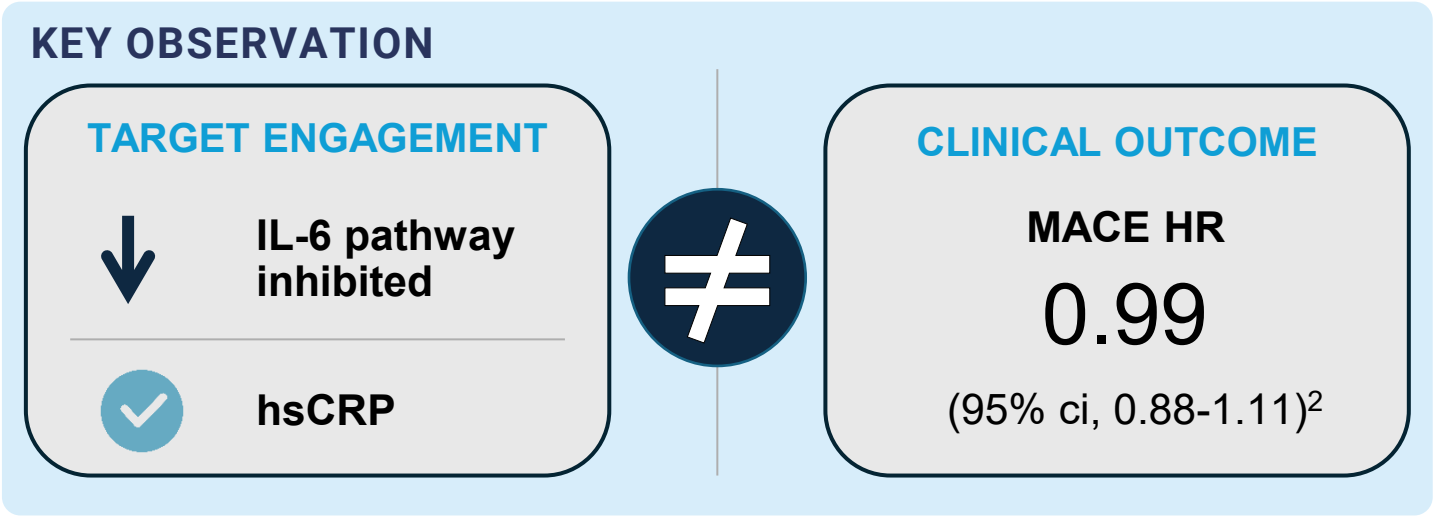
Evolution Research Group

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When the Biomarker Moves but the Outcome Doesn't:
What ZEUS Really Tells Us About Inflammation

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When Novo Nordisk recently announced results from the Phase 3 ZEUS cardiovascular outcomes trial of ziltivekimab, some of the immediate reaction was dramatic, with coverage questioning whether the findings represented a major challenge to the cardiovascular inflammation thesis.[1]



The results certainly warrant attention. ZEUS enrolled more than 6,300 participants with atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), and residual inflammation defined by high-sensitivity C-reactive protein (hsCRP) ≥2 mg/L. Ziltivekimab demonstrated the expected inhibition of the interleukin-6 (IL-6) pathway, including reductions in free IL-6 and hsCRP. Yet that biological activity did not translate into fewer major adverse cardiovascular events (MACE): the hazard ratio versus placebo was 0.99 (95% CI, 0.88-1.11).[2]

That disconnect is important. But declaring the broader inflammatory hypothesis disproven may be asking ZEUS to answer a larger question than it actually tested.

In fact, the result may tell us something equally important about how we use inflammatory biomarkers in clinical development.

hsCRP is a well-established marker of systemic inflammation and cardiovascular risk, but it is also a single, nonspecific hepatic acute-phase protein influenced by numerous inflammatory processes. In ZEUS, hsCRP appears to have performed as expected as a pharmacodynamic biomarker: the drug engaged its intended pathway, and hsCRP decreased accordingly. Work published immediately before the ZEUS readout demonstrated a close relationship between estimated free IL-6 and measured hsCRP during ziltivekimab treatment, supporting hsCRP as a downstream marker of IL-6 pathway inhibition.[3]

What ZEUS challenges is the stronger inference that successful modulation of hsCRP necessarily indicates modification of the inflammatory biology responsible for cardiovascular events. A biomarker can demonstrate target engagement, identify elevated risk, and still not function as a validated surrogate for clinical benefit.

This raises a different question:

> **Are we adequately characterizing inflammation when we rely on a single downstream protein?**

One emerging alternative is GlycA, a nuclear magnetic resonance-derived composite biomarker that integrates signals from multiple circulating acute-phase glycoproteins. Rather than reflecting the concentration of a single inflammatory protein, GlycA captures a broader systemic inflammatory signal

and has demonstrated associations with cardiometabolic and cardiovascular risk across multiple cohorts.[4,5] Importantly, GlycA and hsCRP appear to provide overlapping but nonidentical information. In the Intermountain Heart Collaborative Study, the two biomarkers were only moderately correlated, and both independently and additively predicted future cardiovascular events.[6] Similarly, in PREVEND, GlycA remained associated with incident cardiovascular disease after adjustment for hsCRP, with the greatest risk observed when both biomarkers were elevated.[7]

None of this establishes GlycA as a surrogate for cardiovascular outcomes, nor does ZEUS tell us that GlycA would have identified a population more responsive to IL-6 inhibition. Those remain empirical questions. But the findings suggest that the most productive response to ZEUS may not be to abandon the inflammatory hypothesis. It may be to ask whether our current approaches adequately distinguish the presence of inflammation from the type of inflammatory phenotype that is therapeutically actionable.



ERG RESEARCH PERSPECTIVE

At ERG, this is a question we are increasingly interested in exploring. Over the past several years, we have been building a database of potential clinical trial participants with elevated hsCRP to support inflammatory and cardiometabolic drug development. We are now considering how GlycA sampling could augment that resource, allowing us to examine whether GlycA may provide useful information independently or in combination with hsCRP when characterizing inflammatory phenotypes for future clinical research.

The goal would not be to replace hsCRP. Its accessibility, extensive clinical evidence base, and utility as a risk and pharmacodynamic biomarker remain important. Instead, the opportunity may be to determine whether a broader inflammatory signature can complement what hsCRP already tells us.

Perhaps the lesson from ZEUS is not that inflammation does not matter, but that

"inflammation" may be too biologically complex to characterize with a single downstream protein.

That leaves an important question for cardiometabolic drug development:

THE QUESTION AHEAD

If hsCRP tells us that inflammation is present, could combining it with a more integrated measure such as GlycA help us understand what kind of inflammation is present and, more importantly, which patients have inflammation that is therapeutically actionable?



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REFERENCES

1. Bilodeau K. Did Novo's phase 3 flop kill the inflammation hypothesis in heart disease? PharmaVoice. Published August 10, 2026.
2. Novo Nordisk. Novo Nordisk provides update on the ZEUS phase 3 trial in people with ASCVD, CKD and inflammation. Published July 31, 2026.
3. Nolain P, Fugger M, Hellinghus BT, et al. A quantitative method to estimate free interleukin-6 among patients treated with the interleukin-6 ligand inhibitor ziltivekimab: comparison to C-reactive protein with implications for the ZEUS, HERMES, and ARTEMIS cardiovascular outcomes trials. Atherosclerosis. 2026;417:120742. doi:10.1016/j.atherosclerosis.2026.120742.
4. Connelly MA, Otvos JD, Shalaurova I, Playford MP, Mehta NN. GlycA, a novel biomarker of systemic inflammation and cardiovascular disease risk. J Transl Med. 2017;15:219. doi:10.1186/s12967-017-1321-6.
5. Otvos JD, Shalaurova I, Wolak-Dinsmore J, et al. GlycA: a composite nuclear magnetic resonance biomarker of systemic inflammation. Clin Chem. 2015;61(5):714-723. doi:10.1373/clinchem.2014.232918.
6. Muhlestein JB, May HT, Galenko O, et al. GlycA and hsCRP are independent and additive predictors of future cardiovascular events among patients undergoing angiography: the Intermountain Heart Collaborative Study. Am Heart J. 2018;202:27-32. doi:10.1016/j.ahj.2018.04.003.
7. Gruppen EG, Riphagen IJ, Connelly MA, Otvos JD, Bakker SJL, Dullaart RPF. GlycA, a pro-inflammatory glycoprotein biomarker, and incident cardiovascular disease: relationship with C-reactive protein and renal function. PLoS One. 2015;10(9):e0139057. doi:10.1371/journal.pone.0139057.