



Phase II clinical trial of safety and efficacy of rVA576 (nomacopan) in adult mild to moderate bullous pemphigoid patients

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Current Bullous Pemphigoid (BP) Treatments

None of these treatments has yet been proven effective in randomized controlled clinical trials

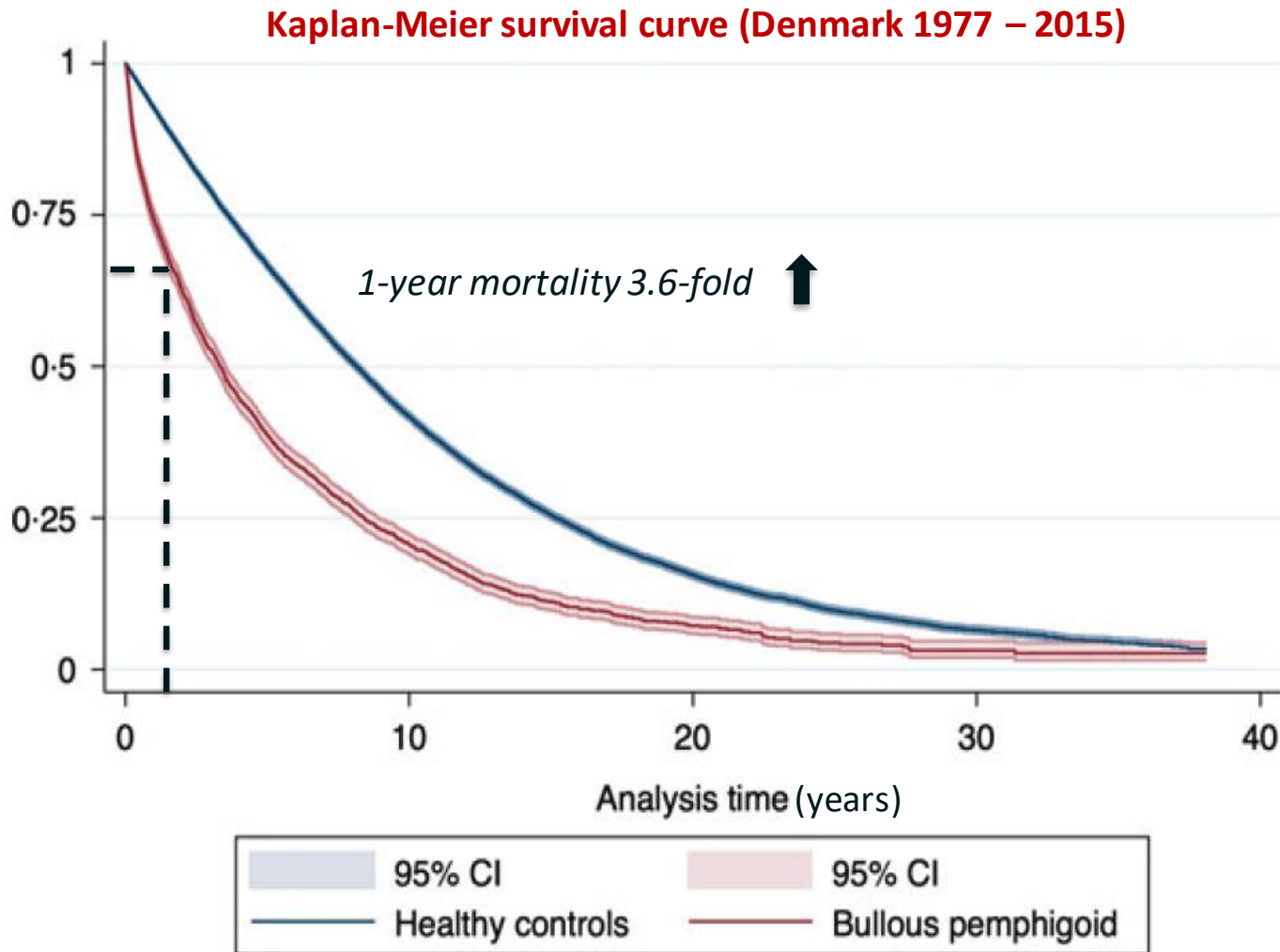
Basis Therapy

- Superpotent topical corticosteroid (clobetasol propionate) 2x daily over entire body
- OR**
- Oral prednisolone/prednisone (0.3-1.0 mg/kg body weight)

Adjuvant Therapy

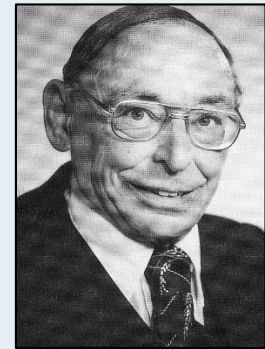
- Immunosuppressants (azathioprine, mycophenolate mofetil, methotrexate)
- Dapsone
- Doxycycline
- Intravenous immunoglobulins (IVIG)
- Rituximab

1-year mortality increased c.3-fold despite treatment



Kibsgaard *et al.*, BJD 176: 1486-1491 (2017)

1953
(precorticosteroid era)



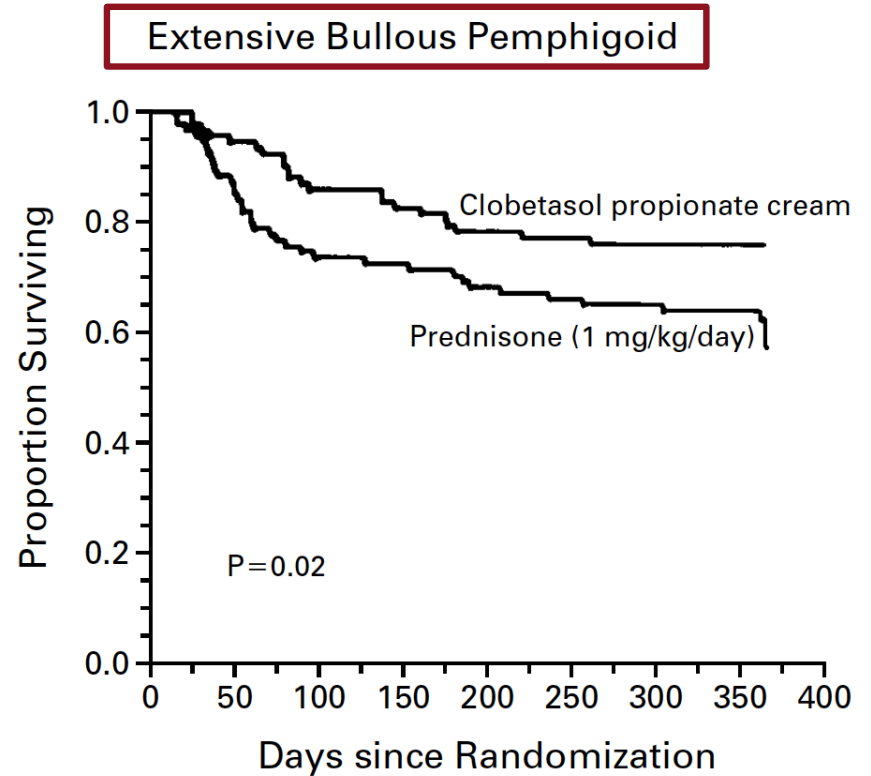
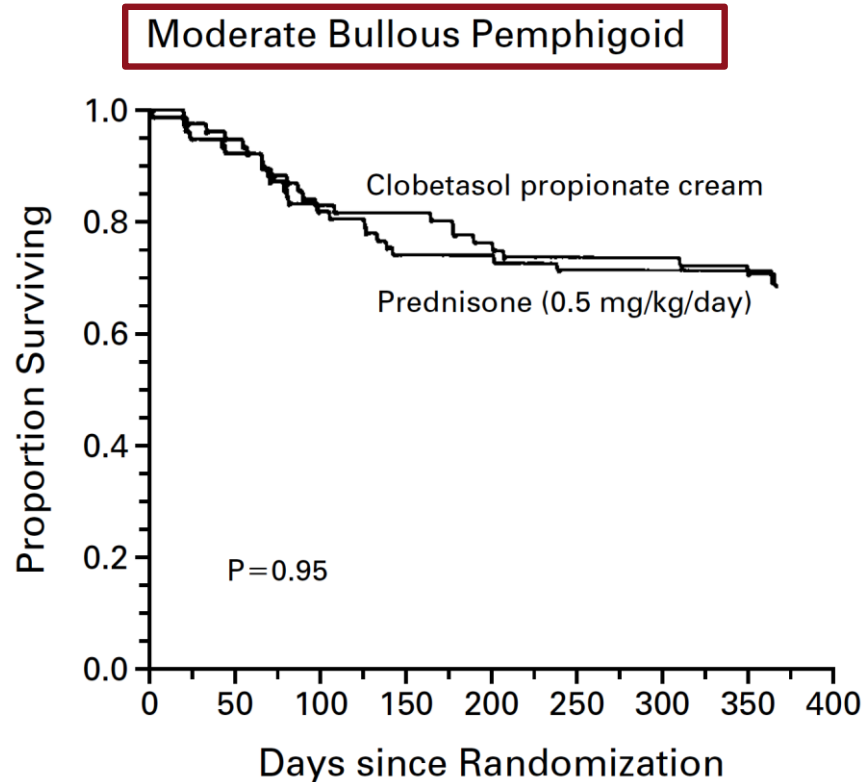
Walter Lever

First description of BP
on 30 patients



1-year mortality: 24%

Systemic Corticosteroids Associated with Higher Mortality than Superpotent Topical Corticosteroids



1-year mortality

30%

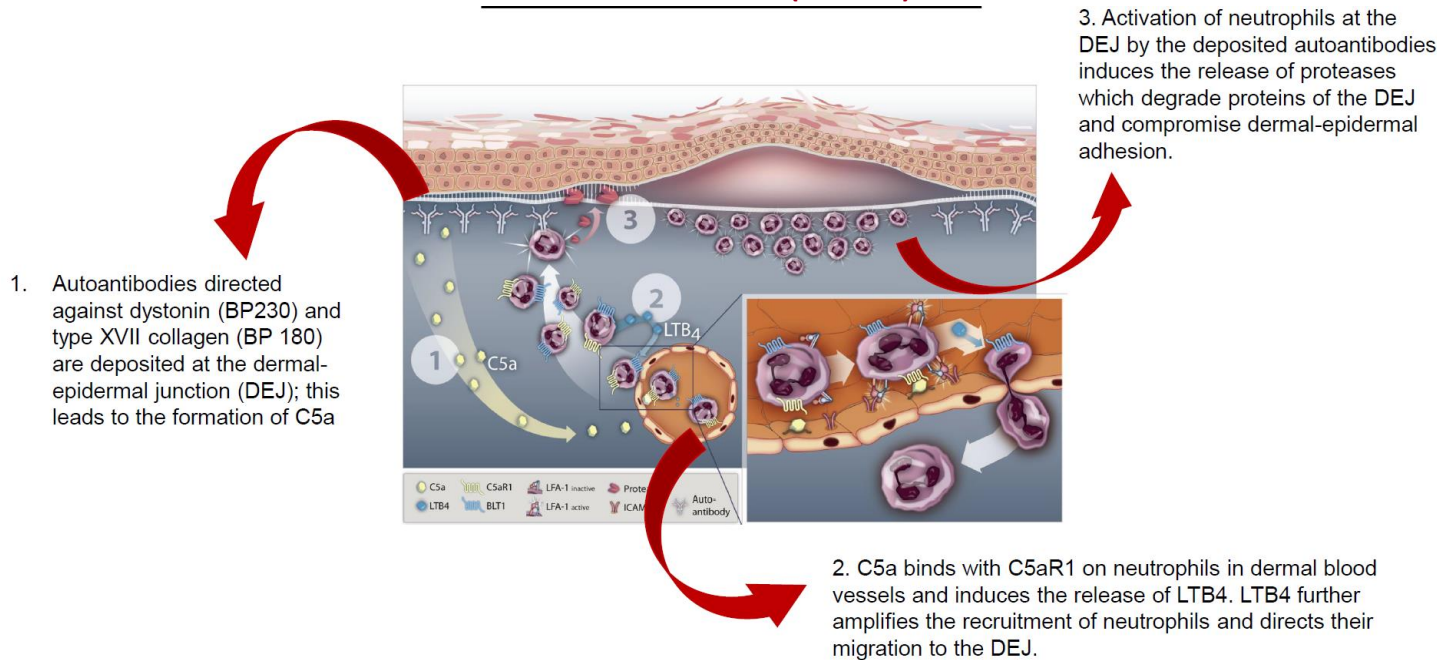
**Clobetasol:
Prednisone:**

**24%
41%**

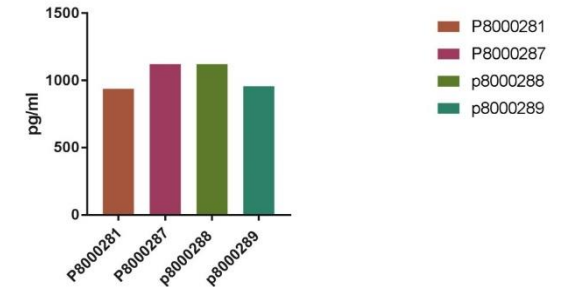
Joly et al., NEJM 346: 321-327 (2017)

Role of complement C5 and LTB4 in BP Pathology

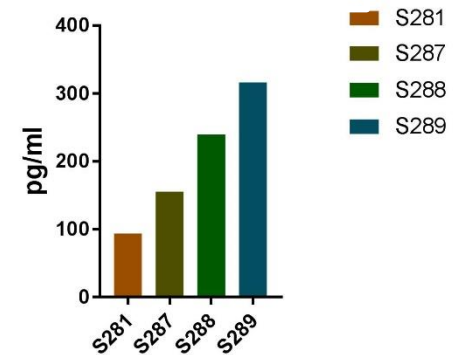
Sadik *et al.*, *Semin Immunol* 37:21-29 (2018)



C5a levels in blister fluid diluted 1:25

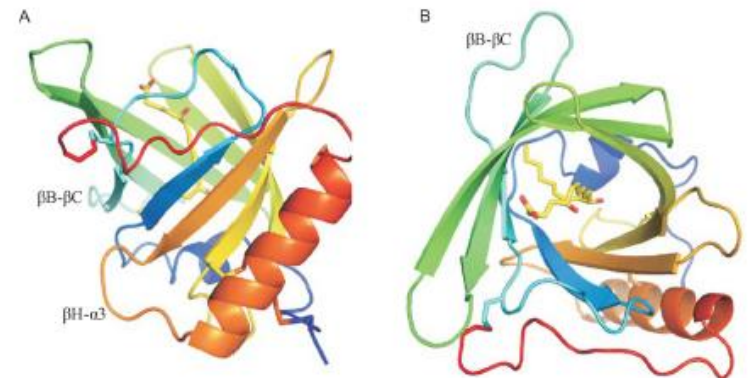


LTB4 levels - human blister fluid



Preclinical evidence for efficacy of nomacopan in BP

- Nomacopan is Phase 3 ready biological bifunctional inhibitor of C5 and LTB4 dosed subcutaneously (s.c.)
- Dose dependent effect in model of BP-like epidermolysis bullosa acquisita (EBA)
- Combined C5/LTB4 found more effective than LTB4 only



Sezin *et al.*, *JCI Insight* 4:e128239 (2019)

Bullous Pemphigoid Phase II Study

Patients with Mild-to-Moderate Disease

Trial approved in Netherlands (2 sites) and Germany (6 sites)

Study design

- Phase II Single arm (n = 9); 42 days treatment
- Test role of C5 & LTB4 dual inhibition in improving BP outcomes
- Active bullous pemphigoid; newly diagnosed or recurrent

Treatment

- Nomacopan s.c. dosing
- Day 1: 60 mg and 30 mg 12 hours later, Day 2-42: 30 mg od

Primary endpoint

Safety

Secondary endpoints

Efficacy evaluated by BPDAl
(BP disease activity index) and QoL at day 42

- Prior to first dose of nomacopan: various SOC drugs used by enrolled patients, including mometasone, clobetasol, dermoxin, dapson, and dexamethasone were stopped at least one week prior to starting nomacopan
- Day 1 to 21: nomacopan (30 mg once daily) + lesional mometasone only
- Day 21 to 42: nomacopan only
- Any use of mometasone or any other steroid after Day 21 considered rescue therapy

Patient demographics & comorbidities

Age (median & range)
71.5 years (55 – 75)

Sex and ethnicity
4 Female, 2 Male; All white

Weight and BMI (median & range)
75kg (64 – 98) and BMI 28 (25 – 40)

Karnofsky performance score (median & range)
75 (60 – 90)

**Wide range of comorbidities
of which most common**

Hypertension: 5 of 6 patients

Diabetes: 4 of 6 patients

COPD: 2 of 6 patients

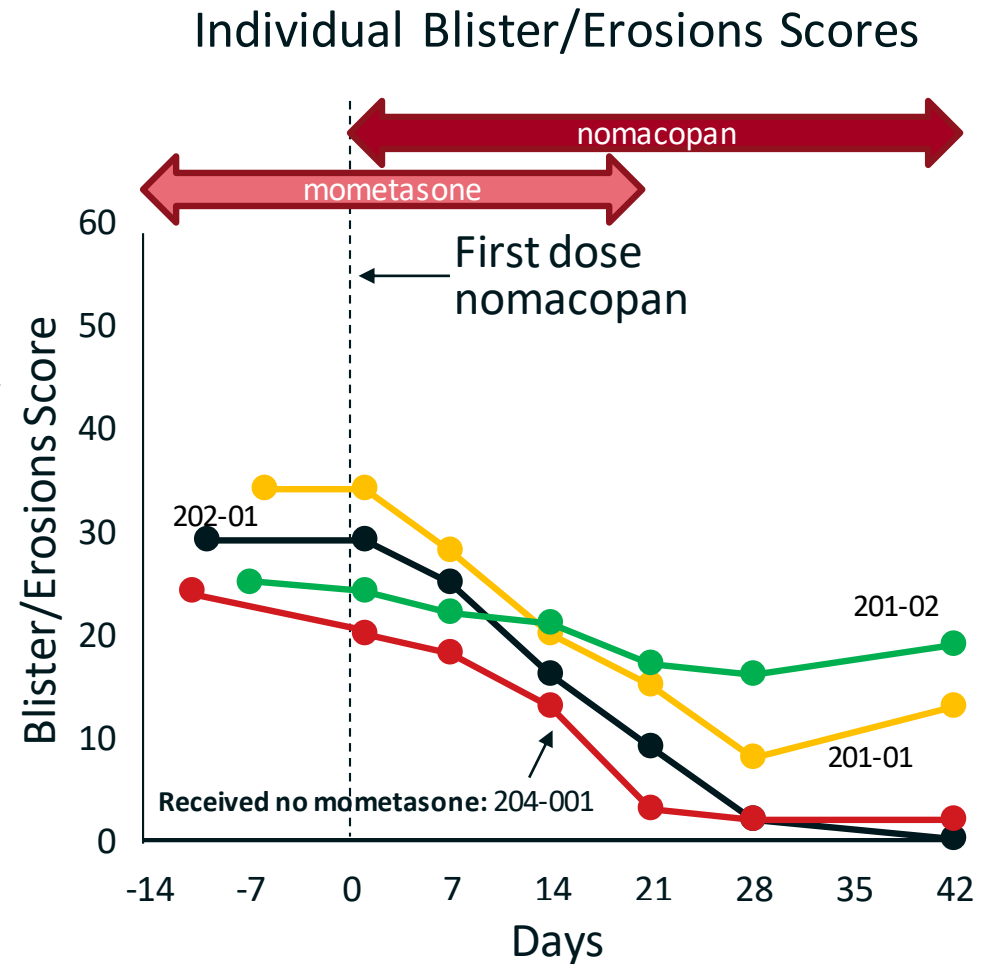
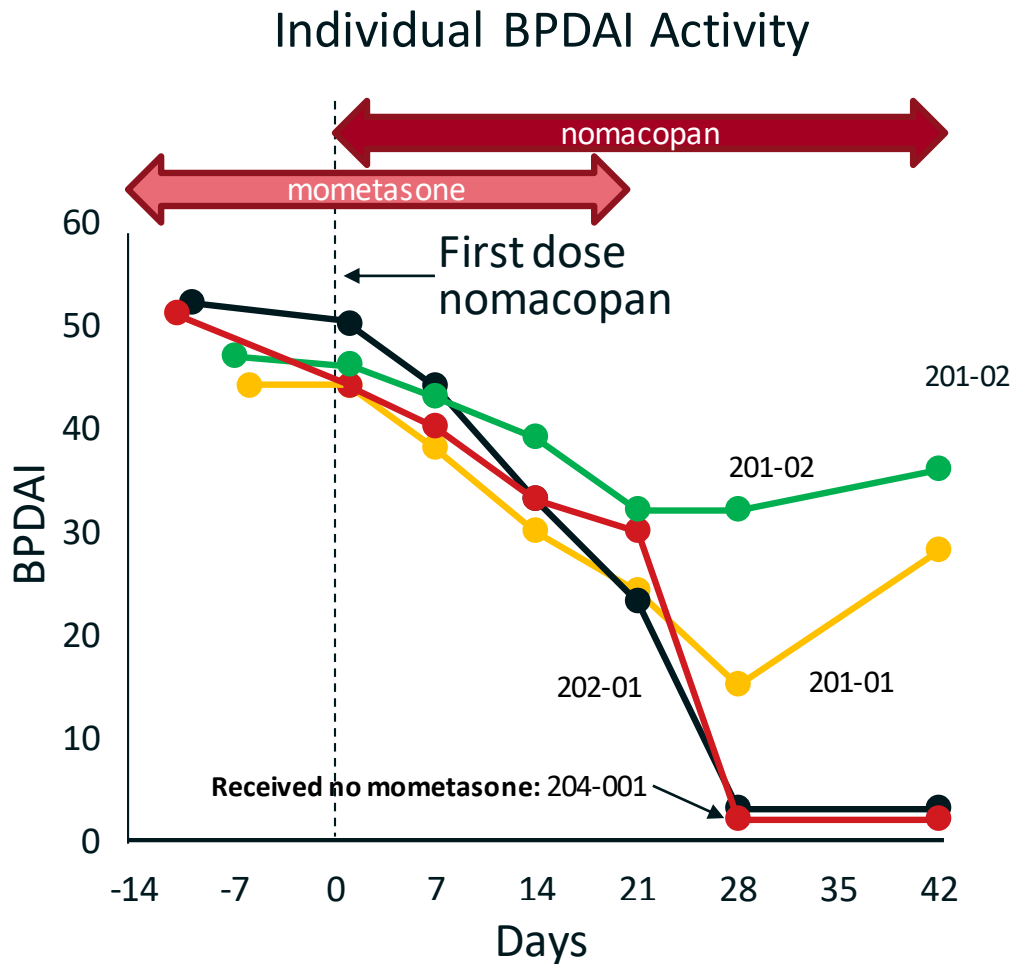
Safety of nomacopan in BP trial

Good tolerability in frail older population (n = 6)

Primary endpoint safety

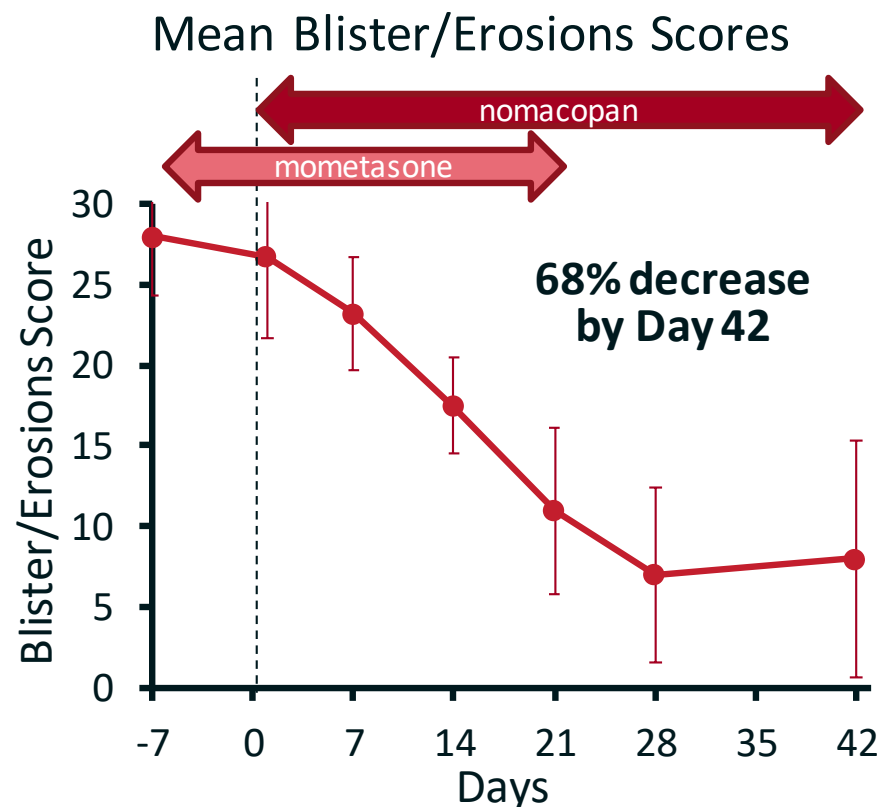
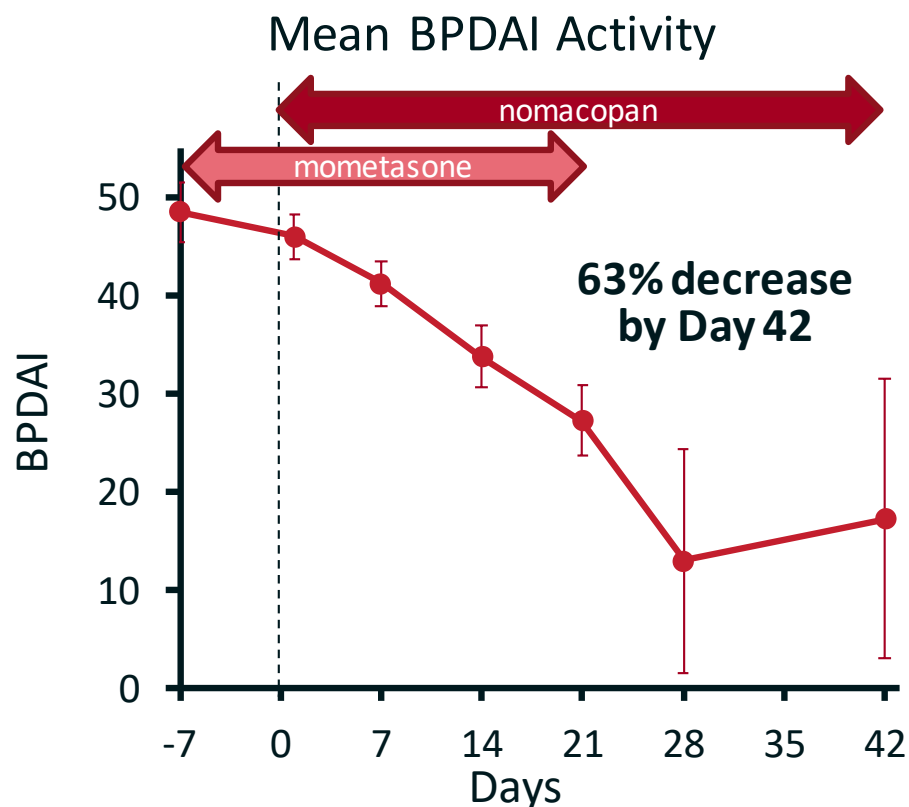
- No drug related SAE
- Five subjects reported a total of 14 AEs including flu symptoms, headache, cut finger, itch, urinary tract infection, cold, leg ulcer, and increasing bullous pemphigoid symptoms
- One subject reported 12 AEs including itch, headache, raised blood pressure, urinary tract infection, injection site erythema, and increasing bullous pemphigoid symptoms.
- Similar good tolerability reported in PNH, AKC trials and extended duration safety studies with over 20 years cumulative patient data

Efficacy Nomacopan Patients with Moderate BP Rapid Improvement - Individual BPDAl & Blisters



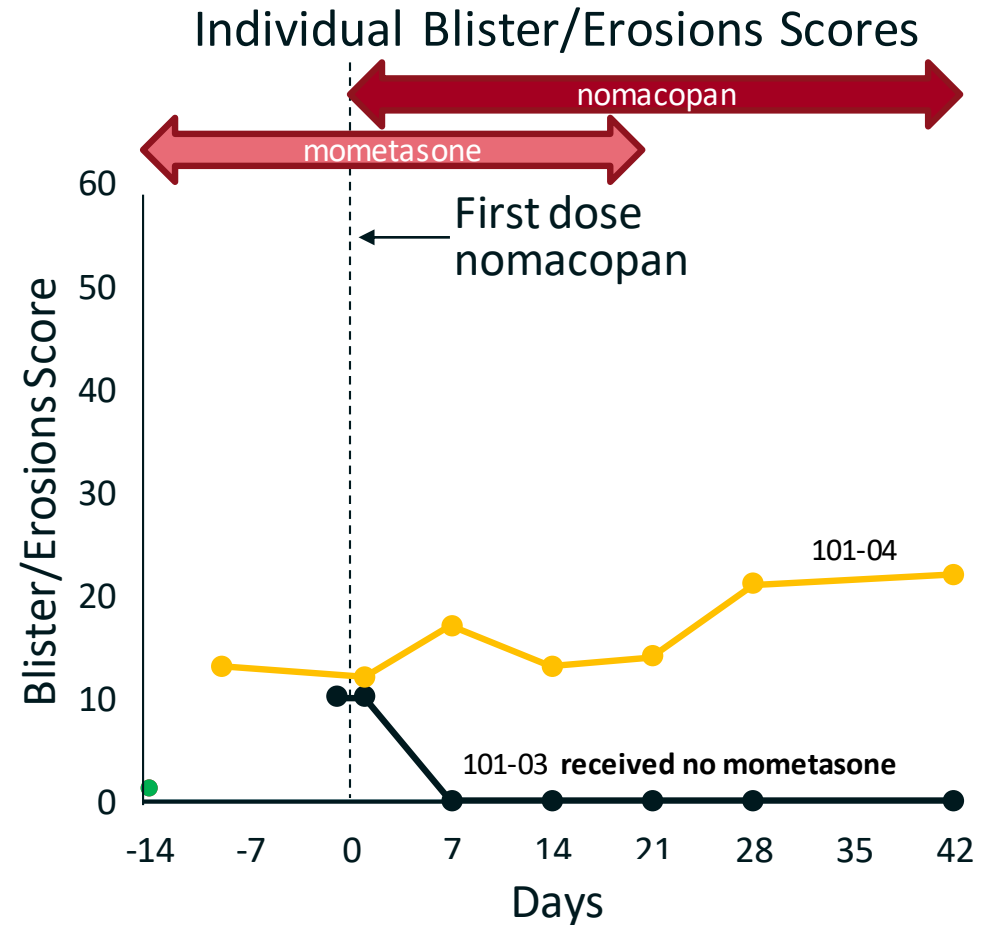
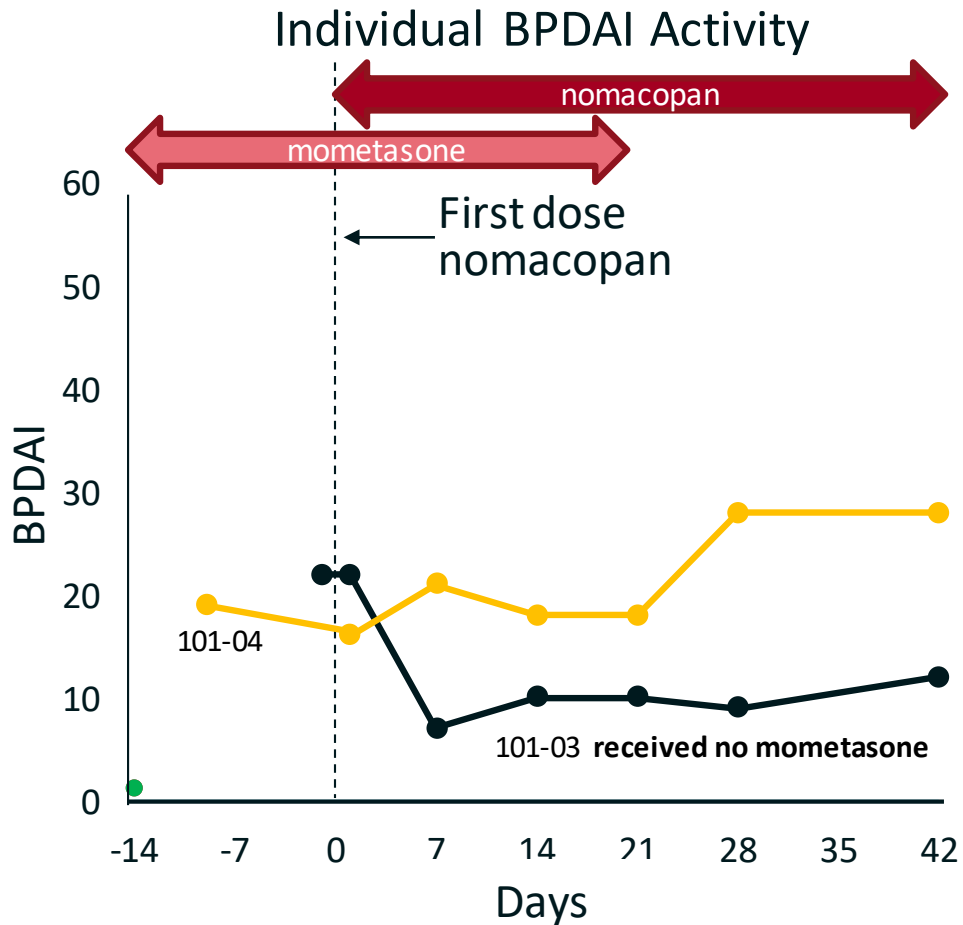
BPDAl global >50 at entry all 4 patients

Marked Improvement in Mean BPDAI & Blister Score in the 4 Moderate Patients Treated with nomacopan



- All four patients were on boundary between moderate and severe, **reflecting patient target group for Phase 3 trial (moderate and severe)**
- All patients saw a rapid decline in BPDAI activity and blister score \pm 90% confidence interval
- Pruritis score (itch) 54% decrease
- Clinical improvement in line with expected SOC response / significant intra-patient variability

Mild Patients Treated with Nomacopan: Individual BPDAI & Blister Scores



- One mild patient responded well with a rapid and complete resolution of blisters
- Second mild patient showed no improvement on nomacopan or while on rescue therapy (lesional clobetasol and oral prednisolone) after day 28
- Unresponsive patient had multiple co-morbidities and entered the trial after a relapse while on multiple topical steroidal treatments for 86 days these steroids were stopped 7 days before starting nomacopan

Nomacopan BP Clinical Study Conclusions

Clinical Response

- Clinical response seen in 5 of 6 treated patients
- 3 of 6 patients showing > 90% improvement blisters/erosions

Steroid-Sparing

- Pronounced corticosteroid-sparing effect; nomacopan suppressed BP in combination with mometasone which is substantially less potent than clobetasol/prednisone which are usually used to treat BP

Monotherapy Potential

- May be effective as monotherapy and may facilitate increased outpatient treatment of BP

Potentially Decreased Mortality

- Due to a favourable safety profile vs. current SOC, nomacopan might decrease BP patient mortality

Acknowledgements

MANY THANKS TO ALL AK801 CLINICAL COLLABORATORS

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- Lübeck
- Groningen
- Dresden
- Kiel
- Würzburg
- Freiburg
- Maastricht

Akari plans to start a Phase 3 trial in H2 2020

www.akaritx.com

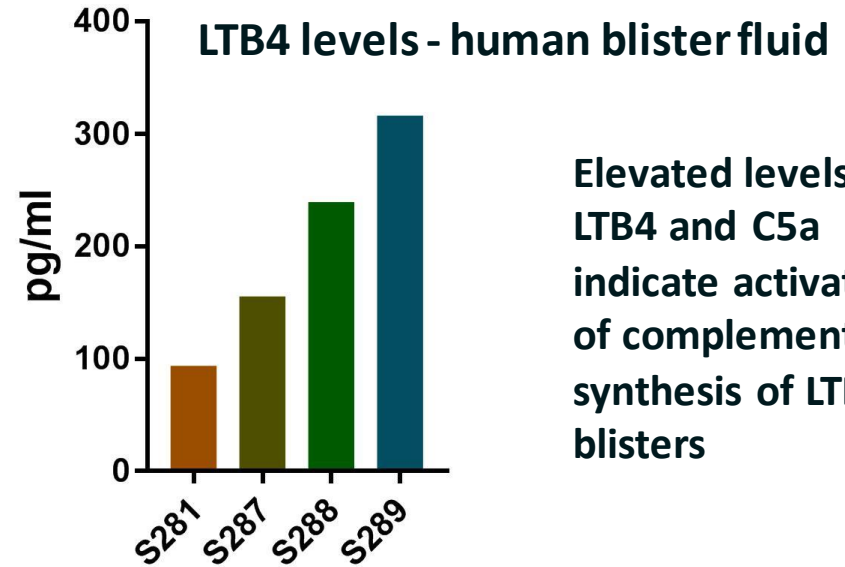
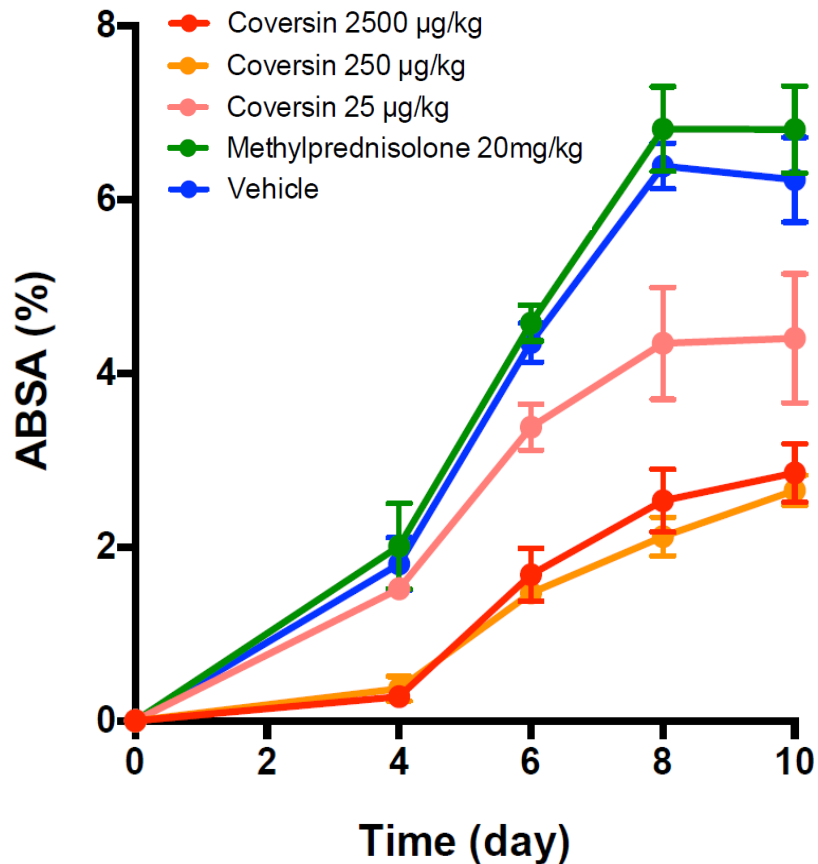
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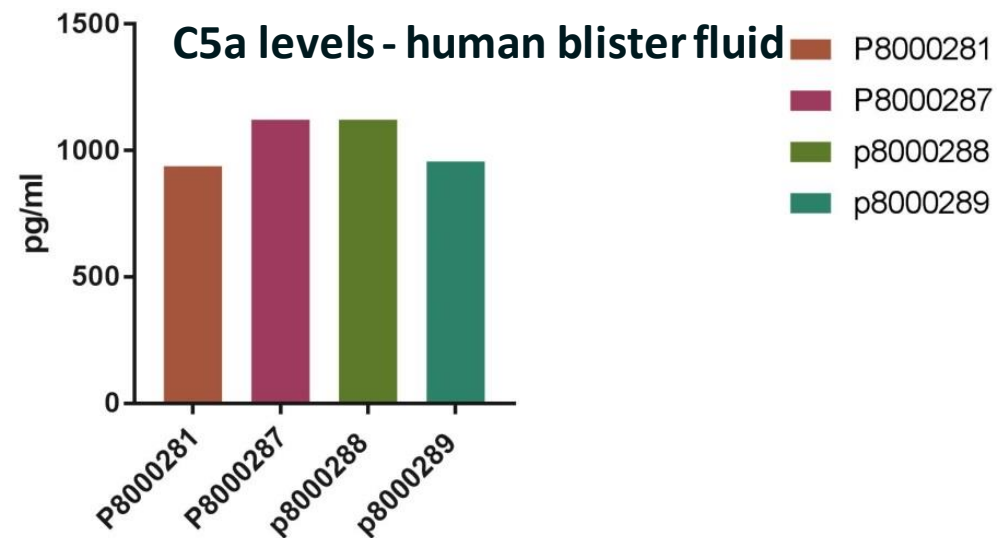
Appendix

Preclinical Efficacy and Elevated C5a/LTB4 (in Man)

Preclinical passive mouse model of epidermolysis bullosa acquisita (EBA) from Dr. Sadik in Lubeck, Germany a leading Bullous Pemphigoid center

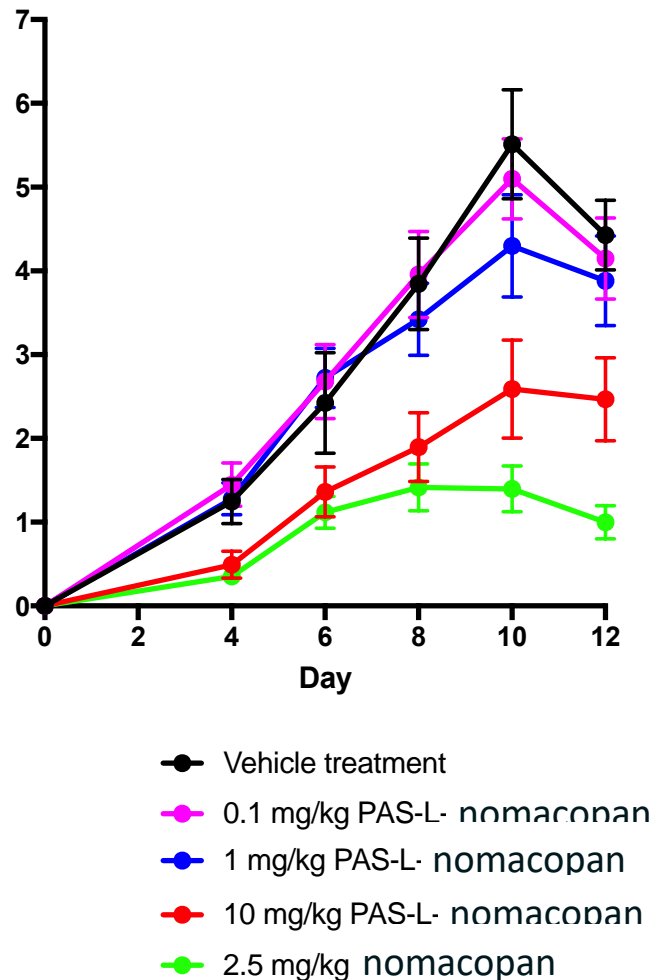


Elevated levels of LTB4 and C5a indicate activation of complement and synthesis of LTB4 in blisters



- Clear dose response
- ~60% reduction in affected area on nomacopan (SC) compared to vehicle or steroid
- P=0.0023 between vehicle and 250 µg/kg

Dual Acting Nomacopan Significantly More Effective Than Long-Acting Nomacopan Only Inhibiting LTB4



- Long acting LTB4 only nomacopan (10mg/kg) ameliorates blister formation but is less effective than the molar equivalent dose of nomacopan (2.5mg/kg) [right panel]
- 0.25mg/kg dose of nomacopan ameliorates blisters but the molar equivalent dose of long acting LTB4 only nomacopan (1mg/kg) is ineffective (see paper)

CONCLUSION:

Both C5 and LTB4 inhibition needed for full efficacy of nomacopan in EBA model

AK801 Nomacopan BP Study

Patient Demographics

Pt #	Age (Yrs)	Sex	Ethnicity	Weight (kg)	Height (cm)	BMI	Karnofsky Score	Medical History
1	70	F	Wh	74	160	29	90	2016: Suspicion of pemphigoid 2010: Lobectomy lung, COPD 2004: Anxiety, Cataract, IBS, Dry eyes, Rhinitis, Reflux, Joint pain, Myalgia, Osteoporosis
2	75	M	Wh	89	172	30	70	2018: Keratosis actinica, Neuropathy 2017: Nephrolithiasis, Neuropathy 2016: Acquired flatfoot; 2011: Metabolic syndrome 2006: Diverticulosis; 2002: Diabetes mellitus II 1999: Iron deficiency anemia 1994: Essential hypertension, COPD
3	66	F	Wh	64	160	25	80	2018: Coronary heart disease 2017: Cerebral infarction, Dyslipidemia 2015: Uterine cysts, Adenoma of adrenal gland 2011: Iatrogenic hypothyreosis (post radio-iodide) 2009: Arterial Hypertension; 1999: Diabetes Type I

AK801 Nomacopan BP Study

Patient Demographics continued

Pt #	Age (Yrs)	Sex	Ethnicity	Weight (kg)	Height (cm)	BMI	Karnofsky Score	Medical History
4	55	F	Wh	98	157	40	80	2018: Thumb joint arthrosis 2014: Hypertension 2012: Hypothyroidism 2011: Depression UNK: Nickel allergy, Cobalt sulfat allergy
5	73	F	Wh	74	163	28	60	2019: Bullous Pemphigoid 2019: Vitamin B&D & folic acid deficiencies 2017: Hyperlipoproteinaemia 2016: Hyperuricemia, Chronic pain syndrome 2013: Leg paresis 2012: Spinal stenosis, Scoliosis 2011: Hypertension, Diabetes Type II, Spondylolisthesis
6	78	M	Wh	75	168	27	70	2012: Nephrolithiasis 2010: Rectal cancer 2005: Diabetes mellitus 1980: Hypercholesterolemia, Hypertension UNK: Tachycardia