# A Phase II Clinical Trial of Safety and Efficacy of Nomacopan (rVA576) in Adult Mild-to-moderate Bullous Pemphigoid Patients

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## Introduction

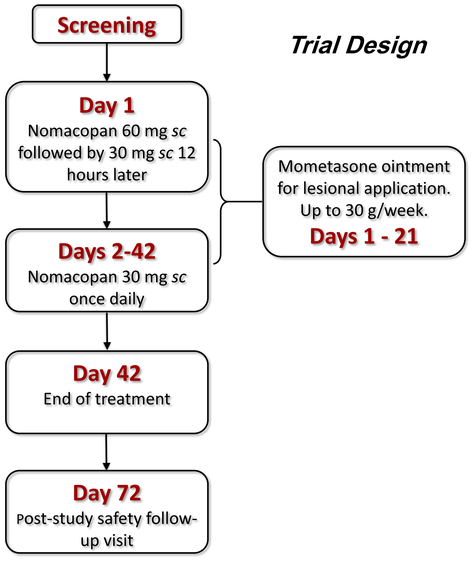
Bullous pemphigoid (BP) is an autoimmune disease characterized by severe itch, urticarial plaques and blisters. Patients are usually treated with systemic and/or topical corticosteroids and immuno-suppressive drugs which are associated with toxicity and are often poorly tolerated in the predominantly elderly patient population. BP patients have significantly elevated mortality compared to their healthy peers and currently there are no drugs approved to treat BP.

Nomacopan (rVA576) directly inhibits complement C5 and leukotriene B4 (LTB4) which are both implicated in the pathogenesis of BP. The safety and efficacy of nomacopan for treatment of BP was investigated in a Phase II study (AK801).

## Materials and Methods

AK801 was a multicenter, single-arm, phase II study of 9 patients with mild to moderate BP. Patients were allowed to use up to 30g/week topical mometasone applied only to lesions during the first 3 weeks of nomacopan treatment; use of any topical steroid thereafter was regarded as rescue therapy. In clinical practice topical mometasone is not used to treat moderate BP as its efficacy is too weak. Eligible patients received a complement ablating dose of nomacopan on day 1, then 30 mg nomacopan once daily (od) by subcutaneous (sc) injection from days 2 to 42. Patients attended the outpatient clinic on days 7, 14, 21, 28, and 42 with a follow up visit on day 72. Patients underwent safety assessments, and PK/PD measurements. Efficacy was assessed using the Bullous Pemphigoid Disease Area Index (BPDAI).

### Trial Design




### Table 1 – Baseline Data

| | | |
|---|---|---|
| **Age** | Median (range) | 75 (55-85) |
| **Gender** | Female | 5 (55.6%) |
| | Male | 4 (44.4%) |
| **Baseline Disease** | New | 5 (55.6%) |
| | Relapsing | 4 (44.4%) |
| **Disease Severity** | Mild (BPDAI < 20) | 2 (22.2%) |
| | Moderate (BPDAI 20-56) | 7 (77.8%) |
| **Comorbidities (>33% of pts)** | Hypertension | 7 (77.8%) |
| | Gastro-oesophageal reflux disease | 3 (33.3%) |
| | Type 2 Diabetes Mellitus | 3 (33.3%) |
| | Chronic Obstructive Pulmonary Disease | 3 (33.3%) |

## Results

The planned set of 9 patients were enrolled; 2 had mild BP (BPDAI <20) and 7 had moderate BP (BPDAI 20-56). The mean total BPDAI score ±95% CI on Day 1 (baseline) of dosing was 32 (±6.6, n=9). The patients were representative of the BP patient population with a median age of 75 years (range 55-85), multiple comorbidities, sex ratio 5F/4M and a 5/4 split of newly presenting or relapsing disease.

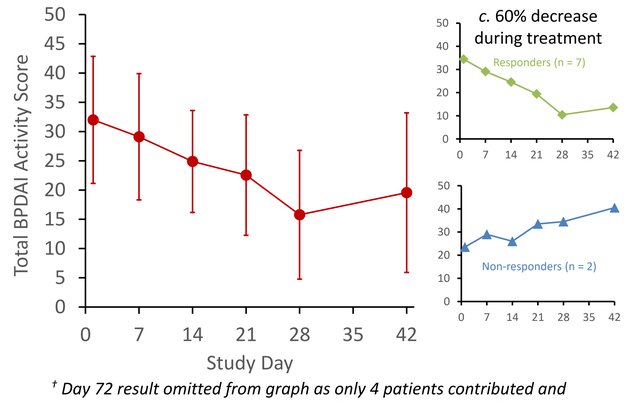
The primary endpoint of the study was safety. No subjects (0%) reported a CTCAE-grade 3, 4 or 5 adverse event which was related/possibly related to nomacopan. There were three SAEs in three subjects (33%), all of which were considered unrelated to nomacopan: two patients had 'condition aggravated' and another patient 'localised infection' of knee.

In 7 of 9 (78%) patients, the BPDAI score decreased by 4 or more points (the minimum clinically important difference) between baseline and Day 42; all but one of these patients had moderate BP. Of the 7 responders, 3 showed an ≥80% reduction and 3 an approximately 40% reduction in BPDAI score. Notably, two of these patients may have entered long term disease remission over this short period of nomacopan treatment as between the last dose of nomacopan (Day 42) and the follow up visit (Day 72), they received no additional therapy for BP. In two patients (22%), considered non-responders, the BPDAI scores increased by 3 or more points between baseline and Day 42. Both of these patients had relapsing disease.

The mean absolute decrease in BPDAI score (±95% CI) between baseline and Day 42 for all 9 subjects was 12.4 (±10.3). For the moderate BP patients (n=7), the mean absolute decrease in BPDAI score was 16 (±12.6). The mean absolute decrease in BPDAI pruritus score between baseline (mean pruritis score 17.6 ±3.0) and Day 42 for all 9 patients was 6.8 (±3.5, n = 9).

These efficacy results are supported by pharmacodynamic measures which showed >90% mean inhibition of terminal complement activity (CH50) in plasma on 30mg od nomacopan and free drug levels that exceed the concentration threshold required for complement inhibition.

### Figure 1
### Mean BPDAI (95% CI) – all patients†



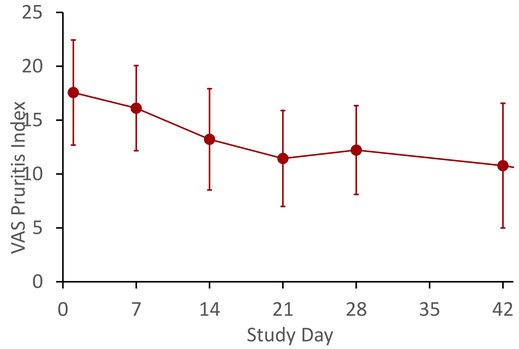

† *Day 72 result omitted from graph as only 4 patients contributed and 95% CI was high - value 28.75 (95% CI -24.33 - 81.83)*

### Table 2 – Safety Data

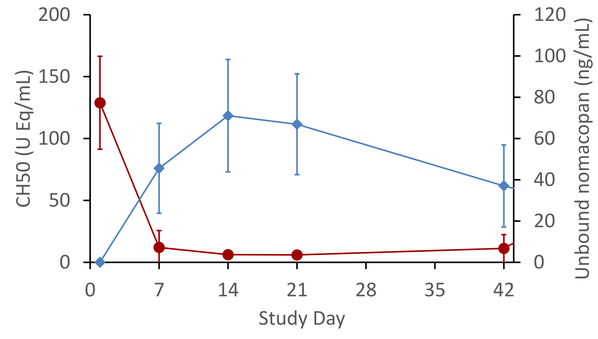
| | |
|---|---|
| **Number of Patients with any TEAEs** | 9 (100%) |
| | |
| **Number of Patients with AEs of Special Interest** | 5 (55.6%) |
| **Infection & Infestations: (urinary tract infection (3), localised infection (1), respiratory tract infection (1), upper respiratory tract infection (1) & influenza (1))** | 4 (44.4%) |
| **Condition aggravated (administration site)** | 1 (11.1%) |
| | |
| **Number of Patients with Serious AEs** | 3 (33.3%) |
| **Condition aggravated (administration site)** | 2 (22.2%) |
| **Localised infection (knee)** | 1 (11.1%) |
| | |
| **Number of Patients with Treatment Related TEAEs** | 3 (33.3%) |
| **Grade 1: taste disorder (1), erythema (1)** | 2 (22.2%) |
| **Grade 2: ventricular extrasystoles** | 1 (11.1%) |
| **Grades 3, 4, or 5** | 0 |

*TEAE = Treatment Emergent Adverse Event*

### Figure 2
### Mean Pruritis VAS Score (95% CI)




### Figure 3
### Mean CH50 & Free Nomacopan (95% CI)




## Discussion

In this single-arm phase II study in BP, nomacopan was demonstrated to be safe and improved BP symptoms in most of the study patients. Nomacopan has the potential to rapidly control BP disease and minimize the use of steroids, which often cause significant complications in the frail BP population.

Following discussion with both the FDA and the EMA, a placebo controlled phase III pivotal study of nomacopan for treatment of moderate to severe BP is planned to start in H1 2021. Patients will receive nomacopan plus oral steroid or placebo plus oral steroid for a period of 24 weeks. The primary endpoint will be achievement of sustained disease remission with important secondary endpoints of measurement of cumulative steroid use and steroid related side effects in the nomacopan versus the placebo arms.