

Development of long-acting PAS-nomacopan for treatment of GA and other retinal diseases

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PURPOSE

- Clinical studies indicate complement inhibitors slow progression of geographic atrophy (GA) but may promote choroidal neovascularisation (CNV). [i] [ii] Treatments slowing progression of GA whilst also inhibiting CNV are needed
- Long-acting 68kda PASylated-nomacopan (PAS-nomacopan) inhibits complement C5 and leukotriene B4 (LTB₄), a potent leukotactic agent that increases retinal VEGF. The addition of a PAS polypeptide to nomacopan increases the effective MW to 580kda which may permit a dosing interval of up to 3 months. Inhibition of LTB₄ may decrease the risk of CNV seen with avincaptad and pegcetacoplan
- Here we report 1.) the effect of IVT administered PAS-nomacopan in a mouse model of laser-induced CNV, and 2.) the pharmacokinetics (PK) of IVT administered PAS-nomacopan in rabbits

[i] Sasaki F, Koga T, Ohba M, Saeki K, Okuno T, Ishikawa K, Nakama T, Nakao S, Yoshida S, Ishibashi T, Ahmadi H, Kanavi MR, Hafezi-Moghadam A, Penninger JM, Sonoda KH, Yokomizo T. Leukotriene B4 promotes neovascularization and macrophage recruitment in murine wet-type AMD models. *JCI Insight*. 2018 Sep 20;3(18)

[ii] Eskandarpour M, Nunn MA, Weston-Davies W, Calder VL. Immune-Mediated Retinal Vasculitis in Posterior Uveitis and Experimental Models: The Leukotriene (LT)B₄-VEGF Axis. *Cells*. 2021 Feb 15;10(2):396

[iii] Sánchez-Taberner S, Fajardo-Sánchez J, Weston-Davies W, Parekh M, Krizan J, Kaye S, Ahmad S. Dual inhibition of complement component 5 and leukotriene B4 by topical rVAS76 in atopic keratoconjunctivitis: TRACKER phase 1 clinical trial results. *Orphanet J Rare Dis*. 2021 Jun 11;16(1):270.

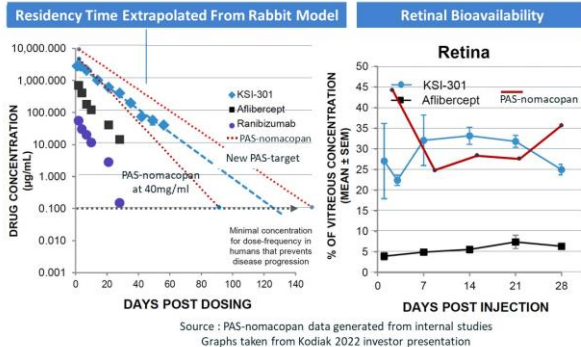
BACKGROUND

- Nomacopan is a recombinant small protein (17kda)
- Nomacopan binds and inactivates complement C5 and leukotriene B4 (LTB₄) and has broad spectrum anti-inflammatory and immunosuppressant activities
- Nomacopan has been in Phase 1 – 3 clinical trials since 2013 with good safety profile
- Ophthalmic clinical development commenced 2017 – topical use of nomacopan for AKC
- Nomacopan was modified for intravitreal injection (IVT) by PASylation[®] to increase functional molecular weight and reduce injection frequency for patient benefit with the added benefit that PAS-nomacopan has a low viscosity
- PAS-nomacopan was tested in a laser-induced CNV model and by studying pharmacokinetics in a rabbit eye to determine suitability for retinal disease development

METHODS

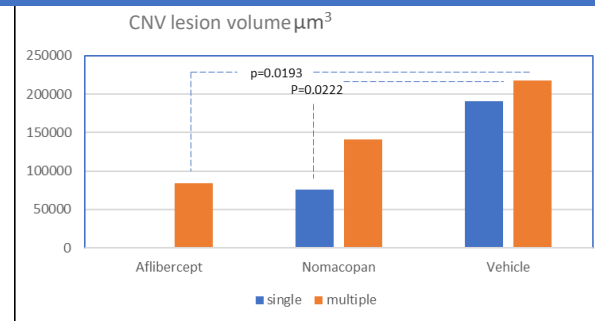
- The study was undertaken by IRIS PHARMA, La Gaude, France.
- For the CNV study, 5 groups of C57BL/6 mice received single or repeat 3µL doses of saline, PAS-nomacopan (20mg/ml) or aflibercept (40mg/ml). CNV was induced by laser in the right eye on Day 0. Retinal angiography was undertaken on Days 7 and 14. CNV volume was measured on Day 16 from flat mount choroid preparations
- Aflibercept was administered 4 times (Days 0, 3, 7, 10) because prior experience indicated that it is not effective in this model if given less frequently. PAS-nomacopan was given to one group once (Day 0) and to a further group four times to match the aflibercept administration. Vehicle was given to different groups once and four times
- To examine PK, pigmented rabbits received a single IVT dose of 50µL PAS-nomacopan on Day 1 to the right eye. Vitreous (V), retina (R) and choroid (CH) were harvested on Days 3, 7, 14, 21, 28 and 56. PAS-nomacopan concentrations in eye tissue were measured using liquid chromatography mass spectrophotometry to derive half-life and bioavailability

PK PD RESULTS



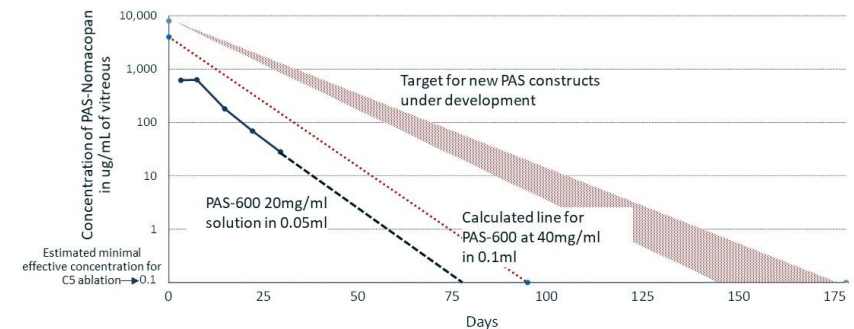
The PK/PD data shown are not the result of a head to head study but are plotted against previously published data using the same species/model. The CNV data are the result of a head to head study.

CNV RESULTS



Effect of single and multiple administrations of PAS nomacopan and aflibercept on CNV lesion volume

PAS-NOMACOPAN HAS POTENTIAL TO EXTEND IVT DOSE INTERVAL TO 3-6 MONTHS



CONCLUSIONS

- These data show that intravitreal PAS-nomacopan is effective in inhibiting CNV in an industry-standard model although, in this experiment it was not as effective as aflibercept in inhibiting vascular leakage
- Clinical trials have demonstrated that complement inhibition by pegcetacoplan (C3 inhibitor) and avincaptad pegol (C5 inhibitor) are effective in slowing the progression of geographic atrophy (GA) but both are complicated by the dose-related development of CNV, possibly secondary to M2 macrophage release of VEGF promoted by LTB₄.
- PAS-nomacopan which combines C5 and LTB₄ inhibition may provide effective treatment for GA whilst also reducing the risk of complications caused related to CNV due to direct inhibition of LTB₄ reducing VEGF
- Initial PK/PD data confirm bioavailability of PAS-nomacopan in R and CH by IVT route and suggest that clinical dose interval may be 3 months or more. Ongoing work exploring tolerability and further half-life extension.