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Phase 2 TRANQUILITY Trial Topline Results

May 20, 2025

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TRANQUIL6ITY results bolster pacibekitug's best-in-class potential for the treatment of cardiovascular disease

Topline results

- **Rapid, deep, durable, and statistically significant reductions in hs-CRP** were seen across all arms vs. placebo
- Pacibekitug becomes the **first and only IL-6 inhibitor** known to achieve deep hs-CRP reductions with **quarterly dosing** in a clinical trial
- Rates of adverse events and serious adverse events for pacibekitug were **comparable to placebo**

Primary and secondary endpoints

Dosing of pacibekitug 50 mg quarterly and 15 mg monthly demonstrated:

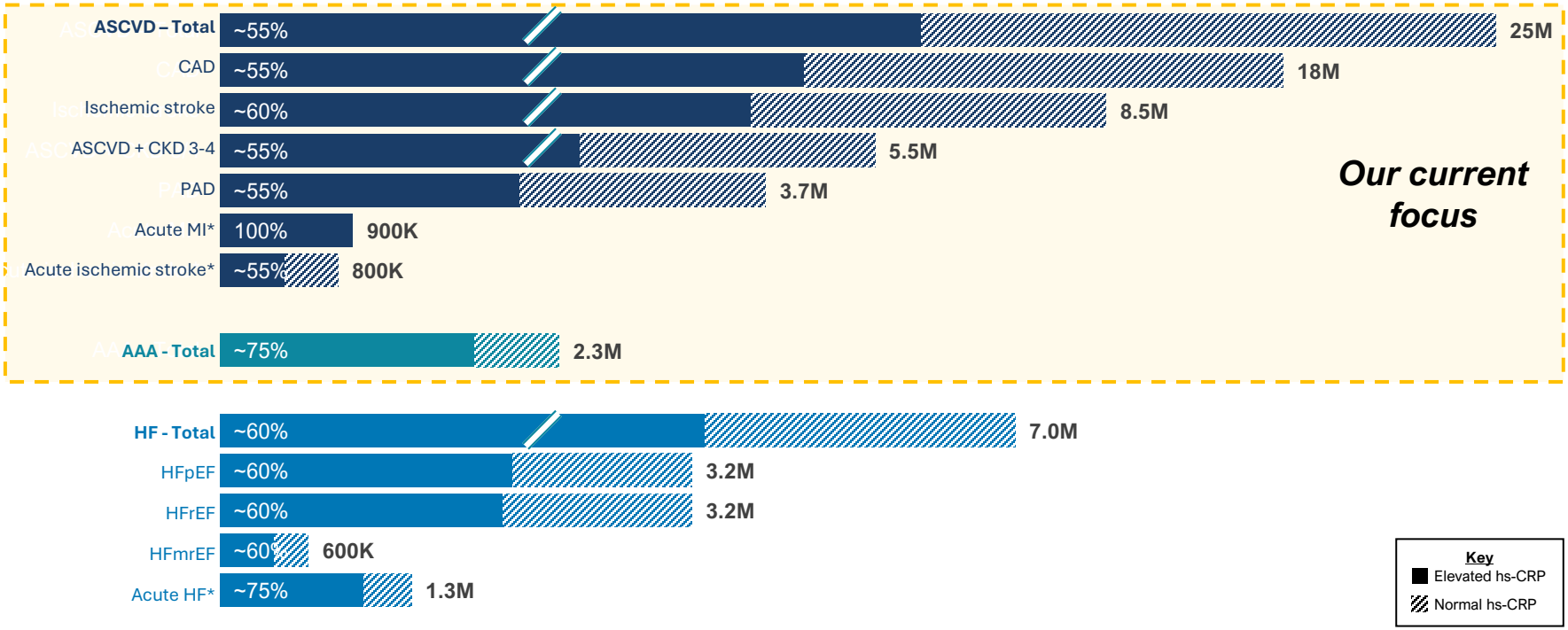
- **86% and 85% median time-averaged reductions in hs-CRP through Day 90**, respectively*
- **85% and 89% reductions in hs-CRP at Day 90**, respectively*
- **83% and 88% of participants achieving hs-CRP below 2 mg/L at Day 90**, respectively*

hs-CRP: high-sensitivity C-reactive protein
* p<0.0001 for all comparisons to placebo.

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

Estimated US prevalence (2024)[1]

Populations are not mutually exclusive



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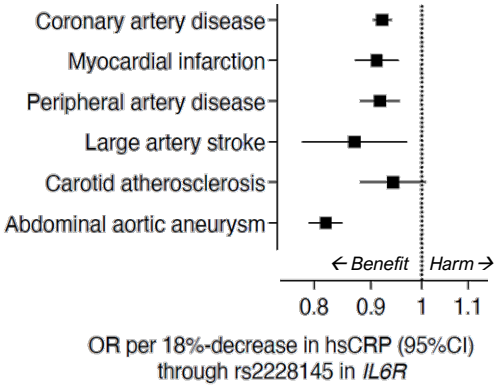
[1]Publications available upon request. Population estimates are adjusted based on US population growth as estimated by the US Census. *Annual incidence
AAA: abdominal aortic aneurysm. ASCVD: atherosclerotic cardiovascular disease. CAD: coronary artery disease. CKD: chronic kidney disease. HF: heart 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

Human genetic evidence

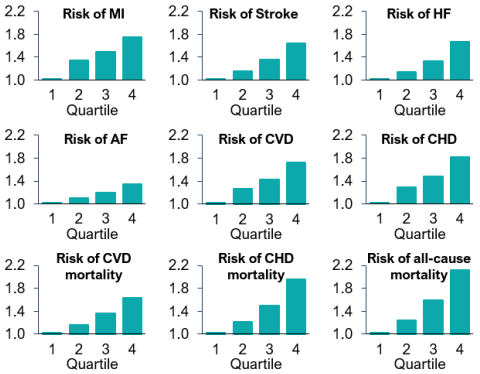
Mendelian randomization studies support a causal relationship between IL-6 pathway and ASCVD[1]



OR per 18%-decrease in hsCRP (95%CI) through rs2228145 in *IL6R*

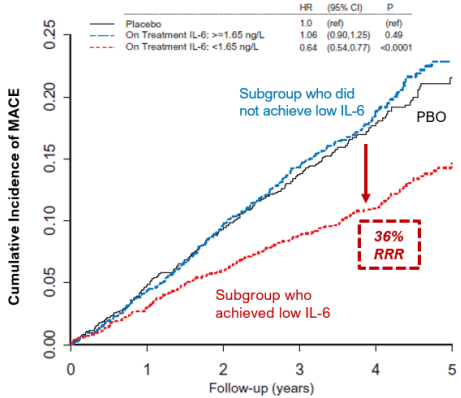
Epidemiological evidence

IL-6 levels were strongly associated with cardiovascular outcomes in Cross-Cohort Collaboration study[2]



Clinical trial evidence

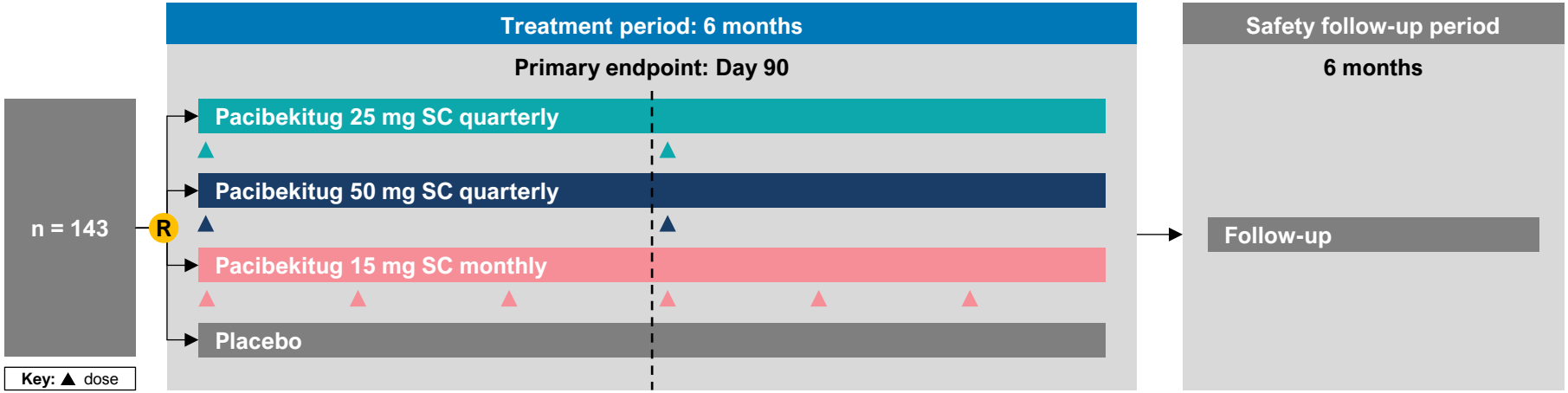
Prespecified CANTOS analysis showed that reductions in IL-6 predicted CV benefit[3]



[1]Analysis based on (i) Georgakis et al., Circ Genom Prec Med (2020), (ii) Levin et al, Circ Res (2021), (iii) Burgess et al, Arterioscler Thromb Vasc Biol (2025), (iv) Omarov et al, medRxiv (2024). [2]Yao et al., The Prognostic Value of Interleukin-6 Levels and Nine Cardiovascular and Mortality Outcomes Insights from the Cross Cohort Collaboration (CCC) 2025. [3]Ridker et al., Eur Heart J (2018). AF: atrial fibrillation. CHD: coronary heart disease. CVD: cardiovascular diseases. HF: heart failure. hs-CRP: high-sensitivity C-reactive protein. MACE: major adverse cardiovascular events. MI: myocardial infarction. OR: odds ratio. PBO: placebo. RRR: relative risk reduction.

TRANQUILITY Phase 2 trial supporting development in CVD

Randomized, double-blind, placebo-controlled Phase 2 trial (NCT06362759)



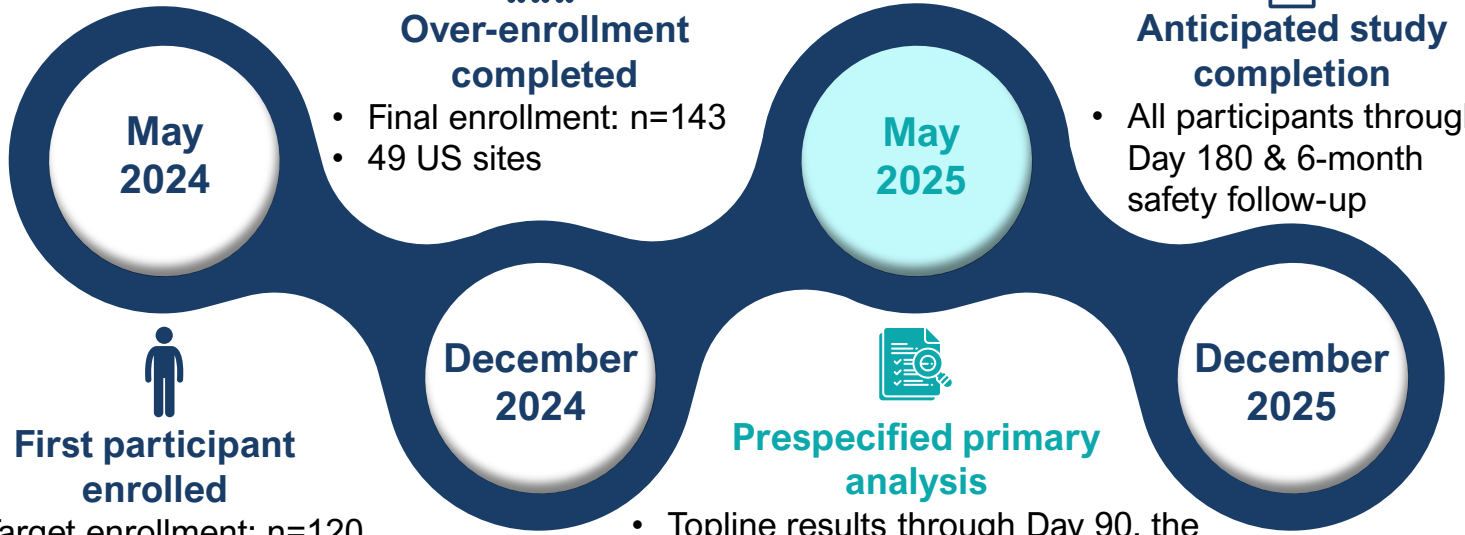
Study population:
- High-sensitivity C-reactive protein (hs-CRP) ≥2 mg/L and <15 mg/L
- CKD stage 3-4 (eGFR 15-59 ml/min/1.73m^2) or UPCR≥200 mg/g
- Exclude patients at higher risk for safety complications (e.g., immunocompromised patients)

Primary endpoint:
- Change from baseline in hs-CRP through Day 90

Secondary endpoints:
- Percentage achieving hs-CRP<2 mg/L through Day 90
- Percentage achieving hs-CRP reduction ≥50% through Day 90
- Change from baseline in hs-CRP through Day 180
- Safety and tolerability

Participants randomized to pacibekitug 25 mg and 50 mg quarterly dosing arms receive matching placebo doses on Days 30, 60, 120, and 150. Participants randomized to placebo receive monthly placebo doses during the treatment period. CKD: chronic kidney disease. CVD: cardiovascular disease. eGFR: estimated glomerular filtration rate. hs-CRP: high-sensitivity C-reactive protein. SC: subcutaneous. UPCR: urine protein-creatinine ratio.

TRANQUILITY trial chronology



First participant enrolled
- Target enrollment: n=120

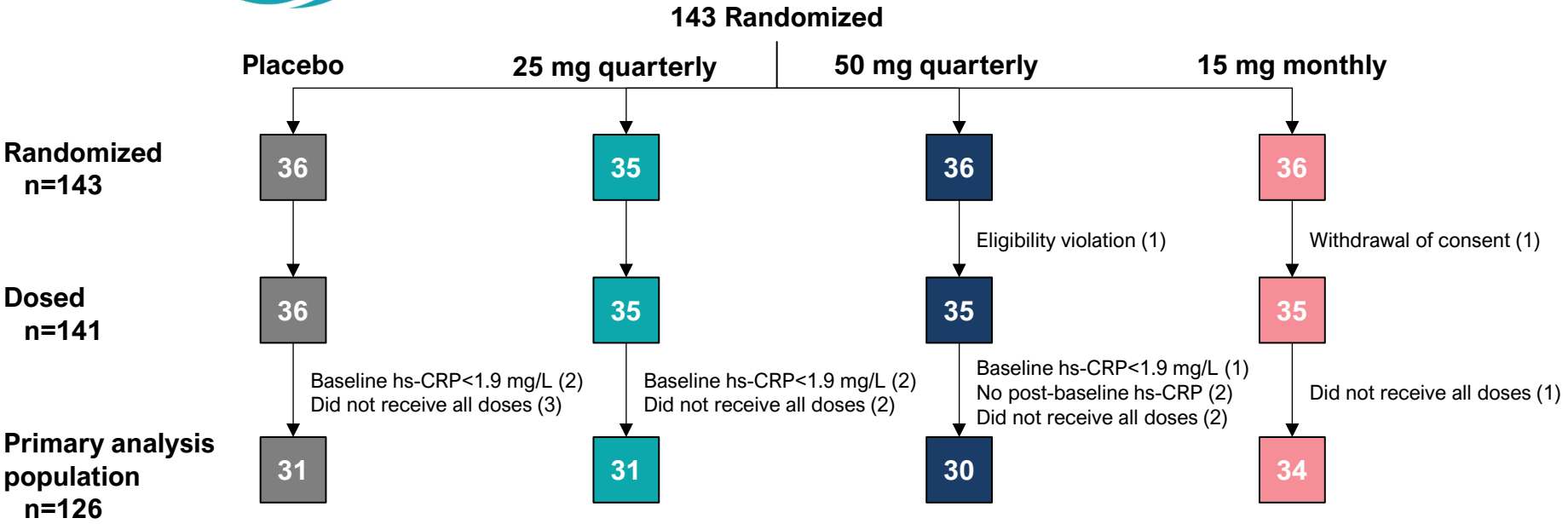
Over-enrollment completed
- Final enrollment: n=143
- 49 US sites

Prespecified primary analysis
- Topline results through Day 90, the primary evaluation period
- Results presented herein reflect a **data extract date of April 23, 2025**

Anticipated study completion
- All participants through Day 180 & 6-month safety follow-up

Data presented herein, and our analyses thereof, are as of the data extract date of April 23, 2025, and therefore do not reflect the complete dataset from the trial, which is ongoing. Cumulative safety data are also presented based upon this same data extract date and are subject to data reflecting any additional safety events as participants complete their study visits and follow-up.

TRANQUILITY trial participant disposition



Prespecified primary analysis population is defined as participants who:

- *Had a baseline hs-CRP of at least 1.9 mg/L♦,*
- *Had at least one post-baseline hs-CRP, and*
- *Received all planned study drug doses during the primary evaluation period*

♦: Baseline hs-CRP defined as average of Screening and Day 1 hs-CRP values.
Data presented herein, and our analyses thereof, are as of the data extract date of April 23, 2025, and therefore do not reflect the complete dataset from the trial, which is ongoing. Cumulative safety data are also presented based upon this same data extract date and are subject to data reflecting any additional safety events as participants complete their study visits and follow-up.

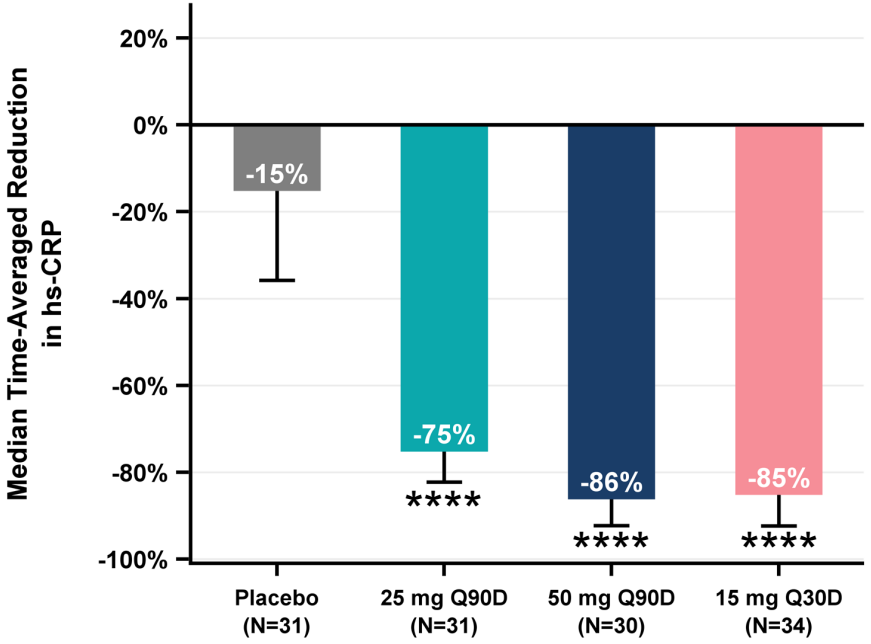
Baseline characteristics in-line with expectations for chronic kidney disease and generally balanced across treatment arms

	Overall N=126	Placebo N=31	Pacibekitug 25 mg quarterly N=31	Pacibekitug 50 mg quarterly N=30	Pacibekitug 15 mg monthly N=34
Age, years	71 (62, 77)	72 (62, 77)	73 (66, 76)	70 (61, 78)	65 (60, 73)
Female	78 (62%)	21 (68%)	17 (55%)	19 (63%)	21 (62%)
Body-mass index, kg/m^2	33.3 (29.7, 36.7)	33.4 (29.7, 36.3)	32.2 (28.1, 35.6)	35.1 (30.7, 39.8)	33.4 (30.2, 36.3)
ASCVD	58 (46%)	15 (48%)	16 (52%)	20 (67%)	7 (21%)
Diabetes [1]	76 (60%)	21 (68%)	16 (52%)	20 (67%)	19 (56%)
Statin use	86 (68%)	20 (65%)	22 (71%)	22 (73%)	22 (65%)
CKD Stage 3a	46 (37%)	12 (39%)	8 (26%)	13 (43%)	13 (38%)
Stage 3b	54 (43%)	12 (39%)	18 (58%)	9 (30%)	15 (44%)
Stage 4	17 (13%)	6 (19%)	4 (13%)	4 (13%)	3 (9%)
eGFR, ml/min/1.73m^2 [2]	42.5 (35.0, 53.0)	43.5 (33.5, 53.0)	37.5 (33.0, 47.0)	48.0 (36.5, 56.5)	42.5 (36.0, 57.0)
IL-6, pg/mL	4.92 (3.14, 8.00)	4.91 (3.32, 5.93)	4.62 (2.87, 7.30)	5.56 (3.58, 10.03)	4.86 (2.39, 7.83)
hs-CRP, mg/L [2]	4.45 (3.00, 6.15)	3.60 (2.70, 5.10)	3.90 (2.35, 5.55)	5.18 (3.60, 7.35)	4.73 (3.80, 7.40)

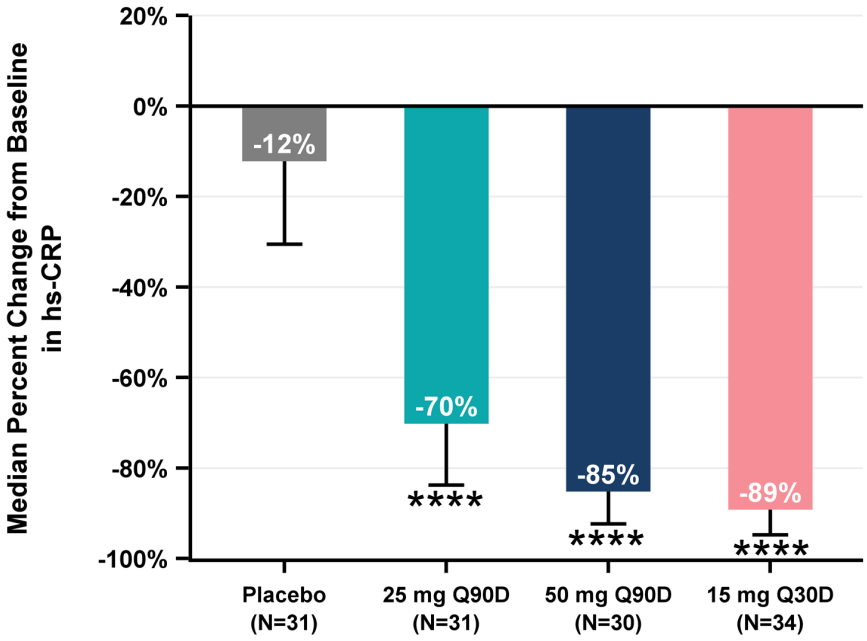
Primary Analysis Population: at least 1 post-baseline hs-CRP, baseline hs-CRP ≥1.9 mg/L, and all planned study drug doses during primary evaluation period.
Data are median (IQR) or n (%). [1] Includes patients with screening hemoglobin A1c ≥6.5% and those with a history of diabetes or on medications for diabetes at baseline.
[2] Baseline values for each participant were calculated as the average of the values at the Screening and Day 1 visits. Data presented herein, and our analyses thereof, are as of the data extract date of April 23, 2025, and therefore do not reflect the complete dataset from the trial, which is ongoing. Cumulative safety data are also presented based upon this same data extract date and are subject to data reflecting any additional safety events as participants complete their study visits and follow-up.

Pacibekitug demonstrated deep and highly statistically significant reductions in hs-CRP across all pacibekitug dosing arms

Percent change from baseline in time-averaged hs-CRP through Day 90



Percent change from baseline in hs-CRP at Day 90



**** *p<0.0001 for all comparisons to placebo*

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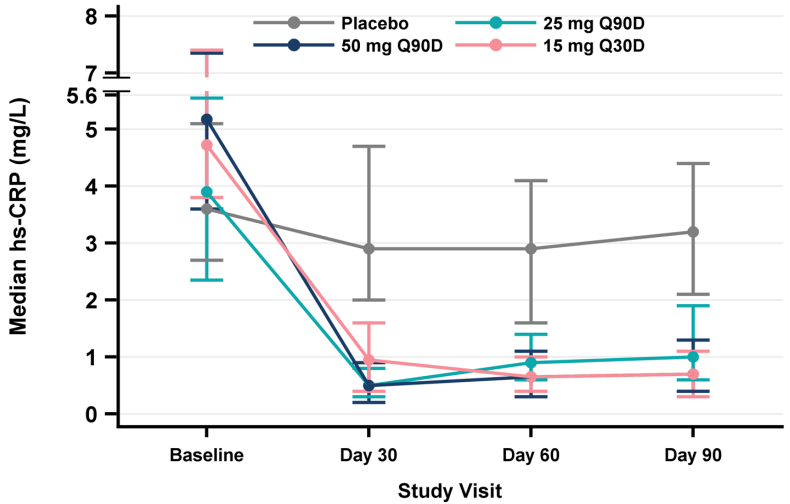
Primary Analysis Population: at least 1 post-baseline hs-CRP, baseline hs-CRP ≥1.9 mg/L, and all planned study drug doses during primary evaluation period.
Error bars represent the 75th percentile for reduction in each dose group. Data presented herein, and our analyses thereof, are as of the data extract date of April 23, 2025, and therefore do not reflect the complete dataset from the trial, which is ongoing. Cumulative safety data are also presented based upon this same data extract date and are subject to data reflecting any additional safety events as participants complete their study visits and follow-up.

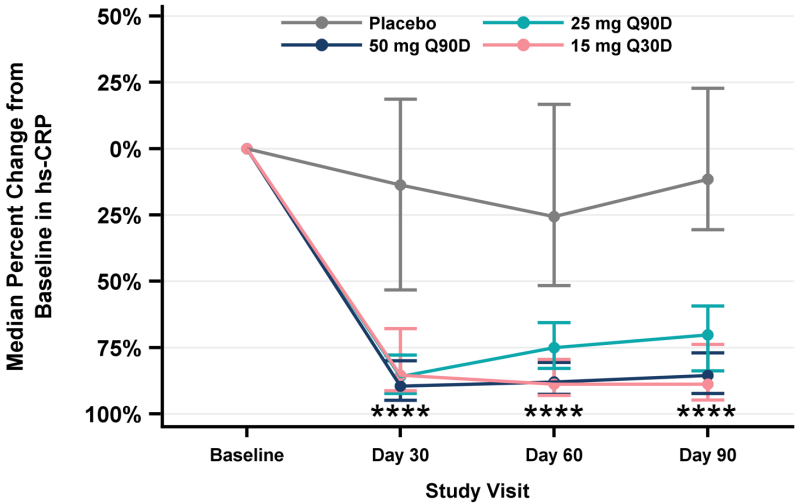
Rapid, deep, and durable suppression of hs-CRP was observed throughout the primary evaluation period

Median (IQR) hs-CRP by visit through Day 90



Number of Participants	Baseline	Day 30	Day 60	Day 90
Placebo	31	31	31	31
25 mg Q90D	31	31	31	31
50 mg Q90D	30	30	30	30
15 mg Q30D	34	34	34	34

Median (IQR) percent change in hs-CRP from baseline by visit through Day 90



Number of Participants	Baseline	Day 30	Day 60	Day 90
Placebo	31	31	31	31
25 mg Q90D	31	31	31	31
50 mg Q90D	30	30	30	30
15 mg Q30D	34	34	34	34

**** *p<0.0001 for all comparisons to placebo*

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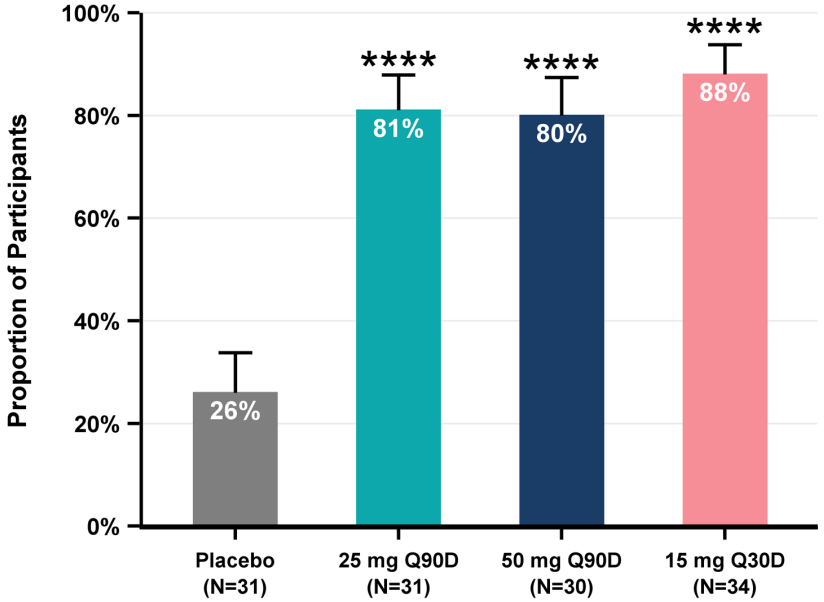
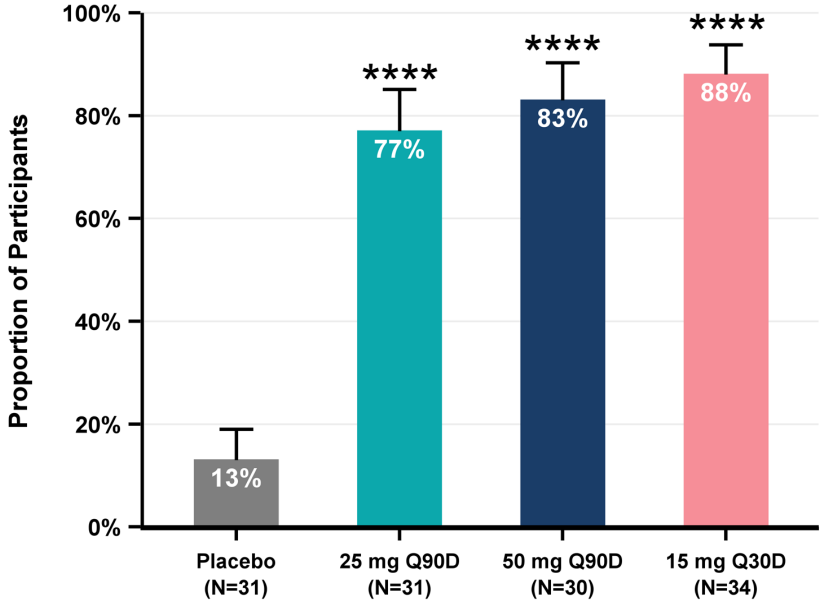
Primary Analysis Population: at least 1 post-baseline hs-CRP, baseline hs-CRP ≥1.9 mg/L, and all planned study drug doses during primary evaluation period.
Data presented herein, and our analyses thereof, are as of the data extract date of April 23, 2025, and therefore do not reflect the complete dataset from the trial, which is ongoing. Cumulative safety data are also presented based upon this same data extract date and are subject to data reflecting any additional safety events as participants complete their study visits and follow-up.

A significant percentage of participants across all pacibekitug dosing arms achieved an hs-CRP of <2 mg/L

Percentage of participants with time-averaged hs-CRP <2 mg/L through Day 90



Percentage of participants with hs-CRP <2 mg/L at Day 90



**** *p<0.0001 for all comparisons to placebo*

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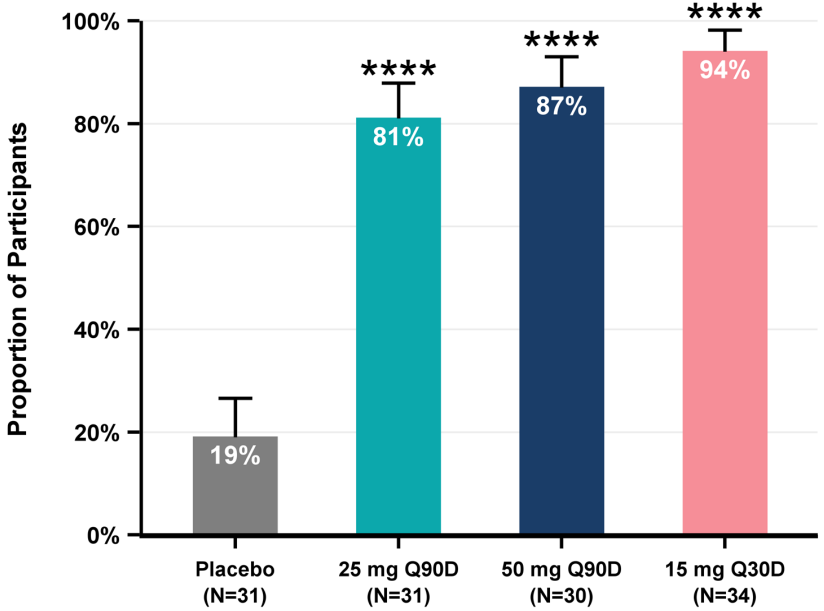
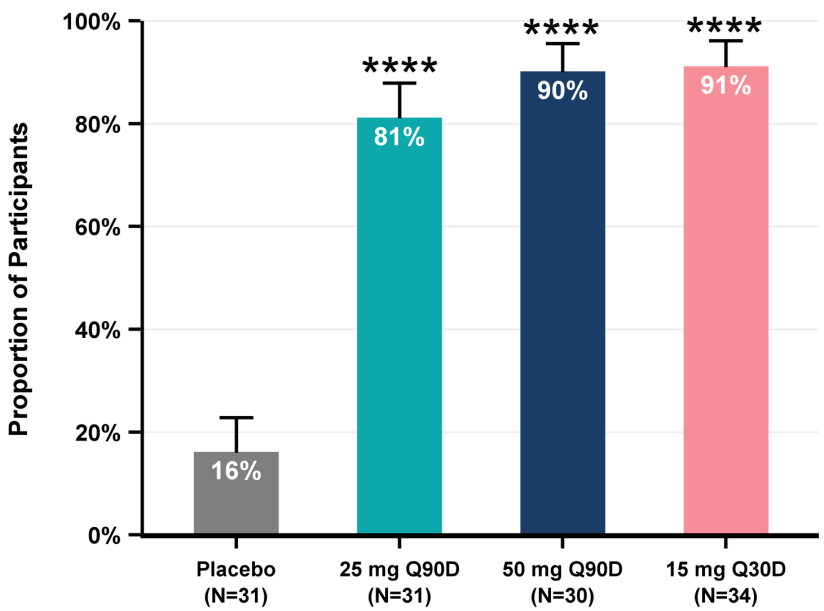
Primary Analysis Population: at least 1 post-baseline hs-CRP, baseline hs-CRP ≥1.9 mg/L, and all planned study drug doses during primary evaluation period.
Error bars represent standard error. Data presented herein, and our analyses thereof, are as of the data extract date of April 23, 2025, and therefore do not reflect the complete dataset from the trial, which is ongoing. Cumulative safety data are also presented based upon this same data extract date and are subject to data reflecting any additional safety events as participants complete their study visits and follow-up.

The vast majority of participants receiving pacibekitug achieved an hs-CRP reduction of ≥50%

Percentage with time-averaged hs-CRP reduction ≥50% through Day 90



Percentage with hs-CRP reduction ≥50% at Day 90



**** *p<0.0001 for all comparisons to placebo*

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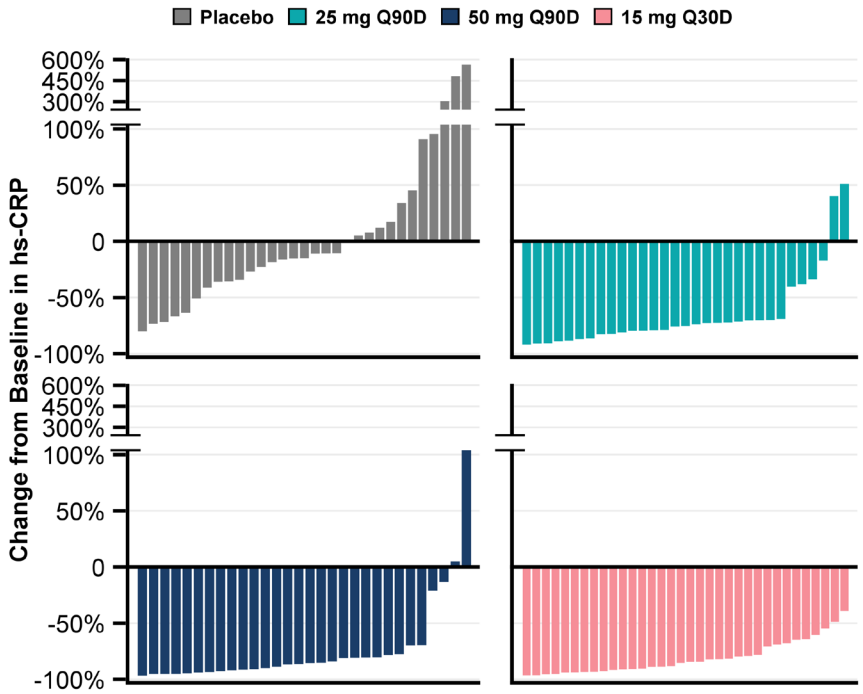
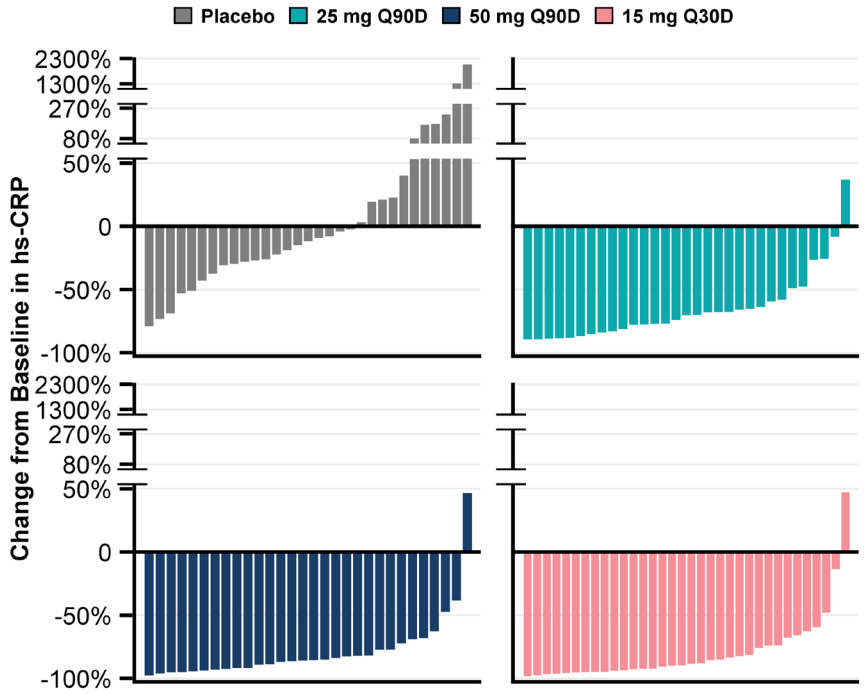
Primary Analysis Population: at least 1 post-baseline hs-CRP, baseline hs-CRP ≥1.9 mg/L, and all planned study drug doses during primary evaluation period.
Error bars represent standard error. Data presented herein, and our analyses thereof, are as of the data extract date of April 23, 2025, and therefore do not reflect the complete dataset from the trial, which is ongoing. Cumulative safety data are also presented based upon this same data extract date and are subject to data reflecting any additional safety events as participants complete their study visits and follow-up.

Participant-level data highlight consistent reduction in hs-CRP through Day 90 for those receiving pacibekitug

Percent change from baseline in time-averaged hs-CRP through Day 90



Percent change from baseline in hs-CRP at Day 90



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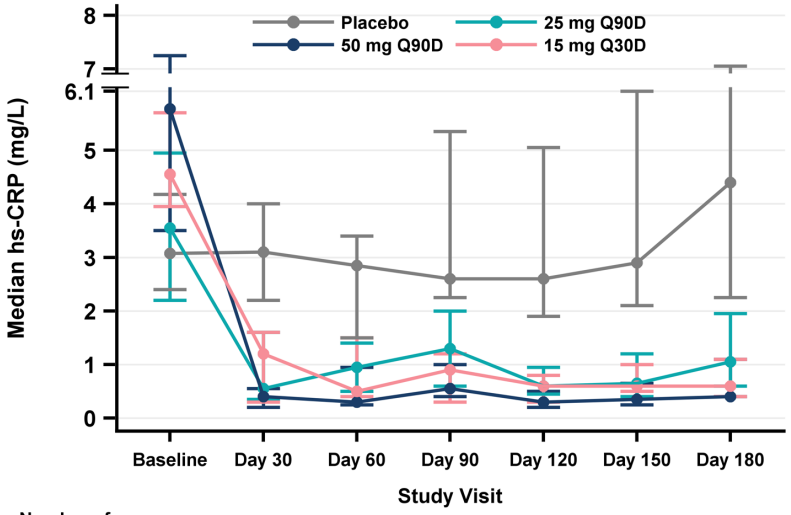
Primary Analysis Population: at least 1 post-baseline hs-CRP, baseline hs-CRP ≥1.9 mg/L, and all planned study drug doses during primary evaluation period.
Data presented herein, and our analyses thereof, are as of the data extract date of April 23, 2025, and therefore do not reflect the complete dataset from the trial, which is ongoing. Cumulative safety data are also presented based upon this same data extract date and are subject to data reflecting any additional safety events as participants complete their study visits and follow-up.

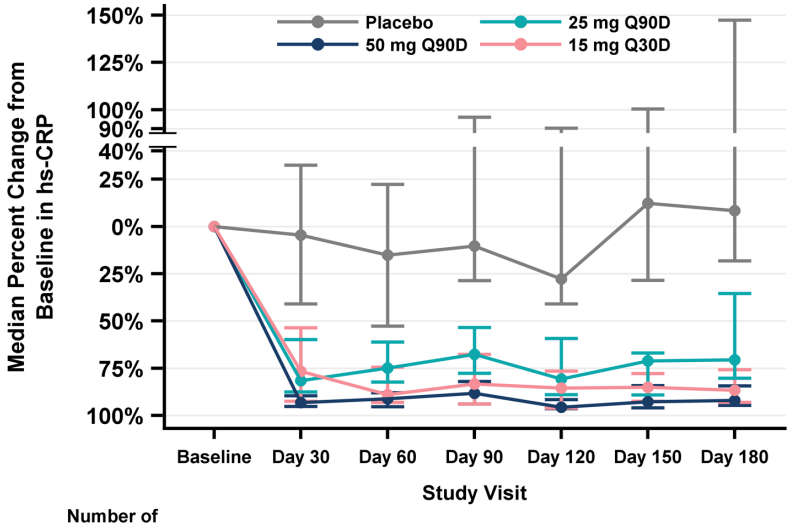
Sustained hs-CRP reductions through Day 180 observed in participants who completed treatment period as of data extract

Median (IQR) hs-CRP by visit through Day 180



Number of Participants	Baseline	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180
Placebo	12	12	12	12	12	12	12
25 mg Q90D	12	12	12	12	12	12	12
50 mg Q90D	12	12	12	12	12	12	12
15 mg Q30D	11	11	11	11	11	11	11

Median (IQR) percent change in hs-CRP from baseline by visit through Day 180



Number of Participants	Baseline	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180
Placebo	12	12	12	12	12	12	12
25 mg Q90D	12	12	12	12	12	12	12
50 mg Q90D	12	12	12	12	12	12	12
15 mg Q30D	11	11	11	11	11	11	11

Primary Analysis Population: at least 1 post-baseline hs-CRP, baseline hs-CRP ≥1.9 mg/L, and all planned study drug doses during primary evaluation period.
Data presented herein, and our analyses thereof, are as of the data extract date of April 23, 2025, and therefore do not reflect the complete dataset from the trial, which is ongoing. Cumulative safety data are also presented based upon this same data extract date and are subject to data reflecting any additional safety events as participants complete their study visits and follow-up. Results through Day 180 presented herein reflect a subset of the primary analysis population as of the data extract date of April 23, 2025. These data and the preliminary analysis presented here are subject to change as additional data are collected through the ongoing trial.

Pacibekitug demonstrated overall incidence rates of adverse events and serious adverse events comparable to placebo

Cumulative incidence through data extract date

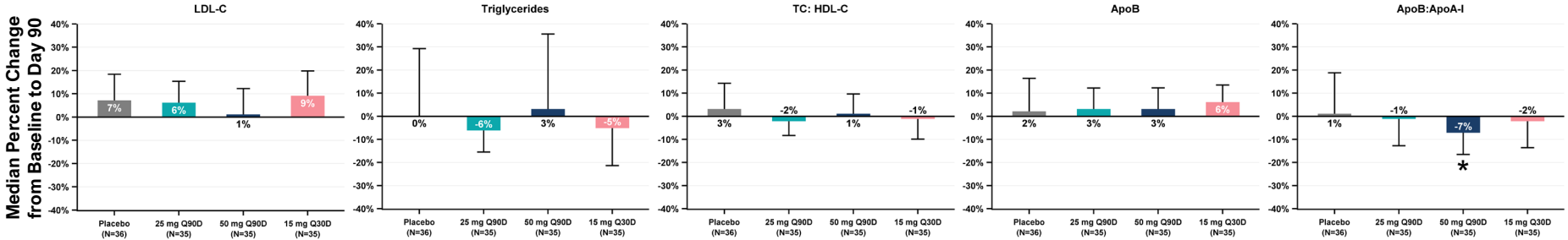
	Placebo N=36	Pacibekitug Pooled N=105	Pacibekitug 25 mg quarterly N=35	Pacibekitug 50 mg quarterly N=35	Pacibekitug 15 mg monthly N=35
Adverse events	20 (56%)	57 (54%)	20 (57%)	18 (51%)	19 (54%)
Serious adverse events	4 (11%)	10 (10%)	6 (17%)	2 (6%)	2 (6%)
AEs leading to discontinuation	0	2 (2%)	0	1 (3%)	1 (3%)
Infection	8 (22%)	25 (24%)	10 (29%)	9 (26%)	6 (17%)
Serious infection	1 (3%)	4 (4%)	4 (11%)	0	0
Death	0	1 (1%)*	1 (3%)*	0	0
Injection site reaction Grade 2+	0	0	0	0	0
Neutropenia Grade 2 [1]	1 (3%)	2 (2%)	1 (3%)	0	1 (3%)
Neutropenia Grade 3+ [1]	0	0	0	0	0
Thrombocytopenia Grade 2+ [1]	0	0	0	0	0

Safety population n=141
**Fatal case of COVID-19*

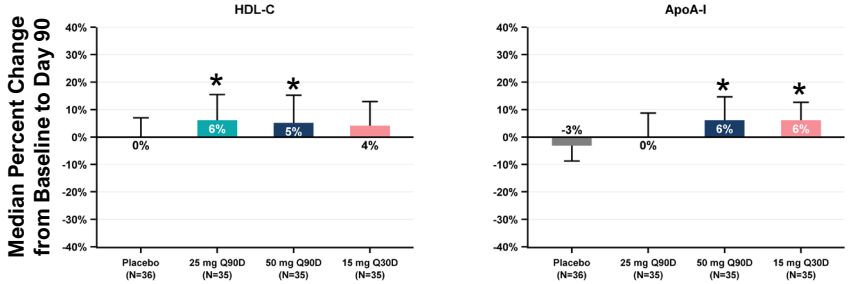
Safety Population: at least 1 dose of study drug. [1] Laboratory abnormalities defined as confirmed low values on 2 consecutive assessments. Neutropenia CTCAE Grade 2: ANC >= 1,000/mm^3 and <1,500/mm^3. Grade 3+: ANC <1,000/mm^3. Thrombocytopenia CTCAE Grade 2+: PLT < 75,000/mm^3. Data presented herein, and our analyses thereof, are as of the data extract date of April 23, 2025, and therefore do not reflect the complete dataset from the trial, which is ongoing. Cumulative safety data are also presented based upon this same data extract date and are subject to data reflecting any additional safety events as participants complete their study visits and follow-up.

No clinically meaningful changes in atherogenic lipids or lipoproteins in pacibekitug arms versus placebo

Atherogenic lipids and lipoproteins



Non-atherogenic lipids and lipoproteins



** p<0.05 for all comparisons to placebo*

Safety Population: at least 1 dose of study drug. Error bars represent the 25th percentile (for negative values) or 75th percentile (for positive values) for changes from baseline seen in each dose group. Data presented herein, and our analyses thereof, are as of the data extract date of April 23, 2025, and therefore do not reflect the complete dataset from the trial, which is ongoing. Cumulative safety data are also presented based upon this same data extract date and are subject to data reflecting any additional safety events as participants complete their study visits and follow-up.

Expert perspective on inflammation and cardiovascular risk

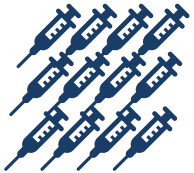
Deepak L. Bhatt, MD, MPH, MBA
Chair of Tourmaline Cardiovascular SAB

SAB: scientific advisory board.

TRANQUILITY 6 results bolster pacibekitug's best-in-class potential

Quarterly dosing viability

Pacibekitug



Ziltivekimab

Development strategy

- **First-in-class**: Pursue high-risk ASCVD populations not being targeted by ziltivekimab
- **First-in-disease**: Tackle AAA, a very high unmet need opportunity

Fast learner

External CV outcomes trials provide critical insights to leverage **additional opportunities to differentiate**

AAA: abdominal aortic aneurysm. ASCVD: atherosclerotic cardiovascular disease. CV: cardiovascular.

With TRANQUILITY results now in hand, Tourmaline is well-positioned to execute on its cardiovascular inflammation strategy

TRANQUILITY data unlocks pacibekitug's potential in CVD

- Demonstrated rapid, deep, and durable hs-CRP reductions
- Confirmed quarterly dosing viability
- Expanded safety database

Key next steps

- In consultation with CV SAB, confirm optimal dose for Phase 3 CVOT in ASCVD and finalize clinical development strategy
- Conduct EOP2 meeting with FDA by end of year
- Initiate Phase 2 proof-of-concept trial in AAA in H2 2025

AAA: abdominal aortic aneurysm. ASCVD: atherosclerotic cardiovascular disease. CVD: cardiovascular disease. CV SAB: cardiovascular Scientific Advisory Board. CVOT: cardiovascular outcomes trial. EOP2: end of Phase 2. FDA: Food & Drug Administration. hs-CRP: high-sensitivity C-reactive protein.

Questions & answers