and proteinuria >1 g/day. In adolescents without a baseline biopsy, eligibility criteria included ≥1 of the following: increased plasma soluble C5b-9, decreased serum C3, presence of hematuria, or presence of C3 nephritic factor. Patients were randomized 1:1 to pegcetacoplan (subcutaneous infusion twice weekly) or placebo for 26 weeks in the RCP. Biopsies were optional for adolescents. The primary endpoint was the log-transformed ratio of urine protein-to-creatinine ratio (UPCR) at week 26 vs baseline. Key secondary endpoints included the proportion of patients achieving a composite renal endpoint criterion (≥50% UPCR reduction and ≤15% eGFR reduction), ≥50% UPCR reduction, and eGFR change from baseline.

**Results:** In total, 28 adolescents were randomized to pegcetacoplan and 27 to placebo. Pegcetacoplan led to significant and clinically meaningful UPCR reductions at week 26, with a 74.5% relative reduction in proteinuria in the pegcetacoplan vs placebo arms (95% CI 58.5, 84.3; nominal $P < .0001$). A greater proportion of adolescents in the pegcetacoplan vs placebo arm achieved the composite renal endpoint (57.1% vs 3.7%; nominal $P = .0016$) and ≥50% UPCR reduction (71.4% vs 3.7%; nominal $P = .0002$). Pegcetacoplan was associated with clinically meaningful eGFR stabilization.

**Conclusions:** In VALIANT, pegcetacoplan was well tolerated in adolescents with C3G and primary IC-MPGN and was the first treatment to induce meaningful proteinuria reduction and eGFR stabilization in this population.

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**P-119**

## Assessing C3 nephritic factor function using Luminex-based formation and stabilization assays

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### Abstract

**Background:** C3 Nephritic factors (Nefs) are autoantibodies that bind to and stabilize the C3 convertase, thereby enhancing complement activity and driving glomerular diseases such as C3 Glomerulopathy (C3G).[1,2] Recently, a Luminex method was developed to evaluate Nefs.[3] Utilizing this technique, the authors proposed that Nefs influence both convertase *formation* and *stabilization*. In this study, we compare the Luminex-based assay to hemolytic-based and surface plasmon resonance (SPR) assays to assess the formation/stabilization model of Nef activity. Method A test population of polyclonal IgG samples were evaluated for C3Nef activity by hemolysis (n = 21)[1] and for convertase formation and stability by SPR analysis (n = 21).[4] Samples were then applied to the Luminex *Formation* (n = 21) and *Stability* assays[3] (n = 12).

**Results:** Nef hemolytic scores ranged from 10% (0+) to 100% (4+). Linear regression between hemolysis and Luminex assays was statistically significant: Luminex *Stability*-Hemolysis yielded $R^2 = 0.46$, $F = 8.6$, $p = 0.015$; Luminex *Formation*-Hemolysis yielded $R^2 = 0.29$, $F = 4.3$, $p = 0.013$. ANOVA test with Dunn's multiple comparisons for Luminex data grouped by hemolytic score (0, 1+, or 4+) showed statistically significant difference between 0 and 4+ Nefs by both *Stability* ($p = 0.0003$) and *Formation* ($p = 0.0012$) assays but no significance between 0 and 1+ Nefs by either Luminex assay.

Linear regression between Luminex *Formation* assay and SPR assay analysis showed significance to the SPR "*Formation*" report point ($R^2 = 0.62$, $F = 29.3$, $p = <0.0001$) and SPR-based *stability* analysis ($R^2 = 0.51$, $F = 18.85$, $p = 0.0004$). The Luminex *Stability* assay correlated weakly with the SPR *Stability* analysis but did not reach significance ($p = 0.15$).

**Conclusion:** Luminex *Formation* correlated better with the SPR *Formation* report point, while Luminex *Stability* showed better correlation to the hemolytic *stability* assay. However, the overall correlations were lower than anticipated, which may point to (1) the small sample size; (2) more nuanced interactions between polyclonal IgG and the C3 convertase; and/or (3) the need for further optimization of the Luminex and SPR methodologies.

**References:** (1) PMID: 22223606, (2) PMID: 35734939, (3) PMID: 39325562, (4) PMID: 22854646.

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**P-120**

## VALIANT: Randomized, multicenter, double-blind, placebo-controlled, phase 3 trial of pegcetacoplan for patients with native or post-transplant recurrent C3G or primary (idiopathic) IC-MPGN

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### Abstract

Aims C3 glomerulopathy (C3G) and primary immune complex-membranoproliferative glomerulonephritis (IC-MPGN) are complement-mediated diseases driven by C3 dysregulation with excessive accumulation of C3 breakdown products in the kidney. Pegcetacoplan (PEG) a C3/C3b inhibitor, targets the central components of the complement pathway, directly inhibiting C3 overactivation and preventing further deposition of C3 breakdown products in the glomeruli. VALIANT (NCT05067127) is the first Phase 3 trial investigating PEG in a broad cohort, including adolescents (≥12 yrs) and adults with native or post-transplant recurrent C3G or primary IC-MPGN.

**Methods:** VALIANT is a randomized, multicenter, double-blind, placebo (PBO)-controlled trial evaluating PEG efficacy and safety. 124 pts were randomized to PEG (n = 63) (twice weekly subcutaneous infusion) or PBO (n = 61) for 26 weeks (wks). The primary endpoint was log-transformed UPCR ratio at wk 26 vs baseline, assessing proteinuria reduction vs PBO. Key secondary endpoints at wk 26 were a composite renal endpoint (proportion of pts achieving ≥50% UPCR and ≤15% eGFR decline), proportion of patients achieving ≥50% UPCR reduction, C3G histologic index activity score change (adjusted LS mean change), reduced C3c renal biopsy staining of ≥2 OOM, eGFR change, (LS mean change), mL/min/1.73 $m^2$. Safety was assessed by treatment-emergent adverse events (TEAE) frequency and severity.

**Results:** The primary endpoint was met, with PEG demonstrating a 68.1% (95% CI: –76.2, –57.3) mean UPCR reduction vs. PBO at wk 26 ($p < 0.0001$). Results were consistent across disease type, age, and transplant status subgroups. PEG also led to robust reductions in C3c staining and clinically meaningful eGFR stabilization vs PBO. Treatment-emergent AE frequency and severity were similar between arms. None of the 4 serious infections (3 PEG; 1 PBO) were attributed to encapsulated bacteria.

**Conclusion:** PEG is the first therapy to achieve significant and clinically meaningful reductions in proteinuria (68.1% vs. PBO), C3c staining and eGFR stabilization in pts ≥12 yrs with C3G or primary IC-MPGN. PEG was well tolerated with no new safety signals observed.

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## P-121

## Metabolic changes in the retinal pigment epithelium of patients with complement factor H haploinsufficiency

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### Abstract

**Background:** Age-related macular degeneration (AMD) is a retinal disease that causes degeneration in the macula – the central part of the retina crucial for visual acuity. The complement system is a well-established contributor to the etiology of AMD, specifically via heightened complement activity at the retinal pigment epithelium (RPE). High penetrant mutations in the complement factor H (CFH) gene are of special interest because it is associated with early onset macular drusen (EOMD), a phenotypically severe subtype of AMD.(1) Recently, we reported a novel CFH SNP in an EOMD family, with A>G substitution at the intron splice site before exon 4, resulting in nonsense mediated decay of the CFH gene. The RPE generated from patient derived induced pluripotent stem cell (iPSC) had 50% reduction of both the CFH and factor H-like protein 1 (FHL-1) protein, which resulted in an increased local complement activity.(2) To further understand non-canonical roles of CFH intracellularly, this study aims to assess the metabolic changes in the RPE during conditions of CFH/FHL-1 insufficiency.

**Methods:** iPSC RPE derived from control patients without retinal degeneration, EOMD patients and Crispr-corrected EOMD (cEOMD) isogenic clones were cultured and collected for targeted metabolomics, mitochondria respiration and glycolytic flux.

**Results:** RPE from EOMD patients were found to have reduced levels of intracellular glucose and glucose 6-phosphate compared to control RPE. Glycolysis stress test revealed increased glycolytic capacity and glycolytic reserve in the EOMD RPE, suggesting changes to glucose consumption. Glutathione to oxidized glutathione ratio (GSH:GSSG) indicative of oxidative stress showed higher oxidative state in the EOMD RPE, consistent with increases in basal and maximum respiration, ATP production, and spare capacity. In contrast, GSH:GSSG was reverted to that of control levels in the cEOMD RPE. EOMD RPE also had reduced tryptophan and kynurenine, which was increased in cEOMD RPE, highlighting alterations in the kynurenine pathway and de novo synthesis of NAD.

**Conclusion:** Oxidative stress, glucose consumption, mitochondria respiration and NAD synthesis were altered in an EOMD patient-derived RPE, suggesting CFH and FHL-1 to have roles in influencing RPE metabolism.

**References:** 1. R.L. Taylor et al., Loss-of-Function Mutations in the CFH Gene Affecting Alternatively Encoded Factor H-like 1 Protein Cause Dominant Early-Onset Macular Drusen. Ophthalmology 126, 1410-1421 (2019).

2. R.R. Lim et al., CFH Haploinsufficiency and Complement Alterations in Early-Onset Macular Degeneration. Investigative Ophthalmology & Visual Science 65 (2024).

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## P-122

## Distinct associations of the lectin pathway proteins MASP-2, MASP-3, and MAP-1 with clinical and serological profiles in Systemic Lupus Erythematosus

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### Abstract

**Background:** The complement system plays an essential role in the pathogenesis of Systemic Lupus Erythematosus (SLE), but most studies have focused on the role of the classical pathway. Recently, we demonstrated a link between the lectin pathway recognition molecule ficolin-3, hematological manifestations, and autoantibody profiles in SLE [1]. In the present study, we expanded the study to include the lectin pathway serine proteases MASP-2 and MASP-3, along with the non-enzymatic splice product MAP-1, proposed to be a lectin pathway regulator.

**Methods:** Serum samples from 531 SLE patients and 322 matched population controls were collected at the Karolinska Institute (KI) in Stockholm, Sweden. The MASP-2, MASP-3, and MAP-1 concentrations were measured by in-house ELISAs. Logistic regression models adjusted for age and sex were used to explore associations between MASP-2, MASP-3, and MAP-1 serum concentrations and SLE disease manifestations and autoantibody specificities.

**Results:** Serum MASP concentrations were significantly higher in patients with SLE compared to control individuals for both MASP-2 ($p < 0.0001$), MASP-3 ($p = 0.0294$), and MAP-1 ($p = 0.0001$). Among these components, serum MAP-1 levels showed the strongest association with clinical manifestations, while associations were weaker for MASP-2 and MASP-3. When comparing patients in the highest vs. the lowest MAP-1 quartile, significant associations were observed for cutaneous (discoid rash OR 2.9, $p = 0.004$) and hematological (leukopenia OR 2.1, $p = 0.006$; lymphopenia OR 1.9, $p = 0.020$) SLE manifestations. Moreover, subjects in the highest MAP-1 quartile had a higher