Preclinical Characterization of BHV-1420:

A Novel TRAP™ Degrader of PLA2R Autoantibodies for Treatment of Membranous Nephropathy

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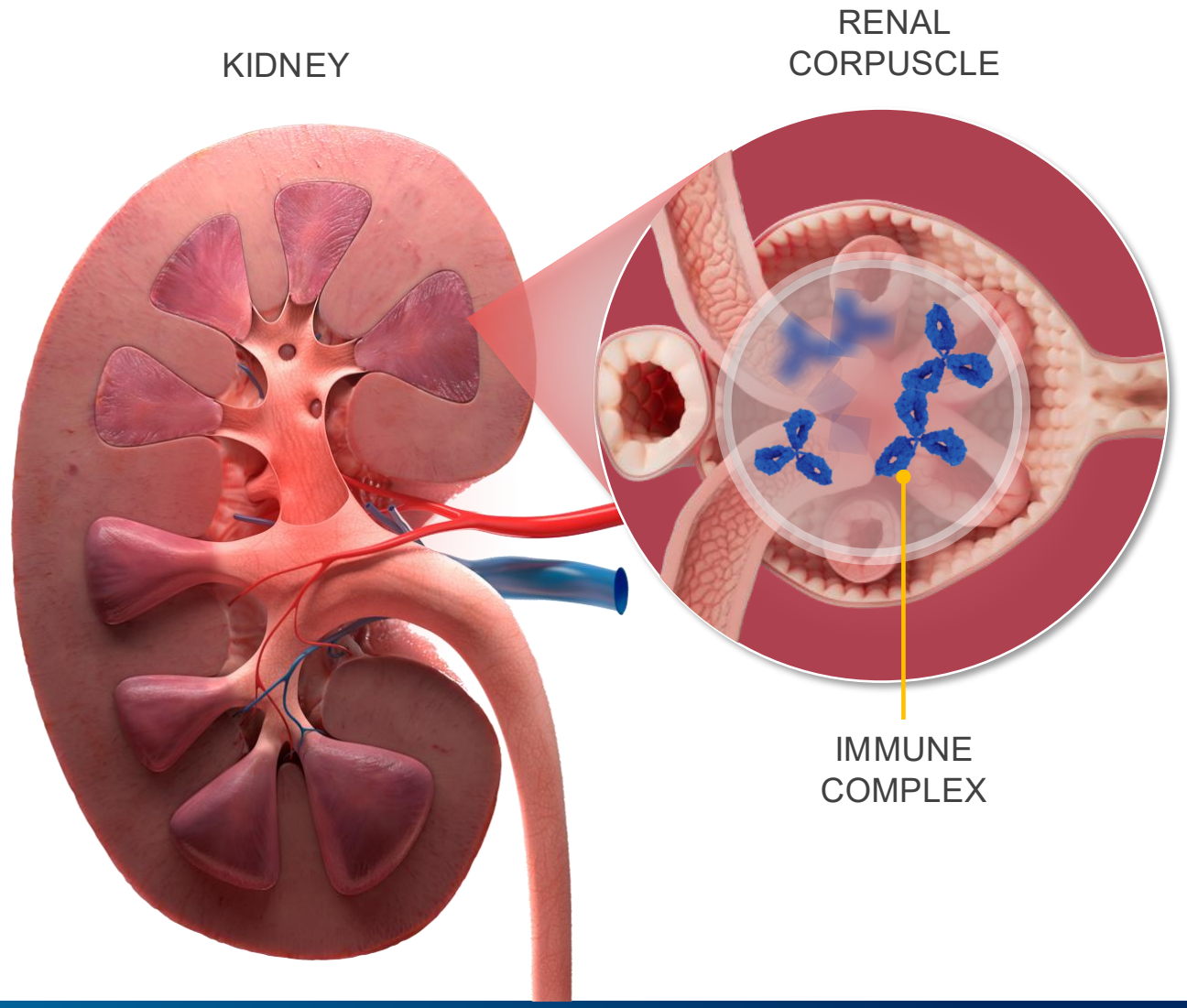
Pathophysiology of Idiopathic Membranous Nephropathy (IMN)

- IMN is a rare glomerular disease affecting 1.2 per 100,000 people per year, causing fatigue, edema, high cholesterol and low protein levels in the blood.[1,2]
- Driven by an autoimmune response that leads to the development of an autoantibody and in situ immune complex formation, thickening of the glomerular basement membrane and changes in podocyte morphology.[3]
- Standard of care is rituximab, cyclophosphamide, corticosteroids and calcineurin inhibitors.[4]

One third of patients eventually develop kidney failure despite treatment.

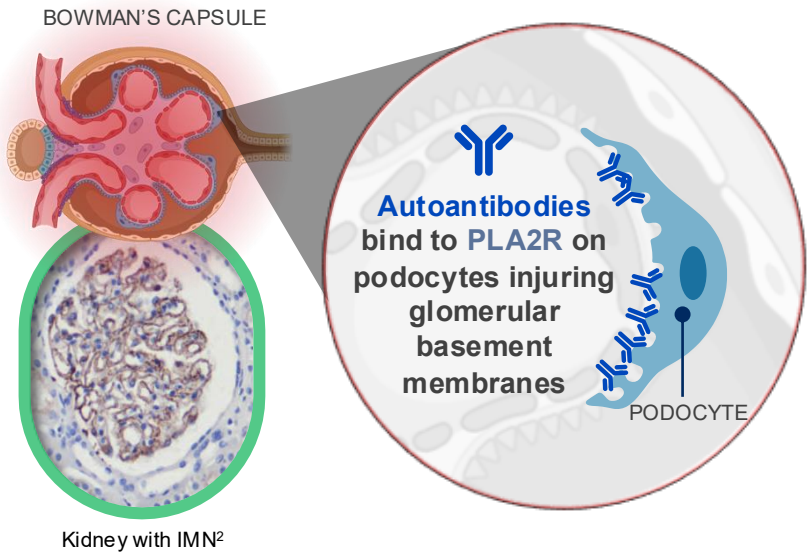


1. McGrogan A, Franssen CF, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrol Dial Transplant. 2011 Feb;26(2):414-30. **2.** Ronco, P.; Plaisier, E.; Debiec, H. Advances in Membranous Nephropathy. J. Clin. Med. (2021) 10, 607. **3.** Beck, L. H. et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N. Engl. J. Med. (2009) 361, 11–21. **4.** Rovin B, Adler S, Barratt J et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases Kidney International. (2021) 100, S1-S276

Anti-PLA2R Autoantibodies Are Pathogenic in IMN

- PLA2R (phospholipase A2 receptor) is the primary autoimmune target in IMN. Anti-PLA2R autoantibodies are detected in 70–80% of patients.[1]
- Anti-PLA2R antibodies are strongly associated with disease severity and remission status.[2]
- Despite treatment, 30–40% of patients fail to sustain long-term remission. These patients often develop ESRD and require kidney transplant.[3,4]
- IMN recurs in up to 50% of kidney allograft recipients.[5]

An anti-PLA2R-specific therapy could be more effective than the current SOC and circumvent the need for immunosuppression.



Subepithelial immune complex deposits

▼

Podocyte injury, thickening of basement membrane

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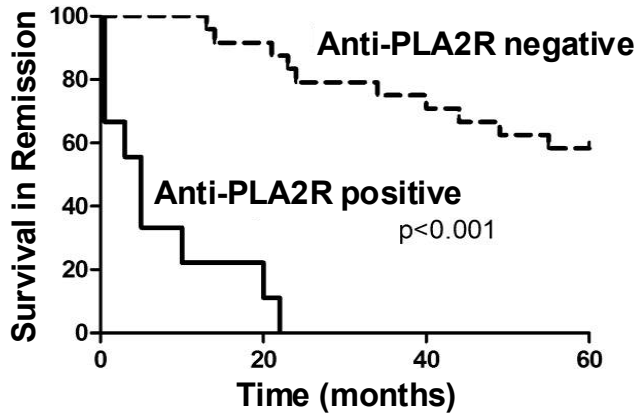
Proteinuria and hyperlipidemia

▼

KIDNEY FAILURE

Patients stratified by anti-PLA2R antibody status after immuno-suppressive treatment[2]



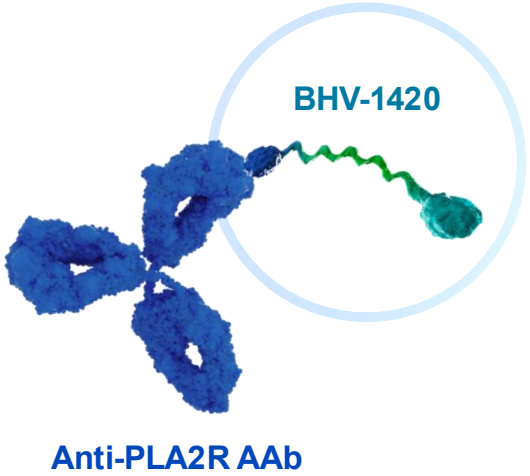
1. Beck LH Jr, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009 Jul 2;361(1):11-21. **2.** Bech AP et al. Clin J Am Soc Nephrol. 2014 Aug 7;9(8):1386-92. **3.** Fervenza FC, et al. Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy. *N Engl J Med*. (2019) 381:36-46. **4.** Nayak et al. Outcomes of primary membranous nephropathy refractory to immunosuppressants. *Clin Kidney J,* (2024) 15;17(5) **5.** Grupper A, Cornell LD, Fervenza FC, Beck LH Jr, Lorenz E, Cosio FG. Recurrent membranous nephropathy after kidney transplantation: treatment and long-term implications. *Transplantation.* (2016) 100:2710–6.

BHV-1420: A Highly-Selective Anti-PLA2R Autoantibody Degrader

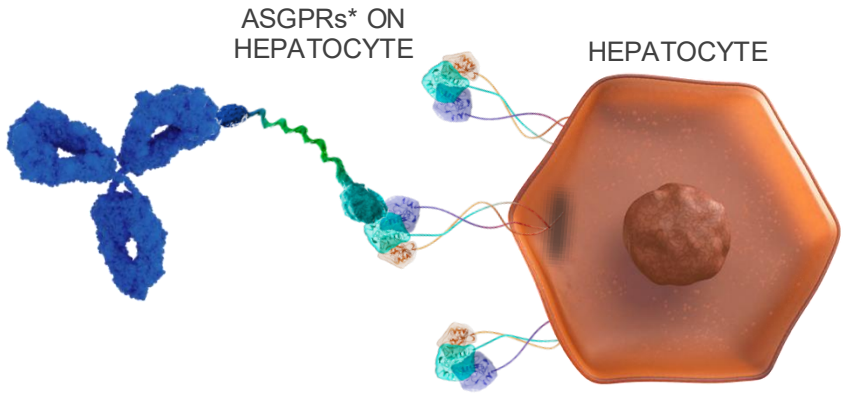
Modality: Heterobifunctional degrader of anti-PLA2R autoantibodies

- Leverages TRAP™ technology platform licensed from Prof. David Spiegel and Yale University
- Exploits ASGPR pathway for internalization and degradation of extracellular proteins
- Selectively binds and degrades anti-PLA2R autoantibodies while avoiding broad immunosuppression

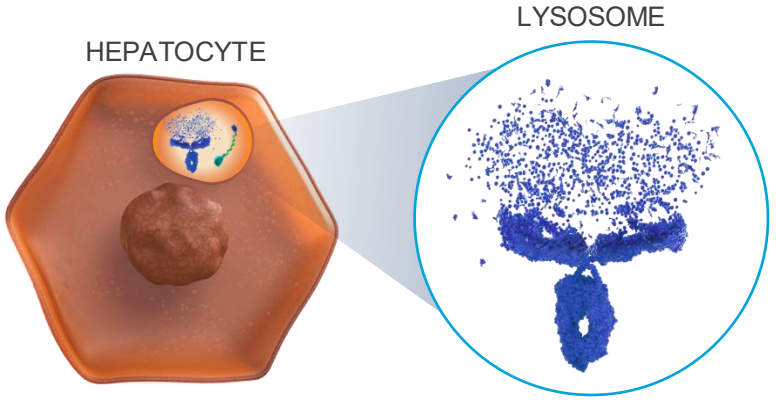
1 Binary complex



2 Ternary complex formation



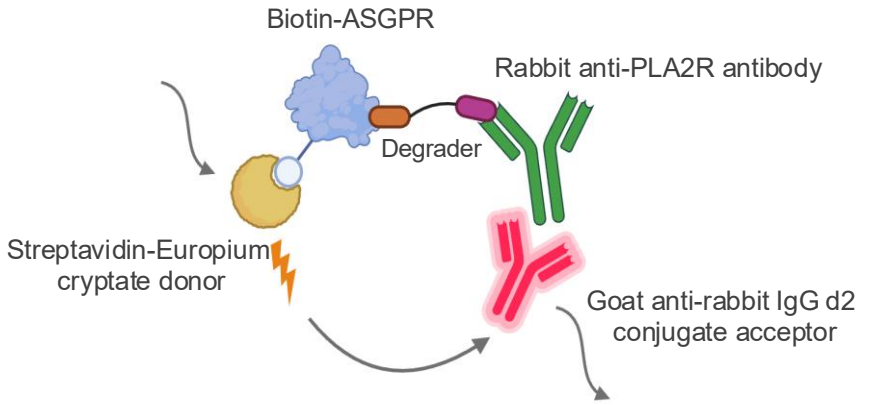
3 Internalization and anti-PLA2R AAb degradation

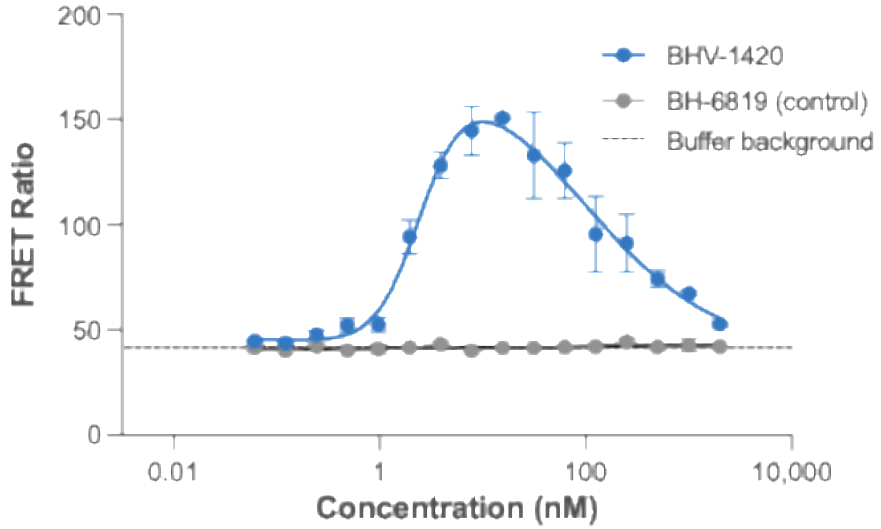


*Stylistic representation
TRAP™, Targeted Removal of Aberrant Protein. **ASGPR,** Asialoglycoprotein Receptor

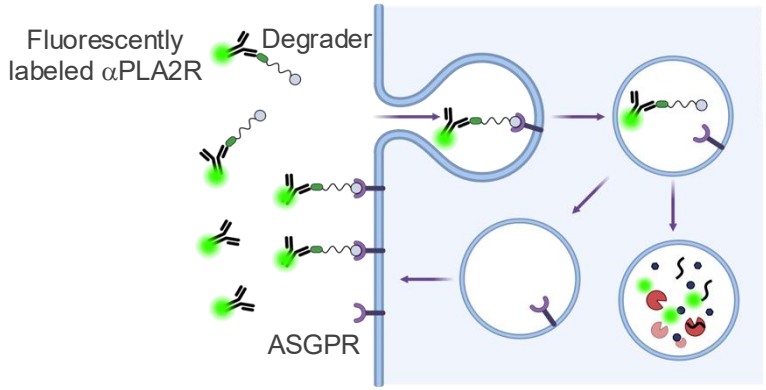
BHV-1420 Induces Ternary Complex and Mediates Anti-PLA2R Internalization

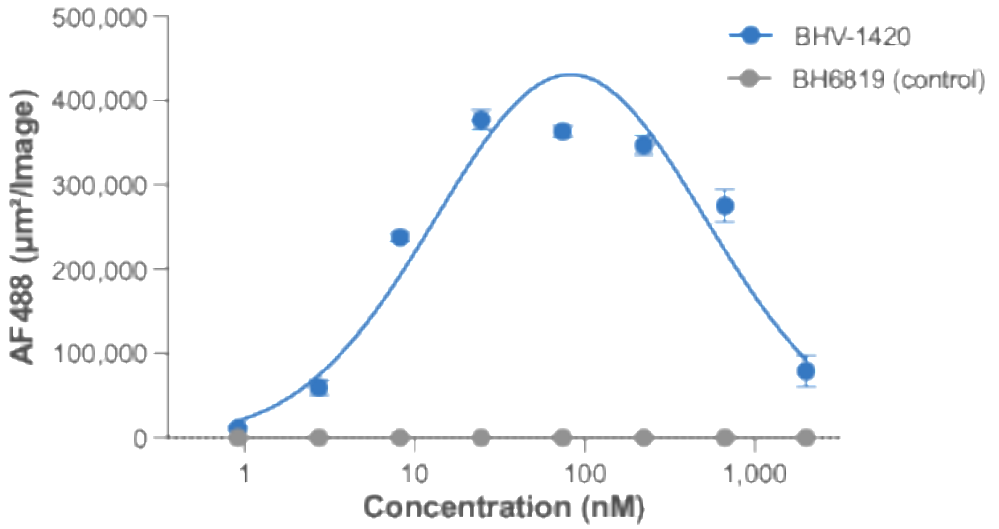
Ternary Complex Formation



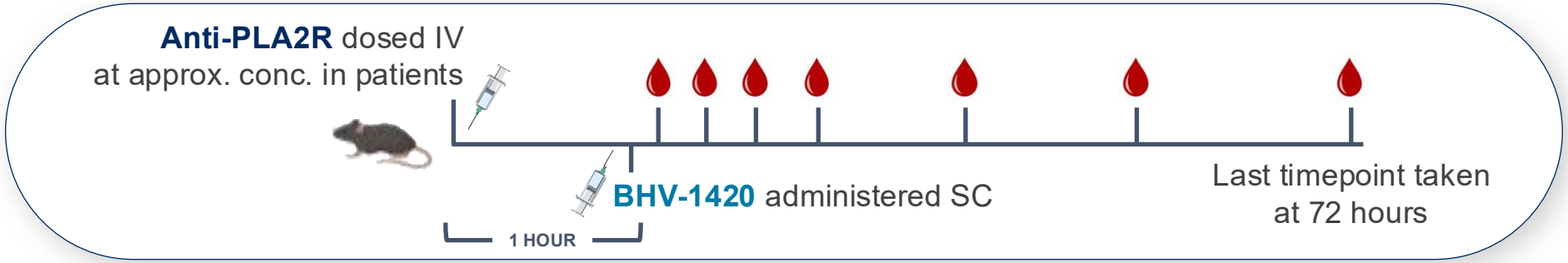


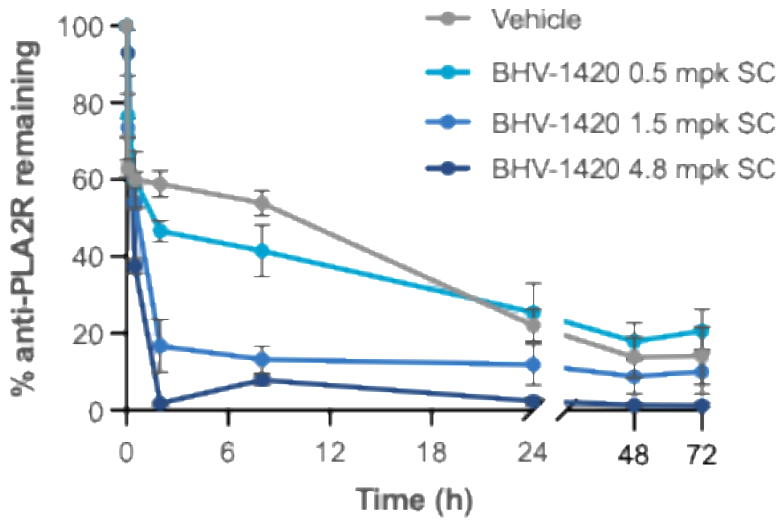
Internalization via ASGPR-Uptake

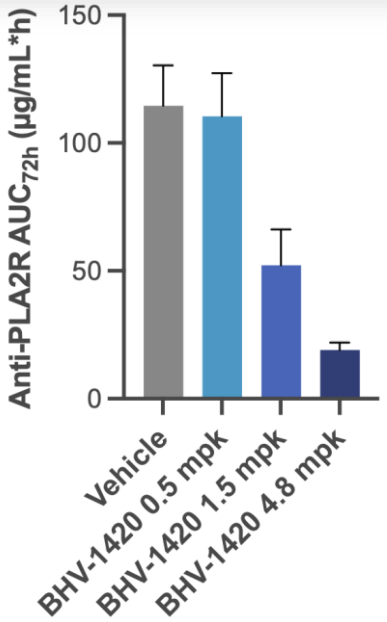




BHV-1420 Induces Rapid, Dose-Dependent Depletion of Anti-PLA2R *In Vivo*

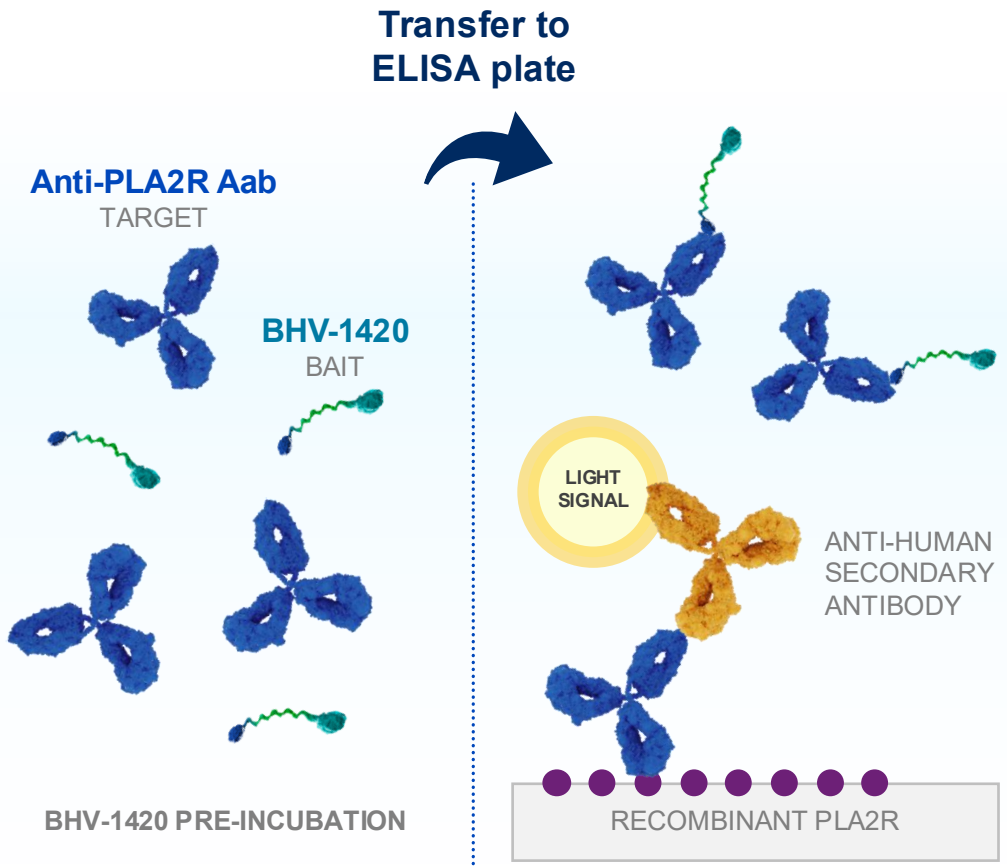


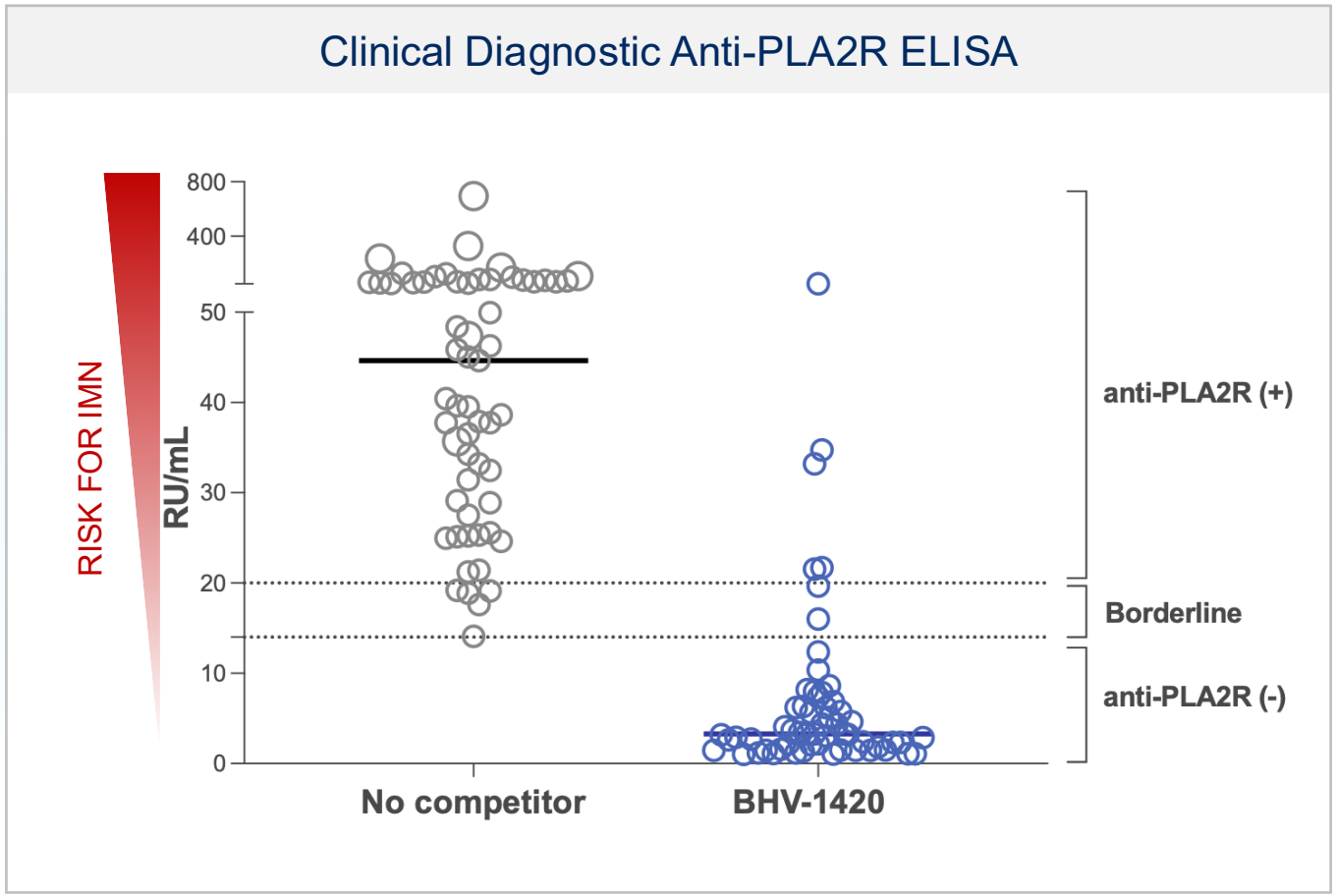




BHV-1420 effectively depletes physiological levels of exogenous anti-PLA2R AAb in mice.

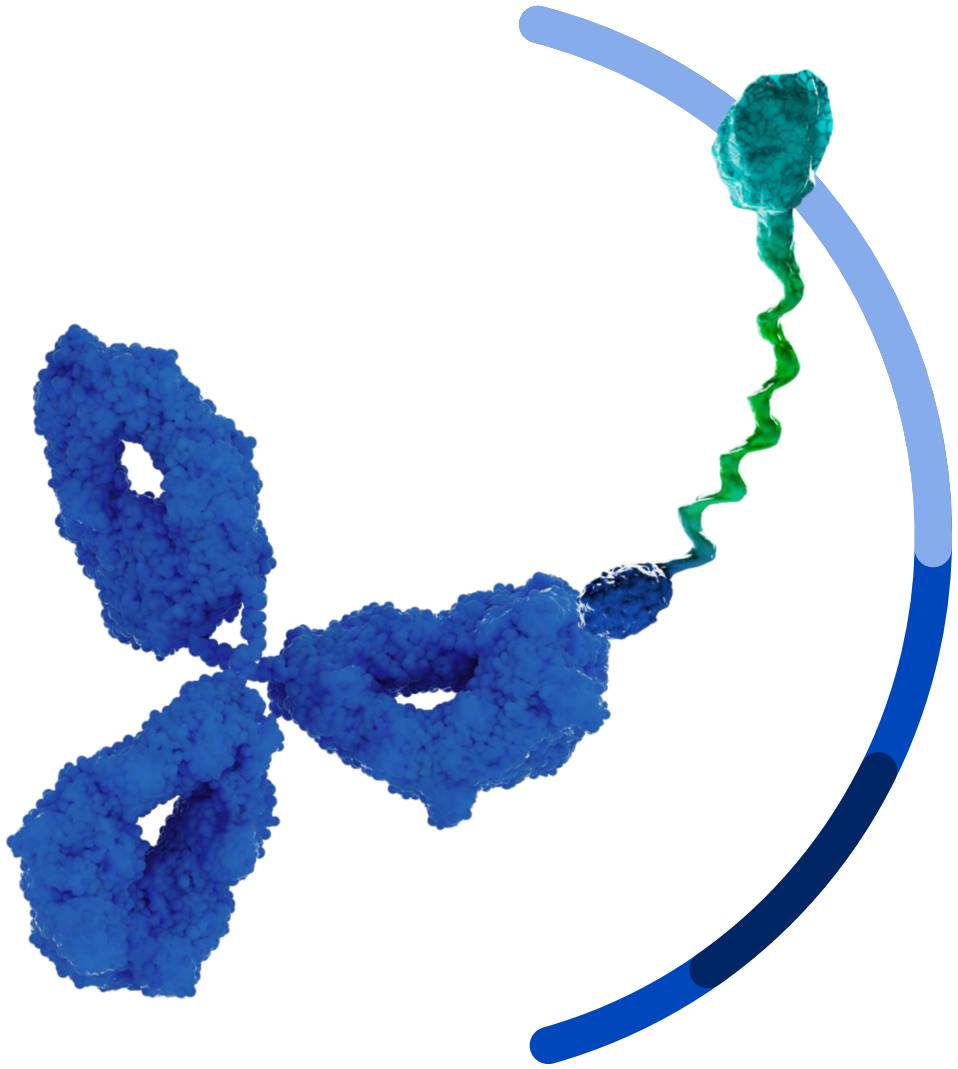
BHV-1420 Effectively Captures Anti-PLA2R Antibodies in IMN Samples





Tested in a competitive ELISA format, BHV-1420 reduced 88% of anti-PLA2R^{+} IMN samples tested (n=59) below the clinical diagnostic limit for anti-PLA2R positivity.

BHV-1420: A Targeted Therapy for IMN With a Novel MOA



- BHV-1420 is a novel heterobifunctional TRAP™ degrader capable of selectively removing pathogenic anti-PLA2R antibodies from circulation.
- Subcutaneous administration of BHV-1420 effectively removes exogenous anti-PLA2R antibodies in a passive transfer mouse model.
- BHV-1420 targets the majority of anti-PLA2R autoantibodies found in IMN patient blood samples.
- BHV-1420 is currently in development as a first-in-class precision therapy for idiopathic membranous nephropathy.