TOURMALINE

Corporate Overview

October 2024

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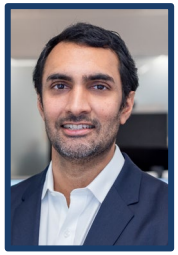
Our mission

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

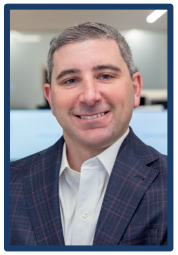
Experienced leadership team

Management Team



Sandeep Kulkarni, MD
Co-founder and Chief Executive Officer

Yung Chyung, MD
Chief Medical 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
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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

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 strategic paths to significant value creation: (1) FcRn+ and (2) cardiovascular inflammation

A late-stage clinical company: pivotal Phase 2b spiriTED TED trial and Phase 2 TRANQUILITY CV trial ongoing, pivotal Phase 3 TED trial also expected to commence in 2H 2024

Accomplished leadership team: extensive experience developing and commercializing antibodies for immune and inflammatory diseases

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

We are in an IL-6 renaissance

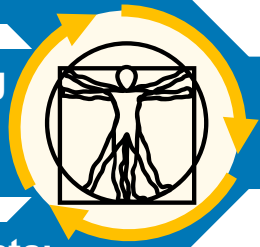
First wave of IL-6 inhibition: focus on rheumatology

2010 – 2023

- RA
- GCA
- sJIA
- CRS
- pJIA
- NMOSD
- MCD
- SSc-ILD
- COVID19
- PMR

Sources of emerging insights:

- Sustained academic and investigator enthusiasm for IL-6
- Hypothesis-generating success from off-label experimentation
- Human translational data: genetic, biomarker, epidemiologic



Second wave of IL-6 Inhibition: driven by emerging insights

2024: Late-stage programs

- AE
- AMI
- ASCVD
- DMD
- HFpEF
- MOGAD
- TED
- UME

2024+: Large body of potential indications

Cardio:	AAA	AM
	Stroke	
Derm:	BP	PV
Endo:	Graves'	
GI:	CD	UC
Hem:	ITP	TTP
Neph:	IgAN	MN
Neuro:	CIDP	IBM
	MG	MS
Ophth:	DME	NIU
Resp:	CHP	IPF
	PAP	Sarcoid
Rheum:	AAV	IgG4-RD
	SjS	

Tourmaline-Selected Indications Key

- Cardiovascular Inflammation
- FcRn+

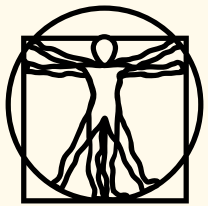
AAA: Abdominal aortic aneurysm; AAV: ANCA-associated vasculitis; AE: Autoimmune encephalitis; AM: Acute myocarditis; AMI: Acute myocardial infarction; ASCVD: Atherosclerotic cardiovascular disease; BP: Bullous pemphigoid; CD: Crohn's disease; CHP: Chronic hypersensitivity pneumonitis; CIDP: Chronic inflammatory demyelinating polyneuropathy; COVID19: Coronavirus disease 2019; CRS: Cytokine release syndrome; DMD: Duchenne muscular dystrophy; DME: Diabetic macular edema; GCA: Giant cell arteritis; FcRn: neonatal Fc receptor; HFpEF: Heart failure with preserved ejection fraction; IBM: Inclusion body myositis; IgAN: IgA nephropathy; IgG4-RD: IgG4 related disease; IPF: Idiopathic pulmonary fibrosis; ITP: Idiopathic thrombocytopenic purpura; MCD: Multicentric castleman's disease; MG: Myasthenia gravis; MN: Membranous nephropathy; MOGAD: Myelin oligodendrocyte glycoprotein antibody-associated disease; MS: Multiple sclerosis; NIU: Non-infectious uveitis; NMOSD: Neuromyelitis optica spectrum disorder; PAP: Pulmonary alveolar proteinosis; pJIA: Polyarticular juvenile idiopathic arthritis; PMR: Polymyalgia rheumatica; PV: Pemphigus vulgaris; RA: Rheumatoid arthritis; Sarcoid: Sarcoidosis; sJIA: Systemic juvenile idiopathic arthritis; SjS: Sjögren's syndrome; SSc-ILD: Systemic sclerosis interstitial lung disease; TED: Thyroid eye disease; TTP: Thrombotic thrombocytopenic purpura; UC: Ulcerative colitis; UME: Uveitic macular edema

Pacibekitug: an anti-IL-6 antibody with the potential to deliver significant value to patients

Pacibekitug attributes observed to date	Potential value to patients
Long-acting with terminal half-life of ~7 weeks[1]	Dosing every 8 weeks[5] or quarterly[6]
>90% pathway inhibition after single 10mg dose[2]	Fast, deep, and durable impact across diseases
Fully human with ADAs in only 0.5% of pt[3]	Durable benefit without need to increase dose
High affinity to IL-6[4]	Volume of ≤1ml for SC injection[5]
Existing data from approximately 450 study participants[1]	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 assessed based on data from prior Phase 2 trials. [6]To be evaluated in CV Phase 2 trial.

Two strategic 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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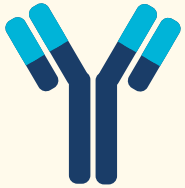


Pacibekitug

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

FcRn+

Pacibekitug has the potential to be a superior therapy for a wide range of autoantibody-driven diseases vs. FcRn inhibitors

Key expected readouts

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

Cardiovascular Inflammation

Pacibekitug has the potential to transform the care of high-risk patients by targeting key inflammatory pathways driving cardiovascular disease

Key expected readouts

- ❑ **H1 2025:** TRANQUILITY Phase 2 topline data
- ➢ **2025:** Zilti ASCVD in CKD Phase 3 (ZEUS) topline data
- ➢ **2026:** Zilti AMI Phase 3 (ARTEMIS) 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; Zilti: ziltivekimab

Clinical development plan for pacibekitug

Strategy	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Expected key milestones
FcRn+	Thyroid Eye Disease (TED)	spiriTED				Phase 2b topline data expected in 2025
						Phase 3 expected to begin in H2 2024
Cardiovascular Inflammation	Atherosclerotic Cardiovascular Disease (ASCVD)	TRANQUILITY				Phase 2 topline data expected in H1 2025

Expect to announce at least one additional indication in 2024

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

FcRn+

FcRn inhibition has garnered substantial attention to date, however significant unmet need persists

What is FcRn?[1]

- Neonatal Fc receptor (FcRn) inhibition observed to lower IgG antibodies
- Mechanism relevant in disorders mediated by pathogenic IgG autoantibodies
- Two anti-FcRn therapies approved for myasthenia gravis with additional supportive data in CIDP, RA, and TED[2,3,4]

FcRn market adoption

- First approved FcRn inhibitor annualizing ~$1.5B sales in 2nd year of launch in MG[5]
- FcRn companies account for >$30B in market capitalization[6]

Key limitations of FcRn inhibition[7]

- **Efficacy limitations:** incomplete clinical response observed
- **Lack of durable efficacy:** clinical worsening occurs soon after cessation of therapy
- **High burden dosing profile:** burdensome weekly or biweekly IV or high-volume SC infusions/injections
- **Unknown long-term safety profile:** uncertain rate of infectious or other complications from sustained non-specific reduction of total IgG

[1]Pyzik et al., Nat Rev Immunol (2023). [2]Chronic inflammatory demyelinating polyneuropathy (CIDP): ARGX, "argenx Reports Posit Topline Data from ADHERE study..." July 17, 2023. [3]Rheumatoid arthritis (RA): Taylor et al., presentation at ACR Convergence (2023). [4]Thyroid eye disease (TED): Kahaly et al., J Clin Endocrinol Metab (2023). [5]ARGX company reports and filings. [6]FactSet as of 12/29/23; assumes Momenta acquisition for $6.5B, UCB market capitalization not included. [7]VYVGART, VYVGART HYTRULO, and RYSTIGGO FDA labels.

Pacibekitug has broad potential beyond autoantibody reduction

An FcRn+ opportunity

Modes of action for IL-6 inhibition[1,2]

IL-6 inhibition impacts:

- Pathogenic B-cell and plasma cell proliferation
- Pathogenic Th17 and Tfh cell proliferation and differentiation
- Acute phase proinflammatory signaling
- Circulation of pathogenic autoantibodies

Potential benefits of IL-6 inhibition versus FcRn inhibition

	IL-6 inhibition[1,2,3]	FcRn inhibition[4,5,6]
Autoantibody reductions	✓	✓
Inhibition of autoantibody production	✓	✗
Anti-inflammatory effects beyond autoantibody reduction	✓	✗
Durability of effect	✓	✗
Low administration burden	✓	✗
Favorable long-term safety profile observed to date	✓	?

[1]Cabezas et al., Front Immunol (2022). [2]Dienz et al., J Exp Med (2009). [3]Tourmaline PK/PD modelling. [4]Howard et al., Lancet Neurol (2021). [5]Patel and Bussel, J Allergy Clin Immunol (2020). [6]VYVGART, VYVGART HYTRULO, and RYSTIGGO FDA labels.

TED: our beachhead indication designed to validate pacibekitug's FcRn+ 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**

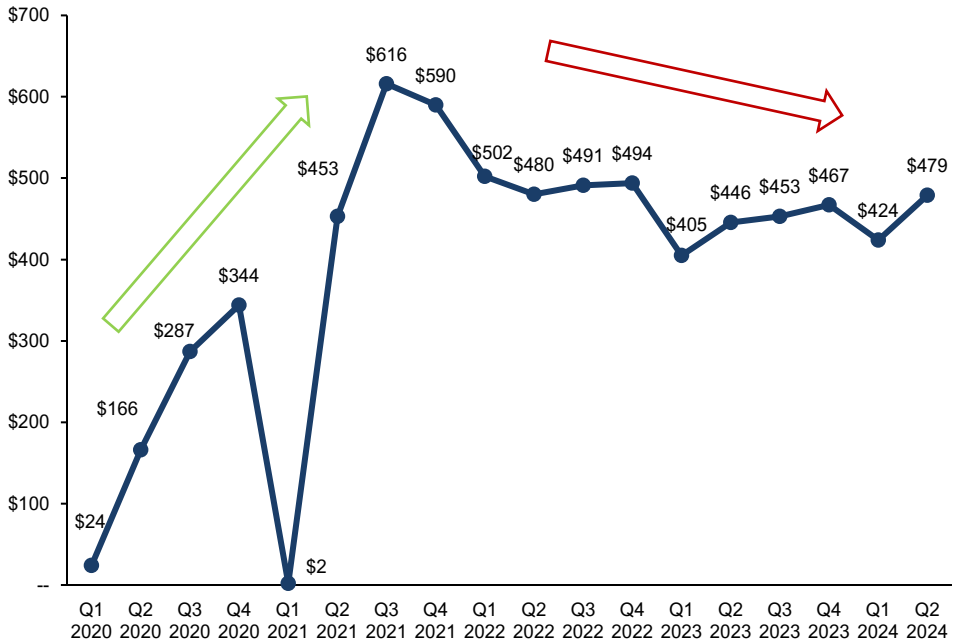
- Deep inhibition of IL-6 pathway observed to date offers potential for durable efficacy across many endpoints
- Existing clinical database supports the potential for a well-tolerated profile at selected doses
- Q8W dosing would allow for a patient-friendly, low burden treatment course

[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]

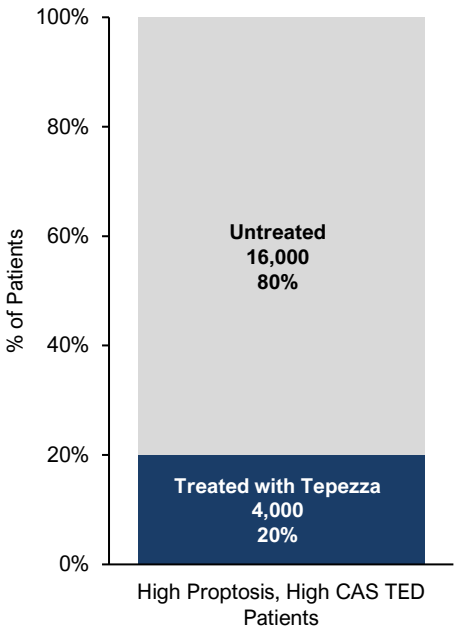
3. **High level of inconvenience & complexity:**
   - IV Q3W (n=8)[2] but limited access to infusion centers[5]
   - Numerous visits and high time commitment (HCPs and patients)[5]
   - Need for serial audiograms, as per label[2,6]
   - Burdensome reimbursement approval process[7]

[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

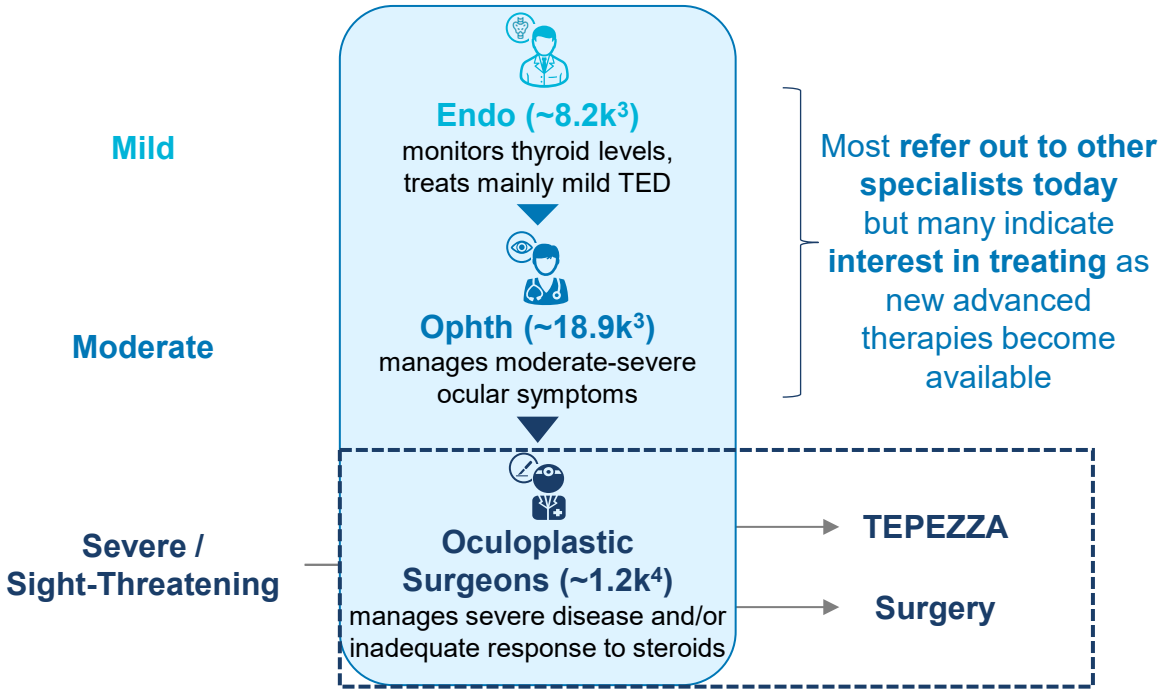
Most TED patients are not receiving TEPEZZA…

TEPEZZA US LTM penetration[1]



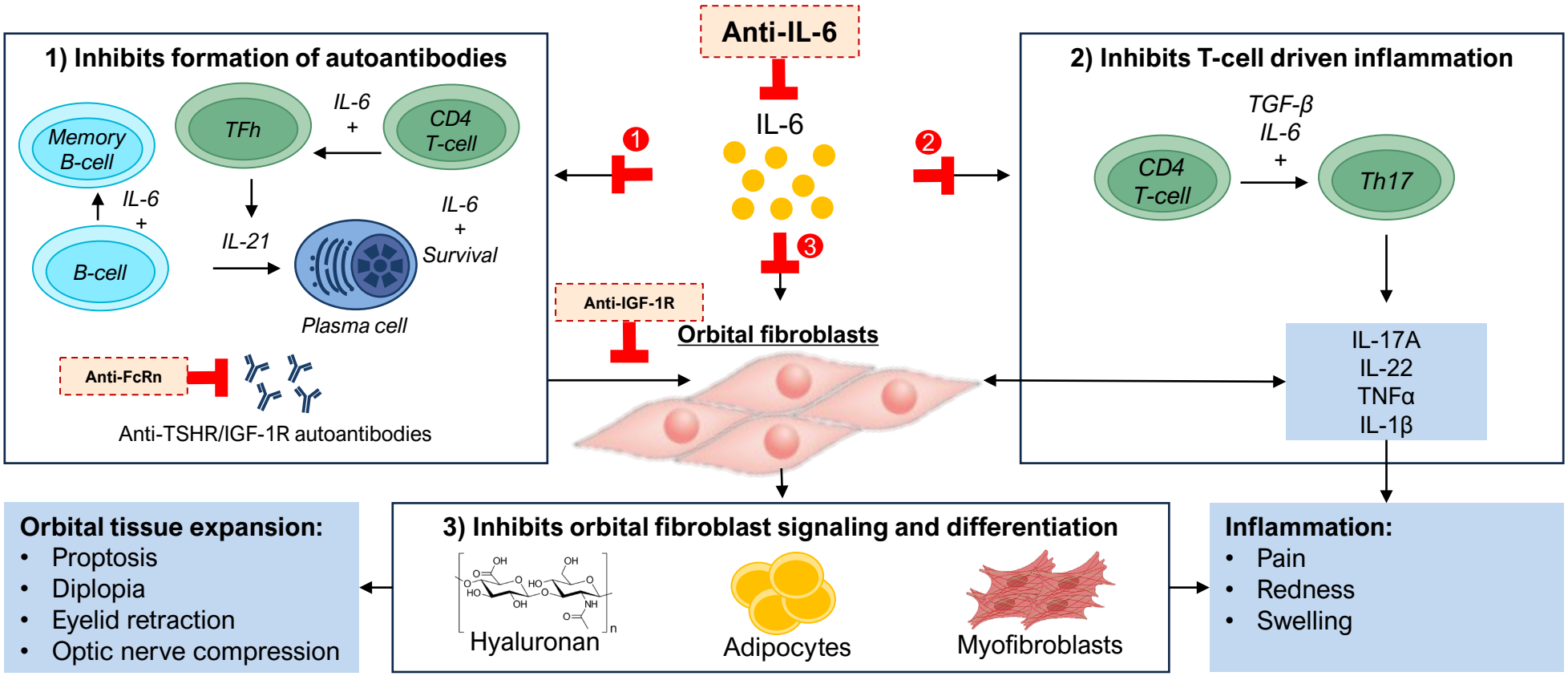
…or only get it relatively late in the treatment journey[2]

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

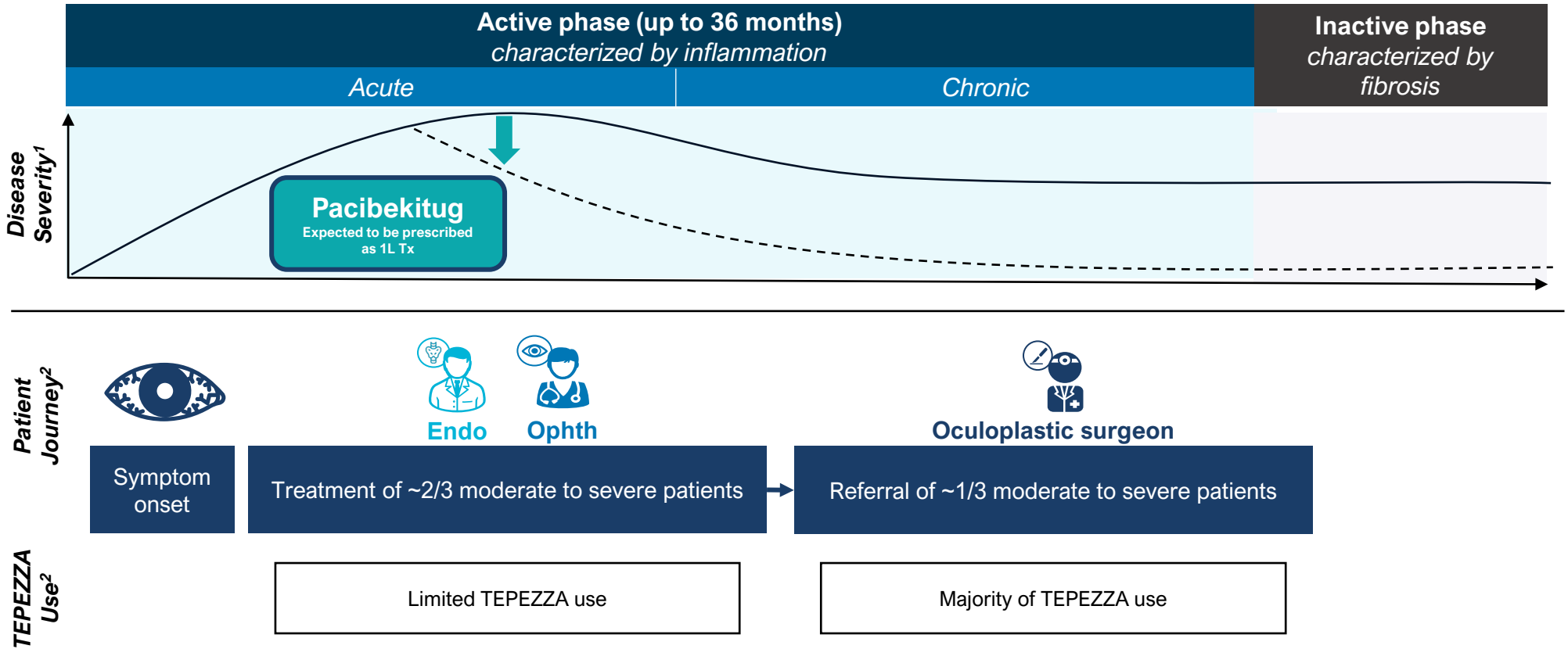
Market research indicates pacibekitug's potential to become an optimal first-line therapy and market leader in TED

Potential target profile of pacibekitug

Deep & broad efficacy	• Meaningful reduction of proptosis • Important improvement of CAS and diplopia
Durable	• Inhibition of production of anti-TSHR auto-antibodies • Durable response, in part due to low immunogenicity
Well-tolerated	• Well-tolerated safety profile, manageable with routine monitoring • Lack of permanent or irreversible side effects
Patient-friendly	• SC, ≤1ml injections, every 8 weeks • Finite treatment for most of patients with flexibility where needed

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.

Pacibekitug offers the potential to stop disease progression in the inflammatory active phase

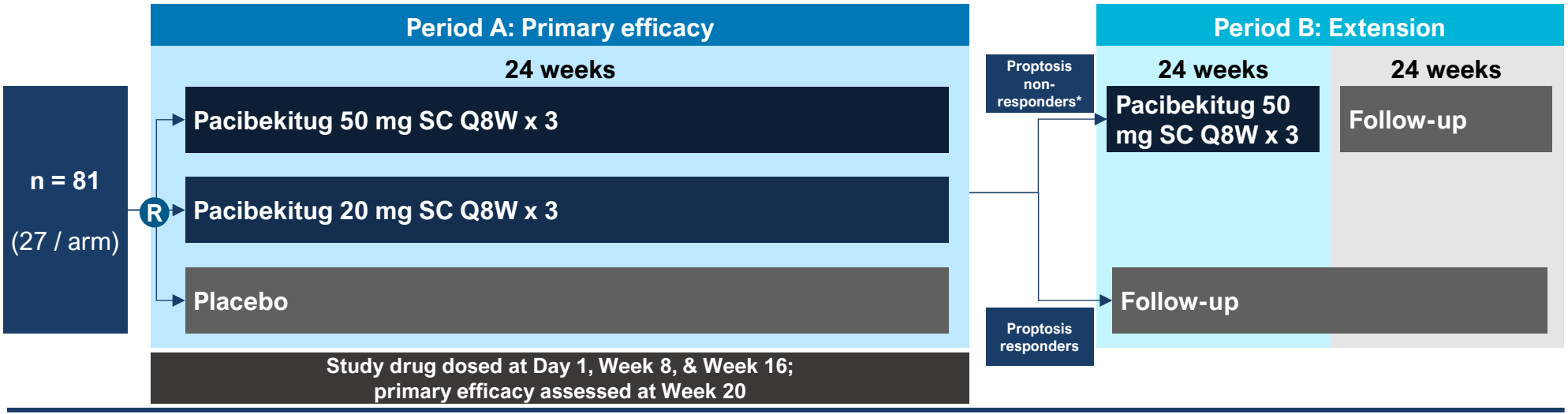


[1]Adapted from Bartley, Arch Ophthalmol. (2011). [2]Tourmaline market research.

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 ≥ 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

Cardiovascular Inflammation

Reducing inflammation: the next frontier in CV diseases

IL-6 driven inflammation has increasingly been validated as a critical and modifiable risk factor driving residual cardiovascular risk

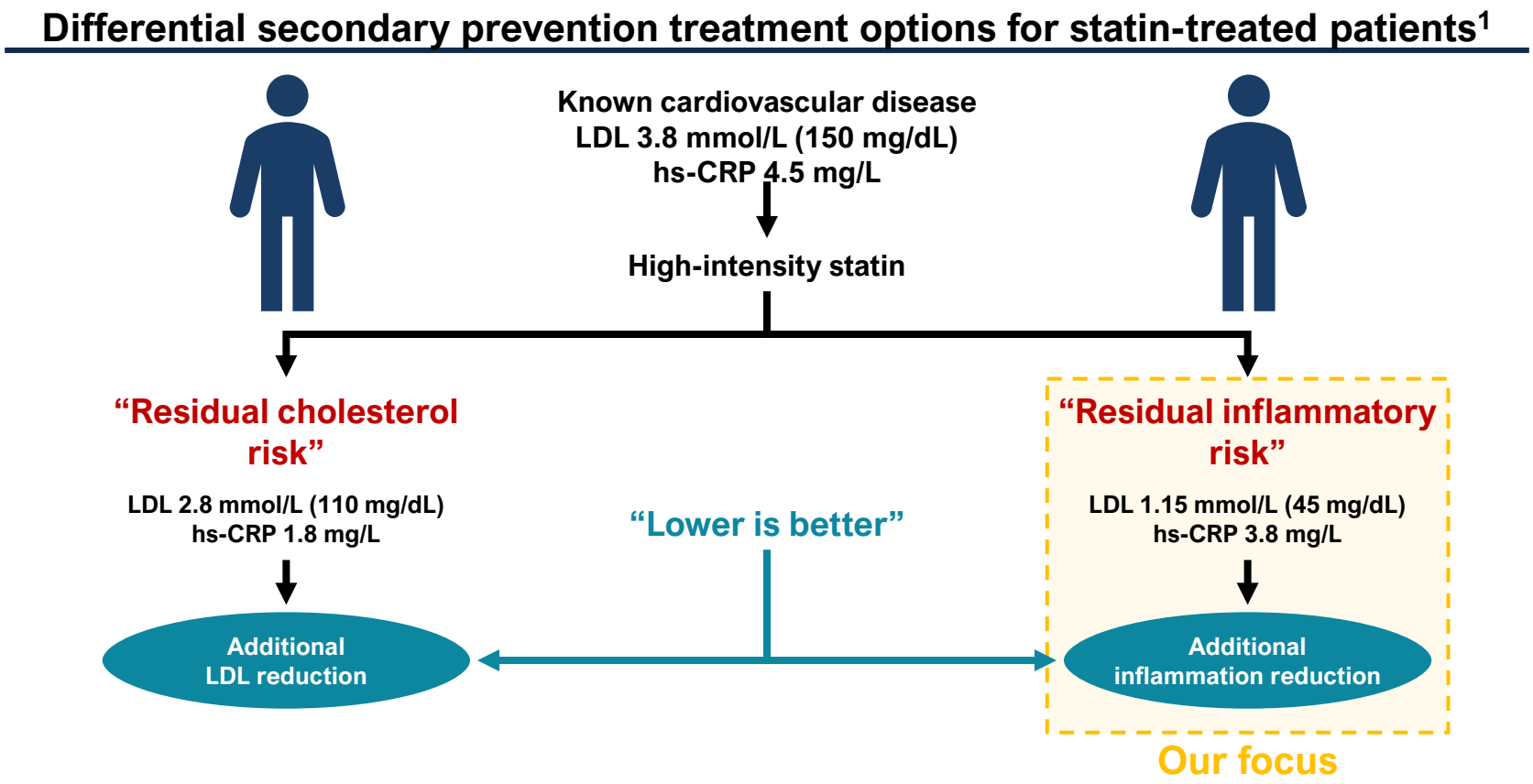
The potential of IL-6 inhibition spans a broad range of cardiovascular indications, affecting tens of millions of patients globally

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, and Tourmaline is well-positioned to capitalize on emerging clinical enthusiasm

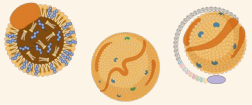
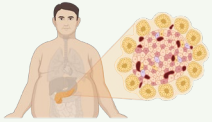
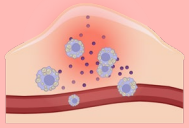
Pacibekitug's potentially best-in-class profile, including quarterly subcutaneous administration, is being evaluated in the Phase 2 TRANQUILITY study and is anticipated to be Phase 3-ready in 2025

Many CV disease patients have residual inflammatory risk



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

Significant unmet need for targeted anti-inflammatory therapies for cardiovascular diseases

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 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.

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

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]

[1] *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*
[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

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

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; Decoroso 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

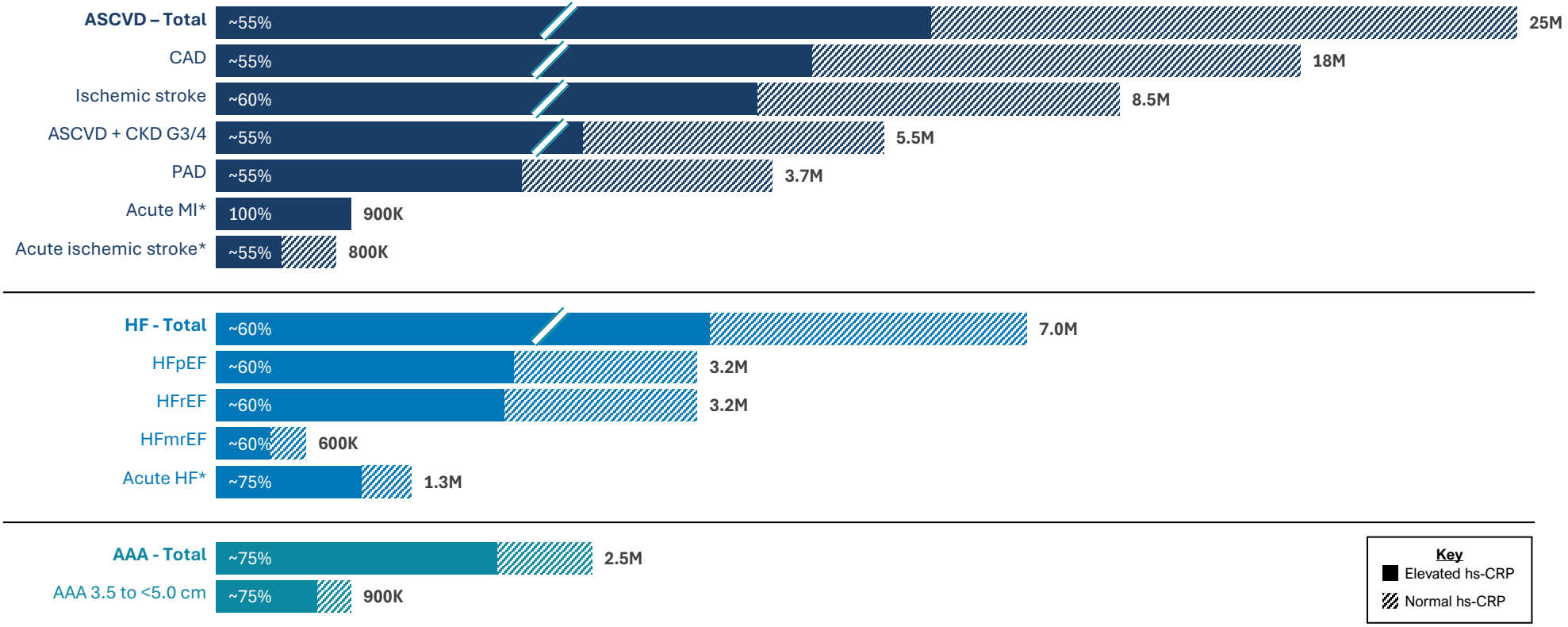
Associations of genetically predicted IL-6 signaling with cardiovascular disease risk across population subgroups

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*]

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



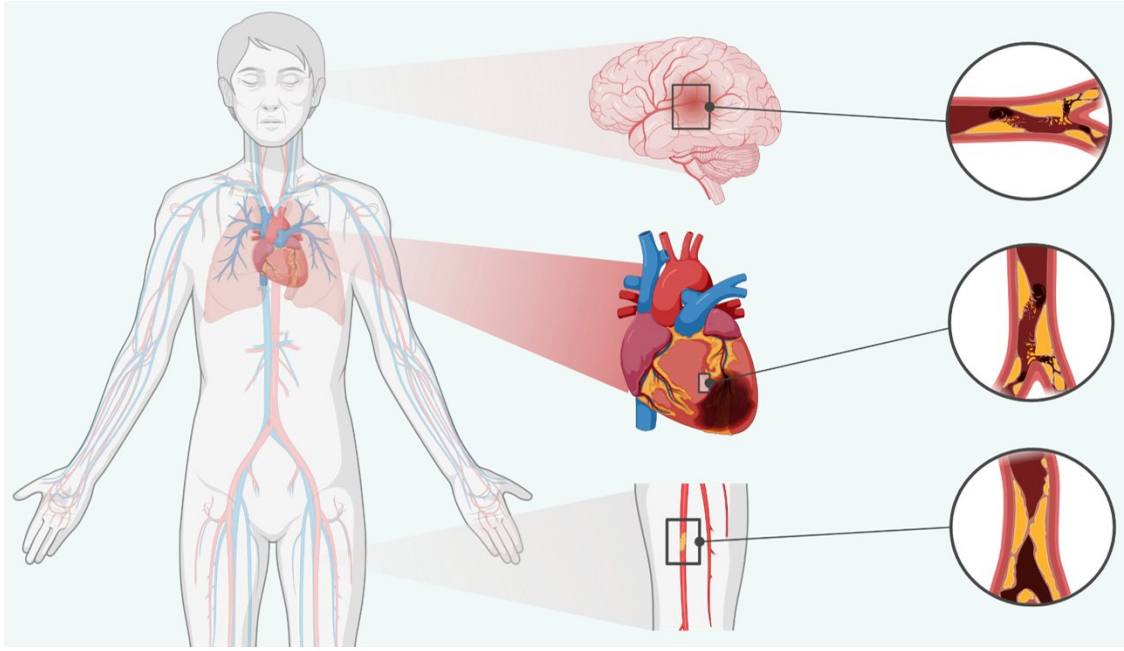
[1]Publications available upon request. *Annual incidence

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

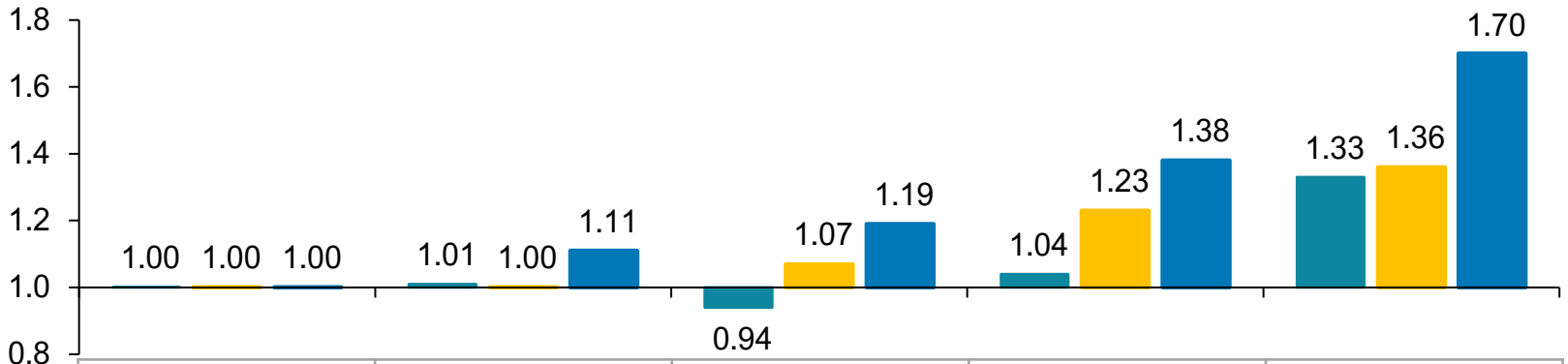
"Probability of success for drug mechanisms with genetic support is 2.6 times greater than those without."[18]

[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).

Analysis of CANTOS implicates IL-6 as a key ASCVD risk factor

Greater IL-6 pathway inhibition associated with greater CV benefit

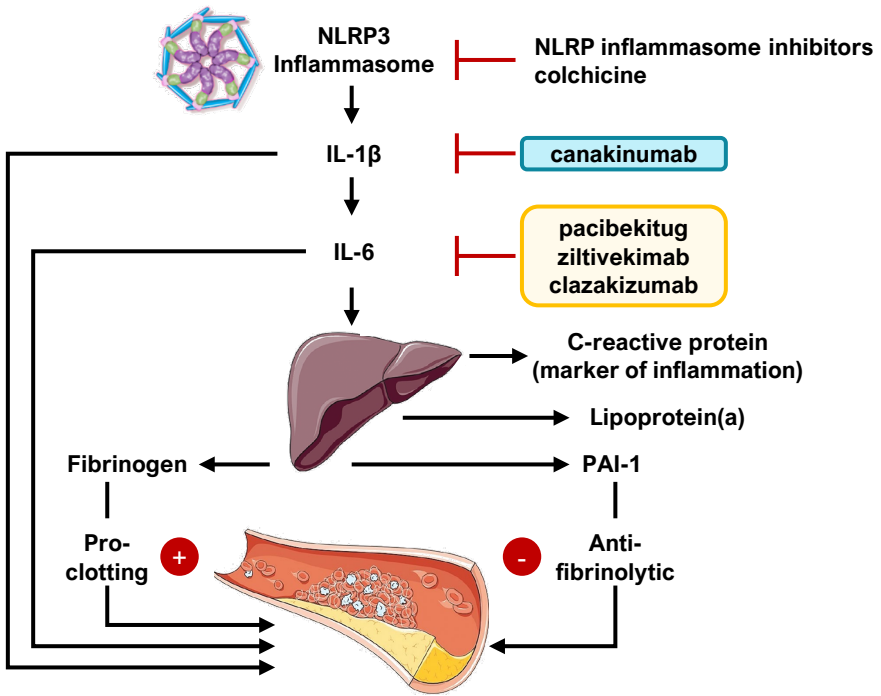
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) Trial Design[1]

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

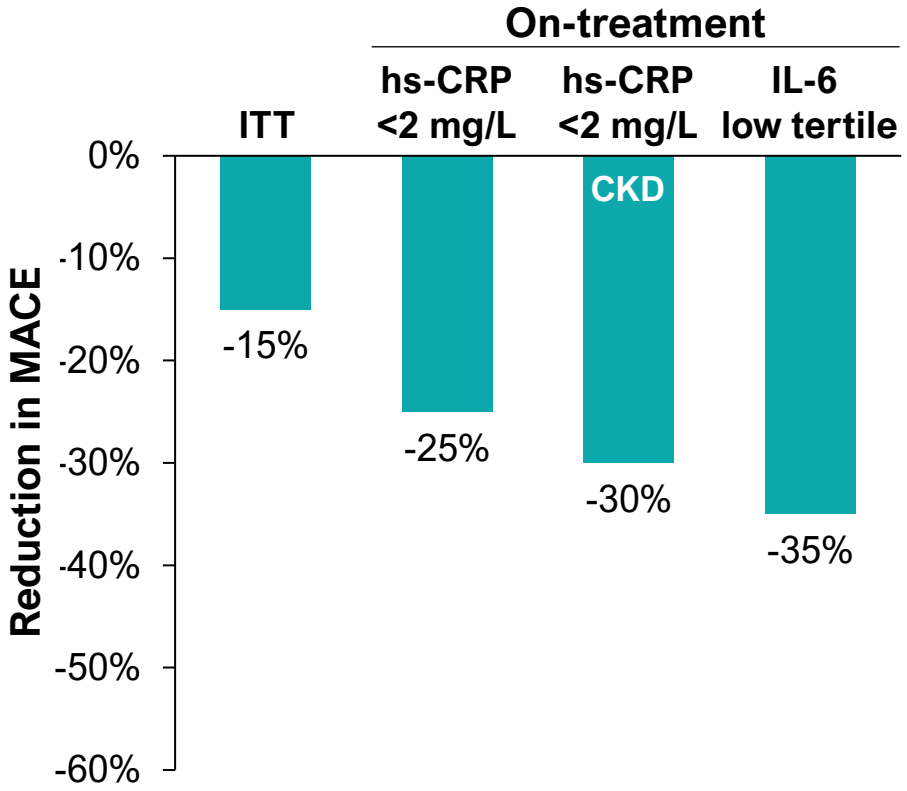
Primary endpoint:
Time to the first occurrence of MACE (CV death, non-fatal MI, or non-fatal stroke)

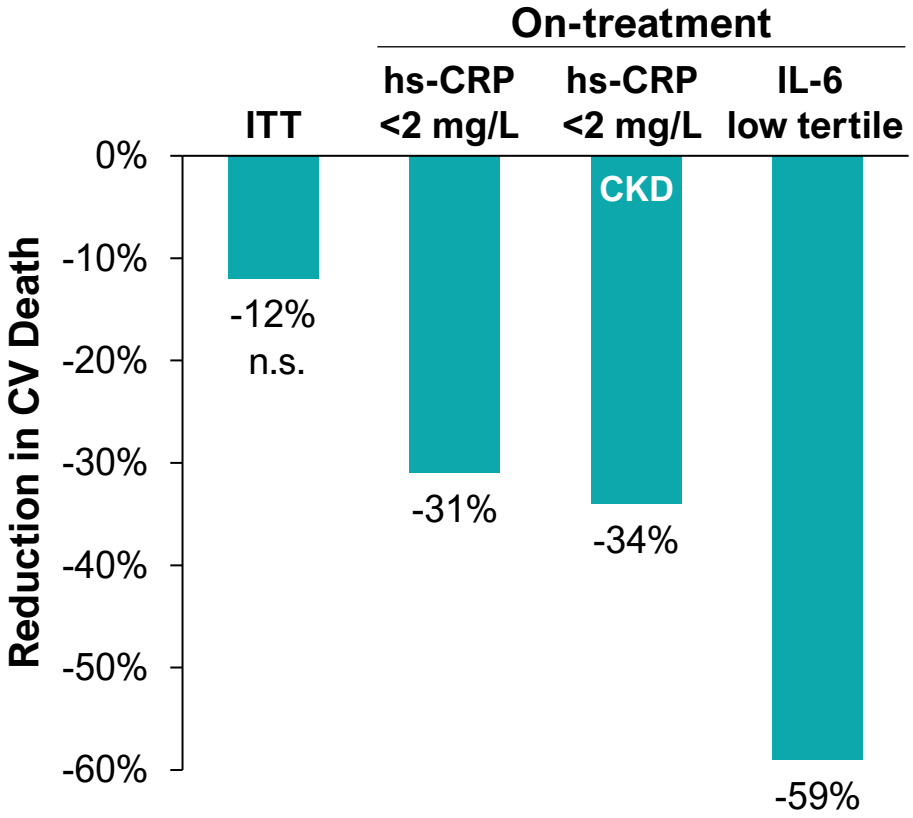
IL-1β is upstream of IL-6[2]



[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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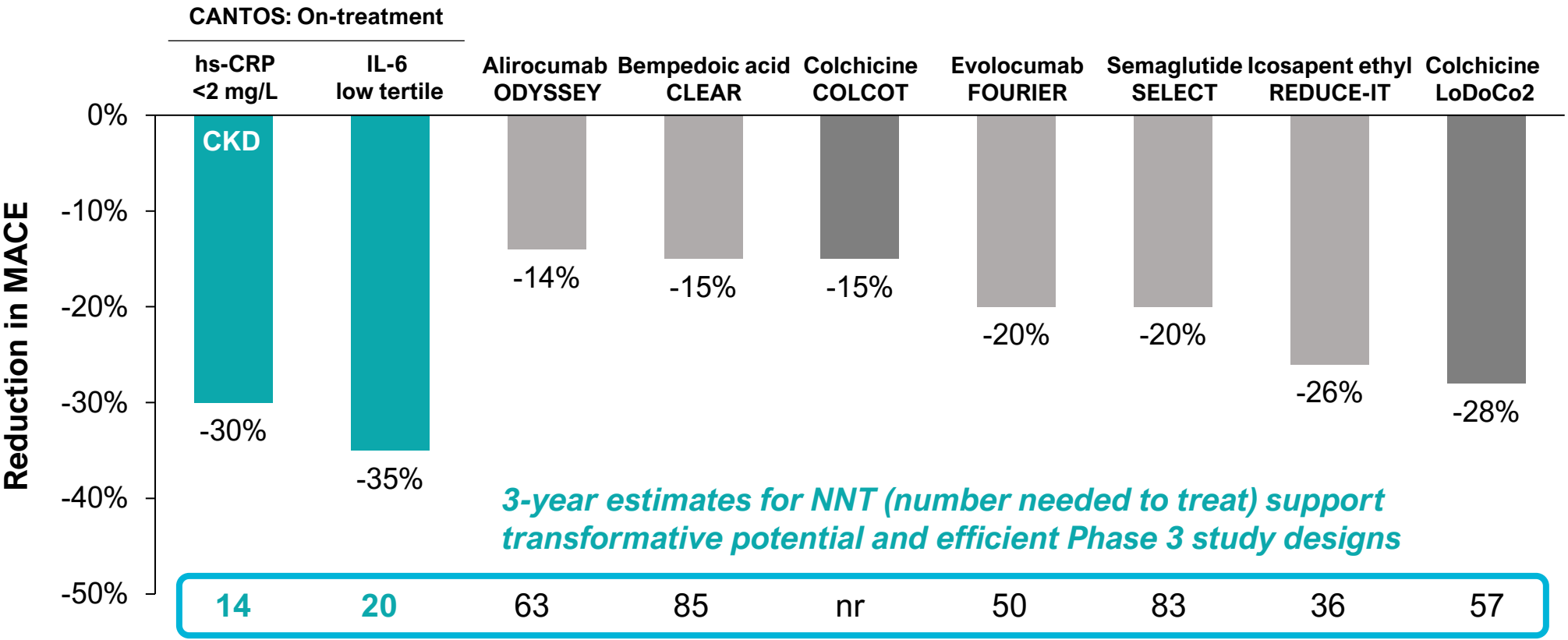
Reduction in MACE shown as 1-Hazard Ratio. ITT: intent to treat. MACE: major adverse cardiovascular events including CV death, myocardial infarction (MI), stroke. n.s.: not statistically significant. ITT CANTOS analysis presents data for 150mg dose group; values for CANTOS subanalyses combine all doses (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).

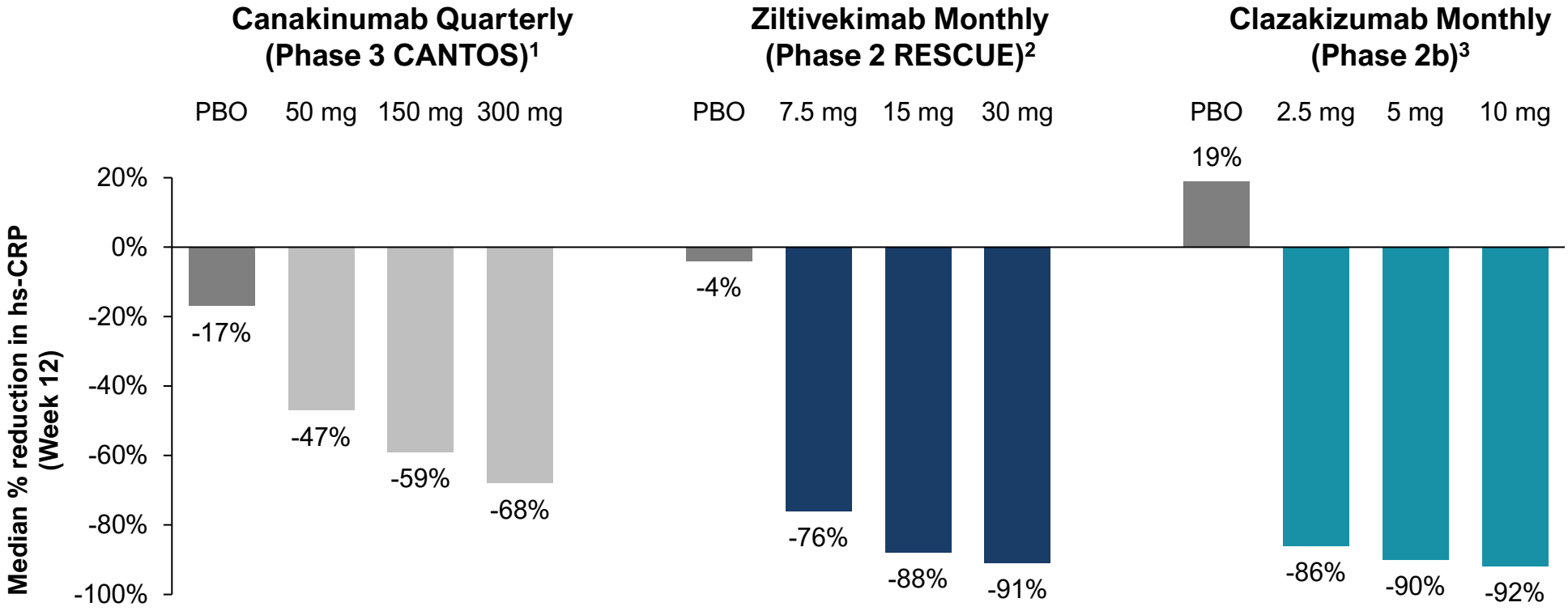
Lessons from canakinumab (anti-IL-1β mAb): Robust inhibition of IL-6 pathway has transformative potential in ASCVD



TOURMALINE

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

[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 24 or 48 hrs

1:1

- Ziltivekimab loading dose 1 followed by dose 2 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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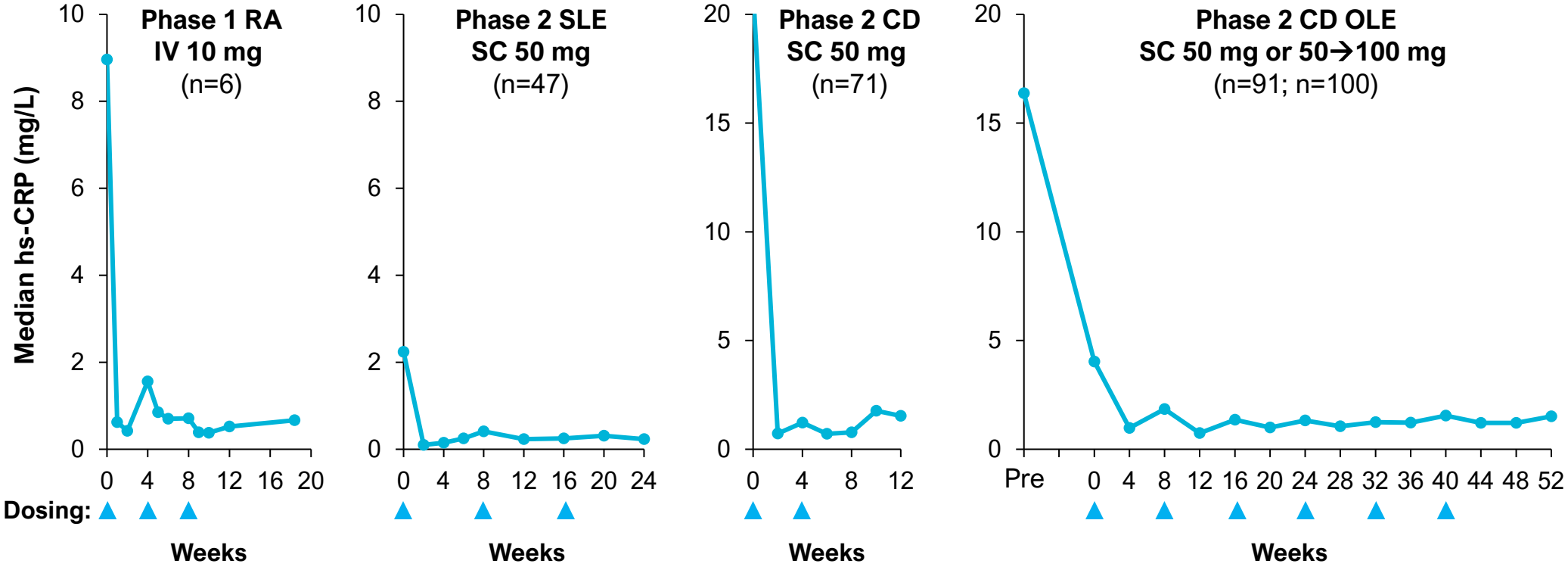
The timing of clinical trial milestones are subject to change.
ASCVD: atherosclerotic cardiovascular disease. CKD: chronic kidney disease. CVOT: cardiovascular outcome trial. ESKD: End Stage Kidney Disease. HFpEF: heart failure with preserved ejection fraction. MACE: major adverse cardiovascular event. 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.

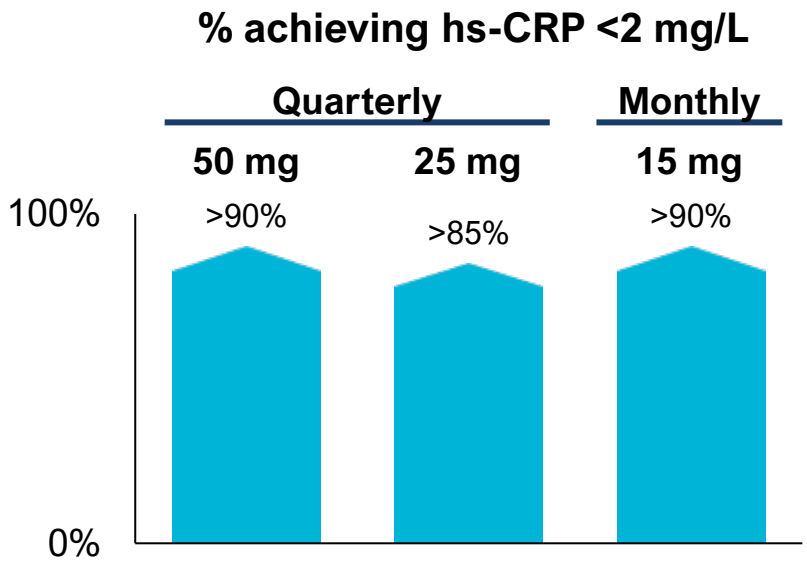
Pacibekitug achieved robust and durable suppression of CRP in patients with high-grade inflammatory autoimmune disorders

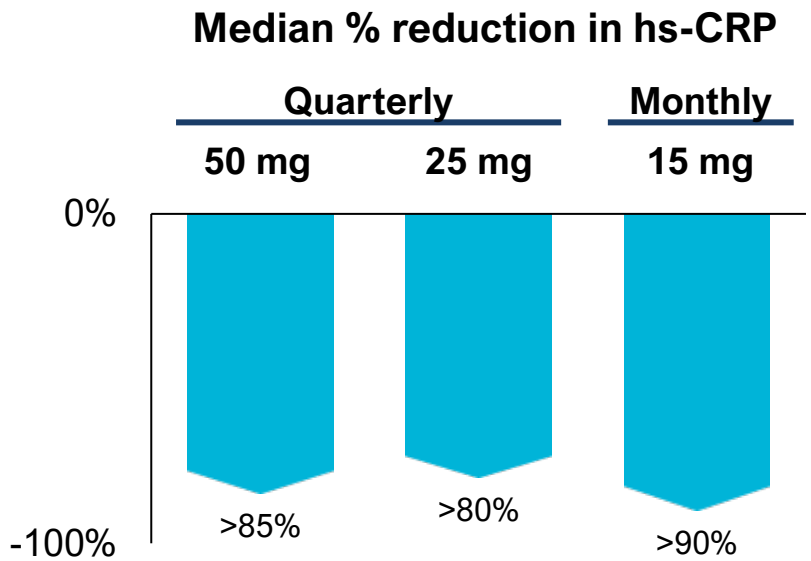


CD: Crohn's disease, OLE: open-label extension, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus. Rheumatoid arthritis: B0151002 study report. Table 14.4.7.1.1. Median baseline CRP 9.0 mg/L. Key eligibility: active disease, background methotrexate. Crohn's disease: B0151003 study report. Table 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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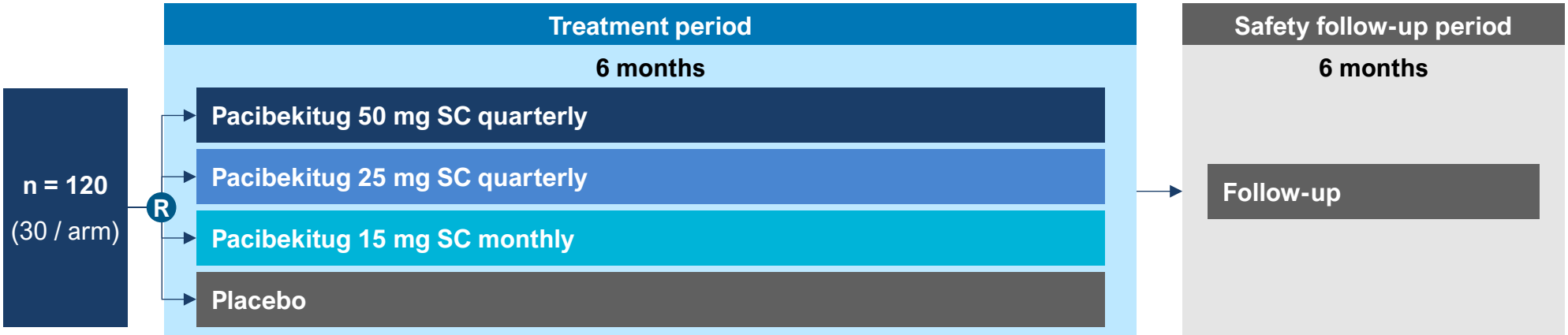
ASCVD: atherosclerotic cardiovascular disease, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, CD: Crohn's disease. The PK and PK/PD models for pacibekitug were developed based on the data from 5 clinical studies (two phase 1 studies in healthy volunteers, one phase 1 study in RA, one phase 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)



Study population:

- CKD stage G3-4 (eGFR 15-59 ml/min/1.73m^2)
- hs-CRP ≥2 mg/L and <15 mg/L
- Exclude patients at higher risk for safety complications (e.g., immunocompromised patients)

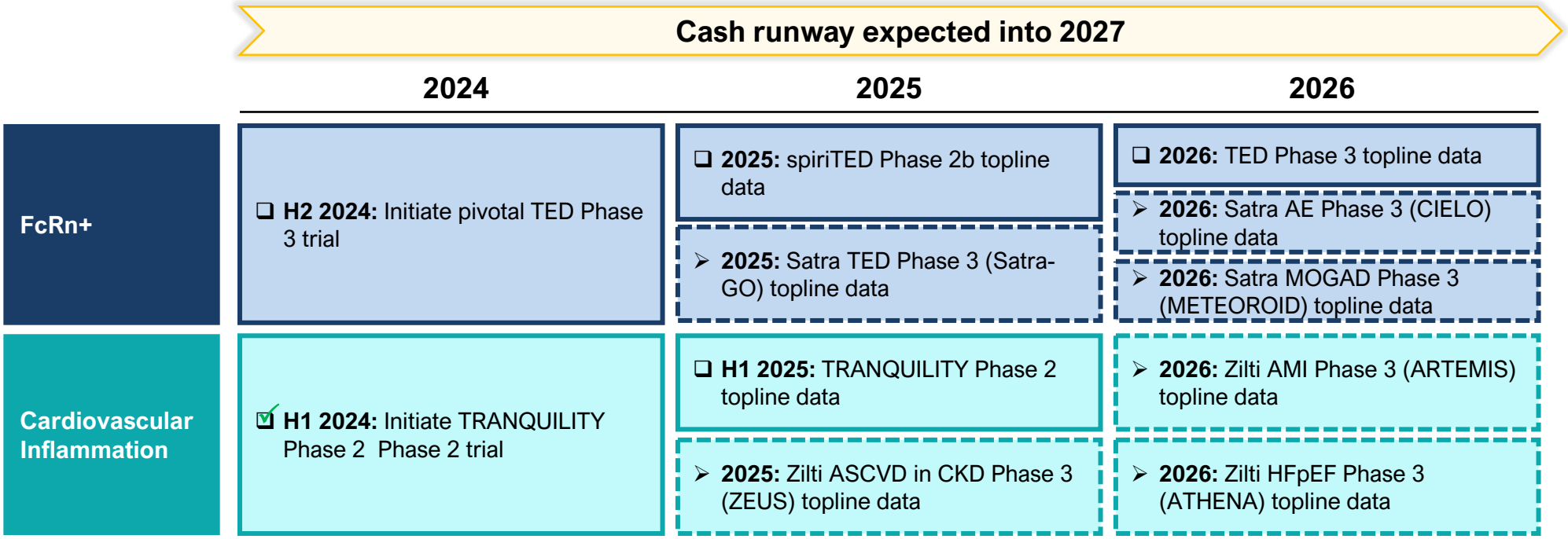
Primary efficacy endpoint:

- Change from baseline in hs-CRP

Additional endpoints:

- Other pharmacodynamic markers: serum amyloid A, fibrinogen, lipoprotein(a), and other biomarkers
- Safety and tolerability

Key milestones expected through 2026



Expect to announce at least one additional indication in 2024

Milestones key: ❑ Internal ➢ External

The timing of regulatory and clinical trial milestones are subject to change and additional discussion with the FDA
AE: autoimmune encephalitis; AMI: acute myocardial infarction; ASCVD: atherosclerotic cardiovascular disease; HFpEF: heart failure with preserved ejection fraction. MOGAD: myelin oligodendrocyte glycoprotein antibody-associated disease; Satra: satralizumab; TED: thyroid eye disease; Zilti: ziltivekimab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