Development of PASylated®-nomacopan for treatment of geographic atrophy (GA) secondary to dry age-related macular degeneration

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BACKGROUND

Complement inhibition is presently the only modality proven to provide benefit for treatment of geographic atrophy (GA) secondary to dry age-related macular degeneration (dAMD) by reducing the growth rate of retinal lesions which destroy photoreceptors and damage sight.

FDA-approved complement-only inhibitors for GA are administered by intravitreal injection once monthly or at intervals of 25 – 60 days (monthly or every other month). However, short dosing intervals of intravitreal injection treatments are associated with poor patient compliance.[1]

The approved complement-only inhibitors for GA treatment are both associated with a 2- to 4-fold increase in the rate of choroidal neovascularisation (CNV) compared to sham in clinical trials. The development of CNV is considered a more immediate risk to sight than GA. When CNV occurs during GA it is treated with additional anti-VEGF-A therapy that is intravitreally injected, which adds to patient burden and increases risk of injection-associated complications.

There is a need for improved therapies to treat GA that provide:

- **A longer dosing interval with similar (or better) efficacy than approved therapies to improve patient compliance and long-term therapeutic outcomes**
- **A therapy that does not increase the risk of treated GA patients developing sight-threatening CNV**

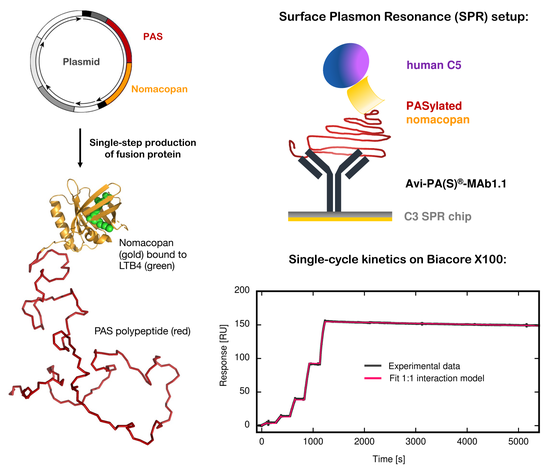
PASylated® nomacopan (PAS-nomacopan) is in the final stages of pre-clinical development targeting both goals – longer dose interval and reduction of CNV risk. PASylation[2] of nomacopan is designed to extend plasma half-life in the eye by in-frame addition of a random coil polypeptide **(FIGURE 1A and 1B)**. As a potent bispecific inhibitor of both complement C5 and leukotriene B4 (LTB4) (**FIGURE 1A**) PAS-nomacopan may offer the known benefits of complement C5 inhibition in the treatment of GA as well as the benefit of LTB4 inhibition (a key driver of VEGF overexpression and CNV) which may reduce the risk of developing sight-threatening CNV. **(FIGURE 2).** Proprietary drug substance (DS) and drug product (DP) manufacturing (**FIGURE 1C**) is on track to support IND submission in 2024 to enable clinical trials of PAS-nomacopan as a potential treatment for GA .

Here, we describe progress toward clinical testing of long-acting PAS-nomacopan that inhibits C5 and LTB4 as a potential treatment for geographic atrophy secondary to dry age-related macular degeneration

FIGURE 1

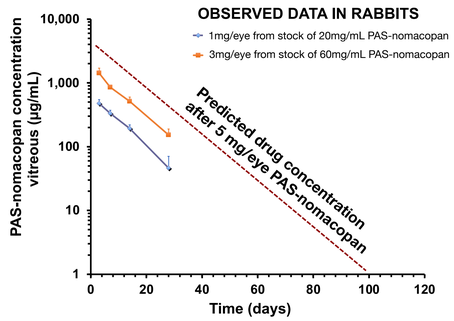
Structure, activity and half-life of PAS-nomacopan

A) PAS-nomacopan expression, structure and binding activity to C5 and LTB4



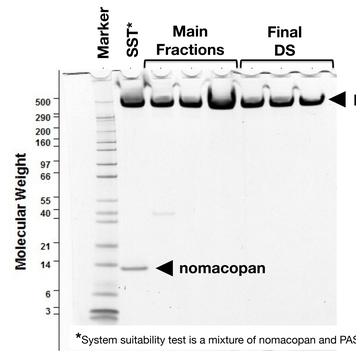
- K_D C5 binding: 25.2 pM
- K_D LTB_4 binding: ~130 pM by fluorescence titration (not shown)

B) PAS-nomacopan vitreous half-life in New Zealand White rabbits – potential for prolonged GA dose interval



- PAS-nomacopan concentration measured using qualified RRLC/MS method with internal reference standard
- Half-life in vitreous 7 – 8 days with relationship between single intravitreal dose of PAS-nomacopan (1 mg or 3 mg/eye) and drug concentration
- Potential (red dotted line) to extend dosing interval to eye by injecting higher concentration of PAS-nomacopan

C) Development of high-yielding manufacturing process for PAS-nomacopan for intravitreal administration



- Manufactured by Wacker Biotech GmbH using a proprietary strain of *E. coli*
- >95% purity by reverse phase HPLC (RP-HPLC) and size exclusion chromatography (SEC)
- Other specifications including endotoxin values on target

*System suitability test is a mixture of nomacopan and PAS-nomacopan

- Development batch manufacturing of DS and DP completed and undergoing stability and toxicology testing
- DS manufacturing process high yielding and considered to have suitable specifications for product for clinical use
- GMP manufacturing scheduled in 2024

FIGURE 2

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

PAS - nomacopan	C5a	Can increase VEGF-A release[3], however anti-C5a therapy alone not effective in a dry AMD model[4]
	MAC (C5b-9)	Accumulates in aging choriocapillaris and associated with death of RPE in AMD patients[5]
	LTB4	Induces VEGF-A & MCP1 which recruit macrophages in laser CNV[6,7,8] and mediate photoreceptor loss in AMD models[9]

SUMMARY

- PAS-nomacopan, a potent inhibitor of complement C5 (C5a and MAC/C5b-9) and leukotriene B4 (LTB4), is in development as a potential treatment for GA
- PAS-nomacopan has been designed to potentially enable an extended dosing interval of 3 months or longer (fewer injections into the eye) using standard fine gauge needles to support improved patient compliance and safety (reduced needle injection complications)
- By inhibiting LTB4, PAS-nomacopan has potential to reduce the CNV safety risk associated with complement-only inhibitors
- Positive pre-clinical results, including an advanced manufacturing process, support the anticipated submission of an IND in 2024 to begin clinical development with Phase 1 single and multiple ascending dose (SAD/MAD) testing to evaluate safety and PK/PD

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