Development of PAS-nomacopan for treatment of geographic atrophy and its protection of retinal function in a blue light model of retinal damage

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Background

PAS-nomacopan (66kDa) is in development for the treatment of geographic atrophy (GA), an advanced form of dry age-related macular degeneration (AMD). The drug is a long acting, PASylated (not PEGYlated) form of nomacopan, a small protein (17kDa) Phase 3 clinical candidate, which is a potent bispecific inhibitor of complement C5 activation and the proinflammatory fatty acid leukotriene B4 (LTB4)[2]. PAS-nomacopan is as potent as the parent molecule[3], has a vitreous half-life in rabbits of 7-8 days and accumulates in retina and choroid at circa 25% of its concentration in vitreous. This profile potentially supports:

- an intra-vitreous dosing (IVT) interval target of 3 months or longer in humans,
- efficacy in GA akin to the clinically approved C5 inhibitor,
- possibility that inhibition of LTB4, which when raised can induce VEGF-A in preclinical models, may prevent elevated rates of choroidal neovascularization (CNV)[4], a harmful side effect in GA patients treated with complement-only inhibitors.

FIGURE 1

PAS-nomacopan may inhibit key immune pathways that are drivers of geographic atrophy (GA) & choroidal neovascularization (CNV)

PAS - nomacopan	C5a	C5a can increase VEGF-A release[5], however anti-C5a therapy alone not effective in a dry AMD model[6]
	MAC (C5b-9)	MAC accumulates in aging choriocapillaris and is associated with death of RPE in AMD patients[7]
	LTB4	LTB4 induces VEGF-A & MCP1, which recruit macrophages in laser CNV[4,8-10] and mediate photoreceptor loss in AMD models[11]

Aim

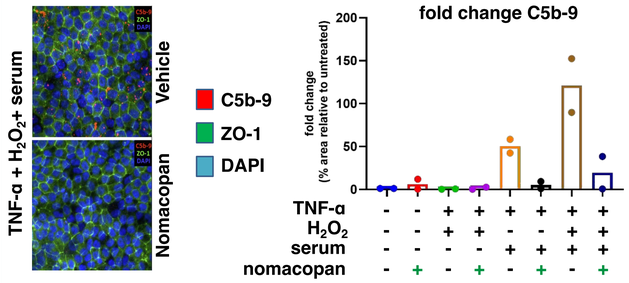
Nomacopan has demonstrated inhibitory activities against drivers of GA and CNV in relevant *in vitro* models (Fig. 1 & 2). To establish the *in vivo* efficacy of PAS-nomacopan in GA, we conducted a pilot study using a blue light (BL)-induced damage model of macular degeneration (Fig. 3). This model is driven by both complement activation and microglial recruitment, making it highly suitable for testing the respective dual inhibitory activities of PAS-nomacopan against C5 and LTB4[12]. Further investigation will involve the use of PAS-nomacopan and variants lacking either C5 or LTB4 inhibition (Fig 4) to elucidate therapeutic mechanisms in this model.

Here, we report on the progress towards efficacy testing of PAS-nomacopan as a potential treatment for geographic atrophy and strategies to discern *in vivo* actions of C5 and LTB4 inhibition

FIGURE 2

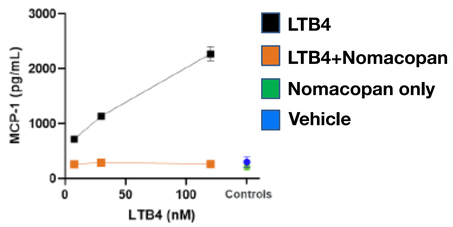
In vitro C5 and LTB4 inhibitory activity of nomacopan

A) Nomacopan inhibits C5b9 formation on iPSC-RPE cells



iPSC-retinal pigment epithelium cells treated with TNF-α, H_2O_2 and serum exhibit maximum C5b-9 deposition, which is associated with RPE cell death. Nomacopan (~600 nM) effectively inhibits C5b-9 formation.

B) Nomacopan inhibits LTB4 stimulated MCP-1 secretion in primary monocytes



Primary monocytes exposed to LTB4 exhibited a dose-dependent increase in MCP-1 secretion, a recruitment factor for macrophages. Nomacopan (600 nM) significantly inhibits LTB4-induced MCP-1 production.

FIGURE 3

Pilot study of PAS-nomacopan efficacy in blue light (BL) damage model

A) Study design and primary measurements

Treatment and dosing schedule:

$$Retinal\ function\ (\%) = \frac{endpoint\ ERG}{baseline\ ERG}\ x\ 100$$

A) Pilot study of rat BL damage model conducted at JOINN Laboratories to determine the efficacy of PAS-nomacopan. Retinal function is calculated as the percentage of dark adapted (DA) endpoint electroretinography (ERG) amplitude remaining after blue light-induced damage. **B)** Endpoint ERG measurements at the recommended light intensities of DA0.015, DA3.0, and DA10.0[13], with means and statistical differences tabulated. **C)** Calculation of retinal function indicates a protective effect of PAS-nomacopan following BL damage.

PAS-nomacopan treated rats demonstrated better retention of ERG response compared to control rats. This information will be used to guide future powered studies to optimize the dosing of PAS-nomacopan.

B) PAS-nomacopan treated eyes - superior ERG response

	endpoint ERG (µV, Day 8)					
	a-wave			b-wave		
	DA0.015	DA3.0	DA10.0	DA0.015	DA3.0	DA10.0
Vehicle	-12.7	-18.9	-16.3	45.4	65.9	80.4
PAS-nomacopan	-15.1	-25.5	-29.5	67.4	92.9	103.0
p - value	0.635	0.057	0.135	0.031	0.055	0.418

trend towards significance * $p < 0.05$

C) PAS-nomacopan treated eyes retained better retinal function

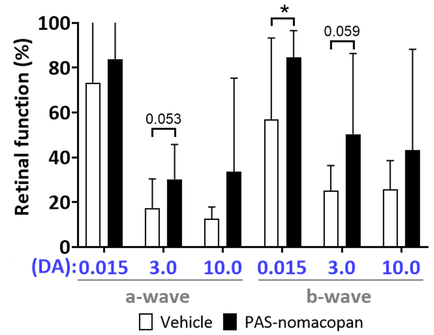
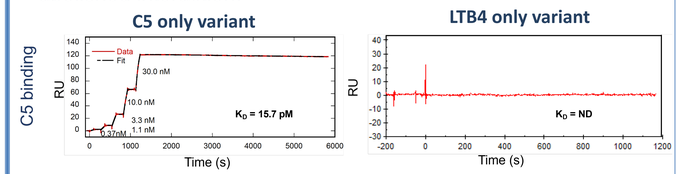


FIGURE 4

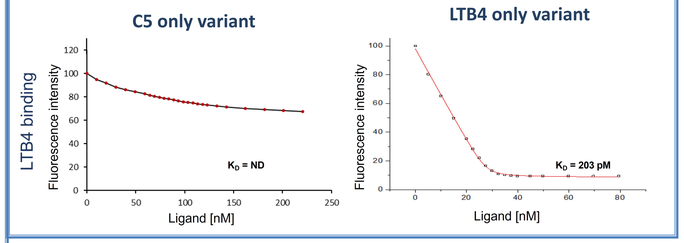
C5 and LTB4 only variants of PAS-nomacopan

PAS-nomacopan and its engineered variants with C5 only or LTB4 only binding activity will be applied to future preclinical models to understand the bispecific inhibitory nature of PAS-nomacopan inhibition.

C5 Binding by surface plasmon resonance**:** The K_D for PAS-nomacopan:C5 binding is 25.2 pM (not shown). C5 only variant demonstrated similar K_D whereas LTB4 only variant completely abolished interaction:



LTB4 Binding by fluorescence titration**:** The K_D for PAS-nomacopan:LTB4 binding is 130 pM (not shown). C5 only variant completely abolished LTB4 interaction whereas LTB4 only variant demonstrate similar K_D:



Summary

- PAS-nomacopan, a long-acting potent inhibitor of both complement C5 (C5a and MAC/C5b-9) and leukotriene B4 (LTB4), is in development as a potential treatment for GA with a **PIND meeting planned H1 2024**
- The **long ocular half-life of PAS-nomacopan** may support improved patient compliance and safety, while **LTB4 inhibition may reduce the risk of CNV** associated with complement-only inhibitors in GA therapy
- Future work will optimize pre-clinical model testing of PAS-nomacopan, and investigate therapeutic mechanisms of bispecific inhibition using engineered variants of nomacopan

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