ARREST-BP: A Randomised Placebo-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of Nomacopan therapy in Bullous Pemphigoid patients

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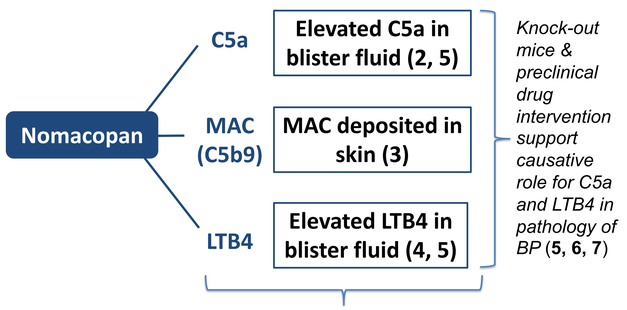
Background

As yet, there are no drugs specifically approved to treat bullous pemphigoid (BP), but there is growing interest in the use of biological drugs to precisely target components of the immune system that may drive BP – akin to the successful development of biologicals for treatment of atopic dermatitis and psoriasis.

Nomacopan is a biological therapy from Akari Therapeutics that specifically inhibits two proinflammatory mediators, complement C5 and leukotriene B4. Both mediators are believed to have important roles in the development, elaboration (via cytokines and other mediators) and maintenance of skin lesions in patients with BP (**Figure 1**).

BP is difficult to treat and achieving disease remission and preventing relapses usually requires aggressive long-term systemic immunosuppressive therapy. However, such treatment with steroids (normal first-line therapy) and immunosuppressants can have severe side effects and is probably a major reason for the 3 – 4-fold increase in the 1-year mortality of BP patients compared to their peers.

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



The safety, pharmacokinetics and efficacy of nomacopan have been investigated in a completed Phase II multicentre, single-arm study in 9 patients with mild-to-moderate BP (NCT04035733). Nomacopan was well tolerated and met the primary and secondary endpoints for safety and efficacy. With the Bullous Pemphigoid Disease Area Index (BPDAI - which provides a measure of lesion intensity and size) decreased, sometimes dramatically and rapidly, in patients receiving nomacopan for only 6 weeks.

Here, we describe the design of the ARREST-BP Phase III trial of nomacopan for treatment of BP which is approved in the USA and targeting to recruit patients in the USA and EU this year

Aim of the Phase III study

The ARREST-BP study will test whether:

- Nomacopan therapy with adjunct oral corticosteroid (OCS) is a more effective therapy than OCS alone
- The adjunct OCS can be tapered more rapidly with than without nomacopan
- Nomacopan therapy with adjunct OCS is at least as safe and well tolerated as OCS alone

If the ARREST-BP trial is successful, the data from the completed study will be used to support a marketing application for nomacopan for treatment of BP.

Trial Design and Opening of Study

ARREST-BP is a multinational, 24-week study of nomacopan for treatment of moderate-to-severe, newly presenting or relapsing BP. Patients will be randomized to either nomacopan plus OCS or placebo plus OCS (**Figure 2**). Following an initial stabilisation phase, steroids will be tapered according to the therapeutic response until patients are on a minimal dose of OCS. ***The primary endpoint will be sustained disease remission on minimal OCS (0.1mg/kg/day) for at least 8 weeks at week 24.***

The study will be in two parts. Part A will examine two different doses of nomacopan. One (45mg once daily) designed to fully inhibit terminal complement activity (TCA) and leukotriene B4 and the other dose (15mg once daily) designed to partially inhibit TCA and fully inhibit leukotriene B4. The latest mechanistic pharmacokinetic model (developed by BAST Inc) indicates that 75% and 98% of patients on once daily doses of 15mg and 45mg, respectively, will have their terminal complement activity inhibited by 90% or more.

The minimally effective dose of nomacopan determined in Part A will be used for Part B the confirmatory study.

Part A is currently opening in 32 sites the USA, Germany, Poland, France and the Netherlands.

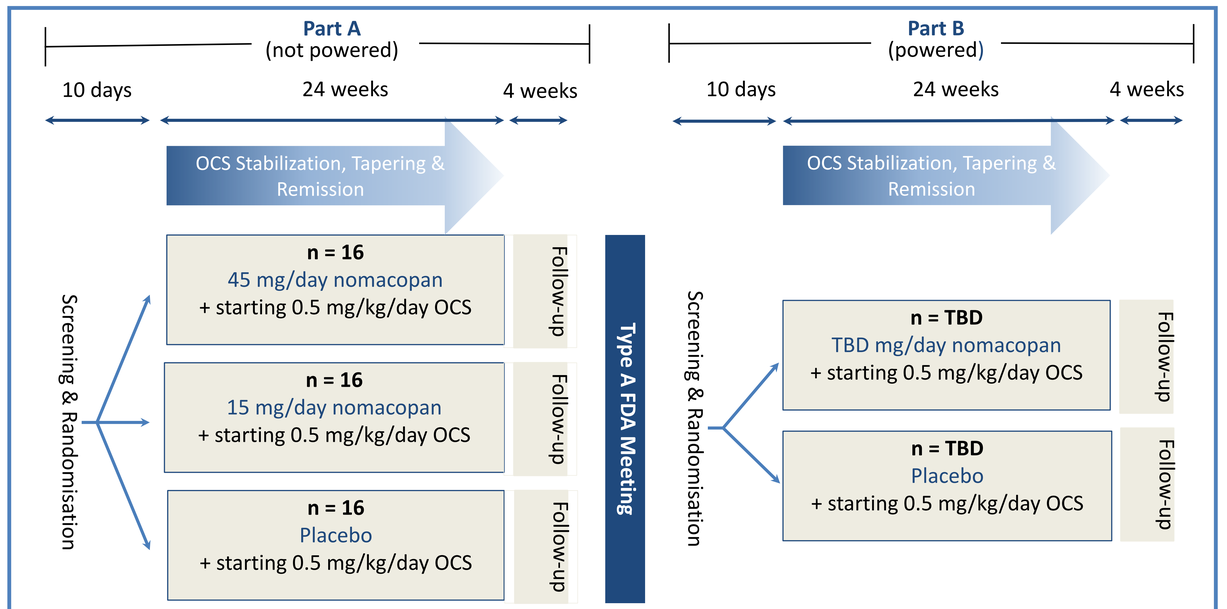
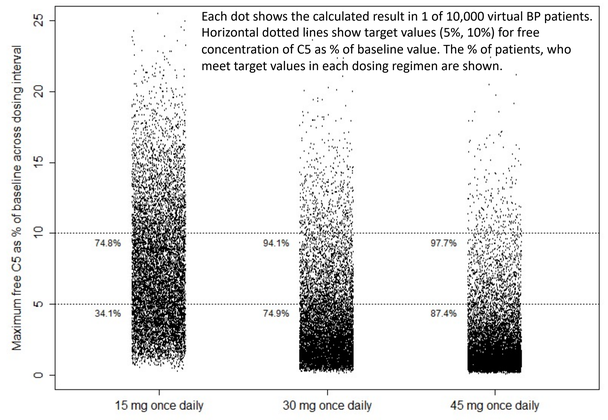


Figure 2 – BP Phase III Design Provides Interim Readout after Part A

Figure 3 – Plot of simulated maximum free C5 at steady state as % of baseline value with once daily dosing



Summary

The multi-national Phase III ARREST-BP trial using nomacopan for treatment of bullous pemphigoid has the potential to redefine the standard of care for BP.

The paradigm shift may be achieved by a treatment that:

a) Has a rapid onset of action
b) Permits rapid reduction of steroid use to reduce morbidity/mortality – as there is the potential to be on minimal steroid by week 6
c) Permits home care rather than treatment in hospital (topical clobetasol propionate)

More details about the Phase III trial and prior presentations on the Phase II trial data are available at https://www.akaritx.com.

REFERENCES: (**1**) Tedbirt et al., *JAMA Dermatol.* 2021;doi: 10.1001/jamadermatol.2020.5598; (**2**) Diaz-Perez & Jordon, *Clin Immunol Immunopathol.* 1976;5:360-370; (**3**) Dahl et al., *J Invest Dermatol.* 1984;82:132-135; (**4**) Kawana et al., *Acta Derm Venereol.* 1990;70:281-285; (**5**) Sezin et al., *JCI Insight.* 2019;4:e128239 https://doi.org/10.1172/jci.insight.128239; (**6**) Sezin et al., *J Invest Dermatol.* 2017;137:1104-1113 doi: 10.1016/j.jid.2016.12.021; (**7**) Edwards et al., *Frontiers Immunol.* 2019;10:1477

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