, the Sponsor or his own copy, supplied in a sealed envelope and decide what, if any, further action to take. Since this will mean that he will be unmasked as to the nature of X and Y, the study as a whole will be unmasked as far as he is concerned but, to the greatest extent possible, other study personnel (e.g. the clinical examiner and study nurses) should remain masked,

The information must not be included in the subject's source files, until the conclusion of the study, to ensure the treatment assignment will remain blinded to the CRO monitor and other study personnel not involved with the subject's immediate care.

Once the study treatment has been unmasked, the subject will complete the Early Termination visit and then discontinue study treatment. The subject will also be seen for post-treatment follow-up.

Proposed text:
In the unlikely event of an emergency where, in the opinion of the investigator, discontinuation of study treatment for an individual patient is not sufficient and the study treatment must be unmasked in order to evaluate further course of action, the investigator ~~should contact the sponsor or designee's Medical Monitor in the first instance to discuss the unmasking and to confirm that unmasking of the subject is necessary and directly impacts the subject's immediate medical management.~~ **will have direct access to the randomisation codes for unmasking.**

The investigator will consult **his own copy of** the randomisation codes ~~held by the CRO, the trial pharmacist, the Sponsor or his own copy,~~ supplied in a sealed envelope**s individually numbered for each patient** and decide what, if any, further action to take. ~~Since this will mean that he will be unmasked as to the nature of X and Y, the study as a whole will be unmasked as far as he is concerned but, to the greatest extent possible, other study personnel (e.g. the clinical examiner and study nurses) should remain masked,~~

~~The information must not be included in the subject's source files, until the conclusion of the study, to ensure the treatment assignment will remain blinded to the CRO monitor and other study personnel not involved with the subject's immediate care~~.

Change 10 section 6.7 Trial Procedures
Previous text:
Screening Period:
Part 2- Randomisation: Upon confirmation of a subject's eligibility at the randomisation visit, the investigator, or designee, will contact the Pharmacist to register the subject as randomised and obtain the assigned medication letter to be dispensed to this subject.

Dosing Period:
Part 2: The remaining 16 patients will be randomised 1:1. Active and placebo drug product will be labelled X and Y, or *vice versa*, in randomised fashion and patients allocated to either group will receive the appropriate medication throughout the trial.

All randomised patients will be seen and assessed at Day 14 and thereafter at 2 weekly intervals by a masked observer who will not know to which group, X or Y, the patients have been randomised and, in any case, will be unaware of the identity of X or Y.

Current text:
Screening Period:
Part 2- Randomisation: Upon confirmation of a subject's eligibility at the Randomisation visit, the investigator, or designee, will contact the Pharmacist to register the subject as randomized and obtain the assigned medication ~~letter to be dispensed to this subject~~ **number.**

Dosing Period:
Part 2: The remaining 16 patients will be randomised 1:1 ~~Active and placebo drug product will be labelled X and Y, or *vice versa*, in randomised fashion and patients allocated to either group will receive the appropriate medication throughout the trial.~~ **to active or placebo and will**

receive the appropriate medication throughout the trial identified by their randomisation number.

All randomised patients will be seen and assessed at Day 14 and thereafter at 2 weekly intervals by a masked observer**.** ~~who will not know to which group, X or Y, the patients have been randomised and, in any case, will be unaware of the identity of X or Y.~~

Justification:
The design of the study has been changed to improve the scientific validity of the study and to protect the trial integrity by complete blinding.

Change 11 Section 7.2 Withdrawal Criteria

Previous text:

All withdrawals must be documented in the eCRF. A patient may be withdrawn in any of the following circumstances:

- Pregnancy unless the patient wishes to consent to a termination.

Current Text:

All withdrawals must be documented in the eCRF. A patient may be withdrawn in any of the following circumstances:

- Pregnancy ~~unless the patient wishes to consent to a termination~~.

Justification: To address the MHRA concerns on pregnancy termination.

Change 12 section 8.2.4 Pregnancy
Previous text:
… If at least one of the above-mentioned examinations is positive, administration of the IMP must be stopped, and the patient must be immediately withdrawn from the study unless the patient consents to a termination in which case treatment would continue.

Current text:
If at least one of the above-mentioned examinations is positive, administration of the IMP must be stopped, and the patient must be immediately withdrawn from the study ~~unless the patient consents to a termination in which case treatment would continue~~.
Justification: To address the MHRA concerns on pregnancy termination.

Change 13 Section 8.2.5 Reporting of Adverse Events
Previous text:
Transfusions of PRBC do not need to be reported as an AE. In the same way, the overnight stay for a transfusion of PRBC does not need to be reported as an SAE.

On the other hand, progression of the underlying disease (at Investigator's discretion) or potential complications have to be reported as adverse events.

New text:

All adverse events, whether in the opinion of the investigator, drug-related or not will be reported in the CRF.

~~Transfusions of PRBC do not need to be reported as an AE. In the same way, the overnight stay for a transfusion of PRBC does not need to be reported as an SAE.~~

~~On the other hand, progression of the underlying disease (at Investigator's discretion) or potential complications have to be reported as adverse events.~~

Justification: This was an error in the protocol and it is now been confirmed that all adverse events will be reported.

SUBSTANTIAL AMENDMENT 2

Change 1: Protocol Signature Page

Previous text: Mr Sajjad Ahmad, Moorfields Eye Hospital, London, EC1V 2PD

Current text: ~~Mr Sajjad Ahmad, Moorfields Eye Hospital, London, EC1V 2PD~~

Justification: Sponsor is looking into opening one additional site in the UK

Change 2: Synopsis

Previous text:

PI(s):	Mr Sajjad Ahmad
Study Center(s):	Moorfields Eye Hospital London EC1V 2PD UK

Current text:

~~PI(s):~~	~~Mr Sajjad Ahmad~~
~~Study Center(s):~~	~~Moorfields Eye Hospital~~ ~~London EC1V 2PD~~ ~~UK~~ **Sites in the United Kingdom**

Justification: Sponsor is looking into opening one additional site in the UK

Previous text:

Duration of Treatment:	56 Days each for active and placebo dosing plus 3 (±2) days between screening and entry and 28 (±2) days between final trial visit and follow up visit. Total trial duration 6-12 months.

Current text:

Duration of Treatment:	56 Days each for active and placebo dosing plus ~~3~~ **7** (±2) days between screening and entry and 28 (±2) days between final trial visit and follow up visit. Total trial duration 6-12 months.

Justification: The screening window has been widened to allow additional time for results and arrival of medication at site.

Change 3: Synopsis. Endpoints: Primary Endpoint and section 5.2.2

- *Previous text:*
- Post-instillation comfort, as graded on patient diary cards at Days 14, 28, 42 and 56
- Improvement from Day 1 in composite clinical scores at Day 14, 28, 42 and 56
- Number and percentage of patients with MMP-9 positive levels at Days 1, 14, 28, 42 and 56
- Comparison of the Conjunctival impression cytology results in each treatment group from Day 1 to Day 56 [NB these investigations will be done for qualitative research information only and will not form part of the statistical analysis since it is unlikely that the reporting will be completed for some months after study datalock]

Current Text:

- Post-instillation comfort, as graded on patient diary cards **at the following intervals** Days **1-**14, Day 1**5-**28, Day **29-**42 and Day **43-**56
- ~~Improvement~~ **Change** from Day 1 in composite clinical scores at Day 14, 28, 42 and 56
- Number and percentage of patients with MMP-9 positive levels at Days 1, ~~14,~~ 28, ~~42~~ and 56
- ~~Comparison of the Conjunctival impression cytology results in each treatment group from Day 1 to Day 56 [NB these investigations will be done for qualitative research information only and will not form part of the statistical analysis since it is unlikely that the reporting will be completed for some months after study datalock]~~

Justification: The language in the endpoints has been adapted:

- **Post instillation comfort will be reviewed by the investigator at the time the patient attends the clinical visit, but the investigator will look at the comfort over the total time since the last visit (intervals) rather than a single timepoint as it was previously suggested in the protocol.**
- **Improvement amended to change: as the sponsor cannot assume there will be an improvement**

- **The number of MMP-9 has been reduced. This is a test which gives a binary result so after reviewing it has been decided that only 3 timepoints are needed.**
- **Deleted conjunctival impression cytology endpoint as this is an exploratory endpoint and it was inadvertently repeated under secondary endpoints.**

Change 4: Section 4.3 Concomitant Therapy

Previous text:
All patients in the study must be receiving maximum topical ciclosporin (Ikervis). This should be administered as late as possible before retiring for the night.
All patients will be receiving a topical antihistamine (olopatadine hydrochloride) once daily. This should be administered in the morning at least 15 minutes before the morning dose of rVA576.

Current text:
All patients in the study must be receiving maximum topical ciclosporin (Ikervis). **This could be up to four times a day at investigator's discretion. The last dose of ciclosporin should be administered as late as possible before retiring for the night.**
All patients will be receiving a topical antihistamine (olopatadine hydrochloride) ~~once~~ **twice** daily. This should be administered ~~in the morning~~ at least 15 minutes before **or after** the ~~morning~~ dose of rVA576.

Justification:
The frequency of antihistamine has been corrected as olopatadine is taken twice daily by all patients.

Ciclosporin is indicated for the treatment of severe keratitis in patients with dry eye disease and the recommended dose is 1 drop of 0.1% to each eye once daily. It has become known that ophthalmologists in tertiary referral centres such as Moorfields Eye Hospital often increase the frequency of topical Ciclosporin to twice, three or four times a day before considering a switch to systemic immunosuppression. Therefore a proportion of patients attending outpatients clinics may be on increased frequency Ciclosporin dosing and the Sponsor would like to be able to include these patients in the study. However, no change in frequency of Ciclosporin dosing will be made once a patient has been selected for the study.

Change 5: 6.3 Dosing Scheme

Previous text:
- Ciclosporin: IKERVIS eye drops 1 mg/ml emulsion one drop to the affected eye(s) at bedtime;
- Topical antihistamine (olopatanol 0.2%, one drop to the affected eye(s) once daily)

Patients will be instructed to use the antihistamine drop (olopatadine 0.2 %) as soon as possible after waking. They will be instructed to instill the first doses of the test eye drops 1 hour later

Current text:

Ciclosporin: IKERVIS eye drops 1 mg/ml emulsion one drop to the affected eye(s) **up to four times a day;**

- Topical antihistamine (**olopatadine** ~~0.2%~~ **1 mg/mL**, one drop to the affected eye(s) ~~once~~ **twice a day**)

Patients will be instructed to use the antihistamine drop (olopatadine **1 mg/mL**) as **prescribed by the investigator.** ~~They will be instructed to instill the first doses of the test eye drops 1 hour later~~

Justification:
Ciclosporin is indicated for the treatment of severe keratitis in patients with dry eye disease and the recommended dose is 1 drop of 0.1% to each eye once daily. It has become known that ophthalmologists in tertiary referral centres such as Moorfields Eye Hospital often increase the frequency of topical Ciclosporin to twice, three or four times a day before considering a switch to systemic immunosuppression. Therefore a proportion of patients attending outpatients clinics may be on increased frequency Ciclosporin dosing and the Sponsor would like to be able to include these patients in the study. However, no change in frequency of Ciclosporin dosing will be made once a patient has been selected for the study.

The frequency of antihistamine has been corrected as this is taken twice daily by all patients. The concentration of olopatadine has been corrected to reflect the fact that it is a 1mg/mL solution

Change 6: section 6.4: Method of Assigning Subjects to Treatments and Masking

Previous text: Upon confirmation of a subject's eligibility at the Randomisation visit, the investigator, or designee, will contact the Pharmacist to register the subject as randomised and obtain the next sequence number to be dispensed to this subject.

Current text: Upon confirmation of a subject's eligibility at the Randomisation visit, the investigator, or designee, will contact the ~~Pharmacist~~ **CRO, Tailored Clinical Research Solution (TCRS),** to register the subject as randomised and obtain the next sequence number to be dispensed to this subject.

Justification: Due to the possibility of a further site being added to the trial then it was decided that the randomisation could no longer be the responsibility of the Pharmacist and has been transferred to the CRO in charge of the study. Since the randomisation is blinded then this will not mean that the CRO risks being unblinded.

Change 7: section 6.7 Trial Procedures

Previous text:

The following investigations and diagnostic procedures will be carried out in this order at clinic visits in accordance with the Schedule of Events (i.e. not all evaluations will be carried out at every visit).

- Medical History, general and indication specific
- Visual acuity by ETDRS
- Clinical examination, gross and slit lamp with clinical scoring
- Tear film break up time (TBUT)
- Conjunctival impression cytology (CIP)
- MMP-9 estimation using the *Inflammadry*® device
- rVA576 blood levels
- Systemic complement activity by serum CH50 ELISA activity.
- Anti-drug antibodies (ADA)
- Pregnancy Test
- Adverse Events
- Post instillation comfort as graded on patient diary cards (five-point grading from 0 (perfectly comfortable) to 4 (Severe, intolerable itching or burning). For full description see Section 17.1.

Current text:

The following investigations and diagnostic procedures will be carried out ~~in this order~~ at clinic visits in accordance with the Schedule of Events (i.e. not all evaluations will be carried out at every visit).

By the Investigator

- Medical History, general and indication specific
- Adverse Events
- Post instillation comfort as graded on patient diary cards (five-point grading from 0 (perfectly comfortable) to 4 (Severe, intolerable itching or burning). For full description see Section 17.1.
- Clinical examination, gross and slit lamp with clinical scoring
- MMP-9 estimation using the *Inflammadry*® device
- Conjunctival impression cytology (CIP)
- Tear film break up time (TBUT)

By the nurse or other qualified person (these may be done on any order and either before or after the Investigator's examination)

- rVA576 blood levels
- Visual acuity by ETDRS
- Systemic complement activity by serum CH50 ELISA activity.
- Anti-drug antibodies (ADA)
- Pregnancy Test

Justification: This has been amended to provide clarity and further information on who will be doing which test.

Previous text:

Screening Period:

Patients may enter the trial within 3 days (±2 days) of screening providing that there has been no change in the inclusion/exclusion criteria.

Current text:

Screening Period:

Patients may enter the trial within ~~3~~ **7** days (±2 days) of screening providing that there has been no change in the inclusion/exclusion criteria.

Justification: The screening window has been increased to allow additional time for results and arrival of medication at site.

Previous text:

Screening Period:
Part 2- Randomisation: Upon confirmation of a subject's eligibility at the Randomisation visit, the investigator, or designee, will contact the Pharmacist to register the subject as randomised and obtain the assigned medication number. This information will be recorded in the patient notes and transcribed eCRF.

Current text:

Screening Period:
Part 2- Randomisation: Upon confirmation of a subject's eligibility at the Randomisation visit, the investigator, or designee, will contact the ~~Pharmacist~~ **CRO, TCRS,** to register the subject as randomised and obtain the assigned medication number. This information will be recorded in the patient notes and transcribed eCRF.

Justification:
Due to the possibility of a further site being added to the trial then it was decided that the randomisation could no longer be the responsibility of the Pharmacist and has been transferred to the CRO in charge of the study. Since the randomisation is blinded then this will not mean that the CRO risks being unblinded.

Change 8: Sections 6.9 Safety and Efficacy Assessment

Previous text:

Conjunctival impression cytology will be done on both eyes at the start of the trial (Day 1) and at the conclusion of the trial (Day 56) for all patients. Analyses of the films will be done at Moorfields Hospital using an immunofluorescent technique (qualitative results only) and/or by flow cytometry (quantitative and qualitative results). These results will not be included in the primary statistical analysis and will be done for research information only as the reporting may not be available until some weeks after conclusion of the trial and database lock.

Current Text:

~~Conjunctival impression cytology will be done on both eyes at the start of the trial (Day 1) and at the conclusion of the trial (Day 56) for all patients. Analyses of the films will be done at Moorfields Hospital using an immunofluorescent technique (qualitative results only) and/or by flow cytometry (quantitative and qualitative results). These results will not be included in the primary statistical analysis and will be done for research information only as the reporting may not be available until some weeks after conclusion of the trial and database lock.~~

Justifications: This was an error as conjunctival impression cytology is an exploratory endpoint and should not be listed under this section.

Change 9: Section 6.9.2 Patient Diary Card

Previous text:

All patients will be issued with a diary card and will be asked to score the least comfortable eye on a scale of 0 to 4 as shown in Table 5 below. A note will be made on the card as to which eye is being scored. If both eyes feel the same, the right eye will be scored.

Current Text:

All patients will be issued with a diary card and will be asked to score **comfort** ~~the least comfortable eye~~ on a scale of 0 to 4 as shown in Table 5 below. **The patient may make further comments (e.g. a difference in comfort between the two eyes) in the diary card.** ~~A note will be made on the card as to which eye is being scored. If both eyes feel the same, the right eye will be scored.~~

Justification: This was an error in the protocol and it is now in line with the patient diary card instructions.

Change 10: section 6.11 Medical Photography

Previous text: none

Current text:
For better assessment of the eye, medical photography may be performed at investigator's discretion and photographs of both eyes may be obtained during the evaluation of the composite score and related ocular adverse events. During the consent obtained at screening the patients will be allowed to opt out of the medical photography. Declining consent for medical photography will not impact patient's participation in the study. Patient's confidentiality will be protected during medical photography of the eye.

Justification: This was added to the protocol as Principal Investigator confirmed it is standard practice for documenting disease progression or improvement.

Change 11: Section 11.1 Statistical Methods

Previous text:
The Baseline value will be defined as the last non-missing measurement collected or derived prior to the Day 1 dose.

New text:
The baseline value will be defined as the pre-dose value on Day 1, if that is missing, it will be defined from the most recent value available.

Justification: This sentence was amended for a more accurate definition of the baseline value

AMENDMENT 3

Summary of changes from Version 4.0 to Version 5.0

Change 1 Exclusion Criteria # 11

Previous Text: Glaucoma

Current Text: **Uncontrolled** glaucoma **(increase in dose of glaucoma medication or surgical intervention for glaucoma within 3 months prior to entry)**

Justification: A high proportion of AKC patients also have glaucoma. The investigators and the sponsor consider that this should not be a reason to exclude a patient from participating in this study providing that the condition has been stable or improving during the 3 months prior to entry as evidenced by there having been no increase in the dose of glaucoma medication or a surgical intervention for glaucoma within that period.

Change 2: Synopsis Treatment Regime

Previous Text: Should not be on topical steroids at start of the trial but may be used as rescue therapy during the trial if necessary.

Current Text: Should not be on topical **ocular** steroids at start of the trial but may be used as rescue therapy during the trial if necessary.

Justification: To add clarification that only topical ocular steroids are not allowed. Patient may continue to use topical steroids other than in the eye (eg steroid cream or ointment for atopic dermatitis).

Change 3 section 6.3: Dosing Scheme

Previous Text: Patients should not have used topical steroids for 1 month prior to entry to the trial but, at the discretion of the investigator, may receive them as rescue medication during the trial.

Current Text: Patients should not have used topical **ocular** steroids for **2 weeks** prior to entry to the trial but, at the discretion of the investigator, may receive them as rescue medication during the trial.

Justification: To add clarification that only topical ocular steroids are not allowed. Patient may continue to use topical steroids other than in the eye (eg steroid cream or ointment for atopic dermatitis).
Wash out period for topical ocular steroids has been reduced. Topical ocular steroids have a short half life i.e. 2.8 hours for lotprednol etabonate (Comstock & DeCory 2012). Therefore, 2 weeks is deemed sufficient time.

Change 4 Section 6.3: dosing Scheme

Previous Text: All patients entering the trial will have been on maximal topical therapy for at least three months before entry on the study and will continue on this therapy (background therapy) for the duration of the study.

Current Text: All patients entering the trial will have been on maximal topical therapy **(meaning the maximal labelled dose or frequency of dosing)** for at least three months before entry on the study and will continue on this therapy (background therapy) for the duration of the study.

Justification: to add clarity on what it is considered maximal topical therapy.

Change 5 section 6.8 Rescue Therapy

Previous Text: Topical steroids will be considered Rescue Therapy.

Current Text: Topical **ocular** steroids will be considered Rescue Therapy.

Justification: To add clarification that only topical ocular steroids are not allowed. Patient may continue to use topical steroids other than in the eye (eg steroid cream or ointment for atopic dermatitis).

AMENDMENT 4

Justification: The three patients in Part 1 who were treated open label and non-comparative have now been treated. The third patient reached the end of week 2 but then withdrew consent for reasons not medication-related but had reached the point in the study at which the safety assessment was scheduled. This assessment has taken place and clearance for the study to proceed to Part 2, the randomised, double-masked, placebo-controlled part, has been given.
The three patients treated found the drops generally comfortable and well-tolerated, although full analysis of the patient diary cards after each instillation has not yet been undertaken. There were no serious or severe treatment emergent adverse events. A mean improvement in signs (55% improvement) and symptoms (62.5% improvement) over

baseline was seen in the two patients who completed the study and the patient who withdrew at 14 days had a 12% improvement from baseline.

During Part 1 recruitment was considerably slower than anticipated at all three study sites. More than 100 patients were pre-screened but only 3 entered the study. Whilst there were a variety of reasons for this, including patients finding the weekly visits at the beginning of Part 1 too frequent and co-morbidities such as uncontrolled glaucoma, a substantial number of patients who were willing to enter the trial failed to meet the threshold score of 22 out of a possible total of 33 in the composite sign/symptom score.

Summary of changes from Version 5.0 to Version 6.0

Change 1 Inclusion Criterion # 2

Previous text: Diagnosis of moderate to severe AKC with a composite symptom/sign score from one eye of ≥ 22 out of 33

Current text: Diagnosis of moderate to severe AKC, **VKC or PKC** with a composite symptom/sign score from one eye of ≥ **18** out of 33

Justification: The entry threshold of 22 in this study was arbitrary and was intended to include patients on the moderate – severe end of the spectrum of severity although there seems to be no agreed definition of what values constitute the boundaries between mild, moderate and severe using this scale.

It is considered that, if the threshold entry score was lowered from 22 to 18, a significant extra number of potential patients would be eligible to join the trial and that all patients so recruited would still be considered to fall into the moderate to severe category of AKC. It is also considered that this change would have no implications as far as safety is concerned.

VKC and PKC are pathophysiologically almost identical conditions to AKC and it is considered that the effect of rVA576 on these conditions will be similar to those seen in AKC. This change is being made to broaden the patient base and increase the rate of recruitment.

Change 2 Exclusion Criterion #1 updated

Previous text: Eye surface disease other than AKC

Current text: Eye surface disease other than AKC**, VKC or PKC**

Justification: As above for Change 2.

Change 3 New Exclusion Criterion #15 added

Previous text: N/A

Current text: **Use of topical ocular steroids within 14 days of Screening visit**

Justification: It was considered that, although the text "Patients should not have used topical ocular steroids for 2 weeks prior to entry to the trial" appears in the body text, additional wording should be included in the eligibility criteria to ensure this is highlighted at the time of screening.

Change 4 Section 4.3 Concomitant Medications

Previous text: The evening dose of rVA576 should be administered at a minimum 30 minutes before ciclosporin.

Current text: The evening dose of rVA576 should be administered at a minimum **15** minutes before ciclosporin.

Justification – To make this easier for the patient to remember.

Change 5 Section 6.3 Dosing Scheme
Previous text: Patients should not have used topical ocular steroids for 2 weeks prior to entry to the trial

Current text: Patients should not have used topical ocular steroids for **14 days** prior to entry to the trial

Justification: To clarify the exact timescale

Change 6 Section 6.7 Trial Procedures
Previous text: Patients may enter the trial within 7 days (±2 days) of screening providing that there has been no change in the inclusion/exclusion criteria.

Current text: Patients may enter the trial within 7 days (±2 days) of screening providing that there has been no change in the inclusion/exclusion criteria. **It must be noted when organizing the first dosing visit that the IMP will take 4 days from the Randomisation to be sent to site and to be ready for dispensing.**

Justification – it was considered pertinent to remind the sites at this juncture that, although theoretically screening may not take 7 days, there is a time constraint placed upon them by the delivery and processing of the IMP

Change 7 Section 6.5

~~In addition, daily automated text messages reminders may be sent to the patient or the clinic staff may call the patient to ensure adherence to taking the study drug at the same time each day.~~

~~Example text as follows (subject to slight changes): *"A gentle reminder - please administer your medicine this morning/evening and record the time in the Patient Dosing Diary.*~~

Justification – Text message is no longer being offered to the patient

Change 8 Section 6.7 Trial Procedures

Previous text: Conjunctival impression cytology (CIP)

Current text: Conjunctival impression cytology (CIP) **(Optional)**

Justification- Making this consistent with the protocol
Change 9 Section 17.2 Schedule of Events and Blood Draws:

Previous text: Serum pregnancy test will be performed at screening, Day 56.

Current text: **Urine** pregnancy test to be performed at **Screening, Day 1, Day 28, Day 56, Day 84 and Unscheduled visit**

Justification: Serum pregnancy test will not be necessary, as urine pregnancy is sensitive enough to justify patient withdrawal from the study

Change 10 Section 6.4
Previous text: At the Screening visit, the investigator, or other site personnel under the direction of the investigator, should access the eCRF to register the subject, obtain the subject identification number. Upon confirmation of a subject's eligibility at the Randomisation visit, the investigator, or designee, will contact the CRO, Tailored Clinical Research Solution (TCRS), to register the subject as randomised and obtain the next sequence number to be dispensed to this subject. This information will be recorded in the patient notes and transcribed eCRF.

Current text: **Upon confirmation of a subject's eligibility** at the Screening visit, the investigator, or other site personnel under the direction of the investigator, should access the eCRF to register the subject **and** obtain the Subject Identification number. **In addition**, the investigator, or designee, will contact the CRO, Tailored Clinical Research Solution (TCRS), to register the subject as randomised. **Sharp Clinical will provide the Randomisation ID to TCRS. TCRS will forward this information to sites for recording** in the patient notes and transcribed eCRF.

Justification- Updated process of randomisation

Change 11 Schedule of Events and Blood Draws Table 17.2
Administration of Drug added to Day 1,7,14,21,28,42 and 56.

Justification: **This had been omitted from previous versions. It was felt that, in order to clarify that sites must leave 4 days between Screening and first dose, in order to allow time for the IMP to be delivered and prepared, this was more easily clarified if IMP administration was overtly listed in this table.**

Change 12 Section 4.1 – Inclusion Criteria

Previous Text: Willing to use adequate contraceptive precautions for the duration of the study and for 90 days.

Current Text: Willing to use highly effective contraceptive precautions for the duration of the study and for 90 days after the last dose of IMP.

Justification: **This make it more clear to the patient that they should use highly effective contraceptive precaution and not just adequate contraception for the duration of the study. Furthermore, the want to clear state that it is 90 days after the last dose and not 90 days after the study.**

AMENDMENT 5

Change 1 – Removal of PKC and addition of severe allergic conjunctivitis (seasonal (SAC) or perennial (PAC)) patients

Section 1 - Indication:

- *Previous Text:* Moderate to severe atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC) and perennial keratoconjunctivitis (PKC)

- *Current Text:* Moderate to severe atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), and ~~perennial keratoconjunctivitis (PKC) and~~ **severe allergic conjunctivitis (seasonal (SAC) or perennial (PAC))**

Section 1 – Primary Objectives:

- *Previous Text:* Safety and tolerability of topical rVA576 for AKC, VKC and PKC

- *Current Text:* Safety and tolerability of topical rVA576 for AKC, VKC ~~and PKC~~ **and severe allergic conjunctivitis (SAC or PAC)**

Section 1 – Secondary Objectives:

- *Previous Text:* Efficacy of topical rVA576 for the treatment of patients with AKC, VKC and PKC

- *Current Text:* Efficacy of topical rVA576 for the treatment of patients with AKC, VKC ~~and PKC~~ **and severe allergic conjunctivitis (SAC or PAC)**

Section 1 – Subject Population:

- *Previous Text:* Patients with moderate to severe AKC, VKC or PKC

- *Current Text:* Patients with moderate to severe AKC, VKC, or ~~PKC~~ **severe allergic conjunctivitis (seasonal (SAC) or perennial (PAC))**

Section 1 and Section 4.1 – Inclusion Criteria:

- *Previous Text:* Diagnosis of moderate to severe AKC, VKC or PKC with a composite symptom/sign score from one eye of ≥ 18 out of 33 (see Clinical Scoring Section 17.1)

- *Current Text:* Diagnosis of moderate to severe AKC, VKC **or severe allergic conjunctivitis (seasonal or perennial). Defined as**:

- AKC, VKC ~~or PKC with~~ - a composite symptom/sign score from one eye of ≥ 18 out of 33 (see Clinical Scoring 17.1)
- **Severe allergic conjunctivitis - a composite symptom/sign score from one eye of ≥ 15 out of 27 (see Clinical Scoring Section 17.1)**

Section 1 and Section 4.2 – Exclusion Criteria:

- *Previous Text:* Eye surface disease other than AKC, VKC or PKC

- *Current Text:* Eye surface disease other than AKC, VKC or ~~PKC~~ **severe allergic conjunctivitis (SAC or PAC)**

Justification: **The term PKC replaced with seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC). As with AKC, these are severe allergic eye diseases unresponsive to topical therapy.**

Justification for adding severe allergic conjunctivitis.
Severe allergic conjunctivitis (SAC) has a similar aetiology to AKC and VKC, the principal differences being that patients may not necessarily have other forms of atopy such as asthma or eczema as manifested in AKC and that, by definition, the cornea is not affected as it is in the keratoconjucitivitides. However, SAC may progress to AKC in time and so it is important that adequate treatment be started before there is significant corneal damage. It is therefore proposed that SAC is added to the list of indications for this study. Since SAC patients do not have corneal involvement it is proposed that a modified form of the composite symptom and sign scoring system is used. This will utilise four symptoms and five signs scored from 0 to 3. In order to enter the study patients will have to score 15 out of a possible 27 instead of 18 out of a possible 33 as for AKC, VKC and PKC patients.

Change 2 – Scoring system added for patients with severe allergic conjunctivitis (SAC or PAC)

Section 1 and Section 4.1 – Inclusion Criteria:

- *Previous Text:* Diagnosis of moderate to severe AKC, VKC or PKC with a composite symptom/sign score from one eye of ≥ 18 out of 33 (see Clinical Scoring Section 17.1)

- *Current Text:* Diagnosis of moderate to severe AKC, VKC **or severe allergic conjunctivitis (seasonal or perennial). Defined as**:
  - AKC, VKC ~~or PKC with~~ - a composite symptom/sign score from one eye of ≥ 18 out of 33 (see Clinical Scoring 17.1)
  - **Severe allergic conjunctivitis - a composite symptom/sign score from one eye of ≥ 15 out of 27 (see Clinical Scoring Section 17.1)**

Section 6.9.1 Clinical Scoring:

- *Previous Text:* A composite score of 5 symptoms and 6 signs will be used

- *Current Text:* A composite score of 5 symptoms and 6 signs will be **used for AKC and VKC patients, and a composite score of 4 symptoms and 5 signs will be used for patients with severe allergic conjunctivitis - SAC or PAC**

Section 6.9.1 ClinicalClincial Scoring:

- *Previous Text:* The maximum possible score for symptoms and signs combined is 33. To qualify for entry to the trial patients must score a minimum of 18 at the Screening visit.

- *Current Text:* The maximum possible score for symptoms and signs combined is 33 **(AKC/VKC) or 27 (severe allergic conjunctivitis)** . To qualify for entry to the trial patients must score:

  AKC or VKC - a minimum of 18 at the Screening visit. .....

  ……..
  Severe allergic conjunctivitis - SAC or PAC - a minimum of 15 at the Screening visit.

  The following symptoms will be scored:

  1. **Itching**
  2. **Tearing**
  3. **Discomfort (burning, stinging or foreign body sensation)**
  4. **Photophobia**

  The following signs will be scored:

  1. **Upper tarsal conjunctival hyperaemia**
  2. **Upper bulbar conjunctival hyperaemia**
  3. **Chemosis**
  4. **Upper tarsal conjunctival papillae**
  5. **Blepharitis**

Section 17.2:

- *Previous Text: N/A*

- *Current Text:* New table inserted for scoring Severe Allergic Conjunctivitis - SAC or PAC

Justification: **Scoring modified in line with the inclusion of patients with seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC)**

Change 3

Section 1:
Previous Text: Sites in United Kingdom

Current Text: Sites in United Kingdom **and Spain**

Justification: **Trial sites to be opened in Spain to increase recruitment**

Change 4
Section 1 and Section 4.1 – Inclusion Criteria:
Previous Text: Will have had maximal topical therapy for at least 3 months without improvement but will not currently be receiving systemic immunotherapy.

Current Text: Will have had **received** ~~maximal~~ **some** topical therapy ~~for at least~~ **during the last** 3 months without improvement but will not currently be receiving systemic immunotherapy. **Topical therapy may be topical cyclosporin, antihistamines or corticosteroids alone or in combination. Lubricants or artificial tears will not a count as topical therapy for these purposes.**

Justification for dropping the medication entry requirements
Since initiating this study it has been found that there is a wide variation in medications that patients with moderate to severe AKC take. In large part this is because of reluctance by patients to use ciclosporin eye drops even when they have been prescribed by their ophthalmologist as a necessary part of their treatment. These drops are well known to cause stinging and burning in some patients and for that reason they often will not use them at all or use them intermittently or with poor compliance. Similarly some patients are reluctant to use antihistamine drops, mainly for perceived lack of efficacy. The previous requirement that patients entering this trial should be on maximal doses of ciclosporin for at least three months prior to entry has proved to be a major barrier to entry.
After discussion with the investigators it has been decided that the strict entry requirements regarding prior medication at entry be dropped and that patients should be allowed to enter whatever topical medication they are taking at that point with the proviso that they should not be taking topical corticosteroids for at least 7 days prior to entry in order to avoid a steroid withdrawal rebound. Patients may continue to take their background medication during the trial if they wish. Any changes will be recorded.

Change 5

Section 1 and Section 4.2 – Exclusion Criteria:

- *Previous Text:* Topical ocular corticosteroid use in the 14 days prior to entry

- *Current Text:* Topical ocular corticosteroid use in the ~~1~~**47** days prior to entry

Justification: **See change 4**

Change 6
Section 1 and Section 4.1 – Inclusion Criteria:
Previous Text: History of atopy other than ocular (dermatitis, asthma, hay fever)

Current Text: ~~History of atopy other than ocular (dermatitis, asthma, hay fever)~~

Justification: **updated in line with inclusion of patients with seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC)**

Change 7
Section 1 and Section 6.3 – Dosing Scheme:
Previous Text: Background therapy:

- Topical ciclosporin
- Topical lubricant
- Topical antihistamine

Current Text: Background therapy:

- Topical ciclosporin
- Topical lubricant
- Topical antihistamine

Patients should continue on whatever topical therapy they are on at the time of screening (ciclosporin or antihistamines) but this should remain stable during the trial. Lubricants and artificial tears may be used ad libitum but should not be administered for 15 minutes before or after the trial medication. In the event of worsening of signs or symptoms that, in the clinician's opinion is so severe as to necessitate a change of medication, ciclosporin and/or antihistamines may be introduced or increased in dose/frequency and this will be considered as a treatment failure for purposes of efficacy analysis. Topical corticosteroids may be added following introduction or increase in ciclosporin/antihistamine therapy if considered necessary.

Justification: **See change 4**

Change 8
Section 6.8 – Rescue therapy:
Previous Text: Topical ocular steroids will be considered Rescue Therapy.

After entry into the trial, subjects will be recommended to not receive Rescue Therapy from the first dose of rVA576 as far as possible unless assessed by PI as needed.

Current Text: Topical ocular steroids will be considered Rescue Therapy.
In the event of worsening of signs or symptoms that, in the clinician's opinion is so severe as to necessitate a change of medication, ciclosporin and/or antihistamines may be introduced or increased in dose/frequency and this will be considered as a treatment failure for purposes of efficacy analysis.

The introduction or increase in dose/frequency of ciclosporin or antihistamines will be considered as Rescue Therapy.

After entry into the trial, subjects will be recommended to not receive Rescue Therapy from the first dose of rVA576 as far as possible unless assessed by PI as needed.

Justification: **Updated to align with the changes in the background therapy.**

AMENDMENT 6 (NON-SUBSTANTIAL)

Change 1
Section 4.3 Concomitant Therapy

Previous Text: All patients in the study must be receiving maximum topical ciclosporin (Ikervis). This could be up to four times a day at investigators discretion. The last dose of ciclosporin should be administered as late as possible before retiring for the night. The evening dose of rVA576 should be administered at a minimum 15 minutes before ciclosporin.

All patients will be receiving a topical antihistamine (olopatadine hydrochloride) twice daily. This should be administered at least 15 minutes before or after the dose of rVA576.

Current Text: These two paragraphs have been removed.

Justification: **These paragraphs should have been removed in protocol v7 to align with the changes in the background therapy**

AMENDMENT 7

Change 1
Protocol synopsis and Section 4.1 - Inclusion criterion 3:

- *Previous Text:* Topical therapy may be topical **cyclosporin**, antihistamines or corticosteroids alone or in combination

- *Current Text:* Topical therapy may be topical ~~**cyclosporin**~~ **calcineurin inhibitors**, antihistamines or corticosteroids alone or in combination

Justification: **In the UK almost all patients using topical ocular calcineurin inhibitors are prescribed ciclosporin A emulsion. This trial has now been expanded to include clinical sites in Spain where it is more usual to use topical tacrolimus. To accommodate this the permitted medications have been changed to allow any topical calcineurin inhibitor.**

Change 2
Section 3.4.2 and 4.0:
Removal of the terms: 'steroid-resistant' and 'resistant to topical corticosteroid treatment'.

Justification: **The intention of this trial is to treat patients with established, moderate to severe allergic conjunctivitis such as atopic keratoconjunctivitis (AKC). Most patients newly presenting with such conditions are normally treated initially with topical antihistamines. If these fail to control the condition the usual next step is to add intermittent topical corticosteroids of ascending potency before adding topical calcineurin inhibitors. Since initiating this trial, it has become apparent that not all patients are treated with topical corticosteroids before progressing to topical calcineurin inhibitors and so the term 'steroid-resistant' may not be appropriate in all cases. The composite clinical sign and symptom score used to assess the suitability of patients for entry to the trial ensures that only patients falling into the moderate to severe categories will in fact be deemed suitable and so the term 'steroid-resistant' is not a necessary or appropriate descriptor and will be removed.**

Change 3
Section 4.3:

- *Previous Text:* All patients may use an eye lubricant *pro re nata* (p.r.n.). This should not be given within 15 minutes before or after rVA576. The exact choice of lubricant is left to the patient but **should be one of the following**:

- *Current Text:* All patients may use an eye lubricant *pro re nata* (p.r.n.). This should not be given within 15 minutes before or after rVA576. The exact choice of lubricant is left to the patient but ~~**should be one of the following**~~ **the following are recommended**:

Justification: **In general ophthalmologists recommend the use of preservative-free lubricants as preservatives, particularly benzalkonium chloride, are known to be associated with eye irritation in some patients. For that reason, when the trial opened at Moorfields Eye Hospital in London, the hospital pharmacy list of non-preserved lubricants was included as permitted medications. Since then it has been found that some patients have their own preferred lubricants, some of which contain preservatives. It has therefore been decided to allow patients to use whatever lubricant or artificial tear they are most comfortable with.**

Change 4
New wording: Interim analyses may also be conducted. Details of any analyses will be outlined in the SAP.

Justification: **When originally planned it was intended that the total duration of the trial would be less than 6 months. However, because the selection criteria were set to include patients on the moderate to severe end of the severity spectrum who had already been shown to be resistant to maximum topical therapy, recruitment has proved to be much slower than anticipated. As the trial has now exceeded its planned duration by more than a year and recruitment of the randomised part has now reached 50% of the planned population, it is now felt that an interim futility analysis is justified to see whether continuing the trial would be futile or would provide further useful information**

2 INTRODUCTION

2.1 Overview of the Disease, treatment options and unmet need

Atopic keratoconjunctivitis (AKC) is a type of allergic conjunctivitis which involves mast cell activation due to the predominance of inflammatory mediators such as eosinophils and Th2-generated cytokines (Mishra et al. 2011). Treatment is initially with topical lubricants, antihistamines, immunomodulators (e.g. ciclosporin A) and intermittent steroids but systemic immunotherapy may become necessary in patients unresponsive to topical therapy. This usually affects 10 - 15% of the population with 5 – 10% of patients who experience severe AKC progressing to complete vision loss. AKC represents a severe chronic allergy primarily in adult population. AKC sufferers usually exhibit symptoms such as itching, burning, tearing, erythematosus and swollen eye lids. The disease may lead to corneal scarring and may also lead to vascularisation of the corneal Both eyes are usually affected equally. There is substantial unmet need for topical agents that will prevent the progression of corneal involvement and the requirement for systemic immunomodulators (La Rosa et al. 2013).

Evidence for LTB4 being an important inflammatory mediator in AKC itself is limited and circumstantial. This is almost certainly because it has not hitherto been a subject of study in this condition since no negative evidence exists. However, there is more evidence for the role of LTB4 in other closely related eye surface inflammatory diseases including vernal keratoconjunctivitis (VKC), Sjögren's syndrome (SS), mucous membrane pemphigus and contact lens-related dry eye. These conditions are histopathologically similar to AKC and the evidence consists mainly of a number of studies demonstrating high tear fluid levels of LTB4 in these conditions. There have been a few attempts to intervene therapeutically by this route using cysteinyl leukotriene receptor antagonists and a meta-analysis of the literature showed that these agents were significantly more effective than placebo although less effective than oral antihistamines (Gane & Buckley 2013). There is less direct evidence for the role of complement activation in eye surface inflammation although complement is known to be an important driver of other forms of eye inflammation such as uveitis (Zhang et al. 2017).

2.2 rVA576

Recombinant rVA576 is a small protein (16.7kDa) which has two independent actions. It inhibits the activation and cleavage of complement C5 and it binds and inactivates leukotriene B4 (LTB4). It is a recombinant version of a near identical native protein isolated from the saliva of the *Ornithodoros moubata* tick where its function is to counteract host immune responses aimed at preventing successful blood feeding by the parasite (Hepburn et al. 2007).

It acts on the complement system by preventing the cleavage of C5 by C5 convertase into C5a and C5b and so is effective in inhibiting terminal complement activity irrespective of the activating pathway. rVA576 is currently in clinical development for the treatment of complement mediated diseases including paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemic syndrome (aHUS). In these conditions, it is administered by subcutaneous injection and has its effect through total blockade of the terminal complement system and prevention of the formation of the membrane attack complex (MAC). In these conditions the contribution, if any, of LTB4 inhibition is unclear and it is thought that complement plays the major role.

LTB4 is a potent pro-inflammatory mediator which has powerful leukocyte attractant properties. It is released predominantly from epithelial cells including bronchoalveolar, conjunctival and naso-pharyngeal mucous membranes. Negligible amounts of LTB4 are found

in circulation and it is believed to achieve its effect mainly through local release and the establishment of concentration gradients. In that respect, topical administration of rVA576, where possible, seems to offer advantages including sparing the infection protective effects of the systemic complement system.

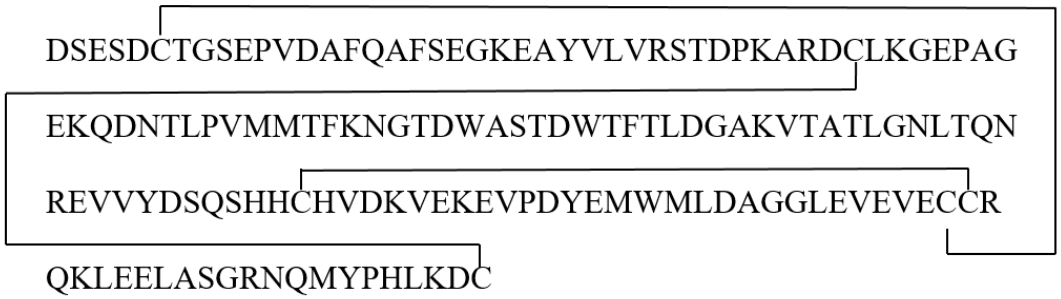
3 PRIOR EXPERIENCE WITH THE INVESTIGATIONAL PRODUCT

3.1 Investigational Product

Recombinant rVA576 0.25% w/v (2.5 mg/mL) eye drops solution is the investigational medicinal product. It is intended for ophthalmic use by topical administration to the eye.

Recombinant rVA576 is a compact small protein molecule with a lipocalin-like structure consisting of alpha helices and a beta barrel. There is a surface-active site which binds to the complement C5 molecule with a high affinity (K_D 1.85 x 10^{-8} M) and an internalised active site which binds the small eicosinoid molecule leukotriene B4 (Hepburn et al. 2007).

The molecular mass of rVA576 as predicted by molecular modelling and confirmed by mass spectrometry is 16.7855 kDa. The amino acid sequence of rVA576 showing disulphide bridges is shown below:



The investigational medicinal product (IMP) solution is a sterile aqueous solution in phosphate buffered saline (PBS) where the Osmolarity and pH correspond to that of the ocular mucosa. The IMP for this clinical trial will be presented as single-use 6 mL glass vials each containing a nominal 1 mL of rVA576 solution at 0.25% w/v (2.5 mg/mL). Administration will be by single-use ocular pipettes.

The IMP can be stored frozen at -20ºC and will have an initial shelf-life of 12 months which may be extended as further stability data becomes available and once defrosted can be stored refrigerated at 2 – 8ºC for 7 days.

The placebo is an identical formulation to the active drug product without rVA576. The placebo solution will be provided as a nominal 1 mL eye drops in 6mL glass vials, and should be stored frozen at -20 ºC with an initial shelf-life of 12 months and then refrigerated at 2-8 ºC and stored for a total of up to 7 days at this temperature.

3.2 Summary of Nonclinical and Clinical Studies Relevant to the Clinical Trial

Recombinant rVA576 is a small protein (MW 16.8kDa) which is derived from a native protein discovered in the saliva of the *Ornithodoros moubata* tick (Nunn et al. 2005). Its function in tick saliva is to assist the parasite in feeding by suppressing the host immune reactions that would otherwise alert the host to the presence of the parasite which could then be removed by scratching or grooming. It has been known for some time that all species of ticks, which can feed undisturbed on their hosts including rodents, cattle, dogs and man, for periods of 14 days or more, secrete an array of immunomodulatory peptides and proteins in their saliva in order

to take control of their hosts' local and systemic immune and inflammatory responses (Francischetti et al. 2009).

The complement system is an important part of the innate immune system in many animal species including all mammals. There are three known pathways in the cascade: the classical, the alternative and the lectin but all converge on a final common pathway. At this point complement C5, a product of the classical pathway is acted upon by the enzyme C5 convertase, a product of the alternative pathway, to form C5a and a cluster of proteins (C5b, C6, C7, C8, and C9) which are collectively known as the membrane attack complex (MAC). It is known that many human autoimmune diseases are associated with inappropriate reactions to products of the final common pathway of the complement system. In particular myasthenia gravis, in which individuals form antibodies to their own acetyl choline receptors (approximately 70% of all myasthenia gravis (MG) patients) is associated with either inappropriate reaction to or over-production of MAC proteins (Lang & Vincent 2009).

Recombinant rVA576 binds to the C5 molecule, preventing C5 convertase from activating and cleaving C5 to form C5a and the MAC. It appears to do this by interfering with a productive interaction between C5 and the C5 convertases, as rVA576 does not directly block the convertase cleavage site on C5 (Jore et al. 2016). The binding of rVA576 to C5 is high affinity (K_D 1.0 x 10^{-9} M) and the rate of dissociation between C5 and rVA576 is very low, but the interaction is not irreversible (Roversi et al. 2013). High resolution X-ray crystallography has resolved the precise details of the binding interaction between rVA576 and C5 (Jore et al. 2016).

Inhibition of the C5 complement system is a therapeutic target in a wide range of autoimmune and inflammatory diseases including rheumatoid arthritis, Crohn's disease, hypersensitivity pneumonitis, ischaemia reperfusion injury, sepsis, myasthenia gravis, paroxysmal nocturnal haemoglobinuria (PNH) and age related macular degeneration (Agostini et al. 2004, de Vries et al. 2003, Godau et al. 2004, Mollnes & Kirschfink 2006, Nozaki et al. 2006, Sarma et al. 2006, Tuzun et al. 2008, Ward et al. 2003).

Independently from complement inhibition, the rVA576 molecule also binds leukotriene B4 (LTB4) at a separate, internalised binding site. This is a high-affinity binding site that outcompetes the natural receptors, BLT1 and BLT2 and results in an effectively irreversibly bound complex (Kuhn et al. 2016). It is thought that natural selection over many millions of years has paired these two activities in a single molecule because of synergies between the complement, eicosanoid and thrombotic pathways which have only recently become recognised but are still not completely elucidated (Hill et al. 2013).

3.2.1 Non-clinical experience:

In mechanistic pharmacology studies rVA576 has been administered to a number of species of laboratory animals including rats, mice, non-human primates, pigs and rabbits. Routes of administration have included intravenous, intraperitoneal, subcutaneous, inhaled and topical ocular. It has been effective in blocking the terminal complement pathway in all species tested to date and, in so doing, alleviating the effects of experimentally induced conditions including asthma, sepsis, adult respiratory distress syndrome (ARDS), myasthenia gravis, experimental autoimmune neuritis (EAN), bullous pemphigoid and myocardial infarction. For full details of these studies refer to the Investigators Brochure (IB).

In toxicology studies rVA576 has been administered to rats, mice and non-human primates by the intravenous and subcutaneous routes and to rabbits by the topical ocular route. In these studies, which have included doses of up to 70 times the highest human equivalent dose (HED)

by the intravenous route, there have been no deaths attributable to the drug and minimal drug-related adverse events. For full details of these studies refer to the IB.

In the 3 day irritation study the average irritation index for the low dose was 0.75, for high dose it was 0.5 and for placebo (PBS vehicle) it was 0.33. All of these values are rated as no irritation. The conclusion was that rVA576 is non-irritable after repeated administration in the concentrations 1.25 and 5 mg/mL into the rabbits' conjunctival sac used under the conditions of the study. A 56 Day ocular tolerance study with ocular irritation test was carried out in white New Zealand rabbits using rVA576 1.25 and 5 mg/mL or placebo (PBS) administered twice a day. The study showed only slight conjunctival redness in some animals from the active group.

3.2.2 Clinical experience

Experience gained with eculizumab (Soliris®) in the treatment of PNH and aHUS in several thousand patients for up to 13 years suggests that long term C5 inhibition is generally safe apart from the increased tendency to *N. meningitidis* infection which results from total blockade of the terminal complement system. The calculated minimum dose of rVA576 in humans required to achieve complete complement blockade is 0.57mg/kg (40mg for a 70kg individual). In this trial, the maximum delivered dose is 0.2mg (40µL per eye x 0.25%), which is two hundredth of the dose required to achieve total complement blockade. In the unlikely event that the entire topical dose will be systemically absorbed it is considered that it would have no impact on the complement blockade and therefore patients participating in this trial will not be required to take prophylactic measures against *Neisseria meningitides* such as vaccination and treatment with antibiotics.

To date (May 2018) rVA576 has been administered to approx. 42 subjects, 32 healthy volunteers and 11 patients. In these patients, rVA576 has generally been found to be well tolerated.

Phase Ia Trial VA576

A single ascending dose (SAD) Phase Ia (VA576) clinical trial of rVA576, administered by s.c. injection, was performed to validate this route of administration and to establish the dose needed to completely inhibit C5 activation in the vascular compartment. The starting dose was one eighth of the dose found to induce total C5 blockade in rodent and non-human primate (NHP) PK studies. The dose was doubled in each of the succeeding 3 cohorts of 6 subjects, until in Cohort 4 the target dose expected to fully inhibit complement (0.57mg/kg) was reached. This s.c. dose of rVA576 was found to produce complete terminal complement blockade, as determined by Classical haemolytic 50% lysis Units Equivalent/ml (CH50 U Eq/ml) assay in all four subjects.

In this study, there were no serious adverse event (SAEs) or dose related adverse events (AE) and the drug was well tolerated.

AK577

A Phase Ib dose range finding study (AK577) was conducted in which 4 cohorts of healthy volunteer subjects were studied. All subjects received ascending doses of 4 x 30 mg doses 12 hourly (or the placebo equivalent), before going on to receive maintenance doses at 1 of 3 dose levels for a further 5-days, or in the case of Cohort 4 for a further 19 days.

There were 6 subjects in each of Cohort 1 (30mg once a day maintenance dose), Cohort 2 (22.5 mg once a day maintenance dose) and Cohort 3 (15 mg once a day maintenance dose)

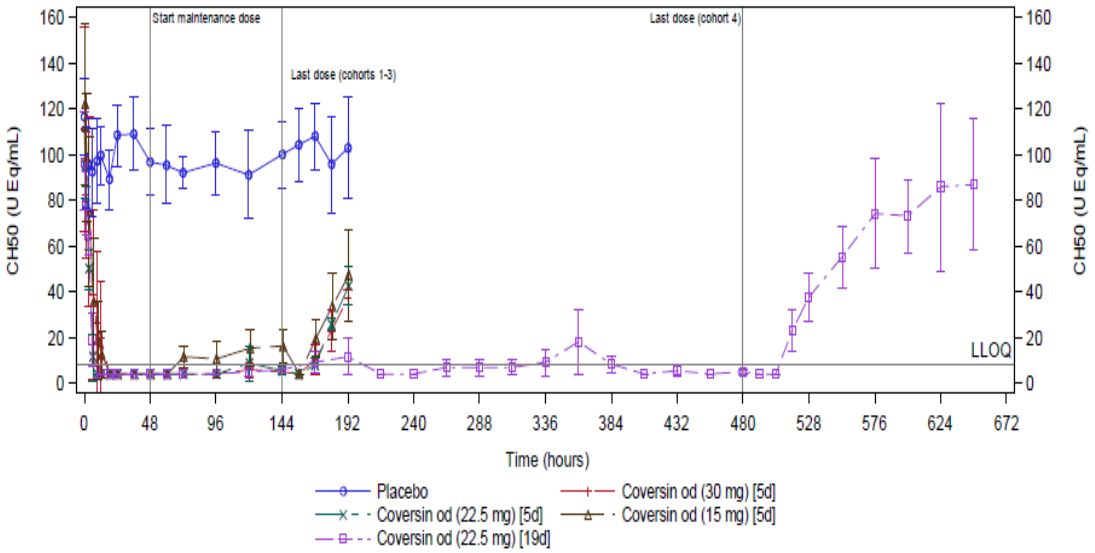
with 4 active subjects receiving rVA576 and 2 subjects receiving placebo in each cohort. Cohorts 1, 2 and 3 subjects were followed during a 2-day recovery period from Day 7 to 9.

Cohort 4 (comprising 4 active subjects only) received ascending doses like Cohorts 1, 2 and 3 and a maintenance dose of 22.5 mg once a day for 19 days. Cohort 4 subjects were followed during a 7-day recovery period from Day 21 to 28.

As shown in Figure 1, the ascending dose rapidly reduced Terminal Complement Activity (TCA) below the lower limit of quantification (LLOQ) for the Enzyme-Linked Immunosorbent Assay (ELISA) CH50 assay and TCA was essentially completely inhibited at maintenance doses of 30mg once daily for 5 days and 22.5 once daily for both 5 and 19 days.

One subject stopped treatment in Cohort 1. The subject, who had received 3 doses of rVA576 and 4 doses of ciprofloxacin, experienced significantly raised creatinine kinase (CK) and serum myoglobin level on Day 2. The Investigator considered that this AE was reported as rhabdomyolysis. The Investigator considered it to be related to the administration of ciprofloxacin, as it is a known, but rare side effect of the drug.

Figure 1 AK577 Mean (+/-SD) CH50-Time Plot



In general, all adverse events were mild to moderate in intensity and all resolved. For further details, please refer to the IB.

In trial AK578, a single PNH eculizumab resistant patient has received daily doses of rVA576 since the 8 February 2016 under protocol AK578. The patient is a 30-year-old male with PNH, (granulocyte clone size: 90%) and severe haemolysis (LDH 3 to 17 x upper limit of normal prior to treatment with rVA576), transient renal failure, extreme fatigue, symptoms of muscle dystonia and no history of thrombosis. He remained severely haemolytic during 6 months of eculizumab treatment despite adequate drug levels and no human anti-drug antibodies. Other causes of haemolysis were excluded. This patient was also shown to have a p.Arg885Ser polymorphism in C5 which rendered him non-responsive to eculizumab therapy.

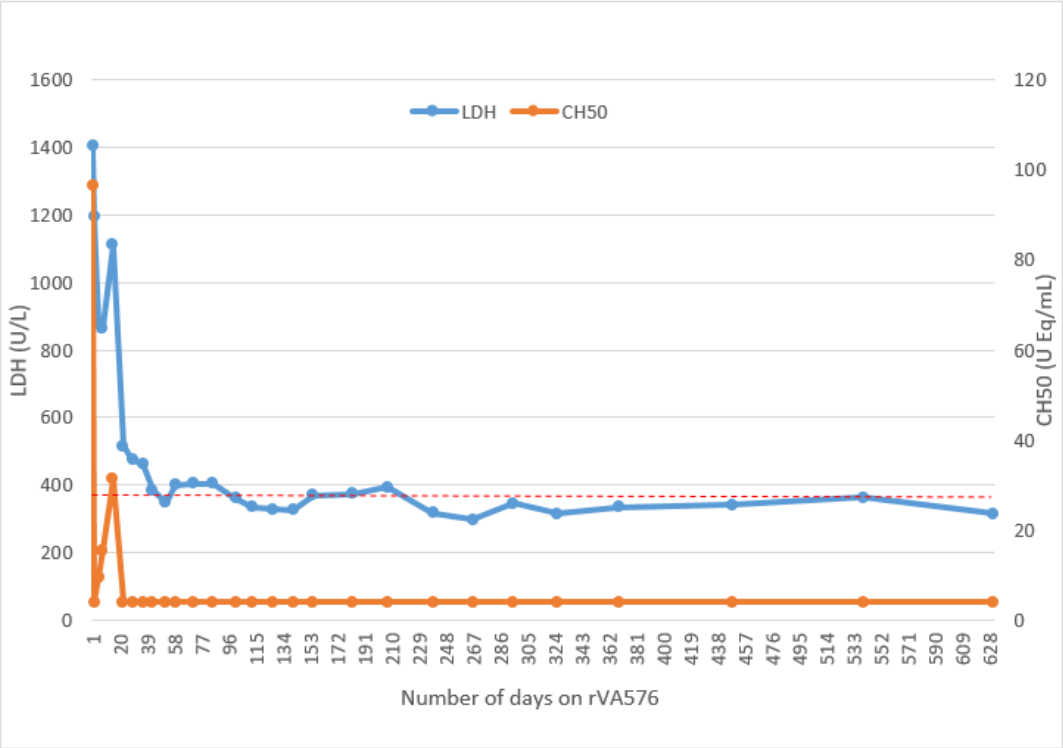
Recombinant rVA576 was initially administered by s.c. injection at an ablating dose of 0.57 mg/kg on day 1, followed by a maintenance dose of 0.14 mg/kg per day thereafter. Peripheral blood samples were drawn for PK/PD. Since this was the first occasion that rVA576

had been administered to a PNH patient, it was important to tailor the dose for best therapeutic effect. The protocol therefore allowed doubling of the dose and/or shortening of the dose interval on the basis of clinical symptoms and CH50 levels to achieve adequate and sustained complement inhibition.

There was a good initial response to the ablating dose of 0.57mg/kg rVA576, with CH50 levels decreasing from baseline 96 U Eq/mL to < 8 U Eq/mL the limit of quantification in the CH50 ELISA. Clinical symptoms and laboratory markers of haemolysis improved during the first few days dosing at 0.14mg/kg every 24 hours. However as shown in Figure 2, 6 days into the treatment, pre-dose CH50 had increased to 20.9 U Eq/ml and the patient experienced haemolysis-associated symptoms with dark urine and no further decrease of his LDH. The same occurred after doubling of the dose to 0.29 mg/kg once per day so the dose and dose interval were changed to 0.14mg/kg administered every 12 hours. This resulted in stable complement inhibition with CH50 levels < 8 U Eq/mL (the limit of quantification) and no breakthrough symptoms. The LDH rapidly decreased to around 500 IU/L and thereafter to approximately 1.5xULN - indicated by the horizontal broken green line at 273 LDH IU/mL.

There have been 7 SAEs to date (May 2018), but no treatment related SAEs and the most commonly reported AEs have been mild injection site reactions. No patient has had to have a dose adjustment or discontinued the trial due to drug related AEs.

Figure 2 Lactate dehydrogenase (LDH) level and complement activity (CH50 U Eq/mL) during treatment with rVA576 for AK578



AK579 (COBALT), a 90 day, open label Phase II trial of rVA576 in complement-inhibitor naïve patients with PNH finished in December 2017 although a full dataset analysis has not yet been completed. Eight patients entered the trial, one of whom was withdrawn after 43 days for a suspected co-morbidity unrelated to the study drug. Preliminary results indicated that a daily dose of 45 mg given either singly or in two divided doses was sufficient to fully inhibit terminal

complement activity and control disease signs and symptoms. This dose was arrived at following an initial exploratory dosing regimen in which escalation to 30mg once daily or 22.5 mg 12 hourly was found to be less effective in reducing and maintaining terminal complement activity. The 45 mg daily dose has been selected for all future clinical trials requiring systemic complement inhibition. All 7 patients who completed the trial remain in the long-term extension study AK581 (CONSERVE) at the current date (21 June 2018).

The most common Treatment Emerging Adverse Events (TEAE) during COBALT was injection site reactions which accounted for the majority of the adverse events, all of which were all mild to moderate in intensity and declined towards the end of the 90-day trial. These reactions were in line with those expected with any drug delivered by the s.c. route. Anti-drug antibody studies have indicated that all patients treated for longer than 21 days develop low titre antibodies but that these are non-neutralising and begin to decline in magnitude from about Day 60 onwards.

3.3 Summary of Known and Potential Risks and Benefits to Human Subjects

The clinical implications of complement C5 blockade can be deduced from a combination of genetic and epidemiological studies, animal studies, clinical experience and experience with eculizumab. Complement C5 deficiency in humans is a rare, familial condition, caused by a variety of genetic defects, including mutations in the C5 exons. Those affected have a predisposition to gram negative infections, particularly meningococcal meningitis (Densen 1989), herpetic infections and seborrheic dermatitis (Bartholomew & Shanahan 1990).

In the SAD trial (VA576) the drug was well tolerated, there were no serious or severe adverse reactions and only mild injection site reactions. A total of three adverse reactions were reported in two of 16 subjects who received the active drug and in one of eight subjects who received placebo. There was no dose relationship, three of the four AEs occurring at the lowest dose and one in the third of four ascending doses. The AEs were mild and self-limiting and consisted of light headedness (1), symptoms of a cold (1), pain in the arm related to the injection site (1) and intolerance to bright light (1).

In the multi-dose Phase Ib study (AK577) there was a subject in Cohort 1 who received three doses of rVA576 and 4 doses of ciprofloxacin and experienced significantly raised CK and serum myoglobin level on Day 2. The subject was clinically stable and troponin was negative. The Principal Investigator (PI) decided to stop rVA576 and ciprofloxacin and withdraw the subject. The subject did not experience any symptoms relating to the raised CK and myoglobin levels. The CK level dropped significantly by Day 6 and had returned to normal by Day 28. The Investigator considered that this AE was related to the administration of ciprofloxacin as it is a known but rare side effect of the drug. He did not consider that it was related to rVA576. (Table 1) shows the treatment-emergent AEs observed in study AK577. In general, all AEs were mild to moderate in intensity and all resolved. As described above, there was one patient who withdrew from treatment.

Table 1 Summary of Treatment-Emergent Adverse Events (TEAEs) from AK577

System Organ Class	Preferred Term	Doses Placebo N= 6 N (%)	rVA576 30 mg od 5d N = 4 N (%)	rVA576 22.5 mg od 5d N = 4 N (%)	rVA576 15 mg od 5d N = 4 N (%)	rVA576 22.5 mg od 19d N = 4 N (%)	Total rVA576 N = 16 N (%)
Number of subjects with AEs		1 (16.7)	2 (50.0)	1 (25.0)	1 (25.0)	3 (75)	7 (43.8)
General disorders and administration site conditions	Total number of subjects	1 (16.7)	0	1 (25.0)	1 (25.0)	2 (50.0)	4 (25)
	Injection site pain	1 (16.7)	0	0	1 (25.0)	2 (50.0)	3 (18.8)
	Injection site reaction	0	0	0	0	2 (50.0)	1(6.3)
	Influenza like illness	0	0	1 (25.0)	0	0	1 (6.3)
	Injection site bruising	0	0	0	0	1 (25.0)	1 (6.3)
	Injection site erythema	0	0	0	0	1 (25.0)	1 (6.3)
	Injection site swelling	0	0	0	0	1 (25.0)	1 (6.3)
Musculoskeletal and connective tissue disorders	Total number of subjects	1 (16.7)	1 (25.0)	1 (25.0)	1 (25.0)	0	3 (18.8)
	Back pain	0	0	0	1 (25.0)	0	1 (6.3)
	Musculoskeletal pain	1 (16.7)	0	0	0	0	0
	Pain in extremity	0	0	1 (25.0)	0	0	1 (6.3)
	Rhabdomyolysis	0	1 (25.0)	0	0	0	1 (6.3)

System Organ Class	Preferred Term	Doses Placebo N= 6 N (%)	rVA576 30 mg od 5d N = 4 N (%)	rVA576 22.5 mg od 5d N = 4 N (%)	rVA576 15 mg od 5d N = 4 N (%)	rVA576 22.5 mg od 19d N = 4 N (%)	Total rVA576 N = 16 N (%)
Nervous system disorders	Total number of patients	0	1 (25.0)	1 (25.0)	0	1 (25.0)	3 (18.8)
	Headache	0	1 (25.0)	1 (25.0)	0	1 (25.0)	3 (18.8)
	Presyncope	0	0	1 (25.0)	0	0	1 (6.3)
Eye Disorders	Total number of subjects	0	2 (50.0)	0	0	0	2 (12.5)
	Lacrimation increased	0	1 (25.0)	0	0	0	1 (6.3)
	Photophobia	0	1 (25.0)	0	0	0	1 (6.3)
Respiratory, thoracic and mediastinal disorders	Total number of subjects	0	1 (25.0)	0	0	0	1 (6.3)
	Cough	0	1 (25.0)	0	0	0	1 (6.3)
	Rhinorrhoea	0	1 (25.0)	0	0	0	1 (6.3)
Injury, poisoning, and procedural complications	Total number of subjects	0	0	0	0	1 (25.0)	1 (6.3)
	Contusion	0	0	0	0	1 (25.0)	1 (6.3)
Skin and s.c. tissue disorders	Total number of subjects	0	0	1 (25.0)	0	0	1 (6.3)
	Rash pruritic	0	0	1 (25.0)	0	0	1 (6.3)

There has been a single patient enrolled in the PNH eculizumab resistant protocol (AK578) to date and one SAE was reported during the first week of treatment. This 30-year-old male patient experienced a PNH-related complaint (fatigue, dark urine) on Day 6 of daily maintenance dosing. He was admitted into the hospital for additional laboratory examinations and discharged on Day 7 and fully recovered. The Investigator considered that this SAE was unrelated to rVA576, but the dose was increased and haemolysis was brought under control. This patient also reported 28 AEs during the 22-month study period (Table 2). All AEs were mild or moderate, resolved spontaneously and no treatments were given.

Table 2 Summary of Adverse Events Observed in AK578

System Organ Class No of subjects with AEs	**Preferred Term**	**Related**	**Possibly Related**
Total number of AEs	31	9 (29%)	22 (71%)
General disorders and administration site reactions	Total no of AE's	9	7
	Injection site reaction	8	0
	Pain injection site	1	0
	Flu-like symptoms	0	4
	Malaise	0	2
	Fatigue	0	1
Nervous system disorders	Total no of AE's	0	7
	Headache	0	6
	Insomnia	0	1
Respiratory and thoracic and mediastinal disorders	Total no of AE's	0	4
	Cough	0	1
	Dyspnoea	0	1
	Sore throat	0	2
Gastrointestinal disorders	Total no of AE's	0	2
	Abdominal pain	0	1
	Nausea	0	1
Skin and s.c. tissue disorders	Total no. of AE's	0	1
	Rash	0	1
Vascular disorders	Total no of AE's	0	1
	Cold fingers and toes	0	1

In the AK579 study, seven out of the eight patients who participated in the study experienced TEAEs. The most common TEAE was injection site reactions which accounted for the majority of the adverse events, which were all mild to moderate in intensity and declined towards the end of the 90-day trial. These reactions were to be expected with a s.c. formulation. It should be noted that the clinical trial is on-going and so the adverse events are not yet finalized and may change once the data is fully cleaned and verified.

Table 3 Summary of Treatment Related Adverse Events from AK579 (COBALT)

System Organ Class	No. of Patients	Related			Possibly Related			TOTAL
	N (%)	Grade 1	Grade 2	Total	Grade 1	Grade 2	Total	
Treatment Related Adverse events	6 (68.5)	42	1	43	72	8	80	123
General disorders and administration site conditions	**6 (68.5)**	**41**	**1**	**42**	**63**	**4**	**67**	**109**
Injection site erythema	5 (62.5)	29	0	29	11	1	12	41
Injection site pruritus	4 (50.0)	5	0	5	6	3	9	14
Injection site bruising	3 (37.5)	5	1	6	1	0	1	7
Injection site pain	3 (37.5)	0	0	0	24	0	24	24
Injection site swelling	2 (25.0)	1	0	1	11	0	11	12
Injection site discharge	1 (12.5)	0	0	0	8	0	8	8
Injection site hypersensitivity	1 (12.5)	0	0	0	1	0	1	1
Injection site induration	1 (12.5)	0	0	0	1	0	1	1
Injection site haematoma	1 (12.5)	1	0	1	0	0	0	1
Gastrointestinal Disorders	**2 (25.0)**	**1**	**0**	**1**	**2**	**0**	**2**	**3**
Abdominal discomfort	1 (12.5)	1	0	1	0	0	0	1
Diarrhoea	1 (12.5)	0	0	0	1	0	1	1
Paraesthesia oral	1 (12.5)	0	0	0	1	0	1	1
Investigations	**1 (12.5)**	**0**	**0**	**0**	**2**	**0**	**2**	**2**
Neutrophil count decreased	1 (12.5)	0	0	0	1	0	1	1
White blood cell count decreased	1 (12.5)	0	0	0	1*	0	1	1
Metabolism and nutrition disorders	**1 (12.5)**	**0**	**0**	**0**	**4**	**0**	**4**	**4**
Hypophosphataemia	1 (12.5)	0	0	0	2	0	2	2
Hypoproteinaemia	1 (12.5)	0	0	0	2	0	2	2
Musculoskeletal and connective tissue disorders	**1 (12.5)**	**0**	**0**	**0**	**0**	**1**	**1**	**1**
Osteoarthritis	1 (12.5)	0	0	0	0	1*	1	1
Nervous System disorders	**1 (12.5)**	**0**	**0**	**0**	**1**	**0**	**1**	**1**
Headache	1 (12.5)	0	0	0	1	0	1	1
Skin and s.c. tissue disorders	**1 (12.5)**	**0**	**0**	**0**	**0**	**3**	**3**	**3**
Pruritus	1 (12.5)	0	0	0	0	1	1	1
Rash	1 (12.5)	0	0	0	0	2	2	2

* AEs on-going, not resolved and not recovered

In AK579 there have been four SAEs to date, none of which were treatment related. These SAEs have occurred in two patients. In one patient (826-001-102), there was a staphylococci

infection which was considered grade 3 and was determined to be a staphylococcus epidermidis infection, which resolved with concomitant medication (conmeds). One patient (826-102-001) has experienced angina pectoris (grade 3), dyspnoea (grade 2) and lethargy (grade 2). The angina pectoris resolved, dyspnoea was resolving and lethargy was on-going at the time of this report. None of the patients needed to have their treatment disrupted or changed.

In the long-term safety study (AK581), only 2 patients have experienced treatment-related adverse events to date. As seen in AK579, these are mostly injection site reactions and they have all resolved.

Table 4 Treatment Related Adverse Events for AK581

System Organ Class	No. of Patients	Related			Possibly Related				TOTAL
	N (%)	Grade 1	Grade 2	Total	Grade 1	Grade 2	Grade 3	Total	
All Related TEAEs	**3/7**	**4**	**0**	**4**	**0**	**4**	**1**	**5**	**9**
General disorders and administration site conditions	**2**	**4**	**0**	**4**	**0**	**0**	**0**	**0**	**4**
Injection site pruritus	1	1	0	1	0	0	0	0	1
Injection site pain	1	2	0	2	0	0	0	0	2
Injection site swelling	1	1	0	1	0	0	0	0	1
Gastrointestinal Disorders	**1**	**0**	**2**	**2**	**0**	**0**	**0**	**0**	**2**
Nausea	1	0	1	1	0	0	0	0	1
Vomiting	1	0	1	1	0	0	0	0	1
Abdominal pain	1	0	0	0	0	1	0	1	1
Investigations	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**2**	**2**
Neutrophil count decreased	1	0	0	0	0	0	1	1	1
White blood cell count decreased	1	0	0	0	0	1	0	1	1

This data is preliminary and not source verified.

Overall, the adverse event profile shows few adverse events other than injection site reactions, which are to be expected with daily s.c. injections. There has been one SAE which was the worsening of paroxysmal nocturnal haemoglobinuria which was classed as Grade 3 and was not related to rVA576.

Going forward, Akari proposes not to report injection site reactions which are classified as Grade 1, but only injection site reactions which are grade 2 or above will be reported. All other adverse events, regardless of grade, will be reported.

rVA576 is a xenologous protein with the recombinant protein originally derived from a cDNA encoding a tick salivary protein. Like other biological drugs (including antibodies), there is a possibility that chronic use of rVA576 may be associated with the formation of ADAs which could neutralise the effect of the drug or cause untoward adverse reactions. Approximately 70% of both mice and NHPs receiving daily doses of rVA576 for 28 days develop detectable ADA. The antibodies were of low titre and did not neutralise the complement inhibitory activity of rVA576. In the AK577 healthy volunteer study, ADA were detected in two of four subjects

dosed with rVA576 for 21 days and in none of the subjects dosed with rV576 for 7 days. The antibodies were of low titre and did not neutralise the complement inhibitory activity of rVA576. All patients (n = 8), except one in AK579, have developed detectable ADA. Dependent on the subject, antibodies were first detectable between Day 14 to Day 90. Again, the antibodies were of low titre and do not neutralise the complement inhibitory activity of rVA576 (the first five of eight subjects in AK579 have been tested to date). The Dutch eculizumab resistant PNH patient who has been receiving rVA576 for more than 21 months first had detectable ADA at Day 16, which peaked at Day 60 and declined thereafter. The appearance of ADA does not appear to be associated with an increase in the rate or severity of injection site reactions. Our experience with rVA576 to date appears similar to patient experience with other parasite derived therapeutic molecules, such as the leech-derived anticoagulant lepirudin (Greinacher & Warkentin 2008), where the majority of patients develop detectable ADA which have no effect on the inhibitory function of the protein.

The potential of rVA576 to induce phototoxicity is at present unknown. For this reason, patients taking rVA576 should be advised to avoid excessive exposure to sunlight or UV light (e.g. sunbeds) for the duration of the study and up to 7 days after last dose.

3.4 Description of/and Justification for the Route of Administration, Dosage Regimen and Treatment Period(s)

The justification for using rVA576 in the treatment of AKC is that it is a disease of the eye surface in which the first line of current treatment is with topical agents. It is only after the failure of such agents that treatment moves on to systemic corticosteroids, antihistamines and immunosuppressants, all of which carry a greater risk of systemic side effects. Recombinant rVA576 has been demonstrated to be bioavailable by the topical ocular route in two preclinical models, Post Corneal Graft and Experimental Immune Conjunctivitis. It has been shown to be well tolerated and non-irritant in rabbit eyes over 56 days and, in view of the association between complement and LTB4 in eye surface inflammation other than AKC it was considered to be justified to trial it by this route in this condition.

The 0.25% (2.5 mg/mL) has been selected for this trial. In the 12-day preclinical experimental immune conjunctivitis (EIC) trial, this dose and 0.5% were equally effective and both were significantly superior to 0.125% and 0.0625%. The lowest of the two most effective doses was therefore selected.

AK701, whilst not a first in man study, is a first study by this route. Additionally, in this early development study, the patients (or their carers) will be using screw top vials and separate pipettes with rubber bulb dispensers with which patients may not be familiar with. For these reasons, the principal investigator (PI) wishes to treat the first three patients in an open-label, non-comparative manner, starting one week apart (Part 1) in order to gain reassurance that subsequent patients will be capable of dosing using these devices.

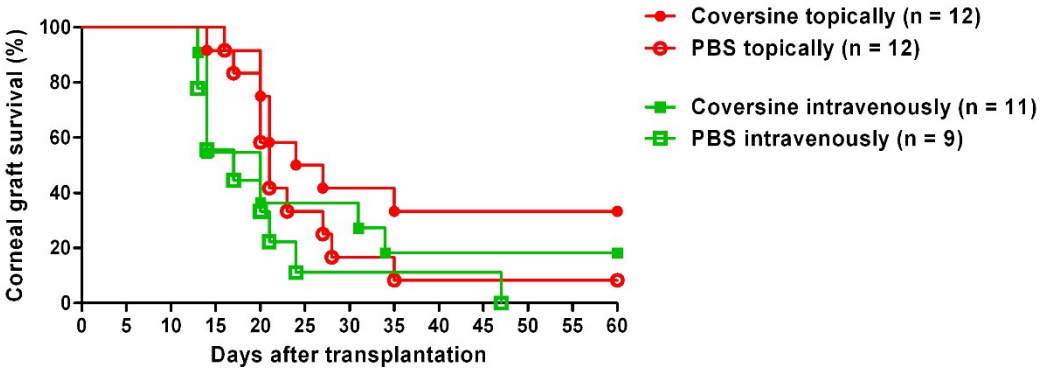
The first dose to these three patients will be given in the clinic observed by the PI. Given the current systemic clinical experience with rVA576 and the favourable ocular irritation and tolerance results, no particular safety issues are anticipated in this or other parts of the study.

Although information on patient device handling could also be obtained using placebo product, there would be no justification for keeping patients on placebo in open-label fashion for 8 weeks and therefore it is proposed that they will all receive active drug which will provide useful safety and tolerability data before proceeding to randomisation in Part 2.

3.4.1 Post corneal graft in mice (personal communication)

This study, conducted by Professor John Forrester in Aberdeen, was designed to examine the effect of rVA576 on mismatched corneal grafts in mice. Recombinant rVA576 was administered as topical ocular drops (0.2%) and systemically (0.6mg/kg) by intravenous injection to BALB/c mice who had received cross-strain mismatched corneal grafts for 14 days once daily after graft. Time to graft rejection was assessed using a Kaplan Meier survival design. The results, shown in Figure 3 below, indicated that rVA576 had a trend towards reducing the rate of graft rejection when used topically but this did not quite reach statistical significance. When used systemically it had no effect.

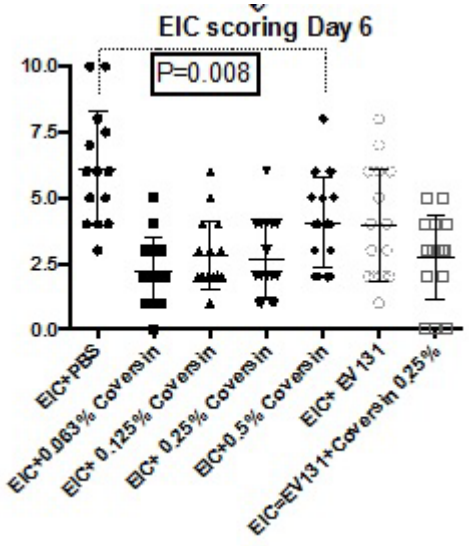
Figure 3 Corneal graft survival in mice



3.4.2 Effect of topical rVA576 on Experimental Immune Conjunctivitis (EIC)

An initial non-GLP study was conducted by Dr Virginia Calder at the Institute of Ophthalmology, London using the method of Adahome (Ahadome et al. 2016) C57 BL6 mice were sensitized to OVA for 14 days by systemic injection with adjuvant and then eyes were challenged daily with topical OVA. The resulting eye surface inflammation was treated from Day 3 onwards with rVA576 at one of four concentrations (0.0625%, 0.125%, 0.25% and 0.5%) or with EV131, a histamine binding protein, or a combination of rVA576 and EV131. No effect was seen from Day 3 to Day 5 but on Day 6 (the final day before the experiment was terminated) a significant fall in inflammation as assessed clinically by a masked observer was seen in mice treated with the three lowest concentrations of rVA576. This correlated with the subsequent eye histology (see Figure 4 below). Flow cytometry confirmed a significant inhibitory effect on the Th9 subset of lymphocytes.

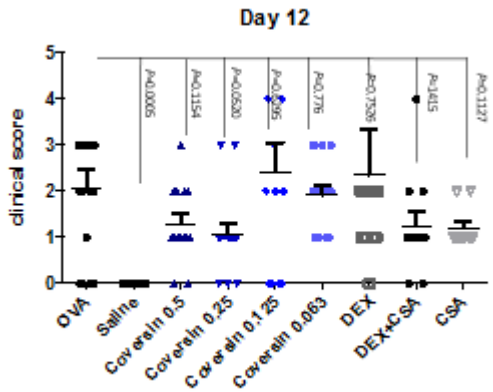
Figure 4 Effect of rVA576 on Experimental Immune Conjunctivitis



Following the study summarised above, a further non-GLP was undertaken by Dr Calder at the Institute of Opthalmology (Personal Communication) in order to confirm the previous results, to determine if the anti-inflammatory effect persisted for longer than 4 days, to further explore the optimum dose and to compare the anti-inflammatory effect to ciclosporin A, corticosteroid (dexamethasone) and the combination of both.

The second EIC study confirmed the earlier result, showed that the duration of effect lasted until at least Day 12 of treatment (the end of the study) and showed that 0.5% and 0.25% were equally effective and superior to the lower concentrations (Calder V. Personal Communication). For that reason 0.25% has been selected as the concentration for the clinical study. The study also showed that topical rVA576 at 0.25% and 0.5% was as effective as topical ciclosporin A alone or in combination with dexamethasone and at Day 12, but not at other time points, was superior to dexamethasone alone (Figure 5).

Figure 5 Effect of rVA576 on Experimental Immune Conjunctivitis at Day 12 (second experiment)



Taken overall, these results suggested that rVA576 has an anti-inflammatory effect on the eye either when injected or used topically.

Current rabbit eye toxicology supports a study of up to 56 days (see Section 3.2.1). The proposed study will last 56 days (8 weeks) per patient since it is considered that in moderate to severe, AKC a study of this length will have the best chance of demonstrating clinical effect.

4 TRIAL POPULATION

The study population will be up to 19 patients above the age of 18 with moderate to severe AKC, VKC or severe allergic conjunctivitis (SAC or PAC). Patients may be male or female.

4.1 Inclusion Criteria

1. Aged 18 and above
2. Diagnosis of moderate to severe AKC,VKC or severe allergic conjunctivitis (seasonal or perennial). Defined as:
    - AKC, VKC - a composite symptom/sign score from one eye of ≥ 18 out of 33 (see Clinical Scoring 17.1)
    - Severe allergic conjunctivitis - a composite symptom/sign score from one eye of ≥ 15 out of 27 (see Clinical Scoring Section 17.1)
3. Will have had received some topical therapy during the last 3 months without improvement but will not currently be receiving systemic immunotherapy. Topical therapy may be topical calcineurin inhibitors, antihistamines or corticosteroids alone or in combination. Lubricants or artificial tears will not a count as topical therapy for these purposes.
4. Will have had at least 7 days without topical ocular corticosteroids prior to entry
5. Willing to give informed consent
6. Willing to use highly effective contraceptive precautions for the duration of the study and for 90 days after the last dose of IMP.
7. Willing to avoid prohibited medications for duration of study (see list of prohibited medications)

4.2 Exclusion Criteria

1. Eye surface disease other than AKC, VKC or severe allergic conjunctivitis (SAC or PAC)
2. Contact lens use during the study
3. Complete or partial tarsorrhaphy. If such a procedure becomes necessary during the course of the trial patients may remain in the trial providing that at least 50% of the eye surface remains visible to slit lamp examination
4. Ankyloblepharon of any degree at entry to the trial
5. Known or suspected ocular malignancy
6. Active ocular infection at entry to the trial. Patients with eye surface bacterial, viral, fungal or protozoal infection may enter the trial after elimination of the infection as confirmed by eye swabs
7. Known or suspected uveitis
8. Participation in any other clinical trial within 1 month of enrolment
9. Use of any of the following prohibited medications:
    - Eculizumab
    - Any other investigational complement inhibitor whether systemic or topical (e.g. RA101495)
    - Montelukast
    - Zafirlukast
    - Pranlukast

- Zileuton
- Hypericum perforatum (St John's wort)

10. Corneal perforation
11. Uncontrolled glaucoma (increase in dose of glaucoma medication or surgical intervention for glaucoma within 3 months prior to entry)
12. Pregnancy (females)
13. Breast feeding (females)
14. Known allergy to ticks or severe reaction to arthropod venom (e.g. bee or wasp venom)
15. Use of topical optical steroids within 7 days of the Screening Visit
16. Failure to satisfy the PI of suitability to participate for any other reason

4.3 Concomitant Therapy

At screening, the PI will ask the patient about any current ongoing medications. During the course of the study, patients should be reminded to record any concomitant medications in their patient diaries and the PI should discuss medications at each visit. All concomitant medications, including herbal and vitamin supplements, must be recorded into the electronic case report form (eCRF).

All patients may use an eye lubricant *pro re nata* (p.r.n.). This should not be given within 15 minutes before or after rVA576. The exact choice of lubricant is left to the patient but the following are recommended:

Unpreserved carmellose 1% (e.g. Cellusan)
Unpreserved sodium hyaluronate ~0.1% (e.g. Hylo-Tear)
Unpreserved sodium hyaluronate ~0.2% (e.g. Hylo-Forte)

4.3.1 Prohibited Medications

Use of systemic immunosuppressives, antihistamines or corticosteroids during the trial is forbidden. Other drugs acting directly on the complement or eicosanoid systems either topically or systemically including;

- Eculizumab
- Any other investigational complement inhibitor whether systemic or topical (e.g. RA101495)
- Montelukast
- Zafirlukast
- Pranlukast
- Zileuton
- Hypericum perforatum (St John's wort)

4.3.2 Neisseria immunisation and antibiotic prophylaxis

Neisseria meningitidis immunisation and antibiotic prophylaxis are not considered necessary for patients participating in this trial because the maximum dose of rVA576 that patients would be exposed, to even if the total dose from both eyes was to be systemically absorbed, would be 0.1mg. The dose needed to completely ablate the terminal complement system in a 70kg adult is approximately 40mg and it is considered that 0.1mg would have no inhibitory effect on systemic innate immunity.

4.4 Contraception

There are no specific, identified risks to mother or foetus from rVA576 therapy. A segment 1 reproductive toxicology study has been undertaken in mice (YUU0001) to assess the effects of 0, 0.5, 5 and 10 mg/kg/day rVA576 on the fertility and early embryonic development of the mouse when administered for at least 14 days before and during pairing, and then to Day 6 of gestation in females and until the day before necropsy for males. The study reported no deaths or clinical signs considered to be associated with the doses of rVA576 test; the causes of death for 1 male and 1 female found dead during the study were considered to be unrelated to test item administration. There was no effect of rVA576 on body weight, food intake, mating activity, fertility and mating, pregnancy or uterine implantation. There were no findings at necropsy considered to be related to rVA576 and group mean ovary and testes weights for animals given the test item were similar to Controls. Segment 2 and 3 reproductive toxicology studies will be undertaken prior to seeking market approval. Until the reproductive toxicology studies are completed, patients being treated with rVA576 should be advised to use the following precautions against sexual exposure and pregnancy.

All trial participants (male and female) of childbearing potential must use, with their partner, a combination of an approved method of highly effective contraception with at least one barrier method of contraception from the time of signing the Informed Consent Form (ICF) until 90 days after the last dose of rVA576. Women of child bearing potential are considered those women who have menarche and until becoming post-menopausal unless permanently sterilised. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative cause.

The following methods of highly effective contraception are acceptable and must be combined with at least one of the barrier method of contraception:

- Surgical sterilisation (i.e. bilateral tubal removal, bilateral ovary removal, hysterectomy for female partners; vasectomy for males)
- Placement of an intrauterine device or intrauterine system
- Hormonal contraception associated with the inhibition of ovulation (implantable, patch, oral)

- Barrier methods:
    - For male patients, this must be a condom; for female patients, either their partner's use of a condom or the patient's use of an occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository
    - Barrier methods must be used in conjunction with a highly effective method of contraception listed above

Alternatively, true abstinence is acceptable when consistent with the patient's preferred and usual lifestyle. Any female patient who becomes pregnant during the course of the trial will be withdrawn from the trial.

Male patients who have been sterilised are required to use one barrier method of contraception (condom).

4.4.1 Exposure of Partners During the Study

There is a risk of drug exposure through ejaculate (which also applies to vasectomised males) which might be harmful to the sexual partners, including pregnant partners of male patients. A

combination of an approved method of highly effective contraception with at least one barrier method of contraception should be used throughout the study and for 90 days after the last day of IMP administration.

4.4.2 Sperm Donation

Male patients should not donate sperm for the duration of the study and for at least 90 days after the last day of IMP administration.

4.4.3 Egg Donation

Female patients should not donate eggs for the duration of the study and for at least 90 days after the last dose of IMP administration.

4.4.4 Breast Feeding

Female patients should not breast feed infants for the duration of the study and for at least 90 days after the last day of IMP administration.

5 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Trial objectives

Part 1: An additional objective for the first 3 patients is to allow the P.I. to assess the patients' ability to use the eye dropper and vials correctly

Part 1 and Part 2: The primary trial objective is to demonstrate the safety and tolerability of rVA576 when given by topical ocular administration to patients with AKC, VKC, and severe allergic conjunctivitis (SAC or PAC).

The secondary objective is to demonstrate efficacy in this patient population in Part 2 of the study.

To assess whether rVA576 0.25% eye drops, solution is effective in mitigating the signs and symptoms of AKC, VKC, and severe allergic conjunctivitis (SAC or PAC) and whether they have any effect on surrogate markers of inflammation.

Efficacy will be defined as a difference in the mean composite clinical score between active and placebo treated patients in part 2 of the study. Clinical assessments and safety assessments in the randomised part of the study will be performed by a masked reviewer

5.2 Endpoints

5.2.1 Primary endpoint

- Incidence of ocular treatment emergent adverse events during the treatment period (adverse events which have occurred during the 56 days following randomisation (Part 2 of the study only) will be considered in the analysis of the primary safety outcome).

5.2.2 Secondary endpoint

- Post-instillation comfort, as graded on patient diary cards at the following intervals Days 1-14, Day 15-28, Day 29-42 and Day 43-56
- Visual acuity by Early Treatment Diabetic Retinopathy Study (ETDRS) charts comparison from Day 1 to Day 56
- Change from Day 1 in composite clinical scores at Day 14, 28, 42 and 56
- Number and percentage of patients with MMP-9 positive levels at Days 1, 28, and 56
- Change from Day 1 in Tear film break up time (TBUT) at Day 14, 28, 42 and 56

5.2.3 Exploratory endpoints

- Systemic absorption by blood sampling
- If enough tear fluid can be collected analysis of complement C3, C5 and LTB4 will be performed
- A comparison of the number of patients requiring rescue therapy at any stage of the trial and the number on such therapy at the end of the trial
- Comparison of the Conjunctival impression cytology results in each treatment group from Day 1 to Day 56 using flow cytometry analysis [NB Because these may not be reported for some time after completion of the trial and database lock, they will not form part of the statistical analysis and will be used for research information only]

6 TRIAL DESIGN AND PROCEDURES

6.1 Trial Design

The trial will comprise 2 parts:

Part 1: The first 3 patients selected for the study will be treated with active drug in open-label manner. They will have weekly clinic visits for up the first 2 weeks and thereafter biweekly visits. When the third of the first 3 patients has completed their first 2 weeks treatment, the PI will review the safety, tolerability and ease of application for each patient before deciding to proceed to the randomised, double masked comparative phase of the study (Part 2). The 3 patients will continue on the study and complete the 8 weeks trial as open label patients.

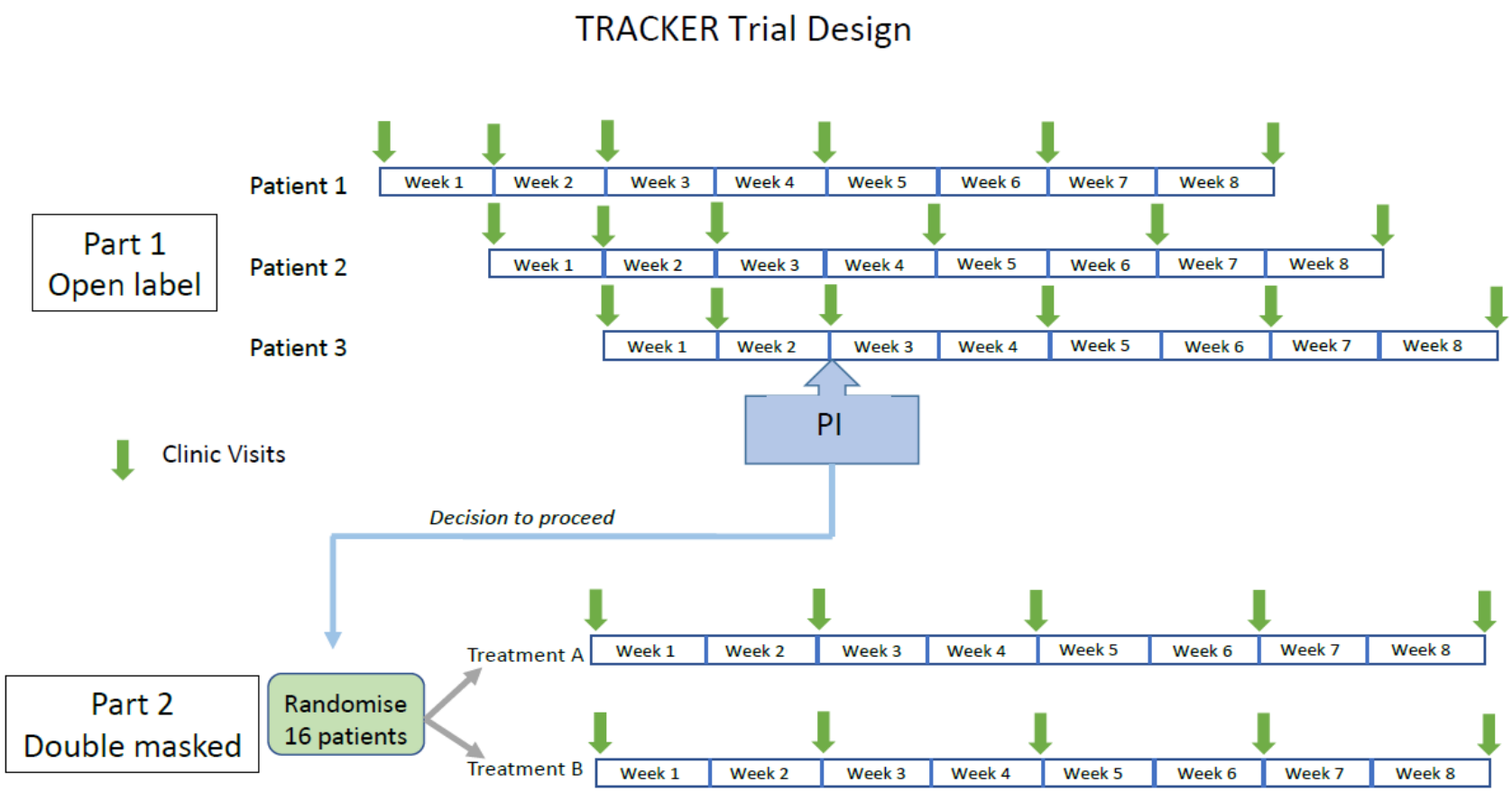
Part 2: A randomised, double-masked, placebo controlled trial of topical rVA576 or placebo eye drops in moderate to severe AKC, VKC and severe allergic conjunctivitis (SAC or PAC). The part 2 trial population will comprise 16 patients who meet all the inclusion and none of the exclusion criteria (Section 4.1 and Section 4.2).

6.2 Duration of trial

The estimated duration of the study for an individual patient is approximately 13 weeks. The duration from the First Patient Screened to Last Patient Last Visit (LPLV) will be approximately 7-8 months.

At the end of the 56 Days the subjects will return to their usual standard of care therapy, as this is the first clinical trial of rVA576 in patients with AKC, VKC and severe allergic conjunctivitis (SAC or PAC) and the long-term efficacy and safety is not yet established.

Figure 6 Trial Design



6.3 Dosing Scheme

Part 1: The product will be supplied as a sterile 0.25% solution in 6 mL glass vials containing 1 mL of rVA576 solution. Single use eye dropper pipettes will also be supplied. The vials are for single use (one drop to each eye) and must be retained and returned to the site at each clinic visit.

Part 2: The product will be supplied as a sterile 0.25% solution in 6 mL glass vials containing 1 mL of solution of either rVA576 or placebo. Eye dropper pipettes will also be supplied. The vials are for single use (one drop to each eye) and must be retained and returned to the site at each clinical visit.

The patients will be randomised to receive either rVA576 active or placebo in double masked fashion. The product should be administered as one drop to each eye every 12 hours (i.e. twice daily) for a total of 56 days.

The product should be stored frozen in the site Pharmacy until the first 7 days' supply is to be given to the patient and then every 7 days thereafter. The product once unfrozen should be kept at 2 -8 °C for a maximum of 7 days.

All patients entering the trial will have been on maximal topical therapy (meaning the maximal labelled dose or frequency of dosing) for at least three months before entry on the study and will continue on this therapy (background therapy) for the duration of the study.

Background therapy:

Patients should continue on whatever topical therapy they are on at the time of screening but this should remain stable during the trial. Lubricants and artificial tears may be used *ad libitum* but should not be administered for 15 minutes before or after the trial medication. In the event of worsening of signs or symptoms that, in the clinician's opinion is so severe as to necessitate a change of medication, ciclosporin and/or antihistamines may be introduced or increased in dose/frequency and this will be considered as a treatment failure for purposes of efficacy analysis. Topical corticosteroids may be added following introduction or increase in ciclosporin/antihistamine therapy if considered necessary.

See Concomitant Medications for further details of choice of eye lubricants.

Patients should not have used topical ocular steroids for 7 days prior to entry to the trial but, at the discretion of the investigator, may receive them as rescue medication during the trial. A comparison of the number of patients requiring rescue therapy at any stage of the trial and the number on such therapy at the end of the trial will be an additional exploratory endpoint.

Use of systemic immunosuppressives, antihistamines or corticosteroids during the trial is forbidden. Patients who, in the opinion of the investigator, require such treatment will be withdrawn from the trial. If the reason for giving such treatment is related to their primary pathology (AKC, VKC, or severe allergic conjunctivitis (SAC or PAC)) they will be regarded as treatment failures.

6.4 Method of Assigning Subjects to Treatments and Blinding (Part 2)

After the initial 3 open label patients (Part 1), subsequent patients entering this clinical trial will be randomised in a 1:1 fashion.

The randomisation will be generated using the 'Prisym Medica Clintrial' software package. The required number of records, along with treatment allocation codes, treatment descriptions and required randomisation block size will be entered into the system according to the study requirements. One master set of codes will be generated within the Prisym system to facilitate printing of labels.

Upon confirmation of a subject's eligibility at the Screening visit, the investigator, or other site personnel under the direction of the investigator, should access the eCRF to register the subject and obtain the Subject Identification number. In addition, the investigator, or designee, will contact the CRO, Tailored Clinical Research Solution (TCRS), to register the subject as randomised. TCRS will forward the Randomisation ID to sites for recording in the patient notes and transcribed eCRF.

6.4.1 Emergency Unmasking for Safety Reasons

In the unlikely event of an emergency where, in the opinion of the investigator, discontinuation of study treatment for an individual patient is not sufficient and the study treatment must be unmasked in order to evaluate further course of action, the investigator will have direct access to the randomisation codes for unmasking.

The investigator will consult his own copy of the randomisation codes supplied in a sealed envelopes individually numbered for each patient and decide what, if any, further action to take.

Once the study treatment has been unmasked, the subject will complete the Early Termination visit and then discontinue study treatment. The subject will also be seen for post-treatment follow-up.

6.5 Compliance

As a measure of compliance, all empty rVA576 vials will be returned by the patient to the site and Patient Dosing Diaries will be reviewed by research staff at each study visit.

6.6 Missed Doses

If a patient misses a dose, it may be taken later unless it is within 3 hours of the next scheduled dose, in which case it should not be taken and the patient should resume normal dosing at the time of the scheduled dose. Precautions about not using other eye drops within 15 minutes before or after the rVA576 dose should continue to be observed.

6.7 Trial Procedures

The total number of clinic visits including screening and follow-up will be a minimum of 7 with additional visits at the discretion of the PI.

The following investigations and diagnostic procedures will be carried out at clinic visits in accordance with the Schedule of Events (i.e. not all evaluations will be carried out at every visit).

<u>By the Investigator</u>

- Medical History, general and indication specific
- Adverse Events
- Post instillation comfort as graded on patient diary cards (five-point grading from 0 (perfectly comfortable) to 4 (Severe, intolerable itching or burning). For full description see Section 6.9.1.

- Clinical examination, gross and slit lamp with clinical scoring. For full description see Section 17.1 (AKC and VKC) and 17.2 (severe allergic conjunctivitis - SAC or PAC).MMP-9 estimation using the *Inflammadry*® device
- Conjunctival impression cytology (CIP) (Optional)
- Tear film break up time (TBUT)

By the nurse or other qualified person (these may be done on any order and either before or after the Investigator's examination)

- rVA576 blood levels
- Visual acuity by ETDRS
- Systemic complement activity by serum CH50 ELISA activity.
- Anti-drug antibodies (ADA)
- Pregnancy Test (Urine)

Screening Period:

Potential trial patients will visit the clinic for an initial visit at which time their suitability for the trial will be assessed by the Principal Investigator (PI) and the purpose, nature and possible benefits and risks will be explained. Patients will be given a detailed patient information leaflet and will be given sufficient time to consider their participation before entering the trial.

Patients may enter the trial within 7 days (±2 days) of screening providing that there has been no change in the inclusion/exclusion criteria. It must be noted when organizing the first dosing visit that the IMP will take 4 days from the Randomisation to be sent to site and to be ready for dispensing.

Part 1- open label: The first 3 patients selected for the study will be treated with active drug in open-label manner at weekly intervals. The first dose to these three patients will be given in the clinic observed by the PI.

Part 2- Randomisation: Upon confirmation of a subject's eligibility at the Randomisation visit, the investigator, or designee, will contact the CRO, TCRS, to register the subject as randomised and obtain the assigned medication number. This information will be recorded in the patient notes and transcribed eCRF.

Dosing Period:

Patients or their carers will collect clinical trial supplies from the clinical trial site at each clinic visit. Between visits new supplies will be delivered from the Pharmacy to the patient's home by a courier service arranged by the Sponsor at a pre-arranged time and date.

Part 1: Patients will be seen by the PI on Day 7 and thereafter every 14 days (±2 days) during the trial or more frequently if necessary. The trial dosing period will terminate after 56 days' treatment at which time patients will return to the clinic for a final assessment.

Part 2: The remaining 16 patients will be randomised 1:1 to active or placebo and will receive the appropriate medication throughout the trial identified by their Randomisation number.

All randomised patients will be seen and assessed at Day 14 and thereafter at 2 weekly intervals by a masked observer.

Part 1 and Part 2:

Patients or their carers will be taught how to administer the eye drops. They will also be taught how to store the drug during the trial.

Patients (or their carers) will remove one vial from the refrigerator 10 minutes before administration to allow the vial to warm to room temperature. One drop will be administered topically to each eye using the same vial and same pipette for both eyes.

The drops will be administered twice a day, as near to 12 hours apart as possible (e.g. 8am and 8pm). Vials will be used only once for administration to both eyes. Used vials will be returned to the trial pharmacy at each clinic visit for compliance checking. A daily diary card will be kept in which administration will be recorded together with a record of comfort and any adverse events.

Patients and their carers will be provided with clear written and illustrated instructions detailing the correct procedure for transporting, storing and administering the IMP.

An attempt will be made to collect tear fluid from patients in the trial using either glass capillary tubes or micropipettes according to the method of Sack et al (Sack et al. 1992). However, this may be difficult or impossible in the clinical trial setting as the induction of reflex tearing would obviate the results of the investigation by dilution of the mediators. If sufficient fluid is collected from individual patients (> 10µL) it will be analysed for complement products and/or LTB4. If insufficient is collected from individual patients any fluid collected may be pooled and analyses done on the total aliquot.

Follow up:

Patient will return again 28 days ±7 days for a follow-up visit.

6.8 Rescue Therapy

Topical ocular steroids will be considered Rescue Therapy.

In the event of worsening of signs or symptoms that, in the clinician's opinion is so severe as to necessitate a change of medication, ciclosporin and/or antihistamines may be introduced or increased in dose/frequency and this will be considered as a treatment failure for purposes of efficacy analysis.

The introduction or increase in dose/frequency of ciclosporin or antihistamines will be considered as Rescue Therapy.

After entry into the trial, subjects will be recommended to not receive Rescue Therapy from the first dose of rVA576 as far as possible unless assessed by PI as needed.

6.9 Safety and Efficacy Assessments

Safety will be assessed by the Investigator from history and clinical examination. Adverse events (AE) will be recorded in the CRFs and in part 2 of the study, a comparison will be made between the number, type and severity of AEs between the treatment groups.

Comfort will be assessed on the basis of the patient diary cards. A comparison of the total comfort scores between the randomised treatment groups in part 2 of the study, will be made at the conclusion of the trial. For each treatment group a total comfort score of < 10 will be deemed to be comfortable/acceptable, 10 - 19 will be moderately uncomfortable, 20 - 29 will be very uncomfortable and > 30 will be severely/unacceptably uncomfortable.

Composite eye sign and symptom scoring will be carried out by the investigator/blind assessor (depending on the part of the study) at each scheduled clinic visit. Symptoms will be scored by the patient in response to specific questioning by the investigator/blind assessor. Signs will be scored by the investigator/blind assessor as a result of the clinical examination. At each visit the patient will be asked which eye feels to be the worst affected at the time of the visit and that eye will be used for the examination. If both eyes seem to the patient to be equally affected the right eye will always be used. The worst affected eye may change from visit to visit.

For each sign/symptom a numerical score 0 – 3 will be awarded (see table in Section 17.1 (AKC and VKC) and 17.2 (severe allergic conjunctivitis - SAC or PAC). These scores will be summed at the conclusion of the examination and this will be known as the composite score. The minimum possible composite score is 0, the maximum 33 (AKC and VKC) or 27 (severe allergic conjunctivitis (SAC or PAC)). All statistical comparisons, in part 2 of the study, will be done on the basis of the composite score for each patient/visit.

MMP-9 detection using the *Inflammadry*® device. This device will give a binary (positive/negative) result which will be recorded in the CRFs at each time point and a comparison of the numbers of positives in each randomised treatment group will be made.

Tear film break up time (TBUT). Tear breakup time (TBUT) is a clinical test used to assess for evaporative dry eye disease. To measure TBUT, fluorescein is instilled into the patient's tear film and the patient is asked not to blink while the tear film is observed under a broad beam of cobalt blue illumination. The TBUT is recorded as the number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film. A TBUT under 10 seconds is considered abnormal.

This test will be performed in one eye only at the time points specified in the Schedule of Events.

6.9.1 Clinical scoring

Clinical scoring will be according to the method described by Akpek (Akpek et al. 2004). This will be carried out at each clinic visit by the PI or his designated sub-investigator(s). A composite score of 5 symptoms and 6 signs will be used for AKC and VKC patients, and a composite score of 4 symptoms and 5 signs will be used for patients with severe allergic conjunctivitis - SAC or PAC. One eye only should be scored which will be the eye judged as worst affected at each visit by the patient. In the event that the patient judges both eyes to be equally affected the right eye will be assessed. Scoring will be on a scale of 0 to 3 where 0 is unaffected, 1 is mildly affected, 2 is moderately affected and 3 is severely affected (see Section 17.1 and 17.2 for full details). The maximum possible score for symptoms and signs combined is 33 (AKC/VKC) or 27 (severe allergic conjunctivitis) . To qualify for entry to the trial patients must score:

AKC or VKC - a minimum of 18 at the Screening visit.

The following symptoms will be scored:

1. Itching
2. Tearing
3. Discomfort (burning, stinging or foreign body sensation)
4. Discharge
5. Photophobia

The following signs will be scored:

1. Bulbar conjunctival hyperaemia
2. Tarsal conjunctival papillary hypertrophy
3. Punctate keratitis
4. Neovascularisation of cornea
5. Cicatrising conjunctivitis
6. Blepharitis

Severe allergic conjunctivitis - SAC or PAC - a minimum of 15 at the Screening visit.

The following symptoms will be scored:

1. Itching
2. Tearing
3. Discomfort (burning, stinging or foreign body sensation)
4. Photophobia

The following signs will be scored:

1. Upper tarsal conjunctival hyperaemia
2. Upper bulbar conjunctival hyperaemia
3. Chemosis
4. Upper tarsal conjunctival papillae
5. Blepharitis

6.9.2 Patient diary card

All patients will be issued with a diary card and will be asked to score comfort on a scale of 0 to 4 as shown in Table 5 below. **The patient may make further comments (e.g. a difference in comfort between the two eyes) in the diary card.**

Table 5 Eye comfort scoring

Score	Description
0	Perfectly comfortable
1	Slight discomfort. Aware of some burning, itching or stinging for up to half a minute after using the eye drop, solution but the discomfort improves without treatment.
2	Moderate discomfort. Burning, itching or stinging lasts for half a minute or longer but improves without treatment.
3	Severe discomfort. Burning, itching or stinging last for at least half a minute and requires washing the eyes to relieve it.
4	Unbearable burning itching or stinging. So severe that you cannot continue treatment.

Scoring will be carried out at 0.5, 1, 2, 3 and 5 minutes after instillation of the drops and, in addition, patients will be asked to insert a brief description (up to 5 words) of how the eyes feel at the 3-minute time point. A list of suggested descriptor words will be provided but patients will be free to use any terminology they wish. Suggested descriptors are:

- Normal, cool, comfortable, smooth, fresh
- Uncomfortable, gritty, dry, sticky
- Burning, itchy, stinging, painful

In addition, there will be space for any other comments the patient may have.

Diary cards will be checked by the trial nurse or the PI/blind assessor at each visit to ensure that they are being filled in correctly and regularly.

6.10 Laboratory Tests

The following laboratory tests will need to be conducted at the applicable visits, per Schedule of Events. The assessments will be conducted at the central laboratory, as indicated in the following table:

Table 6 Laboratory Tests

Central Lab
PK (Unbound rVA576)
Anti-Drug Antibody (ADA)
PD (CH50)

The analyses will be performed in masked fashion as far as the Central; Lab is concerned and unmasking will not be performed until the conclusion of the trial.

6.11 Medical Photography

For better assessment of the eye, medical photography may be performed at investigator's judgement and photographs of both eyes may be obtained during the evaluation of the composite score and related ocular adverse events. During the consent obtained at screening the patients will be allowed to opt out of the medical photography. Declining consent for medical photography will not impact patient's participation in the study. Patient's confidentiality will be protected during medical photography of the eye.

7 REASON FOR WITHDRAWAL / EARLY DISCONTINUATION

7.1 Termination or Suspension of the Study

The Sponsor may prematurely terminate or suspend the study at any time for the following reasons:

- Safety concerns e.g. due to occurrence of many serious ADRs
- Achieving the purpose of the study is considered impossible e.g. due to inadequate recruitment of patients

The Sponsor may prematurely terminate or suspend the study as well at a particular medical institution at any time during the course of the study, if major violations/deviations of the protocol or other procedures have not been improved or International Committee on Harmonisation (ICH) GCP has not been followed.

If the study is prematurely terminated or suspended, the Sponsor should promptly inform the Investigators. The Investigator or designee should promptly inform the participating patients and change the study medication to other appropriate therapy(ies). All supplies must be returned.

The Investigator may prematurely terminate or suspend the study at their medical institution with the agreement of the Sponsor. This may be done at any time during the study if they consider that ensuring patient safety during the study is difficult due to safety concerns (e.g., occurrence of many SAEs).

The party which terminates the study will provide a written statement as to the reason for the termination.

The Sponsor (or CRO) will notify Regulatory Authorities, as appropriate of premature terminations or other suspensions. The Investigator or their designee should promptly inform the corresponding Ethics Committee (EC).

7.2 Withdrawal Criteria

In accordance with applicable regulations, a patient has the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the Institution. Should a patient withdraw from the study, the patient will not undergo any further study-specific procedures or receive any treatment mandated by the protocol.

If a patient fails to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

In the event of the premature withdrawal of a patient from the trial, the end of trial visit should be carried out as completely as possible. Minimally, a safety assessment should be performed.

In the case of withdrawal due to the occurrence of unacceptable toxicity, the patient will be requested to remain under the supervision of the Investigator until the toxicity has resolved or is no longer considered to be clinically significant by the Investigator.

If an AE classified as severe results in patient withdrawal from the study, the patient will be followed until the AE (or SAE) resolves or stabilises, and any interventions required to resolve or stabilise the event will be recorded in the eCRF.

All withdrawals must be documented in the eCRF. A patient may be withdrawn in any of the following circumstances:

- Withdrawal of consent (mandatory withdrawal)
- Intake of non-permitted concomitant medications (may be discussed with the Sponsor and dependent on the nature of the medication)
- Patient is non-compliant with more than three consecutive missed doses and two missed clinic visits, in the opinion of the Investigator (discretionary withdrawal)
- If discontinuation is considered necessary by the Investigator and/or Sponsor (mandatory withdrawal)
- Request of Regulatory Agency (mandatory withdrawal)
- Patient develops an illness that would compromise his participation in the study (may be discussed with sponsor)
- Pregnancy

8 SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication.

8.1.2 Adverse Drug Reaction (ADR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study medication qualify as ADRs.

8.1.3 Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. IB for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

8.1.4 Serious Adverse Event or Serious Adverse Reaction

Any untoward medical occurrence or effect at any dose that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital abnormality / birth defect.

NOTE: *Other events that may not result in death, are not life threatening, or do not require hospitalization, may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include, but are not limited to, severe early onset reaction such as anaphylaxis, vasovagal episodes, episodes of hypotonia, hyporeactivity or hyperventilation, or convulsions.*

All SAEs will be reported to the Sponsor (or designee) within 24 hours of notice of occurrence. The Sponsor (or their designee) will be responsible for reporting the AE to the appropriate regulatory authorities and the ECs within the legally specified period. It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. An AE of severe intensity need not necessarily be considered serious. For example, a migraine headache that incapacitates a patient for many hours may be considered a severe AE, whereas a stroke that results in a limited degree of disability may be considered mild, but should be reported as an SAE.

8.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. IB for an unapproved investigational product or Summary of Product Characteristics for an approved product).

Treatment Emergent Adverse Events (TEAEs)

Treatment emergent adverse events (TEAEs) are undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment.

8.2 Procedures for Recording of Safety Events

8.2.1 General

All adverse events occurring during the Study (from the time point of signing of the ICF until completion of patient`s study participation or premature withdrawal) observed by the

investigator or reported by the patient, whether or not attributed to the IMP, shall be recorded in patient`s medical records and on the eCRF.

The following information shall be recorded:

- Description
- Date of onset and end date
- Severity
- Assessment of relatedness to the IMP
- Seriousness
- Measures taken for management of the AE
- Outcome of the event

Follow-up information should be provided as necessary.

AEs considered as being related to the IMP as judged by a medically qualified Investigator, or the Sponsor, must be followed until their resolution or when patient`s status is considered as stable. All related AEs that result in a patient's withdrawal from the Study or are present at the end of the Study, should be re-evaluated and if needed followed until a satisfactory resolution occurs.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require termination of IMP administration. A patient may also voluntarily withdraw from IMP administration due to AEs perceived as intolerable. If either of these occurs, the patient will be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

The severity of reported events shall be assessed on the following scale:

- 1 = mild
- 2 = moderate
- 3 = severe

The causal relationship of AEs to the IMP must be assessed by the investigator, or by a medically qualified designee, in accordance with the following criteria:

TERM	DEFINITION
Unrelated	Clinical event with an incompatible time relationship to administration of the investigational medical product (IMP), and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the IMP
Possibly related	Clinical event with a reasonable time relationship to IMP administration, and that is unlikely to be attributed to concurrent disease or other drugs or chemicals
Related	Clinical event with plausible time relationship to IMP administration and that cannot be explained by concurrent disease or other drugs or chemicals

The degree of certainty with which an AE is attributed to IMP administration (or alternative causes, e.g. natural history of the underlying disease, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of the IMP
- Reactions of a similar nature have been previously observed with the IMP or this class of drug
- A temporal relationship to IMP administration, terminating with IMP withdrawal or recurring on re challenge
- Alternative cause

At the last scheduled visit, the investigator shall instruct each patient to report any subsequent event(s) that the patient, or her personal physician, believes might reasonably be related to participation in this Study. The investigator should notify the Sponsor (or designee) of any death or SAE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this Study.

8.2.2 Pre-existing Conditions

For purposes of this Study a pre-existing condition means a diagnosed, clinically significant finding, symptom or laboratory abnormality present at screening. Subsequently, during the course of the Study it shall be recorded as an AE/SAE if the frequency, intensity, or the character of the condition worsens during the study period.

8.2.3 Overdose

The total amount of rVA576 in single drops is so small that overdosage by this route is considered to be impossible (1 drop of rVA576 0.25% solution contains 0.15 mg, one three hundredth of the standard systemic therapeutic dose) even if totally systemically absorbed. Since there are no known adverse events associated with systemic overdosage the risk of ocular overdosage, whether accidental or intentional, is therefore considered to be negligible).

8.2.4 Pregnancy

Recombinant rVA576 is contraindicated during pregnancy. If pregnancy is suspected, a blood sample for serum HCG examination must be sent to the sub-contracted laboratory within 48 hours. As during the first pregnancy weeks the test may be negative it may be confirmed by an ultrasound examination. If at least one of the above-mentioned examinations is positive, administration of the IMP must be stopped and the patient must be immediately withdrawn from the study. All pregnancies (even if suspected) must be reported on the appropriate eCRF page (Pregnancy form) within 24 hours from the moment when the investigator became aware of the pregnancy (or suspected pregnancy). In any case each pregnancy must be followed till its termination (either by birth of a child or abortion) and the eCRF Pregnancy form has to be updated.

8.2.5 Reporting of Adverse Events

All adverse events, whether in the opinion of the investigator, drug-related or not will be reported in the CRF.

8.3 Reporting Procedures for Serious Adverse Events

Any SAE occurring during the Study has to be managed by established SoC to protect life and health of participating patients. If such treatment represents a significant deviation from the protocol, the investigator shall immediately notify the study monitor and/or the Sponsor to determine whether the patient should be dropped from the Study, or not.

All SAEs, irrespective of their causality, must be notified to the Pharmacovigilance provider (PVP) of the Sponsor, **within 24 hours** of investigator's knowledge of the event. Reporting shall be done on the corresponding SAE form, provided to each centre during the initiation visit, and sent by fax or e-mail to:

Fax: +420 227 204 958
E-mail: safety@akaritx.com

The provided information shall contain as much detail regarding the event as available. Investigators shall not wait to receive additional information to fully document the event, before notifying the SAE to Akari Therapeutics Plc. The SAE reporting form should detail all relevant aspects of the AEs listed in Section 8.2. Where applicable, information from relevant hospital records or autopsy reports should be obtained and provided to Akari Therapeutics Plc.

8.4 Expedited Safety Reporting

Any SAE, which is unexpected and at least possibly related to the IMP, requiring expedited reporting to the respective regulatory authority, EudraVigilance and ECs / Institutional Review Boards (IRBs) of the sites participating in this Study is patient to following timelines:

- 7 calendar days for SUSARs involving death and life-threatening events,
- 15 calendar days for SUSARs involving hospitalization or prolongation of hospitalization or persistent or significant disability/incapacity or congenital anomaly/birth defect or any other significant clinical/laboratory event of major concern in the opinion of the Investigator.

Day zero (clock start) for expedited reporting purposes is the date of initial information or of the relevant follow-up information received in any form (in writing or verbal) by any personnel of Sponsor or contracted parties including the CRO and the Pharmacovigilance Provider (PVP).

All SUSARs will be reported to the respective competent authorities, ECs (IRBs) and Investigators within specified timelines in accordance with corresponding national legislation.

8.5 Development Safety Update Reports

Development Safety Update Reports will be prepared by Akari Therapeutics Plc on an annual basis and distributed to all competent authorities and to relevant ECs in accordance with the corresponding national regulations.

9 ACCOUNTABILITY PROCEDURES

The PI and the hospital pharmacist are responsible for study medication accountability, reconciliation, and record maintenance. Drug accountability records will be maintained during the study, including the amount of study medication received from the Sponsor, the amount distributed to each patient, and the amount of unused drug returned to the Sponsor or destroyed at Sponsor's request. In addition, in the event of necessary disposal of opened but wasted medication, the disposal should be documented appropriately (i.e. witnessed) in accordance with applicable local regulations, and "Good Clinical Practice" (GCP) procedures.

10 COMPLIANCE

Patients will fill in diary cards recording each dose and the time and date that it was administered. In addition, all used vials should be retained in the container provided and returned to the trial pharmacy at each clinic visit. The trial pharmacist will keep records of the number of vials returned for each patient and a full reconciliation will be carried out at the conclusion of the trial.

11 STATISTICS

11.1 Statistical Methods

A Statistical Analysis Plan (SAP) will be prepared and finalised prior to unmasking of the study for the analysis. The SAP will provide full details of the analyses, data displays, algorithms to be used for data derivations and handling of missing data. SAS® statistical software version 9.3 or above will be used for analysing the data (SAS Institute, Inc., Cary, North Carolina).

Continuous variables will be summarized using the number of patients, number of missing values, mean, median, standard deviation, standard error, minimum, and maximum. Categorical variables will be summarized using number of patients, number of missing values, frequency counts, and percentages. Unless otherwise specified, missing data will not be included in the denominator for percentage calculation. Change from baseline may be substituted with percentage change from baseline or ratio to baseline if the distribution of an individual parameter suggests this.

The baseline value will be defined as the pre-dose value on Day 1, if that is missing, it will be defined from the most recent value available.
The two parts of the study will be reported separately. Data from patients included in Part 1 will only be listed, while the following sections apply for data from patients included in Part 2.

11.2 Primary Analysis

Ocular adverse events which have occurred during the 56 days of treatment following randomisation will be considered in the analysis of the primary safety outcome. The difference between the two treatments in the proportion of patients experiencing any ocular treatment emergent AEs as coded under MedDRA System Organ class: Eye disorders will be reported with its associated 95% Confidence interval.

A treatment-emergent adverse event (TEAE) will defined as an adverse event that started, or increased in severity, after the first dose of study medication was taken. The incidence of TEAEs will be summarized by System Organ Class, Higher Level Term and Preferred Term. Additional summaries will be produced, such as summary of serious TEAEs, summary of TEAEs by intensity/severity, or by relationship to study drug.

11.3 Secondary Analyses

- Post-instillation comfort, as graded on patient diary cards, will be summarised by treatment group at Days 14, 28, 42 and 56. The weekly comfort scores will be compared between treatment groups.
- The observed values and change from Baseline in composite clinical scores, in individual symptom and in sign scores, at Days 14, 28, 42 and 56 will be summarised and plotted by treatment group. The change from Baseline in composite clinical scores will be analysed with a Mixed-effects Model for Repeated Measures. The model will include baseline composite clinical score as a covariate, treatment group, visit and patient group (AKC/VKC or SAC/PAC) as fixed factors and the treatment arm by visit interaction. The Least Square means over time with associated 95% confidence intervals will be plotted, as well as adjusted LS mean difference to placebo and 95% confidence interval.
- The number and proportion of patients with MMP-9 positive levels at Days 14, 28, 42 and 56 will be summarised, and compared between treatment groups.
- The observed values and change from Baseline in Tear film break up time at Days 14, 28, 42 and 56 will be summarised and compared between treatment groups.

Additional analyses will be defined in the SAP. Other endpoints, such as visual acuity, Conjunctival impression cytology results, use of rescue therapy and PK will be analyzed as indicated above depending on whether their outcome measure is a continuous or categorical variable.

Listings will also be used to display data at the individual patient's level.

Interim analyses may also be conducted. Details of any analyses will be outlined in the SAP.

11.4 Number of Subjects

Up to 19 patients (3 in part 1 of the study and up to 16 in part 2), to include active and placebo treated, will be enrolled under this protocol. The sample size for this study was determined based on practical, and not statistical, considerations.

11.5 Significance Level

The primary objective of the study is to assess the safety and tolerability of topical rVA576 for AKC, VKC and severe allergic conjunctivitis (SAC or PAC) and the study is not powered for the primary analysis.

For the secondary efficacy analyses, a nominal level of 5% will be considered significant, and no multiplicity adjustment will be introduced. Some significant findings are expected to occur by chance so undue consideration will not be given to any particular significant difference. Interpretation of the results will be based on patterns of differences and in conjunction with the results of the primary analyses.

11.6 Missing, Unused or Spurious Data

Missing data that cannot be retrieved from source records or other repositories will be recorded as such in the CRFs and will not be entered into the statistical analysis. Spurious data will be examined by the Sponsor's monitor, medical or statistical advisors and a decision made as to how it should be handled. If there is an obvious transcription or data entry error such as a misplaced decimal point in a biochemical parameter this will be discussed with the CRO or the laboratory and, if all parties agree, it will be corrected and endorsed by both the PI and the Sponsor prior to database lock.

No imputations will be made for missing demographic characteristics or disease characteristics. However, rules for handling of outcomes missing data or incomplete dates will be described fully in the SAP. The treatment of outliers will be addressed in the SAP. If applicable, full and modified data sets will be included in the SAP with a complete explanation of data handling and analysis methods to ensure completeness.

Unused data (e.g. superfluous blood pressure recordings or haematological results in addition to those required by the protocol will remain part of the source documentation and only be incorporated into the trial documents and analysis if there is reason for them to be (e.g. an unexpected fall in blood pressure that might constitute an AE).

11.7 Deviations from the Statistical Plan

It is not envisaged that there should be any deviations from the statistical plan since this is primarily a safety study. Any unexpected deviations (e.g. a requirement for a trend analysis not foreseen in planning the trial) will be discussed with the PI and the statistical advisor and the rationale for such an analysis will be included in the trial report.

11.8 Subjects to be Included in the Analysis

Three populations will be considered in the analysis of Part 2 of the study:

1. Full Analysis Set: This population will be defined as all subjects randomized to treatment who received at least one dose of investigational product. This will be the primary population for assessing efficacy. Subjects will be classified by the study medication they were randomised to.

2. Safety Analysis Set: This population will be defined as all subjects randomized to treatment who received at least one dose of investigational product. Randomized subjects will only be excluded if there is clear evidence of failure to take investigational product. This will be the primary population for assessing safety. Subjects will be classified by the actual study medication they receive.

3. Pharmacokinetic Analysis Set: This population will be defined as all subjects who take at least one dose of rVA576 and have at least one PK sample taken and analysed. This will be the primary population for assessing PK.

12 DIRECT ACCESS TO SOURCE DOCUMENTS

The CRO, hospitals and PIs carrying out this study will allow the Sponsor direct access to all source documents and will permit trial-related auditing of clinical, pharmacy and laboratory facilities.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Hospitals/departments taking part in the trial are responsible for maintaining their own SOPs and QA/QC procedures. The Sponsor will also maintain its SOPs, QA and QC procedures and will, at its discretion, carry out a full or partial audit of the trial site facilities and SOPs. The Sponsor will be responsible for monitoring the trial and carrying out full or representative source data verification.

14 ETHICAL CONSIDERATIONS

The application will be reviewed and approved by appropriate Ethics Committees prior to the trial commencing. All ethical aspects of the study will be in accordance with ICH Good Clinical Practice (GCP) guidelines and the requirements of the Declaration of Helsinki.

15 DATA HANDLING, RECORD KEEPING AND SAMPLE COLLECTION

The CRO and hospitals will supply and complete the source documentation and all related documentation (e.g. ECG traces, laboratory data) and at the conclusion of the trial will transfer these to the CRO who will be responsible for data entry and analysis. The original documentation will be returned to the hospitals for archiving (at least 20 years after completing of the trial) and the Sponsor will also keep duplicates for the same purpose.

Biological samples may only be stored indefinitely for the purpose of additional research related to this protocol if the patient has given informed consent for additional scientific research (directly related to this protocol). If no informed consent was obtained, samples must be destroyed after the patient has completed all protocol treatment and procedures.

Storage of biological samples on site is subject to the site's guidelines. When samples are shipped to another facility (e.g. a central laboratory), they should be stripped from any identifying information and labeled with a code (trial name, patient study number, date and time of collection).

16 FINANCING AND INSURANCE

The Sponsor will have a commercial contract in place with the hospital and the PI and the hospitals/universities who will be responsible for any payments to subjects and for payment of travel and other expenses.

The Sponsor has a clinical trials insurance policy in place, underwritten by AON Limited. A copy of the policy/certificate of insurance will be supplied separately.

17 PUBLICATION POLICY

The trial will be registered with EUDRACT or the U.S. National Institutes of Health ClinicalTrials.gov website and the results will be posted when available.

The PI of the clinical units has independent rights of publication but will agree to discuss any intended publications or presentations with the Sponsor and to allow the Sponsor reasonable time to make comments, file or add to patent applications or request changes to the manuscript.

17.1 Scoring of Clinical Signs and Symptoms – AKC and VKC

SYMPTOM	0	1	2	3
Itch	No desire to rub or scratch the eye	Occasional desire to rub or scratch the eye	Frequent need to rub or scratch the eye	Constant need to rub or scratch the eye
Tearing	Normal tear production	Positive sensation of fullness of the conjunctival sac without tears spilling over the lid margin	Intermittent, infrequent spilling of tears over the lid margin	Constant, or nearly constant, spilling of tears over the lid margins
Discomfort (including burning, stinging, and foreign body sensations)	Absent	Mild	Moderate	Severe
Discharge	No abnormal discharge	Small amount of mucoid discharge noted in the lower cul-de-sac	Moderate amount of mucoid discharge noted in the lower cul-de-sac and in the marginal tear strip; presence of crust upon awakening	Eyelids tightly matted together upon awakening, requiring warm soaks to pry lids apart; warm soaks necessary to clean eyelids during the day
Photophobia	No difficulty experienced	Mild difficulty with light causing squinting	Moderate difficulty, necessitating dark glasses	Extreme photophobia, causing the patient to stay indoors; cannot stand natural light even with dark glasses
SIGN	**0**	**1**	**2**	**3**
Bulbar conjunctival hyperaemia	Absent	Mild	Moderate	Severe
Tarsal conjunctival papillary hypertrophy	No evidence of papillary formation	Mild papillary hyperaemia	Moderate papillary hypertrophy with oedema of the palpebral conjunctiva and hazy view of the deep tarsal vessels	Severe papillary hypertrophy obscuring the visualization of the deep tarsal vessels
Punctate keratitis (superficial epithelial keratitis and punctate staining of the cornea with fluorescein)	No evidence of punctate keratitis	One quadrant of punctate keratitis	Two quadrants of punctate keratitis	Three or more quadrants of punctate keratitis
Neovascularization of cornea (new vessel formation, crossing the limbus onto the clear cornea by 2 mm)	No evidence of new vessel Formation	Presence of neovascularization in 1 quadrant of cornea	Presence of neovascularization in 2 quadrants of cornea	Presence of neovascularization in 3 quadrants of cornea
SIGN	**0**	**1**	**2**	**3**
Cicatrizing conjunctivitis (superficial scarring of the conjunctiva)	No evidence of cicatrisation	Presence of subepithelial fibrosis	Presence of fornix foreshortening	Symblepharon formation
Blepharitis (hyperaemia and oedema of eyelid skin with meibomian gland dysfunction)	No evidence of blepharitis	Presence of mild redness and oedema of the eyelid with meibomian gland dysfunction	Moderate inflammation with hyperaemia, scales, and scurf of eyelid skin and toothpaste phenomenon	Severe inflammation, with cracks in the eyelid skin, loss of eyelashes, and lid oedema

17.2 Scoring of Clinical Signs and Symptoms - Severe Allergic Conjunctivitis - SAC or PAC

SYMPTOM	**0**	**1**	**2**	**3**
Itch	No desire to rub or scratch the eye	Occasional desire to rub or scratch the eye	Frequent need to rub or scratch the eye	Constant need to rub or scratch the eye
Tearing	Normal tear production	Positive sensation of fullness of the conjunctival sac without tears spilling over the lid margin	Intermittent, infrequent spilling of tears over the lid margin	Constant, or nearly constant, spilling of tears over the lid margins
Discomfort (including burning, stinging, and foreign body sensations)	Absent	Mild	Moderate	Severe
Photophobia	No difficulty experienced	Mild difficulty with light causing squinting	Moderate difficulty, necessitating dark glasses	Extreme photophobia, causing the patient to stay indoors; cannot stand natural light even with dark glasses
SIGN	**0**	**1**	**2**	**3**
Upper tarsal conjunctival hyperaemia	Absent	Mild	Moderate	Severe
Upper bulbar conjunctival hyperaemia	Absent	Mild	Moderate	Severe
Chemosis	Absent	Mild	Moderate	Severe
Upper tarsal conjunctival papillae	Absent. Normal smooth conjunctival surface	Roughness to appearance of upper tarsal conjunctiva but no papillae ≥1mm	Roughness of upper tarsal conjunctiva and some scattered papillae ≥1mm	Cobblestone appearance of upper tarsal papillae
Blepharitis (hyperaemia and oedema of eyelid skin with meibomian gland dysfunction)	No evidence of blepharitis	Presence of mild redness and oedema of the eyelid with meibomian gland dysfunction	Moderate inflammation with hyperaemia, scales, and scurf of eyelid skin and toothpaste phenomenon	Severe inflammation, with cracks in the eyelid skin, loss of eyelashes, and lid oedema

17.3 Schedule of Events and Blood Draws

	Screening Day -7 – Day 1	Day 1 Baseline Pre-dose	Day 7 (±2 Days) Patients 1 – 3 only	Day 14 (±2 Days)	Day 28 (±2 Days)	Day 42 (±2 Days)	Day 56 (±2 days) End of dosing	Day 84 (±7 days) Follow-up Visit	Unscheduled
Eligibility, ICF & Medical History & Demographics	x								
Visual acuity by ETDRS	x	x	x	x	x	x	x	x	x
CH50		x					x		
rVA576 Drug Level (PK)[5]		x[5]		x[5]			x[5]		
Drug Administration[6]		x	x	x	x	x	x		
Antibodies (ADA)		x		x			x		
Drug Accountability			x	x	x	x	x		x
Pregnancy test (urine)	x	x			x		x	x	x
AEs & Concomitant Medications	x	x	x	x	x	x	x	x	x
Eye Swab	x								
Clinical Scoring[1]	x[2]	x	x	x	x	x	x	x	x
Conjunctival Impression Cytology (Optional)		x					x		
MMP-9 Estimation using an Inflammadry® Device[3]		x			x		x		
Tear film break up time		x	x	x	x	x	x	x	x
Patient Diary Cards[4]			x	x	x	x	x		x

1. The score is a composite of five symptoms and six signs (AKC/VKC) or four symptoms and five signs (severe allergic conjunctivitis), each graded 0 – 3 (0 = absent and 3 = most severe). The eye regarded by the patient as being most severely affected will be assessed. In the event the patient regards both eyes as being equally affected, the right eye will be assessed.
2. A total score of ≥18 out of a possible 33 (AKC/VKC), or ≥15 out of a possible 27 (severe allergic conjunctivitis), is required at the Baseline (Day1) visit for trial inclusion.
3. This test will be performed at every scheduled visit, with one assay performed per eye.
4. The Diary Cards will record the time of every IMP administration, suspected adverse events, comfort and ease of IMP administration. The Diaries will be reviewed by the Investigator at each visit.
5. PK samples should be taken pre- and 1 hour post-dose
6. It should be noted that 4 days should be allowed between Randomisation and first dose for delivery and preparation of the IMP

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