ORAL NLRP3 INHIBITOR RUVONOFLAST PROVIDES RAPID, ROBUST AND REVERSIBLE INFLAMMATION REDUCTION IN PEOPLE WITH RESIDUAL INFLAMMATORY RISK OF ASCVD

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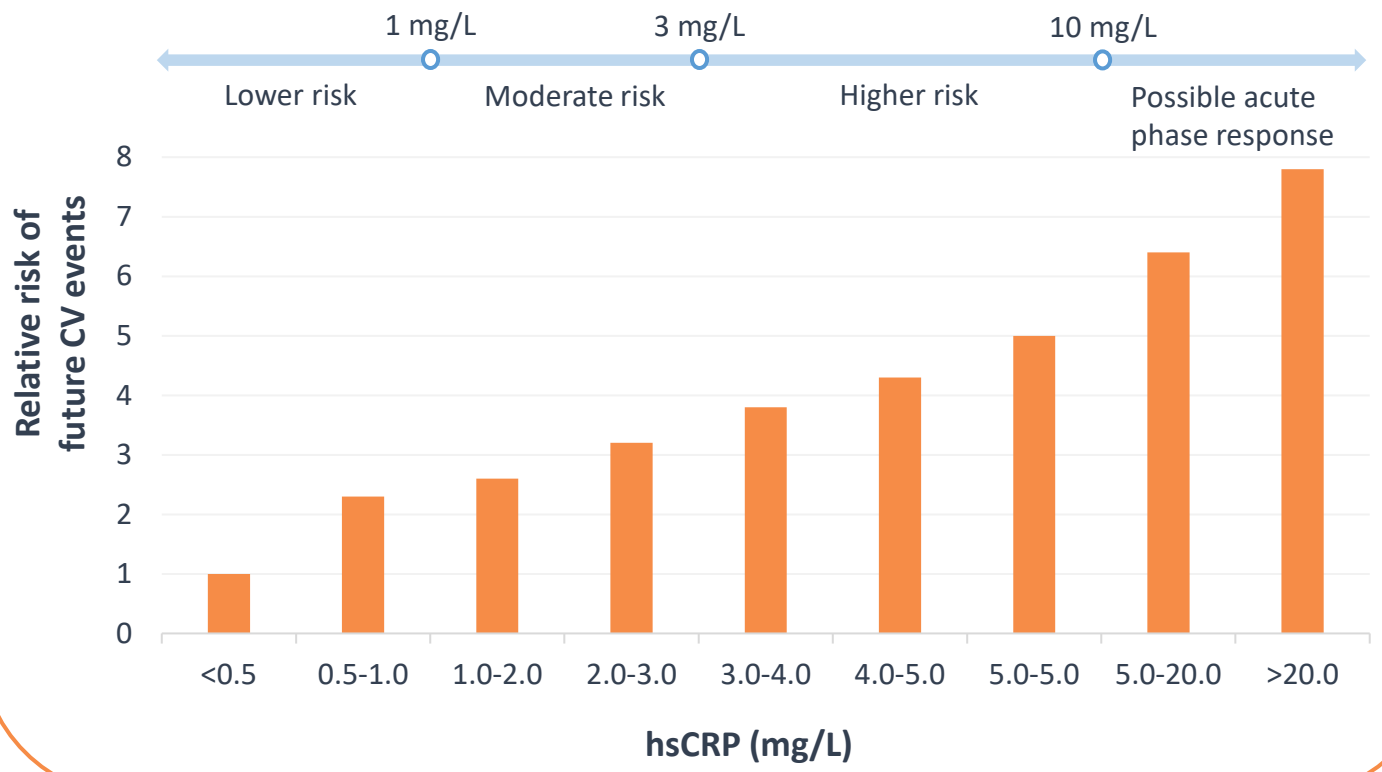
Residual inflammatory risk is a critical unmet need in ASCVD

- Residual cardiovascular risk persists despite treatment of traditional risk factors
- Elevated high-sensitivity C-reactive protein (hsCRP) identifies patients with persistent inflammatory risk despite contemporary preventive therapy
- Inflammatory signaling is mechanistically linked to atherogenesis, plaque progression and recurrent cardiovascular events
- The 2025 ACC Scientific Statement: Inflammation and Cardiovascular Disease prioritizes inflammation-targeted strategies, but there are few approved therapies

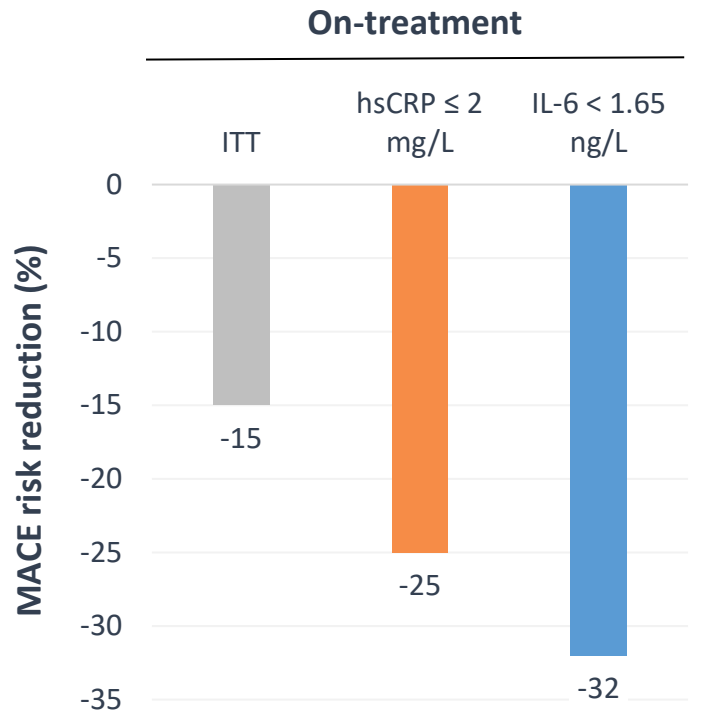
ASCVD, atherosclerotic cardiovascular disease. Mensah GA, et al. *J Am Coll Cardiol*. 2025. https://doi.org/10.1016/j.jacc.2025.08.047.

Inflammation is a proven causal, modifiable CV risk factor

The relationship of inflammation to CV risk is linear across high-sensitivity C-reactive protein (hsCRP) values[1]

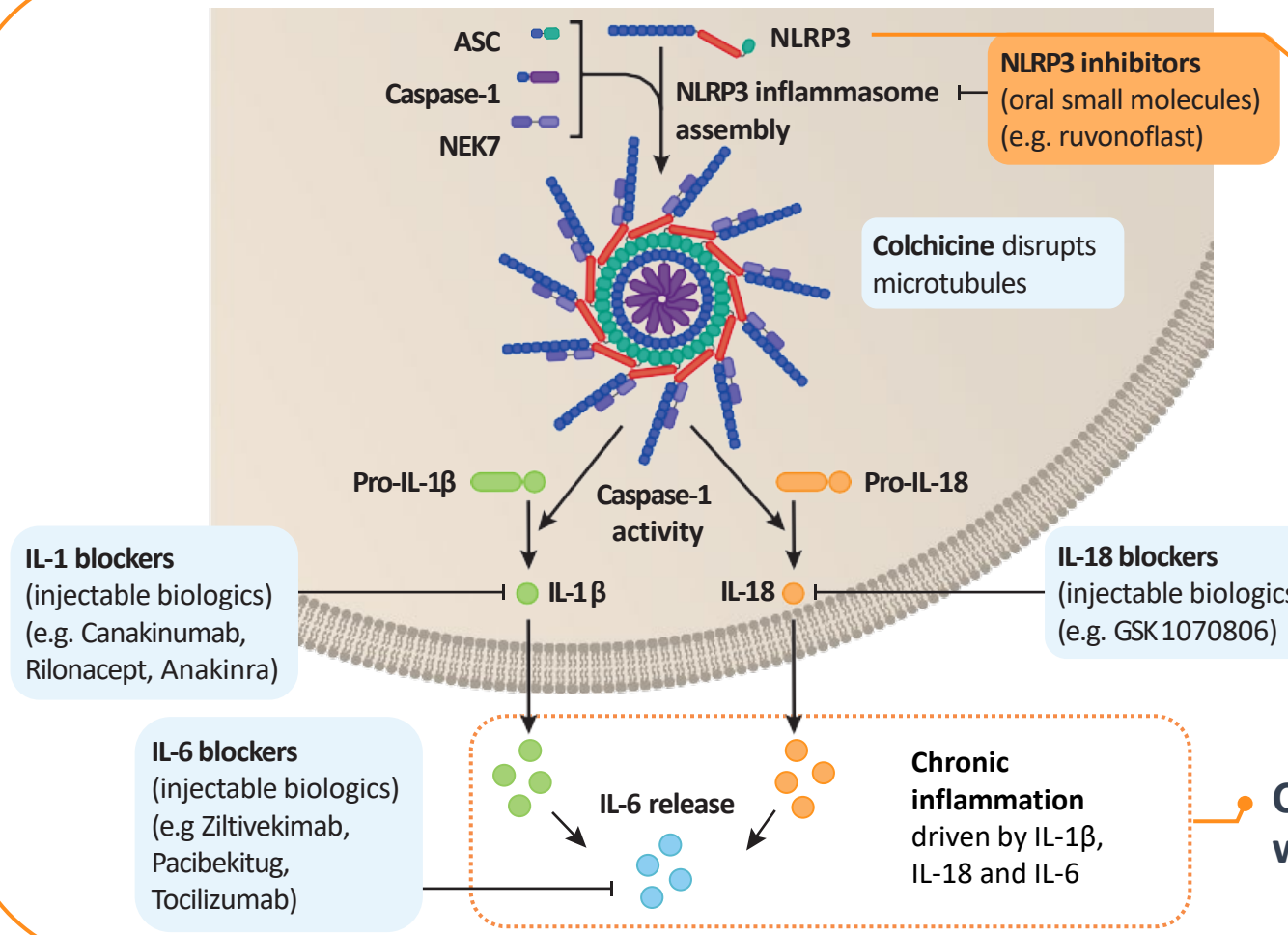


CANTOS (anti–IL-1β)* established hsCRP and IL-6 thresholds for MACE risk reduction[2–4]



*Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) of IL-1β blocker canakinumab. CV, cardiovascular; hsCRP, high-sensitivity C-reactive protein; IL-1β, interleukin-1β; IL-6, interleukin-6; ITT, intent to treat; MACE, major adverse cardiovascular event. 1. Mensah GA, et al. *J Am Coll Cardiol*. 2025. https://doi.org/10.1016/j.jacc.2025.08.047. 2. Ridker PM, et al. *N Engl J Med*. 2017. https://doi.org/10.1056/nejmoa1707914. 3. Ridker PM, et al. *Lancet*. 2018. https://doi.org/10.1016/s0140-6736(17)32814-3. 4. Ridker PM, et al. *Eur Heart J*. 2018. https://doi.org/10.1093/eurheartj/ehy310.

Ruvonoflast targets the innate immunity cascade consisting of the NLRP3 inflammasome–IL-1β, IL-18–IL-6–CRP axis to reduce chronic inflammation



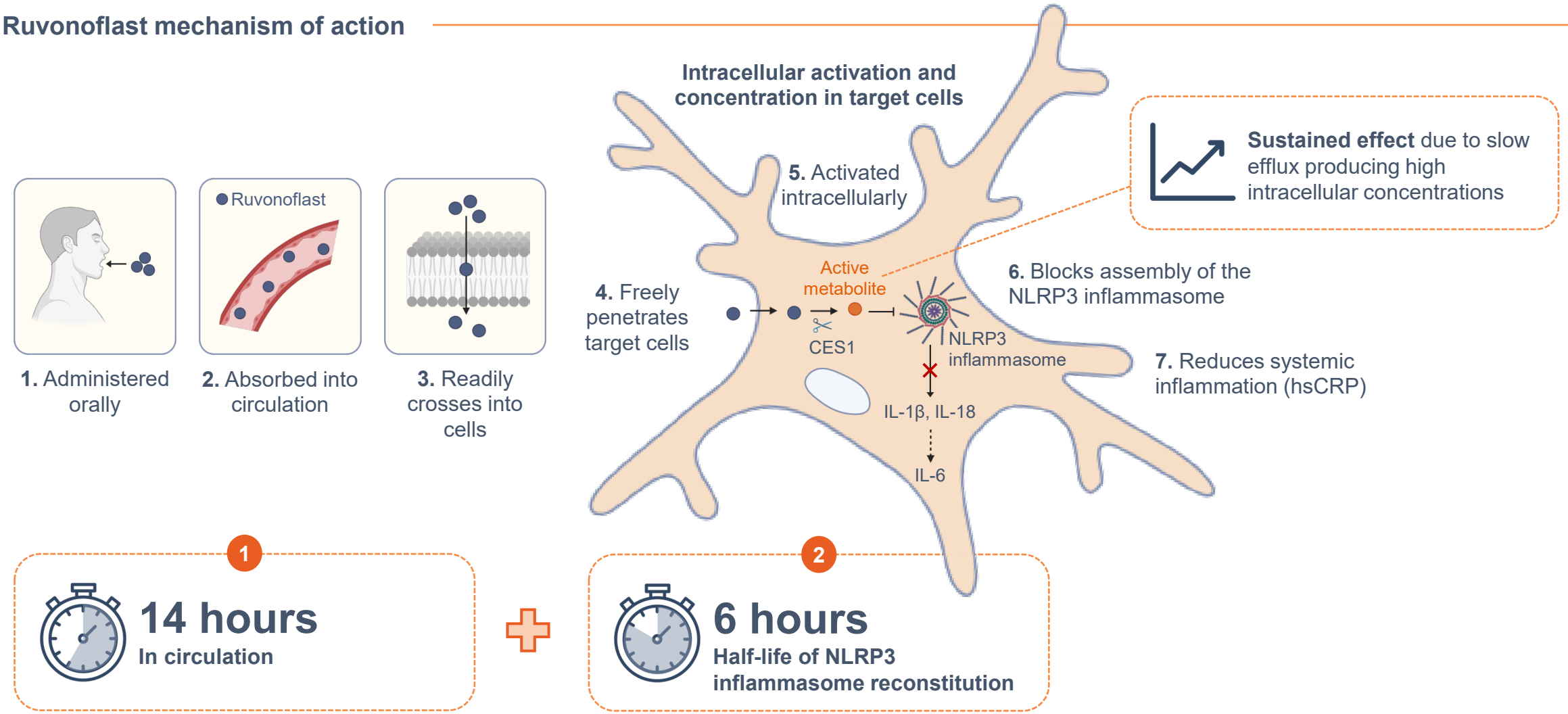
Activators of NLRP3 include cholesterol crystals, oxLDL and other damage-associated molecular patterns (DAMPs)

Clinically assessed with hsCRP

ASC, apoptosis-associated speck-like protein containing a CARD; DAMPs, damage-associated molecular patterns; hsCRP, high-sensitivity C-reactive protein; IL-1, interleukin-1; IL-6, interleukin-6; IL-18, interleukin-18; NEK7, NIMA-related kinase 7; NLPR3, NOD-like receptor family, pyrin domain containing 3; oxLDL, oxidized low-density lipoprotein. Figure adapted from NodThera. *Biopharm Deal*. 2025;19(4) and Ray KK, et al. *JACC*. 2026. https://doi.org/10.1016/j.jacc.2026.05.014.

Ruvonoflast concentrates intracellularly, blocks NLRP3 inflammasome assembly

Ruvonoflast mechanism of action



CES1, carboxylesterase 1; hsCRP, high-sensitivity C-reactive protein; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-18, interleukin-18; NLPR3, NOD-like receptor family, pyrin domain containing 3.

Harrison D, et al. *J Med Chem*. 2023. https://doi.org/10.1021/acs.jmedchem.3c01398. Doedens JR, et al. *Biochem Pharmacol*. 2024. https://doi.org/10.1016/j.bcp.2024.116455.

Ruvonoflast efficacy and safety assessed in 63 cardiometabolic patients with elevated risk of ASVCD

Participants

- Aged ≥ 18 yrs
- hsCRP ≥ 2.5 mg/L
- BMI ≥ 30 to ≤ 40 kg/m^2
- ≥1 ASCVD risk factor: hypertension, dyslipidemia, type 2 diabetes

Major exclusion criteria:

- *History of stroke with residual neuro deficit (<2 yrs) or TIA (<6 mos)*
- *Any history of ACS (incl. unstable angina, acute MI)*
- *Stable angina or CHF*
- *Past or current Hep B or C infection, or positive HIV antibody at screening*
- *Concurrent inflammatory illness*

Phase 1b trial

R 2:1 stratified by baseline hsCRP

Ruvonoflast 225mg Q12H N=40

n=37 completed
n=3 withdrawn
participant choice, n=2
*AE, n=1**

Placebo N=23

n=22 completed
n=1 withdrawn
participant choice, n=1

28 days

Inpatient on a clinical research unit, with **calorie restriction** expected to produce weight loss†

7 days

Outpatient safety follow up

- **Primary endpoint: change in hsCRP at Day 28**, log-transformed ratio to baseline (Bayesian analysis)
  - Sample size provides **80% power** to detect **~31% difference (ruvonoflast vs placebo)**
- **Secondary endpoints:**
  - Change in hsCRP ratio to baseline over time (MMRM)
  - Absolute change in IL-6, total/calculated free IL-18, fibrinogen, CXCL1, IL-1β
  - % change in body weight, absolute fat mass, % body fat, visceral fat volume‡
  - Safety (AEs)
- **Prespecified exploratory analyses:**
  - % change in IL-6, total/calculated free IL-18, fibrinogen, CXCL1, IL-1β
  - % change in Lp(a)
- **Post hoc analyses:**
  - Participants (%) achieving hsCRP ≤ 3, 2, 1 mg/L
  - Absolute change in HbA1c
  - % change in HOMA-IR, total cholesterol, HDL-C, LDL-C, VLDL-C, triglycerides

*Anaphylactic reaction (Grade 3) prior to AM dosing in a participant with a strong family history of food allergy; considered unrelated to study treatment. Participant withdrawn from the study to avoid exposure to possible allergens. †2000 kcal/day (45% carbohydrate, 20% protein, 35% fat). ‡Body composition parameters assessed with bioelectrical impedance. ACS, acute coronary syndrome; AE, adverse event; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHF, congestive heart failure; CXCL1, C-X-C motif chemokine ligand 1; HDL-C, high-density lipoprotein cholesterol; HepB, hepatitis B; HepC, hepatitis C; HIV, human immunodeficiency virus; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; hsCRP, high-sensitivity C-reactive protein; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-18, interleukin-18; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein A; MI, myocardial infarction; MMRM, mixed-effects model with repeated measures; Q12H, every 12 hours; TIA, transient ischemic attack; VLDL-C, very low-density lipoprotein cholesterol. Ray KK, et al. *JACC*. 2026. https://doi.org/10.1016/j.jacc.2026.05.014.

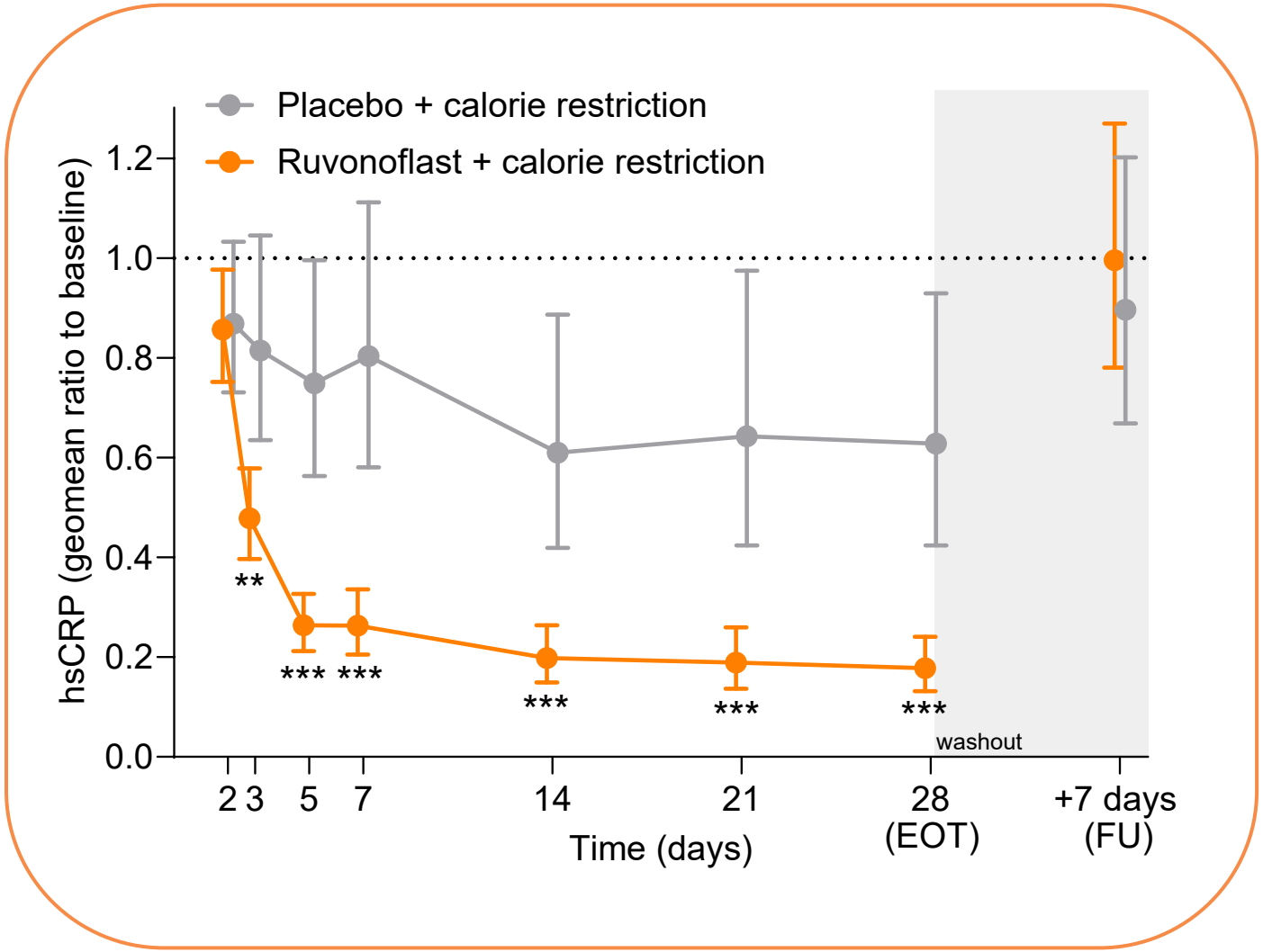
Treatment groups were generally well balanced

	Placebo (N=23)	Ruvonoflast 225mg Q12H (N=40)	Total (N=63)
Age, years; mean (min, max)	52.8 (36, 75)	52.5 (30, 69)	52.6 (30, 75)
Sex, n (%)			
Male	8 (34.8%)	10 (25.0%)	18 (28.6%)
Female	15 (65.2%)	30 (75.0%)	45 (71.4%)
Race, n (%)			
White	16 (69.6%)	28 (70.0%)	44 (69.8%)
Black or African American	7 (30.4%)	12 (30.0%)	19 (30.2%)
BMI, kg/m²; mean (SD)	34.4 (2.6)	35.2 (2.6)	34.9 (2.6)
Controlled type 2 diabetes*, n (%)	6 (26.1%)	5 (12.5%)	11 (17.5%)
History of controlled hypertension, n (%)	19 (82.6%)	31 (77.5%)	50 (79.4%)
History of hypercholesterolemia or screening LDL-C >130 mg/dL, n (%)	15 (65.2%)	35 (87.5%)	50 (79.4%)
History of hypercholesterolemia, n (%)	6 (26.1%)	11 (27.5%)	17 (27.0%)
Statin use, n (%)	3 (13.0%)	8 (20.0%)	11 (17.5%)
LDL-C, mg/dL; mean (SD)	121.2 (30.8)	132.8 (28.5)	128.6 (29.7)
HDL-C, mg/dL; mean (SD)	53.2 (13.6)	50.7 (13.0)	51.6 (13.2)
Total cholesterol, mg/dL; mean (SD)	199.1 (35.6)	205.7 (34.2)	203.3 (34.6)
Triglycerides, mg/dL; median (IQR)	120.0 (91.0–244.0)	120.5 (99.8–164.0)	120.0 (99.0-180.0)
Systolic blood pressure mmHg; mean (SD)	125.5 (11.6)	126.5 (9.5)	126.1 (10.2)
HbA1c %; mean (SD)	6.0 (0.8)	5.9 (0.7)	6.0 (0.8)
hsCRP, mg/L			
Mean (SD)	6.31 (4.63)	7.94 (5.08)	7.35 (4.95)
Median (IQR)	5.16 (3.93–6.87)	6.42 (3.89–10.85)	5.70 (3.93–9.80)
IL-6, pg/ml; median (IQR)	1.80 (1.45–2.16)	1.81 (1.36–2.22)	1.80 (1.43–2.22)

No significant between-group differences in baseline characteristics, except for documented history of hypercholesterolemia or screening LDL-C >130 mg/dL

*HbA1c ≤8%. BMI, body mass index; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; Q12H, every 12 hours. Ray KK, et al. *JACC*. 2026. https://doi.org/10.1016/j.jacc.2026.05.014.

Ruvonoflast demonstrated early, sustained and reversible hsCRP reduction versus placebo



The primary endpoint of hsCRP reduction was met with a posterior probability of >99% for superiority of ruvonoflast over placebo at Day 28

hsCRP reduction at Day 28 in the ruvonoflast group was 82.2% versus 37.2% in the placebo group (45% between-group difference)

Significant between-group differences favoring ruvonoflast observed from Day 3 ($p \leq 0.001$) and maintained through Day 28

hsCRP returned to near baseline levels ~7 days after treatment discontinuation during the washout period

EOT, end of treatment; FU, follow up; hsCRP, high-sensitivity C-reactive protein. Ray KK, et al. *JACC*. 2026. https://doi.org/10.1016/j.jacc.2026.05.014.

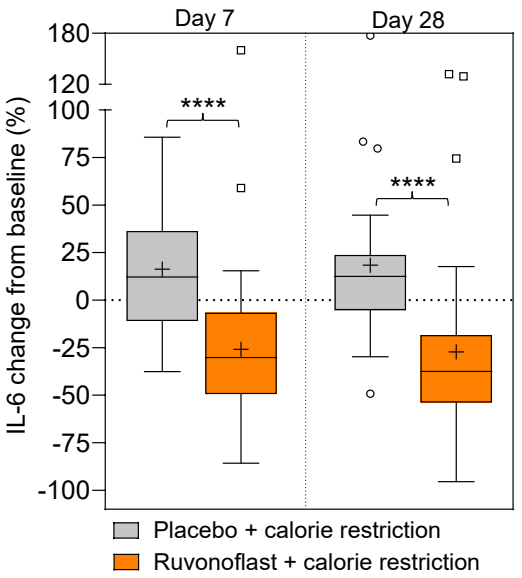
Ruvonoflast significantly reduced IL-6 and fibrinogen (absolute change from baseline) vs placebo at Day 28

Secondary endpoints	Baseline		Day 28			
	Placebo (N=23)	Ruvonoflast 225mg Q12H (N=40)	Placebo (N=22)	Ruvonoflast 225mg Q12H (N=37)	Treatment group differences, ruvonoflast vs placebo (ANCOVA/MMRM)	
Body weight and body composition	**Actual value, mean (SD)**		**Percentage change from baseline, LSmean (95% CI) or mean (SD)**		**LSmean difference (95% CI)***	**p-value**
Body weight, kg	90.7 (12.8)	91.8 (10.1)	−3.65 (−4.34, −2.95)	−3.62 (−4.15, −3.09)	0.03 (−0.85, 0.90)	0.953
Absolute fat mass, kg	40.4 (7.2)	42.2 (5.4)	−5.2 (3.7)	−4.3 (2.7)	n/a	n/a
Body fat %	44.6 (5.3)	46.2 (5.0)	−1.6 (3.1)	−0.7 (2.0)	n/a	n/a
Visceral fat, L	3.3 (1.6)	3.1 (1.4)	−15.5 (22.1)	−12.7 (10.3)	n/a	n/a
Key inflammatory biomarkers	**Actual value, mean (SD)**		**Absolute change from baseline, LSmean (95% CI)**		**LSmean difference (95% CI)†**	**p-value**
IL-6, pg/ml	1.89 (0.64)	2.97 (4.54)	−0.28 (−0.70, 0.14)	−1.27 (−1.59, −0.95)	−0.99 (−1.52, −0.46)	<0.001
Total IL-18, pg/mL	798.7 (247.3)	913.3 (325.0)	−148. 8 (−241.4, −56.2)	−132.8 (−204.0, −61.6)	16.0 (−101.1, 133.1)	0.785
Calculated free IL-18, pg/mL	148.4 (64.7)	159.9 (55.8)	−19.0 (−35.3, −2.7)	−34.3 (−46.8, −21.8)	−15.3 (−35.8, 5.3)	0.142
Fibrinogen, g/L	3.44 (0.77)	3.78 (0.82)	0.19 (−0.09, 0.46)	−0.93 (−1.14, −0.72)	−1.12 (−1.47, −0.77)	<0.001
CXCL1, pg/mL	1810.0 (789.6)	1950.8 (764.1)	−196.6 (−519.8, 126.5)	−121.7 (−368.5, 125.2)	75.0 (−332.1, 482.1)	0.714
IL-1β, fg/mL	571.1 (226.7)	680.0 (503.6)	−132.8 (−219.1, −46.5)	−115.2 (−181.3, −49.1)	17.6 (−91.5, 126.7)	0.748

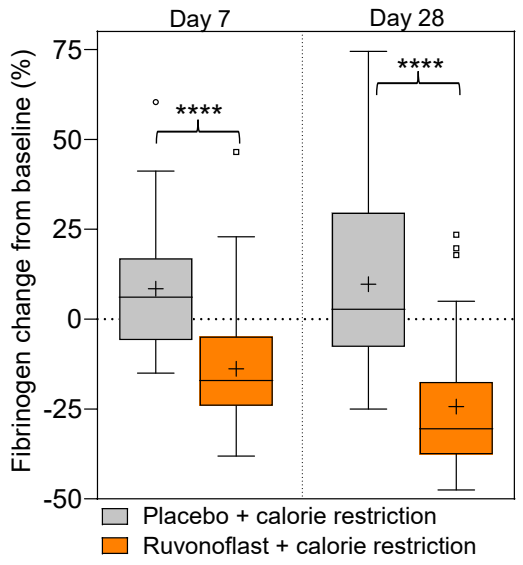
*Analyzed using an analysis of covariance with treatment group as a fixed effect and baseline weight as a covariate. †Analyzed using a mixed-effect model with repeated measures (MMRM) with fixed effects for baseline, treatment group, visit, and treatment*visit interaction. ANCOVA, analysis of covariance; CI, confidence interval; CXCL1, C-X-C motif chemokine ligand 1; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-18, interleukin-18; LSmean, least-squares mean; MMRM, mixed-effects model with repeated measures; SD, standard deviation; Q12H, every 12 hours. Ray KK, et al. *JACC*. 2026. https://doi.org/10.1016/j.jacc.2026.05.014.

Exploratory Analyses: Treatment effects favoring ruvonoflast were observed for % change from baseline in IL-6, fibrinogen, calculated free IL-18 and Lp(a)

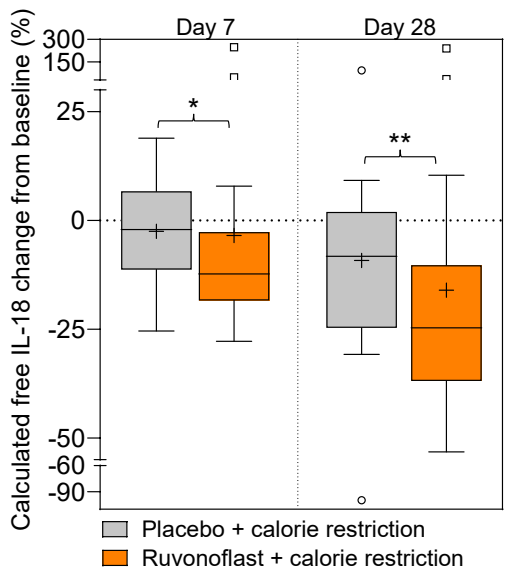
IL-6



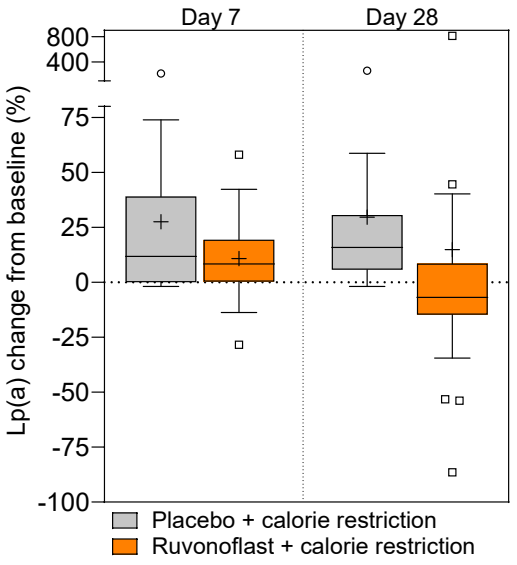
Fibrinogen



Calculated free IL-18



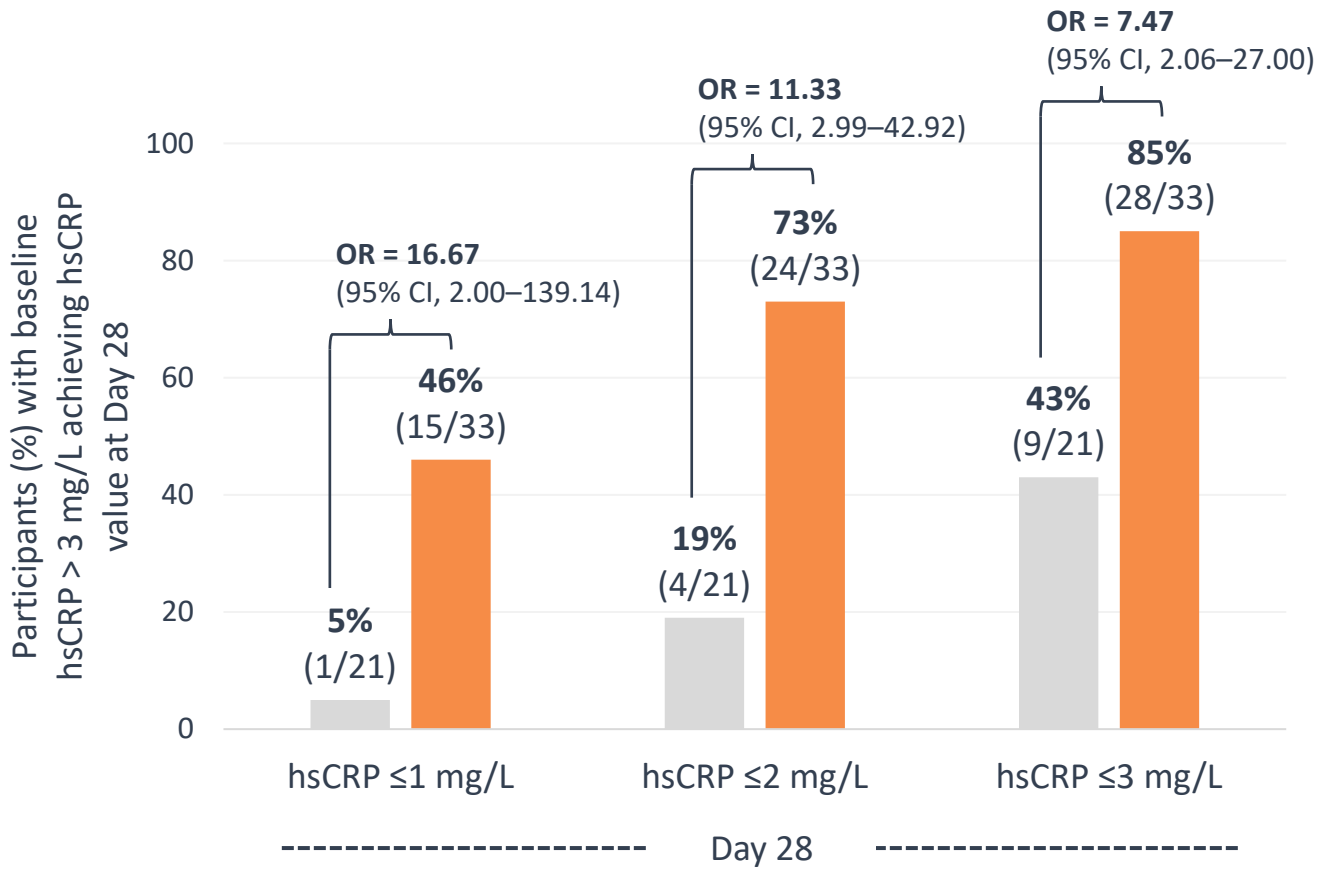
Lp(a)



IL-6, fibrinogen and calculated free IL-18 were prespecified exploratory analyses supporting the corresponding secondary endpoints (absolute change from baseline); treatment group differences analyzed post hoc using Mann-Whitney U tests. Lp(a) was a prespecified exploratory endpoint analyzed descriptively. Interquartile range (IQR) is indicated by the box, median by the horizontal bar, and mean by the plus sign. Whiskers extend to extreme values within 1.5xIQR, with outliers beyond shown as open circles (placebo) or squares (ruvonoflast). IL-6, interleukin-6; IL-18, interleukin-18; Lp(a), lipoprotein(a). Ray KK, et al. *JACC*. 2026. https://doi.org/10.1016/j.jacc.2026.05.014.

Post hoc Analyses: Magnitude of the reductions in hsCRP with ruvonoflast may be clinically meaningful

Participants (%) with baseline hsCRP > 3 mg/L (n=33 ruvonoflast, n=21 placebo) achieving hsCRP ≤ 3, 2, 1 mg/L at Day 28:



Participants may appear in multiple hsCRP categories if they meet more than one threshold.

All participants (n=37 ruvonoflast, n=22 placebo):

76% hsCRP ≤ 2 mg/L at Day 28 with ruvonoflast
versus 23% with placebo

43% hsCRP ≤ 1 mg/L at Day 28 with ruvonoflast
versus 9% with placebo

CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; OR, odds ratio (ruvonoflast vs placebo); Q12H, every 12 hours. Ray KK, et al. *JACC*. 2026. https://doi.org/10.1016/j.jacc.2026.05.014.

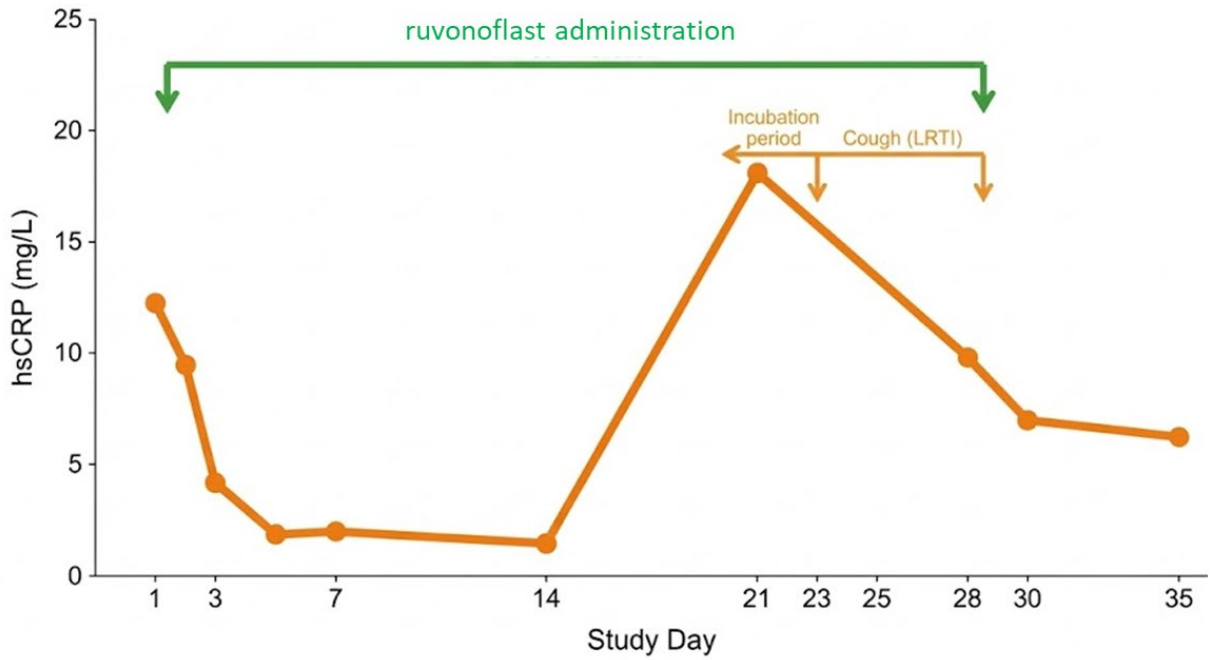
SAEs were similar between groups, but more ruvonoflast-treated participants discontinued treatment due to transient, reversible TEAEs

	Placebo (N=23) n (%)	Ruvonoflast 225mg Q12H (N=40) n (%)	Total (N=63) n (%)
Any TEAE	9 (39.1)	20 (50.0)	29 (46.0)
Any Treatment-Related TEAE	1 (4.3)	7 (17.5)	8 (12.7)
Any TEAE Leading to Treatment Discontinuation	0	4 (10.0)*	4 (6.3)
Any TEAE Leading to Death	0	0	0
Any TEAE Grade 3 or Higher	1 (4.3)	6 (15.0)	7 (11.1)
Any Treatment-Related Grade 3 or Higher TEAE	0	3 (7.5)	3 (4.8)
Any Treatment-Emergent SAE	1 (4.3)	0	1 (1.6)
Any Treatment-Related SAE	0	0	0

- The majority of TEAEs were Grade 1 or 2 and generally mild and self-resolving
- All TEAEs had resolved by study end, excluding one event of Grade 1 eosinophilia considered unrelated to study drug
- There were no treatment-related serious AEs (SAEs) and no events leading to death
- One (4.3%) participant receiving placebo experienced a treatment-emergent SAE (bacterial food poisoning) considered unrelated to study treatment

*[1] Anaphylactic reaction (Grade 3) prior to AM dosing in a participant with a strong family history of food allergy; considered unrelated to study treatment and resolved the same day following treatment with epinephrine, corticosteroids and antihistamines. Participant withdrawn from the study to avoid exposure to possible allergens. [2] Asymptomatic increased ALT (Grade 3) and GGT (Grade 2) considered related to study drug; study treatment discontinued, resolved within 4 days. Asymptomatic increased ALT, AST and GGT (all Grade 3) and elevated LDH (Grade 1) considered related to study drug; study treatment discontinued, laboratory values normalized within 6 weeks. For [2] and [3], multiple possible confounding or contributing factors associated with liver function test abnormalities were present. [4] Urticaria (Grade 2) considered related to study treatment; study treatment discontinued, resolved 3 days post treatment with diphenhydramine hydrochloride. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; hsCRP, high-sensitivity C-reactive protein; LDH, lactate dehydrogenase; Q12H, every 12 hours; SAE, serious adverse event; TEAE, treatment-emergent adverse event. Ray KK, et al. *JACC*. 2026. https://doi.org/10.1016/j.jacc.2026.05.014.

Ruvonoflast-treated participant was able to mount an infection response while on study drug



- **Selective NLRP3 inhibition** preserves parallel pathways for pathogen response
- **No increased risk of infections** observed in this trial
- **Potential differentiation from IL-1/IL-6 biologics**

hsCRP, high-sensitivity C-reactive protein; IL-1, interleukin-1; IL-6, interleukin-6; LRTI, lower respiratory tract infection; NLPR3, NOD-like receptor family, pyrin domain containing 3.

Limitations and future directions

Limitations

Limitations reflective of a Phase 1b trial:

- Selected population
- Limited sample size (n=59 completed)
- Short duration of treatment (28 days)

Larger and longer studies in broader populations and in the absence of calorie restriction are needed to provide more robust evidence for safety and efficacy.

Together form the largest clinical dataset for an NLRP3 inhibitor

Phase 1

Completed

Phase 2

RESOLVE-1 and RESOLVE-2 reading out mid-to-late 2026

RESOLVE-1 (NCT07055516; n=176, 24 wks): Ruvonoflast monotherapy w/o calorie restriction in cardiomet pts, incl. with type 2 diabetes

RESOLVE-2 (NCT07220629; n=82, 32 wks): Ruvonoflast as an adjunct to GLP-1 RA in cardiomet pts

Phase 3

Phase 3 launch planned for early 2027

Cardiomet, cardiometabolic; GLP-1 RA, glucagon-like peptide-1 receptor agonist; NLPR3, NOD-like receptor family, pyrin domain containing 3; pts, patients; w/o, without.

Conclusions

- Ruvonoflast significantly reduced hsCRP versus placebo at Day 28, with rapid and quickly reversible effects that may help balance inflammation control with maintaining immune responsiveness when needed
- Ruvonoflast significantly lowered putative causal biomarkers IL-6 and fibrinogen versus placebo
- Improvements in weight and metabolic/lipid parameters occurred in both groups with calorie restriction, suggesting that ruvonoflast's anti-inflammatory effects are weight independent and potentially additive to lifestyle modification
- Over 28 days, no SAEs occurred with ruvonoflast; AEs leading to treatment discontinuation were more common than with placebo, but transient and reversible
- Compelling efficacy and safety support ongoing Phase 2 and forthcoming Phase 3 trials of ruvonoflast in cardiometabolic patients

Simultaneously published in *JACC*

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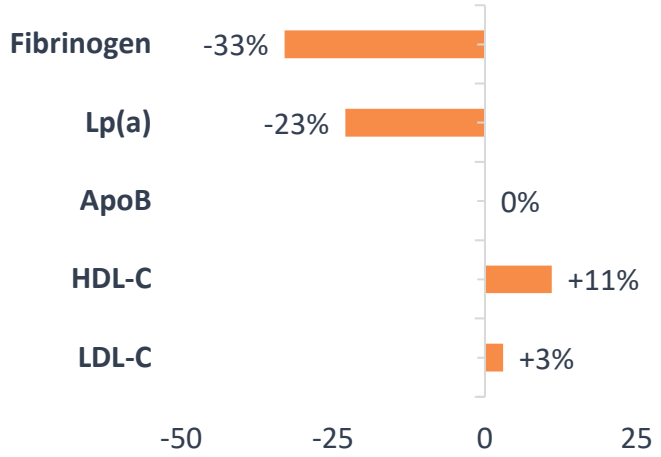
AEs, adverse events; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; NLRP3, NOD-like receptor family, pyrin domain containing 3; SAEs, serious adverse events.

Q&A

Biomarker profile of ruvonoflast is comparable to injectable biologics targeting IL-1β and IL-6

Ruvonoflast 225mg
oral NLRP3 inhibitor

82% hsCRP reduction
versus 37% with calorie-restricted placebo (4 weeks)[1]

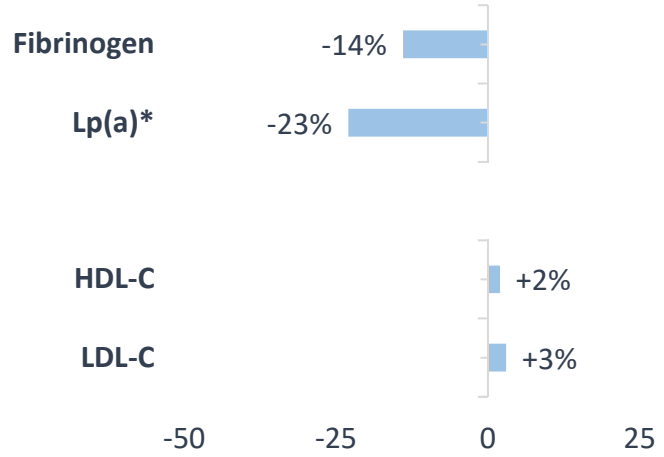


Placebo-adjusted % change from baseline[1,2]

hsCRP reduction (%) derived from the geometric LSmean ratio to baseline. Biomarker values reported at 4 weeks, as median % change from baseline, except for HDL-C and LDL-C (mean % change from baseline).

Canakinumab 150mg
anti-IL-1β monoclonal antibody

54% hsCRP reduction
versus 17% with placebo (48 months)[3]

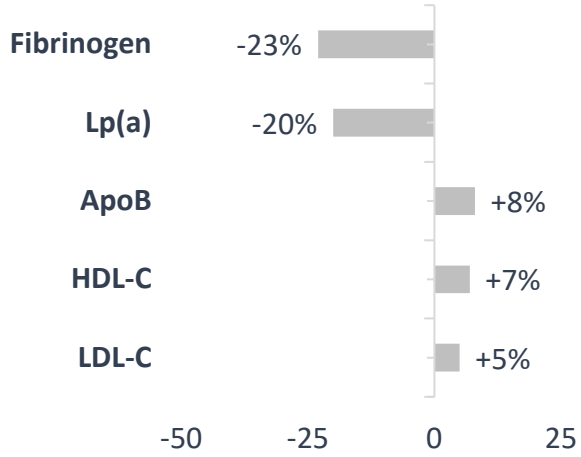


Placebo-adjusted % change from baseline[3–5]

**Not placebo-adjusted. Median % change from baseline reported at 48 months for hsCRP, HDL-C and LDL-C and at 4 months for fibrinogen. Dose and time of endpoint assessment not reported for Lp(a).*

Ziltivekimab 15mg
anti-IL-6 monoclonal antibody

88% hsCRP reduction
versus 4% with placebo (12 weeks)[6]



Placebo-adjusted % change from baseline[6]

Median % change from baseline reported at 12 weeks.

ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IL-1β, interleukin-1β; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); NLPR3, NOD-like receptor family, pyrin domain containing 3; 1. Ray KK, et al. *JACC*. 2026. https://doi.org/10.1016/j.jacc.2026.05.014. 2. Data on file for ApoB. 3. Ridker PM, et al. *N Engl J Med*. 2017. https://doi.org/10.1056/nejmoa1707914. 4. Ridker PM, et al. *Circulation*. 2012. https://doi.org/10.1161/circulationaha.112.122556. 5. Schrock C. *Atherosclerosis*, 331e36. 6. Ridker PM, et al. *Lancet*. 2021. https://doi.org/10.1016/s0140-6736(21)00520-1.