TOURMALINE

Corporate Overview

January 2025

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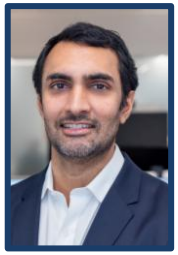
Our mission

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

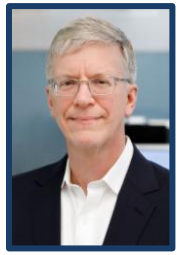
Experienced leadership team

Management Team



Sandeep Kulkarni, MD
Co-Founder and Chief Executive Officer

Ryan Robinson, CPA
Chief Financial Officer



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Key highlights

- **An IL-6 renaissance is underway:** new insights emerging about a broad range of indications where IL-6 may be clinically validated
- **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
- **Two paths to significant value creation:** (1) cardiovascular inflammation and (2) thyroid eye disease
- **A late-stage clinical company:** Phase 2 TRANQUILITY trial in CV and pivotal Phase 2b spiriTED trial in TED ongoing
- **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
- **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

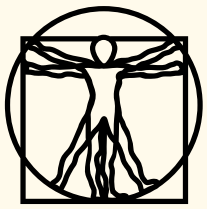
- **Long-acting** with terminal half-life of ~7 weeks[1]
- **>90% pathway inhibition** after single 10mg dose[2]
- **Fully human** with ADAs in only 0.5% of patients[3]
- **High affinity** to IL-6[4]
- Existing data from approximately **450 study participants**[1]

Potential value to patients

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

[1]Across six clinical trials in healthy volunteers and RA, SLE, and CD patients. [2]Data on file; single intravenous 10mg dose in Ph1 MAD study in RA patients; as measured by C-reactive protein (CRP), a pharmacodynamic marker of IL-6 signaling. [3]Generated from Medarex transgenic mouse platform; across approximately 450 subjects dosed with pacibekitug, only 2 subjects generated anti-drug antibodies (ADAs) following treatment. [4]Data on file. [5]To be evaluated in CV Phase 2 trial. [6]To be evaluated in TED Phase 2 trial. Every 8-week dosing was achieved in prior Phase 2 trials. CD: Crohn's Disease. CV: cardiovascular. SC: subcutaneous. RA: rheumatoid arthritis. SLE: systemic lupus erythematosus. TED: thyroid eye disease.

Two paths to unlock major value creation



IL-6 Renaissance

Emerging insights implicating IL-6 in a wide range of rare & large diseases

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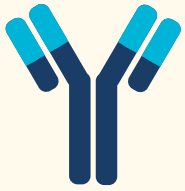


Pacibekitug

- ✓ Long-acting
- ✓ Low immunogenicity
- ✓ Low volume, SC

Key expected readouts

Cardiovascular Inflammation

- ❑ **Q2 2025:** TRANQUILITY Phase 2 topline data
- ➢ **2025 / 2026:** Zilti ASCVD in CKD Phase 3 (ZEUS) topline data
- ➢ **2026:** Zilti AMI Phase 3 (ARTEMIS) topline data

Thyroid Eye Disease

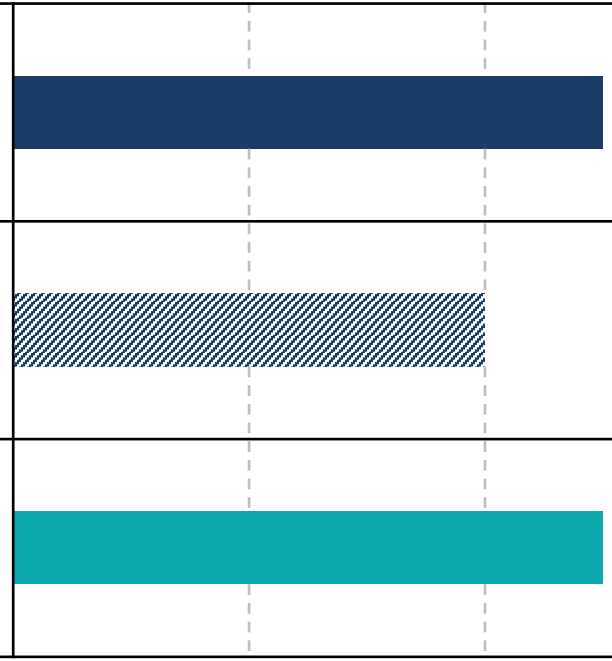
- ❑ **H2 2025:** spiriTED Phase 2b topline data
- ➢ **2026:** Satra TED Phase 3 (Satra-GO) topline data

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)					TRANQUILITY 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)					spiriTED 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

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

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

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

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 guiding our development strategy for pacibekitug

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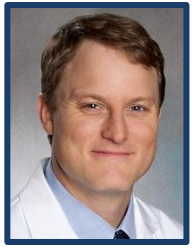

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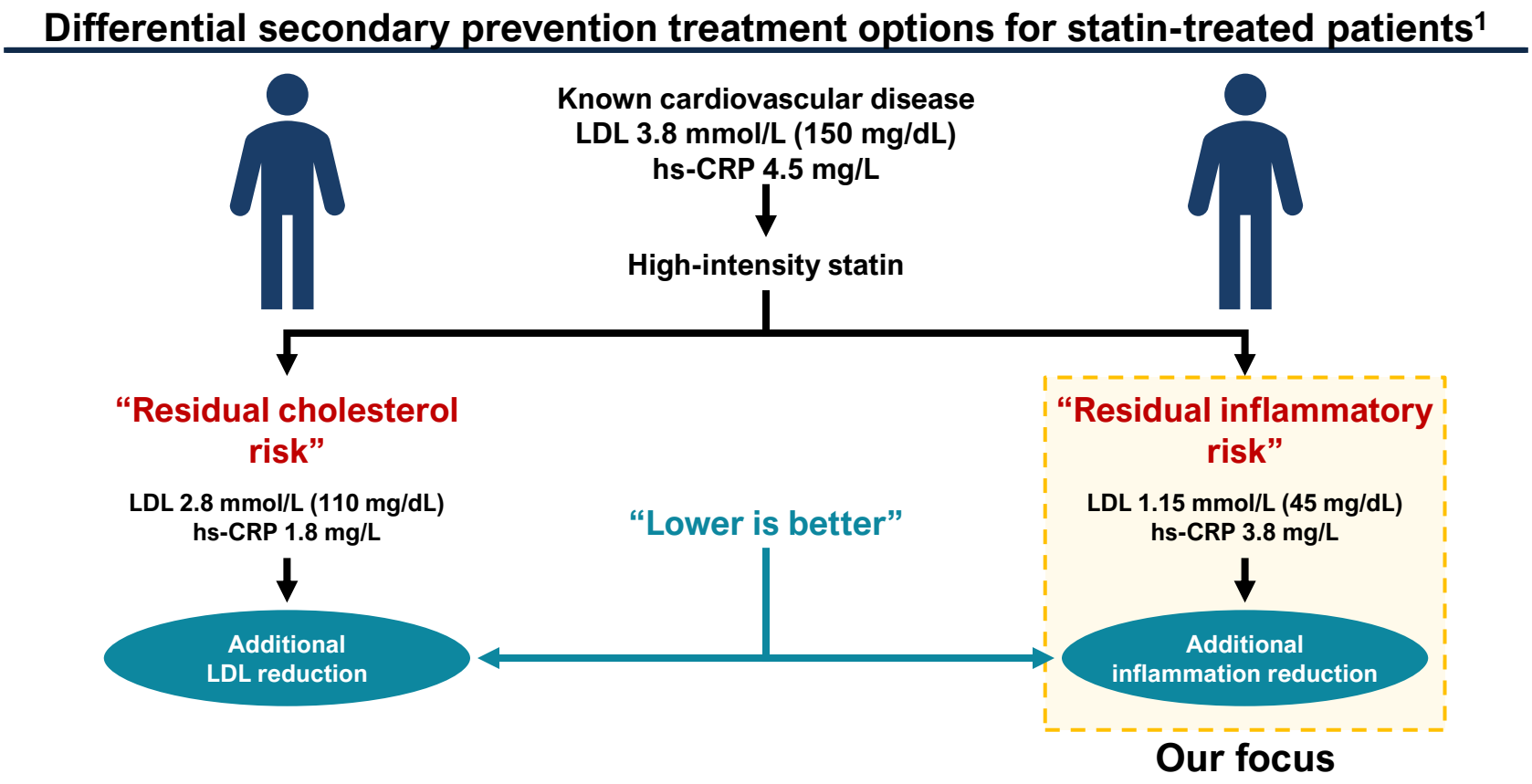
Residual inflammation remains a key driver of CV risk despite optimized management of cholesterol



[1]Adapted from Ridker, Eur Heart J (2016).

Increasing recognition of inflammation & IL-6 as drivers of CV risk

RESEARCH LETTER

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

A Phenome-Wide Association Study

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

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

Alessio Alogna, MD, PhD,[a,b,c] Katlyn E. Koepp, PhD,[a] Michael Sabbah, MD,[a] Jair M. Espindola Netto, PhD,[d] Michael D. Jensen, MD,[e] James L. Kirkland, MD, PhD,[d,f] Carolyn S.P. Lam, MBBS,[g] Masaru Obokata, MD, PhD,[a] Mark C. Petrie, MD,[h] Paul M. Ridker, MD, MPH,[i] Hidemi Sorimachi, MD, PhD,[a] Tamara Tchkonia, PhD,[d] Adriaan Voors, MD, PhD,[j] Margaret M. Redfield, MD,[a] Barry A. Borlaug, MD[a]

Research Letter

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

Sizheng Steven Zhao[1,*], Dipender Gill[2]

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[2] *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 Palaiopanos, MD, Harry Björkbacka, PhD, Annette Peters, PhD, James A. de Lemos, MD, Sudha Seshadri, MD, Martin Dichgans, MD, and Marios K. Georgakis, MD, PhD

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Neurology® 2022;98:e1002-e1012. doi:10.1212/WNL.0000000000013274

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

Eleni Michou[1†], Desiree Wussler[1,2†], Maria Belkin[1], Cornelia Simmen[1], Ivo Strebel[1], Albina Nowak[3,4], Nikola Kozhuharov[1], Samyut Shrestha[1], Pedro Lopez-Ayala[1], Zaid Sabti[1], Constantin Mork[1], Matthias Diebold[1], Tiffany Péquignot[1], Katharina Rentsch[5], Arnold von Eckardstein[6], Danielle M. Gualandro[1], Tobias Breidthardt[1,2], and Christian Mueller[1*]

ORIGINAL RESEARCH

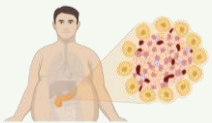
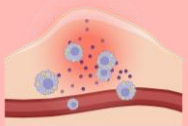
Elevated Interleukin-6 Levels Are Associated With an Increased Risk of QTc Interval Prolongation in a Large Cohort of US Veterans

Pietro Enea Lazzerini, MD; Michael Cupelli, PhD; Alessandra Cartocci, MSc; Iacopo Bertolozzi, MD; Viola Salvini, MD; Riccardo Acciai, MD; Fabio Salvadori, MD; Tommaso Marzotti, MD; Decorosо Verrengia, MD; Gabriele Cevenini, BioEng; Stefania Bisogno, MD; Maurizio Bicchi, MD; Giovanni Donati, MD; Sciaila Bernardini, MD; Franco Laghi-Pasini, MD; Maurizio Acampa, MD; Pier Leopoldo Capecchi, MD, PhD; Nabil El-Sherif, MD; Mohamed Boutjdir, PhD

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

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

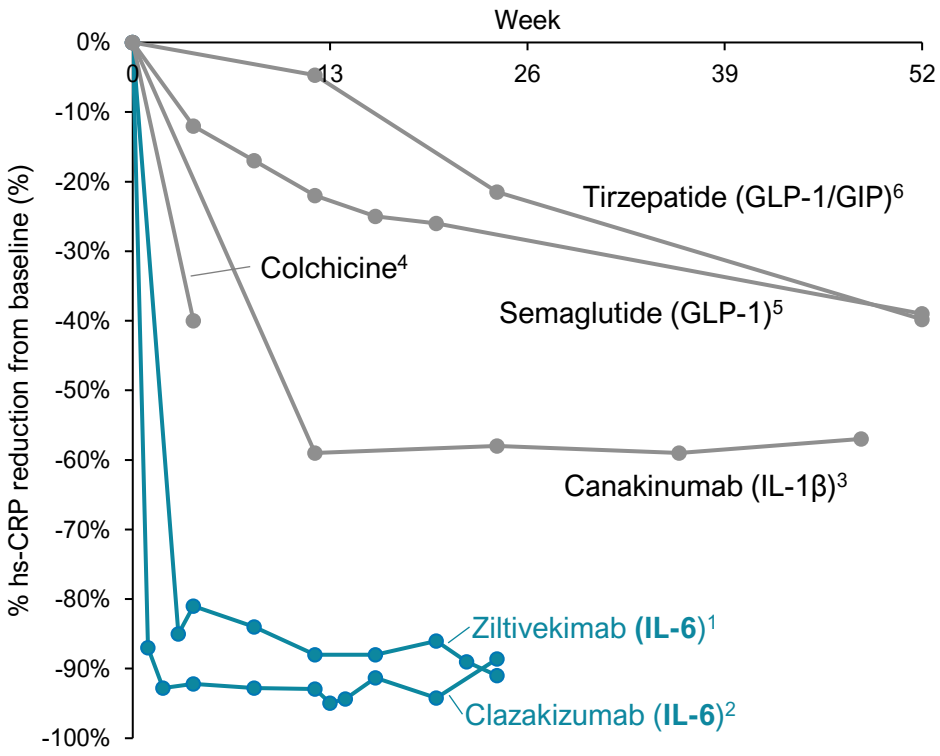
Cardiovascular inflammation largely unaddressed by existing treatments

Atherothrombotic Pathways	Thrombosis	Hypertension	Atherogenic lipoproteins	Diabetes, Insulin resistance, Obesity	Inflammation
					
Biomarkers	**None readily available**	**Blood pressure**	**ApoB, Non-HDL-C, LDL-C, Triglycerides, Lipoprotein(a)**	**HbA1c, Fasting glucose, Weight**	**C-reactive protein**
Approved Therapies	Aspirin P2Y12R inhibitors Factor Xa inhibitors PAR-1 antagonists	ACEI/ARB Calcium channel blockers Thiazide diuretics Renin inhibitors Beta-blockers Mineralocorticoid antagonists	Statins PCSK9 inhibitors Icosapent ethyl NPC1L1 inhibitors ACL inhibitors Bile acid sequestrants MTP inhibitors ANGPTL3 inhibitors Apheresis	SGLT2 inhibitors GLP-1 agonists GIP/GLP-1 agonists	Colchicine
Therapies in Late-Stage Development	Factor XI inhibitors Factor XIa inhibitors	Angiotensinogen inhibitors Aldosterone synthase inhibitors Endothelin antagonists Renal denervation Baroreceptor activation	CETP inhibitors Lipoprotein(a) inhibitors ApoC3 inhibitors Fibrates CRISPR PCSK9 base editing	GIP/GLP-1/glucagon agonists Amylin agonists GIP-1/amylin agonists	**IL-6 inhibitors** NLRP3 inhibitors

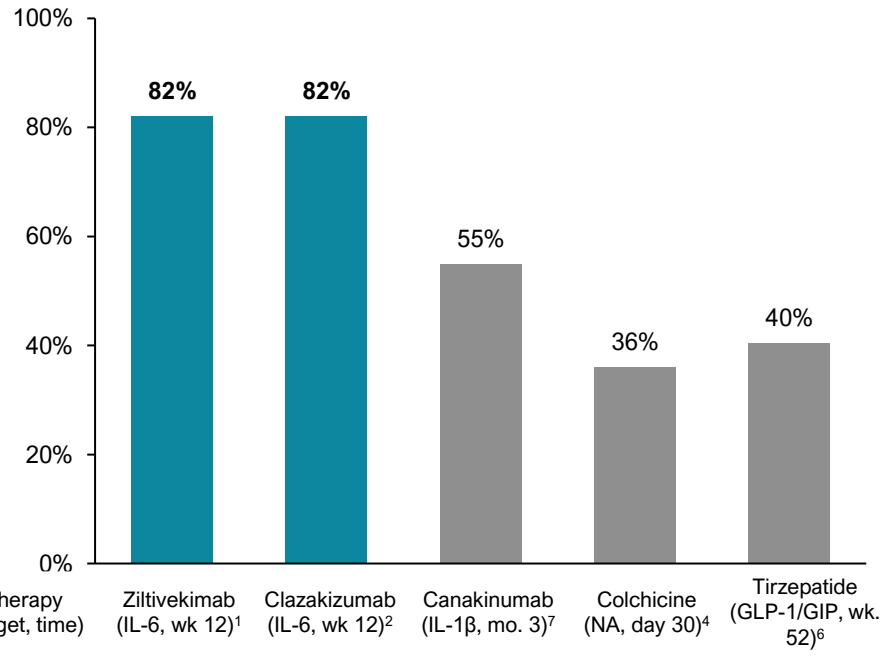
List of therapies not exhaustive. ACEI: angiotensin-converting enzyme inhibitor. ACL: adenosine triphosphate-citrate lyase. ANGPTL3: angiopoietin-like protein 3. ApoB: apolipoprotein B. ApoC3: apolipoprotein C3. ARB: angiotensin receptor blocker. CETP: Cholesteryl ester transfer protein. CRISPR: clustered regularly interspaced short palindromic repeats. GIP: gastric inhibitory polypeptide. GLP-1: glucagon-like peptide-1. IL-6: Interleukin-6. MTP: microsomal triglyceride transfer protein. NLRP3: nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3. NPC1L1: Niemann-Pick C1-Like 1. PAR: protease-activated receptors. PCSK9: proprotein convertase subtilisin/ kexin type 9. P2Y12R: purinergic 2Y type 12 receptor. SGLT2: sodium-glucose cotransporter 2.

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



Therapy (target, time)	Ziltivekimab (IL-6, wk 12)[1]	Clazakizumab (IL-6, wk 12)[2]	Canakinumab (IL-1β, mo. 3)[7]	Colchicine (NA, day 30)[4]	Tirzepatide (GLP-1/GIP, wk. 52)[6]
Baseline hs-CRP (mg/L), median	**5.70**	**7.2**	**4.25**	**4.40**	**3.1**

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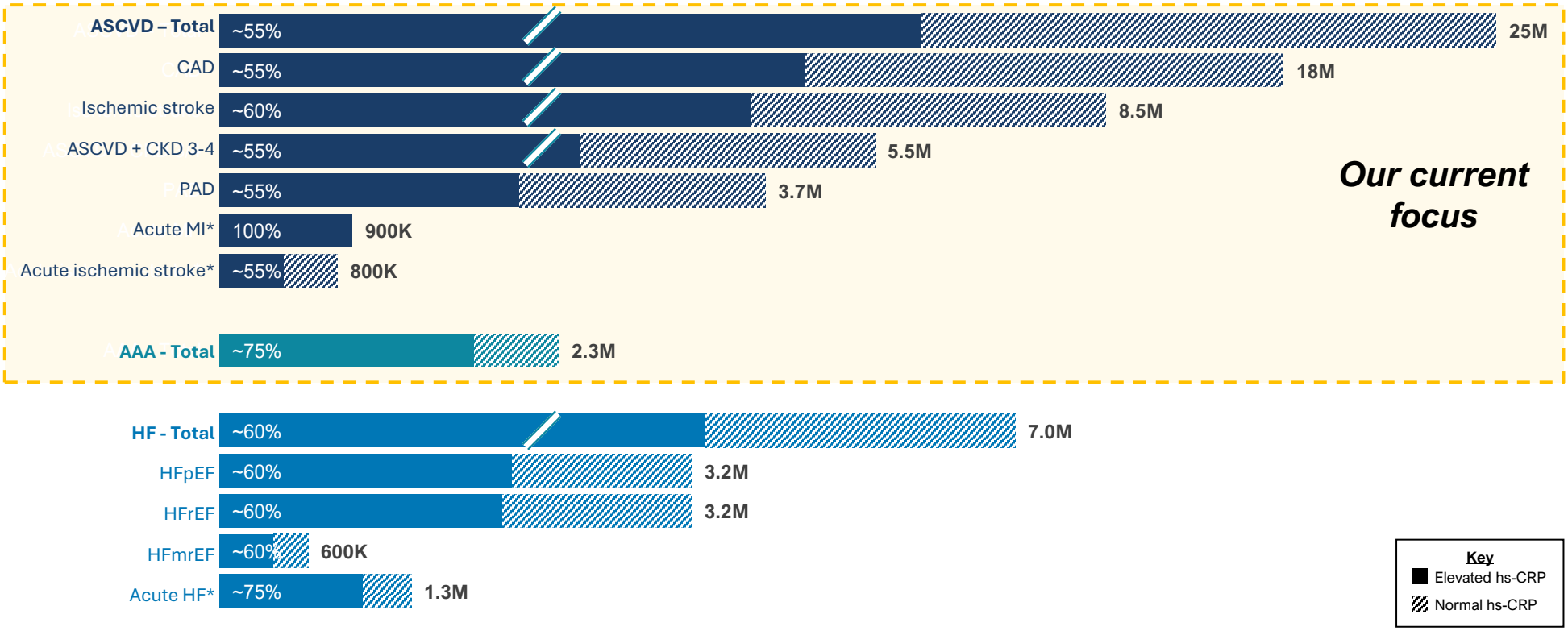
[1]RESCUE: Ridker et al., Lancet (2021). Ziltivekimab 15mg q4w arm. [2]Chertow et al., Nat Med (2024). Clazakizumab 5mg q4w arm. [3]CANTOS: Ridker et al., N Eng J Med (2017). 150mg q3m arm. [4]Fiolet et al., PLOS ONE (2020). Colchicine 0.5mg QD. [5]SELECT: Plutzky et al., EAS Congress (2024). Semaglutide 2.4mg QW maintenance. [6]Borlaug et al., Nat Med (2024). Tirzepatide up to 15mg QW. [7]Ridker et. al., Lancet (2017). Time course values obtained by webplotdigitizer. Values are not placebo adjusted. CVD: cardiovascular disease. GIP: gastric inhibitory polypeptide. GLP-1: glucagon-like peptide-1. hs-CRP: high sensitivity C-reactive protein. Certain data in this presentation 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.

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

Estimated US prevalence (2024)[1]

Populations are not mutually exclusive

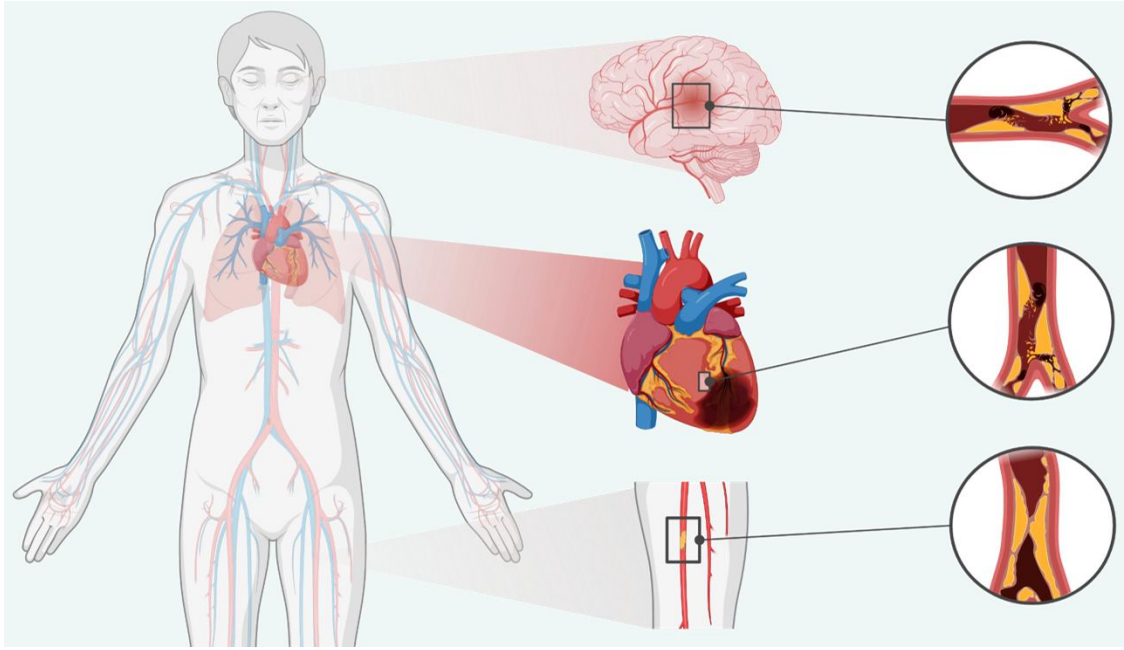


[1]Publications available upon request. *Annual incidence
AAA: abdominal aortic aneurysm. ASCVD: atherosclerotic cardiovascular disease. CAD: coronary artery disease. CKD: chronic kidney disease. HF: heart failure. HFmrEF: Heart Failure with Mid-Range Ejection Fraction. HFpEF: heart failure with preserved ejection fraction. HFrEF: heart failure with reduced ejection fraction. MI: myocardial infarction. PAD: peripheral artery disease.

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

- Human genetic evidence
- Epidemiological evidence
- Clinical trial evidence

Evidence suggests IL-6 may drive ASCVD risk



ASCVD: atherosclerotic cardiovascular disease

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[1,2]	Positive	Positive
Inhibiting IL-6 to treat polymyalgia rheumatica[3,4]	Positive	Positive
Lowering blood pressure to lower ASCVD risk[5,6]	Positive	Positive
Raising HDL-C to lower ASCVD risk[7,8]	Negative	Negative
Inhibiting LpPLA2 to lower ASCVD risk[9,10]	Negative	Negative
Inhibiting TNFα to treat multiple sclerosis[11,12]	Negative (harm)	Negative (harm)
Inhibiting IL-6 to lower ASCVD risk[13-17]	Positive	Trials Ongoing

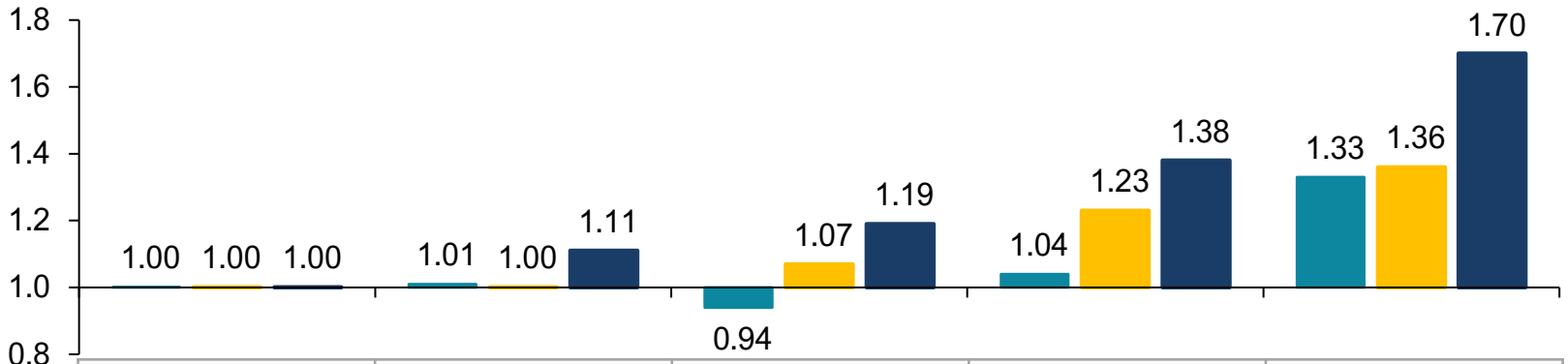
"Probability of success for drug mechanisms with genetic support is 2.6 times greater than those without."[18]

[1]Ference et al., J. Am. Coll. Cardiol. (2012). [2]Casula et al., Pharm. Res. (2019). [3]Zhao et al., Ann Rheum Dis (2022). [4]Spiera eta al. N Engl Med (2023). [5]Wan et al., Hypertension (2021). [6]The Blood Pressure Lowering Treatment Trialists' Collaboration, Lancet (2021). [7]Voight et al., Lancet (2012). [8]Keene et al., BMJ (2014). [9]Gregson et al., Eur J Prev Cardiol. (2017). [10]Fras et al., Arch Med Sci. (2021). [11]Kang et al., Neurology (2021). [12]Lenercept Multiple Sclerosis Study Group, Neurology (1999). [13]Levin et al, Circulation Research (2021). [14]Georgakis et al., Circulation (2021). [15]Swerdlow et al., Lancet (2012). [16]Georgakis et al., Circ Genom Precis Med. (2020). [17]Georgakis et al., BCM Med. (2022). [18]Minikel et al., Nature (2024).

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[1]
(n=27,929)



	Quintile (reference)	Quintile 2	Quintile 3	Quintile 4	Quintile 5
hs-CRP mg/L baseline	<0.65	0.65 to <1.47	1.47 to <2.75	2.75 to <5.18	≥5.18
LDL-C mg/dL baseline	<96.1	96.1 to <113.5	113.5 to <129.7	129.7 to <150.7	≥150.7
Lp(a) mg/dL baseline	<3.6	3.6 to <7.6	7.6 to <15.5	15.5 to <44.1	≥44.1

[1]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

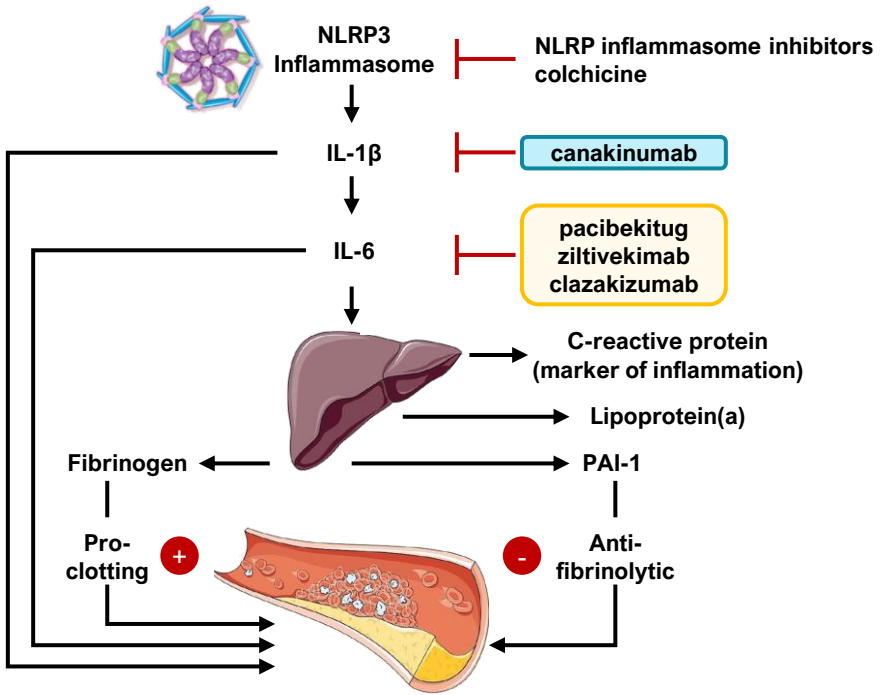
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) Trial Design[1]

10,061 patients
- Stable CAD (post MI)
- On Statin, ACE/ARB, BB, ASA
- hs-CRP ≥2 mg/L

- Canakinumab 50 mg Q3M n = 2,170
- Canakinumab 150 mg Q3M n = 2,284
- Canakinumab 300 mg Q3M n = 2,263
- Placebo Q3M n = 3,344

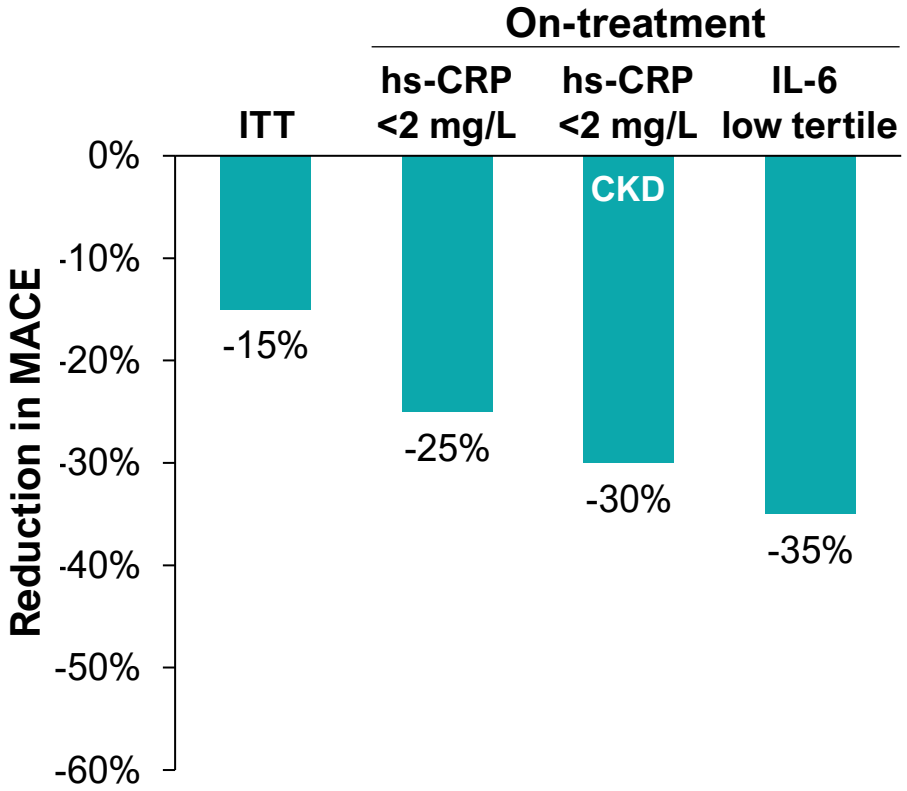
Primary endpoint:
Time to the first occurrence of MACE (CV death, non-fatal MI, or non-fatal stroke)

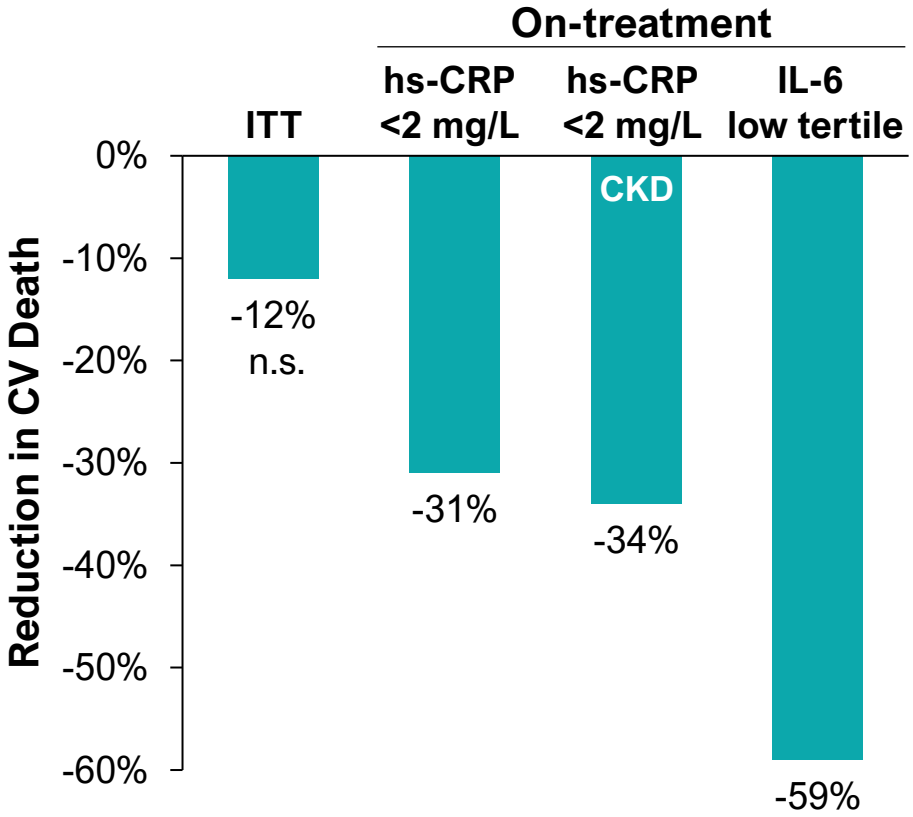
IL-1β is upstream of IL-6[2]



[1]Ridker et al., N. Engl. J. Med. (2017). [2]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-1β mAb):
"Lower is better" for downstream biomarkers of IL-6 activity





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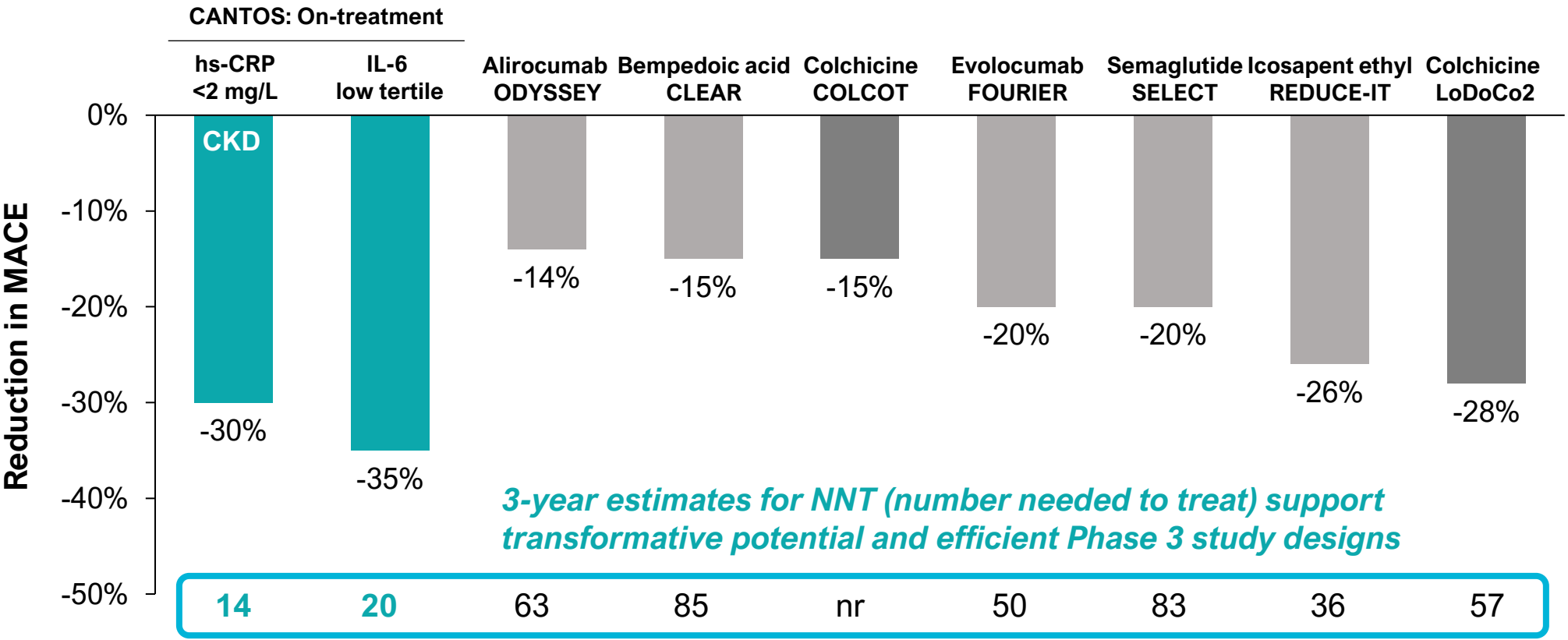
Reduction in MACE shown as 1-Hazard Ratio. ITT: intent to treat. MACE: major adverse cardiovascular events including CV death, myocardial infarction (MI), stroke. n.s.: not statistically significant. ITT CANTOS analysis presents data for 150mg dose group; values for CANTOS subanalyses combine all doses (50, 150, 300 mg). Ridker et al., NEJM (2017). Ridker et al., Lancet (2018). Adjusted for age, gender, smoking, hypertension, diabetes, BMI, baseline hs-CRP, baseline LDL-C. Ridker et al., Eur Heart J (2018). Adjusted for age, gender, smoking, hypertension, diabetes, BMI, baseline IL-6, baseline LDL-C. Ridker et al., JACC (2018).

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



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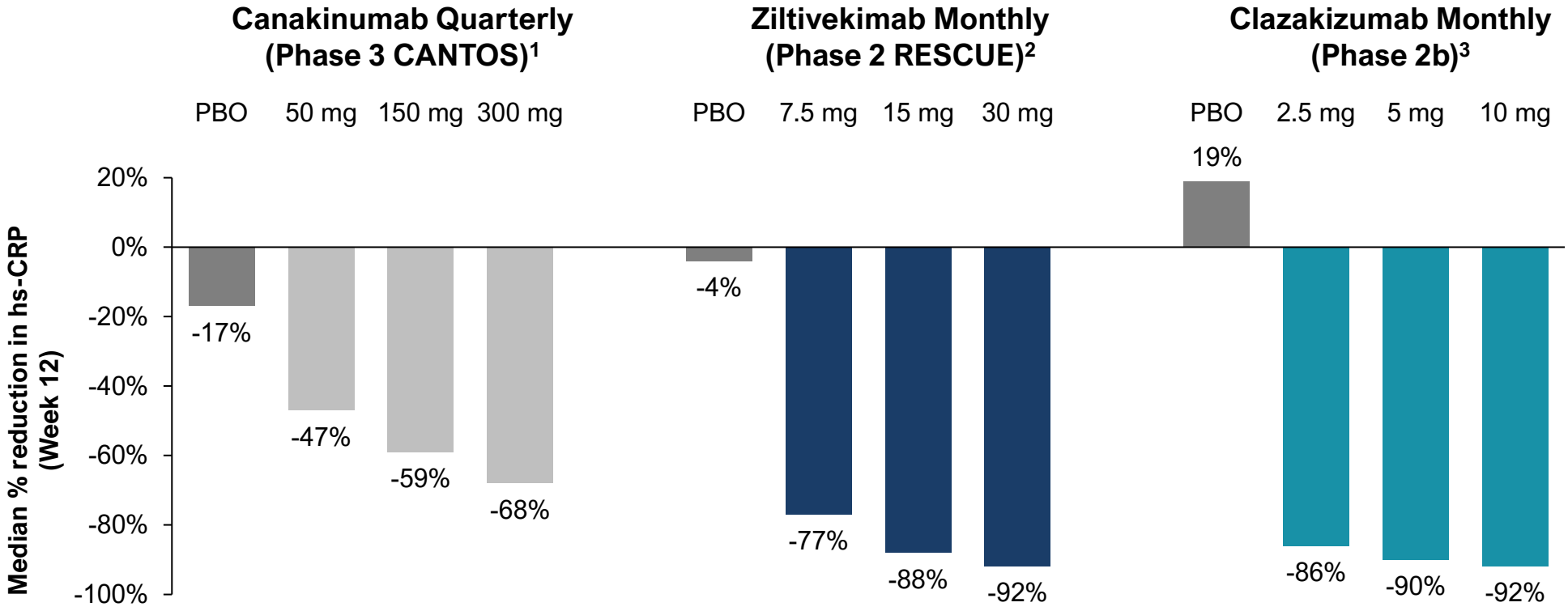
Reduction in MACE shown as 1-Hazard Ratio. MACE: major adverse cardiovascular events including CV death, myocardial infarction (MI), stroke except for: ODYSSEY OUTCOMES (all death, MI, ischemic stroke); COLCOT (CV death, MI, stroke, resuscitated cardiac arrest); LoDoCo2 (CV death, MI, ischemic stroke); 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-1β blockade



Direct IL-6 inhibition achieved ~2x placebo-adjusted reductions in hs-CRP compared to upstream IL-1β

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[1]Ridker et al., NEJM (2017). [2]Ridker et al., Lancet (2021). [3]Chertow, Nature (2024).
Certain data in this presentation 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.

Five Phase 3 CVOTs enrolling >24,000 patients

ZEUS: ASCVD w/CKD[1]

6,200 patients
- ASCVD
- CKD stage 3-4
- hs-CRP ≥2 mg/L

1:1

- Ziltivekimab 15 mg QM + Standard of Care
- Placebo QM + Standard of Care

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

ARTEMIS: acute MI[2]

10,000 patients
- Acute MI
- First dose within 36 or 48 hrs

1:1

- Ziltivekimab loading 30mg followed by 15mg QM + Standard of Care
- Placebo QM + Standard of Care

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

ATHENA: HFpEF[3]

680 patients
- HF Class II-III
- hs-CRP ≥2 mg/L

1:1

- Ziltivekimab QM + Standard of Care
- Placebo QM + Standard of Care

Primary endpoint:
Change in KCCQ-CSS at 1 year

HERMES: HFpEF[4]

5,600 patients
- HF Class II-IV
- hs-CRP ≥2 mg/L

1:1

- Ziltivekimab 15 mg QM + Standard of Care
- Placebo QM + Standard of Care

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

POSIBIL6: ESKD[5]

2,310 patients
- ESKD
- Diabetes or ASCVD
- hs-CRP ≥2 mg/L

1:1

- Clazakizumab 5 mg Q4W + Standard of Care
- Placebo Q4W + Standard of Care

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

Topline data readouts expected

2025 / 2026	2026	2026	2027	2028

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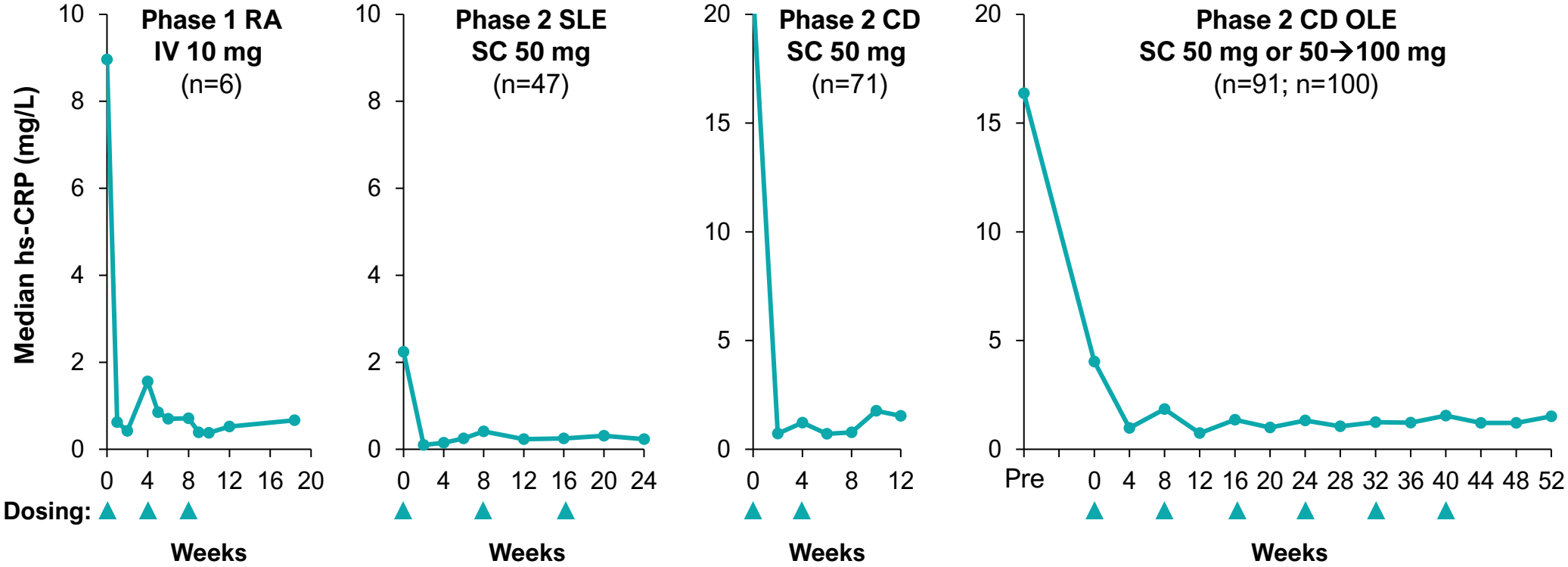
The timing of clinical trial milestones are subject to change.
ASCVD: atherosclerotic cardiovascular disease. CKD: chronic kidney disease. CVOT: cardiovascular outcome trial. ESKD: End Stage Kidney Disease. HFpEF: heart failure with preserved ejection fraction. MACE: major adverse cardiovascular event. MI: myocardial infarction.
[1]Clinicaltrials.gov: NCT05021835. [2]Clinicaltrials.gov: NCT06118281. [3]Clinicaltrials.gov: NCT06200207 [4]Clinicaltrials.gov: NCT05636176 [5]Clinicaltrials.gov: NCT05485961 (Phase 3 portion only)

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

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

CD: Crohn's disease, CKD: chronic kidney disease, HD: hemodialysis, NDD: non-dialysis dependent, SLE: systemic lupus erythematosus. [1]Incidence of ADAs in repeat-dose studies calculated as reported per dosing arm. [2]Route of administration in planned or ongoing studies in patients with or at high-risk of ASCVD. [3]Clinicaltrials.gov NCT03926117. [4]Pergola et al., JASN (2021). [5]Ridker et al., Lancet (2021). [6]Wada et al., J Cardiol (2023). [7]Clinicaltrials.gov NCT01490450. [8]Clinicaltrials.gov NCT01545050. [9]Weinblatt et al., Arthritis Rheum (2015). [10]Clinicaltrials.gov NCT05485961.
Data reported in publications or on clinicaltrials.gov as detailed above. No head-to-head studies have been conducted between the mabs shown here, which have each been evaluated in different populations.

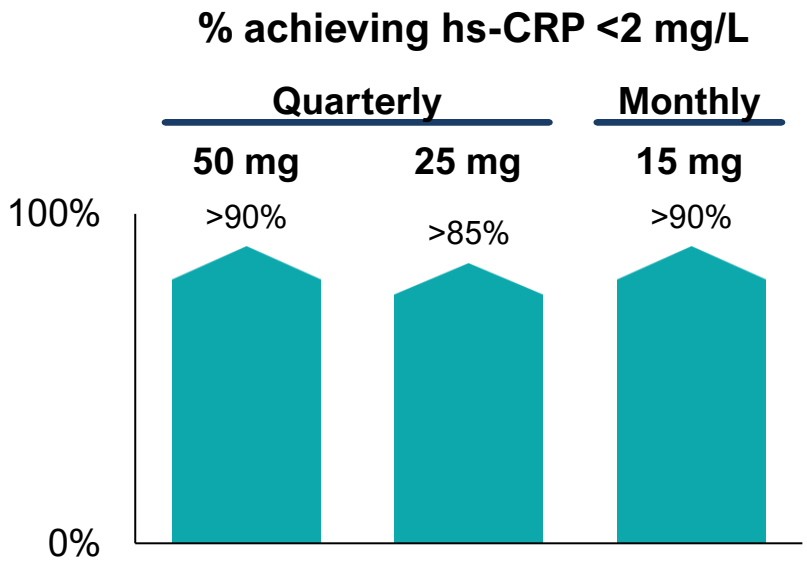
Pacibekitug achieved robust and durable suppression of CRP in patients with high-grade inflammatory autoimmune disorders

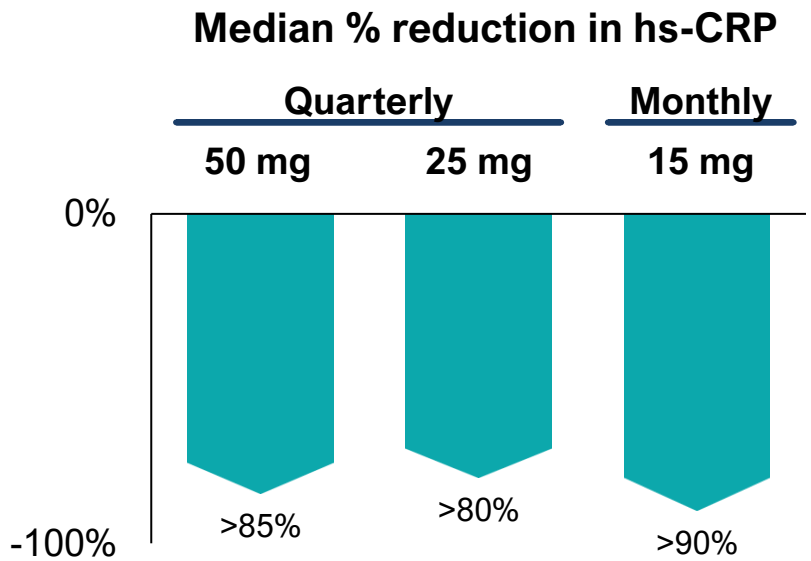


CD: Crohn's disease, OLE: open-label extension, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus. Rheumatoid arthritis: B0151002 study report. Table 14.4.7.1.1. Median baseline CRP 9.0 mg/L. Key eligibility: active disease, background methotrexate. Crohn's disease: B0151003 study report. Table 14.2.4.1.3. Median baseline hs-CRP 21.1 mg/L. Key eligibility: active disease, failed/intolerant to anti-TNFα. CD OLE B0151005 study report. Table 14.2.4.1. Median pre-baseline hs-CRP 16.4 mg/L, baseline hs-CRP 4.0 mg/L. Systemic lupus erythematosus: B0151006 study report. Table 14.3.4.1.5. Median baseline hs-CRP 2.2 mg/L.

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[1]

% achieving hs-CRP<2 mg/L: 82%

median % reduction: 88%

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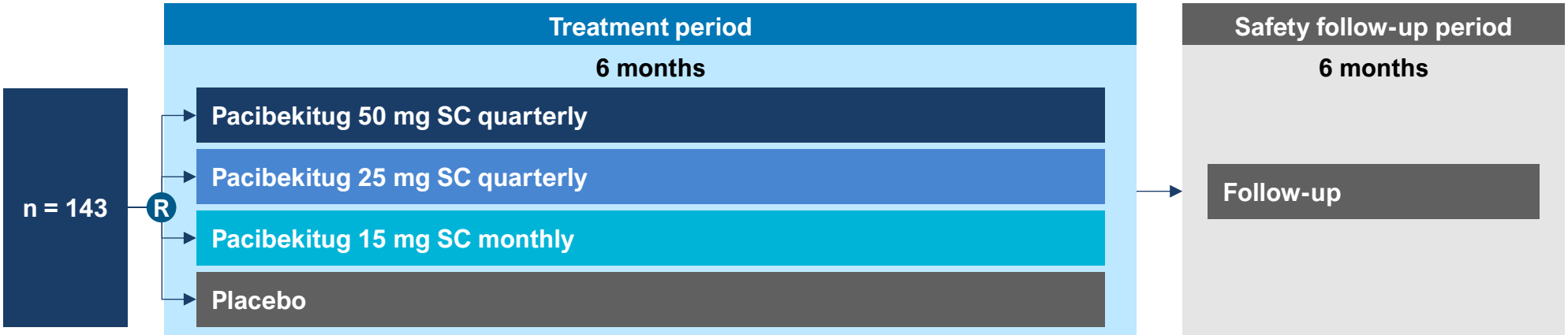
ASCVD: atherosclerotic cardiovascular disease, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, CD: Crohn's disease. The PK and PK/PD models for pacibekitug were developed based on the data from 5 clinical studies (two phase 1 studies in healthy volunteers, one phase 1 study in RA, one phase 2 study in SLE, and one phase 2 study in CD). A two-compartment model with first-order absorption and linear elimination and a mechanism-based indirect response model (in a relationship on CRP) adequately described the PK and PK/PD relationships, respectively. Simulations were performed assuming an RA-like population with baseline CRP >2 mg/L to 10 mg/L. Results at Day 90 are shown. [1]Ridker et al., Lancet (2021). Results after 12 weeks of treatment are shown. 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.

TRANQUILITY 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^2) or UPCR>200 mg/g
- hs-CRP ≥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

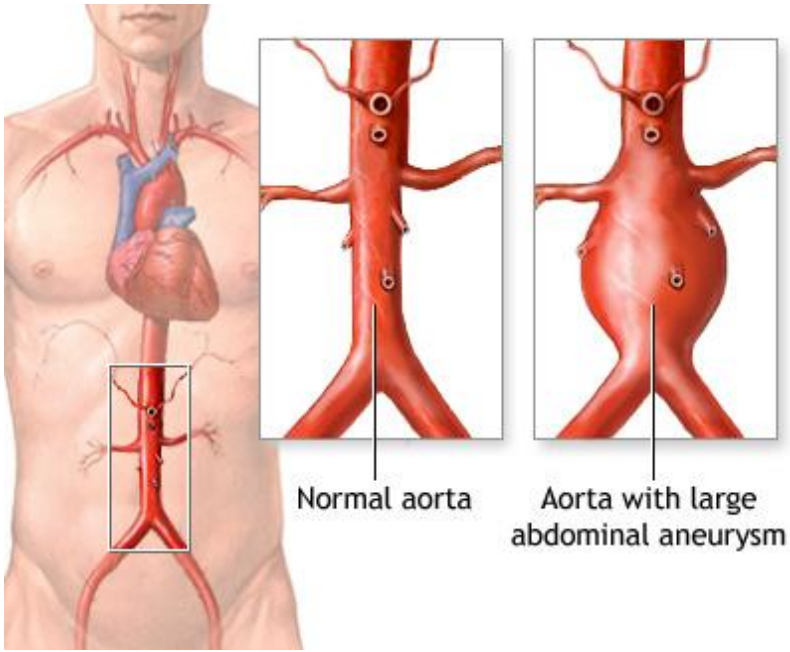
Additional endpoints:

- 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**[1]
- **Strong strategic fit** with ASCVD due to overlapping prescribers
- Progressive disease with increasing risk of **rupture, usually a fatal event**[2]
- **In less than 5 years**, majority of medium-sized AAA grow to threshold for surgical repair[3,4]
- Surgical repair, recommended for large AAA to prevent rupture, is **associated with complications**[5-9]



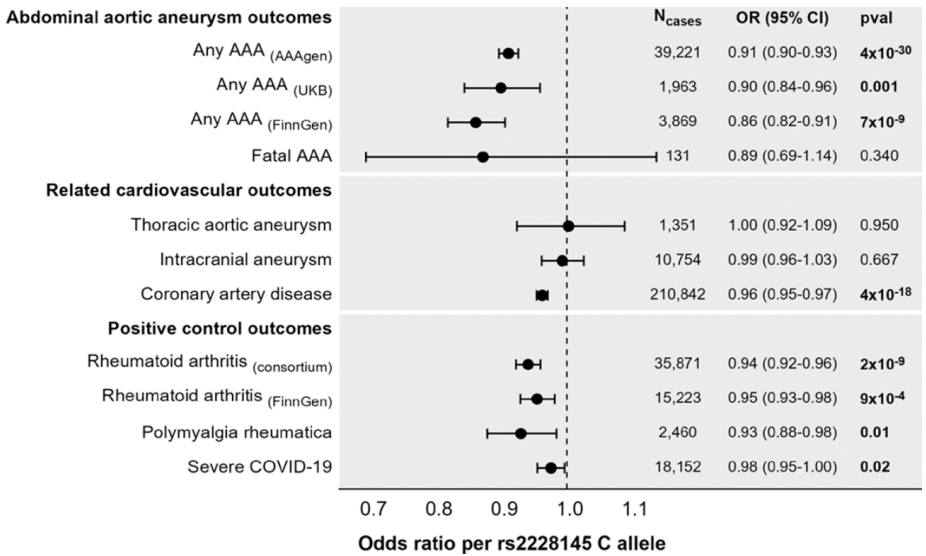
No FDA approved treatment

[1]Stuntz, Cardiology (2016). [2]Golledge et al., Eur Heart J (2023). [3]UKSAT, NEJM (2002). [4]Lederle et al., NEJM (2002). [5]Chaikof et al., J Vasc Surg (2018). [6]Isselbacher et al., Circulation (2022). [7]Schermerhorn et al., NEJM (2008). [8]Yei et al., JAMA Netw Open (2022). [9]Gilmore et al., Circ Cardiovasc Qual Outcomes (2024). Figure from https://medlineplus.gov/ency/article/000162.htm.
AAA: abdominal aortic aneurysm. ASCVD: atherosclerotic cardiovascular disease. HCP: healthcare professional.

Compelling evidence supports IL-6 inhibition to slow AAA growth

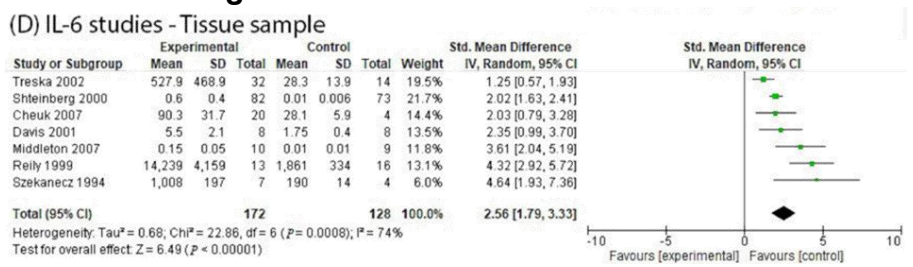
Human genetic evidence

Genetic variant associated with reduction in risk of AAA[1]

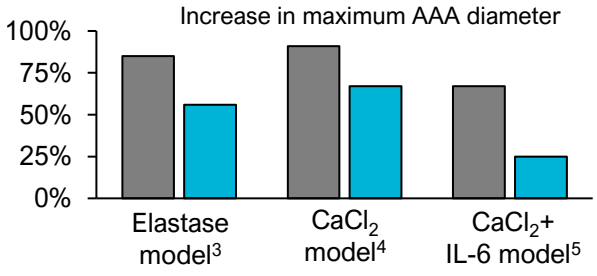


Epidemiological evidence

Higher IL-6 levels associated with AAA[2]



Experimental evidence



Inhibition of IL-6 pathway signaling decreased AAA expansion in multiple preclinical models[3]

[1]Burgess et al., ATVB 2024. [2]Thanigaimani et al., Biomedicine (2022). [3]Kokje et al., Atherosclerosis (2016). Results at day 14. [4]Nishihara et al., PLoS One (2017). Results at day 42. [5]Patel et al., Vasc Endovascular Surg (2023). Results at day 21.
AAA: abdominal aortic aneurysm.

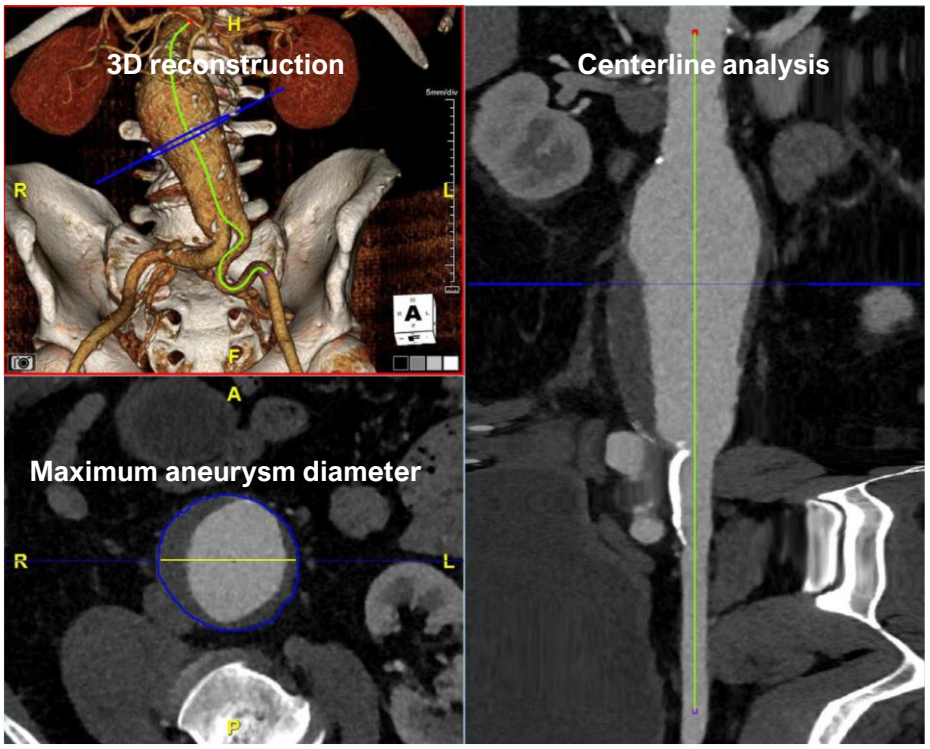
Phase 2 PoC study expected to use imaging to evaluate the ability of pacibekitug to inhibit AAA growth

- Serial imaging is the foundation of clinical care[1]
- 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

CT



[1]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)[1,2]
- ~80%[3] 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)[4]

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[4]

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

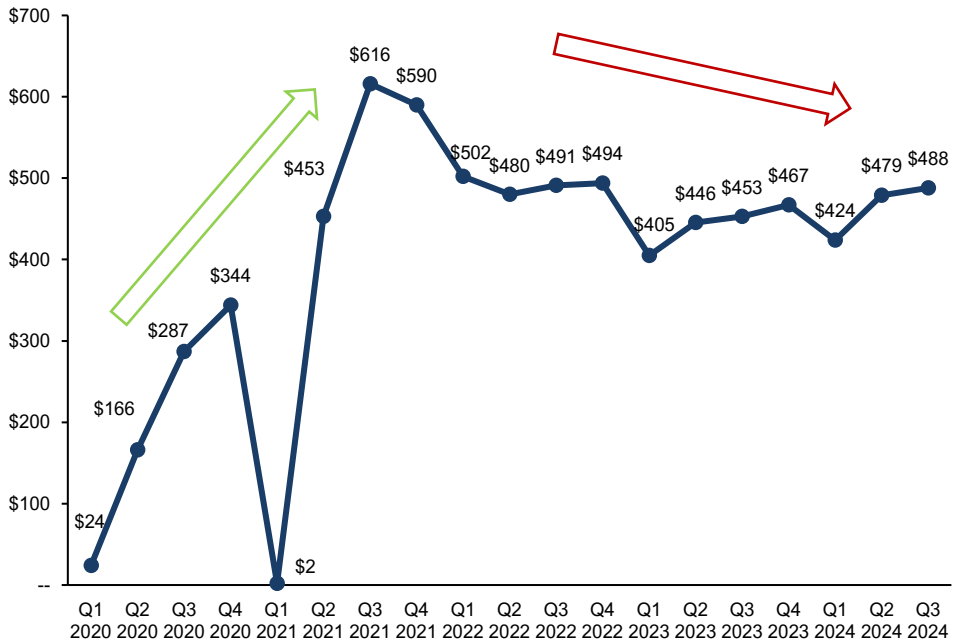
- Deep inhibition of IL-6 pathway observed to date offers potential for durable efficacy across many endpoints
- Existing clinical database supports the potential for a well-tolerated profile at selected doses
- Q8W dosing would allow for a patient-friendly, low burden treatment course

[1]Lazarus, Best Pract. Res. Clin. Endocrinol. Metab. (2012). [2]Bartalena et al., Front. Endocrinol. (2020). [3]Horizon Q3 2022 earnings call. [4]Tourmaline market research.

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)[1]



…believed to be due to real-world experience

1. **Safety issues:** Risk of potentially permanent hearing loss[2]

> **----------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[3,4]

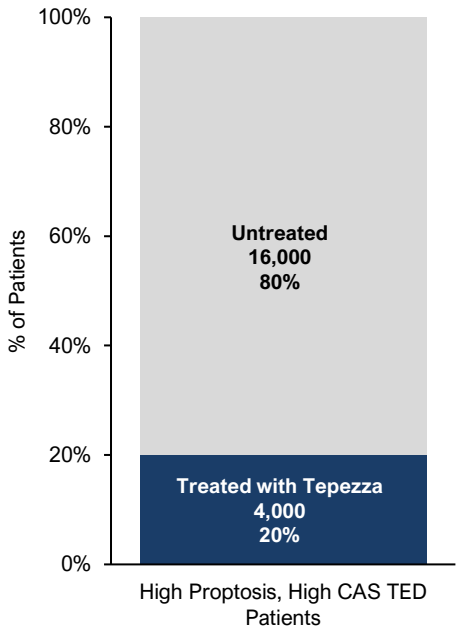
3. **High level of inconvenience & complexity:**
   - IV Q3W (n=8)[2] but limited access to infusion centers[5]
   - Numerous visits and high time commitment (HCPs and patients)[5]
   - Need for serial audiograms, as per label[2,6]
   - Burdensome reimbursement approval process[7]

[1]Horizon and Amgen company reports and filings. [2]TEPEZZA FDA label. [3]Kahaly et al., Thyroid (2021) (ATA 2021 presentation). [4]Rosenblatt et al., Ophthalmic Plast Reconstr Surg (2023). [5]Tourmaline market research. [6]Chow and Silkiss, BMJ Case Rep (2022). [7]Horizon Therapeutics Public Ltd. Co. Q2 2023 Form 10-Q.

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

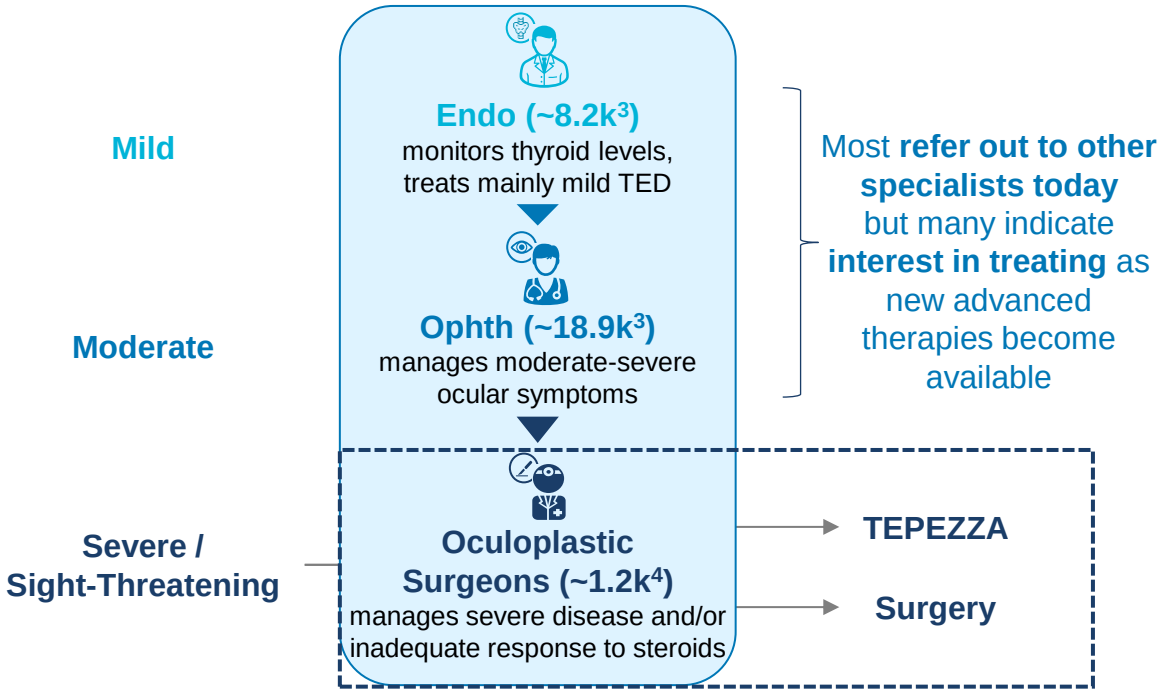
Most TED patients are not receiving TEPEZZA…

TEPEZZA US LTM penetration[1]



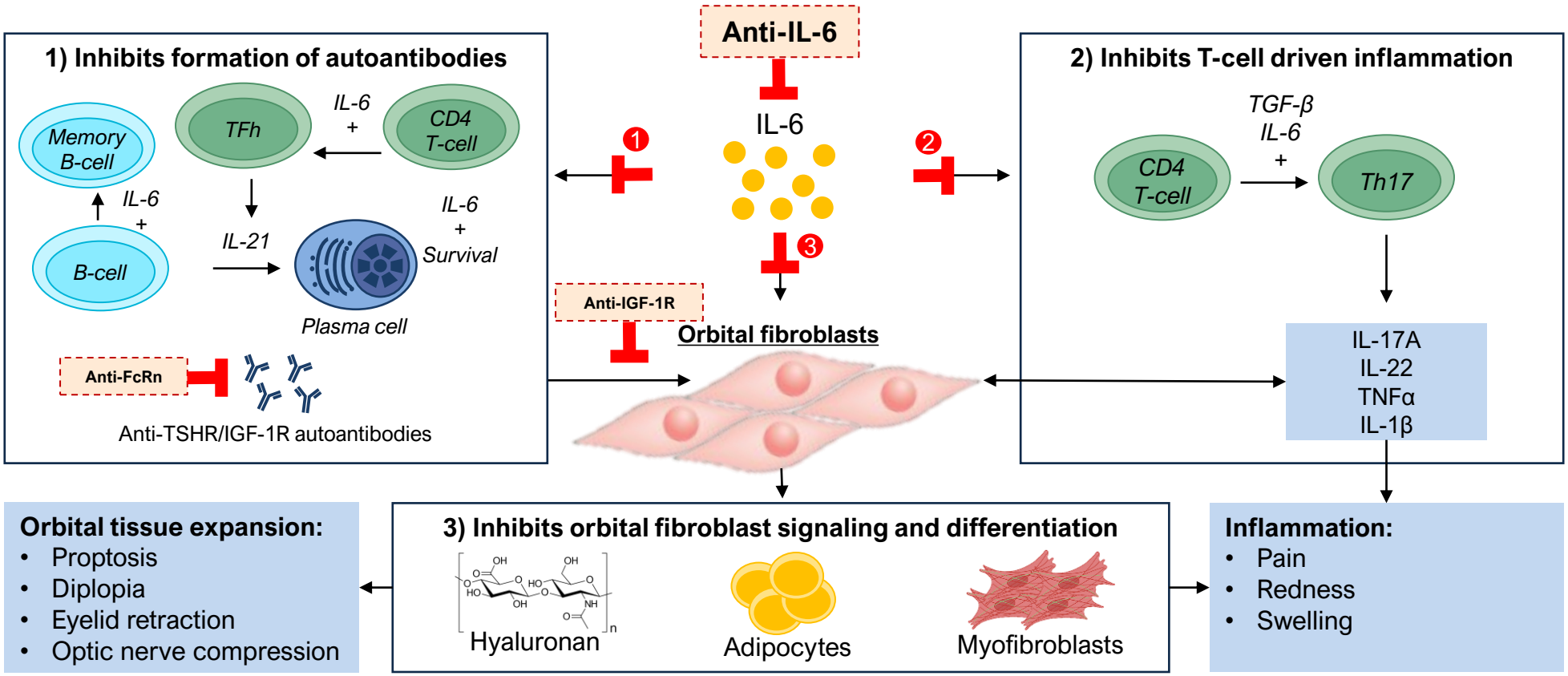
…or only get it relatively late in the treatment journey[2]

Simplified Treatment Journey[2]



[1]Horizon Q3 2022 earnings call; LTM = last twelve months. [2]Tourmaline market research; endo = endocrinologist; ophth = ophthalmologist. [3]AAMC 2022 Physician Specialty Data Report. [4]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
Bennedjai	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
Weighted Mean				**68%**	**72%**	**71%**
Smith 2017 (tepro Phase 2)				**71%**	**69%**	**N/A**
Douglas 2020 (tepro Phase 3)				**83%**	**59%**	**N/A**

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

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Proptosis response rate is generally defined in the data outlined here as a ≥2 mm proptosis improvement in the worse eye at baseline without any worsening in the other eye. CAS response rate is generally defined in the data outlined here as a CAS of 0 or 1. Studies referenced in this table represent investigator-led studies and were not designed with the intent of generating evidence for an approval of tocilizumab or sarilumab in TED. The majority of these studies were not designed with power to detect statistical significance. Retro: retrospective. Obs: observational. Prosp: prospective. RCT: randomized controlled trial. CS: case series. CR: case report. NR: not reported. NS: not significant. CI: clear improvement. Tepro: teprotumumab. Publications available upon request

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

Target product profile in TED*

Study population		• Moderate-to-severe active TED patients
MOA		• **IL-6 inhibition**
Efficacy	Primary endpoint	• **Proptosis**
Efficacy	Secondary endpoints	• **Diplopia, clinical activity score (CAS), inflammation, and lid retraction**
Efficacy	Additional measures	• Lower **rate of relapse** and retreatment • **Rapid time to response** • Lower rate of **surgical intervention**
Safety	Warnings & precautions	• **No anticipated risk of permanent hearing loss** or warnings beyond typical IL-6 safety considerations
Dosing & administration		• **Every 8-week, low volume subcutaneous injection** through pre-filled syringe • Finite dosing

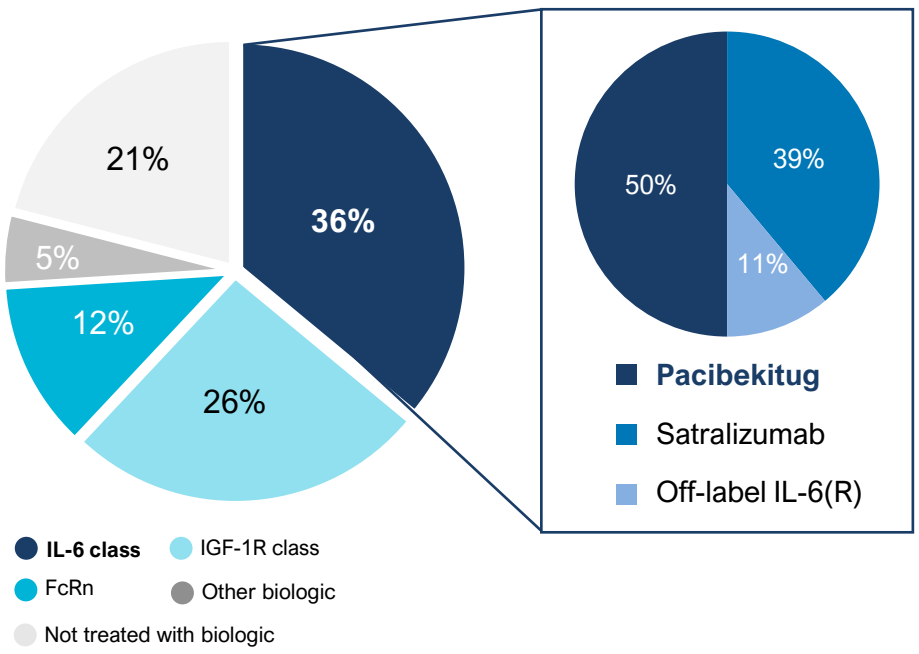
Targeted points of differentiation

- **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**

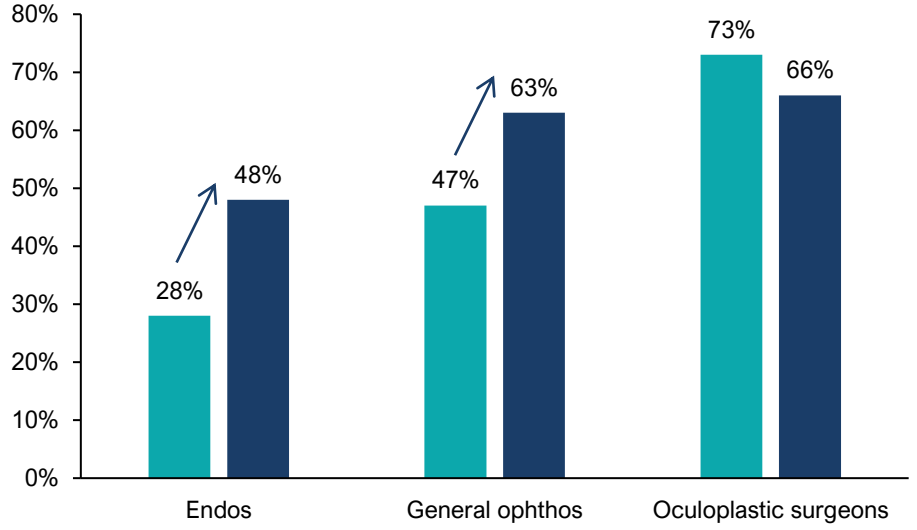
*This target product profile outlines the desired characteristics of pacibekitug in TED. It will be informed by clinical data from Phase 2b and Phase 3 and additional evidence generated from other programs including from the real world. The characteristics presented reflect outcomes that may not be representative of pacibekitug. The results of past clinical trials may not be indicative of future results, and the results of future or ongoing clinical trials may not demonstrate some or any of the characteristics presented.
MOA: mechanism of action. QoL: quality of life. TED: thyroid eye disease. SC: subcutaneous

…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[1]



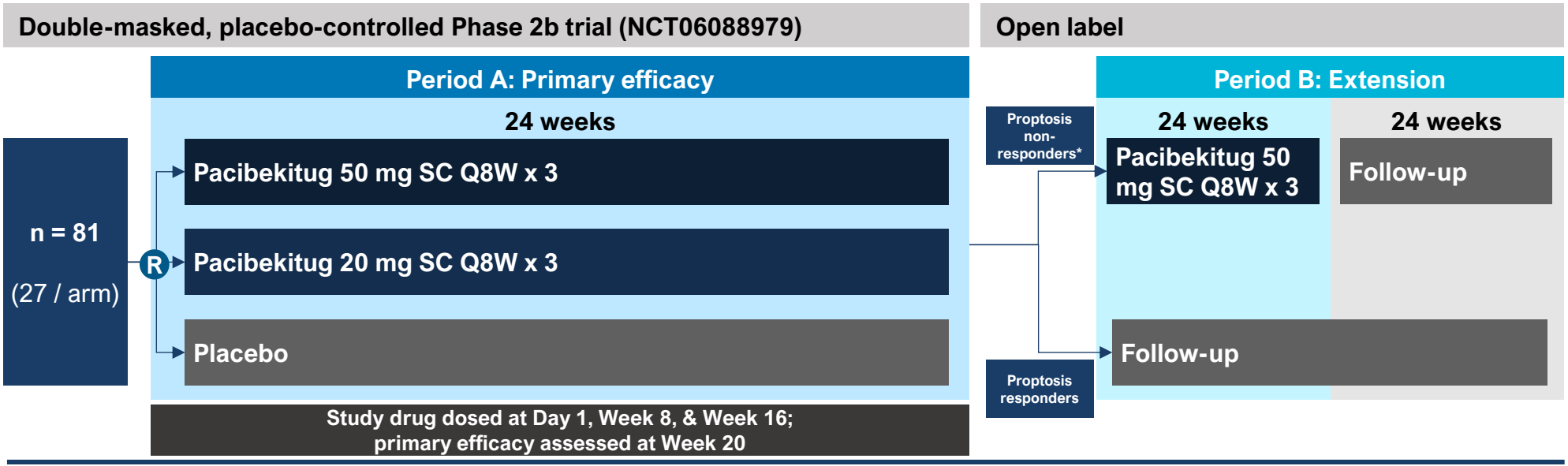
Impact on Rx if SC therapies are available[1]



- 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

[1]In a masked survey of future potential product entrants - HCP Quant Research with N = 60 General Ophthos, N = 40 Endos and N = 40 Oculoplastic Surgeons (February 2024). FcRn: neonatal fragment crystallizable receptor. IGF-1R: insulin-like growth factor 1 receptor. IL-6: interleukin-6. Rx: prescriptions. SC: subcutaneous. TED: thyroid eye disease.

spiriTED pivotal trial in first-line TED



Study population:
- Moderate-to-severe TED, with proptosis ≥ 3mm above normal (based on race and gender)
- Active phase, with symptom onset ≤ 15 months, CAS ≥ 4 and positive TSI
- First-line setting, with cap on prior corticosteroid use (< 1g 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	TRANQUILITY Phase 2 topline data	Q2 2025
	AAA	Phase 2 trial start	Post-TRANQUILITY topline data
Autoimmune disease	TED	spiriTED Phase 2b topline data	H2 2025

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