A Phase IIa open label single arm study of safety and efficacy of rVA576 in adult mild to moderate Bullous Pemphigoid subjects

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SPONSOR: **Akari Therapeutics Plc**

EudraCT NUMBER: **2017-002836-18**

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LIST OF ABBREVIATIONS

Abbreviation	Definition / Term
β-HCG	Human Chorionic Gonadotropin
ABSA	Absolute Body Surface Area
ADA	Anti-Drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
aHUS	atypical Haemolytic Uraemic Syndrome
ALT	Alanine Aminotransferase
AST	Aspartase aminotransferase
AD	Ablating Dose
BLT1	Leukotriene B4 Receptor 1
BP	Bullous Pemphigoid
BP180	Bullous Pemphigoid 180kDa protein
BP230	Bullous Pemphigoid 230kDa protein
BPDAI	Bullous Pemphigoid Disease Area Index
BPI	British Pharmaceutical Industry
CRF (eCRF)	Case Report Form (electronic Case Report Form)
CH50	Classical haemolytic 50% lysis
U Eq	Units Equivalent
CK	Creatinine Kinase
CRO	Contract Research Organisation
CRH	Corticotropin-Releasing Hormone
CRP	C-reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
ECG	Electrocardiogram
ED	Effective Dose
EDC	Electronic Data Capture
ELISA	Enzyme-Linked Immunosorbent Assay
EQ-5D-5L	EuroQol 5 Dimensional 5 Level
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hb	Haemoglobin
HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medical Product
IRB	Institutional Review Board (or equivalent, e.g. Ethics Committee)
ITT	Intention to Treat
i.v.	Intravenous
K_D	Dissociation Constant
LEC	Local Ethics Committee
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal

Abbreviation	Definition / Term
LPLV	Last Patient Last Visit
LTB_4	Leukotriene B4
MAC	Membrane Attack Complex
MCHC	Mean Cell Haemoglobin Concentration
MCP	Membrane Cofactor Protein
MCV	Mean Cell Volume
MedDRA	Medical Dictionary of Regulatory Activities
MG	*Myasthenia Gravis*
MW	Molecular Weight
NHP	Non-human primate
NOAEL	No Observable Adverse Event Level
OmCI	*Ornithodoros moubata* Complement Inhibitor
PBS	Phosphate Buffered Saline
PD	Pharmacodynamic(s)
PI	Principal Investigator
PK	Pharmacokinetic(s)
PNH	Paroxysmal Nocturnal Haemoglobinuria
PP	Per Protocol
QA	Quality Assurance
QC	Quality Control
QMG	Quantitative Myasthenia Gravis (score)
QoL	Quality of Life
SAE	Serious Adverse Event
SAD	Single ascending dose
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
S.Cr	Serum Creatinine
TABQOL	Treatment of Autoimmune Bullous Disease Quality of Life
TEAEs	Treatment-Emergent Adverse Events
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper Limit of Normal
WFI	Water for Injection
WOCBP	Woman of child bearing potential

PROTOCOL SIGNATURE PAGE

Protocol Title:	A Phase IIa open label single arm study of Safety and Efficacy of rVA576 in adult mild to moderate Bullous Pemphigoid subjects
Protocol Number:	AK801

Authorized Sponsor Representative Signature:

Signature: _____ Date: _____

[redacted]
75-76 Wimpole Street,
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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: _____

This study will be conducted according to the principles of Good Clinical Practice.

CONFIDENTIAL

CONTENTS

1. PROTOCOL SYNOPSIS

Protocol Title:	**A Phase IIa Open Label Single Arm Study of Safety and Efficacy of rVA576 in Adult Mild to Moderate Bullous Pemphigoid Subjects**		
Protocol Number:	AK801		
EudraCT No.:	2017-002836-18		
Sponsor:	Akari Therapeutics Plc. 75-76 Wimpole Street London W1G 9RT UK		
Investigational Product(s):	rVA576 powder for solution for subcutaneous injection 30mg/mL		
Phase of Development:	IIa	**Indication:**	Mild to Moderate Bullous Pemphigoid
Study Centre(s):	Approximately 4-6 sites in Germany, UK and Netherlands		
Objectives:	**Primary Objective:** To assess the safety of rVA576 in adult subjects with mild to moderate bullous pemphigoid (BP). **Secondary Objectives:** To assess the efficacy of rVA576 and its effect on the quality of life of adult subjects with mild to moderate BP.		
Study Design: **Phase IIa**	Open-label single arm study. BP subjects will be treated with 30 mg once daily rVA576 regime for 6 weeks.		
Planned Number of Subjects:	Up to 9		
Subject Population:	New onset or relapsing mild to moderate BP subjects. The study population will consist of patients above the age of 18 years with active episode of BP, confirmed by inclusion and exclusion criteria as below and who, in the opinion of the Investigator, would benefit from treatment with rVA576, a combined complement C5 and leukotriene B_4 (LTB_4) inhibitor.		

Criteria for Inclusion and Exclusion:	**Inclusion Criteria:** 1. Adult male or female ≥18-year-old patients 2. Subject with newly presenting mild to moderate cutaneous bullous pemphigoid (BP) not on any current systemic corticosteroid or immunomodulator treatment. (Subjects on topical corticosteroids will stop use of these on or before Day1) 3. BPDAI global score at screening of 10-56 (≥ 10 but <56) 4. Subjects with a relapse of mild to moderate bullous pemphigoid are eligible if their disease was quiescent without any systemic treatment for at least 2 months before the current relapse. 5. Cutaneous bullous pemphigoid (BP) per standard diagnostic criteria: a. Clinical presentation (cutaneous blistering and/or itchy dermatosis), AND b. Direct immunofluorescence (DIF) studies performed on perilesional skin collected approximately 1 cm away from a fresh blister, an erosion or papule showing linear (n-serrated) deposition of IgG and/or C3 along the epidermal basement membrane zone, AND/OR Indirect immunofluorescence (IIF) studies performed with patient serum on 1.0M NaCl human salt split skin, showing IgG along the roof of the blister. 6. Karnofsky performance status > 60% 7. Adequate cardiac, renal, hepatic, neurological and psychiatric function as determined by the Investigator and demonstrated by screening laboratory evaluations, vital sign measurement, ECG recording and physical examination results. 8. Women of childbearing potential (WOCBP) must agree to use effective contraception consistently throughout the study (such as hormonal contraception or two forms of barrier contraception) and have a negative serum pregnancy test at screening and a negative urine pregnancy test per the schedule of visits. Women are considered post-menopausal and not of childbearing potential if they have had 12 months of amenorrhea or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks previously. 9. Males with a childbearing potential partner must agree to use effective contraception consistently OR have had a vasectomy

	10. Willing and able to adhere to the study visit schedule and other protocol requirements including self-injection. 11. Willing and able to provide voluntary written informed consent 12. Willing to receive immunisation against *Neisseria meningitidis* and antibiotic prophylaxis in accordance with applicable guidelines and local standard of care of the PI at the trial site

	Exclusion Criteria: **Bullous Pemphigoid Exclusion criteria** 1. Patients with severe BP. Severe disease to defined as global BPDAI ≥ 56. 2. Patients with refractory BP. Refractory BP may be defined as failure or loss of response to maximal topical or oral steroids. 3. Concomitant skin conditions preventing physical evaluation of BP. **rVA576 and mometasone related exclusion criteria** 4. Participation in a clinical trial of an investigational product within 6 weeks of screening. 5. Known hypersensitivity to tick or to rVA576 and any of its excipients. 6. BP patients on systemic corticosteroid or systemic immunomodulator treatment (including azathioprine, dapsone, rituximab etc). 7. Treatment with biologics (e.g. etanercept, adalimumab, ustekinumab, infliximab, intravenous immunoglobulin (IVIG) and rituximab or other anti-CD20 therapies) within 5 half-lives of the drugs prior to screening. 8. Known hypersensitivity to mometasone furoate or to other corticosteroids or to any excipients in mometasone furoate 9. Received rVA576 or other recognised systemic medications for the treatment of the current episode of BP prior to study entry. Prior topical treatment with corticosteroids is permitted. This must be discontinued and study medications started on Day 1 **General Exclusion Criteria** 10. Patients with severe medical or surgical conditions at screening or Day 1 including, but not limited to cardiac, respiratory, renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, psychiatric, or any other severe acute or chronic medical condition that may increase the risk associated with study participation/treatment or may interfere with the interpretation of study results and, in the Investigator's opinion, would make the patient inappropriate for study entry. 11. Presence of any malignancy that has been under active treatment or in previous 5 years except for patients with removal of uncomplicated basal cell carcinoma or cutaneous squamous cell carcinoma, who may take part in the study.

<table>
<tr><td></td><td>
12. Congenital or acquired immunodeficiency (e.g. common variable immunodeficiency, organ transplantation).
13. Clinically significant vital sign measurements or ECG findings as determined by the Investigator.
14. Clinically significant abnormal laboratory test results including but not limited to:
• Haemoglobin level <10.0 g/dL
• White blood cell count < 3 x 10^3/μL
• Lymphocyte count < 0.5 x 10^3/μL
• Platelet count <100 x 10*9 /L or >1200 x 10*9/L
• Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN)
• Alkaline phosphatase >3 x ULN
• Serum creatinine (S.Cr) >2 x ULN
15. Active or recent history of clinically significant infection within 1 month of Screening.
16. Pregnant or breast-feeding, or planning to become pregnant during the study.
17. Evidence of an active disease of hepatitis B (HBsAg positive or HBcAg positive) or hepatitis C (HCV ab positive), CMV (IgM positive) or human immunodeficiency virus (HIV) infection (HIV1/2 Ab positive)
18. Active abuse of alcohol or drugs.
</td></tr>
<tr><td>Concurrent medication:</td><td>Subjects are permitted to receive topical mometasone (up to 30 grams per week)</td></tr>
<tr><td>Treatment Regimen:</td><td>rVA576
<table>
<tr><td>Treatment Phase</td><td>Day</td><td>Dose</td></tr>
<tr><td>Ablation</td><td>Day 1</td><td>60 mg
30 mg 12hrs later</td></tr>
<tr><td>Maintenance</td><td>Day 2-Day 42</td><td>30 mg (To be administered in the morning around same time everyday ± 1 hours)</td></tr>
</table>
TOPICAL MOMETASONE (lesional application only)
Topical mometasone is allowed as background therapy for first 21 Days only, after this it will be considered Rescue Therapy.
Topical mometasone furoate 0.1% cream or ointment (30g /week) will be permitted with participants preferably using ointment applied as a thin film.</td></tr>
</table>

	Participants will be instructed to apply the topical mometasone furoate to blisters / lesions as required (not to areas of unaffected skin). If the participant is allergic to mometasone furoate or the hospital pharmacy does not stock it, then an alternative topical steroid may be prescribed but this must be in the same potency class. In addition, participants will be advised that they can apply a light moisturiser to blisters / lesions at any time during the study.
Duration of Treatment and study:	42 Days (6 weeks) days of active treatment. Estimated study duration including enrolment (FPFV to LPLV) period is 6-12 months.
Endpoints:	**Endpoints:** **Primary:** Proportion of participants reporting grade 3, 4 and 5 adverse events, which are related/possibly related to rVA576 during the treatment period. The Common Terminology Criteria for Adverse Events (CTCAE v4.03) will be used to grade adverse events by the investigator. At each study visit, participants will be questioned about adverse events they have experienced since the last study visit. **Secondary:** • Mean absolute change in BPDAI activity scores between baseline (Day 1) and Day 42. • Proportion of patients whose BPDAI activity score decreases by 4 or more points between baseline (Day 1) and Day 42. • Proportion of patients whose BPDAI activity score increases by 3 or more points between baseline (Day 1) and Day 42. • Mean absolute change in BPDAI pruritus index between Day 1(baseline) and Day 42 • Mean change in Dermatology Life Quality Index (DLQI) between baseline (Day 1) and Day 42 • Mean change in Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL) between baseline (Day 1) and Day 42
Statistical Methods:	There will be no statistical testing in the study. Descriptive statistics will be used to summarise the data. Adverse events (AEs) of grade 3, 4 and 5 which have been assigned a causal relationship to rVA576 of 'related/possibly related' and have

	occurred during the treatment period will be considered in the analysis of the primary safety outcome. The proportion of patients experiencing such AEs will be reported with its associated 95% confidence interval. Safety analysis will be performed using the safety analysis set.

2. INTRODUCTION

The study will be conducted and completed per study protocol and the guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki (2004).

2.1. Overview of the Disease: Background of Bullous Pemphigoid, treatment options and unmet need

Bullous pemphigoid (BP) is the most common of the autoimmune blistering skin diseases in Western Europe. [Joly 2012]

BP is a serious condition with significant associated morbidity and mortality [Swerlick and Korman 2004]. Widespread tense and haemorrhagic blisters, skin erosions and severe itching cause patients a great deal of distress and pain. It occurs mainly in the elderly (>65 years).

Untreated, BP may be a self-limiting disease in a proportion of patients with periods of spontaneous remissions and exacerbations. In most patients who are treated, BP remits within 1.5-5 years but may recur once medication is stopped.

Patients are often admitted to hospital for initial treatment. The estimates of admission rates for patients with BP vary, but they are generally high, thus representing a significant burden and cost to the healthcare systems, as well to the patients' and their families / carers. The severity of symptoms and lesions in BP make treatment mandatory. Corticosteroids are often administered and frequent hospital visits are needed for dose adjustments.

During the active stage, BP is associated with morbidity and a mortality that is twice that of the general elderly population. Older age at onset and frail general condition are poor prognostic factors.

Many available treatments are associated with toxicity and may be poorly tolerated in patients with BP. Mortality during the first year is significantly higher in patients treated with high doses of systemic corticosteroids (prednisolone equivalent >40 mg daily) [Joly 2012]

Treatment should aim to control symptoms with minimum adverse effects where possible. Options are broadly divided into anti-inflammatory drugs, immunosuppressive or immunomodulating drugs, and procedures that aim to remove circulating pathogenic antibodies and inflammatory mediators (Venning 2012).

Corticosteroids are the most commonly used anti-inflammatory drugs given for treatment of BP. They are administered systemically, for example prednisolone, or topically application of very potent steroids such as clobetasol. Anti-inflammatory antibiotics such a tetracyclines are used as well. Long term use of potent steroids is associated with several adverse effects such as severe skin atrophy, osteoporosis, diabetes, glaucoma, cataract formation, weight gain, and psychologic disturbances.

Azathioprine and methotrexate are still commonly used to treat BP. Intravenous immunoglobulins have been used as immunomodulatory agents in BP as well as other auto immune blistering skin diseases.

The choice of treatment depends on the individual patient's circumstances especially the severity of the BP and presence of comorbidities. All of these treatment options have limited applicability due to reasons associated with efficacy, safety or both. And thus, there exists a need for a safe and effective therapy for BP patients.

A Cochrane systematic review [Kirtschig 2010] addressed the treatment of BP and highlighted the lack of the evidence informing current treatment paradigms as well as the unmet need and the need for better evidence based therapies.

The mortality rate in treated patients is estimated to range from [redacted] at one year. It is thought that in this susceptible elderly population, corticosteroid treatment contributes to the high mortality rate. This is due, at least in part, to the significant adverse events associated with the use of steroids, such as hypertension, diabetes, infections and osteoporosis. Management of these conditions can be difficult and their treatment represents a significant burden. Therefore, the avoidance of systemic corticosteroids in this vulnerable group of patients is highly desirable and a safer, effective, evidence based alternative is needed.

As seen in the recent BLISTER study [Williams 2017] there is now evidence that tetracyclines may be effective in treating BP. Tetracyclines are readily available broad-spectrum antibiotics which have other anti-inflammatory non-antibiotic properties. In this study mometasone was allowed as background steroid therapy in the doses of up to 30 grams per week

This AK801 proof of concept study will try to estimate the safety and efficacy of rVA576 as a complement C5 and LTB_4 inhibitor for the treatment of mild to moderate BP patients.

A significant obstacle in guiding evidence-based management of BP has been a lack of a standardised, validated scoring system for the condition. This had led to difficulties in sharing multicentre-based evidences for therapeutic efforts as there was a lack of generally accepted definitions for the clinical evaluation of patients with BP.

Common terms and end points for BP were needed so that experts in the field can accurately measure and assess disease extent, activity, severity, and therapeutic response, and thus facilitate and advance clinical trials.

This is the aim of the recently published recommendations from the International Pemphigoid Committee that represent 2 years of collaborative efforts to attain mutually acceptable common definitions for BP and proposes a disease extent score, the BP Disease Area Index. (BPDAI) (Murrell et al 2012)

As this index is new, there is paucity of data on cut-offs to be used for differentiating between mild, moderate and severe disease. Also, various definitions of response and remission will develop over time.

The current AK801 study aims to use BPDAI for identification of mild to moderate BP patients. Based on research by Levy-Sitbon 2014 et al a global BPDAI cut off of 56 has been used to exclude severe BP.

A reduction of 4 points in BPDAI activity score as a minimal clinically important difference (MCID) for improvement and an increase of 3 points as an MCID for disease worsening has

been proposed by Wijayanti et al [Wijayanti et al 2017]. These cut offs for assessment will be used in the current study AK801.
A global BPDAI score of 10 as minimal entry criteria has been chosen based on consultation with the experts in the field.
As this is a study of short duration, a single arm study and a first study of rVA576 in BP, change from baseline will be used as efficacy criteria.

This study will not only help the sponsors to design further clinical studies in BP if appropriate but will provide important data to help use of BPDAI in management of BP for the experts and other researchers.

The global BPDAI is composed of 2 scores: total BPDAI activity and total BPDAI damage. The total BPDAI activity score is the arithmetic sum of the 3 subcomponents – cutaneous blisters/ erosions, cutaneous urticaria/erythema, and mucosal blisters/ erosions. The total BPDAI damage score is the arithmetic sum of the items rated regionally for damage caused by more permanent features such as post-inflammatory hyperpigmentation, scarring and other. BPDAI quantifies lesion number and size thresholds.

Lesions are rated based on the regions affected. BPDAI gives additional weighting to areas of the skin primarily affected in BP, such as the limbs, and less emphasis to scalp and face, to better differentiate clinical response in BP.

The global BPDAI scores can range from 0 to 372. For BPDAI activity up to 360 (maximum 240 for total skin activity and 120 for mucosal activity), and 0 to 12 for BPDAI damage, with higher scores indicating greater disease activity or damage. BPDAI also has a separate subjective measure known as BPDAI-pruritus measured separately as VAS with the score between 0 and 30.

2.2. rVA576

Recombinant rVA576 is a small protein complement C5 inhibitor, which prevents the cleavage of C5 by C5 convertase and thereby inhibits generation of C5b-9 the membrane attack complex (MAC), as well as preventing the release of the anaphylatoxin C5a. rVA576 is effective in inhibiting terminal complement activity irrespective of the activating pathway (classical, lectin or alternative). In an *in vitro* experiment, it has been found to be as effective as eculizumab (*Soliris*®), at a molar equivalent dose, in preventing the haemolysis of red blood cells taken from patients with paroxysmal nocturnal haemoglobinuria (PNH). Furthermore, rVA576 has demonstrated substantial therapeutic effects in animal models, in which the pathology is dependent on the release of C5a and/or the formation of the MAC. As well as inhibiting C5 activation, rVA576 binds and inhibits leukotriene B4 (LTB_4), which can be in induced by signals independent of complement but works in conjunction with C5a as a white blood cell attractant and activator. Following successful Phase Ia and Ib clinical trials in healthy human volunteers, rVA576 is being developed for treatment of patients with [redacted] diseases such as BP. Its high solubility makes rVA576 suitable for [redacted] s.c. injection with the advantage that patients can self-administer the drug. Therefore, unlike the anti-C5 monoclonal antibody Soliris® which is marketed for treatment of PNH, patients receiving rVA576 are not tied to intravenous (i.v.) infusions twice a month. Infusions necessitate either attendance at a hospital clinic or a home visit by a suitably qualified nurse so being able to self-inject may add to patient convenience and comfort, because they have more control over their treatment which may lead to improved compliance.

3. PRIOR EXPERIENCE WITH THE INVESTIGATIONAL PRODUCT

3.1. Investigational Product

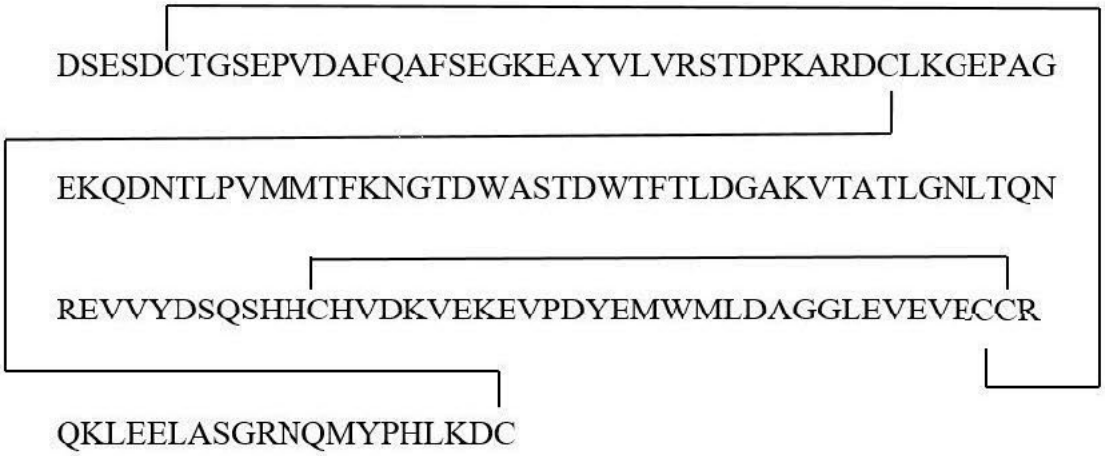
3.1.1.rVA576 powder for solution for injection 30mg/mL

rVA576 is a compact small protein molecule with a lipocalin-like structure consisting of two alpha helices and an eight-stranded beta barrel. There is a surface-active site, which binds to the complement C5 molecule with a high affinity (K_D 1.0 x 10^{-9} M) and an internalised active site capable of specifically and very tightly (KD 0.2 x 10-9 M) binding LTB_4 (Roversi 2013).

[redacted]

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 and disulphide bridging pattern is shown below:



rVA576 drug product is presented in 6mL vials containing lyophilised powder comprising sodium phosphate, sodium chloride and 18mg rVA576 per vial. The vials are stored at 2 to 8°C. Prior to injection the drug product is reconstituted with 0.6mL of sterile water for injection (WFI) to give a solution of 30mg/ml rVA576 in PBS pH 7.2. After reconstitution, the drug will normally be injected immediately [redacted] The extractable volume from each vial using a standard syringe is ≥0.5ml permitting administration of 15mg rVA576 per vial.

Dose	Number of Vials	Volume Administered	s.c injection
60 mg	**4 vials**	**2.0 mL**	**Two injections**
30mg	2 vials	1.0 mL	single injection

The drug product solution will be prepared for s.c. administration by drawing up the requisite volume from one or more vials to deliver the desired dose in one or more syringes.
Doses of rVA576 will be given at the same time each day [redacted] preferably in the morning. The subject will be given a patient card where time when drug was administrated and location of injection will be recorded daily.

3.1.2. Packaging and Labelling of the Investigational Medicinal Product

Packaging and labelling of the IMP will be provided by Akari Therapeutics PLC and will comply with Annex 13 of the European Union Good Manufacturing Practice (GMP) regulations and local regulatory requirements.

3.2. Summary of non-clinical and clinical studies relevant to the clinical trial

Recombinant rVA576 is a protein derived from a native protein discovered in the saliva of the *Ornithodoros moubata* tick [Nunn 2005]. Its function in tick saliva is to assist the parasite in feeding by suppressing host immune reactions, which would otherwise alert the host to the presence of the parasite that 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 up to 14 days, secrete an array of immunomodulatory peptides and proteins in their saliva to take control of their hosts' local and systemic immune and inflammatory responses [Francischetti 2009].

The complement system is an important part of the innate immune system in vertebrates, 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. Complement C5 is acted upon by the enzyme complex C5 convertase, to form C5a and C5b. The latter then recruits a set of proteins (C6, C7, C8, and C9), which assemble to form the membrane attack complex (MAC). Many human autoimmune diseases are associated with over activation of complement causing inflammation and tissue damage, most significantly via the products of the final common pathway C5a and the MAC. For example, in myasthenia gravis (MG) individuals form auto-antibodies to their own acetyl choline receptors (approximately 70% of all MG patients), which activate complement at the neuromuscular junction causing damage via the MAC [Lang 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 C5 convertase, rather than by blocking the convertase cleavage site on the C5 molecule [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 [Hepburn 2007]. X-ray crystallographic studies have revealed the precise binding interaction rVA576 complexed with human complement 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 Crohn's disease, hypersensitivity pneumonitis, ischaemia reperfusion injury, sepsis, myasthenia gravis, paroxysmal nocturnal haemoglobinuria (PNH), atypical haemolytic uraemic syndrome (aHUS) and age related macular degeneration [Agostini 2004; de Vries 203; Godau 2004; Mollnes 2006; Nozaki 2006; Sarma 2006; Tüzün 2008; Ward 2003; Lennon 1975; Soltys 2009].

3.2.1.Non-clinical

THERAPEUTIC POTENTIAL OF rVA576 IN A PASSIVE TRANSFER MOUSE MODEL OF EPIDERMOLYSIS BULLOSA ACQUSITA

Using BLT1 receptor deficient mice, it has been shown that leukotriene B_4 (LTB_4) and its receptor BLT1 are indispensable for neutrophil recruitment into the skin and consequently for skin inflammation using the antibody transfer mouse model of BP-like epidermolysis bullosa acquisita (EBA) (Sezin et al 2017). In addition, it is known that complement component C5 and the receptor for C5a, C5aR1, are required for full EBA pathology (Sitaru et al 2005, Karsten et al 2012).

These findings suggest that rVA576, with its dual inhibition of C5 and LTB_4, may be a promising novel therapeutic strategy in the treatment of pemphigoid diseases.

Recombinant rVA576 was tested by assessing its therapeutic effect on the course of disease in the passive EBA mouse model. In this model, rVA576 dose-dependently ameliorated the severity of skin inflammation, highlighting the potential of the drug for treatment of human pemphigoid diseases.

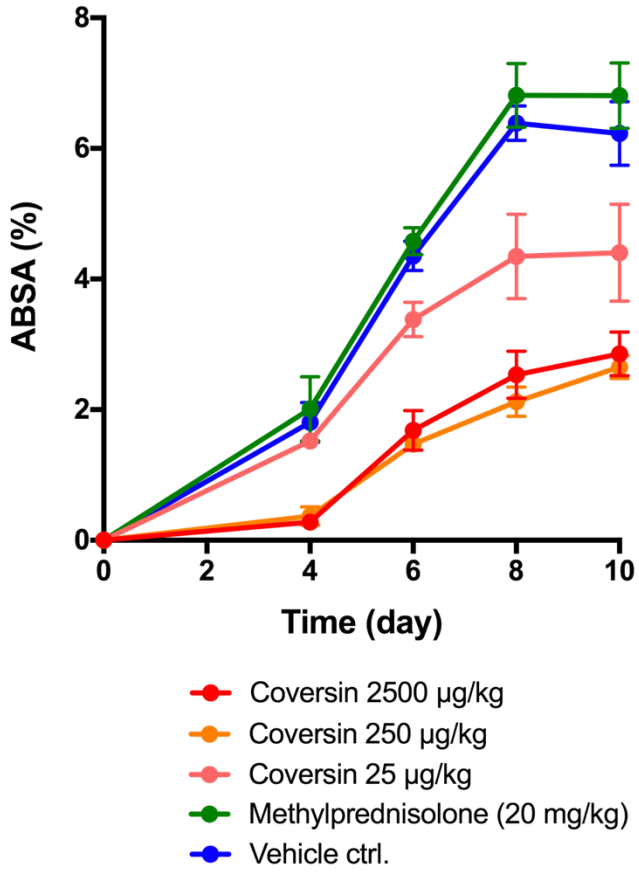
Two duplicate studies have been performed looking at the effect of rVA576 on the course of skin inflammation in a mouse (C57B1/6JRj WT) model of EBA induced by passive transfer of purified Col7 IgG. [redacted] All mice used in the experiments were female because they generally exhibit more intense skin inflammation than male mice in response to passive transfer of Col7 IgG.

Antibody transfer EBA-like skin inflammation was induced by injecting mice in the scapular region SC with 50 μg affinity purified anti-Col7 Ig on Days 0, 2 and 4 of the experiments. The antibodies were produced in New Zeland White rabbts by immunising them with 200 μg of protein containing a mix of three different recombinant proteins (Col7A, B and C) derived from non-collagenous 1 (NC1) domain of collagen VII together with incomplete Freund's adjuvant. IgGs were isolated by use of protein G and affinity purified with histidine-tagged Col7.

Prophylactic treatment with rVA576 was started four days prior to the first application of anti-Col7 IgG to induce phemphigoid disease-like skin inflammation. [redacted]

Serum samples were taken from the mice at baseline and immediately prior to the doses on Days -4, 0, 6 and the day after the last dose Day 10 in experiment 1 and Days -4, 0, 6, and the day after the last dose Day 12 in experiment 2 to assess the terminal complement activity using a sheep red blood cell lytic CH50 assay. The animals were scored for the disease severity by a trained examiner who was blinded to treatment group and the percentage of absolute body surface area (ABSA) affected by skin lesions was calculated.

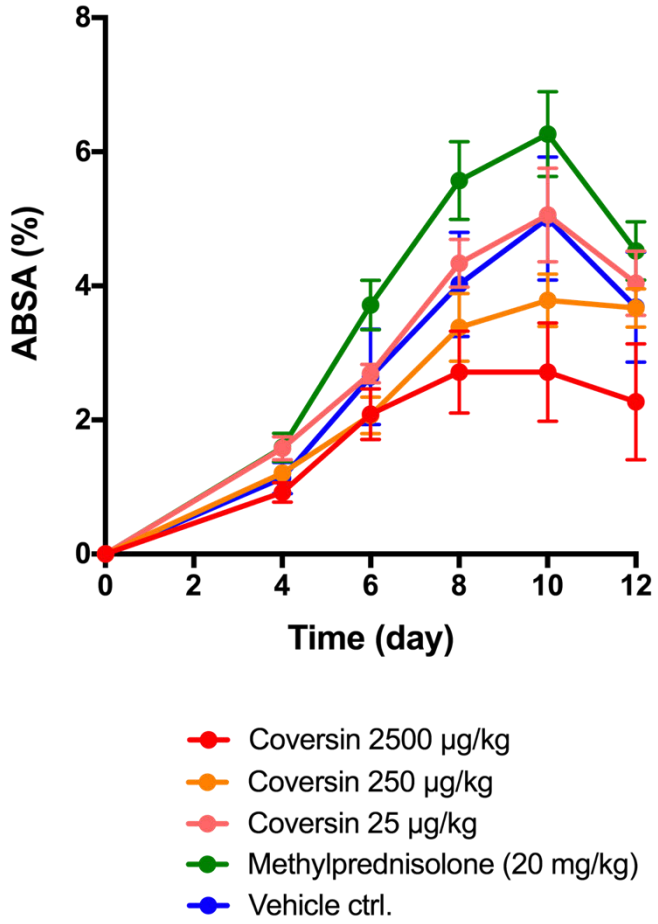
[redacted] rVA576 dose dependently and significantly (P<0.01) ameliorated skin inflammation measured by ABSA. All three doses of rVA576 were effective with 25µg/kg rVA576 reducing ABSA by approximately 30% compared to the negative control (PBS treatment) and 250µg/kg and 2500µg/kg both reducing ABSA by approximately 60% compared to negative control (**Figure *1***). The ABSA in the negative control (vehicle) group was about 7% in [redacted] which is a typical value for this model which normally achieves between 5-10% ABSA at peak. All mice in the negative control group showed a similar inflammatory response. Interestingly, the positive control 2000 µg/kg methylprednisolone IP, previously shown to reduce ABSA at this dose in the mouse model of EBA (Hellberg et al, 2013), had no effect on ABSA in the investigator's hands.



Data are presented as means +/- SEM; N = 5 mice per group; Two-way ANOVA testing for statistical significance confirms significant differences between the vehicle control and rVA576 (Coversin) at all doses.

Figure 1: [redacted] – Effect of rVA576 on the course of pemphigoid disease-like skin inflammation in the passive EBA mouse model

[redacted]

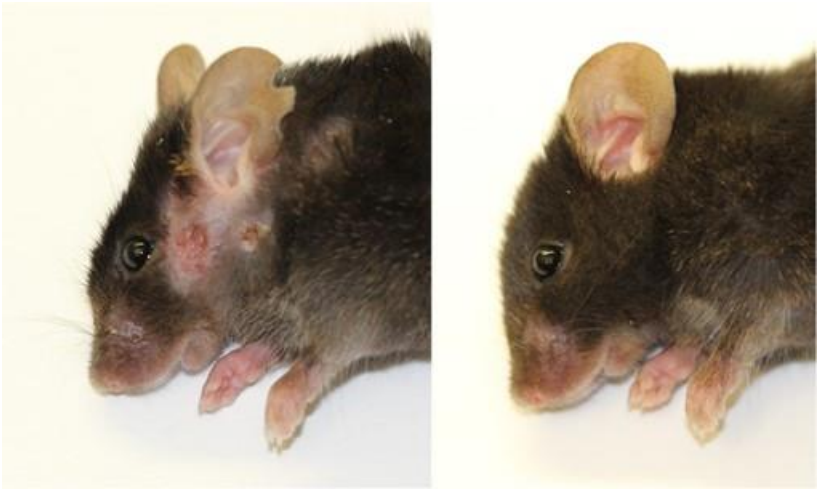


Data are presented as means +/- SEM; [redacted] in the vehicle control and the methylprednisolone group, [redacted] in the coversin groups; In comparison to the first experiment, rVA576 (Coversin) does not cause a marked difference compared to the vehicle control group. Notably, in this experiment, several mice in the control group did not develop a significant level of disease, [redacted]

Figure 2: [redacted] – Effect of Coversin on the course of pemphigoid disease-like skin inflammation in the passive EBA mouse model.

Combining the full dataset [redacted] shows that both the 250µg/kg (***Figure 3***) and 2500µg/kg doses of rVA576 significantly ($P<0.01$) prophylactically ameliorated skin inflammation measured by ABSA. The results indicate that rVA576 may have the potential to treat bullous pemphigoid (BP) in humans.

Figure 3 Comparison of mice treated with vehicle (left) and 250µg/kg rVA576 (right)



3.2.2. *Clinical*

VA576

A single ascending dose (SAD) Phase I (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 all C5 in the vascular compartment. [redacted] in Cohort 4 the dose expected from preclinical development studies, to fully inhibit complement ([redacted] was reached. This s.c. dose of rVA576 was found to produce complete terminal complement blockade, as determined by CH50 Units Equivalent/ml (CH50 U Eq/ml) assay in all four subjects treated with rVA576 (**Figure *4***).

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

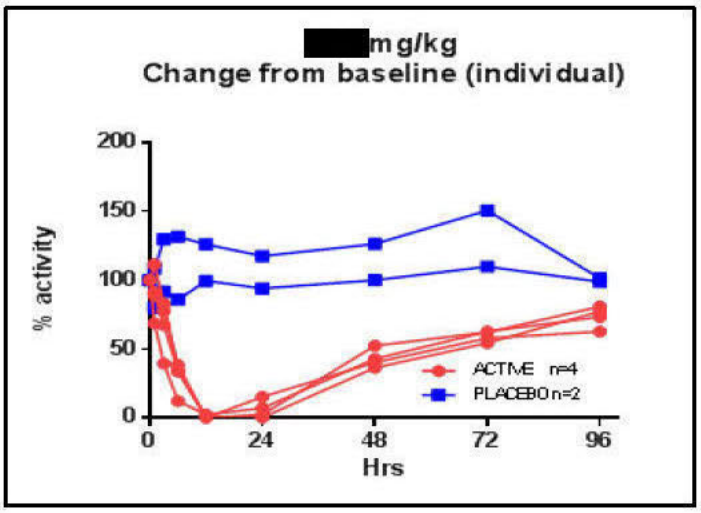


Figure 4: VA576 Phase I SAD clinical trial in normal volunteers (terminal complement activity (% of baseline) measured by CH50 in 4 active and 2 placebo treated subjects dosed at [redacted]mg/kg)

Phase 1 trial AK577

A Phase 1 dose ranging study (AK577) was conducted in which the effects of multiple doses of rVA576 in healthy volunteer subjects was studied. All subjects received an ablating dose of 4 x [redacted]mg followed by 3 further [redacted]mg doses at 12 hour intervals (or the placebo equivalent), before going on to receive maintenance doses at one 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 ([redacted]mg once a day maintenance dose), Cohort 2 ([redacted]mg once a day maintenance dose) and Cohort 3 ([redacted]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 Day 9.

Cohort 4 (comprising 4 active subjects only) received the same ablating dose as Cohorts 1, 2 and 3 and a maintenance dose of [redacted]mg once a day for 19 days. Cohort 4 subjects were followed during a 7-day recovery period from Day 21 to 28.

The effect rVA576 on terminal complement activity measured by CH50 are shown in **Figure 5**. [redacted]

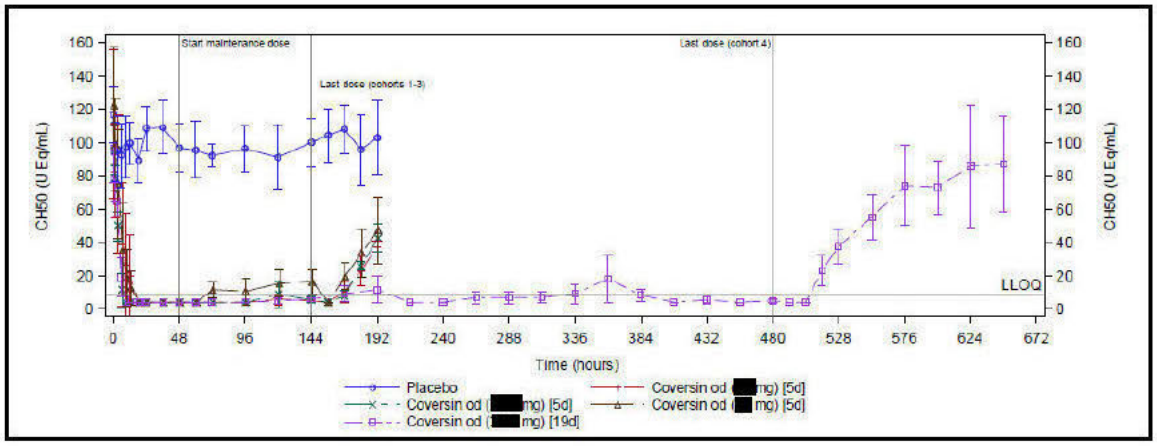


Figure 5: AK 577 Mean (+/-SD) CH50-Time Plot

3.3. Previous experience in patients

A 4-year-old child with a thrombotic microangiopathy (TMA), secondary to graft versus host disease (GVHD) following a bone marrow transplant, was treated with rVA576 on a named patient basis for 58 days during which time there was improvement in LDH and the thrombocytopenia [Goodship et al, 2017]. The drug supply ran out and the patient died 24 days later. During the period of treatment, the drug was well tolerated, there were no injection site reactions [redacted]

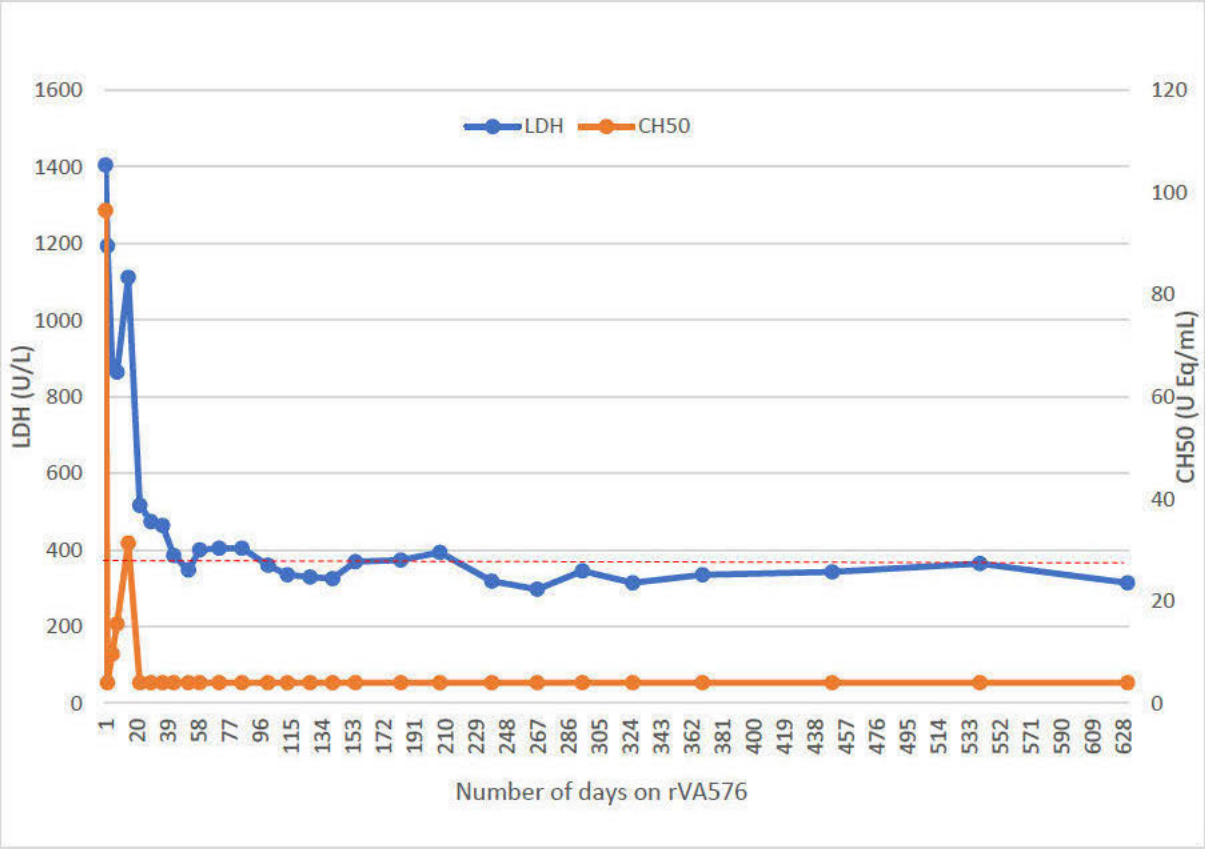
A single PNH eculizumab (Soliris®) resistant patient has received daily doses of rVA576 since the 8 Feb 2016 under clinical trial protocol AK578. At enrolment, the patient was a 32-year-old male with PNH, (granulocyte clone size: 90%) and severe haemolysis (LDH 3 to 17 x upper limit of normal, ULN, prior 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 (Soliris®) treatment despite adequate drug levels and no human anti-drug antibodies (ADA). Other causes of haemolysis were excluded. The patient was shown to have a p.Arg885Ser polymorphism in C5 which rendered him non-responsive to eculizumab (Soliris®) therapy.

In trial AK578, rVA576 was initially administered by s.c. injection at an ablating dose (AD) of [redacted]mg/kg on Day 1, followed by a maintenance dose of [redacted]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 AD 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. [redacted] 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 in **Figure *6***

Figure 6: Lactate dehydrogenase (LDH) level and terminal complement activity (CH50 U Eq/mL) during treatment with rVA576 for AK578



The ULN for this site is 250 U/L.

A Phase II COBALT open label study (AK579) in PNH patients has enrolled eight patients. [redacted]

[redacted] At the current date (15 Nov 2017) the trial overall has met its primary endpoint (median LDH at Day 28 ≤1.8 x upper limit of normal (ULN)). [redacted]

[redacted]

3.3.1. Summary of known and potential risks and benefits to human subjects

[redacted] the clinical implications of complement C5 blockade can be deduced from a combination of genetic and epidemiological studies, animal studies and experience with eculizumab (*Soliris*®). 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].

[redacted] rVA576 has generally been found to be well tolerated.

In the single ascending dose trial (VA576) the drug was well tolerated, [redacted]

[redacted]

Table 1 shows the treatment-emergent AE observed in study Phase 1b AK577. In general, all AEs were mild to moderate in intensity and all resolved. [redacted]

Table 1: Summary of Treatment-Emergent Adverse Events from AK577

[redacted]	[redacted]	[redacted]					
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

System Organ Class	Preferred term	Doses
[redacted]		

There has been a single patient enrolled in the PNH eculizumab resistant protocol (AK578) to date [redacted]

Table 2: Summary of Adverse Events Observed in AK578

System Organ Class	Preferred Term	Related	Possibly Related	Not Related
[redacted]				

System Organ Class	Preferred Term	Related	Possibly Related	Not Related
[redacted]				

[redacted]

Table 3: Summary of 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	
[redacted]								

System Organ Class	No. of Patients	Related			Possibly Related			TOTAL
	N (%)	Grade 1	Grade 2	Total	Grade 1	Grade 2	Total	
[redacted]								

[redacted]

[redacted]

Table 4: Adverse Events for AK581

System Organ Class	No. of Patients	Related			Possibly Related			TOTAL
	N (%)	Grade 1	Grade 2	Total	Grade 1	Grade 2	Total	
[redacted]								

[redacted]

In a retrospective review of PNH patients on long term treatment with eculizumab (*Soliris*®), two of ninety-six patients developed meningococcal meningitis [Hillmen et al, 2013]. Currently subjects taking eculizumab are advised to maintain prophylaxis against *Neisseria meningitidis* either by active immunization or by taking long term antibiotics or both [Dmytrijuk et al, 2008]. In this study, the anti-meningococcal measures employed in individual cases will be at the discretion of the Investigators and in accordance with local practice. In limited duration, toxicological studies with both eculizumab (*Soliris*®) and rVA576, no AEs or findings attributable to C5 blockade have been reported but Investigators are advised to be alert for possible infectious events, even in subjects who have received meningococcal immunisation.

GLP-compliant daily s.c. repeat dose studies in mice (1, 3 and 6 months) and cynomolgus monkeys (1 month) have been completed. [redacted]

[redacted]

[redacted]

3.3.2. Description of and justification of route of administration, dosage regimen and treatment period(s)

[redacted]

[redacted] rVA576 complexed with C5 has a circulating half-life of ~30 hours in rats (Hepburn et al, 2007). The rate of production of C5 by humans is not known precisely. Sissons *et al*. 1976 using the Fick Principle and ^{125}I labelled C5 injected intravenously calculated a daily turnover in normal humans of between 65 and 196 µg/kg/hr (mean 90 µg/kg/hr) (Sissons et al, 1977). It is It is considered that turnover in autoimmune disease is not substantially different to that in normal subjects. On this basis, the mean amount of C5 produced daily is roughly 151.2 mg [redacted]

[redacted]

[redacted]

Once daily repeat dose toxicology studies in mice (1-, 3- and 6-months) and cynomolgus monkey (1-month) have been performed [redacted]

Table 5:Safety Factor Calculation

PK Parameter	NHP[a]	Human[b]	Safety factor[c]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

In the Phase I SAD study VA576 at [redacted]mg/kg rVA576 complete inhibition of terminal complement activity was seen by approximately 9 hours after injection and lasted until 24 hours after injection. Recovery due to gradual replenishment of C5 by the liver and other tissues was such that at 96 hours post-dose CH50 had only returned to about 75% of baseline. [redacted]

In the Phase Ib study (AK577) in all placebo-treated subjects, CH50 results remained at around baseline levels throughout the dosing period. In contrast, the rVA576 AD fully inhibited complement activity. CH50 results were inhibited by >90% from 24 h after the start of the AD period until the end of the AD period (i.e. the morning of Day 3). [redacted] To further explore this effective dose, a longer dosing period was tested in Cohort 4, in which all subjects received a maintenance dose of [redacted] mg rVA576 for 19 days. In all 4 subjects, complement activity was almost completely inhibited throughout the maintenance dosing period and for the 24h after maintenance dose (**Figure *5***). Recovery to baseline complement activity took approximately 5 days.

Based on this data and that which we obtained from AK579 phase 2 PNH trial (described above) the proposed dosing for the current phase 2 BP study is an ablating dose of 60mg followed 12 hours later by a 30mg dose and then 30 mg once daily up to Day 42 (± 3 days). The proposed once daily maintenance dose is lower for BP (30mg) than for PNH or aHUS (45mg) as the latter two diseases require absolute control of complement activation, whereas in BP it may be sufficient to 'turn-down' terminal complement activation to low levels and LTB_4 binding may also have more effect on the pathology of BP than of PNH or aHUS.

4. TRIAL OBJECTIVES AND ENDPOINTS

4.1. Trial objectives

The primary objective of the study is to assess the safety of rVA576 in adult subjects with mild to moderate BP.

Secondary Objectives:
To assess the efficacy of rVA576 and its effect on the quality of life of adult subjects with mild to moderate BP.

4.2. Endpoints

4.2.1. Primary Endpoint:

4.2.2. Secondary Endpoints:

- Mean absolute change in BPDAI activity scores between Day 1(baseline) and Day 42
- Proportion of patients whose BPDAI activity score decreases by 4 or more points between baseline (Day1) and Day 42.
- Proportion of patients whose BPDAI activity score increases by 3 or more points between baseline (Day1) and Day 42.
- Mean absolute change in BPDAI pruritus index between Day 1 (baseline) and Day 42
- Mean Change in DLQI between baseline (Day 1) and Day 42
- Mean Change in TABQOL between baseline (Day 1) and Day 42

4.2.3. Additional Endpoints:

- Percentage change in BPDAI activity scores between baseline (Day1) and Day 42
- Proportion of patients who achieve a reduction in BPDAI activity score of at least 50%, at Day 42
- Proportion of patients who achieve a reduction in BPDAI activity score of at least 75% at Day 42
- Time to achieve 50% reduction in BPDAI activity score from Baseline (Day 1)
- Time to achieve 75% reduction in BPDAI activity score from baseline (Day 1)
- Proportion of subjects with Disease control at Day 21 (defined as the absence of new bullae for 3 consecutive days)
- Proportion of subjects with Disease control at Day 42 (defined as the absence of new bullae for 3 consecutive days)
- Change in percentage BP 180 antibody titre at Day 42 compared to baseline (Day 1)
- Change in percentage BP 230 antibody titre at Day 42 compared to baseline (Day 1)

- Change in the perilesional skin biopsy parameters at Day 42 compared to baseline (Day 1). Assessing density of granulocytes within the dermal infiltrate at Day 42 compared to screening/ historical data.
- PK (unbound rVA576) and PD (terminal complement activity measured by CH50 U Eq/mL) parameters during ablation and maintenance phases of treatment
- Change in LTB_4 level in serum between baseline (Day 1) and Day 42
- Proportion of subjects with positive Anti-drug antibody at Day 42.
- Treatment emergent adverse events (TEAEs);
- Change from baseline in physical examination
- ECG
- Clinical laboratory tests
- Vital signs

5. TRIAL POPULATION

The study population will consist of patients above the age of 18 years with an acute episode of mild to moderate BP defined as in the inclusion criteria, using clinical features and immunofluorescence and who, in the opinion of the Investigator, would benefit from treatment with dual inhibition by a combined complement C5 /LTB_4 inhibitor.

Patients may have received local steroid therapy prior to a definitive diagnosis of BP being made and can continue to receive local steroid therapy until screening and signing the informed consent form. However, subjects have to discontinue such treatment on Day 1 of dosing and only use permitted medications during the study.

[redacted]

At the end of 6 weeks, the subjects will return to their usual standard of care therapy, as this is the first clinical trial in BP patients with rVA576 and the long-term efficacy and safety is not yet established.

5.1. Inclusion Criteria

1. Adult male or female ≥18 -old patients
2. Subject with newly presenting mild to moderate BP not on any current systemic corticosteroid or immunomodulator treatment. (Subjects on topical corticosteroids will stop use of these on or before Day1)
3. BPDAI global score at Screening of 10-56 (≥ 10 but <56)

4. Subjects with a relapse of mild to moderate BP are eligible if their disease was quiescent without any systemic treatment for at least 2 months before the current relapse.

5. Cutaneous BP per standard diagnostic criteria:
   a. Clinical presentation (cutaneous blistering and/or itchy dermatosis),
      AND
   b. Direct immunofluorescence (DIF) studies performed on erythematous perilesional skin collected approximately 1 cm away from a fresh blister, an erosion or papule showing linear (n-serrated) deposition of IgG and/or C3 along the epidermal basement membrane zone,
      AND/OR
      Indirect immunofluorescence (IIF) studies performed with patient serum on 1.0M NaCl human salt split skin, showing IgG along the roof of the blister.

6. Karnofsky performance status > 60%

7. Adequate cardiac, pulmonary, renal, hepatic, neurological and psychiatric function as determined by the Investigator and demonstrated by screening laboratory evaluations, vital sign measurement, ECG recording and physical examination results.
8. Woman of childbearing potential (WOCBP) must agree to use effective contraception consistently throughout the study (such as hormonal contraception or two forms of barrier contraception) and have a negative serum pregnancy test at screening and a negative urine pregnancy test per the schedule of visits. Women are considered post-menopausal and not of childbearing potential if they have had 12 months of amenorrhea or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks previously.
9. Males with a childbearing potential partner of must agree to use effective contraception consistently OR have had a vasectomy
10. Willing and able to adhere to the study visit schedule and other protocol requirements including self-injection.
11. Willing and able to provide voluntary written informed consent.
12. Willing to receive immunisation against *Neisseria meningitidis* and antibiotic prophylaxis in accordance with the applicable guidelines and local standard of care of the PI at the trial site

5.2. Exclusion Criteria

Disease related (BP) Exclusion criteria

1. Patients with severe BP where severe disease is defined as global BPDAI $\geq$ 56.
2. Patients with refractory BP. Refractory BP may be defined as failure or loss of response to maximal doses of topical or oral steroids.
3. Concomitant skin conditions preventing physical evaluation of BP.

rVA576 and Mometasone related exclusion criteria

4. Participation in a clinical trial of an investigational product within 6 weeks of screening.
5. Known hypersensitivity to tick or to rVA576 and any of its excipients.
6. BP patients on systemic corticosteroid or systemic immunomodulator treatment (including azathioprine, dapsone, rituximab etc).
7. Treatment with any biologics (e.g. etanercept, adalimumab, ustekinumab, infliximab, intravenous immunoglobulins (IVIG) and rituximab or other anti-CD20 therapies) within its 5 half-lives from screening.
8. Known hypersensitivity to mometasone furoate or to other corticosteroids or to any of the excipients in mometasone furoate
9. Received rVA576 or any other recognised systemic medications for the treatment of the current episode of BP prior to study entry. Prior topical treatment with corticosteroids is permitted. This must be discontinued and study medications started on Day 1

General Exclusion Criteria

10. Patients with severe medical or surgical conditions at screening or baseline including, but not limited to cardiac, respiratory, renal, hepatic haematological, gastrointestinal,

endocrine, pulmonary, cardiac, neurologic, cerebral, psychiatric, or any other severe acute or chronic medical condition that may increase the risk associated with study participation/treatment or may interfere with the interpretation of study results and, in the Investigator's opinion, would make the patient inappropriate for study entry.

11. Presence of any malignancy that has been under active treatment or in previous 5 years with the exception of patients with removal of uncomplicated basal cell carcinoma or cutaneous squamous cell carcinoma, who may take part in the study.
12. Congenital or acquired immunodeficiency (e.g. common variable immunodeficiency, organ transplantation).
13. Clinically significant vital sign measurements or ECG findings as determined by the Investigator.
14. Clinically significant abnormal laboratory test results including but not limited to:
    - Haemoglobin level <10.0 g/dL
    - White blood cell count < 3 x $10^3/\mu L$
    - Lymphocyte count < 0.5 x $10^3/\mu L$
    - Platelet count <100 x 10*9 /L or >1200 x 10*9/L
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x the upper limit of normal (ULN)
    - Alkaline phosphatase >3 x ULN
    - Serum creatinine >2 x ULN
15. Active or recent history of clinically significant infection within 1 month of screening.
16. Pregnant or breast-feeding, or planning to become pregnant during the study.
17. Evidence of an active disease of hepatitis B (HBsAg positive or HBcAb positive) or hepatitis C (HCV ab positive), CMV (IgM positive) or human immunodeficiency virus (HIV) infection (HIV1/2 Ab positive
18. Active abuse of alcohol or drugs.

5.3. Concomitant Medications

At Screening visit, PI will ask subject about any medication that is currently ongoing. Subjects should be reminded to record any concomitant medication in their patient diaries and PI should discuss medications at each visit. Concomitant medications must be recorded into the eCRF.

Any use of mometasone for local application is not permitted after Day 21. Any such use after Day 21 is considered rescue therapy. In addition, any use of other local steroids at any time during the study will be considered a protocol deviation.

5.3.1.Meningitis Prophylaxis

Based on experience with the C5 complement inhibitor eculizumab (*Soliris*®) and on data in patients with constitutional C5 deficiency, it is expected that any C5 inhibitor including rVA576 may increase the risk of infection with *Neisseria meningitidis*. Therefore, all subjects taking part in clinical trials with rVA576 should receive *N. meningitidis* immunization (including anti-B serotype vaccine) and prophylactic oral antibiotics (Penicillin V or alternative antibiotic in case of allergy) for at least 14 days post first dose of rVA576.
Indefinite oral antibiotic prophylaxis throughout eculizumab (*Soliris*®) treatment has been recently recommended by the KDIGO aHUS meeting report (Goodship 2017). The PI should consider this as well as local and national guidance for antibiotic prophylaxis beyond a minimum of 14 days after vaccination.

[redacted]

For penicillin allergy, an alternative antibiotic prophylaxis may be used consistent with local antimicrobial policy. Doses and precautions to follow will be per the manufacturers' recommendations. Patients will complete diary cards to monitor compliance.

A dose of the conjugated quadrivalent vaccine against meningitis A, C, W-135 and Y as well as the initial/first dose of Bexsero, (if Bexsero is available) should be given as soon as patient has been found eligible and before start of rVA576 treatment. [redacted] A second dose of *Bexsero*® meningitis B vaccine should then be given around 1 month later. [redacted]

The exact nature, doses, timing of doses and details of meningococcal prophylaxis will be recorded in the eCRFs.

5.3.2. Prohibited Medications

The following medications are not allowed while subject is taking part in this study. The PI should discuss at each visit with the subject.

- Any steroid for local application or systemic use (other than mometasone for first 21 Days)
- Any use of immunosuppressants or immunomodulators, such as azathioprine or methotrexate or rituximab
- Any use of antibiotics for treatment of BP, such as, doxycycline
- Any other drug acting directly on the complement system

The subject will receive a Patient Alert card as soon as participation in the study is confirmed. This card has a list of all prohibited medications.

5.4. Throat and Nasal Swabs

All patients selected for entry into this trial will have throat and nasal swabs taken once they have consented. A positive *Neisseria sp*. results will exclude subjects from the trial. [redacted]

5.5. Contraception

There are no specific, identified risks to mother or foetus from rVA576 therapy. [redacted] Until the results from complete

reproductive toxicology studies are known patients being treated with rVA576 should be advised to use the following precautions against sexual exposure and pregnancy.
Subjects who are or become sexually active must use, with their partner, 2 approved methods of highly effective contraception from the time of IMP administration until 90 days after the last dose of IMP.
WOCBP 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.
Two or more of the following methods are acceptable and must include at least one barrier method:

- 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 subjects, this must be a condom; for female subjects, either their partner's use of a condom or the subject'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 another method

Alternatively, true abstinence is acceptable when consistent with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, they and their partner should use two of the contraceptive methods listed above.
Male subjects who have been sterilised are required to use one barrier method of contraception (condom).

5.5.1. Exposure of partners during the study

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

5.5.2. Sperm donation

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

6. TRIAL DESIGN AND PROCEDURES

6.1. Trial design

This is an open label, single arm study in up to 9 patients with newly diagnosed or relapsing BP, who meet the inclusion and exclusion criteria, as defined in Section 5.1 and 5.2. The study design is depicted in **Figure *7***.

6.2. Duration of trial

The estimated duration of the study for an individual subject is 42 Days and a follow-up visit a month after. **The end of study is defined as the date of the last patients last visit (LPLV).** The duration of the First Patient Screened to LPLV will be approximately 12 months.

At the end of the study the subjects will return to the standard of care (SOC) at their site. No additional rVA576 will be available beyond Day 42.

6.3. Dosing Scheme

6.3.1. rVA576

6.3.2. Mometasone furoate

6.4. Trial procedures

6.4.1. Screening Period- (Day -14 to -1)

- ✓ Obtain subject's ICF
- ✓ Collection of demographic data
- ✓ Collection of medical history including any relevant medical condition
- ✓ Assessment of prior and concomitant therapy
- ✓ Physical examination and vital signs **(see Section 6.7 for details)**
- ✓ Perform a 12-lead electrocardiogram (ECG) **(see Section 6.7 for details)**
- ✓ Nasal and Throat Swab **(see Section 5.4 for details)**
- ✓ Assess Karnofsky Performance status
- ✓ Complete global BPDAI and Visual Analogue Pruritus scale
- ✓ Subject completes Quality of Life instrument **(see Section 'Appendix' for details)**

- Blood draws:
  - Serum for beta-human chorionic gonadotropin (β-HCG) pregnancy test for all WOCBP unless surgically sterile or post-menopausal. This will be analysed in the local laboratory
  - Haematology, chemistry and urinalysis for the local laboratory (**see Section 6.7 for details**)
  - Collect BP 180 and BP 230 for the central laboratory. Please refer to the Laboratory Manual for further details
  - Skin Biopsy: Perform skin biopsy to establish diagnosis and obtain a baseline (see section 6.6.6 for details) if not performed within 1 month of screening date.

- ✓ Evaluate results of the above procedures and review inclusion and exclusion criteria before proceeding to next visit
- ✓ If eligibility criteria are met, vaccinate against *N. meningitidis* **(see Section 5.3 for details)**

6.4.2. Ablation Day 1 Baseline (Pre-dose):

- ✓ Physical examination and vital signs **(see Section 6.7 for details)**
- ✓ Perform a 12-lead electrocardiogram (ECG) **(see Section 6.7 for details)**
- ✓ Complete global BPDAI and Visual Analogue Pruritus scale
- ✓ Record any new, or changes to adverse events and (AEs) concomitant medications that have occurred since the last visit
- ✓ Subject to start taking prophylactic antibiotics to reduce risk of *N. meningitides* infection

- Blood draws:
  - Collect haematology, chemistry and urinalysis for the local laboratory **(see Section 6.7 for details).**
  - Collect, serum for measurement of antidrug antihuman antibody (ADA), Total C5 and blood EDTA for measurement of LTB_4 for the central laboratory. For instructions and order of sampling please refer to the Laboratory Manual
  - Collect serum for PK and PD samples for the central laboratory. Collect sample 5-60 minutes before first dose of IMP. For instructions and handling of the samples please refer to the Laboratory Manual
- ✓ Administer first dose of rVA576 60mg
- ✓ Subject to be given patient diary and taught how to complete it
- ✓ Remind the subject to return all used rVA576 vials and the used mometasone tubes at each visit and keep a record of how many unused rVA576 vials remain in their fridge at home.
- ✓ Instruct the subject on the signs and symptoms of *N. meningitidis* infection. Provide an Identification Card to the subject which explains that the subject is participating in a clinical trial with a description of rVA576 and emergency contact information.

  Administer second dose of rVA576 30mg 12h after the morning dose

6.4.3. Day 7 – Pre-dose assessments and blood draws

- ✓ Physical examination and vital signs **(see Section 6.7 for details)**
- ✓ Perform a 12-lead electrocardiogram (ECG) **(see Section 6.7 for details)**
- ✓ Complete global BPDAI and Visual Analogue Pruritus scale
- ✓ Assessment of disease control

- ✓ Record any new, or changes to AEs and concomitant medications that have occurred since the last visit
- ✓ Check subject diary card to confirm antibiotic compliance, rVA576 administration and body temperature
- ✓ Perform drug accountability and record compliance. Remind the subject to bring all used rVA576 vials and mometasone tubes at each visit and record the number of unused rVA576 vials remaining in their fridge

- Blood Draws:
  - Collect haematology, chemistry and urinalysis for the local laboratory **(see Section 6.7 for details)**
  - Collect, serum for measurement of antidrug antihuman antibody (ADA) and Total C5, and blood EDTA for measurement of LTB_4 for the central laboratory. For instructions and order of sampling please refer to the Laboratory Manual
  - Collect serum for PK and PD samples for the central laboratory. Collect sample 5-60 minutes before the daily dose of IMP. For instructions and handling the samples please refer to the Laboratory Manual

- ✓ Administer 30mg of rVA576

6.4.4.Day 14 – Pre-dose assessments and blood draws

- ✓ Physical examination and vital signs **(see Section 6.7 for details)**
- ✓ Perform a 12-lead electrocardiogram (ECG) **(see Section 6.7 for details)**
- ✓ Complete global BPDAI and Visual Analogue Pruritus scale
- ✓ Assessment of disease control
- ✓ Record any new, or changes to AEs and concomitant medications that have occurred since the last visit
- ✓ Check subject diary card to confirm antibiotic compliance, rVA576 administration and body temperature
- ✓ Perform drug accountability (vials and mometasone) and record compliance. Remind the subject to bring all used rVA576 vials and mometasone tubes at each visit and record the number of unused rVA576 vials remaining in their fridge

- Blood Draws:
  - Collect haematology, chemistry, and urinalysis for the local laboratory **(see Section 6.7 for details)**
  - Collect, serum for measurement of antidrug antihuman antibody (ADA), Total C5, and blood EDTA for measurement of LTB_4 for the central laboratory. For instructions and order of sampling please refer to the Laboratory Manual
  - Collect serum for PK and PD samples for the central laboratory. Collect sample 5-60 minutes before the daily dose of IMP. For instructions and handling the samples please refer to the Laboratory Manual

- ✓ Administer 30mg of rVA576

Post dose:

- ✓ At intervals 3h, 6h, 9h,12h and 18h (±0.5h) after the 30mg dose please complete the following:
  - ➢ Collect serum for PK and PD samples for the central laboratory. For instructions and handling samples please refer to the Laboratory Manual.
  - ➢ At 12h only collect blood EDTA for measurement of LTB_4 for the central laboratory. For instructions and order of sampling please refer to the Laboratory Manual
  - ➢ Assess the subject for any adverse events

6.4.5.Day 21 – Pre-dose (±1 day) assessments and blood draws

- ✓ Physical examination and vital signs **(see Section 6.7 for details)**
- ✓ Perform a 12-lead electrocardiogram (ECG) **(see Section 6.7 for details)**
- ✓ Complete BPDAI and Visual Analogue Pruritus scale
- ✓ Subject completes Quality of Life instrument **(see Section 'Appendix' for details)**
- ✓ Assessment of disease control
- ✓ Record any new, or changes to AEs and concomitant medications that have occurred since the last visit
- ✓ Check subject diary card to confirm antibiotic compliance (if applicable), rVA576 administration and body temperature
- ✓ Perform drug accountability (vials and mometasone) and record compliance. Remind the subject to bring all used rVA576 vials at each visit and record the number of unused rVA576 vials remaining in their fridge

- Blood draws:
  - ➢ Collect haematology and chemistry for the local laboratory **(see Section 6.7 for details)**
  - ➢ Collect BP 180 and BP 230 for the central laboratory. Please for further details refer to the Laboratory Manual.
  - ➢ Collect serum for measurement antihuman antibody (ADA), Total C5 and blood EDTA for measurement LTB_4 for the central laboratory. For instructions and order of sampling please refer to the Laboratory Manual.
  - ➢ Collect serum for PK and PD samples for the central laboratory. Collect sample 5-60 minutes before IMP. For instructions and handling of the samples please refer to the Laboratory Manual.

- ✓ The subject should prepare and administer 30mg of rVA576 at the clinic visit

6.4.6.Day 28 – Pre-dose assessments and blood draws (±1days)

- ✓ Physical examination and vital signs **(see Section 6.7 for details)**
- ✓ Perform a 12-lead electrocardiogram (ECG) **(see Section 6.7 for details)**
- ✓ Complete global BPDAI and Visual Analogue Pruritus scale
- ✓ Assessment of disease control
- ✓ Record any new, or changes to AEs and concomitant medications that have occurred since the last visit
- ✓ Check subject diary card to confirm antibiotic compliance (if applicable), rVA576 administration and body temperature
- ✓ Perform drug accountability and record compliance. Remind the subject to bring all used rVA576 vials at each visit and record the number of unused rVA576 vials remaining in their fridge

- Blood Draws:
  - ➢ Collect haematology, chemistry, and urinalysis for the local laboratory **(see Section 6.7 for details)**
- ✓ The subject should prepare and administer 30mg of rVA576 at the clinic visit

6.4.7.Day 42 - Pre-dose assessments and blood draws (±3 day)

- ✓ Physical examination and vital signs **(see Section 6.7 for details)**
- ✓ Perform a 12-lead electrocardiogram (ECG) **(see Section 6.7 for details)**
- ✓ Complete global BPDAI and Visual Analogue Pruritus scale
- ✓ Subject completes Quality of Life instrument and **(see Section 'Appendix' for details)**
- ✓ Assessment of disease control
- ✓ Record any new, or changes to adverse events and concomitant medications that have occurred since the last visit
- ✓ Check subject diary card to confirm antibiotic compliance (if applicable), rVA576 administration and body temperature
- ✓ Perform drug accountability and record compliance.
- ✓ Perform biopsy

- Blood draws:
  - ➢ Collect haematology including B-HCG pregnancy test for WOCBP, chemistry, BP and urinalysis for the local laboratory **(see Section 6.7 for details)**
  - ➢ Collect BP 180 and BP 230 for the central laboratory. Please for further details refer to the Laboratory Manual.

- Collect serum for measurement of antihuman antibody (ADA), Total C5 and blood EDTA for measurement of LTB_4 for the central laboratory. For instructions and order of sampling please refer to the Laboratory Manual.
- Collect samples for PK and PD assays for the central laboratory. Collect sample 5-60 minutes before IMP. For instructions and handling of the samples please refer to the Laboratory Manual.

6.4.8. Unscheduled visit:

- ✓ Physical examination vital signs **(see Section 6.7 for details);**
- ✓ Perform a 12-lead electrocardiogram (ECG) **(see Section 6.7 for details)**;
- ✓ Complete global BPDAI and Visual Analogue Pruritus scale
- ✓ Subject completes Quality of Life instrument and **(see Section 'Appendix' for details)**
- ✓ Record any new, or changes to adverse events and concomitant medications that have occurred since the last visit
- ✓ Check subject diary card to confirm antibiotic compliance (if applicable), rVA576 administration and body temperature
- ✓ Perform drug accountability and record compliance. Remind the subject to bring all used rVA576 vials at each visit and record the number of unused rVA576 vials remaining in their fridge

- Blood draws:
  - Collect samples for haematology, chemistry and urinalysis **(see Section 6.7 for details).**
  - Collect serum for measurement of antihuman antibody (ADA), Total C5 and blood EDTA for measurement of LTB_4 for the central laboratory. For instructions and order of sampling please refer to the Laboratory Manual.
  - Collect samples for PK and PD assays for the central laboratory. Collect sample 5-60 minutes before IMP. For instructions and handling of the samples please refer to the Laboratory Manual.

6.4.9. Follow- up Day 72 (±3 days)

- ✓ Physical examination and vital signs **(see Section 6.7 for details);**
- ✓ Record any new, or changes to adverse events and concomitant medications that have occurred since the last visit

- Blood draws:
  - Collect haematology, chemistry and urinalysis (**see Section 6.7 for details)**.
  - Collect serum for measurement of antihuman antibody (ADA), Total C5 and blood EDTA for measurement of LTB_4 for the central laboratory. For instructions and order of sampling please refer to the Laboratory Manual.
  - Collect samples for PK and PD assays for the central laboratory. For instructions and handling of the samples please refer to the Laboratory Manual.

Table 6: Schedule of Events and Blood Draws for AK801 Screening to Day 42

		60mg followed by 30 mg 12 hr later		30 mg once daily										
	Screening	Day 1	Day 7 (±1 day)	Day 14 (±1 day)						Day 21 (±1 day) Pre-dose	Day 28 (±1 day) Pre-dose	Day 42 (±1 day)	Day 72	Unscheduled
	Up to Day-14	Pre-dose	Pre-dose	Pre-dose	3h	6h	9h	12h	18h			Study End Early Termination	Follow-up Visit	(if needed at any time)
Eligibility, ICF & Medical History & Demographics	x													
Physical Examination[1]	x	x	x	x						x	x	x	x	x
ECG	x	x	x	x						x	x	x		x
Nasal & Throat Swabs[2]	x													
Vital Signs[3] (including height & weight)	x	x	x	x						x	x	x	x	x
CH50 (PD)		x*	x*	x*	x*	x*	x*	x*	x*	x*		x*	x*	x*
rVA576 Drug Level (PK)		x*	x*	x*	x*	x*	x*	x*	x*	x*		x*	x*	x*
Antibodies (ADA)		x*	x*	x*						x*		x*	x*	x*
LTB_4		x*	x*	x*				x*		x*		x*	x*	x*
Total C5		x*	x*	x*						x*		x*	x*	x*
Chemistry & Haematology[4]	x	x	x	x						x	x	x	x	x
Urinalysis – Pregnancy Test[5]	x	x	x	x							x	x	x	x
DLQI- TABQOL	x									x		x		x
Assessment of disease control			X	X						x	X	x		
Bullous Pemphigoid Disease Area Index (BPDAI)	x	x	x	x						x	x	x		x
Meningitis prophylaxis6	Vaccine	Antibiotics/Vaccine as per site schedule												
Drug Accountability			x	x						x	x	x		x
AEs & Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Karnofsky Performance Status	x													
Visual Analogue Scale PRURITUS	x	x	x	x						x	x	x		x
BP180 & BP230 Antibody Titres	x*									x*		x*		
Skin Biopsy[7] and Immunofluorescence [8]	x*											x*		
Dosing		x	x	x						x	x	x		

* Central Labs

(1) Physical Examination – Inclusive of injection site inspection.

(2) Nasal & Throat swabs - All patients selected for entry into this trial will have throat and nasal swabs taken once they have consented. Any positive Neisseria sp. results will exclude that patient from the trial. Repeat throat and nasal swabs during the screening period are allowed at weekly intervals. If the organism has been eradicated before planned Day 1 patient can be included.

(3) Vitals – Diastolic and Systolic blood pressure, pulse rate and oral temperature (weight only required at Screening, pre-dose Day 1, Day 21 and Day 42 and height is only required at Screening).

(4) Serum Pregnancy test will be performed at screening and end of treatment Day 42 or early termination.

(5) A urine pregnancy test should be performed at Day 1, Day 28, follow up and unscheduled.

(6) [redacted]

(7) Diagnostic skin biopsy may be used for this study as baseline unless it is older than 1 month in which case it will need to be repeated. At the end of treatment or early termination skin biopsy should be performed in the same area as the diagnostic biopsy area. It should be a peri-lesional tissue specimen for DIF examination.

(8) Immunofluorescence studies should be performed on perilesional skin, approximately 1cm away from the skin lesion. It is considered positive when showing linear deposition of IgG and / or C3 along the basement membrane zone.

6.5. CH50 assay

Inhibition of terminal complement activity measured by CH50 may improve clinical control of the disease. Serum CH50 assay is currently the most sensitive and quickest means of detecting inadequate control during anti-complement therapy. In practice, the Quidel ELISA assay that is used to measure complement activity in units of CH50 U Eq/mL has a lower limit of quantification of [redacted] CH50 U Eq/mL with individual normal baseline values ranging from 79-187 CH50 U Eq/mL. Thus, the assay is insensitive to differences in CH50 when there is < [redacted] CH50 U Eq/mL residual complement activity. Therefore, for practical purposes the Central Laboratory (which will conduct all CH50 assays during the trial) considers values less than [redacted] CH50 U Eq/mL as completely inhibited.

6.6. Efficacy assessments

6.6.1. Bullous Pemphigoid Disease Area Index (BPDAI)

BPDAI **(**see Appendix for details) will performed at screening and pre-dose at baseline and at every visit until Day 42.

The global BPDAI is composed of 2 scores: total BPDAI activity and BPDAI damage.

The total BPDAI activity score is the arithmetic sum of the 3 subcomponents – cutaneous blisters/ erosions, cutaneous urticaria/erythema, and mucosal blisters/ erosions.

The BPDAI damage score is the arithmetic sum of the items rated regionally for damage caused by more permanent features such as post-inflammatory hyperpigmentation, scarring and other.

BPDAI quantifies lesion number and size thresholds. Lesions are rated based on the regions affected. BPDAI gives additional weighting to areas of the skin primarily affected in BP, such as the limbs, and less emphasis to scalp and face, to better differentiate clinical response in BP.

The global BPDAI scores can range from 0 to 372. For BPDAI activity up to 360 (maximum 240 for total skin activity-[120 for erosions/blisters, 120 for urticaria/ erythema] and 120 for mucosal activity), and 0 to 12 for BPDAI damage, with higher scores indicating greater disease activity or damage. The global BPDAI score will be used to assess the inclusion of subjects.

BPDAI also has a separate subjective measure known as BPDAI-pruritus Index.

The BPDAI pruritus component is based on a visual analogue scale, measuring the severity of itch during the past 24 h (0–10), the past week (0–10) and the past month (0–10) with a total score of 30. If the patient is unable to complete a reliable visual analogue scale rating, as a result of dementia, for instance, the degree of pruritus will be based on the extent of excoriations alone (total score 30).

6.6.2. Quality of Life Instrument –DLQI / TABQOL assessment

DLQI and TABQOL **(**see Appendix for details) will always be performed at screening, pre-dose on Day 1 Day 21- and Day 42.

The subject will complete the paper questionnaires at the time points specified on the Schedule of Events during the study. The data will be transcribed to the eCRF and subsequently analysed as a secondary efficacy endpoint.
The patient will complete a non-validated questionnaire at Day 14, Day 28 and Day 42 to determine whether self-injection by patients with BP is well-accepted and the support provided sufficient.

6.6.3.LTB4

Measurement of LTB_4 in serum will be used to collect information on effect of rVA576. LTB_4 levels and will be collected at Day 1 (pre-dose), Day 2 (pre-dose) Day 14 (pre-dose) and Day 42 or the early termination visit, if applicable.

6.6.4.BP 180 / BP 230

There is increased level of circulating IgG antibodies against two antigens in the BP patients. These are BP antigen 180 (BP180) and BP antigen 230 (BP230).
In patients with BP this has led to serologic testing for the levels of these two antibodies.
This testing detects circulating IgG that reacts with BP180 (specifically, the NC16A domain of BP180, which is the most common antigenic target and which also has been known as BP antigen 2 (BPAg2)) and with BP230 (specifically, fused antigenic targets from the N-terminal domain, central rod domain, and C-terminal domain of human BP230 and which also is known as BP antigen 1 (BPAg1)).

6.6.5.Assessment of Disease control

Pemphigoid is characterised by formation of new bullae/ vesicles / papules / plaques or erythema. When the disease starts to come under control, the formation of new lesions decreases to the point where there are no new lesions observed and established lesions have begun to heal or healed.

Having no new lesions for at least 3 consecutive days is considered one of the efficacy measures to monitor therapy and improvement. Similarly, the established lesions not extending to new lesions (bullae, vesicles, papules, plaques or erythema) after healing can be an efficacy measure too.

This will be assessed by the PI/ designee at baseline and all subsequent visits when the PI does the BPDAI calculation, by asking the subject if they have noticed any new lesions form over last 3 days and note down the numbers of new lesions if developed. PI/designee will also assess on visit 7 and all subsequent visits, if the established lesions extended to no new lesions and/or considered as healed.

6.6.6. Skin biopsy for direct/ indirect immunofluorescence

The initial evaluation of both new and recurrent blistering skin diseases requires a skin biopsy. It is assumed that a biopsy report will be available at baseline and will be transferRED in the study CRF.

A baseline skin biopsy (punch biopsy) may be performed during screening if no biopsy had been performed to establish diagnosis or the detailed report of the biopsy is not available. If the diagnostic biopsy has been carried out within one month to the screening visit, a baseline biopsy will not be carried out. This will decrease the burden on an additional procedure on the BP patients, who are mostly old and likely to have many co-morbid conditions and disabilities. The baseline biopsy is performed to establish diagnosis, obtain baseline immunofluorescence data.

The baseline biopsy will be performed by the PI/designee (suitably qualified) and will be sent to Central Laboratory for analysis. Direct immunofluorescence (DIF) studies performed on perilesional erythematous skin collected approximately 1 cm away from a blister, erosion or papule showing linear (n-serrated) deposition of IgG and/or C3 along the epidermal basement membrane zone will establish the diagnosis of BP.

Another skin biopsy will be carried out at the end of the study treatment at Day 42 or at early termination visit. At the end-of-study skin biopsy should be performed in the same area as the diagnostic biopsy area. It should include both a lesional tissue specimen for routine (fixed tissue) a perilesional tissue specimen for DIF examinations a peri-lesional biopsy.

6.7. Safety Assessments

6.7.1. Adverse Events

All clinical AEs (defined in Section 8 occurring after the subject has signed the ICF and after the last dose of study medication (i.e. the follow-up period), whether observed by the Investigator or reported by the subject, will be recorded on the AE eCRF page. Medical conditions (including laboratory values and/or vital signs that are out of range and found clinically significant) that exist prior to Informed Consent will be recorded as part of medical history.

All laboratory, vital sign, or ECG values should be reviewed by the Investigator to determine clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings should be reported as AEs if they are symptomatic, lead to study drug discontinuation, require corrective treatment.

All SAEs are to be reported according to the procedures in Section 8. Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary signs or symptoms as the AE or SAE term with additional details included in the SAE narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report as individual entries of AE or SAE. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). Pre-planned (prior to signing the ICF) procedures or hospitalizations for pre-existing conditions which do not worsen in severity should not be reported as SAEs (see Section 8 for Definitions). For deaths, the underlying or immediate cause of death should always be reported as an SAE. In addition, any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE, unless the subject is transferred to and followed up in the long-term safety study.

At each visit, the Investigator should determine whether any AEs have occurred by evaluating the subject. AEs may be directly observed, reported spontaneously by the subject, or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 8 The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

Investigators should follow subjects with AEs until the event has resolved or the condition has stabilized. Unresolved AEs, including significant abnormal laboratory values at the end of the study, should be followed up until resolution or until no longer clinically relevant. Subjects with unresolved AEs who are transferred to the long-term safety study will continue to be followed in that study until event resolution.

6.7.2.Medical History and Present Conditions

A complete medical history will include evaluation (past and present) of the following:

General	Heart / cardiovascular
Chest / respiratory	Dermatological / skin
Past (or plans for future) surgeries	Alcohol use or Substance abuse
Neurological/ Psychiatric	Haematological / lymphatic
Abdominal/Urogenital	Endocrine / metabolic
Medications	Smoking
Allergies / drug sensitivities	

6.7.3.Physical Examination

Should minimally include clinical evaluations of the head, neck, thyroid, eyes, ears, nose, throat, heart, lungs, lymph nodes, neurological, abdomen, skin, extremities, and musculoskeletal system.

6.7.4.Electrocardiogram

Twelve-lead ECG data will be collected per the schedule of assessments. Investigative sites will utilize local ECG equipment and preserve the ECG tracing as subject source documentation. The ECG will be interpreted as normal, abnormal-not clinically significant(NCS) or abnormal-clinically significant(CS).

6.7.5.Vital Signs

Blood pressure, pulse and respiratory rate will be measured in the supine position after the subject has rested comfortably. Body temperature will be recorded using whatever device is routinely used in the Investigator's clinic (e.g. oral, ear etc.). Body weight (only at screening and end of treatment and height (only at screening) will also be recorded using scale available at site.

6.7.6.Pregnancy Test

All WOCBP, unless surgically sterile, must have a serum negative pregnancy test at screening visit. This test will be performed at the local laboratory. Urine pregnancy test will be performed as detailed in the schedule of events on all WOCBP unless surgically sterile throughout the

study. The patient will be discontinued from the study if she becomes pregnant during the study and will be followed up until resolution.

6.7.7.Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures at the time points specified in the schedule of events.
Details of these procedures and required safety monitoring will be given in the laboratory manual. Clinical laboratory tests to be performed in this study are summarized in **Table *7***. Refer to the Schedule of Events (**Table 6**) for timing of all assessments. See Laboratory Manual for testing regimen.
Additional, non-genetic, testing may be conducted on retained samples if deemed appropriate by the Investigator or should additional research suggest further investigation is required to improve disease evaluation and drug response. Consent for additional, currently undetermined, exploratory analysis will be in place prior to further analysis. The patient may refuse additional testing on their retained samples at any point and this will not influence their participation in the study.
Additional and repeat blood draws considered necessary for safety and well-being of the subject may be performed at the discretion of the Investigator. All clinical laboratory safety tests will be performed locally by each clinical unit.

Table 7: Clinical Laboratory Test

Complete Blood Count and Differential	Chemistry	Urinalysis	Other Test
White blood cell count with differential	Sodium	Leukocytes	**Anti-Drug Antibody (ADA)**
Mean Cell Haemoglobin Concentration (MCHC)	Potassium	Bilirubin	**PK (Unbound rVA576)**
Mean Cell Volume (MCV)	Glucose (Random)	Glucose	**PD (CH50)**
Red blood cell count	Alkaline phosphatase	pH	**Human Chorionic Gonadotropin (β-HCG)**
Haemoglobin	Alanine Aminotransferase (ALT)	Microbiology	**LTB_4**
Mean Cell Haemoglobin (MCH)	Bicarbonate	Urine Microscopy	**Total C5**
Haematocrit	Urea	Pregnancy testing	
CRP	Aminotransferase (AST)	Ketones	
Platelets	Creatine Kinase (CK)	Nitrates	
	Total Bilirubin	Blood	
	Chloride	Specific gravity	
	Albumin	Urobilinogen	
	Calcium		
	Gamma Glutamyl Transpeptidase (GGT)		
	Bilirubin (Direct) (only if Total is elevated)		
	Phosphate (Inorganic)		
	Protein (Total)		
	Serum Creatinine		
	Urine Protein		

6.8. Additional assessments

6.8.1. Pharmacokinetics (PK) and Pharmacodynamics (PD)

Blood samples will be collected at the specified times in the schedule of events to study the PK of rVA576. PK parameters such as maximum concentration, trough concentration at various time points after the first dose, and during the maintenance treatment phase will be performed. Clearance and terminal half-life will be estimated.

The subject may require an overnight stay in hospital to have some of the PK and PD samples taken. This will remain at PI discretion. PK/PD samples at 12h and 18h not taken will not be recorded as a protocol deviation.

Blood samples for PD analysis will be collected at specified time points to assess pre-and post-treatment serum haemolytic activity and therefore complement activity inhibition.

The date and exact time of collection must be recorded.

6.8.2. Antibodies (ADA)

Antibodies immunogenicity evaluation will be analysed for anti-drug antibody (ADA) formation to rVA576, as per schedule of events or the early termination, if applicable.

6.8.3. Medical Photography

For better assessment of skin lesions, medical photography may be performed at investigator's judgement and photographs of skin lesions may be obtained during assessment of BPDAI, new bullae and adverse events related to skin. 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 skin lesions.

6.9. Missed doses

In the event of one missed dose (defined as a dose not taken within a two-hour time window either side of the specified time) the following procedure should be adopted by the patient:

- [redacted]

In the event of more than one missed dose the CRO and the Investigator's clinic should be informed as soon as possible and the following procedure should be adopted:

- [redacted]

Inform the home care nurse or the Investigator's clinic at the next opportunity (this is important in order that extra medication can be supplied to replace the additional dose).

If [redacted] or more consecutive doses have been missed the patient's ability or willingness to comply with the protocol should be discussed and consideration should be given as to whether that subject should continue in the study. Further home care nursing support or even administration by a home care nurse may be offered to support patient compliance throughout the study if required.

6.10. Rescue Therapy

All subjects will receive topical mometasone cream or ointment up to 30 gram/ week, as maximal background therapy until Day 21, in addition to rVA576 30 mg s.c. od.
Any use of mometasone that is higher than permitted use during first 21 Days will be considered as rescue therapy.
Any use of topical mometasone after Day 21 will be considered rescue therapy.
Any use of other topical steroids, oral steroids, immunomodulators or such medications would be considered as rescue therapy.

The weight of the topical mometasone returned by the patient at each visit should be recorded in the medical notes at the clinical visits on days 7, 14 and 21.

At any time during the trial, the clinical condition of the subject may necessitate the clinician/ investigator to change or increase the background steroid therapy.
Any form of this escalation will be deemed as 'rescue therapy' and will be noted in the eCRF as a protocol deviation.
In addition, participants will be advised that they can apply a light moisturiser (emollients such as Vaseline or similar creams or ointments without any steroids) to blisters / lesions at any time during the study. This is not considered to be rescue therapy.

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:

- Difficulty ensuring the safety of subjects due to safety concerns (e.g. occurrence of many serious ADRs)
- Achieving the purpose of the study is considered impossible (e.g. inadequate recruitment of subjects)

If the study is prematurely terminated or suspended, the Sponsor should promptly inform the Investigators. The Investigator or designee should promptly inform the participating subjects and change the study medication to other appropriate therapy(ies).
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 Sponsor may prematurely terminate or suspend the study at a particular medical institution at any time during the course of the study if major violations/deviations of the protocol or other procedures has not been improved or ICH GCP has not been followed.

If the study is prematurely terminated or suspended, the Investigator or their designee should promptly inform the corresponding Ethics Committee (EC), any participating subjects, and change the study medication to another appropriate therapy. All supplies must be returned.
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.

7.2. Withdrawal Criteria

In accordance with applicable regulations, a subject 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 subject withdraw from the study, the subject will not undergo any further study-specific procedures or receive any treatment mandated by the protocol.
If a subject 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 subject 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 subject withdrawal from the study, the subject 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 subject may be withdrawn in any of the following circumstances:

- Withdrawal of consent (mandatory withdrawal)
- Intake of non-permitted concomitant medication (may be discussed with the Sponsor and dependent on the nature of the medication)
- Subject is non-compliant more than three consecutive missed doses with study procedures in the opinion of the Investigator (mandatory withdrawal)
- If discontinuation is considered necessary by the Investigator and/or Sponsor (mandatory withdrawal)
- Request of Regulatory Agency (mandatory withdrawal)
- Subject develops an illness that would compromise his participation in the study (may be discussed with sponsor)
- Patient is not achieving complete inhibition at the maximum assigned dose
- Pregnancy.

7.3. Accountability Procedures

In accordance with Good Clinical Practice (GCP), the clinical unit will account for all study medication. The clinical unit 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 subject, and the amount of unused drug returned to the Sponsor or destroyed at Sponsors 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 GCP procedures.

Subjects are required to return used and unused vials to the clinical unit. Storage bags will be provided to each subject. For all unused study medication, the subject should adhere to the storage instructions until the study medication is returned to the clinical unit.

7.4. Compliance

Reasonable levels of compliance are assumed as a condition of entry (prior enrolment in and completion of a rVA576 clinical trial). As an additional measure of compliance, all empty rVA576 vials will be returned to the Sponsor or the clinical unit. At the end of the study all vials including unused vials will be returned.

8. SAFETY REPORTING

8.1. Definitions

8.1.1. Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable 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

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 related/possibly related causal relationship to the study medication qualify as adverse drug reactions.

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. Investigator's Brochure for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

8.1.4. Serious Adverse Event (SAE) or Serious Adverse Reaction

Any untoward medical occurrence or effect that at any dose results in:

- 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 anomaly/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, convulsions, etc.

All SAEs will be reported to the Sponsor (or designee) within 24 hours of occurrence. The Sponsor (or their designee) will be responsible for reporting the SAE 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. Investigator's Brochure for an unapproved investigational product or Summary of Product Characteristics for an approved product).

8.2. Procedures for Recording of Adverse Events

8.2.1. General

All AEs occurring during the Study (from the timepoint of signing of the Informed Consent Form 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,
- 4 = life-threatening
- 5 = death

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

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 be related/possibly related to this Study.

8.2.2. Pre-existing Conditions

For purposes of this Study a pre-existing condition means a diagnose, clinically significant finding, symptom or laboratory abnormality present at baseline (Visit 1). 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

All overdoses with or without associated symptoms, should be reported as AEs on the appropriate eCRF page. An overdose is defined as dose exceeding the specified dose for each week. If sequelae meeting the criteria for a SAE have occurred in association with the overdose, the case must be reported immediately, within 24 hours. An assessment whether the overdose was accidental or intentional should be recorded. If the overdose was a suicide

attempt, this fact should be clearly stated. The AEs and SAEs that occur as a result of an overdose should be recorded on the eCRF.

8.2.4.Pregnancy

[redacted] If pregnancy is suspected, administration of the IMP must be immediately interrupted. A blood sample for serum HCG examination has to be sent to the sub-contracted laboratory. 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, the patient must be immediately withdrawn from the study. If the patient is not pregnant, use of the IMP may be restarted. All pregnancies (even if suspected) must be reported on the appropriate eCRF page (Pregnancy form) within 24 hours from the moment when the investigator got 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.

8.3. Reporting Procedures for Serious Adverse Events

Any SAE occurring during the Study has to be managed by established Standards of Care 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 out 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 center during the initiation visit, and sent by fax or e-mail to:

Fax: [redacted]
E-mail: [redacted]

The provided information shall contain as much details regarding the event as actually 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 8.2.1. 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 Ethics Committees/IRBs of the sites participating in this Study is subject 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. DATA HANDLING AND SOURCE DOCUMENTS

Subject data will be collected on eCRFs and will be substantiated by source documents at the clinical site. The eCRFs will be completed according to guidelines provided by the CRO and their SOPs. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of all study procedures, AEs and patient status.

The Investigator must maintain source documents, such as laboratory reports, complete medical history, ECG read outs and physical examination reports. All source documents should be accessible for verification by the site monitor, auditor, the EC, or for inspections by the regulatory authorities. In addition, the site will allow the Sponsor and assigned CRO direct access to all source documents and will permit trial-related auditing of clinical, pharmacy and laboratory facilities.

Direct access to these documents must be guaranteed by the Investigator or their designee, or the study coordinator, who must provide support at all times for these activities.

The nature and location of all sources of original data required to complete the eCRF will be identified by the CRO and the site staff.

The Study Monitor will perform 100% source data verification to ensure adequate quality control and assurance of subject data. An explanation of missing data must be given.

All data entered into the eCRF will be saved directly into the study database. This data will be validated both manually and programmatically. Clarification of data will be requested from the study site as requested. The database will be quality assured and will be available for statistical analysis.

Subject data will be reviewed for major protocol deviations by the Study Monitor during site visits and the entire team will review the database at timed intervals prior to the database lock.

9.1. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by sponsor and, if required, by the regulatory authority(ies), and which was given approval/favourable opinion by the IRB/IEC.

A protocol deviation to eliminate any apparent immediate hazard to a subject(s) may be implemented immediately. The sponsor and the IRB/IEC must be notified of the deviation and reason. The sponsor must be notified of all intended or unintended deviations to the protocol (e.g. inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

If a subject received at least one dose of study medication but was subsequently determined to be ineligible or to have received the wrong dose or investigational treatment, all appropriate safety and Early Termination procedures should be performed, with data collected for inclusion in the safety and efficacy analysis, as appropriate. The protocol deviation should be appropriately documented.
The Investigator should notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

10. STATISTICS

10.1. Statistical Methods

A Statistical Analysis Plan (SAP) will be prepared and finalised prior to enrolment of patients in the study. 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 summarised using the number of patients, number of missing values, mean, median, standard deviation, standard error, minimum, maximum, and 95% confidence intervals where applicable. Categorical variables will be summarized using number of patients, number of missing values, frequency counts, percentages, and 95% confidence intervals where applicable. Absolute change from baseline may be substituted with percentage change from baseline or ratio to baseline if the distribution of an individual parameter suggests this.

Baseline will be the measurement made on Day 1 immediately prior to the first ablating dose, unless this measurement is missing in which case baseline will be the most recent measurement made prior to Day 1.

Demographics and Baseline characteristics, such as Karnofsky performance status, medical history, and prior medications will be described.

Extent of exposure, compliance, concomitant medications, and use of rescue therapy will be described.

10.1.1. Primary Analysis

Adverse events (AEs) of grade 3, 4 and 5 which have been assigned a causal relationship to rVA576 of 'related/possibly related' and have occurred during the treatment period will be considered in the analysis of the primary safety outcome. The primary endpoint will be analysed in terms of the proportion of subjects reporting safety events. The proportion of patients experiencing such AEs will be reported with its associated Clopper-Pearson (exact) 95% confidence interval.

10.1.2.Secondary Analysis

- Bullous Pemphigoid Disease Area Index score (BPDAI)

The mean observed values and absolute mean change from Baseline in BPDAI activity scores and BPDAI pruritus index will be plotted over time and summarised with their associated 95% confidence interval using t-distributions.

The proportion of patients whose BPDAI activity score decreases by 4 or more points between baseline and Day 42, and the proportion of patients whose BPDAI activity score increases by 3 or more points between baseline and Day 42 will also be described.

- DLQI - TABQOL

The observed values and absolute change from Baseline in Quality of life scores will be summarised and plotted over time.

10.1.3. Additional Analyses

• BPDAI

The percentage change from Baseline in BPDAI activity scores will be calculated for each patient and plotted overtime. The mean percentage change in BPDAI activity score at Day 42 compared to baseline will be presented with its associated 95% confidence interval. The proportion of patients who achieve a reduction in BPDAI activity score of at least 50% (and 75%) at Day 42. The time to achieve such reductions will also be described.

The BPDAI global score and BPDAI damage score will also be summarized with observed values and absolute change from Baseline summarised and plotted over time. Results may also be presented separately for patients who completed the treatment period with and without using any rescue therapy

The proportion of subjects with Disease control at Day 21 (defined as the absence of new bullae for 3 consecutive days) and at Day 42 will be described.

For BP 180, BP 230 antibody titres, and LTB_4, the mean observed values and change from Baseline will be plotted and summarised overtime. Spaghetti plots (individual line plots) over time, will be produced.

• ADA

[redacted]

• PK and PD

PK parameters will be analyzed using summary statistics and lines and mean plots as appropriate for both ablation and maintenance treatment period.

PD parameters will be analyzed using summary statistics and graphical displays such as waterfall plots and line plots as appropriate.

• Skin biopsy

[redacted]

Other efficacy endpoints not listed above will be summarised as indicated above depending on whether its outcome measure is a continuous or categorical variable.

10.1.4. Safety Analyses

10.2. Number of Patients

A maximum of 9 patients will be enrolled. The sample size for this study was determined based on practical, and not statistical, considerations.
The Sponsor reserves the right to review accruing safety and efficacy data from the study as a management aid to assist in conduct of the current study and the design of future studies.

10.3. Significance Level

There will be no statistical testing in the study. Analyses will be purely descriptive with no hypothesis testing and no multiplicity adjustment will be introduced.

10.4. Missing, Unused or Spurious Data

Missing data that cannot be retrieved from source records or other repositories will be recorded as such in the eCRFs and presented as missing in 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.

10.5. Deviation from the Statistical Analysis Plan

It is not envisaged that there should be any deviations from the SAP. Any unexpected deviations (e.g. a requirement for a trend analysis not foreseen in planning the trial) will be discussed with regulatory agencies and the rationale for such an analysis will be included in the SAP, or SAP amendment and Final Study Report.

10.6. Subjects to be Included in the Statistical Analysis

Two populations will be considered in the analysis:

Safety Analysis Set: This population will be defined as all subjects who received at least one dose of rVA576. This will be the primary population for assessing safety and efficacy.

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.

11. QUALITY CONTROL AND ASSURANCE

The hospitals/departments taking part in the trial are responsible for maintaining their own SOPs and QA/QC procedures. The Sponsor or their delegate will also implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) to ensure that the study is conducted and data are generated, documented and reported

in compliance with the protocol and ICH GCP and all applicable regulatory requirements. The Sponsor or delegate will be responsible for monitoring the trial and carrying out 100% source data verification.
The study will be in accordance with the provisions of the Declaration of Helsinki and all revisions thereof, in accordance with ICH GCP and as required by applicable regulatory requirements.
Any necessary training for the study will be provided to Investigators and study personnel by the Sponsor or their designee prior to study initiation.

12. ETHICAL CONDUCT OF THE STUDY

12.1. Ethical Considerations and EC Approval

The study will be conducted in accordance with all appropriate regulatory requirements and under an approved protocol. The study will be conducted in accordance with current ICH GCP, all appropriate patient privacy requirements and the ethical principles outlined in the Declaration of Helsinki.

12.2. Subject Confidentiality

The investigators and the sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The investigator must ensure that the subject's anonymity is maintained. On the electronic case report forms (eCRFs) or other documents submitted to the sponsor or designee, subjects should be identified by a unique subject identifier as designated by the sponsor. Documents that are not for submission to the sponsor or designee (eg, signed informed consent forms [ICF]) should be kept in strict confidence by the investigator.

In compliance with applicable regulations and ICH GCP guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the independent ethics committee (IEC) or institutional review board (IRB) direct access to review the subject's original medical records for verification of study-related procedures and data. The investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the subject.

13. FINANCING, INDEMNITY AND INSURANCE

The Sponsor will have a commercial contract in place with the CRO and the hospitals/universities will be responsible for any payments to subjects for payment of travel and other expenses reimbursable by the Sponsor on delivery of receipts.
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. Provision is made for (1) The indemnity or compensation in the event of injury or death attributable to the clinical trial and (2) Insurance or indemnity to cover the liability of the Investigator or Sponsor
Akari Therapeutics Plc will indemnify the Investigators from all or any claims arising out of this study except for their negligence or malpractice and providing that the study is conducted according to the standards established by the protocol.

In the event that it can be demonstrated that a subject suffers any significant deterioration in health or well-being or any harmful susceptibility or toxicity as a direct result of their participation in this study then Akari Therapeutics Plc will agree to abide by the current Association of the British Pharmaceutical Industry (BPI) Guidelines with regard to compensation payable to the subject residing in the UK. The amount of compensation will be calculated by reference to the level of damages commonly awarded according to local law for similar injuries occurring in subjects residing outside the UK.

14. PUBLICATION POLICY

The key design elements of this protocol will be posted in a publicly accessible database.
The CRO has no independent publication rights.
Akari Therapeutics Plc actively encourages publication of clinical trial data in reputable peer reviewed journals. Authorship will be discussed and agreed in advance. If the Investigator drafts a publication, he/she agrees to send it to Akari Therapeutics Plc for review and comment before its submission to the journal. In cases where Akari Therapeutics Plc considers that the proposed publication contains information which should be protected as valuable confidential information or is out of compliance with applicable laws and regulations, Akari Therapeutics Plc reserves the right to delay submission for publication, until the required deletion of the confidential information from the proposed publication has been done.

15. STUDY RECORD RETENTION

The Investigators shall ensure that the documents contained in the Investigator Site File are retained for 25 years after the conclusion of the trial. The Sponsor shall ensure that the documents contained in the Trial Master File are retained for 25 years after the conclusion of the trial. The Sponsor and Investigators will ensure that during this period the files are complete, legible and readily available to the licensing authority on request.
All data derived from the study will remain the property of Akari Therapeutics Plc.
All correspondence (e.g. with the Sponsor, or designee, Ethics Committee) relating to this study should be kept in the appropriate files. Records of subject's source documents, eCRF's, IMP inventory pertaining to the study must be kept on file.
If the Investigator moves, withdraws from the study or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

15.1. Clinical Study Report

The results of this clinical study must be summarised by the Sponsor (or designee) and a final audited report must be retained on file. This report will include discussions on the study objectives, methodology, findings and conclusions. The PI(s) will be asked to review and comment on the draft report and the Chief Investigator will be required to sign the final version. All Investigators will be provided with a final copy of the Clinical study report. The report must be archived with all other study documents.

15.2. Handling and retention of blood and pathological samples

Samples should be handled according to the instructions provided in the Laboratory Manual. The duration of retention of blood and pathological samples will be in accordance with details provided in the patient information leaflet and agreed to by signing the ICF.

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17. APPENDICES

- Appendix A : DLQI
- Appendix B: TABQOL
- Appendix C: BPDAI
- Appendix D: BPDAI Pruritus Index
- Appendix E: World Health Organization Classification of topical Corticosteroids
- Appendix F: Karnosksy Performance Status

APPENDIX A: DLQI questionnaire

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

Appendix B : TABQOL

Tjokrowidjaja A, Daniel BS, Frew JW, Sebaratnam DF, Hanna AM, Chee S, Dermawan A, Wang CQ, Lim C, Venugopal SS, Rhodes LM, Welsh B, Nijsten T, Murrell DF.
Br J Dermatol. 2013 Nov;169(5):1000-6.

1. As a result of your blistering disease treatment, do you notice you bruise or bleed easily?	I notice this all the time I notice this a lot I notice this sometimes I have not had this problem
2. As a result of your blistering disease treatment, can you still tolerate hot or cold temperatures?	I am very sensitive to changes in temperature I am sometimes sensitive to changes in temperature I am occasionally sensitive to changes in temperature I have not had this problem
3. Do you have to take your medications for your blistering disease at a specific time?	Yes it is very frustrating – I have to change my meal times and/or sleeping patterns Yes it is a little annoying Yes however I do not mind No
4. Do you take many medications for your blistering disease?	Yes, it is very frustrating Yes, it is quite annoying Yes, but I do not mind No
5. Does the treatment for your blistering disease result in you feeling bloated?	All the time A lot of the time Some of the time Not at all
6. Does the treatment for your blistering disease make it difficult to walk?	All the time A lot of the time Some of the time Not at all
7. As a result of your blistering disease treatment, can you think as quickly or as clearly as you used to?	No, it is very frustrating No, it is quite annoying No, but I do not mind Yes, I do not have this problem
8. Do you find your blistering disease treatments very time-consuming?	Yes, it is very frustrating Yes, it is quite annoying Yes, but I do not mind No
9. Do you mind the needles or blood tests involved in the treatment of your blistering disease?	Yes, I really hate and dread every needle Yes, I dislike needles Yes, I sometimes worry about it No, I Never worry about it
10. Do you worry your blistering disease will get worse when you drop the dosages of your medications?	Yes, I worry about it all the time Yes, I worry about it a lot Yes, I sometimes worry about it No, I never worry about it
11. Do you worry about your blistering treatment being dangerous?	I worry all the time about side effects I sometimes worry about side effects I occasionally worry about side effects I never worry about it
12. Do you feel tired and lethargic as a result of the treatment for your blistering disease?	All the time A lot of the time Some of the time Not at all
13. Do you worry about getting sick (with the flu, etc) due to your depressed immunity because of the treatment for your blistering disease?	Yes, I worry about it all the time Yes, I worry about it a lot Yes, I sometimes worry about it No, I never worry about it
14. As a result of your blistering disease treatment, have you stopped doing many activities to avoid getting sick?	Yes, I no longer do any of the activities I enjoy Yes, I cannot do many of the activities I enjoy Yes, I cannot do some of the activities I enjoy No, I can still do everything I enjoy
15. Do you have nightmares or bad memories as a result of your blistering disease treatment?	All the time A lot of the time Some of the time Not at all
16. Does your blistering disease treatment affect your holidays?	I cannot go on holidays anymore – it is too tiring and inconvenient Going on holidays is difficult Going on holidays is a little harder than before My blistering disease does not affect me going on holidays at all
17. Is your blistering disease treatment giving you financial difficulties?	Yes, I cannot afford my treatment Yes, I have had to make major changes in spending Yes, I have had to make some small changes in spending No

Please indicate the time taken to finish the survey: _____ minutes _____seconds

APPENDIX C: Bullous Pemphigoid Disease Activity Index

BPDAI					
SKIN	ACTIVITY		ACTIVITY		DAMAGE
Anatomical location	Erosions/Blisters	Number of Lesions if <3	Urticaria/ Erythema / Other	Number of Lesions if <3	Pigmentation / Other
	0 absent		0 absent		Absent 0, present 1
	1 1-3 lesions, none > 1 cm diameter		1 1-3 lesions, none >6 cm diameter		
	2 1-3 lesions, at least one > 1 cm diameter		2 1-3 lesions, at least one lesion > 6 cm diameter		
	3 >3 lesions, none > 2 cm diameter		3 >3 lesions, or at least one lesion > 10 cm		
	5 >3 lesions, and at least one >2 cm		5 >3 lesions and at least one lesion > 25 cm		
	10 >3 lesions, and at least one lesion >5 cm diameter or entire area		10 >3 lesions and at least one lesion > 50 cm diameter or entire area		
Head					
Neck					
Chest					
Left arm					
Right arm					
Hands					
Abdomen					
Genitals					
Back/Buttocks					
Left leg					
Right leg					
Feet					
Total skin	/120		/120		
MUCOSA	Erosions/Blisters				
	1 1 lesion				
	2 2-3 lesions				
	5 >3 lesions, or 2 lesions >2cm				
	10 entire area				
Eyes					
Nose					
Buccal mucosa					
Hard palate					
Soft palate					
Upper gingiva					
Lower gingiva					
Tongue					
Floor of Mouth					
Labial Mucosa					
Posterior Pharynx					
Anogenital					
Total Mucosa	/120				

Murrell et al Definitions and outcome measures for bullous pemphigoid: Recommendations by an international panel of experts. J Am Acad Dermatol. 2012 Mar;66(3):479-85

APPENDIX D: Bullous Pemphigoid Disease Activity Index: Pruritus Component-VAS

BPDAI PRURITUS COMPONENT - VAS

DATE: ……..

☐ **Baseline**	☐ **Beginning Consolidation**
☐ **Consolidation phase**	☐ **End of Consolidation**
☐ **Tapering phase**	☐ **Partial remission on minimal therapy**
☐ **Complete remission on minimal therapy**	☐ **Partial remission off therapy**
☐ **Complete remission off therapy**	☐ **Flare**

A. How severe has your itching been over the last 24 hours?

0 1 2 3 4 5 6 7 8 9 10
None Severe

Score out of 10 =

B. How severe has your itching been the past week?

0 1 2 3 4 5 6 7 8 9 10
None Severe

Score out of 10 =

C. How severe has your itching been in the past month?

0 1 2 3 4 5 6 7 8 9 10
None Severe

Score out of 10 =

Average INTENSITY SCORE FOR PAST MONTH = (A+B+C) = /30

OR

For BP patients with impaired mental functioning:

	No evidence of itch (no excoriations)	0
	Mild itch (isolated excoriations up to two body sites)	10
	Moderate itch (excoriations on ≥ 3 body sites, impairment of daily activity	20
	Severe itch (generalized excoriation, sleep impairment)	30
	TOTAL SCORE	/30

Murrell et al Definitions and outcome measures for bullous pemphigoid: Recommendations by an international panel of experts. J Am Acad Dermatol. 2012 Mar;66(3):479-85

APPENDIX E: WORLD HEALTH ORGANIZATION CLASSIFICATION OF TOPICAL CORTICOSTEROIDS

Potency	Group	Name
Ultra-high	I	Clobetasol propionate cream (0.05%) Diflorasone diacetate ointment (0.05%)
High	II	Amcinodine ointment (0.1%) Betamethasone dipropionate ointment (0.05%) Desoximetasone (cream or ointment) (0.025%) Fluocinonide (cream, ointment, or gel) (0.05%) Halcinonide cream (0.1%)
	III	Betamethasone dipropionate cream (0.05%) Betamethasone valerate ointment (0.1%) Diflorasone diacetate cream (0.05%) Triamcinolone acetonide ointment (0.1%)
Moderate	IV	Desoximetasone cream (0.05%) Fluocinonide acetonide ointment (0.025%) Hydrocortisone valerate ointment (0.2%) Triamcinolone acetonide cream (0.1%)
	V	Betamethasone dipropionate lotion (0.02%) Betamethasone valerate cream (0.1%) Fluocinonide acetonide cream (0.025%) Hydrocortisone butyrate cream (0.1%) Hydrocortisone valerate cream (0.2%) Triamcinolone acetonide lotion (0.1%)
Low	VI	Betamethasone valerate lotion (0.05%) Desonide cream (0.05%) Fluocinolone acetonide solution (0.01%)
	VII	Dexamethasone sodium phosphate cream (0.1%) Hydrocortisone acetate cream (1%) Methylprednisolone acetate cream (0.25%)

Appendix F: KARNOFSKY PERFORMANCE STATUS

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

References:

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Summary of Amendments to the Originally Approved Protocol AK801 Version 1.0

Protocol Amendment (non-substantial) 23rd March 2018 - Protocol Version 2.0 (The Netherlands only)

- Update to the home care nursing solution - home care nurses were not to perform administration of IMP
- Dapsone added as prohibited medication
- Mometasone wording updated - new tubes to be supplied at each visit and tubes including empty tubes from previous visit to be returned

Protocol Amendment 1 (24th April 2018) - Protocol Version 1.1 (Germany only)

- Changes in the inclusion criteria related to contraception and pregnancy testing recommendations to comply with German legislation.
- Addition of text to record use of rescue therapy (mometasone, or any use of other topical steroids, oral steroids, immunomodulators or such medications).
- Addition of text within exclusion criteria about suspected drug induced BP
- Additional exploratory endpoint added to the protocol by recording the use of topical steroids and rescue medications.

Protocol Amendment 2 (26th April 2018) - Protocol Version 3.0 (The Netherlands only)

- Removal of text in additional endpoint as it was already defined in disease control.
- Modification of the responsibilities of the home nurse vendor within the trial population and missed dose sections.
- More clarification added for the patient's medication and rescue therapy.
- Vital signs section amended to be consistent with the rest of the protocol.
- Removal of non-validated quality of life questionnaire.
- Clarification of physical examination assessments.

Protocol Amendment (non-substantial) (18th May 2018) - Protocol Version 1.2 (Germany only)

- Further changes relating to contraception and pregnancy testing recommendations to comply with German legislation.

Protocol Amendment 3 (16th August 2018) - Protocol Version 4.0 (Germany & The Netherlands)

- To allow patients help with dosing at home, if required.

Protocol Amendment 4 (8th May 2019) - Protocol Version 5.0 (Germany & The Netherlands)

- To allow enrolment of patients receiving systemic treatment for the current episode of BP, provided current treatment was stopped before Day 1.
- Change of exclusion criterion from 'oral' steroids to 'systemic' steroids.
- To allow patient visits to be conducted at home by suitable staff, to decrease patient burden.
- Inclusion Criteria: Clarification added for patients with disability.
- Addition of disease control assessment at Baseline, any unscheduled and follow-up visits.
- Addition of global BPDAI and Visual Analogue Pruritus assessments at follow-up visit.

CONFIDENTIAL

AKARI
THERAPEUTICS

STATISTICAL ANALYSIS PLAN

A Phase IIa open label single arm study of safety and efficacy of rVA576 in adult mild to moderate Bullous Pemphigoid subjects

Drug Name:	**Coversin**
Study Number:	**AK801**
EudraCT Number:	**2017-002836-18**
Name of Sponsor:	**Akari Therapeutics Plc**
Address:	**75-76 Wimpole Street** **London W1G 9RT** **UK**
Protocol Version (Date):	**Protocol Version 5.0 DE and NL (8 May 2019)**
SAP Version:	**Final v2.0**
SAP Date:	**6 November 2019**

SAP SIGNATURE PAGE

STUDY TITLE: A Phase IIa open label single arm study of safety and efficacy of rVA576 in adult mild to moderate Bullous Pemphigoid subjects

We, the undersigned, have reviewed and approved this statistical analysis plan.

Signature	Date
[redacted] Consultant Statistician, [redacted]	
[redacted] Clinical Project Manager Akari Therapeutics Plc	
[redacted] Medical Director Akari Therapeutics Plc	
[redacted] Chief Scientific Officer Akari Therapeutics Plc	

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADA	Anti-drug Antibodies
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BP	Bullous Pemphigoid
BPDAI	Bullous Pemphigoid Disease Area Index
CFB	Change from baseline
CH50	Classical haemolytic 50% lysis
CH50 U Eq/ml	Classical haemolytic 50% lysis units equivalent / ml
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
LLN	Lower limit of normal
LOCF	Last Observation Carried Forward
LTB_4	Leukotriene B4
MedDRA	Medical Dictionary for Regulatory Activities
MCID	Minimal Clinically Important Difference
PD	Pharmacodymanics
PK	Pharmacokinetics
SAE	Serious adverse event
SAP	Statistical analysis plan
SDTM	Study Data Tabulation Model
TABQOL	Treatment of Autoimmune Bullous Disease Quality of Life
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

1 Introduction

This document provides a description of the statistical methods and procedures to be implemented for the analysis and reporting of data from the Akari Therapeutics study with protocol number AK801. Any deviations from this Statistical Analysis Plan (SAP) after the database lock will need to be substantiated by sound statistical rationale and will be documented in the final clinical study report (CSR).

This SAP is based on Global Clinical Study Protocol Version 5.0, dated 08 May 2019, and is an amendment to the initial SAP version 1.0 dated 15 May 2018. Changes between version 1.0 and this version 2.0 of the SAP are described briefly in Appendix 2.

2 Study Objectives and Study Design

2.1 Study Objectives

The study objectives, as specified in section 4 of the protocol, are as follows:

2.1.1 Primary Objective

The primary objective of the study is to assess the safety of rVA576 in adult subjects with mild to moderate bullous pemphigoid (BP).

2.1.2 Secondary Objectives

The secondary objective of this study is to assess the efficacy of rVA576 and its effect on the quality of life of adult subjects with mild to moderate BP.

2.2 Study Design

This is an open label, single arm study in up to 9 patients with newly diagnosed or relapsing BP, who meet the inclusion and exclusion criteria, as defined in Section 5.1 and 5.2 of the protocol.

Table 1: Schedule of Events and Blood Draws for AK801 Screening to Day 72

	Screening	60mg followed by 30 mg 12 hr later Day 1	Day 7 (±1 day)	30 mg once daily										
				Day 14 (±1 day)						Day 21 (±1 day)	Day 28 (±1 day)	Day 42 (±1 day)	Day 72	Unscheduled[10]
	Up to Day-14	Pre-dose	Pre-dose	Pre-dose	3h	6h	9h	12h	18h	Pre-dose	Pre-dose	Study End Early Termination	Follow-up Visit	(if needed at any time)
Eligibility, ICF & Medical History & Demographics	x													
Physical Examination[1]	x	x	x	x						x	x	x	x	x
ECG	x	x	x	x						x	x	x		x
Nasal & Throat Swabs[2]	x													
Vital Signs[3] (including height & weight)	x	x	x	x						x	x	x	x	x
CH50 (PD)		x*	x*	x*	x*	x*	x*	x*	x*	x*		x*	x*	x*
rVA576 Drug Level (PK)		x*	x*	x*	x*	x*	x*	x*	x*	x*		x*	x*	x*
Antibodies (ADA)		x*	x*	x*						x*		x*	x*	x*
LTB4		x*	x*	x*				x*		x*		x*	x*	x*
Total C5		x*	x*	x*						x*		x*	x*	x*
Chemistry & Haematology[4]	x	x	x	x						x	x	x	x	x
Urinalysis – Pregnancy Test[5]	x	x	x	x							x	x	x	x
DLQI- TABQOL	x									x		x		x
Assessment of disease control		x	x	x						x	x	x	x	x
Bullous Pemphigoid Disease Area Index (BPDAI)	x	x	x	x						x	x	x	x	x
Meningitis prophylaxis[6]	Vaccine	Antibiotics/Vaccine as per site schedule												
Drug Accountability			x	x						x	x	x		x
AEs & Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Karnofsky Performance Status[7]	x													
Visual Analogue Scale PRURITUS	x	x	x	x						x	x	x	x	x
BP180 & BP230 Antibody Titres	x*									x*		x*		
Skin Biopsy[8] and Immunofluorescence [9]	x*											x*		

* Central Labs

(1) Physical Examination – Inclusive of injection site inspection.

(2) Nasal & Throat swabs - All patients selected for entry into this trial will have throat and nasal swabs taken once they have consented. Any positive Neisseria sp. results will exclude that patient from the trial. Repeat throat and nasal swabs during the screening period are allowed at weekly intervals. If the organism has been eradicated before planned Day 1 patient can be included.

(3) Vitals – Diastolic and Systolic blood pressure, pulse rate and oral temperature (weight only required at Screening, Day 21 and Day 42 and height is only required at Screening).

(4) Serum Pregnancy test will be performed at screening and end of treatment Day 42 or early termination.

(5) A urine pregnancy test should be performed at Day 1, Day 28, follow up and unscheduled.

(6) [redacted]

(7) The patient with disability can be included in the study on the investigator's judgement if the score is ≥ 60

(8) Diagnostic skin biopsy may be used for this study as baseline unless it is older than 1 month in which case it will need to be repeated. At the end of treatment or early termination skin biopsy should be performed in the same area as the diagnostic biopsy area. It should be a peri-lesional tissue specimen for DIF examination.

(9) Immunofluorescence studies should be performed on perilesional skin, approximately 1cm away from the skin lesion. It is considered positive when showing linear deposition of IgG and / or C3 along the basement membrane zone.

(10) The patient may attend the study centre for unscheduled visit in case of new lesions after obtaining disease control, between day 42 and day 72 for the disease status assessment or other reasons (e.g. missed blood sample, missed assessment)

2.3 Study Endpoints

2.3.1 Primary Endpoint

Proportion of participants reporting grade 3, 4 and 5 adverse events, which are related/possibly related to rVA576 during the treatment period.

The Common Terminology Criteria for Adverse Events (CTCAE v4.03) will be used to grade adverse events. At each study visit, participants will be questioned about adverse events they have experienced since the last study visit.

2.3.2 Secondary Endpoints

The secondary efficacy endpoints of this study are the following:

- Mean absolute change in BPDAI activity scores between Day 1(baseline) and Day 42
- Proportion of patients whose BPDAI activity score decreases by 4 or more points between baseline (Day1) and Day 42.
- Proportion of patients whose BPDAI activity score increases by 3 or more points between baseline (Day1) and Day 42.
- Mean absolute change in BPDAI pruritus index between Day 1 (baseline) and Day 42
- Mean Change in Dermatology Life Quality Index (DLQI) between baseline (Day 1) and Day 42
- Mean Change in Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL) between baseline (Day 1) and Day 42

2.3.3 Additional Endpoints

- Percentage change in BPDAI activity scores between baseline (Day1) and Day 42
- Proportion of patients who achieve a reduction in BPDAI activity score of at least 50%, at Day 42
- Proportion of patients who achieve a reduction in BPDAI activity score of at least 75% at Day 42
- Time to achieve 50% reduction in BPDAI activity score from Baseline (Day 1)
- Time to achieve 75% reduction in BPDAI activity score from baseline (Day 1)
- Proportion of subjects with Disease control at Day 21
- Proportion of subjects with Disease control at Day 42
- Percentage change in BP 180 antibody titre at Day 42 compared to baseline (Day 1)
- Percentage change in BP 230 antibody titre at Day 42 compared to baseline (Day 1)
- Change in the perilesional skin biopsy parameters at Day 42 compared to baseline (Day 1).
- PK (unbound rVA576) and Pharmacodymanics (PD terminal complement activity measured by CH50 U Eq/mL) parameters during ablation and maintenance phases of treatment

- Use of topical steroids and rescue medications
- Change in Leukotriene B4 (LTB_4) level in serum between baseline (Day 1) and Day 42
- Proportion of subjects with positive Anti-drug antibody at Day 42.
- Treatment emergent adverse events (TEAEs);
- Change from baseline in physical examination
- Electrocardiogram (ECG)
- Clinical laboratory tests
- Vital signs

3 Efficacy and Safety Variables

3.1 Screening and Baseline

Written informed consent will be obtained before any study procedures are performed. The following procedures will be performed exclusively at the Screening visit:

3.1.1 **Medical History**

Medical conditions (including laboratory values and/or vital signs that are out of range and found clinically significant) that exist prior to Informed Consent will be recorded as part of medical history.

A complete medical history will include evaluation (past and present) of the following:

General	Heart / cardiovascular
Chest / respiratory	Dermatological / skin
Past (or plans for future) surgeries	Alcohol use or Substance abuse
Neurological/ Psychiatric	Haematological / lymphatic
Abdominal/Urogenital	Endocrine / metabolic
Medications	Smoking
Allergies / drug sensitivities	

All medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 19.0.

3.1.2 **Demographics**

Demographic information (date/year of birth, age, sex, ethnicity and race) will be collected at Screening. Karnofsky Performance status, nasal and throat swab, smoking status and alcohol/substance use and chilbearing potential will also be collected.

3.1.3 **Eligibility**

Evaluation of the study inclusion/exclusion criteria will be assessed at Screening.

3.2 Efficacy Measurements and Variables

3.2.1 Bullous Pemphigoid Disease Area Index

The BPDAI will be performed at screening and pre-dose on Day 1 and at every visit (scheduled and unscheduled) until the Follow-up visit (Day 72). The global BPDAI is composed of 2 scores: total BPDAI activity and total BPDAI damage.

- The total BPDAI activity score is the arithmetic sum of the 3 subcomponents – cutaneous blisters/ erosions, cutaneous urticaria/erythema, and mucosal blisters/ erosions.
- The total BPDAI damage score is the arithmetic sum of the items rated regionally for damage caused by more permanent features such as post-inflammatory hyperpigmentation, scarring and other. BPDAI quantifies lesion number and size thresholds. Lesions are rated based on the regions affected. BPDAI gives additional weighting to areas of the skin primarily affected in BP, such as the limbs, and less emphasis to scalp and face, to better differentiate clinical response in BP.

The global BPDAI score can range from 0 to 372. For BPDAI activity up to 360 (maximum 240 for total skin activity and 120 for mucosal activity), and 0 to 12 for BPDAI damage, with higher scores indicating greater disease activity or damage.

BPDAI also has a separate subjective measure known as BPDAI-pruritus Index. The BPDAI pruritus component is based on a visual analogue scale, measuring the severity of itch during the past 24 h (0–10), the past week (0–10) and the past month (0–10) with a total score of 30.

The current AK801 study aims to use BPDAI for identification of mild to moderate BP patients. A global BPDAI minimum cut off of 10 and maximum of 56 (based on research by Levy-Sitbon 2014 et al) will be used to exclude severe BP. A reduction of 4 points in BPDAI activity score as a minimal clinically important difference (MCID) for improvement and an increase of 3 points as an MCID for disease worsening will be used.

The pre-dose Day 1 assessment will be regarded as the Baseline value. If the Day 1 assessment is unavailable then the value from the Screening assessment will be used as Baseline.

The BPDAI activity score will be calculated at each visit. Given the novelty of this endpoint, both the absolute change from Baseline and the percentage change from Baseline will be calculated. This will allow identification of patients with a 50% reduction (and 75% reduction) from the Baseline value.

The BPDAI pruritus index, BPDAI global score and BPDAI damage score will also be calculated at each visit, with their absolute change from Baseline.

The scores will be calculated at each visit, provided that all items are available. Every effort will be made to collect all items and calculate the scores, however, it is possible that some items remain missing. Given the novelty of these endpoints, sensitivity analyses will be produced using a last observation carried forward (LOCF) approach. In these analyses, any item that is missing will be imputed by carrying forward the previous result for this item, as long as it was measured post-baseline. Imputation will only be applied during the treatment period, i.e. no imputation will be performed if Day 72 is missing,

3.2.2 **DLQI**

The DLQI will be performed at screening, Day 21 and Day 42. The screening assessment will be regarded as the Baseline value. The DLQI score will be calculated at each visit, provided that no more than 1 answers are missing or 'not done' in the questionnaire. The absolute change from Baseline will also be calculated. The LOCF approach, as described in Section 3.2.1, will also be applied to items in the DLQI questionnaire, if the DLQI score was not calculated due to more than 1 missing answer.

3.2.3 **TABQOL**

The TABQOL will be performed at screening, Day 21 and Day 42. The screening assessment will be regarded as the Baseline value. The TABQOL score will be calculated at each visit, provided that all answers are available in the questionnaire. The absolute change from Baseline will also be calculated. The LOCF approach, as described in Section 3.2.1, will also be applied to items in the TABQOL questionnaire.

3.2.4 **Disease control**

This will be assessed by the PI/designee at all applicablevisits when the PI does the BPDAI calculation, by asking the subject if they have noticed any new lesions form over last 3 days and note down the numbers of new lesions if developed. The PI will also assess if healed lesions have developed into new lesions and whether existing lesions are considered healed (yes/no). Subjects with Disease control at Day 21 and at Day 42 will be identified.

3.2.5 **LTB_4**

LTB_4 will be used to collect information on the effect of rVA576. LTB4 levels in serum will be collected pre-dose at Day 1, Day 7, Day 14 (pre-dose and 12h post-dose), Day 21 and Day 42 or the early termination visit, if applicable, and at the Follow-up visit (Day 72), and analysed in the Central Laboratory.

LTB_4 analyses may be performed at a later stage and results reported separately from the main CSR.

3.2.6 **BP180 and BP230 antibody titres**

BP antigen 180 and BP antigen 230 antibody titres levels will be collected at screening, Day 21 and Day 42 or the early termination visit, if applicable, and analysed in the Central Laboratory.

The screening assessment will be regarded as the Baseline value. The percentage change from Baseline to each subsequent assessment will be derived.

3.2.7 **Skin biopsy**

A skin biopsy will be performed at screening to establish diagnosis and obtain a baseline

[redacted]

3.3 Safety Measurements and Variables

3.3.1 Adverse Events

All clinical AEs occurring after the subject has signed the ICF and after the last dose of study medication (i.e. the follow-up period), whether observed by the Investigator or reported by the subject, will be recorded on the AE Electronic Case Report Form (eCRF) page. The following details will be reported for each adverse event:

- Name
- Start and stop dates
- Severity, using CTCAE grading:
  - Mild
  - Moderate
  - Severe
  - Life-threatening
  - Death
- Relationship with the investigational product:
  - Unrelated
  - Possibly Related
  - Related
- Serious:
  - Yes
  - No

  - Action taken with study treatment (rVA576)
  - Dose not changed
  - Dose reduced
  - Drug interrupted
  - Drug withdrawn
  - Not applicable
  - Unknown
  - Other
- Outcome
  - Fatal
  - Not recovered/not resolved
  - Recovered/resolved
  - Recovered/resolved with sequelae
  - Recovering/resolving
  - Unknown

If the AE was judged serious, additional data will be recorded such as: whether the AE caused study discontinuation, caused death, was life threatening, was in-patient hospitalisation or prolonged hospitalisation, was persistent or significant disability/incapacity, congenital abnormality or birth defect.

Adverse events will be coded using MedDRA.

Treatment emergent adverse events (TEAEs) will be defined as any adverse event with a recorded start date/time on or after the date/time of start of study medication. AEs with partial start dates or times will be evaluated for treatment-emergent status using all available start date/time information. If the available incomplete start date/time information is insufficient to determine treatment-emergent status then the AE will be assumed to be a TEAE.

3.3.2 Physical Examination

A physical examination, covering the following aspects, will be performed at Screening and repeated on Day 1, 7, 14, 21, 28, 42 and the Follow-Up assessment Day 72 and any unscheduled visits: clinical evaluations of the cardiovascular, respiratory, endocrinology, neurology, gastrointestinal, dermatological, ophthalmic, blood and lymphatic, extremities, and musculoskeletal system... If the result is abnormal or clinically significant at screening, the corresponding condition will be recorded in the medical history. If the overall interpretation is abnormal and clinically significant at any subsequent visits, the corresponding condition will be recorded as an adverse event.

3.3.3 Clinical Laboratory Samples (Local Laboratories)

All samples will be collected at the time of Screening, Day 1, Day 7, Day 14, Day 21, Day 28, Day 42 and Follow-up visit (Day 72). All clinical laboratory safety tests (haematology, chemistry and urinalysis) will be performed locally by each clinical unit.

<u>Haematology</u>

- White blood cell count [10^9/L]
- Red blood cell count [10^12/L]
- Haemoglobin [g/L]
- Haematocrit [%]
- Mean corpuscular volume [fL]
- Mean corpuscular haemoglobin [pg]
- Mean corpuscular haemoglobin concentration [g/L]
- Platelets [10^9/L]
- Neutrophils absolute [10^9/L] and %
- Lymphocytes absolute [10^9/L] and %
- Monocytes absolute [10^9/L] and %
- Eosinophils absolute [10^9/L] and %
- Basophils absolute [10^9/L] and %
- C-reactive protein [nmol/L]

<u>Chemistry</u>

- Sodium [mmol/L]

- Potassium [mmol/L]
- Glucose (random) [mmol/L]
- Alkaline phosphatase [U/L]
- Alanine aminotransferase [U/L]
- Bicarbonate [mmol/L]
- Urea [mmol/L]
- Aminotransferase [U/L]
- Creatine kinase [U/L]
- Total Bilirubin [µmol/L]
- Chloride [mmol/L]
- Albumin [g/L]
- Calcium [mmol/L]
- Gamma-glutamyl transpeptidase [U/L]
- Bilirubin (Direct) (only if Total is elevated) [µmol/L]
- Phosphate (Inorganic) [mmol/L]
- Total protein [g/L]
- Serum Creatinine [µmol/L]

For each of the haematology, chemistry, and renal function parameters, values from the locally reported laboratory will be converted to the standardised units shown in parenthesis during statistical programming of the Study Data Tabulation Model (SDTM) datasets.

Urinalysis

- Leukocytes [/µl]
- Bilirubin [negative/positive]
- Glucose [mg/dl]
- pH
- Microbiology
- Urine microscopy
- Ketones
- Nitrates [negative/positive]
- Blood [/µl]
- Specific gravity [g/l]
- Urobilinogen [negative/positive]
- Urine protein [mg/d]

Urine pregnancy test data will be listed.

Out-of-range laboratory data will be flagged as low or high according to gender and laboratory specific normal ranges. Interpretation of the laboratory data will be performed by the investigator and reported as normal, abnormal clinically significant or abnormal not clinically significant.

The pre-dose Day 1 assessment will be regarded as the Baseline value for each laboratory parameter. If the Day 1 assessment is unavailable then the value from the Screening assessment will be used as Baseline. The change from Baseline to each subsequent laboratory assessment will be derived for each of the continuous laboratory parameters.

3.3.4 Vital Signs

Vital signs, comprising systolic and diastolic blood pressure measurements, pulse rate. respiratory rate, and body temperature, will be measured at Screening and also repeated pre-dose on Day 1, 7, 14, 21, 28, 42, Follow-Up visit (Day 72) and any unscheduled visits. Body weight (only at screening, Day 21 and Day 42) and height (only at screening) will also be recorded using scales available at site.

The pre-dose assessment on Day 1 will be regarded as the Baseline value for each vital signs parameter. If the Day 1 assessment is unavailable then the value from the Screening assessment will be used as Baseline. The change from Baseline to each subsequent assessment will be derived for each vital signs parameter.

3.3.5 Electrocardiogram

Twelve-lead ECG data will be collected at screening and also repeated pre-dose on Day 1, 7, 14, 21, 28, and Day 42. The following ECG parameters will be recorded in the eCRF:

- Heart rate (beats/min)
- PR interval (msec)
- QRS duration (msec)
- QT interval (msec)
- QTc interval (msec)
- Overall interpretation

Interpretation of the ECG will be performed by the investigator and reported as normal, abnormal, inderterminate, not evaluable or unknown and if deemed abnormal, whether the abnormality is clinically significant or not clinically significant.

The ECG conducted before the first dose of study medication will be regarded as the Baseline ECG. Changes in each ECG parameter from Baseline or any additional unscheduled ECGs, will be derived.

3.4 Additional assessments

3.4.1 CH50 Levels

Blood samples for CH50 will be collected at Day 1 (pre-dose), Day 7 (pre-dose), Day 14 (pre- and 3, 6, 9, 12, and 18 hours post-dose), Day 21 (pre-dose), Day 42 or the early termination visit, if applicable, and at the Follow-up visit (Day 72), and analysed in the Central Laboratory.

The pre-dose Day 1 assessment will be regarded as the Baseline value. The absolute change and percentage change from Baseline to each subsequent assessment will be derived.

3.4.2 Anti-drug antibody (ADA)

Blood samples for Antibodies immunogenicity evaluation to be performed at the Central Laboratory will be collected pre-dose at Day 1, Day 7, Day 14, Day 21 and Day 42 or the early termination visit, if applicable, and at the Follow-up visit (Day 72).

ADA analyses may be performed at a later stage and results reported separately from the main CSR.Pharmacokinetics (PK) (unbound rVA576)

Blood samples will be collected at the specified times in the schedule of events to study the PK of rVA576. Samples for PK will be taken 5 – 60 minutes before IMP administration at Day 1 (pre-dose), Day 7 (pre-dose), Day 14 (pre- and 3, 6, 9, 12, and 18 hours post-dose), Day 21 (pre-dose), Day 42 or the early termination visit, if applicable, and at the Follow-up visit (Day 72). The date and exact time of collection will be recorded.

PK analyses may be performed at a later stage and results reported separately from the main CSR.

3.4.3 Throat and Nasal Swabs

All patients selected for entry into this trial will have throat and nasal swabs taken once they have consented. A positive Neisseria sp. results will exclude subjects from the trial. Repeat throat and nasal swabs is allowed during screening at weekly intervals. Subject might be enrolled if the organism has been eradicated.

No derivations will be performed on this data. This data will only be listed.

3.4.4 Total C5

Blood samples for complement protein levels and/or activity (Total C5) to be performed at the central laboratory will be collected pre-dose at Day 1, Day 7, Day 14, Day 21, Day 42 or the early termination visit, if applicable, and at the Follow-up visit (Day 72).

No derivations will be performed on this data. This data will only be listed.

3.5 Study Medication, Compliance and Exposure

Study medication will be administered over 42 days as described below:

Treatment Phase	Day	Purpose	Dose
Ablation	Day 1	To rapidly inhibit all terminal complement activity	60 mg followed by 30 mg 12 hours later
Maintenance dosing	Day 2 to Day 42	To maintain stable and complete complement inhibition	30 mg (at approximately same time every day, ± one hour)

Exposure will be derived as the number of days between the first and last dose of study medication.

Study medication compliance will be derived as the proportion of the total planned dose received (total injected volume in mL) in order to reflect both the proportion of doses and days that the patient received the intended injection during the exposure period.

3.6 Mometasone furoate

All subjects will receive topical mometasone cream or ointment up to 30 gram/ week, as maximal background therapy until Day 21 and the weight of the topical mometasone returned by the patient should be recorded in the medical notes at the scheduled clinical visits on days 7, 14 and 21. The amount of topical mometasone used each week will be calculated.

3.7 Prior and Concomitant Medications

Details of any relevant prior medications, or any changes or additional medications that were taken during the study will be recorded on the eCRF. Assessment of prior and concomitant therapies will be performed at each study visit.

Medication start and stop dates recorded on the Prior and Concomitant Medications eCRF will be used to determine whether the medications are prior or concomitant to the treatment period. Concomitant medications are defined as those used during the treatment period (i.e., start date is after the first dose of study drug, or start date is prior to the date of first dose and stop date is either after the date of first dose or marked as continuing). Prior medications are defined as those used prior to and stopped before the first dose of study drug.

All prior/concomitant medication will be coded with Anatomical Therapeutic Chemical (ATC) class and preferred term.

3.8 Rescue therapy

Any use of mometasone that is higher than 30 gram/week permitted during the first 21 Days and any use of mometasone after Day 21 will be considered as rescue therapy. In addition, any use of other local steroids at any time during the study will be considered a protocol deviation and any use of other topical steroids, oral steroids, immunomodulators or such medications after day 1 will be identified and recorded in the eCRF as rescue therapy.

Subjects who have used any rescue therapy for every week between Day 1 and 42, and overall will be identified.

3.9 Presentation

Statistical analyses will be performed using SAS® (Version 9.3 or later). All available data will be presented in patient data listings, which will be sorted by site number, patient identifier and where appropriate, visit number and/or visit date.

Descriptive statistics (n, mean, standard deviation, median, first quartile, third quartile minimum, and maximum) will be used to summarise the continuous efficacy and safety data. Discrete measures will be summarised using count and percentage. Unless otherwise stated, descriptive statistics showing the mean and median will be displayed to one decimal place more than the original data; the standard deviation will be displayed to two decimal places more than the original data; minimum and maximum will be displayed to the same number of decimal places as the original data.

Any significance tests or confidence intervals will be purely descriptive.

Unless otherwise stated, all data will be listed.

4 Statistical Methods Planned

4.1 Changes from Protocol

In the protocol version 5.0, dated 8 May 2019, the treatment period to be considered for the analysis of the primary safety outcome was not clearly defined. Wording has been added in this SAP to clarify that the treatment period to be considered for the analysis of the primary safety outcome is defined as the period starting at the first dose date and up to the follow-up visit, scheduled 4 weeks after the last dose date of the study drug. This is in-line with Section 10.1.4 of the protocol which defined a TEAE as an AE that started after the first dose of study medication was taken.

Descriptive summaries of the proportion of patients whose BPDAI activity score decreases or increases have been added as an additional analysis.

PK, ADA and LTB_4 analyses may be performed at a later stage. If available before finalisation of the CSR the results will be reported in the CSR, otherwise results will be reported separately from the main CSR. Analyses of these endpoints are not covered in this SAP.

4.2 Analysis Sets

4.2.1 Screened Set

The Screened Set will include all patients who signed the informed consent form and are assigned a screening number.

4.2.2 Safety Analysis Set

The Safety Analysis Set will include all screened patients who received at least 1 dose of rVA576. This will be the primary population for assessing safety and efficacy.

4.3 Review of Data and Analysis Plan Finalisation

A review of the electronic data will be performed prior to database lock. Decisions on the composition of analysis datasets will be made and documented prior to database lock.

Data tables will be reviewed for outliers, implausibility and spurious values. Outliers identified may be excluded and the results of the analysis will be repeated on the modified dataset, excluding outliers. A listing will be produced summarising the details of any outliers identified. Full and modified data sets will be described in the Statistical Appendix for the CSR with a complete explanation of data handling and analysis methods to ensure completeness. The clinical importance of changes to the results on exclusion of these observations will be assessed and any important differences will also be reported in the Statistical Appendix for the CSR.

4.4 Statistical Methods, definitions

Baseline	Baseline measurements refer to all data collected at Day 1.

Change from baseline (CFB)	Difference between the timepoint value and the baseline value. CFB = Timepoint value – Baseline value
% Change from baseline (%CFB)	%CFB = 100*[(Timepoint value – Baseline value)/Baseline value]
Exposure to the study medication	Exposure will be calculated as the time, in days, between the first and the last dose of the study medication. Exposure (days) = Last dose – Start dose + 1
Compliance to the study medication	Compliance will be calculated as the % between the planned dose and the real dose. Compliance (%) = 100*(Real dose/Planned dose)
BPDAI activity score	Arithmetic sum of the 3 subcomponents – cutaneous blisters / erosions, cutaneous urticarial / erythema, and mucosal blisters / erosions.
BPDAI damage score	Arithmetic sum of the items rated regionally for damage caused by more permanent features such as post-inflammatory hyperpigmentation, scarring and other.
Global BPDAI score	Arithmetic sum of the BPDAI activity score and BPDAI damage score.
Time until BPDAI reduction	Time until BPDAI reduction will be calculated as the time, in days, between the first dose date and the first visit in which patient presents a reduction of at least 50% (and 75%) in the BPDAI activity score. If a patient will not present any reduction then he will be censored at the last available Follow-up information. Time until BPDAI reduction = First reduction dose – Start dose + 1

4.5 General Data Handling Rules

Values from the locally reported laboratory will be converted to the standardised units at the SDTM level.

Laboratory values recorded as below the limit of quantification or above the limit of quantification will be handled as follows: results recorded as below will be imputed using half of the lower limit of quantification for the purpose of calculating change from baseline, or percentage change from baseline, for summaries and figures. Measurements recorded as above will be imputed using the quantification limit. The raw data will be displayed in the listings.

The data may be log transformed, this will be guided by the degree of skewness and variability in the data within and between subjects across time.

4.6 Patient Disposition

Patient disposition will be provided, showing the number and percentage of patients who received study drug, completed the study visit schedule or withdrew early. For patients who withdraw from the study, the primary reason for the withdrawal will also be summarized.

The total number of patients who were screened and the number who failed screening will be tabulated. Screen failures and screen failure reasons will be listed in a data listing.

The number of patients Screened and the number and percentage of patients included in the Safety Analysis Set will be presented.

4.7 Demographics and Baseline Characteristics

Demographic characteristics (age, sex, ethnicity and race), Karnofsky Performance Status, height, weight, body mass index, smoking status, alcohol/substance use and childbearing potential will be summarized for the Safety Analysis Set.

4.8 Medical History

Medical history findings at screening will be summarized for the Safety Analysis Set.

4.9 Study Drug Exposure and Compliance

Exposure to the study medication will be summarized for the Safety Analysis Set. In addition the number and percentage of patients with exposure in the following categories will be summarised:

- 1-7 days
- 8-28 days
- 29-42 days
- >42 days

The derived compliance for the period of time that each patient received study medication will be categorised and summarised as:

- <90%
- 90% to <95%
- 95% to 100%
- >100%

If more data is captured in the CRF through a comment such as missed doses, reason missed dose, or full amount not administered, it will listed in the exposure listing.

4.10 Prior/Concomitant Medications

The numbers and percentages of patients taking concomitant medications (including oral antibiotic prophylaxis as requested per protocol) will be summarised by ATC and preferred term for the Safety Analysis Set. Prior medications will not be summarised but will be listed separately from concomitant medications.

The mean weekly amount (grams) of topical mometasone used will be summarised for each week between Day 1 and 42. Use of any rescue therapy (mometasone, or any use of other topical steroids, oral steroids, immunomodulators or such medications) will be summarised for each week between Day 1 and 42, and overall. i.e. At each weekly interval, the proportion of patients who have used rescue therapy will be summarised

4.11 Analysis of Efficacy

Efficacy analyses will also be performed using the Safety Analysis Set. All efficacy data will be listed.

4.11.1 Primary Efficacy Analysis

Not Applicable.

4.11.2 Secondary Efficacy Analysis

BPDAI

The BPDAI activity score and BPDAI pruritus index will be presented as a (spaghetti) line plot over time for all patients in the Safety Analysis Set.

The mean observed values and absolute mean change from Baseline in BPDAI activity score and BPDAI pruritus index will be plotted over time and summarised with their associated 95% confidence interval using t-distributions.

The proportion of patients whose BPDAI activity score decreases by 4 or more points between baseline and Day 42, and the proportion of patients whose BPDAI activity score increases by 3 or more points between baseline and Day 42 will also be described.

DLQI

The observed values and absolute change from Baseline in Quality of life scores will be summarised and plotted over time.

TABQOL

The observed values and absolute change from Baseline in Quality of life scores will be summarised and plotted over time.

4.11.3 Additional Efficacy Analysis

BPDAI

The percentage change from Baseline in BPDAI activity scores will be calculated for each patient and plotted overtime. The mean percentage change in BPDAI activity score at Day 42 compared to baseline will be presented with its associated 95% Confidence Interval.

The proportion of patients who achieve a reduction in BPDAI activity score of at least 50% (and 75%) at Day 42 will be reported.

The time to achieve at least 50% reduction (and 75%) will also be described: Kaplan-Meier estimates of the proportion of patients achieving a reduction in BPDAI activity score will be displayed with 95% two-sided confidence limits. For this purpose, PROC

LIFETEST in SAS will be used. The median, 95% Confidence Interval of the median, 25th and 75th percentiles of the time to achieving such reduction will be produced.

Patients who have not achieved such reduction will be censored at their last available follow-up information, i.e. a patient who does not experience at least a 50% reduction for the duration of the study will be right censored: the time to achievement for this person will be considered to be at least as long as the duration of the study, up to their last available follow-up information.

The BPDAI global score, BPDAI damage score, and three sub-components of the BPDAI pruritus index (last 24 hours, last week, last month) will also be summarized with observed values and absolute change from Baseline summarised and plotted over time.

In addition, different levels of reduction and increase in BPDAI activity scores will be described as multiples of the MCID: The proportion of patients whose BPDAI activity score decreases by 2xMCID, 3xMCID etc… and the proportion of patients whose BPDAI activity score increases by 2xMCID, 3xMCID etc… between baseline and Day 42 will also be described.

Disease Control

The proportion of subjects with Disease control at Day 21 and at Day 42 will be described. The following summaries will be produced: proportion of subjects without any new bullae for the last 3 consecutive days, proportion of subjects with established lesions considered as healed at the visit and the proportion of subjects reporting healed lesions that have developed into new lesions.

BP180 and BP230

For BP 180, BP 230 antibody the mean observed titres and percentage change from Baseline will be plotted and summarised overtime. Spaghetti plots (individual line plots) over time, will be produced.

Skin Biopsy

Results from the Baseline and Day 42 biopsies will be summarised: The proportion of subjects with positive/negative results at Day 42 will be described. In addition, for biopsies reported with a score between 0 and 3, a shift table will be produced comparing values at Baseline versus Day 42: The number and percentage of subjects with results shifting by 0 (no change), or -1, -2 and -3 (improvement), or +1 and +2 (worsening) will be presented. Note, that the value can only worsen by +1 and +2, not worsen by +3, as all subjects entering the trial must have a positive biopsy which is represented by the score 1, 2 or 3.

Sensitivity analyses

As a sensitivity analysis, the mean observed values and mean change from Baseline in BPDAI activity score and in BPDAI pruritus index will be calculated after applying the LOCF approach to the scores, and will be summarised with their associated 95% Confidence Intervals. Results may also be presented separately for patients who completed the treatment period with and without using any rescue therapy.

The observed values and absolute change from Baseline in Quality of life scores (DLQI and TABQOL) will also be summarised after applying the LOCF approach to the scores.

4.12 Analysis of Safety

Safety analyses will be performed using the Safety Analysis Set. All safety data will be listed.

4.12.1 Primary Safety Analysis

Adverse events of grade 3, 4 and 5 which have been assigned a causal relationship to rVA576 of 'related/possibly related' and have occurred during the treatment period (on or after the first dose date and up to the Follow-up visit, scheduled 4 weeks after the last dose date of the study drug) will be considered in the analysis of the primary safety outcome.

The primary endpoint will be analysed in terms of the proportion of subjects reporting safety events. The proportion of patients experiencing such AEs will be reported with its associated Clopper-Pearson (exact) 95% confidence interval.

4.12.2 Additional Safety analysis

Adverse Events

A summary overview of AEs will be provided, which presents the number and percentage of patients from the Safety Analysis Set satisfying each of the following categories:

- Any TEAEs
- AEs of special interest (i.e. malignancies, injection site reactions >CTCAE Grade 2, infection, hypersensitivity)
- SAEs that occur on or after the first dose date and up to 4 weeks after the last dose date of the study drug
- Treatment-emergent SAEs leading to death
- TEAEs leading to discontinuation

The number and percentage of patients with TEAEs will be summarised by MedDRA System Organ Class, High Level Term, and Preferred Term. In these summaries, any patient reporting multiple episodes of the same TEAE (i.e. same preferred term), will be counted once.

TEAEs will also be summarized by severity, and by relationship to study drug. Separate summaries will also be generated for treatment-related AEs overall and by severity. The number and percentage of patients with TEAEs will be summarised by reported severity (*Severity = 'Mild', 'Moderate', 'Severe', 'Life-threatening', 'Death'*) within each preferred term within system organ class. In this summary, any patients reporting multiple episodes of the same TEAE (i.e. same preferred term), will be counted once against the most severely reported category.

Separate summaries will also be generated for TEAEs that have been assigned a causal relationship to rVA576 of 'related/possibly related' overall and by severity.

A list of patients reporting any treatment emergent SAEs and a list of patients reporting any TEAEs that led to an interruption or withdrawal of the study medication will be provided. A list of patients reporting AEs of special interest (i.e. malignancies, injection site reactions >CTCAE Grade 2, infection, hypersensitivity) and AEs leading to death will also be provided.

Clinical Laboratory Assessments (local laboratories)

Observed values and change from baseline will be summarised at each applicable study visit for the Safety Analysis Set for the parameters listed in Section 3.3.3. Counts and percentages of patients in each category will be used to summarise categorical urinalysis parameters for the baseline visit and each post-baseline assessment.

Counts and percentages of patients with haematology and chemistry observations that are below Lower limit of normal (<LLN) or above Upper limit of normal (>ULN) at any post baseline visit will be summarised. Patients with haematology or chemistry observations that are below (<LLN) or above (>ULN) the limit of normal at *any* post baseline visit will be listed, as well as patients with markedly abnormal values.

A shift table will present the number and percentage of patients who are low, normal, or high at Baseline and Day 42 together, describing patients shifting from one category (e.g. normal) to another (e.g. low).

Vital Signs

Observed values and change from baseline of Vitals signs measurements (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, temperature, weight) will be summarised at each applicable study visit for the Safety Analysis set. Also, a (spaghetti) line plot over time for all patients in the Safety Analysis Set will be presented.

Subjects with markedly abnormal values for vital signs will be listed.

Electrocardiogram

The number and percentage of patients who have an ECG post-baseline Overall interpretation that falls within each category ('Normal'; 'Abnormal, Not Clinically Significant'; 'Abnormal, Clinically Significant') will be tabulated for the Safety Analysis Set at day 42.

Observed values and change from baseline of ECG measurements (heart rate, PR interval, QRS duration, QT interval and QTc interval) will be summarised at each applicable study visit for the Safety Analysis set. Also, a (spaghetti) line plot over time for all patients in the Safety Analysis Set will be presented.

Physical Examination

The number and percentage of patients, from the Safety Analysis Set, with any reported abnormal findings ('Not Clinically Significant' or 'Clinically Significant') at their screening physical examination assessments will be presented along with reported changes to physical examination findings post-screening.

4.13 Pharmacodynamic Analysis

Observed values, change from baseline, and ratio to baseline expressed as a percentage (also called % activity) in CH50 will be summarised at each applicable study visit for the Safety Analaysis Set.

The number and proportion of patients achieving maintenance of pre-dose serum complement activity at ≤10 CH50 U Eq/ml between Day 2 and Day 42 will be summarised at each study visit.

CH50 levels will be presented as a (spaghetti) line plot over time for all patients in the Safety Analysis Set.

4.14 Interim Analysis

A formal interim analysis will not be performed but results may be reviewed and reported periodically. The Sponsor reserves the right to review accruing safety and efficacy data from the study as a management aid to assist in conduct of the current study and the design of future studies.

4.15 Data Safety Monitoring Board (DSMB)

No DSMB will be convened.

5 Sample Size Determination

A maximum of 9 patients will be enrolled. The sample size for this study was determined based on practical, and not statistical, considerations.

6 Programming Specifications

The programming specification, including the mock-up analysis tables, figures, and data listings, as well as the derived database specification, will be prepared in stand-alone documents.

7 References

• Wijayanti A, Zhao CY, Boettiger D et al 2017 The Reliability, Validity and Responsiveness of Two Disease Scores (BPDAI and ABSIS) for Bullous Pemphigoid: Which One to Use? Acta Derm Venereol. 2017 Jan 4;97(1):24-31.Levy-Sitbon et al. Assessment of bullous pemphigoid disease area index during treatment: a prospective study of 30 patients. Dermatology. 2014;229(2):116-22

8 APPENDIX 1

8.1 Tables

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8.3 Figures

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9 APPENDIX 2

Changes from Final version 1.0 to 2.0

Rationale for change(s)	**Section(s) amended**
Update per protocol version 5.0	2.2 Table 1 updated
	2.3.3 endpoint added
	3.3.2 Updated list of Physical examination
	3.3.4 Correction of Vital signs timepoints
	3.8 Clarification of rescue therapy
	4.1 updated
Analyses of LTB_4, ADA and PK removed as some analyses may be performed at a later stage and results reported separately from the main CSR.	3.2.5, 3.4.2 and 3.4.3 amended
	4.2.3, and 4.12 sections deleted
	4.6 and 4.11.3 sentences deleted
Clarification of compliane calculation and of listed data	3.5 and 4.9 text added
Addition of Q1 and Q3 in planned summary statistics	3.9 addition of Q1 and Q3
Addition of definitions to help review of SAP	4.4 addition of whole section
Addition of summary tables for Vital signs and ECGs results	4.12.2 text added
Addition of summary table of increases and decreases in BPDAI activity scores	4.11.3 text added
Addition of Appendix 1, Table of Contents for Tables, Listings and Figures as per ICH E3	Appendix 1 added
Appendix 2 added	Appendix 2 added
Minor formatting updates	Various