Akari Therapeutics

August 2022

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THERAPEUTICS

Forward—Looking Statements

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Overview: Akari Therapeutics (Nasdaq: AKTX)

AUTOIMMUNE AND INFLAMMATORY	BISPECIFIC NOMACOPAN	NEAR-TERM INFLECTION POINT, PROMISING PRE-CLINICAL PROGRAM	DE-RISKED PATHWAYS
• Akari is a biotechnology company developing nomacopan and PAS-nomacopan for autoimmune and inflammatory diseases • Established in 2015	• Akari's lead asset is late-stage nomacopan, a bispecific recombinant protein inhibitor of complement C5 and leukotriene-B4 (LTB4) • Dual mode of action prevents inflammation and tissue damage	• Nomacopan Phase 3 program in severe pediatric hematopoietic stem cell transplant-related thrombotic microangiopathy (HSCT-TMA) • Positive results of long-acting PAS-nomacopan pre-clinical program support the potential of IND/IMPD for clinical trials in in geographic atrophy (GA)	• Strong late-stage development foundation set with extensive pre-clinical and early clinical research • Two development programs addressing areas of significant unmet patient need • Potential regulatory pathway on late-stage program • Extensive experience in the complement market supports development and go-to-market

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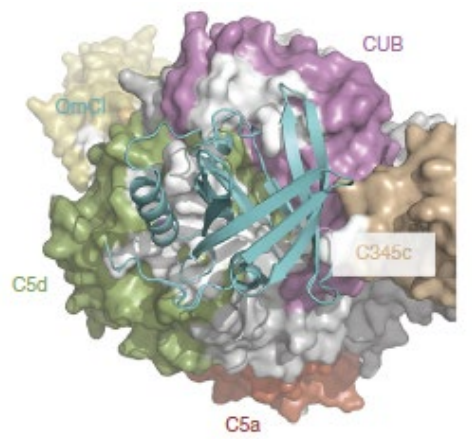
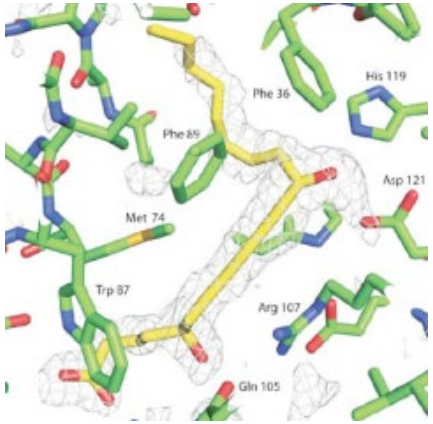
Nomacopan: First-in-Class Bispecific Anti-Inflammatory Biologic



High resolution structure of nomacopan (cyan) bound to the CUB, C5d, and C345C domains of C5 – Jore, et al. Nat Struct Mol Biol. 2016



High resolution structure of nomacopan capture of LTB4 (yellow) – Roversi, et al. J Immunol. 2013

Two Modes of Action

- Inhibits C5 activation in a similar way to eculizumab, but binds a different highly conserved region of C5 (K_D <1nM)
- Unique mode of action against LTB4 by very tightly sequestering LTB4 within body of protein 'ligand capture' (K_D 0.13nM) thereby preventing receptor mediated cell activation
- By binding to C5 the LTB4 inhibitory activity of nomacopan is greatly prolonged since the nomacopan C5 complex has a half-life of > 60h and is present in great excess to LTB4, so nomacopan circulates through the body and absorbs LTB4 disrupting cell recruitment and activation

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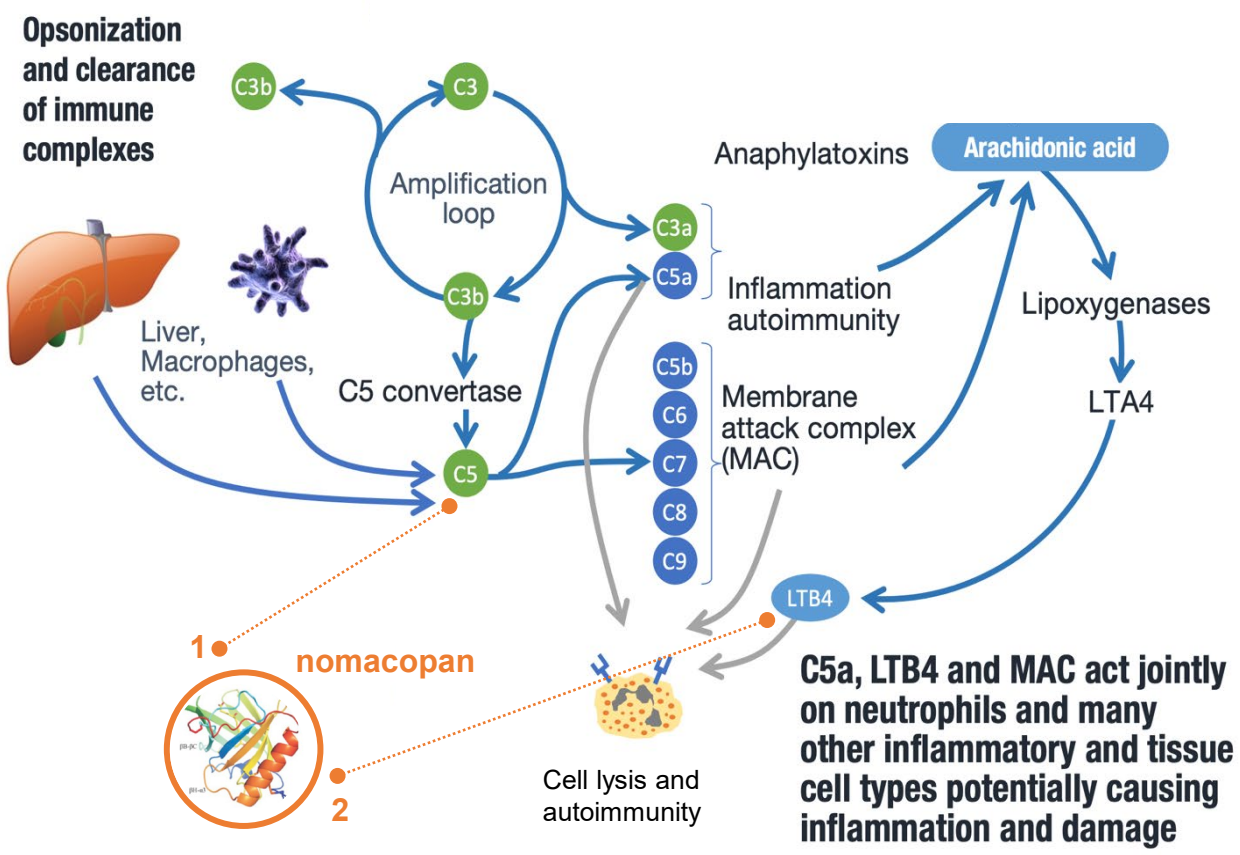
Nomacopan Inhibits Damaging Cell Lysis and Inflammation While Preserving Opsonization and Clearance of Immune Complexes

- Prevents activation of C5 and binds LTB4 which prevents proinflammatory and potentially tissue-damaging effects mediated by C5a, the MAC and LTB4
- Opsonization and clearance of immune complexes remain intact
- Inhibiting C5 activation prevents formation of the MAC and C5a that signals through 2 cell surface G protein-coupled receptors (GPCRs)
- Sequestering LTB4 prevents interaction of proinflammatory eicosanoid with cell surface GPCRs (BLT1 high affinity and BLT2 low affinity)



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Akari Pipeline Overview: Near-Term Inflection Point, Promising Pre-Clinical Program

Indication	Candidate/ Formulation	Market	Pre-Clinical	Phase 1&2	Phase 3 Part A	Phase 3 Part B
Current Areas of Focus						
Pediatric hematopoietic stem cell transplant–related thrombotic microangiopathy (HSCT-TMA)	Nomacopan/ subcutaneous	Rare				
Geographic atrophy (GA)	Long-acting PAS-nomacopan/ intravitreal injection	Mass				
Other Areas of Research *(not currently active)*						
Bullous pemphigoid (BP)	Nomacopan/ subcutaneous	Rare				
Paroxysmal nocturnal hemoglobinuria (PNH)	Nomacopan/ subcutaneous	Rare				
Atopic keratoconjunctivitis (AKC)	Nomacopan/topical distillation	Rare				
Lung	Nomacopan/ nebulized	Mass				

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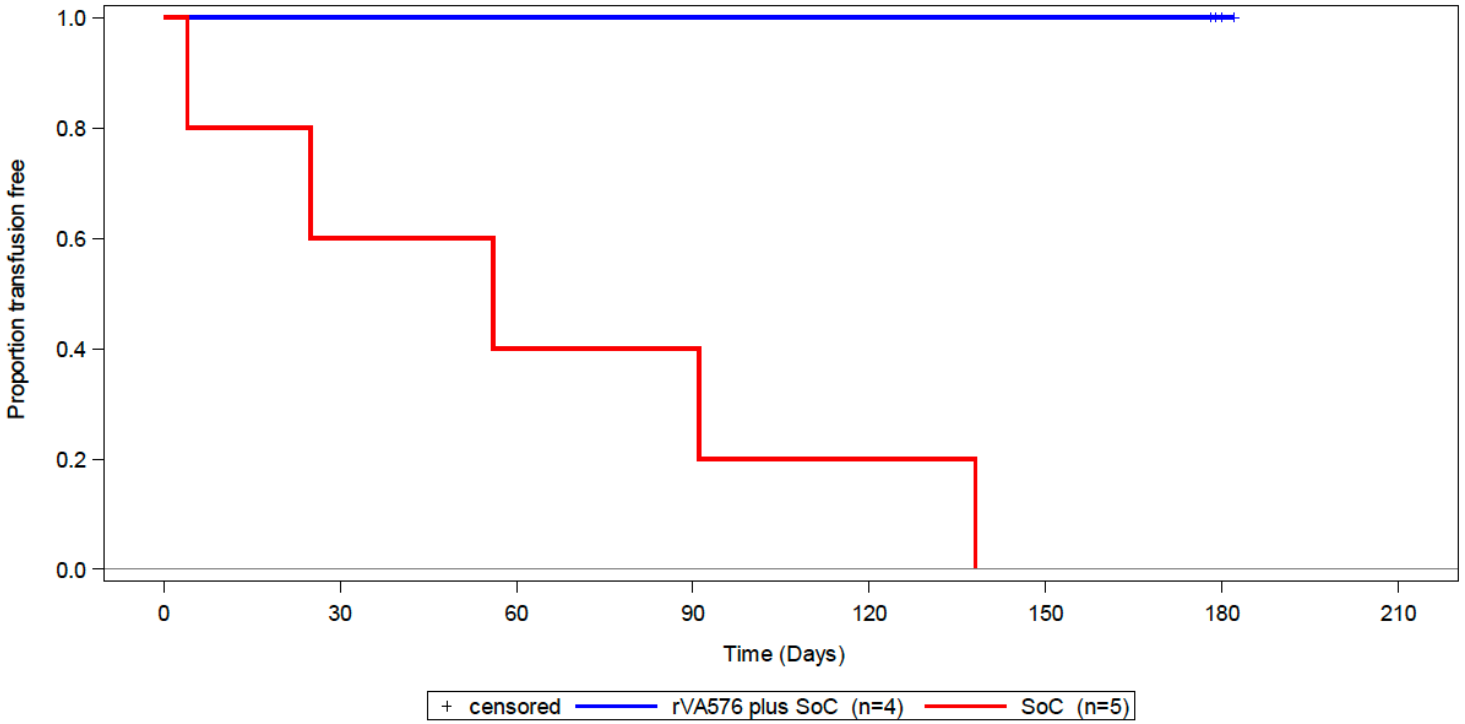
De-Risking Nomacopan Development Pathways

- Akari believes nomacopan pre-clinical and early clinical work, and Phase 3 program in PNH, helped to de-risk and set a solid foundation for registration-directed Phase 3 program in severe pediatric HSCT-TMA
  - Clinical PNH studies showed nomacopan binds tightly to LTB4 and likely prevents LTB4-mediated cell activation
  - >32 patient years of nomacopan exposure in PNH
- Optimized manufacturing, improving secretion/expression efficiency, increasing yield of nomacopan 12-fold and reducing costs of the clinical trial
- Pre-clinical work to date on long-acting PAS-nomacopan on dosing interval and volume, while achieving manufacturing scalability, positions Akari well to advance the program toward clinical trials in GA



Transfusion independence in PNH patients treated with nomacopan

Reference
Akari Therapeutics data on file

Leadership Team

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Strategic Priorities

1. Advance late-stage nomacopan HSCT-TMA Phase 3 program toward regulatory approval
2. Focus on rapid advancement of long-acting PAS-nomacopan program for geographic atrophy (GA) in dry age-related macular degeneration (dAMD)
3. Cultivate partnerships that will allow Akari to realize the promise of nomacopan in larger patient populations with significant unmet need
4. Further expand Akari's regulatory, medical, and commercial capabilities to execute pivotal clinical trial, and BLA/MAA filings

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THROMBOTIC MICROANGIOPATHIES (TMAs)

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Pediatric HSCT-TMA

- TMA following a stem cell transplant procedure is a rare but serious complication of HSCT that appears to involve complement activation, inflammation, tissue hypoxia and blood clots, leading to progressive organ damage and death
- Mortality in patients who develop severe transplant-related TMAs is 80%.[1]
- Currently, there are no approved treatment options in the U.S. or Europe.

Reference

1. Rosenthal J. Hematopoietic cell transplantation-associated thrombotic microangiopathy: a review of pathophysiology, diagnosis, and treatment. J Blood Med. 2016;7:181-186. Published 2016 Sep 2.

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Rationale for Bispecific Nomacopan in HSCT-TMA

- C5 activation is a key driver of HSCT-TMA
  - Elevated baseline complement activity
  - Chronic complement present during active TMA
  - With endothelial injury and progressive organ damage, especially in kidneys
- LTB4 in HSCT-TMA
  - LTB4 activity in endothelial surfaces[1] and neutrophil extracellular traps (NETs)[1,2,3,4] resulting in a prothrombotic state and elevated inflammation, which further activates complement
  - LTB4 is elevated in patients with graft-versus-host disease (GVHD) and may impact GVHD progression[5]
- FDA granted Orphan and Fast Track designations
- Phase 3 Part A trial has enrolled 4 patients and has a recruitment goal of 7 patients

1. Folco EJ, et al. Neutrophil Extracellular Traps Induce Endothelial Cell Activation and Tissue Factor Production Through Interleukin-1α and Cathepsin G. Arterioscler Thromb Vasc Biol. 2018;38(8):1901-1912.
2. Carestia A, et al. NETosis before and after Hyperglycemic Control in Type 2 Diabetes Mellitus Patients. PLoS One. 2016 Dec 22;11(12):e0168647.
3. Mawhin MA,. The receptor EP3 to PGE2: A rational target to prevent atherothrombosis without inducing bleeding. Prostaglandins Other Lipid Mediat. 2015 Sep;121(Pt A):4-16.
4. Klopf J, et al. Neutrophil Extracellular Traps and Their Implications in Cardiovascular and Inflammatory Disease. Int J Mol Sci. 2021 Jan 8;22(2):559.
5. Takatsuka H, et al. Predicting the severity of intestinal graft-versus-host disease from leukotriene B4 levels after bone marrow transplantation. Bone Marrow Transplant. 2000;26(12):1313-1316.

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Pediatric HSCT-TMA Phase 3 Open-Label Study Now Underway

	Part A	Part B
Purpose	• Dose confirmation by age cohort • Safety	• Efficacy • Safety
Study Population	• 7 total **Age cohorts** 0.5 to <2 years ≥2 to <9 years ≥9 to <18 years	• TBD
Sites	• US, UK and Poland	• TBD

Primary Endpoints

- **Independence of red blood cell transfusion** maintained over ≥ 28 days immediately prior to any scheduled clinical visit up to Week 24

OR

- **Urine protein creatinine ratio of ≤ 2 mg/mg** maintained over ≥ 28 days immediately prior to any scheduled clinical visit up to Week 24

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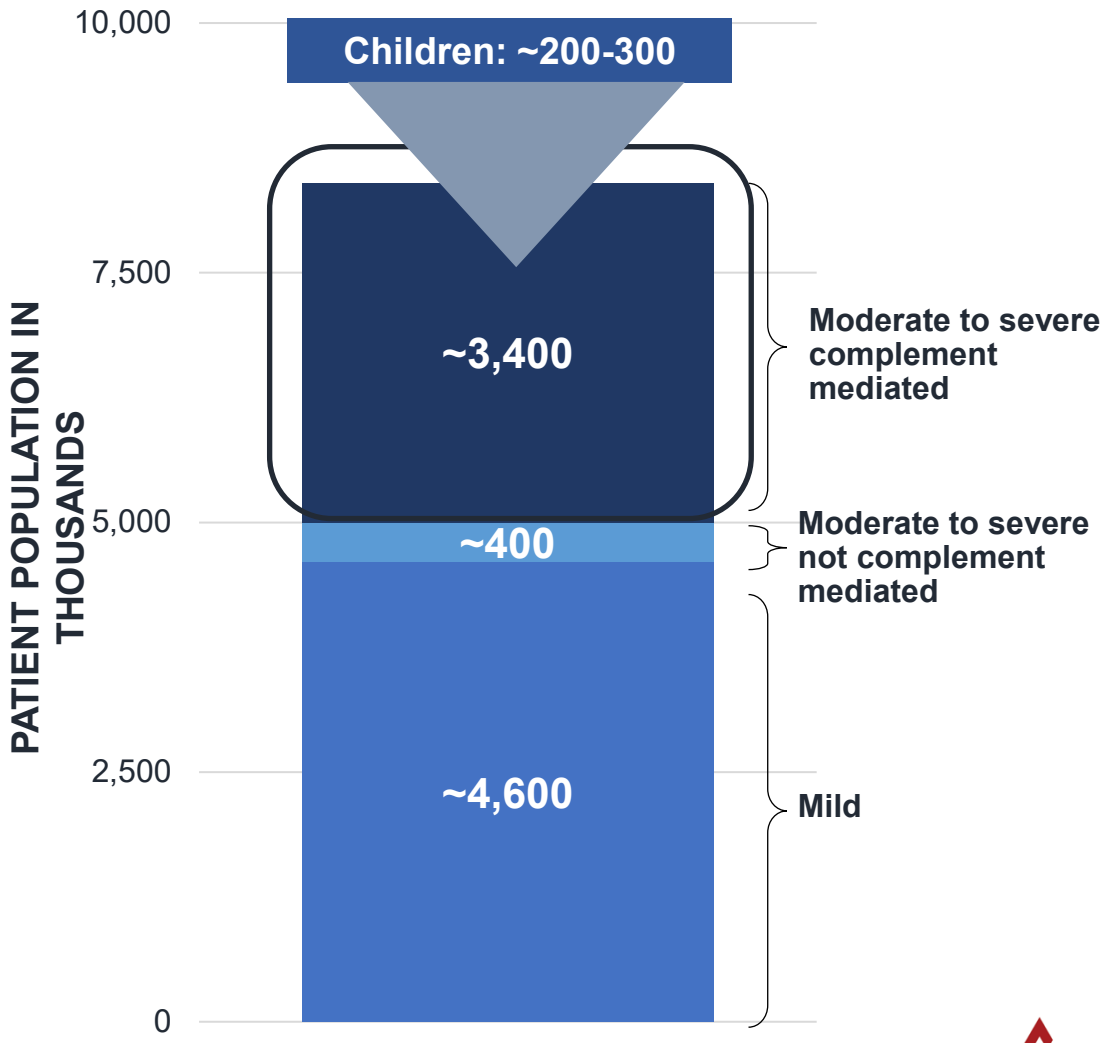
HSCT-TMA U.S. Market Opportunity

~22,000	HSCTs occur annually in the U.S.
~8,400	(38%) lead to TMAs
~3,400	TMAs are moderate to severe complement-mediated ○ 200-300 pediatrics ○ 3,100-3,200 adult

References

- Health Resources and Services Administration (HRSA), 2020
- Jodele S, et al. Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults. Blood. 2014;124(4):645-653.
- Jodele S, et al. Complement blockade for TA-TMA: lessons learned from a large pediatric cohort treated with eculizumab. Blood. 2020;135(13):1049-1057.

HSCT-TMA U.S. Population
(incidence in adults and children in the U.S. 2022)



SEVERE PROGRESSIVE RETINAL DISEASES

Geographic Atrophy (GA)

- Geographic atrophy (GA) manifests as a chronic progressive degeneration of the macula, which occurs during late-stage dry age-related macular degeneration (dAMD) and can lead to irreversible vision loss
- Approximately 5 million people worldwide are affected,[1,2] with nearly 1 million in the U.S.[3]
- There are no approved treatment options

References

1. Wong WL, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2(2):e106-e116.
2. Rudnicka AR, et al. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. Ophthalmology. 2012;119(3):571-580.
3. Friedman DS, et al. Prevalence of age-related macular degeneration in the United States [published correction appears in Arch Ophthalmol. 2011 Sep;129(9):1188]. Arch Ophthalmol. 2004;122(4):564-572.

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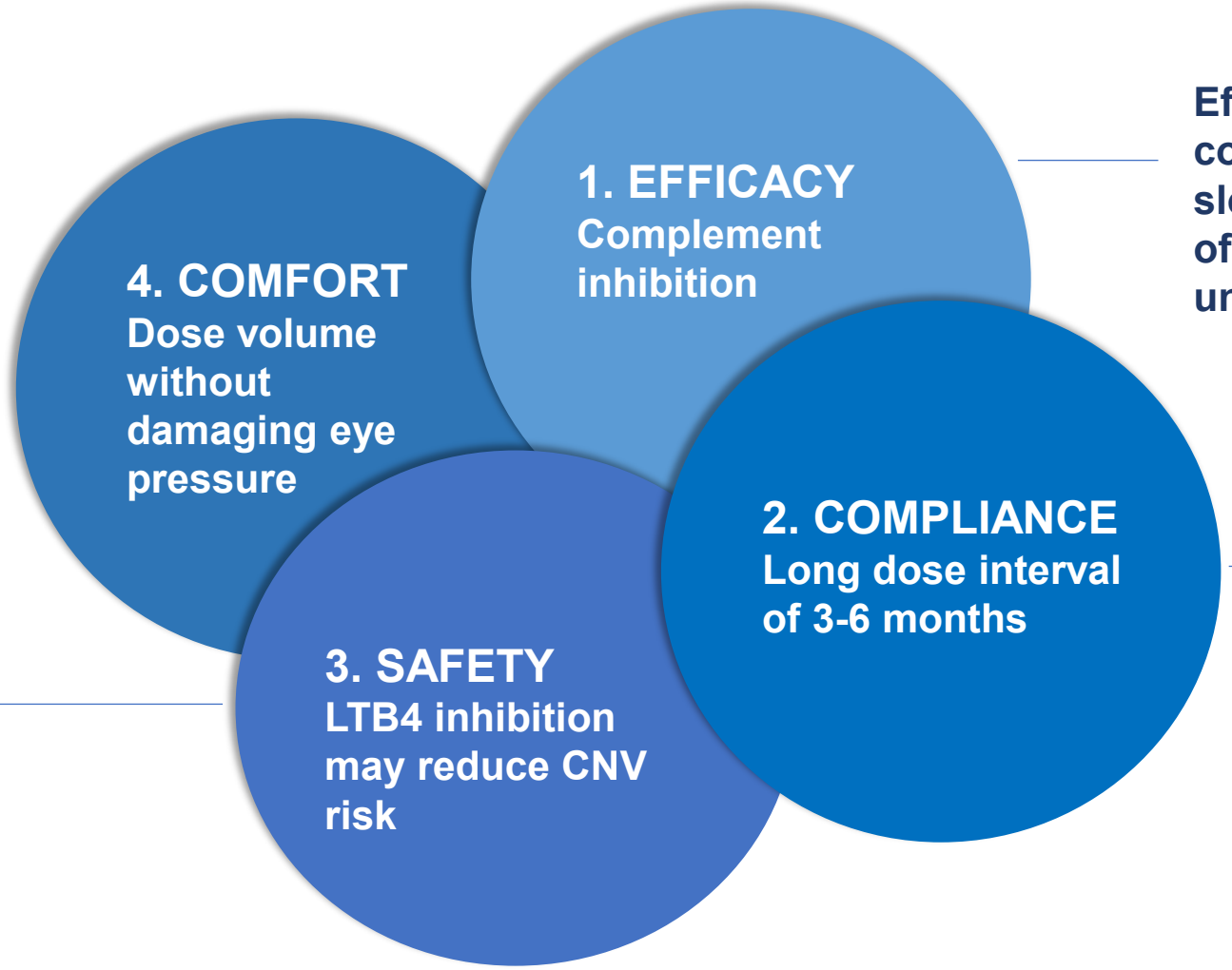
Long-Acting PAS-Nomacopan Development Focused on Four Key Needs in GA

Longer half-life allows lower dose volume with little impact on intraocular pressure (IOP) that can be damaging at high levels over time



Efficacy of complement inhibition slowing progression of GA lesions is well understood

Potential for extended dose intervals and less frequent needle injections into the back of the eye, a source of fear, discomfort and disruption for patients[1]

LTB4 inhibition shown to address a key driver of sight-threatening CNV, a safety risk associated with certain complement-only inhibitors

References

1. McClard CK, et al. Questionnaire to Assess Life Impact of Treatment by Intravitreal Injections (QUALITII): Development of a patient-reported measure to assess treatment burden of repeat intravitreal injections. BMJ Open Ophthalmol. 2021;6(1):e000669.

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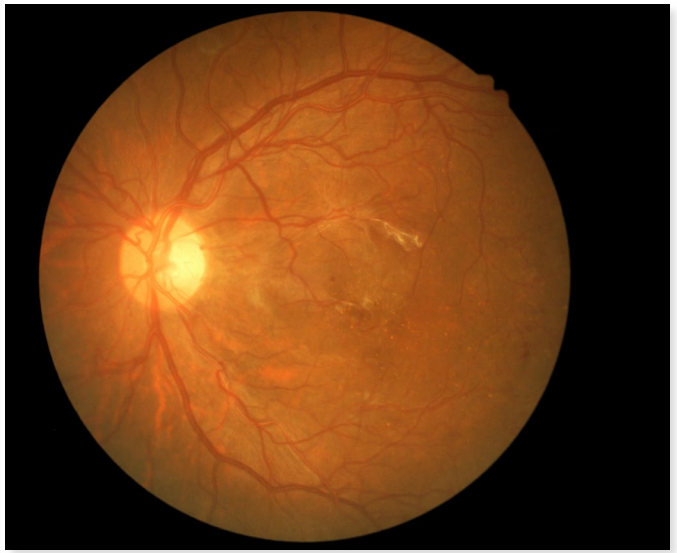
Value Proposition in Long-Acting PAS-Nomacopan in GA

- Complement inhibitors shown in multiple clinical studies to be effective at slowing the progression of GA lesions[1,2]
- Pre-clinical studies support the potential of long-acting PASylated® nomacopan in GA and its advancement toward IND/IMPD for clinical trials
  - Half-life of intravitreally (IVT) injected PAS-nomacopan may enable dosing intervals of 3-6 months (other therapies in clinical trials have been dosed monthly or every other month)[1,2]
  - Half-life may also support a dose volume with little impact on intraocular pressure, which at high levels over time can be damaging[3]
  - Pre-clinical data show LTB4 inhibition by PAS-nomacopan may also reduce risk of sight-threatening choroidal neovascularization (CNV), a safety risk associated with certain complement-only inhibitors[1,2,4,5]



References

1. Liao DS, et al. Complement C3 Inhibitor Pegcetacoplan for Geographic Atrophy Secondary to Age-Related Macular Degeneration: A Randomized Phase 2 Trial. Ophthalmology. 2020
2. Jaffe GJ, et al. C5 Inhibitor Avacincaptad Pegol for Geographic Atrophy Due to Age-Related Macular Degeneration: A Randomized Pivotal Phase 2/3 Trial. Ophthalmology. 2021;128(4):576-586.
3. Medeiros FA, Alencar LM, Zangwill LM, Sample PA, Weinreb RN. The Relationship between intraocular pressure and progressive retinal nerve fiber layer loss in glaucoma. Ophthalmology. 2009;116(6):1125-33.e333.
4. Sasaki F, et al. Leukotriene B4 promotes neovascularization and macrophage recruitment in murine wet-type AMD models. JCI Insight. 2018;3(18):e96902. Published 2018 Sep 20.
5. Eskandarpour et al. Immune-Mediated Retinal Vasculitis in Posterior Uveitis and Experimental Models: The Leukotriene (LT)B4-VEGF Axis. Cells. 2021;10(2):396. Published 2021 Feb 15.

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Next Steps for PAS-Nomacopan

- Conduct additional IND-enabling studies and advance the program toward the clinic
  - Optimize PAS-nomacopan for extended dosing interval of 3+ months, and a dose volume with minimal impact on IOP
  - Achieve manufacturing scalability
- Clarity on IND / IMPD timing by year end 2022

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PROGRESS & PRIORITIES

Akari Anticipated Milestones

4 patients dosed in Phase 3 Part A study of nomacopan in severe pediatric HSCT-TMA

Data readout: Phase 3 Part A study of nomacopan in severe pediatric HSCT-TMA

1H 2022 **2H 2022** **1H 2023**

Pre-clinical studies of long-acting PAS-nomacopan for GA

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Discussion / Questions

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