A randomized, part A partial blinded and part B double blinded, placebo-controlled 24-week clinical study to evaluate the efficacy and safety of nomacopan therapy in adult patients with bullous pemphigoid receiving adjunct oral corticosteroid therapy (ARREST-BP)

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Primary Objective:* confirm the dose of nomacopan and sample size for Part B and evaluate the rank order of secondary endpointsOther Objectives:* compare nomacopan with adjunct OCS to placebo with adjunct OCS in achievement of Complete Remission of...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON51799

Source
ToetsingOnline

Brief title
The ARREST-BP study for patients with Bullous Pemphigoid

Condition

- Autoimmune disorders

Synonym
bullous pemphigoid, skin blistering diesease

Research involving
Human

Sponsors and support

Primary sponsor: Akari Therapeutics Plc
Source(s) of monetary or material Support: Funded by the Sponsor Akari Therapeutics Plc

Intervention

Keyword: adjunct oral corticostroid therapy, bullous pemphigoid, partially blinded, placebo controlled

Outcome measures

Primary outcome

Primary Endpoint

Proportion of patients in Complete Disease Remission on (CRon) minimal OCS

therapy (0.1 mg/kg/day) for 8 weeks or more at week 24 [Time Frame: weeks 16 *

24].

Secondary outcome

Other Endpoints (Exploratory for Part A, Secondary for Part B)

1. Cumulative OCS dose during treatment [Time Frame: randomization to 24 weeks].

2. Proportion of patients requiring rescue therapy during the 24 weeks of

treatment [Time Frame: randomization to 24 weeks].

3. Proportion of patients in Partial Disease Remission on (PRon) minimal OCS

therapy (0.1 mg/kg/day) for 8 weeks or more at week 24 [Time Frame: weeks 16 *

24].

4. Time (weeks) to onset of Complete Remission on (CRon) Minimal OCS and

Partial Remission on (PRon) Minimal OCS [Time Frame: from week 6 to end of

study].

5. Duration (weeks) of Complete Remission on (CRon) Minimal OCS and Partial Remission on (PRon) Minimal OCS [Time Frame: from week 6 to end of study].

6. Proportion of patients with Investigator Global Assessment (IGA) score of 0 or 1 (clear or almost clear) at 6 weeks, 12 weeks and end of treatment [Time Frame: weeks 6 * 24].

7. Frequency, type and relationship of AEs to treatment [Time Frame: randomisation to end of study].

8. Incidence of steroid-related AEs [Time frame randomisation to end of study].

9. Change from baseline in Dermatology Life Quality Index (DLQI) [Time Frame: randomisation to week 24].

10. Incidence of treatment-emergent anti-drug antibody (ADA) responses and titre and neutralising potential assessed in vitro at baseline and every 4 weeks [Time Frame: randomisation to end of study].

Exploratory Endpoints (Exploratory for Part A and Part B)

11. Time (weeks) to first occurrence of Control of Disease Activity [Time Frame: randomization to 24 weeks].

12. Time (weeks) to first occurrence of 100% epithelialisation [Time Frame: randomization to 24 weeks].

13. Cumulative duration (weeks) of Complete Remission on (CRon) Minimal OCS and Partial Remission on (PRon) Minimal OCS [Time Frame: from week 6 to end of study].

14. Proportion of patients with BPDAI activity score reduction of >50%, >90% and complete cessation of lesions from baseline at 1, 3, 6, 12 and 24 weeks

[Time Frame: randomisation to 24 weeks].

15. Proportion of patients with pruritus VAS score reduction of >50%, >90% and complete cessation of itch from baseline at weeks 8, 16, 24 and 28 [Time Frame: randomisation to end of study].

16. Change and percent change from baseline (average during screening period) in the weekly average of daily PP-NRS [Time Frame: screening to week 24]

17. Proportion of patients achieving at least a 4-point reduction from baseline (average during screening period) in weekly average of the daily PP-NRS [Time Frame: screening to week 24]

18. Change from baseline in total BPDAI activity score over time [Time Frame: randomisation to end of study].

19. Change from baseline in total BPDAI pruritus VAS score over time [Time Frame: randomisation to end of study].

20. Proportion of patients requiring *0.5mg/kg/day OCS after Control Disease Activity established. [Time Frame: randomisation to end of study].

21. Time to relapse/flare while on Minimal OCS on first occasion that patient is on Minimal OCS [Time Frame: from week 6 to end of study].

22. Proportion of patients on Minimal OCS at weeks 8, 16, 24 and 28 [Time Frame: from week 6 to end of study].

23. Proportion of patients requiring an increase in SOC therapy for BP after study drug treatment has stopped [Time frame: weeks 24 * end of study].

24. Change in anti-BP180 and anti-BP230 autoantibody (IgG) titres [Time Frame: randomisation to end of study].

25. Concentrations of inflammatory markers that may be associated with active

BP disease including IL1 alpha, IL1beta, IL2, IL4, IL5, IL6, IL8, IL10, IL13,

IL17, TNF and eotaxin-1 (CCL11) at baseline and at 4, 12 and 24 weeks [Time

Frame: randomisation to 24 weeks].

26. Histopathology of cell infiltrate in skin tissue biopsy at baseline and 2

weeks [Time Frame: randomisation to 2 weeks].

27. Trough concentrations of nomacopan, and inhibition of terminal complement

activity in serum, and total LTB4 concentration in plasma [Time Frame:

randomisation to end of study].

28. LTB4 concentration from skin tissue biopsy [Time Frame: randomisation to 2

weeks]

The primary endpoint (CRon) will remain the same in Part A and Part B. The

number of secondary endpoints in Part B will be reduced and they will be

ranked.

Study description

Background summary

Bullous pemphigoid (BP) is the most common subtype of autoimmune blistering disease (AIBD). The pathogenesis of BP is not fully understood but it is likely that there is an interaction between predisposing genetic factors and environmental triggering factors.

BP treatment has 3 main goals: stopping blister formation and pruritus, promoting healing of blisters and erosions, and improving quality of life. First-line therapy consists of high potency topical or systemic glucocorticosteroids.

Due to numerous AEs and symptoms associated with current therapeutic options and the increased risk of morbidity and mortality, the need for a safe and

effective treatment of BP remains. Newer therapeutic agents targeting molecules involved in the inflammatory cascade associated with BP represent future alternatives to classical immunosuppressant drugs. There is currently no approved targeted therapy for treatment of BP.

Nomacopan, a recombinant small protein therapeutic, is being developed as a treatment for BP with the intention that it will have fewer adverse effects than traditional corticosteroid therapies.
In Part A, a higher 45 mg once daily dose of nomacopan and a lower 15 mg once daily dose of nomacopan will be compared. In Part B of the study, all patients will receive either a 45mg or a 15mg once daily dose. The single dose to be used for all patients will be selected based on the results seen in Part A.

A treatment period of 24 weeks will be used in Part A. Nomacopan will be administered with adjunct oral corticosteroid therapy (OCS) tapered according to disease response.

Study objective

Primary Objective:
* confirm the dose of nomacopan and sample size for Part B and evaluate the rank order of secondary endpoints

Other Objectives:
* compare nomacopan with adjunct OCS to placebo with adjunct OCS in achievement of Complete Remission of disease on minimal OCS (CRon)
* test whether cumulative OCS is lower in the nomacopan than the placebo arm.
* assess steroid use testing whether fewer nomacopan than placebo treated patients require rescue therapy during treatment.
* assess disease control by testing whether nomacopan arm is superior to placebo arm in achieving Partial Remission of disease on minimal OCS (PRon).
* evaluate how long it takes to achieve initial CDA and full disease control assessed by time to achievement of CRon or PRon.
* evaluate duration of CRon or PRon.
* evaluate the effect of treatment on disease intensity measured by bullous pemphigoid disease area index (BPDAI)
* evaluate the effect of treatment on itch reported by the weekly average daily peak pruritis Numerical Rating Scale (PP-NRS) and separately by the BPDAI pruritus score.
* evaluate the effect of treatment on disease intensity measured by Investigator Global Assessment (IGA).
* assess the safety and tolerability of nomacopan with adjunct OCS compared to placebo and adjunct OCS.
* evaluate health-related quality of life (QoL) measures.
* characterize nomacopan PK and terminal complement activity in serum and total LTB4 in plasma.
* record time taken until patient is receiving minimal OCS.

* evaluate time to relapse/flare from date that patient is first on minimal OCS.
* assess cumulative steroid use after treatment stops until week 28.
* evaluate BP180 and BP230 autoantibody titres.
* measure inflammatory markers associated with active BP disease by examining cytokine profiles in serum.
* assess inflammation by skin tissue biopsy to measure leukotriene B4 (LTB4) and cell infiltrate.
* assess the immunogenicity of nomacopan.

Study design

Study Design:
This is a randomized, placebo-controlled clinical study in two parts - Part A and Part B. Part A is blinded for placebo/active but not for low/high dose; part B is double blinded.

The objectives of the study are:

* In Part A: to confirm the dose of nomacopan and sample size for Part B and also rank the order of secondary endpoints for Part B
* In Part A: to compare nomacopan with adjunct OCS to placebo with adjunct OCS in achievement of Complete Remission of disease on minimal OCS (CRon)
* In Part A and Part B: to evaluate the safety of nomacopan with adjunct OCS
* In Part B: to test drug efficacy and in particular whether treatment with nomacopan and adjunct oral corticosteroid (OCS), with steroid tapered (between weeks 2 and 24) according to disease response, leads to a higher proportion of patients in complete disease remission than treatment with placebo and adjunct OCS.
* In Part B: to examine whether there is a reduction in cumulative OCS use and fewer steroid related adverse events in the nomacopan than the placebo arm.

The primary endpoint of both Parts of the study is achievement of Complete Disease Remission on (CRon) minimal OCS (0.1 mg/kg/day) for 8 weeks or more at week 24.

The only OCS permitted in this trial is prednisone or prednisolone.

Part A (48 patients):
Part A will have four arms in which patients will be randomised to receive either:

* high dose nomacopan (standard complement ablating doses on Day 1 followed by 45 mg qd) plus a starting dose of 0.5 mg/kg/day OCS, n = 16,
or
* low dose nomacopan (standard complement ablating doses on Day 1 followed by 15 mg qd) plus a starting dose of 0.5 mg/kg/day OCS, n = 16,
or

* placebo injections (matching standard complement ablating doses on Day 1 and then matching injection volume of 45mg dose) plus a starting dose of 0.5 mg/kg/day oral corticosteroid (OCS) qd, n = 8,
or
* placebo injections (matching standard complement ablating doses on Day 1 and then matching injection volume of 15mg dose) plus a starting dose of 0.5 mg/kg/day oral corticosteroid (OCS) qd, n = 8.

Randomisation in Part A will be stratified by newly presenting/relapsed patients. Either 4 or 6 relapsing patients will be allowed into each of the nomacopan treatment arms, and 2 or 3 relapsing patients will be allowed into each of the placebo treatment arms, while maintaining the 2:2:1:1 randomization scheme for high dose nomacopan: low dose nomacopan: placebo 45mg: placebo 15mg. Twelve (12) or eighteen (18) relapsing patients will be recruited.

Part B (pivotal):
The dose of nomacopan and patient numbers in Part B will be determined following completion and analysis of Part A, a Type A meeting with the FDA and a Scientific Advice Meeting with the EMA. The sample size for Part B is expected to be approximately 100 patients. Part B will have two arms.

* placebo plus oral corticosteroid (OCS), n = TBD,
or
* single selected dose of nomacopan (standard complement ablating doses on Day 1 followed by either 15 or 45 mg [TBD] qd) and OCS, n = TBD.

Randomisation in Part B will be stratified by moderate/severe disease based on IGA score at Day 1 (Baseline) and by newly presenting/relapsed patients.

Part A and Part B will have a similar design and the same study periods:
In both Parts A and B patients will receive study drug once daily for 24 weeks. Both parts can each be considered to have three periods:

* Disease Control (Period 1): patients will remain on a fixed OCS starting dose (0.5 mg/kg/day) for a minimum of 2 weeks until Control of Disease Activity (CDA) is achieved, when OCS tapering begins. With CDA defined as the time at which new lesions cease to form and established lesions begin to heal, or pruritic symptoms start to abate.

* OCS Tapering (Period 2): OCS tapering will begin once CDA is achieved, and after a minimum of 2 weeks of OCS study treatment. OCS tapering will continue until the patient is on minimal OCS (0.1 mg/kg/day), at which point the patient is eligible for assessment of the duration of disease remission. It is important to note, that OCS tapering can begin once CDA is achieved and does not require that the patient has 80% epithelialization of lesions. If CDA is not maintained during tapering the OCS dose is kept constant if there are transient lesions. If the disease is worsening the OCS dose may be increased,

to a maximum dose of 0.75 mg/kg/day, until disease control is re-established when OCS tapering can be resumed. Rules for OCS taper and increase are presented in the main body of the Protocol.

* Remission (Period 3): patients who remain in complete disease remission (no lesions) will stay on minimal OCS (0.1 mg/kg/day) for the rest of the treatment period (24 weeks). If there is onset of new disease activity (except transient lesions) the OCS dose may be increased until disease control is re-established when OCS tapering can be resumed. If patients are on 0.1 mg/kg/day and in complete remission (CRon) for the entire period between weeks 16 to 24 they meet the primary endpoint regardless of the patient*s OCS doses before week 16.

Definitions of disease worsening, and relapse/flare are provided in the main body of the protocol.

In both Parts A and B there will be a follow-up period of four weeks, between weeks 24 and 28, during this time patients will receive standard of care (SOC) treatment without nomacopan.

Safety and Extension Study for Part B:
A separate one-year safety and extension study will be offered to patients from either arm of the Part B study who have achieved the primary endpoint of CRon or have achieved partial disease remission on (PRon) minimal OCS (0.1 mg/kg/day) for 8 weeks or more at the end of nomacopan treatment (week 24 of the parent study AK802). If patients are in CRon when they enter the safety and extension study or achieve CRon during the safety and extension study the OCS dose may be gradually tapered to 0mg/kg/day OCS. The study will follow the patients to assess total duration of CR on minimal or no OCS, PRon, cumulative steroid use and safety after discontinuation of nomacopan. The study will also monitor the response of patients to re-treatment with nomacopan if they experience a relapse/flare. An interim analysis of safety will be undertaken when all patients have reached six months in the extension study and a final analysis at 12 months. Patients in CR or PRon who relapse/flare will be treated with nomacopan (with the nomacopan dose used in Part B) plus a starting dose of up to 0.5 mg/kg/day OCS determined by treating physician depending on disease severity. Patients entering the safety and extension study will not be receiving nomacopan but may do so at entry or anytime thereafter if they exhibit relapse/flare. All patients, carers and staff treating the patients who enter the safety and extension study will remain blinded to Part B treatment allocation.

Intervention

Study Procedures (Parts A and B):
Part A and B of the study will have similar study procedures. A patient who has been in Part A of the trial cannot enter Part B.

Patients can be screened up to 10 days prior to randomization and should generally not receive any treatment other than emollients until the randomisation visit. For ethical reasons patients can be treated with 30-60g potent topical corticosteroids (eg triamcinolone or mometasone furoate), but not super-potent topical steroids, and no more than 0.3 mg/kg/day OCS during the screening period. It is advised that the OCS dose is minimized during the screening period to help ensure that healing does not begin before patients are randomized to treatment. Patients will then be randomized on Day 1 to receive study drug or placebo with OCS at a starting dose of 0.5 mg/kg/day. At screening and on Day 1 subjects will have markers of disease activity measured (including BPDAI, IGA, QOL, PP-NRS scores and BP180/BP230 antibody titres) to gauge how their condition has changed between screening and trial entry.

Patients will have scheduled clinical visits for assessment (including disease control and OCS dose assessment) at baseline (Day 1) and at Weeks 1, 2, 3 and 4 and then every four weeks thereafter until the end of treatment (Week 24). The week 3 assessment may be either a clinical visit or a home assessment if the patient has control of disease activity at the week 2 clinic visit. A safety follow-up visit will be performed at the end of study (Week 28). Home assessments (usually a televisit) will also be performed by trained staff at Weeks 10, 14, 18, 22 and 26. Once a patient is in complete remission on minimal OCS, a home consultation (by phone) will be undertaken once weekly during the weeks that the patient is not having a full home assessment or being seen at the clinic, to determine that disease control is being maintained during the period of assessment of sustained disease remission. If during a home assessment, it is considered that the patient may no longer be in disease remission an unscheduled clinic visit will take place to confirm that the patient is no longer in remission and to raise the OCS dose if required.

For the first 14 days of the study (minimum duration of period 1), the OCS dose will usually remain the same (0.5 mg/kg/day), unless patients have severe disease (IGA score of 4) and do not have CDA at their Week 1 assessment in which case OCS may be raised to 0.75mg/kg/day at Week 1. If patients have moderate disease at Week 1 (IGA score of 3) whether or not the disease has worsened they should remain on 0.5mg/kg/day OCS until the Week 2 assessment. At Week 2 and thereafter OCS taper can begin if there is CDA. At each subsequent clinical or home assessment (ie on weeks 3, 4 and 6 and then every 2 weeks thereafter until week 24):

1. Dose decreased by one step if there is CDA.
2. Dose remains the same if there are transient lesions.
3. Dose increased by one step if there is Mild New Activity.
4. Dose increased by one or more steps if disease is exhibiting more than Mild New Activity including Disease Relapse/Flare.

Any change in OCS dose can only be performed at a clinical assessment (either at clinic or at home usually by televisit) from Week 1 onward (severe patients

only for dose increase * see above) or from Week 2 (all patients permitted dose increase or decrease), and once weekly until Week 4, and then every two weeks thereafter. If a home assessment is being performed and it is considered there may be increased disease activity that mandates an increase of the OCS dose, an unscheduled clinical visit should be arranged to assess disease activity and whether there is a need to raise the OCS dose.

Once the patient is on minimal OCS (0.1 mg/kg/day), they are eligible for assessment of duration of disease remission.

As described above, if patients do not achieve initial CDA on an OCS dose of 0.5 mg/kg/day their OCS dose can be raised to 0.75 mg/kg after one week if IGA indicates they have worsening severe disease at Week 1 or at two weeks if they have moderate disease. If CDA has not been achieved after three or four weeks on the highest OCS dose of 0.75 mg/kg/day, the patient will be regarded as a treatment failure and study treatment will be withdrawn. Whether the period is three or four weeks depends on the timing of the shift to the highest dose of OCS and the subsequent schedule of clinical assessments.

Stopping study IMP and use of rescue therapy does not constitute withdrawal from the trial. The Investigator will start rescue therapy for treatment failure according to their normal practice. Rescue therapy comprises any therapy for treatment of BP administered because study treatment is considered to have failed.

Patients who require rescue therapy for treatment failure will be requested to attend clinic visits and have home assessments (usually televisits) as described in Section 18.3 and 18.4 until week 28 or until complete remission off steroid is achieved. In clinic visits will assess BPDAI, IGA, concomitant medications (including all therapies for treatment of BP), cumulative OCS dose and safety. Patients who are treatment failures will not be eligible to enter the safety and extension study.

Topical emollients are permitted throughout the trial to relieve dry skin (xerosis), which is not a symptom of BP, but is a very common cause of itch in the elderly. The use of topical corticosteroids, even for a short period, is not permitted after randomization.

Blood samples for assessment of blood chemistry, haematology, biomarkers of inflammation, PKPD and anti-drug antibodies (ADA) will be taken throughout the study.

Nasal and throat swabs will be taken neisseria sp. testing at screening. ECGs, physical examinations and bullous pemphifoid related assessments will be conducted throughout the study.

Biopsy sampling twice during the study is optional.

Study burden and risks

Treatment by daily subcutaneous injections, elaborate preparation of IMP, several questionnaires adn daily diary entries as well as frequent efficacy assessments are rather time consuming and in part painful. Treatment may also be associated with the occurrance of side effects.
Different doses are accomplished by adapting the applied volume. For the higher dose two injectiosn per application are necessary.

Nomacopan associated risks:
Nomacopan was well tolerated in normal volunteers, adults with paroxysmal nocturnal hemoglobinuria (PNH), and severe allergic conjunctivitis and keratoconjunctivitis, and an older adult BP population with many comorbidities. The most commonly reported treatment emergent adverse events (TEAEs) were injection site reactions of mild or very occasionally moderate severity that required no specific treatment.

One serious adverse reaction of urinary tract infection caused by Escherichia coli was reported in a PNH patient treated with nomacopan. This event was assessed by the investigator as possibly related to nomacopan. The subject*s medical history of urinary tract infection and cystitis potentially confounded causality for the reported event making causality not related to nomacopan in the opinion of the sponsor. There have been no other reports of treatment-related serious infections.

There have been nine further serious infections reported in the nomacopan clinical development program to date (August 2020); all of these were considered unrelated to nomacopan by both the investigator and the sponsor. In only a few instances were organisms cultured: Escherichia coli was cultured from urine in a catheterised patient, and in another patient Staphylococcal epidermis was cultured from a peripherally inserted central catheter.

There have been no treatment-related study withdrawals.

As Neisseria meningitidis has been reported as a risk with a C5 complement inhibitor (Soliris®) all subjects have received meningitis prophylaxis either by antibiotics or vaccine prior to nomacopan therapy. No events of meningococcal infection have been reported to date.

Anti-Drug Antibodies
Nomacopan is a xenologous protein with the recombinant protein originally derived from a cDNA encoding a tick salivary protein. In the AK577 dose ranging study healthy volunteer study, anti-drug antibodies (ADAs) were detected in two of four subjects dosed with nomacopan for 21 days and in none of the 12 subjects dosed with nomacopan for 7 days. The antibodies were of low

titre and did not neutralise the complement inhibitory activity of nomacopan. The eculizumab resistant PNH patient who received nomacopan for more than 21 months in Study AK578 first had detectable ADA at Day 16, which peaked at Day 60 and declined thereafter. All patients (n=8) in AK579 developed ADAs, which were first detectable between Day 14 to Day 90. Again, the antibodies were of low titre and did not neutralise the complement inhibitory activity of nomacopan.

The appearance of ADA does not appear to be associated with an increase in the rate or severity of injection site reactions.

The most compelling data supporting that the human ADA are non-neutralising is that in PNH patients from trials AK578, AK579, AK581 and AK585, over a daily dosing period of years, terminal complement activity has been found to be below the lower limit of quantification at all time points after Day 1 of nomacopan dosing. Furthermore, ADA are not associated with a decrease in the concentration of unbound nomacopan in patients.

Experience with nomacopan to date appears similar to patient experience with other parasite derived therapeutic molecules, such as the leech-derived anticoagulant hirudin, where most patients develop detectable ADA which have no effect on the inhibitory function of the protein.

Assessment/trial measure related risks:
Non-invasive measures like ECG, vital sign measurements and BPDAI assessments do not pose any risk or burden to the subject.

Blood sampling during the trial poses the same small risk for pain through skin puncture, hematoma, infection or venous inflammation as normally induced by this technique. Risks will be mitigated by delegating this task to experienced study personnel.

Biopsy sampling is associated with an increased risk of scaring, infection of the wound, damage of superficial nerves with resulting insensitivity of surrounding areal and discomfort or pain. Serious side-effects are rare and biopsy sampling will only be performed by experienced medical trial team members to reduce any risk.

Given the unmet need, efficacy observed in the Phase 2 study, and the benign safety profile of nomacopan demonstrated to date - the benefit: risk of the AK802 study is considered positive.

Participants my benefit by improvement of their conditions when being randomized to active treatment. Overall, the study results will support insight into the mechanism of pathogenisis of the diesase and the effectiveness and side effects of the investigational medicinal product wihc will serve future

research and help mitigating the unmet needs for effective therapy.

Contacts

Public
Akari Therapeutics Plc

Wimpole Street 75-76
London W1G 9RT
GB
Scientific
Akari Therapeutics Plc

Wimpole Street 75-76
London W1G 9RT
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female between 18 and 89 years of age inclusive at the time of consent with Karnofsky score of 50% or more at screening.
2. Male or female * 90 years of age at the time of consent with Karnofsky score of 70% or more at screening.
3. Diagnosis of Bullous Pemphigoid (either newly diagnosed or relapsing); if relapsing they may have previously been shown to satisfy these diagnostic criteria for BP:
a. blisters alone, or blisters and/or urticaria or papules or erythema with or without itch,

AND
b. direct immunofluorescence of perilesional skin collected near a fresh blister, erosion or papule showing linear deposition of immunoglobulin G (IgG) and/or C3 along the epidermal basement membrane zone,
AND
c. indirect immunofluorescence studies performed with patient serum on 1.0M NaCl human salt split skin, showing anti-basement membrane zone antibodies binding the epidermal side of the salt split skin OR anti-BP180 or anti-BP230 antibody positive by enzyme linked immunosorbent assay. Note, if the serum binds both the epidermal and dermal side of the salt split skin the serum must also be anti-BP180/BP230 antibody positive by ELISA for inclusion of the subject.
4. Patients with atypical Bullous Pemphigoid (ie without blisters) if they have positive direct immunofluorescence AND positive indirect immunofluorescence AND are anti-BP180 antibody positive.
5. Bullous Pemphigoid classified as either moderate or severe on the basis of the Investigator Global Assessment (IGA) at randomisation. Moderate BP classified as an IGA score of 3 and severe BP classified as an IGA score of 4.
6. Willing to receive immunisation against Neisseria meningitidis and/or antibiotic prophylaxis in accordance with applicable guidelines and local standard of care (SOC).
7. Ability to travel to site for scheduled clinic visits and be available for scheduled assessments to be performed in their place of residence by trained healthcare practitioners.
8. Provision of voluntary written informed consent. Note: Consent must be obtained prior to any study-related procedures.
9. Women of childbearing potential must agree to use two methods of contraception, one highly effective and one effective (barrier), consistently throughout the study and have a negative serum pregnancy test at screening and a negative urine pregnancy test per the schedule of events. Women are considered post-menopausal and not of childbearing potential if they have had 12 months of amenorrhea, without an alternative medical cause, or have had permanent sterilisation methods (including hysterectomy, bilateral salpingectomy and bilateral oophorectomy) at least six weeks before randomisation.
10. Males with a childbearing potential partner must agree to use two methods of contraception, one highly effective and one effective, consistently throughout the study including a barrier method.

Exclusion criteria

1. Patients with recalcitrant BP that have never achieved CDA or who have never been in complete disease remission with persistent disease after a period of 12 months from the start of super potent steroid or OCS treatment.
2. Epidermolysis bullosa acquisita, mucous membrane pemphigoid, or anti p200

pemphigoid.
3. Mucosal lesion BPDAI score accounts for >or = 30% of total BPDAI activity score at randomisation.
4. BP considered to be drug induced, in particular diagnosis of BP made within two months of starting a drug well known to induce BP * notably including, but not limited to, dipeptidyl peptidase-4 (DDP-4) inhibitor, anti-PD1 inhibitors, and certain diuretics and neuroleptics.
5. Participation in a clinical trial of an investigational product within 6 weeks of screening.
6. Treatment with BP-directed biologics as follows:
a. Any cell-depleting agents including, but not limited to, rituximab within 12 months prior to baseline.
b. Other biologics within five half-lives (if known) or 16 weeks prior to the baseline, whichever is longer.
c. Intravenous immunoglobulin within 16 weeks prior to the baseline.
7. Taking > 0.3 mg/kg/day OCS at screening.
8. Treatment with systemic immunomodulators such as dapsone or doxycycline within four half-lives of the drugs prior to baseline Day 1 (5 days for dapsone, 3 days for doxycycline).
9. Treatment with immunosuppressants (such as methotrexate, azathioprine, mycophenolate, calcineurin inhibitors) within the last two weeks prior to baseline (Day 1).
10. Treatment with an anti-complement therapy or with Zileuton (Zyflo) within the last three months prior to baseline (Day 1).
11. OCS dose no more than 0.3mg/kg/day in the 7 days before screening visit.
12. Taking super-potent topical corticosteroids (such as clobetasol propionate, augmented betamethasone dipropionate, siflucortolone valerate, fluocinonide, flurandrenolide and halobetasol propionate) and unable to discontinue them at or before the screening assessment.
13. Medical or surgical conditions at screening or Day 1, that in the Investigator's opinion would make the patient inappropriate for study entry; this might include severe medical conditions such as stroke, heart failure, or serious neoplasia with a very high risk of mortality.
14. Impaired neurological function which, in the investigator*s opinion, will prevent participation in the study.
15. Active systemic or organ system bacterial or fungal infection or progressive severe infection (including unresolved or untreated N. meningitidis infection and Escherichia coli Shiga toxin).
16. Known congenital immunodeficiency or a history of acquired immunodeficiency including a positive human immunodeficiency virus (HIV) test.
17. Active infection with hepatitis B or C.
18. Positive nasal throat swab for Neisseria species.
19. Planned major surgical procedures during the conduct of the study.
20. Known hypersensitivity to nomacopan and any of its excipients.
21. Contraindication to OCS including uncontrolled diabetes mellitus, uncontrolled hypertension, cardiac insufficiency, recent serious infection and allergy to OCS.

22. Receipt of live attenuated vaccines for example yellow fever vaccine or some influenza vaccines within 2 weeks of Day 1 (Baseline).
23. Pregnant or breast feeding or planning to become pregnant during the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	nomacopan
Generic name:	rVA576

Ethics review

Approved WMO

Date:	24-11-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	22-04-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-005987-67-NL
ClinicalTrials.gov	NCT05061771
CCMO	NL79150.042.21