American Heart Association Saturday November 7, 2026

Interleukin-6 Inhibition for Atherosclerotic Disease: Primary Report of the Ziltivekimab Cardiovascular Outcomes Study (ZEUS)

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Mass General Brigham
Heart and Vascular Institute

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ZEUS : Conduct and Design I

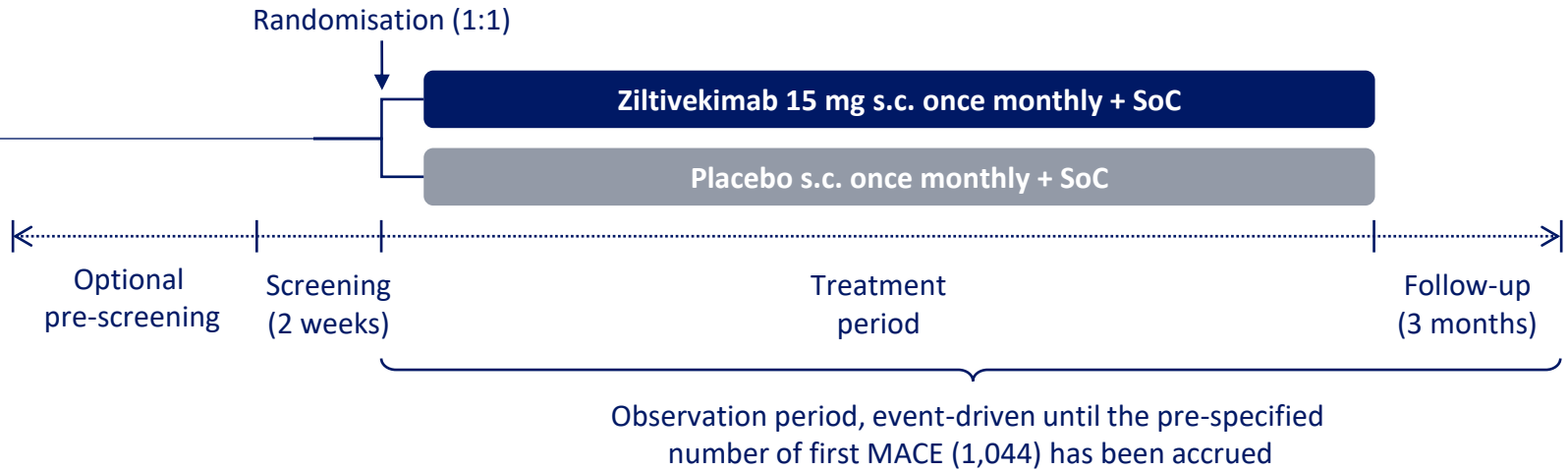
The Ziltivekimab Cardiovascular Outcomes Study (ZEUS) was designed as a global, randomized, double-blind, placebo-controlled trial to evaluate whether IL-6 inhibition would reduce rates of cardiovascular events among high-risk individuals with ASCVD, CKD, and evidence of cardiovascular inflammation defined as hsCRP ≥ 2 mg/L.

6,376 participants

Serum hsCRP ≥2 mg/L

Established ASCVD*

CKD defined as either eGFR ≥15 to <60 mL/min/1.73 m^2 or eGFR ≥60 mL/min/1.73 m^2 with UACR ≥200 mg/g



Objective

To demonstrate the superiority of ziltivekimab 15 mg s.c. once-monthly in reducing the risk of MACE compared with placebo

Primary endpoint ★

Time to first occurrence of 3-point MACE:

- CV death
- Non-fatal MI
- Non-fatal stroke

Confirmatory secondary endpoints ★

- Time to first occurrence of expanded 4-point MACE
- Number of hospitalisations for HF or urgent HF visit or CV death
- Time to first occurrence of a composite CKD endpoint*
- Time to occurrence of all-cause mortality

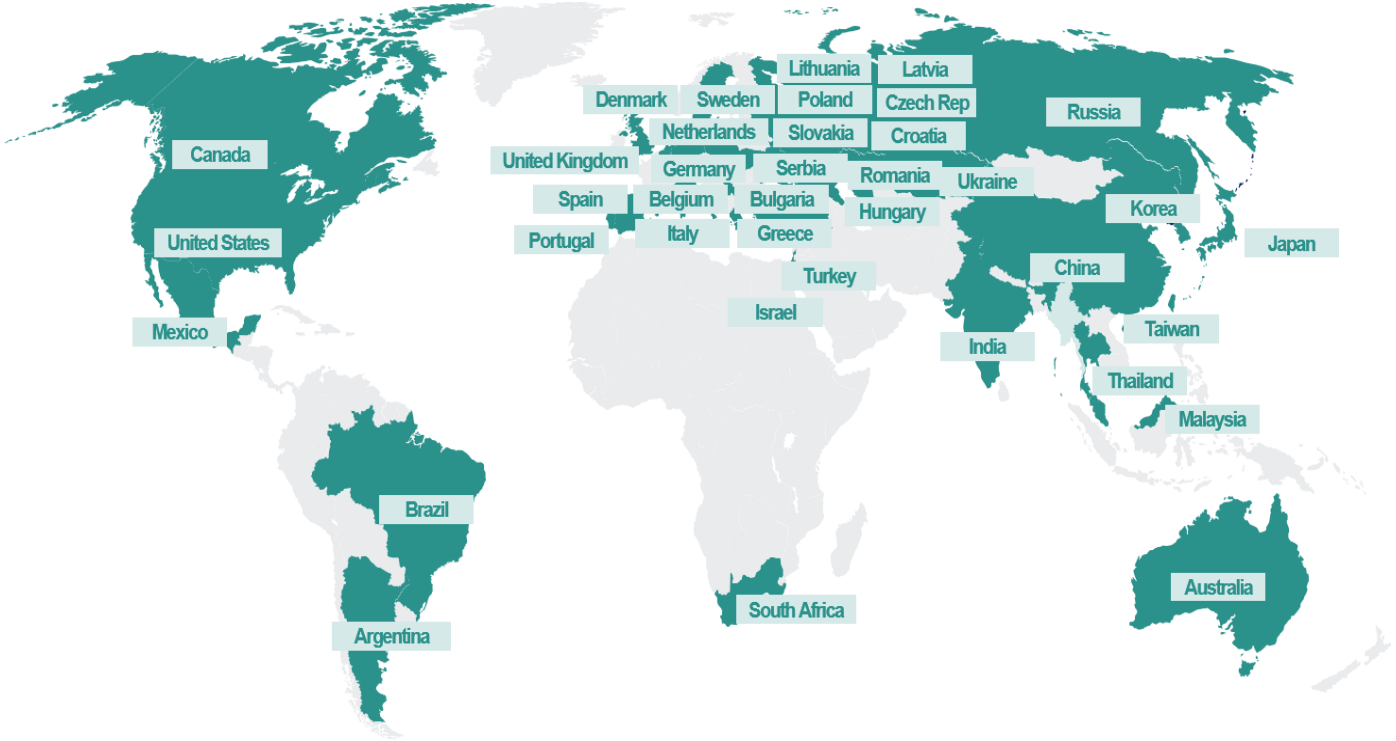
JAMA Cardiol 2026;11:89–97

* sustained reduction in eGFR of at least 40% from baseline, death from kidney failure or cardiovascular causes, or kidney failure

ZEUS : Conduct and Design II

6,376 participants at 757 sites in 38 countries

Median on-treatment period 33 months (IQR 27 – 42, max 55)
Adherence to trial regimen averaged 85.6% over time
1.3% lost to follow-up, vital status known for 99.1%



ASCVD, CKD, hsCRP ≥2 mg/L

Screened
N = 16,016

Screen Failures

hsCRP < 2 mg/L	60.0%
eGFR not in range	32.4%
Untreated latent TB	10.6%

Randomized
N = 6,376

Ziltivekimab
15 mg SC monthly
N = 3,184

Placebo
00 mg SC monthly
N = 3,192

97.6% Completed trial (97.6%)
1.3% Lost to follow-up (1.3%)
0.9% Withdrawn

97.4% Completed trial (97.6%)
1.2% Lost to follow-up (1.3%)
1.2% Withdrawn

99.1% Vital Status Known at Tral Completion

99.0% Vital Status Known at Tral Completion

ZEUS : Baseline Characteristics

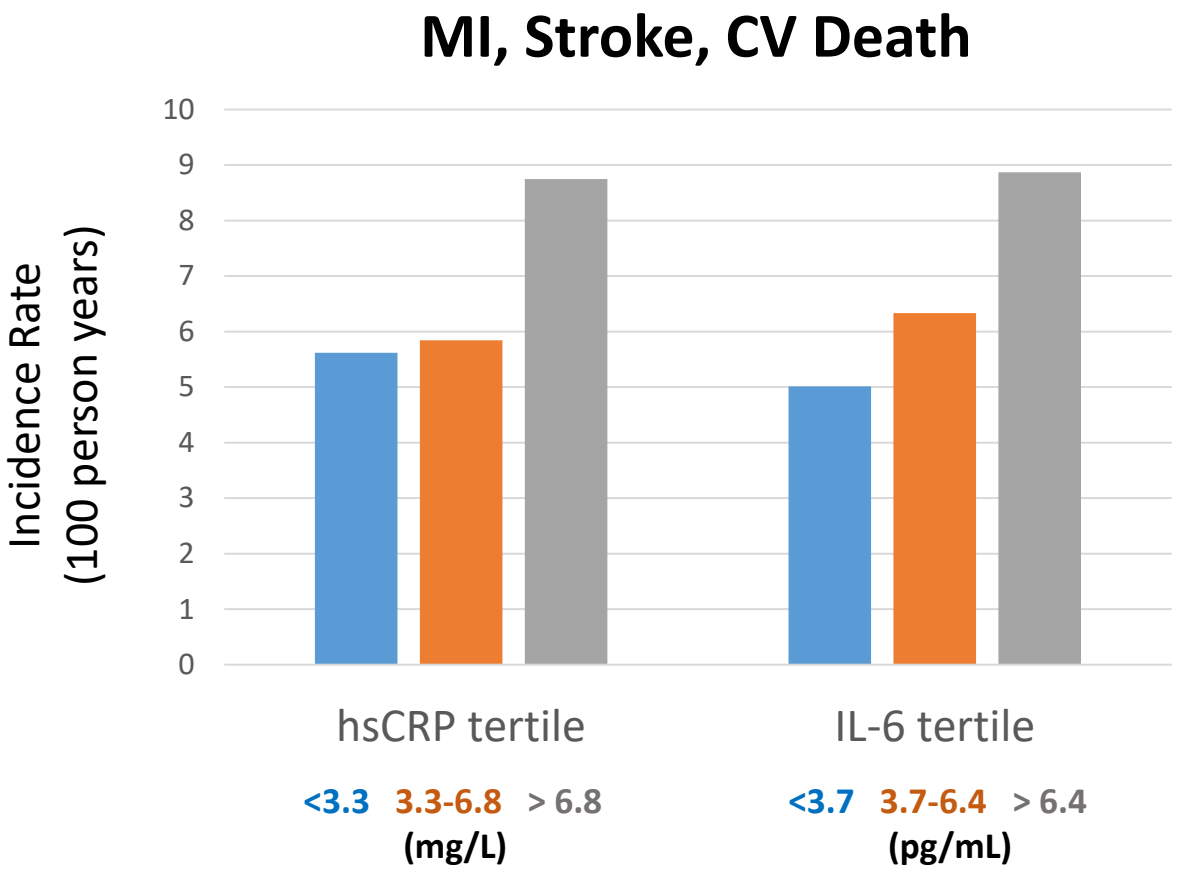
All Participants With Prevalent ASCVD, CKD, and hsCRP ≥ 2 mg/L

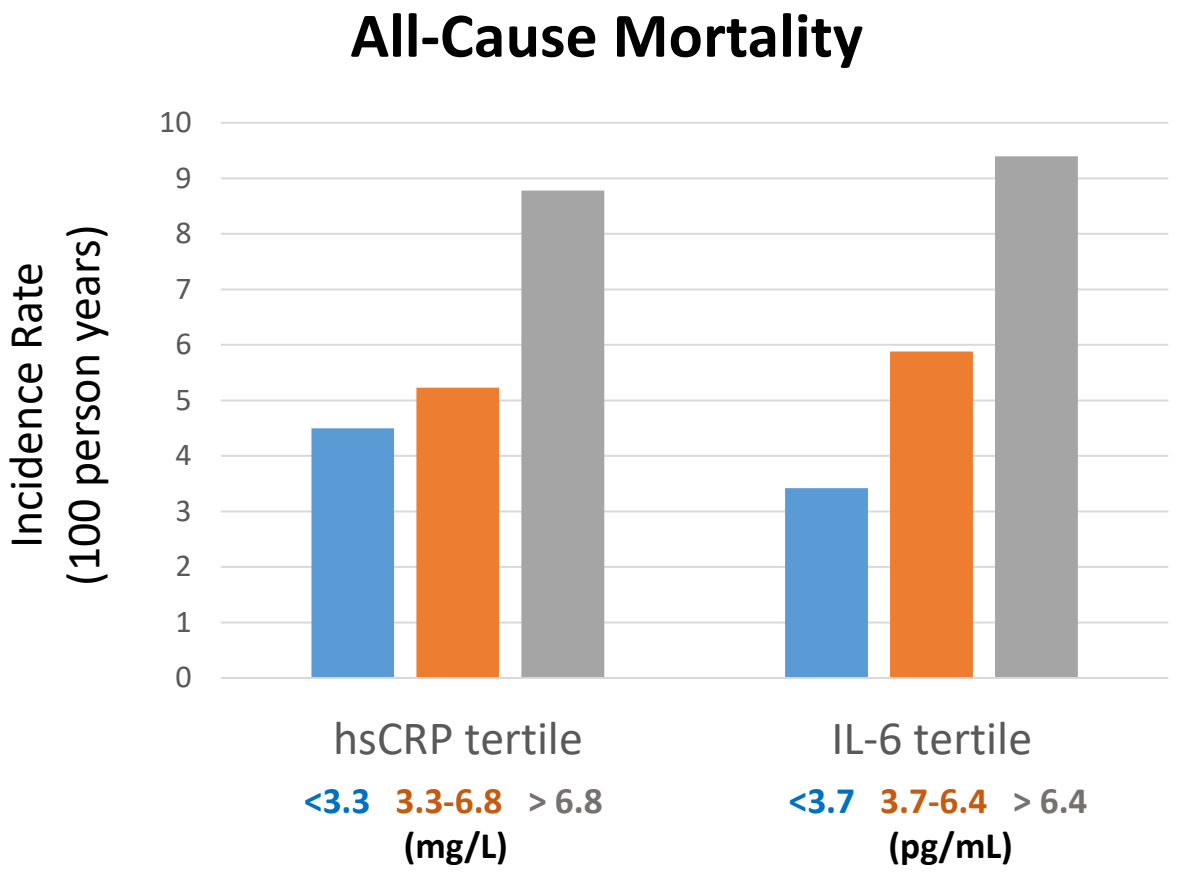
Characteristic	Ziltivekimab (N = 3184)	Placebo (N = 3192)
Age (years)	69.4	69.4
Female sex, (%)	27.9	27.1
Body mass index (kg/m²)	30.3	30.2
Current smoker, (%)	13.9	13.2
Diabetes, (%)	66.5	65.1
Hypertension, (%)	92.3	92.1
Heart failure, (%)	42.8	41.5
eGFR (mL/min/1.73 m²)	44.5	44.5
hs-CRP (mg/L), median (IQR)	4.5 (2.8–8.5)	4.5 (2.7–8.5)
IL-6 (pg/mL), median (IQR)	4.9 (3.2–7.7)	4.8 (3.2–7.7)
LDL-C (mg/dL), median (IQR)	72 (54–96)	71 (54–94)

Concomitant Medications	%
Lipid Lowering	92.6
RAAi	76.4
SGLT2i (beginning)	37.1
(completion)	52.1
GLP1rA (beginning)	11.4
(completion)	18.6

ZEUS : Results I

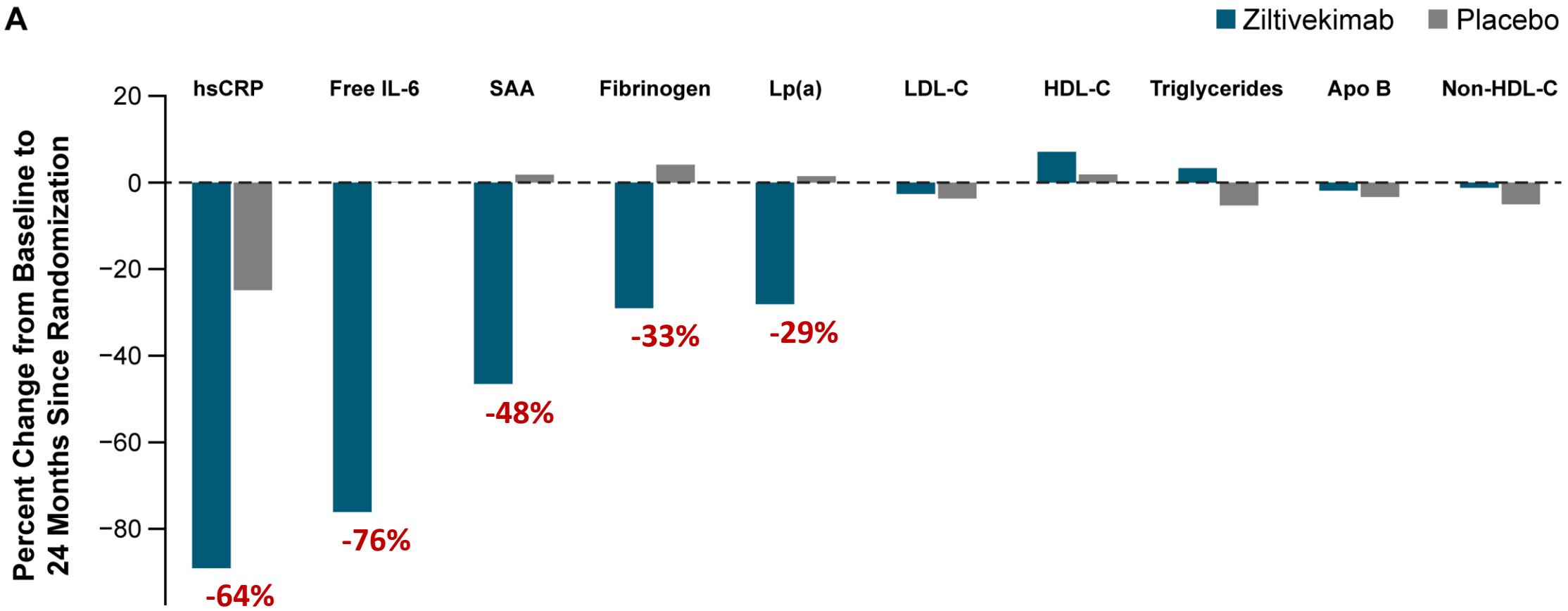
Increasing Tertiles of Both hsCRP and IL-6 Associate with Increasingly High Risks of Major Adverse Cardiovascular Events and Death





ZEUS : Results II

Placebo-Adjusted Effects of Ziltivekimab on Inflammatory and Other Biomarkers

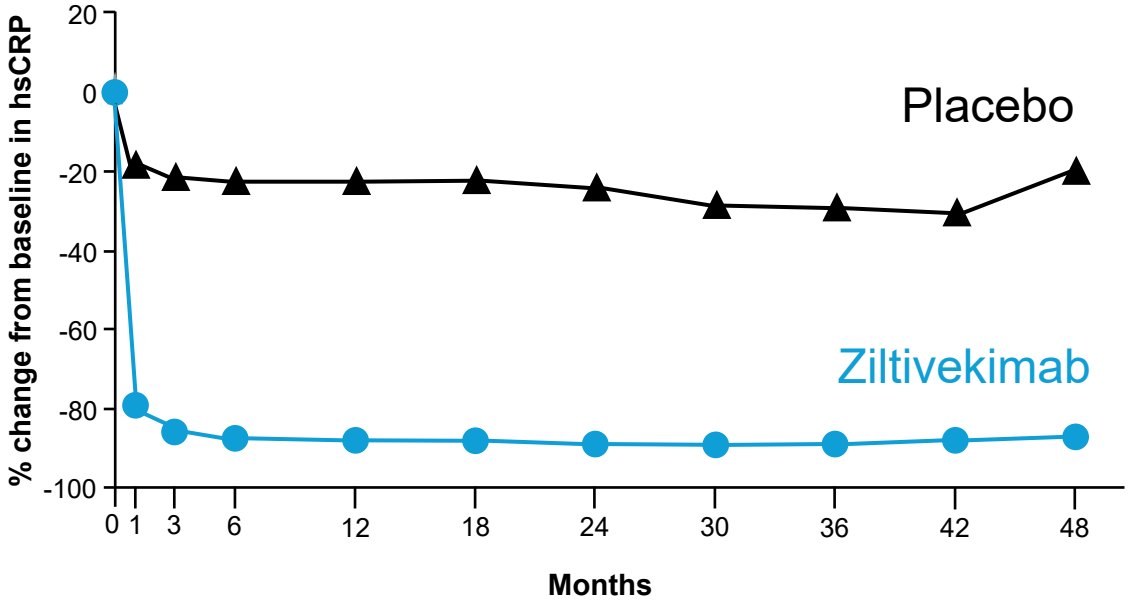


Placebo adjusted percent change from baseline

ZEUS : Results III

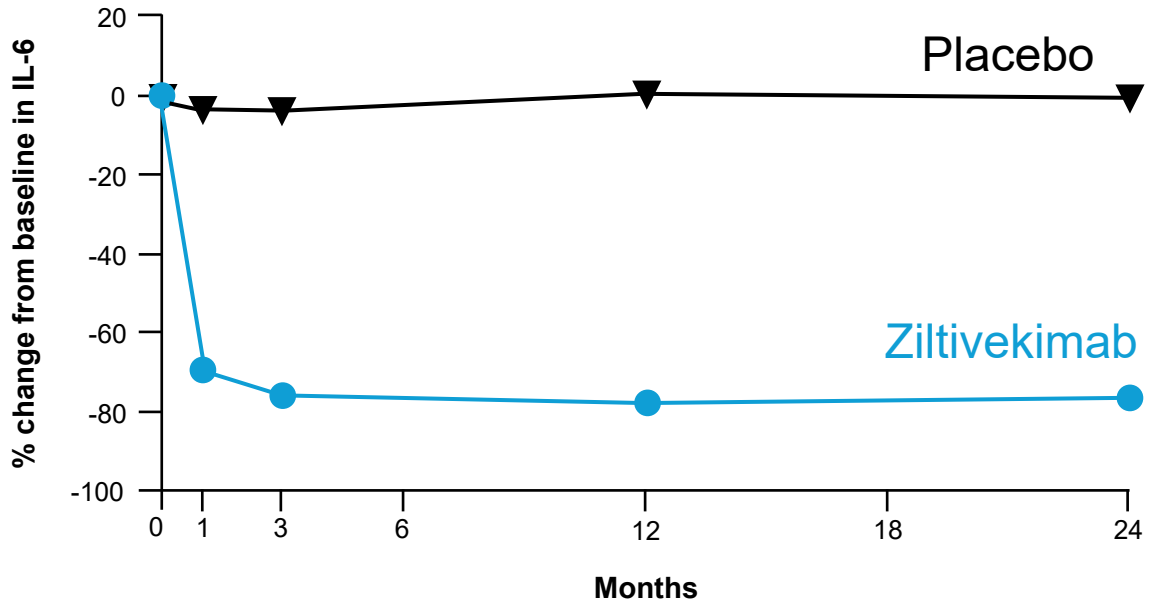
Evidence of Target Engagement - Long-term effects of ziltivekimab on hsCRP and free IL-6

Median Percent Change in hsCRP



64% Placebo-Adjusted Change in hsCRP

Median Percent Change in free IL-6



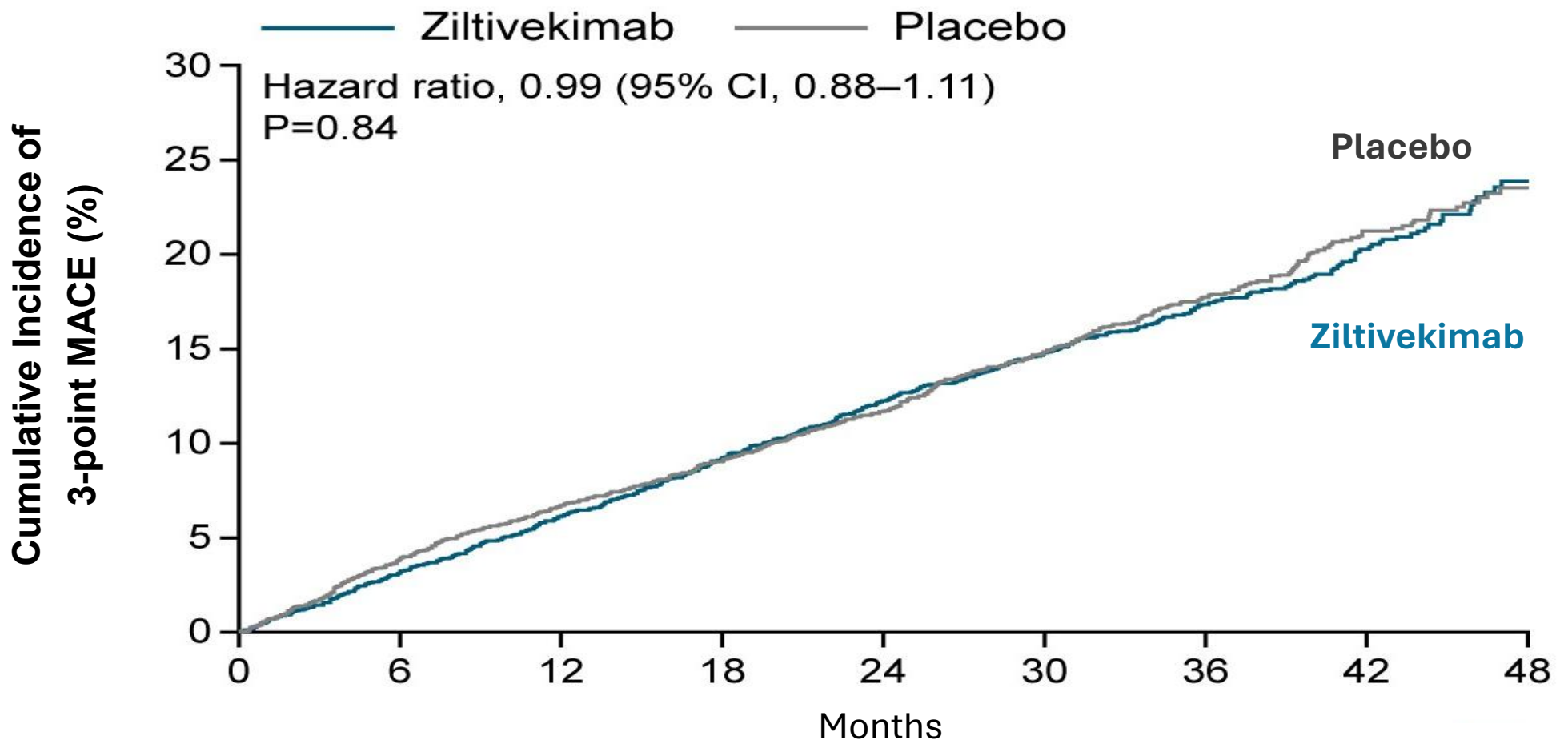
76% Placebo-Adjusted Change in free IL-6

ZEUS : Primary and Secondary Endpoints

Endpoint	Ziltivekimab N (%) IR*	Placebo N (%) IR*	HR (95%CI)
Primary Endpoint: 3-point MACE	**561 (17.6) 6.7**	**565 (17.7) 6.8**	**0.99 (0.88–1.11)**
Cardiovascular death	353 (11.1) 4.0	356 (11.2) 4.1	0.99 (0.86–1.15)
Nonfatal myocardial infarction	143 (4.5) 1.7	148 (4.6) 1.7	0.97 (0.77–1.22)
Nonfatal stroke	114 (3.6) 1.3	124 (3.9) 1.4	0.92 (0.71–1.18)
Expanded 4-point MACE**			
Number of heart failure hospitalizations, urgent heart failure visits, or CV death			
Composite kidney endpoint***			
All-cause mortality			

***IR = incidence rate per 100 participant years of observation. ** inclusive of hospitalization for unstable angina requiring urgent revascularization**
***** sustained reduction in eGFR of at least 40% from baseline, death from kidney failure or cardiovascular causes, or kidney failure (onset of sustained eGFR <15ml per minute per 1.73m2 or initiation of chronic kidney replacement therapy).**

ZEUS : Primary Endpoint: Non-fatal MI, Non-fatal Stroke, Cardiovascular Death



No. at risk									
Ziltivekimab	3,184	3,050	2,920	2,772	2,583	1,897	1,163	600	198
Placebo	3,192	3,027	2,911	2,778	2,605	1,868	1,126	578	208

ZEUS : Primary Endpoint, Selected Pre-Specified Subgroups

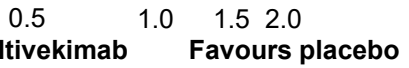
Subgroup	HR (95% CI)	No. of events / analysed participants
Sex		
Female	0.93 (0.74; 1.17)	*292/1,754*
Male	1.01 (0.88; 1.16)	*834/4,622*
Age		
<65 years	1.03 (0.81; 1.30)	*276/1,690*
65–<75 years	0.97 (0.81; 1.16)	*481/2,711*
≥75 years	0.98 (0.80; 1.20)	*369/1,975*
BMI (kg/m²)		
<25	0.76 (0.57; 1.00)	*203/1,150*
25–<30	1.03 (0.84; 1.26)	*381/2,243*
≥30	1.06 (0.90; 1.26)	*539/2,969*
hsCRP		
<median	0.88 (0.74; 1.06)	*470/3,188*
≥median	1.07 (0.92; 1.25)	*656/3,188*
IL-6		
<median	0.92 (0.76; 1.10)	*449/3,141*
≥median	1.04 (0.89; 1.21)	*659/3,147*



Subgroup	HR (95% CI)	No. of events / analysed participants
T2D		
No	1.00 (0.79; 1.26)	*293/2,180*
Yes	0.98 (0.85; 1.12)	*833/4,196*
SGLT2i		
No	1.00 (0.86; 1.16)	*677/4,013*
Yes	0.98 (0.82; 1.18)	*449/2,363*
Incretins		
No	1.00 (0.88; 1.13)	*999/5,651*
Yes	0.89 (0.63; 1.26)	*127/725*
ASCVD subtype		
CHD	0.97 (0.84; 1.13)	*687/4,228*
Cerebrovascular disease	0.91 (0.65; 1.27)	*140/766*
PAD	1.24 (0.78; 1.97)	*73/453*
Polyvascular disease	1.01 (0.77; 1.31)	*224/916*



Subgroup	HR (95% CI)	No. of events / analysed participants
Heart failure		
No	0.88 (0.74; 1.05)	*512/3,687*
Yes	1.08 (0.92; 1.27)	*614/2,689*
eGFR (mL/min/1.73 m²)		
<30	0.99 (0.79; 1.24)	*298/1,157*
30–<45	0.91 (0.75; 1.11)	*404/2,130*
≥45	1.05 (0.87; 1.27)	*424/3,089*
KDIGO groups at baseline		
Very high risk	0.98 (0.84; 1.14)	*655/2,847*
High risk	1.02 (0.81; 1.29)	*283/1,727*
Low/moderate risk	0.90 (0.68; 1.20)	*188/1,795*



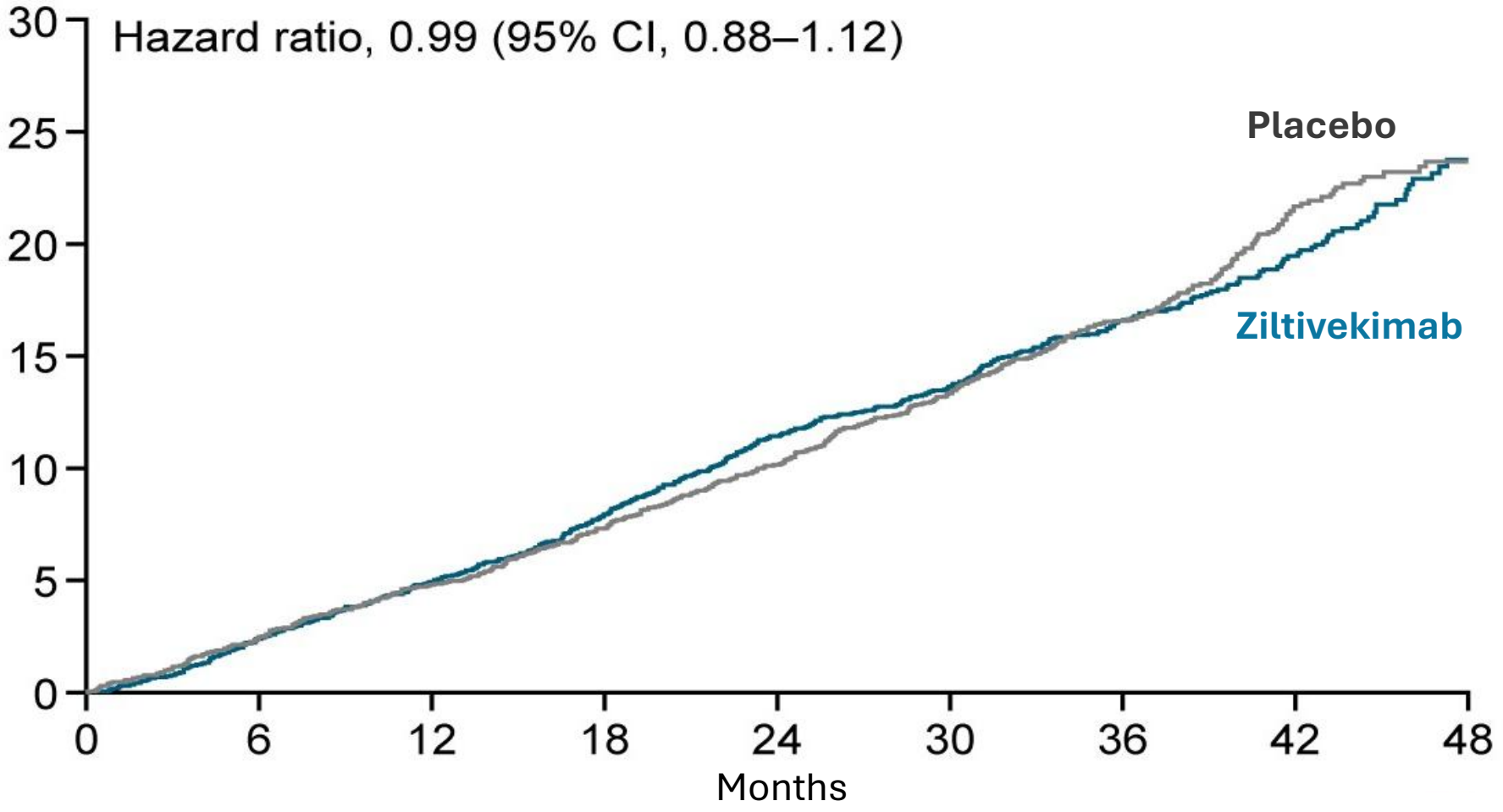
Median high-sensitivity CRP was 4.5 mg/liter.
Median interleukin-6 was 4.88 pg/l.

ZEUS : Primary and Secondary Endpoints

Endpoint	Ziltivekimab N (%) IR*	Placebo N (%) IR*	HR (95%CI)
Primary Endpoint: 3-point MACE	**561 (17.6) 6.7**	**565 (17.7) 6.8**	**0.99 (0.88–1.11)**
Cardiovascular death	353 (11.1) 4.0	356 (11.2) 4.1	0.99 (0.86–1.15)
Nonfatal myocardial infarction	143 (4.5) 1.7	148 (4.6) 1.7	0.97 (0.77–1.22)
Nonfatal stroke	114 (3.6) 1.3	124 (3.9) 1.4	0.92 (0.71–1.18)
Expanded 4-point MACE*	**586 (18.4) 7.0**	**592 (18.5) 7.1**	**0.99 (0.88–1.10)**
Number of heart failure hospitalizations, urgent heart failure visits, or CV death**	**794 (17.1) 9.1**	**842 (17.6) 9.6**	**0.94 (0.83-1.07)**
Composite kidney endpoint***	**643 (20.2) 7.8**	**617 (19.3) 7.4**	**1.05 (0.94-1.17)**
All-cause mortality	**538 (16.9) 6.2**	**542 (17.0) 6.2**	**0.99 (0.88–1.12)**

*** inclusive of hospitalization for unstable angina requiring urgent revascularization. ** Mean ratio rather than hazard ratio**
***** sustained reduction in eGFR of at least 40% from baseline, death from kidney failure or cardiovascular causes, or kidney failure (onset of sustained eGFR <15ml per minute per 1.73m2 or initiation of chronic kidney replacement therapy).**

ZEUS : All-Cause Mortality



No. at risk									
Ziltivekimab	3,184	3,096	3,007	2,889	2,712	2,010	1,241	653	214
Placebo	3,192	3,090	3,010	2,903	2,752	1,995	1,222	636	233

ZEUS : Safety and Adverse Events

Adverse Event	Ziltivekimab N (%)	Placebo N (%)	
Serious adverse event	**1738 (54.6%)**	**1750 (54.8%)**	
Serious adverse event of infection	**651 (20.4%)**	**571 (17.9%)**	*
Cellulitis	93 (2.9%)	31 (1.0%)	*
Infection as primary cause of hospitalization	544 (17.1%)	472 (14.8%)	*
Opportunistic infection	87 (2.7%)	71 (2.2%)	
Death due to infection	101 (3.2%)	80 (2.5%)	
Malignant neoplasms	**205 (6.4)**	**213 (6.7)**	
Serious adverse event of Hemorrhage	**161 (5.1%)**	**129 (4.0%)**	
Serious adverse event of Venous thromboembolism	**51 (1.6%)**	**20 (0.6%)**	*

*** Fisher's exact p-value < 0.05**

ZEUS : Controversies and Possible Reasons for Neutral Findings I

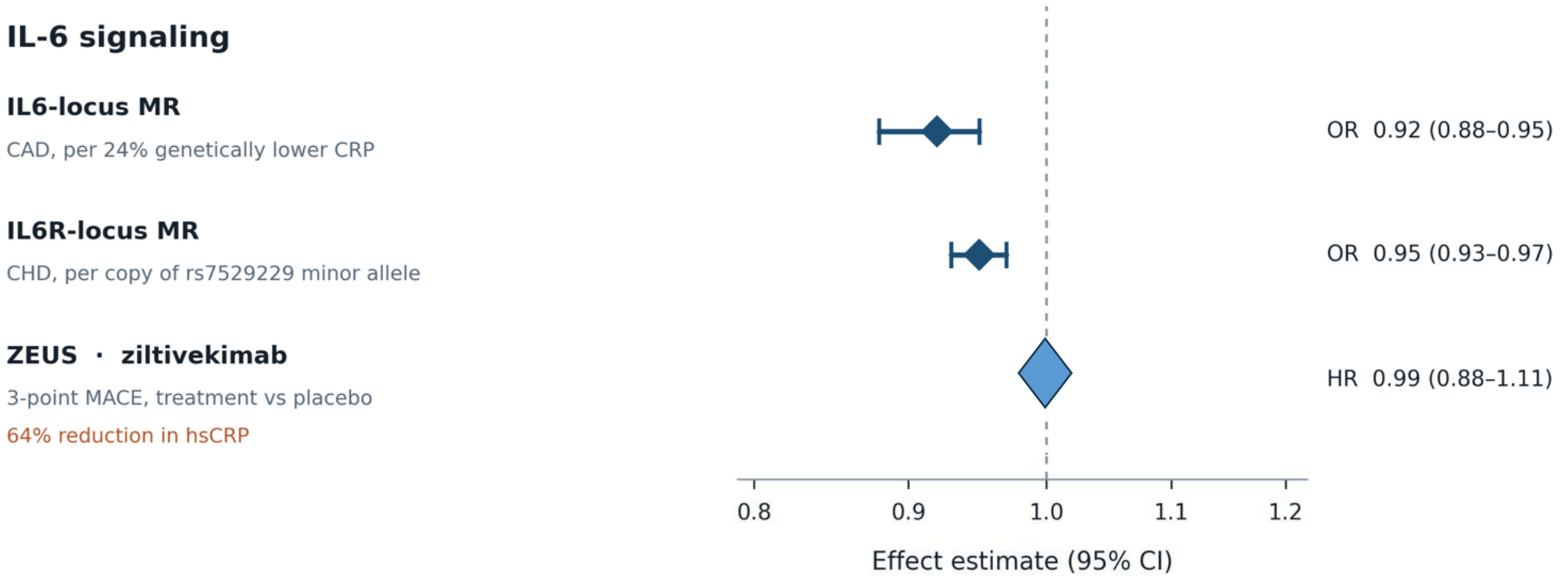
Wrong Target or Non-Modifiable Disease?

Compared to CANTOS (a positive trial of IL-1β inhibition), ZEUS (a neutral trial of IL-6 inhibition) evaluated a much higher risk population raising the possibility that advanced disease may be less amendable to modification by anti-inflammatory therapy.

Characteristic	CANTOS (IL-1β) ASCVD + hsCRP ≥ 2	ZEUS (IL-6) ASCVD + hsCRP ≥ 2 + CKD
Age (years)	61	69
Diabetes (%)	40	66
Heart Failure (%)	22	42
KDIGO Class High or Very High (%)	11.4	71.8
eGFR (ml/min/1.73m^2)	80	45
Endpoint		
3-Point MACE (IR/100 PY)	4.5	6.8
All Cause Mortality (IR/100 PY)	**3.0**	**6.2**

ZEUS : Controversies and Possible Reasons for Neutral Findings II

Genetic Causality is Not Therapeutic Reversibility
Conflicting Evidence from Mendelian Randomization Studies and Randomized Control Trials



Courtesy of M. Shapiro

ZEUS : Conclusions and Considerations of a Neutral Trial

Cardiovascular inflammation is highly prevalent and remains a mechanistically compelling therapeutic target beyond lipid lowering.

The CANTOS, LoDoCo2 and COLCOT trials have proven that anti-inflammatory therapy can reduce cardiovascular event rates. The relevant question moving forward is what drug in which patient group?

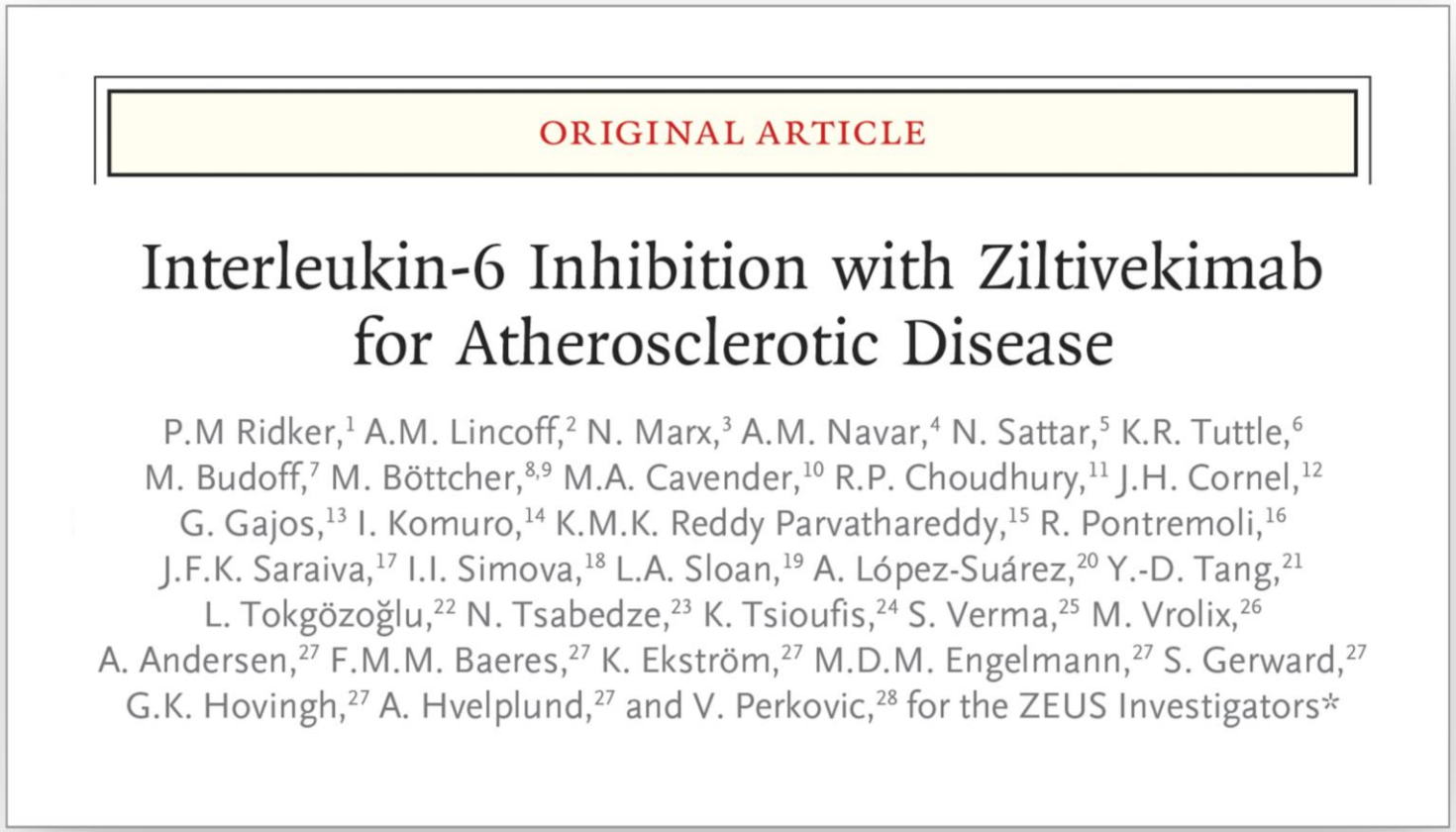
ZEUS evaluated a selected population with established ASCVD and significant CKD raising the possibility that highly advanced disease may be less amendable to anti-inflammatory modification.
"The horse may already have been out of the barn"

The HERMES and ARTEMIS trials will provide further insights on the effect of ziltivekimab in very different trial populations, HFpEF/HFmrEF and acute coronary ischemia, respectively.

In addition to diet, exercise, and smoking cessation - all of which lower hsCRP - statins, colchicine, canakinumab, and GLP1rAs positively impact patients with residual inflammatory risk.

The NLRP3 to IL-1 to IL-6 signaling process is complex but biologically compelling. Several promising opportunities for downstream IL-6 inhibition remain in earlier modifiable disease as well as multiple opportunities for direct targeting of the upstream NLRP3 inflammasome.

The ZEUS Executive Committee wishes to thank the trial sponsor, the trial staff at our 757 clinical sites in 38 countries, and most importantly the 6,376 participants in our trial



ORIGINAL ARTICLE

Interleukin-6 Inhibition with Ziltivekimab for Atherosclerotic Disease

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The NEW ENGLAND JOURNAL of MEDICINE

Science in Depth ZEUS Presentation: Sunday November 8, N230B 9:45 AM