

Disease Remission During a Short-term Treatment Phase II Study of Nomacopan in Mild-to-moderate Bullous Pemphigoid - with Final Plan for Phase III Trial

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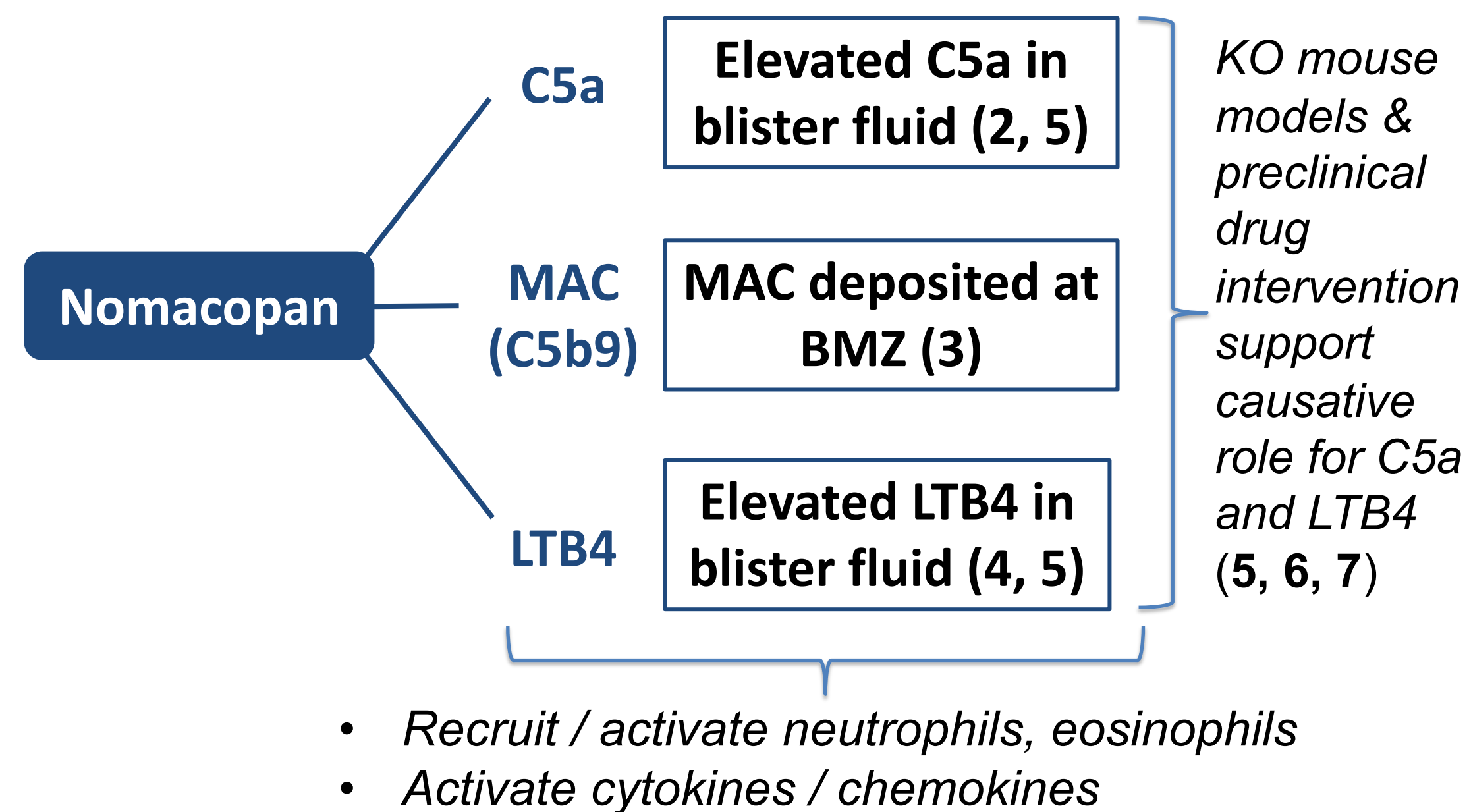


Introduction

Bullous pemphigoid (BP) is the most common of the autoimmune blistering skin diseases. It is a chronic relapsing disease characterized by severe itch, urticarial plaques and blisters. Patients are usually treated with potent systemic and/or topical corticosteroids and immunosuppressive drugs which are associated with steroid related adverse events and are poorly tolerated by the predominantly elderly patients. Mortality of BP patients is approximately 3-fold higher than their healthy peers (1). Currently there are no drugs specifically approved to treat BP, but there is a growing interest in the use of biological drugs to precisely target components of the immune system that may drive disease - in the same way that specific biologicals have been successfully developed for treatment of atopic dermatitis and psoriasis.

Nomacopan (rVA576) directly inhibits complement C5 (MAC and C5a) and leukotriene B4 (LTB4) which are both implicated in the pathogenesis of BP (Figure 1).

Figure 1 – Mode of action of nomacopan for BP: inhibition of 3 pathways that may drive disease



The safety and efficacy of nomacopan for treatment of BP was investigated in a Phase II multicentre, single-arm 42 day treatment study in 9 patients with mild-to-moderate BP. The safety, PK/PD and BPDAl data have previously been reported and showed that nomacopan appeared well tolerated and Bullous Pemphigoid Disease Area Index (BPDAl) decreased, sometimes dramatically, in patients on nomacopan.

Here, we specifically report on the disease control recorded at each clinical visit during the 6-week treatment Phase II trial. Disease control is an important variable, as it will be used to decide when to taper the adjunct oral corticosteroid dose (OCS) to be used in the planned 24 week nomacopan treatment Phase III BP randomised controlled trial whose design is also presented in this poster.

Materials and Methods

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 were permitted to use topical 0.1% mometasone (<30g/week) applied to lesions only during the first 21 days of nomacopan treatment. Patients underwent safety assessments, and PK/PD measurements. Efficacy was assessed using the BPDAl. BP disease control was also assessed by the clinician at each visit by considering three questions: 1) The number of new lesions over the last 3 days? 2) Established lesions considered healed? 3) Healed lesions extended into new lesions?

Results

The planned set of 9 patients were enrolled; 2 had mild BP (BPDAl <20) and 7 had moderate BP (BPDAl 20-56). The mean total BPDAl score \pm 95% CI on Day 1 (baseline) of dosing was 32 (\pm 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 safety and efficacy data in this paragraph were presented at the EADV 2020 meeting. In brief, the primary endpoint of study, safety, was met with no subjects (0%) reporting a CTCAE-grade 3, 4 or 5 adverse event related/possibly related to nomacopan. In 7 of 9 (78%) patients, the BPDAl score decreased by 8 or more points (the minimum clinically important difference is 4) between baseline and Day 42; all but one of these patients had moderate BP. The BPDAl decreased by a mean of c.60% in the 7 patients who showed an improvement in disease while on nomacopan treatment. Two patients were non-responders and their symptoms did not improve during treatment.

The new analysis of BP disease control during the 42 days of nomacopan treatment shows:

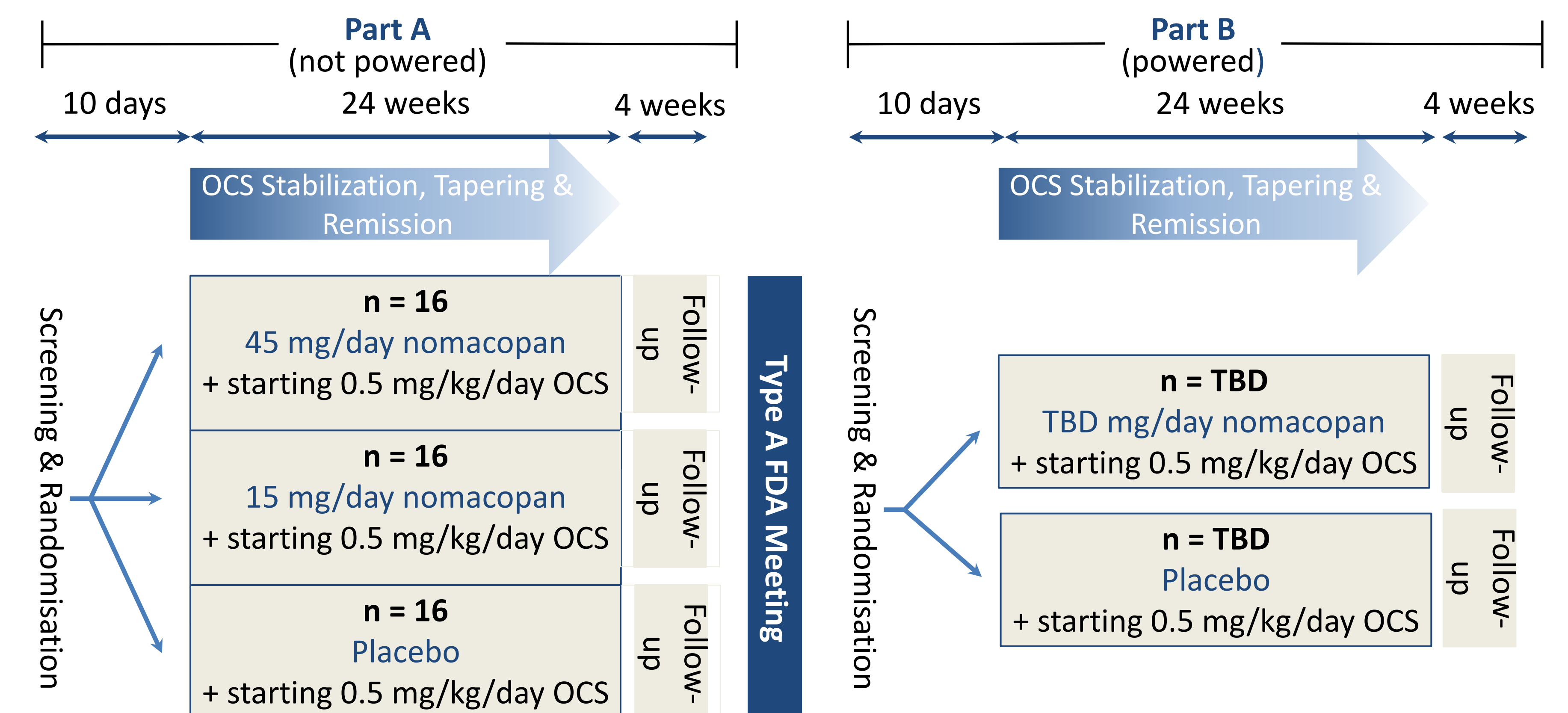
- 5 of 9 (56%) patients had no new lesions for the last 14 days of the 42-day treatment period.
- In 7 of 9 (78%) patients established lesions were healed for the last 14 days of treatment.
- In 4 of 9 (44%) patients healed lesions did not extend into new lesions for the last 14 days of treatment.
- 3 patients (33%) had evidence of complete disease remission on the basis of complete disease control over the last 14 days of treatment.
- 2 of these 3 patients were still in disease remission at Day 72 follow up as they received no further meds for BP.

Table 1 – Summary of Disease Control (and number of new lesions) by Day of Nomacopan Treatment

Patient (n = 9)	DAY 7	DAY 14	DAY 21	DAY 28	DAY 42	Predicted Ph 3 OCS dose Wk 6
Good responder	Yes	Yes	Yes	Yes	Yes	Minimal
Good responder	Yes	Yes	Yes	Yes	Yes	Minimal
Good responder	No	Yes	No (1)	Yes	Yes	0.2mg/kg/day
Responder	Yes	Yes	Yes	Yes	No (NC ^A)	0.3mg/kg/day
Responder	Yes	Yes	Yes	No (1)	No (2)	0.4mg/kg/day
Responder	No	No	Yes	Yes	No	0.4mg/kg/day
Responder	No (2)	No (2)	No (NC ^A)	No (4)	No (NC ^A)	0.75mg/kg/day
Non-responder	No (4)	No (3)	No (3)	No (5)	Yes	0.4mg/kg/day
Non-responder	No (15)	No (12)	No (7)	No (7)	No (12)	Treatment failure

^ANC – not counted

Figure 2 – BP Phase III Design Provides Interim Readout after Part A



Phase 3 trial design

The data from AK801 has informed the design of a 24-week treatment controlled study of nomacopan in moderate-to-severe BP to start H1 2021. The trial design (Figure 2) has been discussed with FDA and EMA. Patients will be randomized to nomacopan plus OCS or placebo plus OCS. After an initial stabilisation phase, steroids will be tapered if patient has ongoing disease control to a minimal dose of OCS (0.1mg/kg/d). The primary endpoint is disease remission for at least 8 weeks at week 24 on minimal OCS.

The trial has a Part A / Part B structure. Part A will confirm the safe and effective dose of nomacopan in BP patients receiving adjunct OCS. Part B is planned to be pivotal using a single fixed dose of nomacopan/OCS versus placebo/OCS.

Discussion

Nomacopan appears to have the potential to rapidly control disease and minimize the use of steroids in BP patients.

The phase III steroid tapering design discussed with the FDA and EMA is supported by the phase II data which shows, if the steroid taper rules for the phase III trial had been followed, 3 patients would likely have been on minimal steroid or 0.2mg/kg/day by week 6, and 3 further patients on 0.3 or 0.4mg/kg/day by week 6 (Table 1). In the phase III trial with adjunct steroid patients will have until week 16 to be on minimal steroid and eligible to assess primary endpoint.

Importantly, the phase III design permits a read out after Part A to select a fixed dose to use in pivotal Part B, rank secondary endpoints and define minimal patient numbers.