

# TOURMALINE

## Corporate Overview

December 2024

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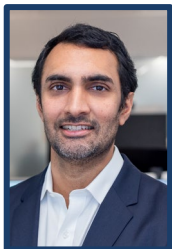
# Our mission

*We are driven by our mission to develop transformative medicines that dramatically improve the lives of patients with life-altering immune and inflammatory diseases*

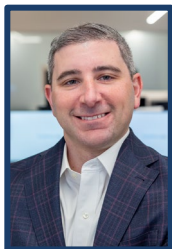


# Experienced leadership team

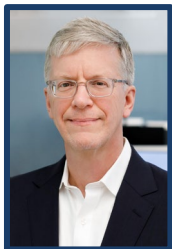
## Management Team



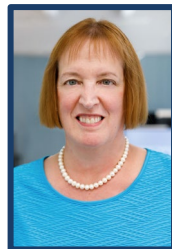
**Sandeep Kulkarni, MD**  
*Co-Founder and  
Chief Executive Officer*



**Ryan Robinson, CPA**  
*Chief Financial Officer*



**Brad Middlekauff, JD**  
*Chief Business Officer and  
General Counsel*



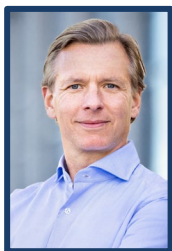
**Susan Dana Jones, PhD**  
*Chief Technology Officer*



**Kevin Johnson, PhD**  
*Chief Regulatory Officer*



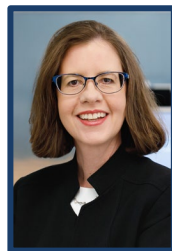
**Emil deGoma, MD**  
*Senior Vice President,  
Medical Research*



**Gerhard Hagn**  
*Senior Vice President,  
Head of Commercial & BD*



**Don Fitch**  
*Senior Vice President,  
Product Development*



**Dora Rau**  
*Senior Vice President,  
Head of Quality*

## Board of Directors

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*Chairman*

**Caley Castelein, MD**

**Aaron Kantoff**

**Mark McDade**

**Sapna Srivastava, PhD**

**Parvinder Thiara**

**Sandeep Kulkarni, MD**

# Key highlights



**An IL-6 renaissance is underway:** new insights emerging about a broad range of indications where IL-6 may be clinically validated

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**Pacibekitug (also referred to as TOUR006) has demonstrated best-in class potential:** long-acting, low immunogenicity, and low-volume subcutaneous administration observed in clinical trials to date

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**Two paths to significant value creation:** (1) cardiovascular inflammation and (2) thyroid eye disease

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**A late-stage clinical company:** Phase 2 TRANQUILITY trial in CV and pivotal Phase 2b spiriTED trial in TED ongoing

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**Two potentially transformative data readouts expected in 2025:** Topline data from TRANQUILITY trial expected in Q2 2025 and topline data from spiriTED trial expected in H2 2025

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**Well-financed:** cash expected to fund operations into 2027, enabling the delivery of key anticipated milestones for both paths

# Pacibekitug: a long-acting anti-IL-6 monoclonal antibody with best-in-class potential



## Attributes observed to date

**Long-acting** with terminal half-life of ~7 weeks<sup>1</sup>

**>90% pathway inhibition** after single 10mg dose<sup>2</sup>

**Fully human** with ADAs in only 0.5% of patients<sup>3</sup>

**High affinity** to IL-6<sup>4</sup>

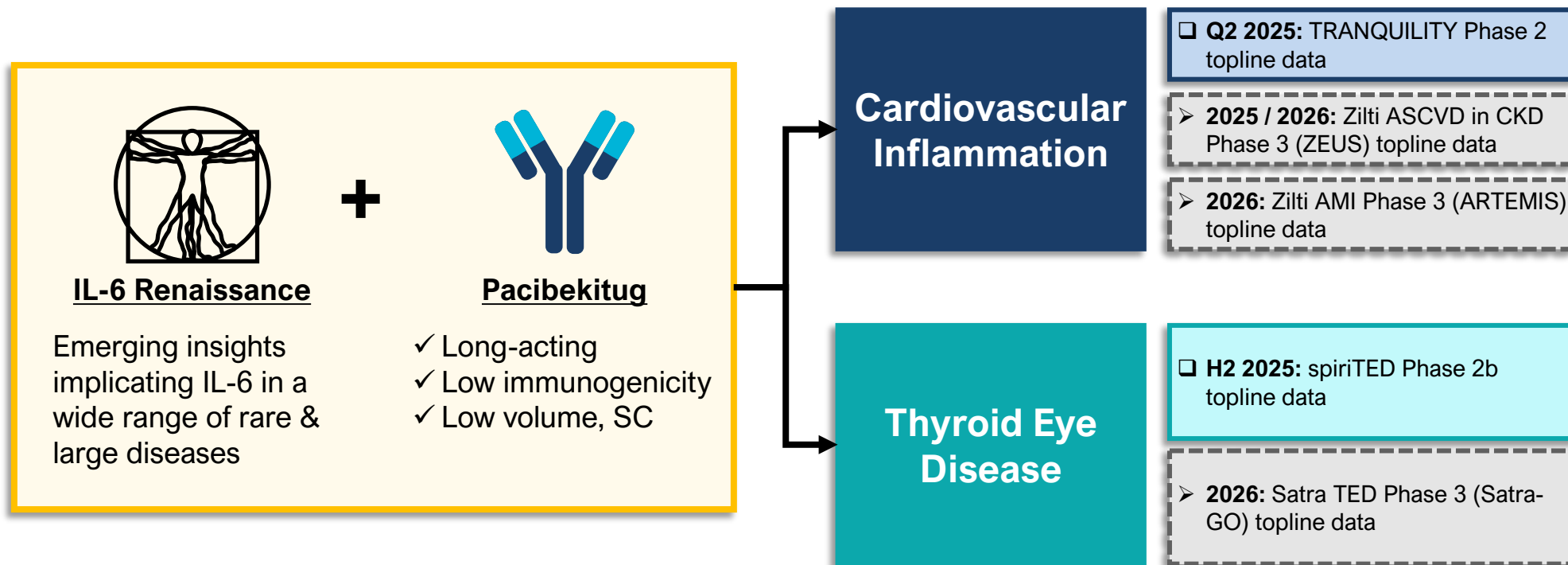
Existing data from approximately **450 study participants**<sup>1</sup>



## Potential value to patients

- **Dosing quarterly**<sup>5</sup> (CV) or **every 8 weeks**<sup>6</sup> (TED)
- **Rapid and robust impact** across diseases
- Durable benefit **without need to increase dose**
- Volume of ≤1ml for **SC injection**<sup>5,6</sup>
- Generally **well-tolerated safety profile** observed to date

# Two paths to unlock major value creation





Milestones key:

☐ Internal

➤ External

The timing of regulatory and clinical trial milestones are subject to change and additional discussion with the FDA  
AMI: acute myocardial infarction. ASCVD: atherosclerotic cardiovascular disease. CKD: chronic kidney disease. Satra: satralizumab. TED: thyroid eye disease. Zilti: ziltivekimab

# Clinical development plan for pacibekitug

Disease Focus	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Expected key milestones
Cardiovascular inflammation	Atherosclerotic Cardiovascular Disease (ASCVD)					 Phase 2 topline data expected in Q2 2025
	Abdominal aortic aneurysm (AAA)					Phase 2 PoC trial initiation expected after TRANQUILITY topline data
Autoimmune disease	Thyroid Eye Disease (TED)					 Phase 2b topline data expected in H2 2025

Note: Hatched bars represent trials that have not yet commenced

The timing of regulatory submissions and clinical trial milestones are subject to change and additional discussion with the FDA



# Cardiovascular Inflammation

# Reducing inflammation: the next frontier in CV diseases



Increasing validation for IL-6 driven inflammation as a critical and modifiable risk factor driving residual cardiovascular risk

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Potential of IL-6 inhibition spans a broad range of cardiovascular indications, affecting tens of millions of patients globally

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Converging lines of human evidence across multiple settings support the transformative potential of IL-6 inhibition

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IL-6 inhibition is being evaluated in multiple cardiovascular outcomes trials with external readouts expected over the next 12 to 24 months

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Pacibekitug's potentially best-in-class profile, including quarterly SC administration, is being evaluated in the Phase 2 TRANQUILITY trial – over-enrollment completed, topline data expected in Q2 2025

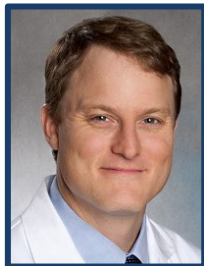
# World-class Cardiovascular Scientific Advisory Board providing insight on our development strategy for pacibekitug



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**SAB Chair**  
*Mount Sinai Fuster Heart Hospital*



**Joshua A. Beckman, MD, MSc**  
*University of Texas Southwestern*



**Marc P. Bonaca, MD, MPH**  
*University of Colorado*  
*CPC Clinical Research*



**Robin Choudhury, MA, DM**  
*University of Oxford*



**Dipender Gill, MD, PhD**  
*Sequoia Genetics*



**Douglas L. Mann, MD**  
*Washington University*  
*School of Medicine*



**James Min, MD**  
*Cleerly, Inc.*



**Pradeep Natarajan, MD, MMSC**  
*Massachusetts General Hospital*  
*Harvard Medical School*



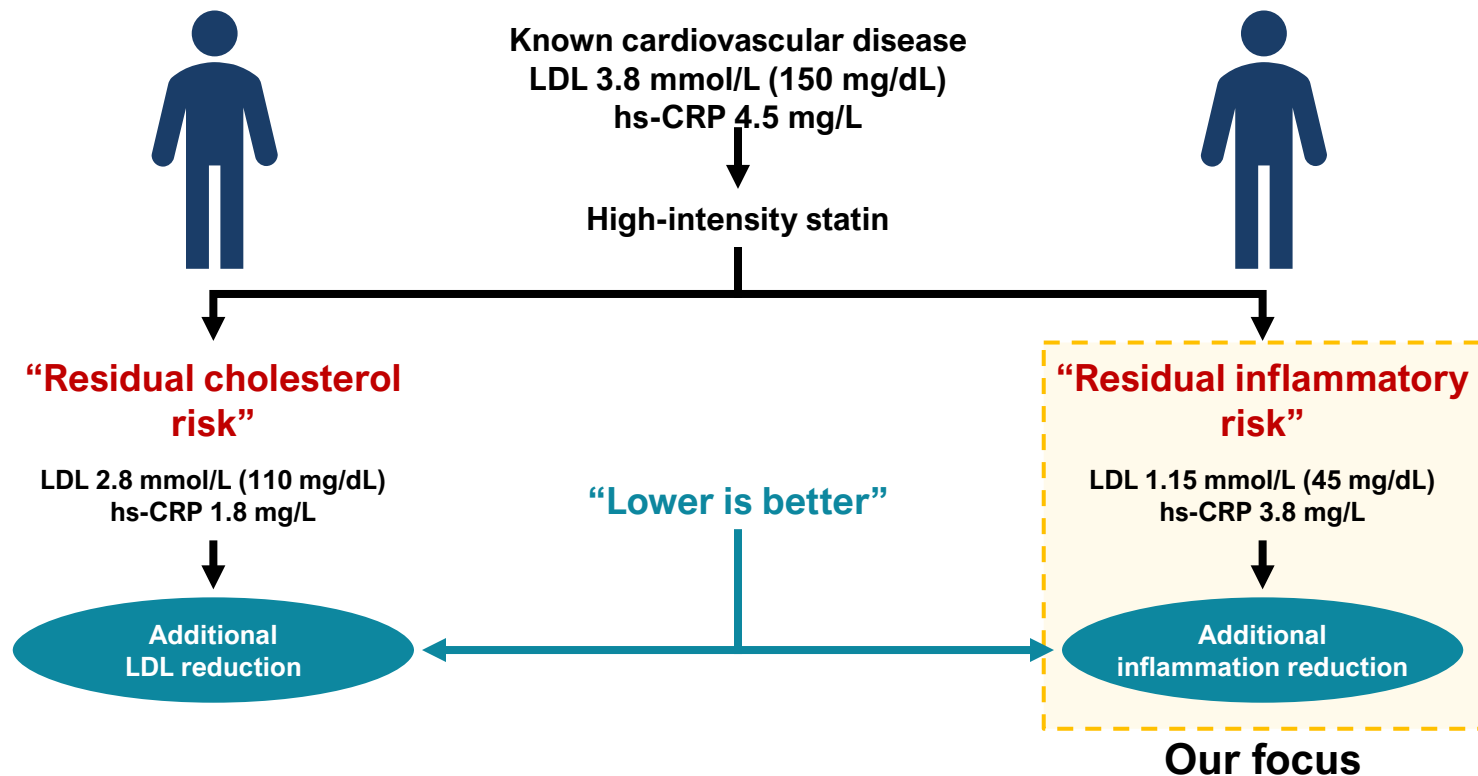
**Michael D. Shapiro, DO, MCR**  
*Wake Forest University*



**Michael Szarek, PhD**  
*University of Colorado*  
*CPC Clinical Research*

# Many CV disease patients have residual inflammatory risk

## Differential secondary prevention treatment options for statin-treated patients<sup>1</sup>



<sup>1</sup>Adapted from Ridker, Eur Heart J (2016).

# Research increasingly highlights inflammation as a driver of CV risk and supports therapeutic potential of IL-6 inhibition



## Association of Interleukin 6 Receptor Variant With Cardiovascular Disease Effects of Interleukin 6 Receptor Blocking Therapy A Phenome-Wide Association Study

Tianxi Cai, ScD; Yichi Zhang, PhD; Yuk-Lam Ho, MPH; Nicholas Link, BA; Jiehuan Sun, PhD; Jie Huang, MS; Tianrun A. Cai, MD; Scott Damrauer, MD; Yuri Ahuja, BS; Jacqueline Honerlaw, RN, BSN, MPH; Jie Huang, PhD; Lauren Costa, MPH; Petra Schubert, MPH; Chuan Hong, PhD; David Gagnon, MD, MPH; Yan V. Sun, PhD; J. Michael Gaziano, MD, MPH; Peter Wilson, MD; Kelly Cho, PhD, MPH; Philip Tsao, PhD; Christopher J. O'Donnell, MD, MPH; Katherine P. Liao, MD, MPH; for the VA Million Veteran Program

### RESEARCH LETTER

## A Missense Variant in the IL-6 Receptor and Protection From Peripheral Artery Disease

Michael G. Levin<sup>1</sup>, Derek Klarin<sup>1</sup>, Marios K. Georgakis<sup>1</sup>, Julie Lynch, Katherine P. Liao<sup>1</sup>, Benjamin F. Voight, Christopher J. O'Donnell<sup>1</sup>, Kyong-Mi Chang, Themistocles L. Assimes, Philip S. Tsao<sup>1</sup>, Scott M. Damrauer<sup>1</sup>, on behalf of the VA Million Veteran Program

## Interleukin-6 in Patients With Heart Failure and Preserved Ejection Fraction

Alessio Alogna, MD, PhD,<sup>1,2,\*</sup> Katlyn E. Koepp, PhD,<sup>2</sup> Michael Sabbah, MD,<sup>2</sup> Jair M. Espindola Netto, PhD,<sup>1</sup> Michael D. Jensen, MD,<sup>1</sup> James L. Kirkland, MD, PhD,<sup>1,2</sup> Carolyn S.P. Lam, MBBS,<sup>2</sup> Masaru Obokata, MD, PhD,<sup>1</sup> Mark C. Petrie, MD,<sup>1</sup> Paul M. Ridker, MD, MPH,<sup>1</sup> Hidemi Sorimachi, MD, PhD,<sup>2</sup> Tamara Tchukonia, PhD,<sup>1</sup> Adriaan Voors, MD, PhD,<sup>1</sup> Margaret M. Redfield, MD,<sup>1</sup> Barry A. Borlaug, MD<sup>1</sup>

### Research Letter

## Genetically Proxied IL-6 Receptor Inhibition and Coronary Artery Disease Risk in a Japanese Population

Sizheng Steven Zhao<sup>1,\*</sup>, Dipender Gill<sup>2</sup>

<sup>1</sup> Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Science, School of Biological Sciences, Faculty of Biological Medicine and Health, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK  
<sup>2</sup> Department of Epidemiology and Biostatistics, Imperial College London, London, UK

### RESEARCH ARTICLE

## Circulating Interleukin-6 Levels and Incident Ischemic Stroke

A Systematic Review and Meta-analysis of Prospective Studies

Andreas Papadopoulos, MD, Konstantinos Palaiopoulos, MD, Harry Björkbacka, PhD, Annette Peters, PhD, James A. de Lemos, MD, Sudha Seshadri, MD, Martin Dichgans, MD, and Marios K. Georgakis, MD, PhD

Neurology<sup>®</sup> 2022;98:e1002-e1012. doi:10.1212/WNL.00000000000013274

Correspondence  
Dr. Georgakis  
marios.georgakis@  
med.uni-muenchen.de

## Quantifying inflammation using interleukin-6 for improved phenotyping and risk stratification in acute heart failure

Eleni Michou<sup>1</sup>, Desiree Wussler<sup>1,2</sup>, Maria Belkin<sup>1</sup>, Cornelia Simmen<sup>1</sup>, Ivo Strebel<sup>1</sup>, Albina Nowak<sup>2,4</sup>, Nikola Kozuharov<sup>1</sup>, Samyut Shrestha<sup>1</sup>, Pedro Lopez-Ayala<sup>1</sup>, Zaid Sabti<sup>1</sup>, Constantin Mork<sup>1</sup>, Matthias Diebold<sup>1</sup>, Tiffany Péquignot<sup>1</sup>, Katharina Rentsch<sup>5</sup>, Arnold von Eckardstein<sup>6</sup>, Danielle M. Gualandro<sup>1</sup>, Tobias Breidhardt<sup>1,2</sup>, and Christian Mueller<sup>1\*</sup>

### ORIGINAL RESEARCH

## Elevated Interleukin-6 Levels Are Associated With an Increased Risk of QTc Interval Prolongation in a Large Cohort of US Veterans

Pietro Enea Lazzarini<sup>1</sup>, MD; Michael Cupelli, PhD; Alessandra Caricci<sup>1</sup>, MSc; Iacopo Bertolozzi, MD; Viola Salvin, MD; Riccardo Accioli<sup>1</sup>, MD; Fabio Salvadori<sup>1</sup>, MD; Tommaso Marzotti, MD; Deoconso Vermeiga<sup>1</sup>, MD; Gabriele Cewerinn<sup>1</sup>, BioEng; Stefania Biogno, MD; Maurizio Blochi, MD; Giovanni Donati, MD; Scialele Bernardini<sup>1</sup>, MD; Franco Lugli-Pastri<sup>1</sup>, MD; Maurizio Acampa<sup>1</sup>, MD; Pier Leopoldo Capocchi<sup>1</sup>, MD, PhD; Nabil El-Sherif, MD; Mohamed Bouajdir<sup>1</sup>, PhD

## Associations of genetically predicted IL-6 signaling with cardiovascular disease risk across population subgroups

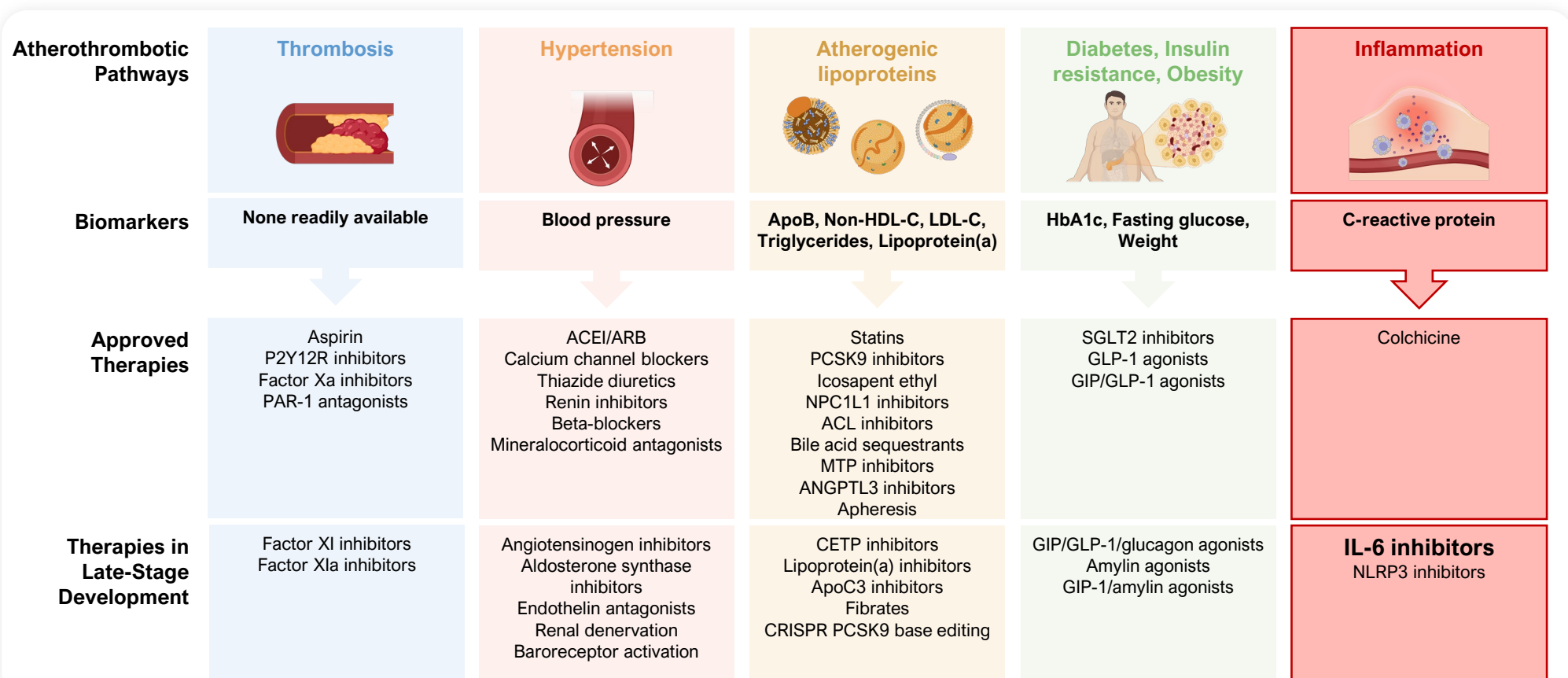
Marios K. Georgakis<sup>1,2,3\*</sup>, Rainer Malik<sup>2</sup>, Tom G. Richardson<sup>4</sup>, Joanna M. M. Howson<sup>4</sup>, Christopher D. Anderson<sup>1,2,5</sup>, Stephen Burgess<sup>6,7</sup>, G. Kees Hovingh<sup>8,9</sup>, Martin Dichgans<sup>3,10,11</sup> and Dipender Gill<sup>4,6,12,13\*</sup>

### RESEARCH LETTER

## Genetically Downregulated Interleukin-6 Signaling Is Associated With a Favorable Cardiometabolic Profile

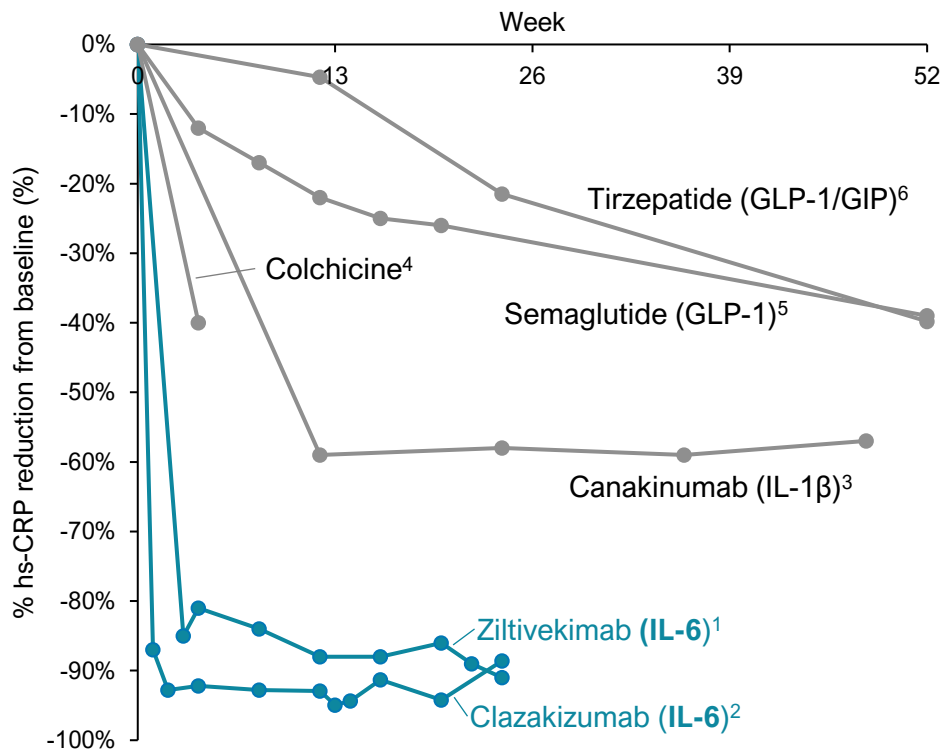
A Phenome-Wide Association Study

# Cardiovascular inflammation largely unaddressed by existing treatments

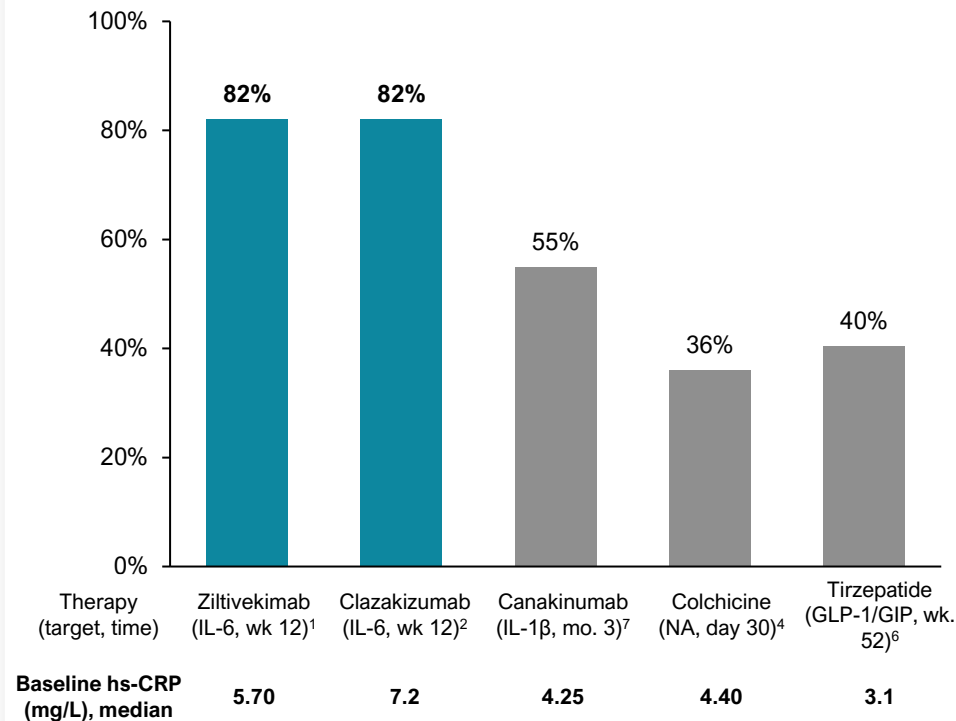


# IL-6 inhibition has produced rapid and robust hs-CRP reductions in patients with established or at high-risk of CVD

## Percent reduction in hs-CRP



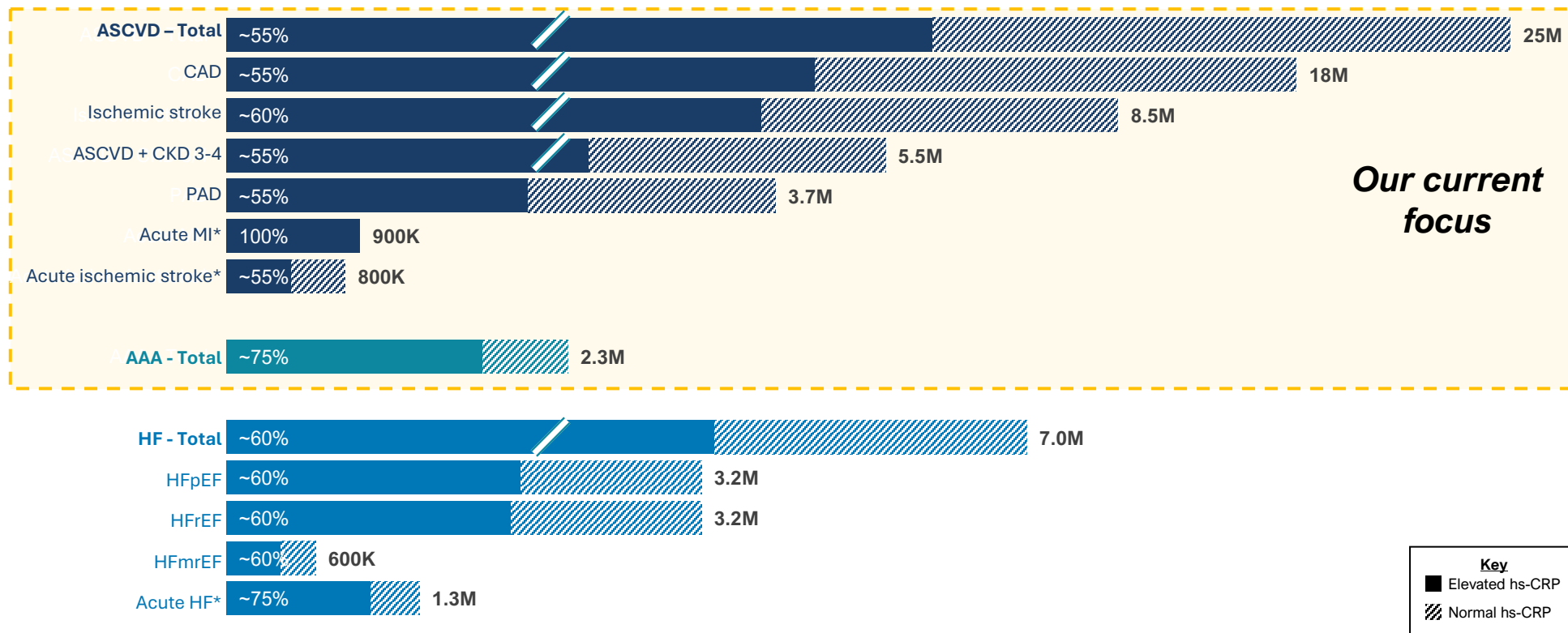
## % of patients with hs-CRP <2 mg/L



# IL-6 inhibition has the potential to address millions of patients across a wide range of inflammation mediated CV conditions

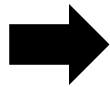
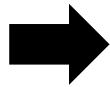
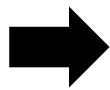
## Estimated US prevalence (2024)<sup>1</sup>

Populations are not mutually exclusive

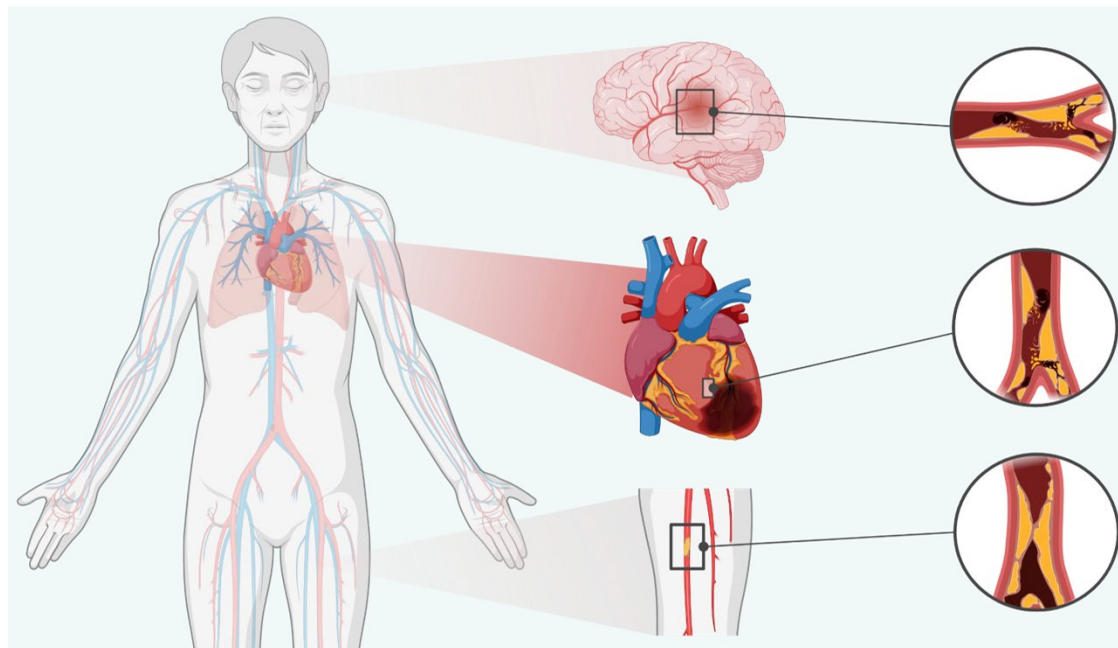




# Convergence of human evidence supports therapeutic potential of IL-6 inhibition for ASCVD



**Evidence suggests IL-6 may drive ASCVD risk**



# Human genetic studies provide initial support for IL-6 pathway inhibition to lower ASCVD risk



## Concordance between results of human genetic studies and randomized clinical trials

Therapeutic target	Genetic Result	RCT Result
Lowering LDL-C to lower ASCVD risk <sup>1,2</sup>	Positive	Positive
Inhibiting IL-6 to treat polymyalgia rheumatica <sup>3,4</sup>	Positive	Positive
Lowering blood pressure to lower ASCVD risk <sup>5,6</sup>	Positive	Positive
Raising HDL-C to lower ASCVD risk <sup>7,8</sup>	Negative	Negative
Inhibiting LpPLA2 to lower ASCVD risk <sup>9,10</sup>	Negative	Negative
Inhibiting TNF $\alpha$ to treat multiple sclerosis <sup>11,12</sup>	Negative (harm)	Negative (harm)
Inhibiting IL-6 to lower ASCVD risk <sup>13-17</sup>	Positive	Trials Ongoing

“Probability of success for drug mechanisms with genetic support is 2.6 times greater than those without.”<sup>18</sup>

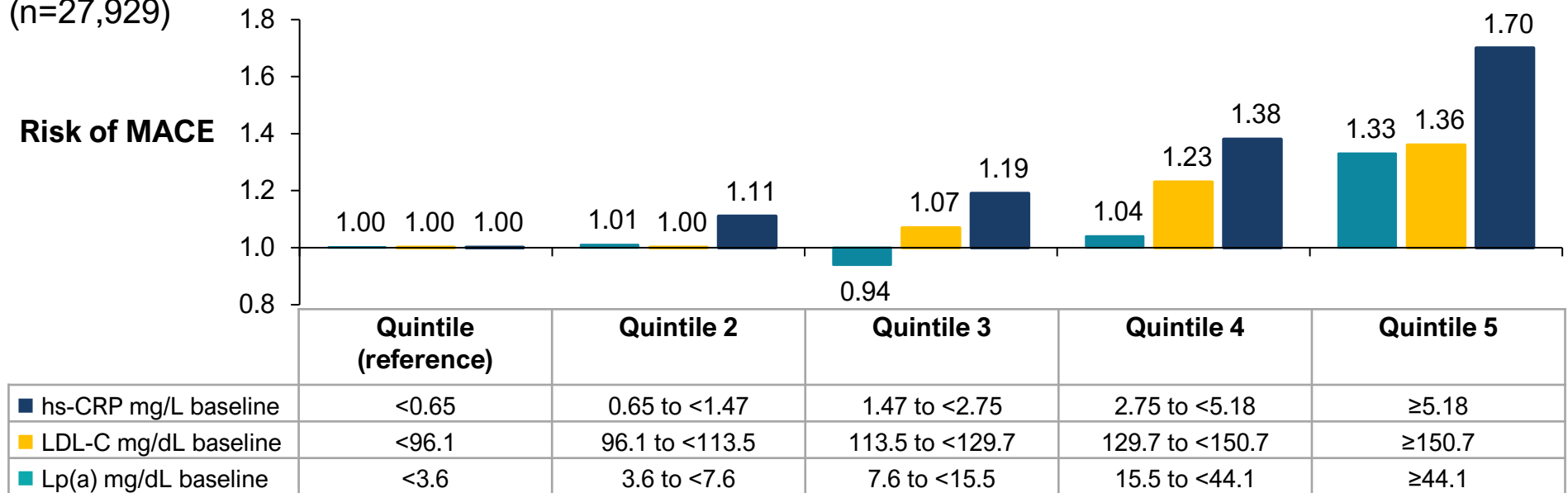
# Emerging evidence suggests that hs-CRP is more strongly associated with MACE than both LDL and Lp(a)



Late breaking data presented at European Society of Cardiology 2024 Congress and simultaneously published in the New England Journal of Medicine

## 30-year longitudinal data from the Women's Health Study<sup>1</sup>

(n=27,929)



<sup>1</sup>Women's Health Study. MACE: CV death, MI, stroke, coronary revascularization. Increased risk defined as 1-relative risk, compared to lowest quintile of Lp(a) and hs-CRP population, adjusted for age, initial randomization treatment group, smoking (current, past, never), presence of diabetes, and Framingham blood pressure categories. Table 2. Ridker et al, NEJM (2024).

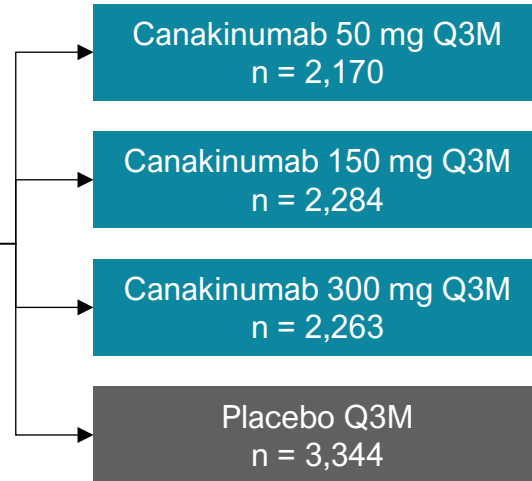
# Landmark CANTOS study validated therapeutic potential of addressing inflammation in ASCVD



## Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) Trial Design<sup>1</sup>

**10,061 patients**

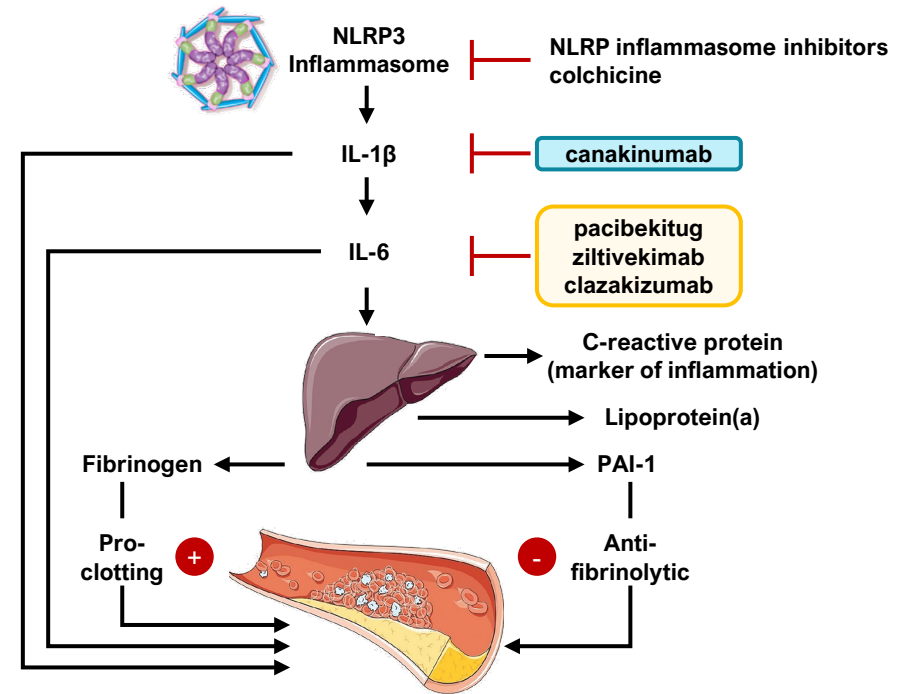
- Stable CAD (post MI)
- On Statin, ACE/ARB, BB, ASA
- hs-CRP  $\geq 2$  mg/L



### Primary endpoint:

Time to the first occurrence of MACE (CV death, non-fatal MI, or non-fatal stroke)

## IL-1 $\beta$ is upstream of IL-6<sup>2</sup>

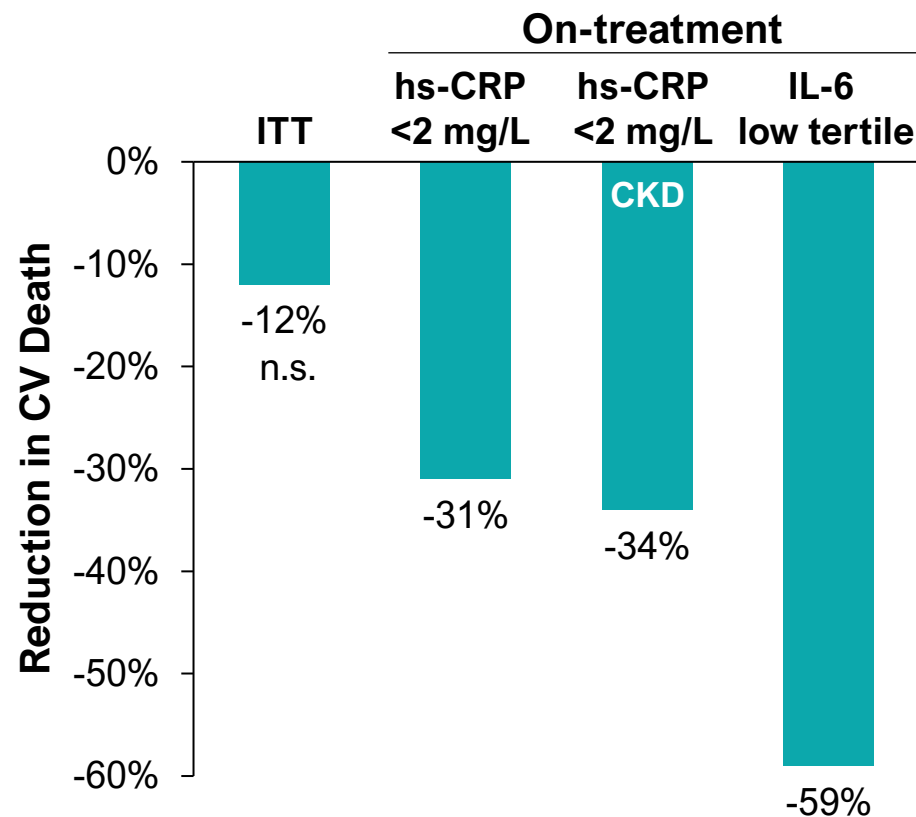
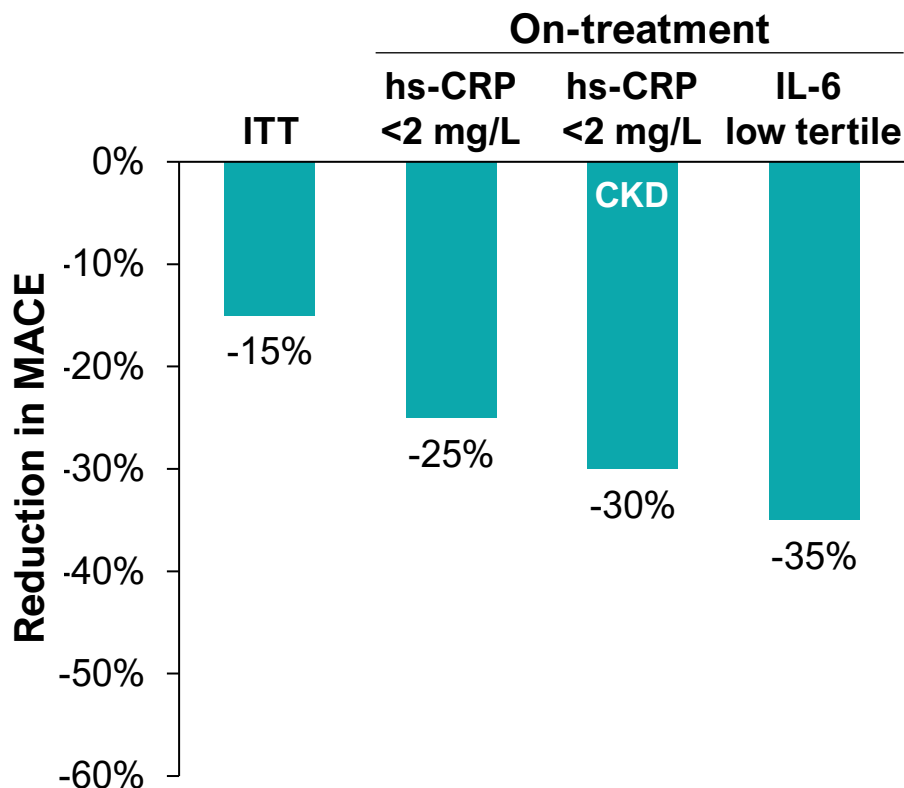


<sup>1</sup>Ridker et al., N. Engl. J. Med. (2017). <sup>2</sup>Adapted from Ridker et al., Circ. Res. (2016), Arnold et al., Eur. J. Cardiol. (2021) and Muller et al., J Lipid Res (2015)

# Lessons from canakinumab (anti-IL-1 $\beta$ mAb):



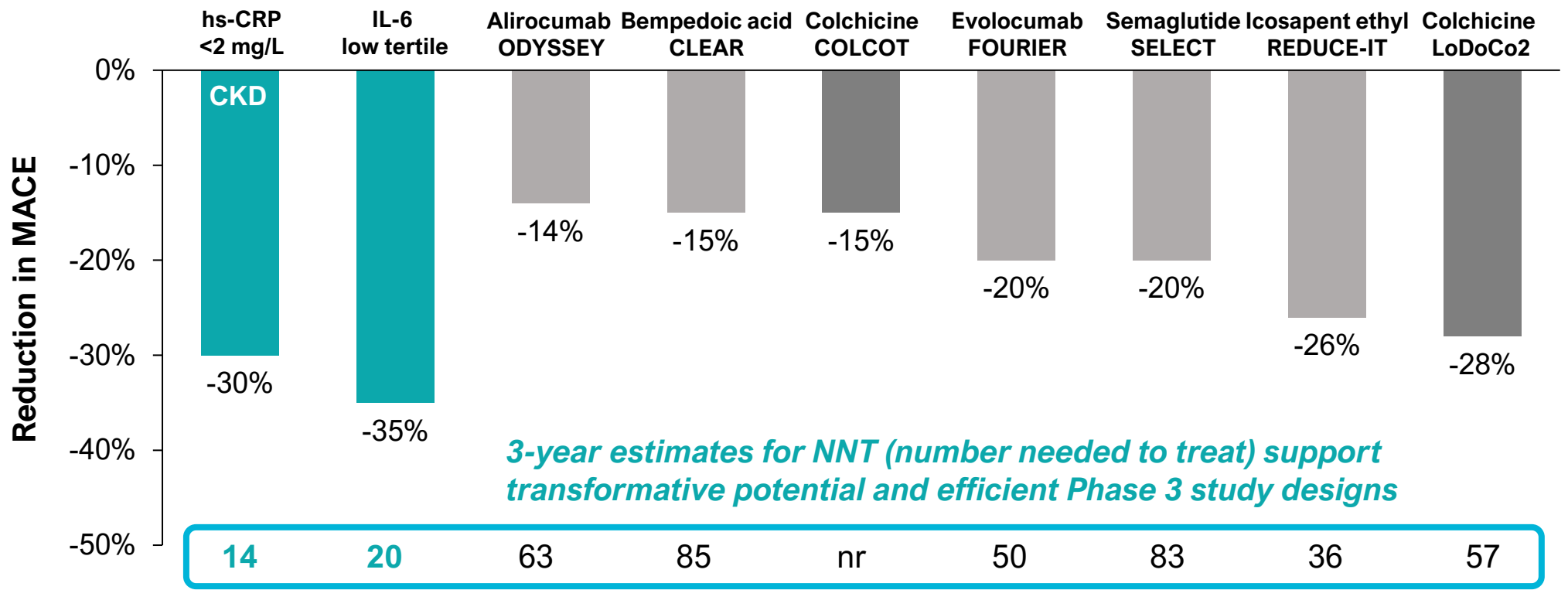
## “Lower is better” for downstream biomarkers of IL-6 activity



# Lessons from canakinumab (anti-IL-1 $\beta$ mAb): Robust inhibition of IL-6 pathway has transformative potential in ASCVD

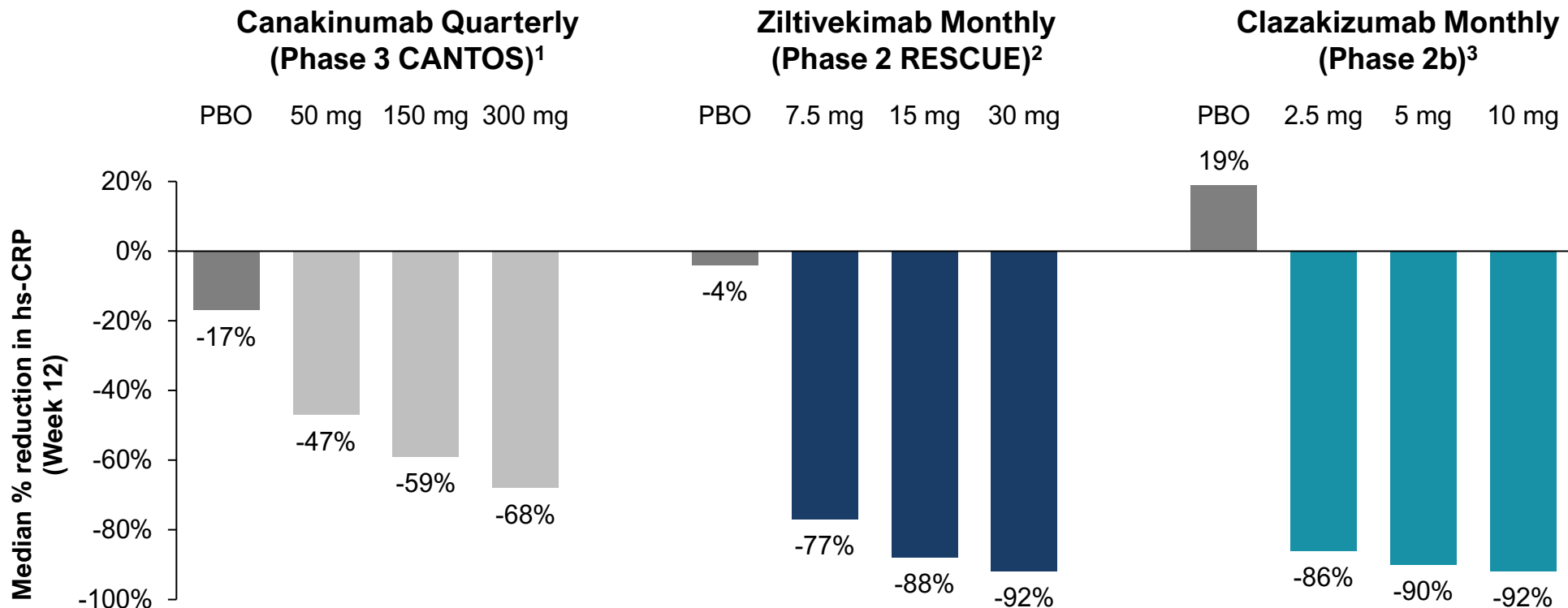


CANTOS: On-treatment



Reduction in MACE shown as 1-Hazard Ratio. MACE: major adverse cardiovascular events including CV death, myocardial infarction (MI), stroke except for: ODYSSEY OUTCOMES (all death, MI, ischemic stroke); COLCOT (CV death, MI, stroke, resuscitated cardiac arrest); LoDoCo2 (CV death, MI, ischemic stroke); main CANTOS analysis presents data for 150mg dose group; values for CANTOS subanalyses combine all doses (50, 150, 300mg); control arms were placebo + background SoC. Certain data in this slide are based on a cross-trial comparison and are not based on head-to-head clinical trials. Cross-trial comparisons are inherently limited and may suggest misleading similarities or differences in outcomes. Results of head-to-head comparisons may differ significantly from those set forth herein. NNT (number needed to treat) values obtained from absolute risk extracted from Kaplan-Meier figures via webplotdigitizer, unless directly reported. NNT for IL-6 < median shown; not reported for IL-6 low tertile. The information on this slide is based on Tourmaline-generated analysis of third-party data and is being presented for hypothesis generating purposes only. As a result, the actual MACE risk reduction hypothesized may be more or less than the data presented in this slide. Publications available upon request.

# In independent studies, direct IL-6 inhibition lowered hs-CRP more than upstream IL-1 $\beta$ blockade

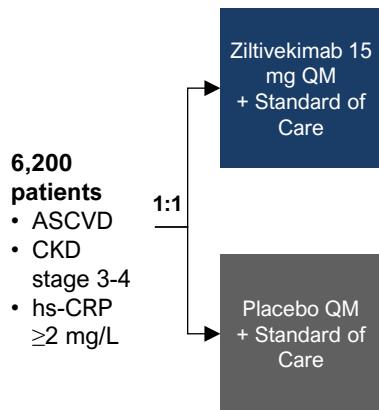


*Direct IL-6 inhibition achieved ~2x placebo-adjusted reductions in hs-CRP compared to upstream IL-1 $\beta$*

# Five Phase 3 CVOTs enrolling >24,000 patients



## ZEUS: ASCVD w/CKD<sup>1</sup>

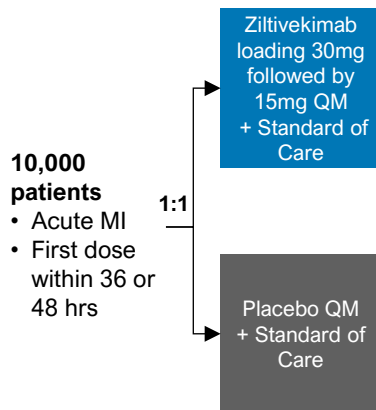


**Primary endpoint:**  
Time to the first occurrence of MACE (CV death, non-fatal MI, or non-fatal stroke)

2025 / 2026



## ARTEMIS: acute MI<sup>2</sup>

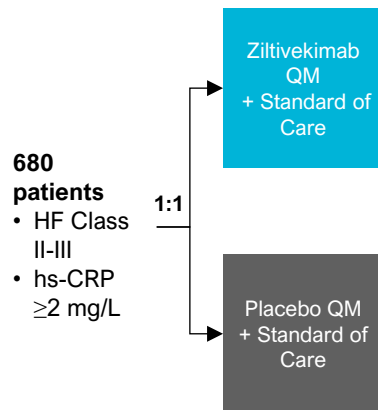


**Primary endpoint:**  
Time to the first occurrence of MACE (CV death, non-fatal MI, or non-fatal stroke)

2026



## ATHENA: HFpEF<sup>3</sup>

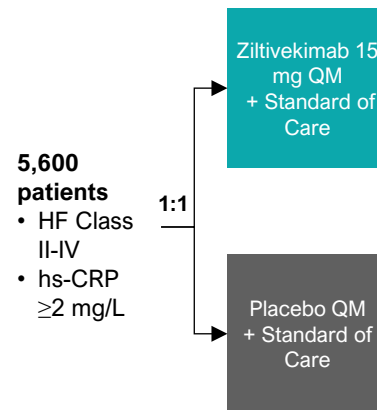


**Primary endpoint:**  
Change in KCCQ-CSS at 1 year

2026



## HERMES: HFpEF<sup>4</sup>

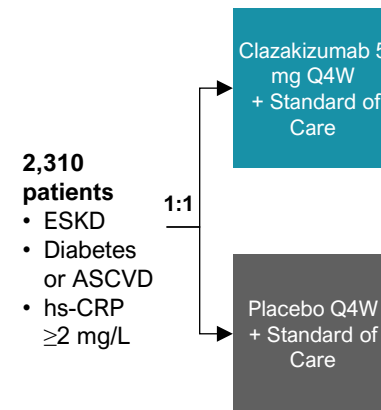


**Primary endpoint:**  
Time to first occurrence of a composite HF endpoint (CV death, HF hospitalization, or urgent HF visit)

2027



## POSIBIL6: ESKD<sup>5</sup>





**Primary endpoint:**  
Time to first occurrence of CV death or MI

2028

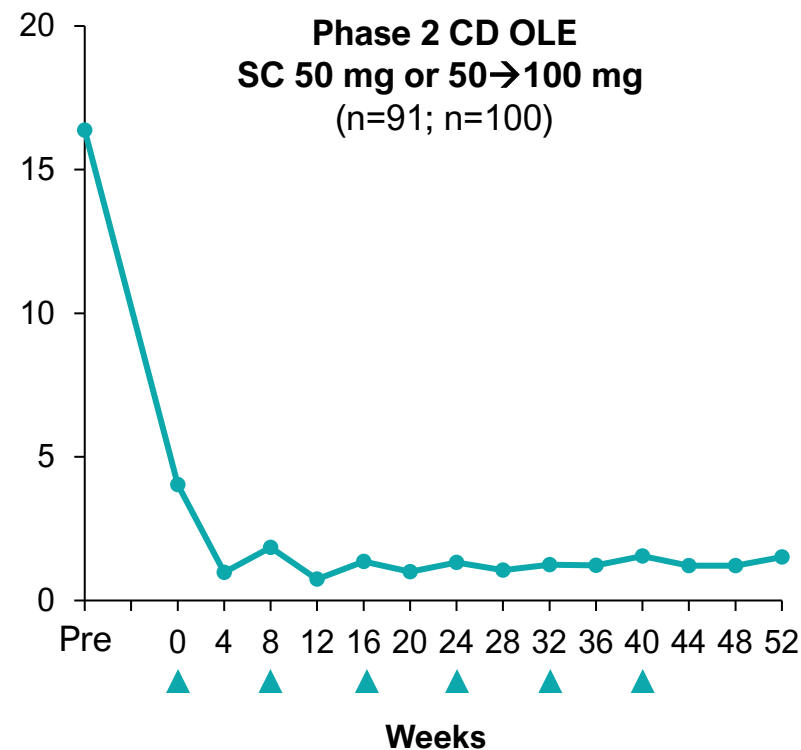
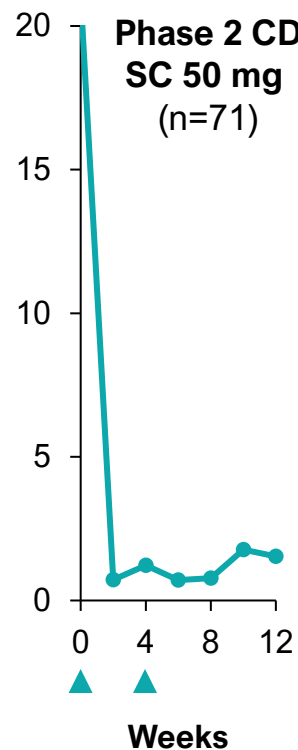
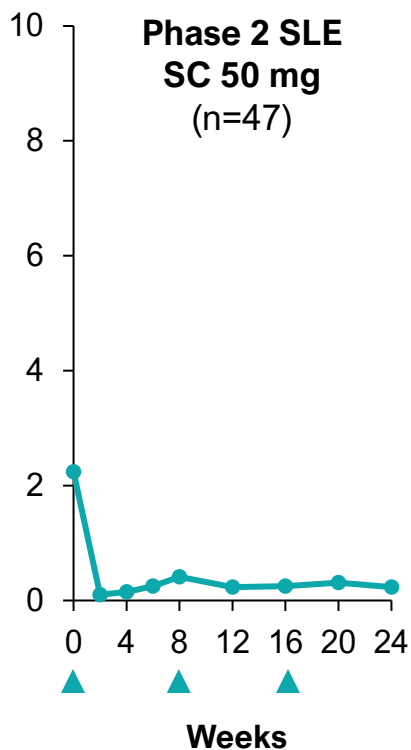
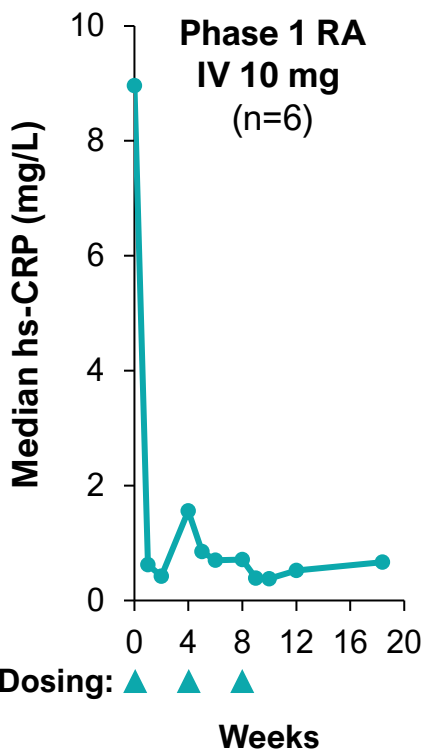
Topline data readouts expected



# Pacibekitug designed to offer best-in-class potential profile in cardiovascular diseases

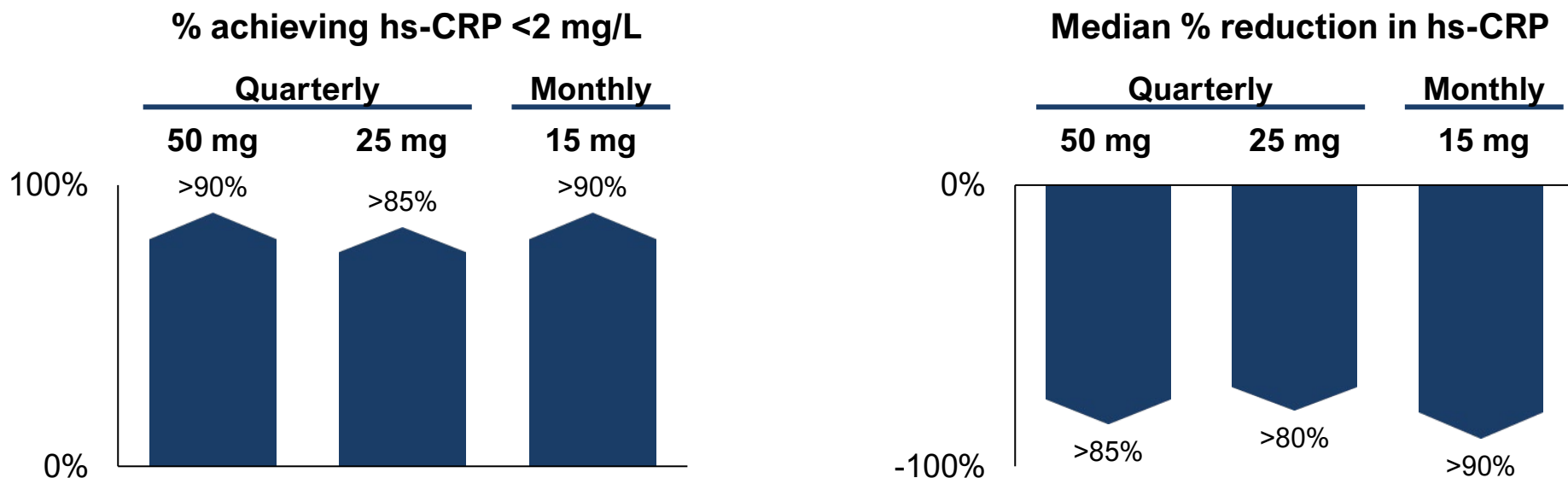
	Pacibekitug	Ziltivekimab	Clazakizumab
Company	TOURMALINE	 novo nordisk®	
Monoclonal antibody	fully human (IgG2)	fully human (IgG1k, YTE mutation)	humanized rabbit (IgG1k)
Anti-drug antibodies <sup>1</sup>	0-1%	6-13% <sup>3,4</sup>	0-10% <sup>7-9</sup>
Route of administration <sup>2</sup>	SC 0.6 mL	SC <sup>5,6</sup> 1.0 mL	IV <sup>10</sup>
Longest dosing intervals in completed studies	Q8W (SLE, CD)	Q4W (NDD-CKD) <sup>5,6</sup>	Q4W <sup>10</sup> (HD-CKD)
Targeted dosing intervals	Quarterly	Monthly	Monthly

# Pacibekitug achieved robust and durable suppression of CRP in patients with high-grade inflammatory autoimmune disorders



# PK/PD modeling supports potential for quarterly dosing of pacibekitug SC in ASCVD

*Results of PK/PD model developed from five studies in patients with RA, SLE, CD and healthy volunteers*

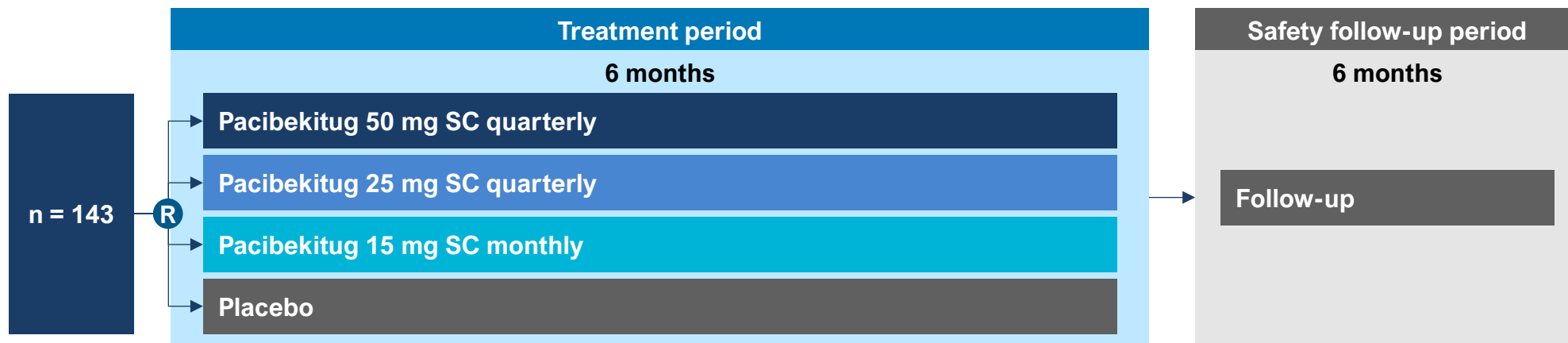


**Ziltivekimab 15 mg monthly<sup>1</sup>**  
% achieving hs-CRP < 2 mg/L: 82%

median % reduction: 88%

# TRANQUILITY<sup>6</sup> Phase 2 trial supporting development in ASCVD

Double-blinded, placebo-controlled Phase 2 trial (NCT06362759) | Status: **over-enrollment completed**



## Study population:

- CKD stage 3-4 (eGFR 15-59 ml/min/1.73m<sup>2</sup>) or UPCR>200 mg/g
- hs-CRP  $\geq$ 2 mg/L and <15 mg/L
- Exclude patients at higher risk for safety complications (e.g., immunocompromised patients)

## Primary pharmacodynamic endpoint:

- Change from baseline in hs-CRP through Day 90

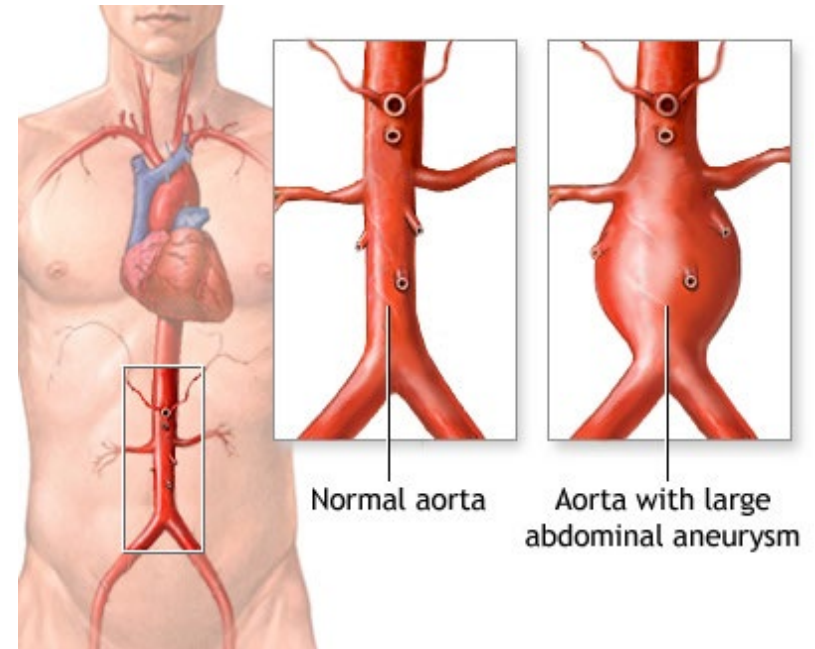
## Additional endpoints:

- Percent of participants who achieve hs-CRP <2 mg/L
- Other pharmacodynamic markers, including lipoprotein (a)
- Safety and tolerability

ASCVD: atherosclerotic cardiovascular disease. CKD: chronic kidney disease. eGFR: estimated glomerular filtration rate. hs-CRP: high-sensitivity C-reactive protein. UPCR: urine protein-creatinine ratio.

# Abdominal aortic aneurysm: a high-mortality, first-in-disease opportunity for pacibekitug

- High-risk vascular disease with **significant unmet need in approximately 2M people in US<sup>1</sup>**
- **Strong strategic fit** with ASCVD due to overlapping prescribers
- Progressive disease with increasing risk of **rupture, usually a fatal event<sup>2</sup>**
- **In less than 5 years**, majority of medium-sized AAA grow to threshold for surgical repair<sup>3,4</sup>
- Surgical repair, recommended for large AAA to prevent rupture, is **associated with complications<sup>5-9</sup>**

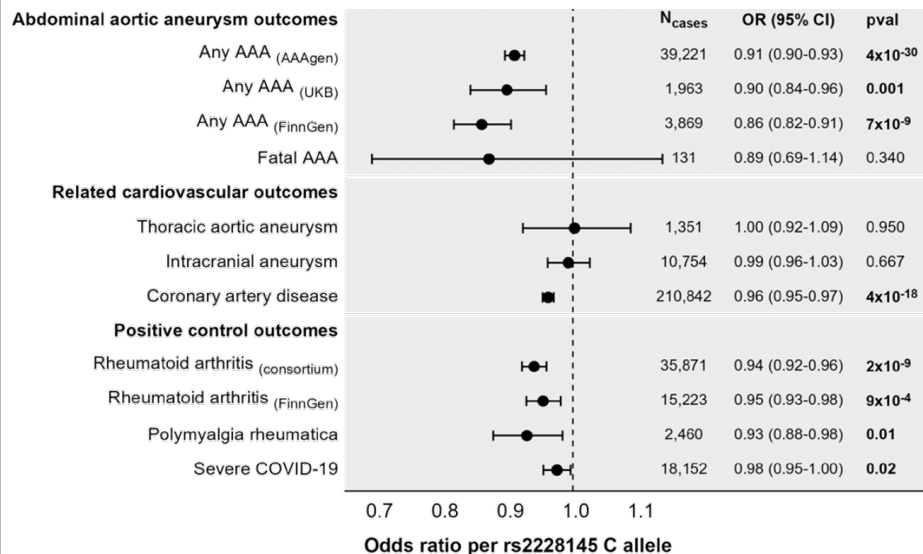


**No FDA approved treatment**

# Compelling evidence supports IL-6 inhibition to slow AAA growth

## Human genetic evidence

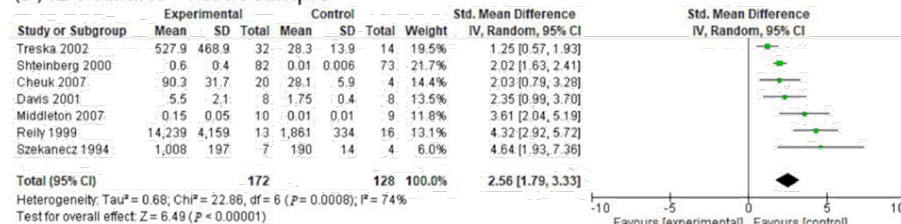
### Genetic variant associated with reduction in risk of AAA<sup>1</sup>



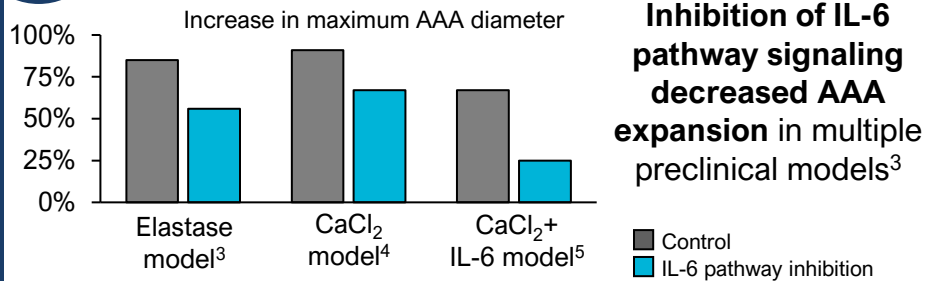
## Epidemiological evidence

### Higher IL-6 levels associated with AAA<sup>2</sup>

#### (D) IL-6 studies - Tissue sample



## Experimental evidence

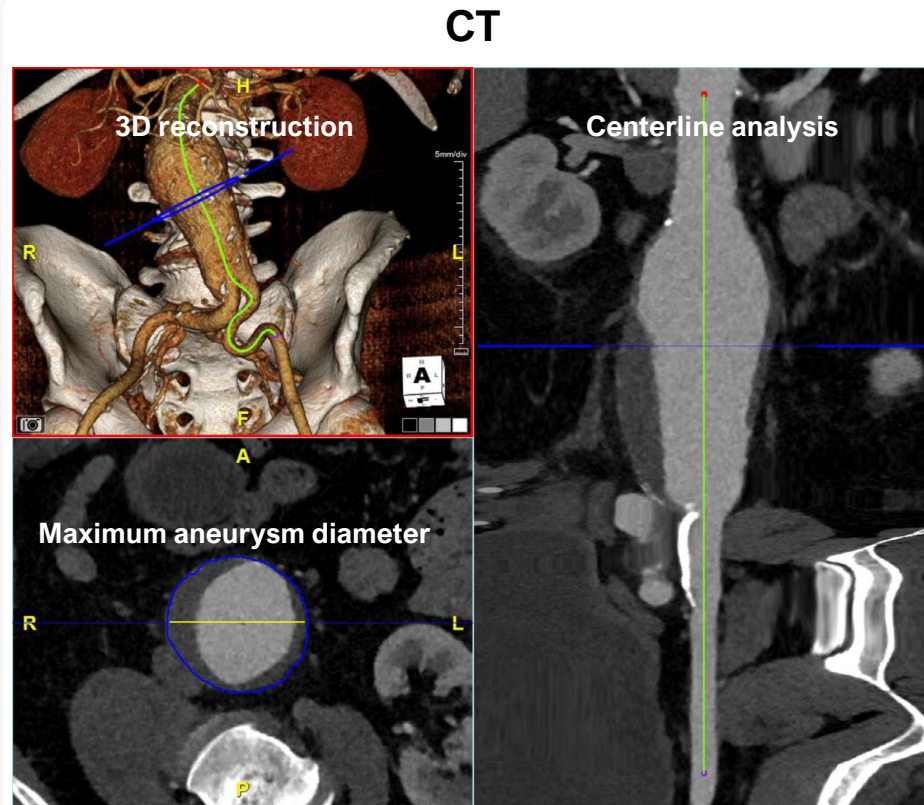


# Phase 2 PoC study expected to use imaging to evaluate the ability of pacibekitug to inhibit AAA growth

- Serial imaging is the foundation of clinical care<sup>1</sup>
- Phase 2 PoC expected to use multimodality imaging to efficiently characterize pacibekitug

## Next steps:

- TRANQUILITY topline data in Q2 2025
- Alignment with FDA on Phase 2 PoC design
- Details to be shared prior to study start



<sup>1</sup>Chaikof et al., J Vasc Surg (2018). Isselbacher et al., Circulation (2022). Figure adapted from Perry et al., Ann Vasc Surg (2022). AAA: abdominal aortic aneurysm. PoC: proof of concept.

# Thyroid Eye Disease



# TED: our beachhead indication designed to validate pacibekitug's potential in autoantibody-driven diseases

## 1 High unmet medical need with significant market opportunity

- TED patients experience significant disease burden driven by inflammation, proptosis, double-vision, and pain
- ~30k new patients each year in the U.S. (average age at diagnosis is ~45)<sup>1,2</sup>
- ~80%<sup>3</sup> of moderate-to-severe TED patients not receiving an FDA-approved treatment, which we believe may be related to significant limitations such as risk of permanent hearing impairment / loss:
  - Vast majority of US treaters report unmet need across all aspects of treatment (efficacy, safety, administration)<sup>4</sup>

## 2 Extensive third-party clinical support that IL-6 inhibition may address key unmet needs

- 50+ publications with 350+ patients demonstrate the therapeutic potential of IL-6 pathway inhibition in TED
- IL-6 may play a more central and upstream role in TED pathogenesis than IGF-1R or FcRn
- Many TED treaters already routinely utilize IL-6 inhibition in their practice<sup>4</sup>

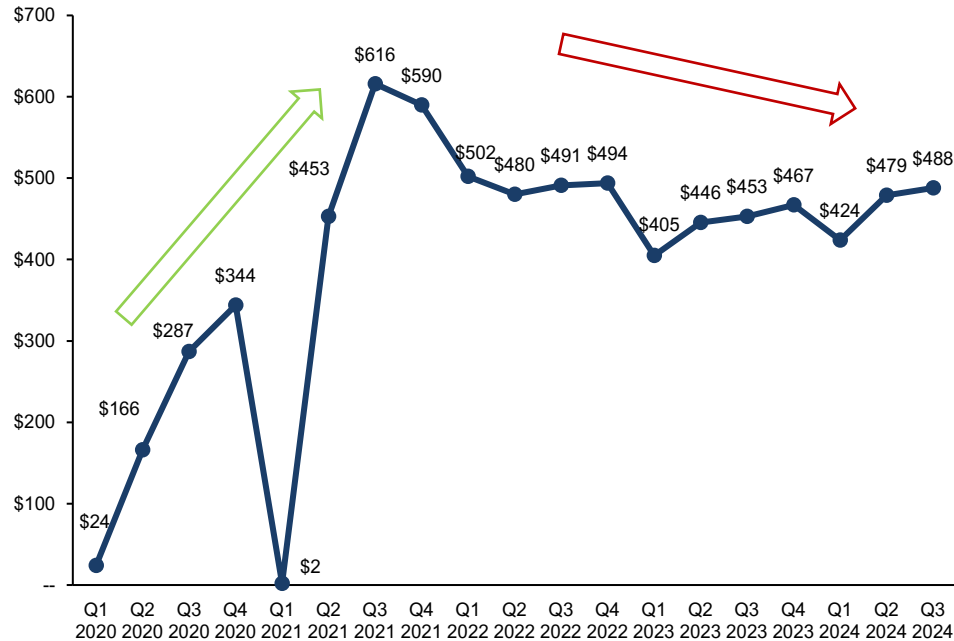
## 3 Pacibekitug has best-in-disease potential in TED

- Deep inhibition of IL-6 pathway observed to date offers potential for durable efficacy across many endpoints
- Existing clinical database supports the potential for a well-tolerated profile at selected doses
- Q8W dosing would allow for a patient-friendly, low burden treatment course

# IGF-1R class limitations present a significant opportunity for novel therapeutic approaches in TED

TEPEZZA U.S. revenues have been stagnating since 2021...

Sales (\$M)<sup>1</sup>



...believed to be due to real-world experience

## 1. Safety issues: Risk of potentially permanent hearing loss<sup>2</sup>

**-----WARNINGS AND PRECAUTIONS-----**

- **Hearing Impairment Including Hearing Loss:** TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients

## 2. Limited durability: Growing real-world effectiveness data reveals larger than anticipated number of non-responders / high relapse rate<sup>3,4</sup>

## 3. High level of inconvenience & complexity:

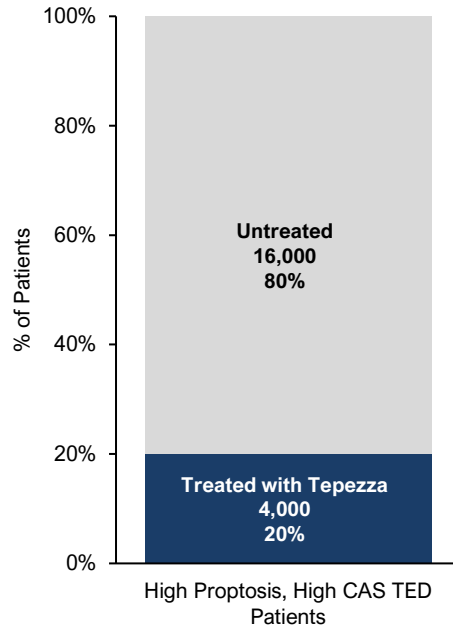
- IV Q3W (n=8)<sup>2</sup> but limited access to infusion centers<sup>5</sup>
- Numerous visits and high time commitment (HCPs and patients)<sup>5</sup>
- Need for serial audiograms, as per label<sup>2,6</sup>
- Burdensome reimbursement approval process<sup>7</sup>

# Despite an FDA-approved medicine, the vast majority of moderate-to-severe TED patients remain untreated

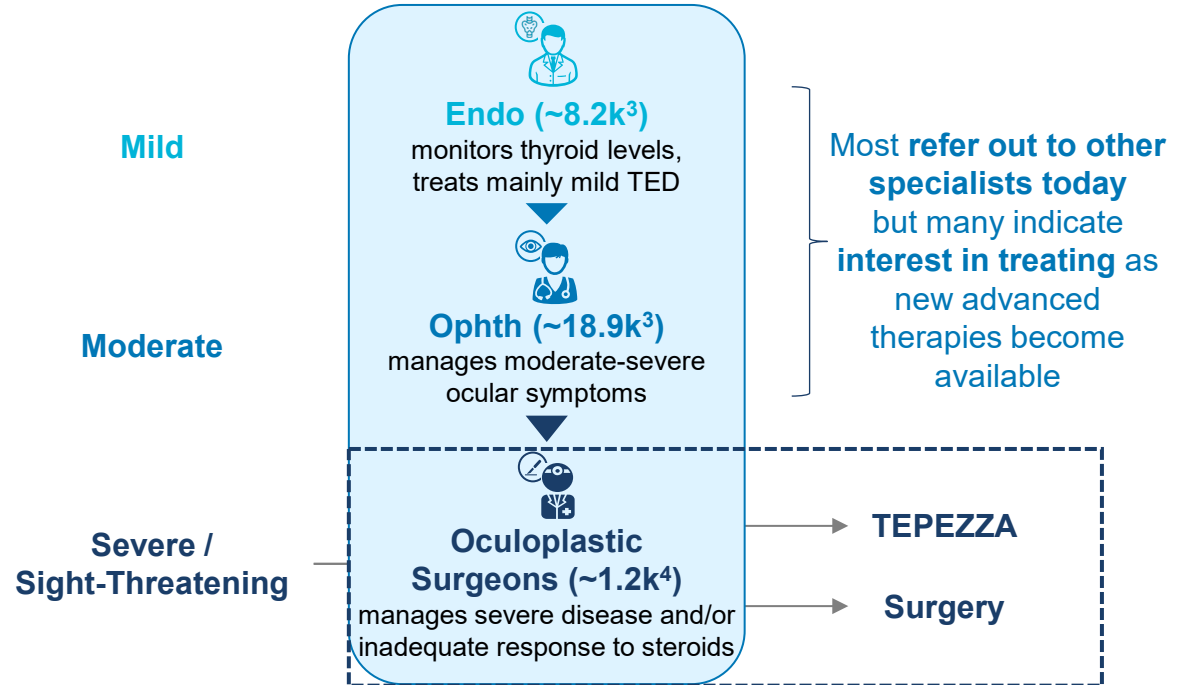
Most TED patients are not receiving TEPEZZA...

...or only get it relatively late in the treatment journey<sup>2</sup>

TEPEZZA US LTM penetration<sup>1</sup>

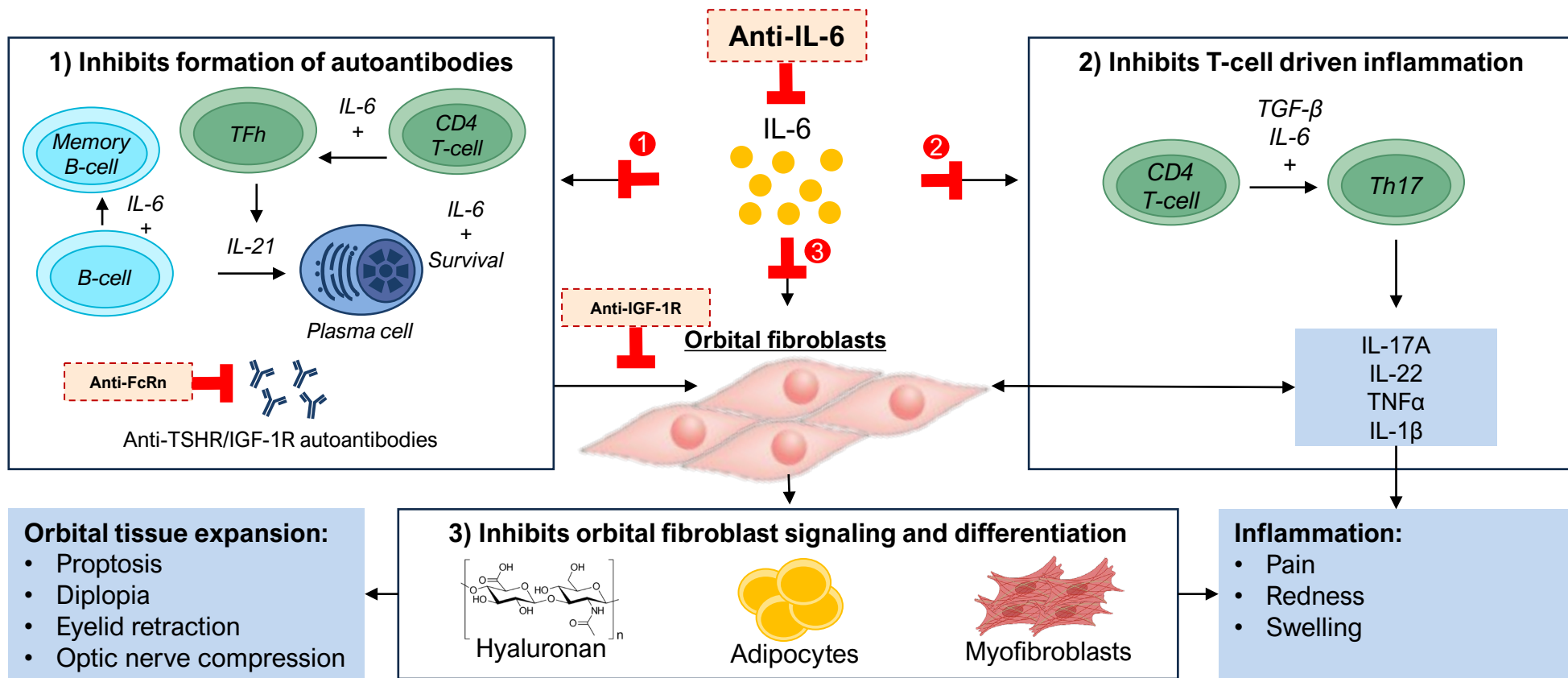


Simplified Treatment Journey<sup>2</sup>



<sup>1</sup>Horizon Q3 2022 earnings call; LTM = last twelve months. <sup>2</sup>Tourmaline market research; endo = endocrinologist; ophth = ophthalmologist. <sup>3</sup>AAMC 2022 Physician Specialty Data Report. <sup>4</sup>Hussey and Tao, Orbit (2022).

# IL-6 inhibition has the potential to address a central and upstream driver of TED



Adapted from Huang et al., Eye (2018); Hodgson and Rajaii, Ophthalmol Ther (2020); Fang et al, Front Endocrinol (2021); Smith et al., Eye (2019); and Cabezas et al., Front. Immunol. (2022)

# Over 50 publications support the therapeutic potential of IL-6 pathway inhibition in TED

Study Details				Key Endpoints		
First author	Year	Study type	N treated	Proptosis response rate	CAS response rate	% autoantibody reduction
Pérez-Moreiras	2021	Retro	54	78	89	75
Sánchez-Bilbao	2020	Obs	48	NR	NR	NR
Atienza-Mateo	2018	Retro	29	NR	NR	NR
Lee	2024	Prosp	19	11	47	56
Pérez-Moreiras	2014	Prosp	18	72	100	76
Pérez-Moreiras	2018	RCT	15	93	60	NS
de la Fuente Bursón	2020	Retro	15	NR	NR	NR
Pereira	2023	Retro	14	NR	NR	NR
Habroosh	2024	Prosp	13	100	31	68
Boutzios	2023	Obs	12	NR	NR	84
Pampín-Sánchez	2022	Retro	11	75	73	NR
Moi	2022	Retro	10	CI	80	75
Cortez	2022	Prosp	10	10	100	81
Silkiss	2020	CS	9	CI	56	74
Smith	2021	Retro	9	78	100	54
Bielefeld	2019	Obs	8	NR	NR	NR
Ceballos-Marcias Jose	2020	CS	8	NR	75	41
Benedjai	2020	Retro	7	NR	NR	73
Moás	2022	Obs	7	NR	NR	92
Toro-Tobon	2023	Retro	6	50	NR	NR
de Pablo Gomez	2018	CS	5	NR	60	NR
Navarrete	2022	Retro	5	NR	NR	NR
Ribi	2017	CS	3	33	67	NR
Maldiney	2020	CS	3	67	NR	NR
Stevens	2022	Retro	3	100	67	NR
Russell	2017	CS	2	NR	0	NR
Sy	2017	CS	2	CI	50	69

Study Details				Key Endpoints		
First author	Year	Study type	N treated	Proptosis response rate	CAS response rate	% autoantibody reduction
Copperman	2019	CS	2	100	0	NR
Coy	2019	CS	2	NR	50	NR
Sierra Osorio	2020	CS	2	100	100	NR
Park	2021	CS	2	100	100	NR
Abeillon-du Payrat	2022	CS	2	100	50	NR
Butnaru	2013	CR	1	NR	100	NR
Gómez Rodríguez	2014	CR	1	NR	100	NR
Bielefeld	2017	CR	1	CI	NR	NR
Canas	2018	CR	1	100	NR	NR
Pascual-Camps	2018	CR	1	NR	NR	NR
Garreta Fontelles	2019	CR	1	NR	NR	93
Mehmet	2020	CR	1	0	NR	NR
Kaplan	2020	CR	1	NR	0	85
Cayon-Blanco	2020	CR	1	NR	100	NR
Tran	2020	CS	1	NR	NR	NR
Ruiz	2021	CR	1	NR	NR	NR
Albrashdi	2022	CR	1	100	NR	NR
Cezara	2022	CR	1	NR	0	NR
Mohamed	2022	CS	1	0	0	NR
Moleiro	2022	CR	1	100	NR	86
Almazrouei	2023	CR	1	NR	NR	NR
Cuculescu	2023	CR	1	CI	0	NR
Nirmalan	2023	CS	1	NR	NR	NR
Pramono	2023	CR	1	NR	NR	NR
Rymuza	2024	CR	1	100	0	8
<b>Weighted Mean</b>				<b>68%</b>	<b>72%</b>	<b>71%</b>
<b>Smith 2017 (tepro Phase 2)</b>				<b>71%</b>	<b>69%</b>	<b>N/A</b>
<b>Douglas 2020 (tepro Phase 3)</b>				<b>83%</b>	<b>59%</b>	<b>N/A</b>

We believe many of these reports may underestimate the true efficacy of IL-6 inhibition

- 350+ mostly steroid-refractory patients
- Late IL-6 inhibition (>9 months post symptom onset) when disease may have exited active phase
- Exposure to IL-6 inhibition may have been suboptimal (<6 months)
- Tourmaline market research with over 100 TED treaters suggests many HCPs already routinely utilize IL-6 inhibition in their practice

# Pacibekitug's target product profile is expected to be well-differentiated in TED...

## Target product profile in TED\*

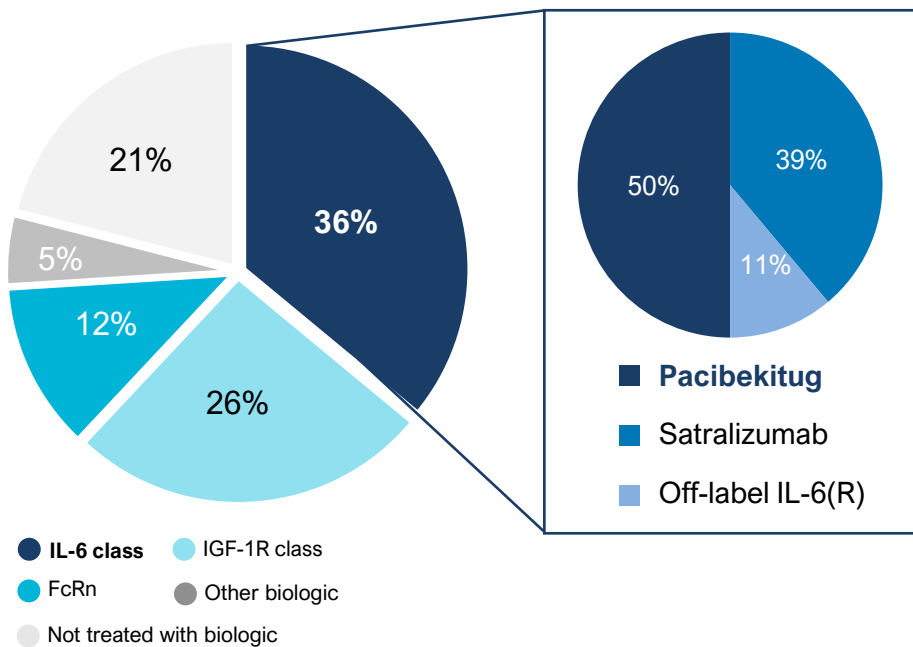
Study population		<ul style="list-style-type: none"> <li>Moderate-to-severe active TED patients</li> </ul>
MOA		<ul style="list-style-type: none"> <li><b>IL-6 inhibition</b></li> </ul>
Efficacy	Primary endpoint	<ul style="list-style-type: none"> <li><b>Proptosis</b></li> </ul>
	Secondary endpoints	<ul style="list-style-type: none"> <li><b>Diplopia, clinical activity score (CAS), inflammation, and lid retraction</b></li> </ul>
	Additional measures	<ul style="list-style-type: none"> <li>Lower <b>rate of relapse</b> and retreatment</li> <li><b>Rapid time to response</b></li> <li>Lower rate of <b>surgical intervention</b></li> </ul>
Safety	Warnings & precautions	<ul style="list-style-type: none"> <li><b>No anticipated risk of permanent hearing loss</b> or warnings beyond typical IL-6 safety considerations</li> </ul>
Dosing & administration		<ul style="list-style-type: none"> <li><b>Every 8-week, low volume subcutaneous injection</b> through pre-filled syringe</li> <li>Finite dosing</li> </ul>

## Targeted points of differentiation

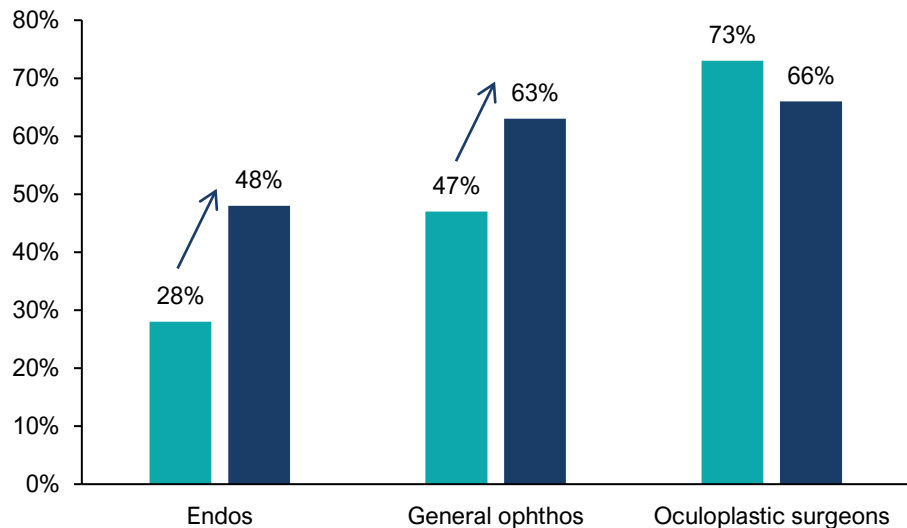
- **Targeting inflammation** which is at core of disease
- **Holistic impact** on many QoL-impacting symptoms
- Emphasis on **response durability**
- **Well-tolerated** without the risk of hearing loss
- Least frequent and **most patient-friendly SC dosing**

# ...resulting in leading market share, capitalizing on increasing Rx from endocrinologists and ophthalmologists

## Pacibekitug ranked highest in future market share among 140 TED treaters in US<sup>1</sup>



## Impact on Rx if SC therapies are available<sup>1</sup>



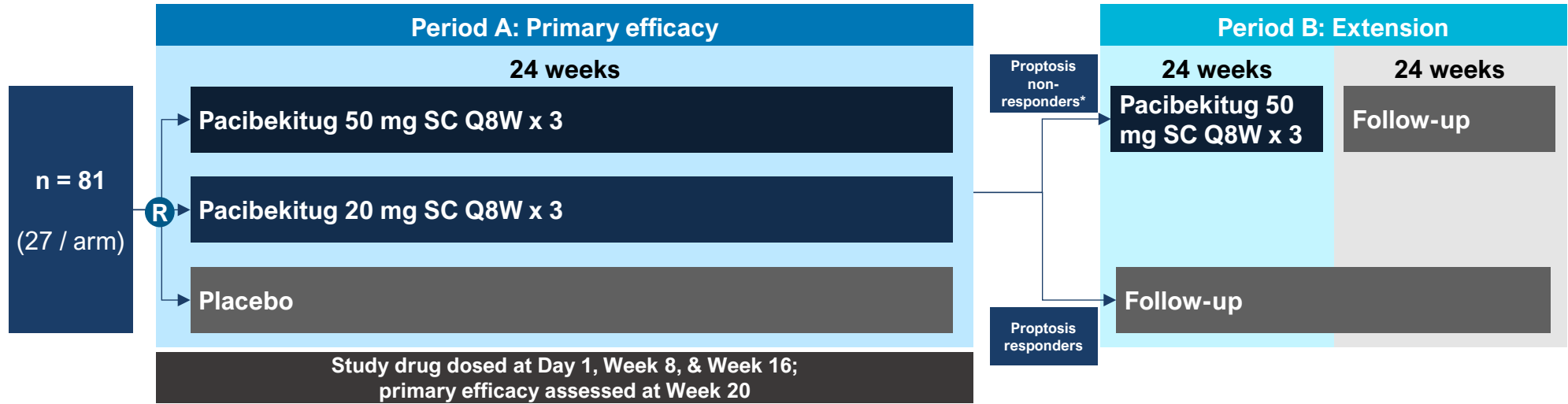
- I treat and manage moderate to severe active TED patients rather than referring out to another physician today
- As additional treatments become available for TED, including SC therapies, I will treat and manage moderate to severe active TED patients rather than referring out to another physician



# spiriTED pivotal trial in first-line TED

Double-masked, placebo-controlled Phase 2b trial (NCT06088979)

Open label



## Study population:

- Moderate-to-severe TED, with proptosis  $\geq 3$ mm above normal (based on race and gender)
- Active phase, with symptom onset  $\leq 15$  months, CAS  $\geq 4$  and positive TSI
- First-line setting, with cap on prior corticosteroid use ( $< 1$ g methylprednisolone or equivalent)

## Primary efficacy endpoint:

- Proptosis response rate at week 20



## Additional endpoints:

- CAS
- Diplopia
- QoL, safety, PK/PD/ADA

\*Any patient who receives rescue therapy/intervention in Period A will not receive pacibekitug in Period B and will instead undergo follow-up only



# Key upcoming milestones

Disease focus	Indication	Milestone	Expected timing
Cardiovascular inflammation	ASCVD	 Phase 2 topline data	Q2 2025
	AAA	Phase 2 trial start	Post-TRANQUILITY topline data
Autoimmune disease	TED	 Phase 2b topline data	H2 2025

AAA: abdominal aortic aneurysm. ASCVD: atherosclerotic cardiovascular disease. TED: thyroid eye disease.

TOURMALINE