A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial of Pacibekitug Subcutaneous Quarterly or Monthly in Patients With Elevated hs-CRP and Chronic Kidney Disease: TRANQUILITY 90-Day Results

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PURPOSE

- Pacibekitug (TOUR006; formerly PF-04236921) is a long-acting, fully human, anti–interleukin-6 (IL-6) monoclonal antibody with a naturally long half-life, low immunogenicity, and high binding affinity for IL-6.

Objective:

- The ongoing Phase 2 TRANQUILITY trial (TOUR006-C01; NCT06362759) is designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of quarterly (Q90D) and monthly (Q30D) subcutaneous (SC) administration of pacibekitug in patients with elevated high-sensitivity C-reactive protein (hs-CRP) and chronic kidney disease (CKD).

METHODS

- Enrollment completed in December 2024 and the prespecified primary analysis data were extracted on April 23, 2025; study completion is anticipated in December 2025 (**Figure 1**).

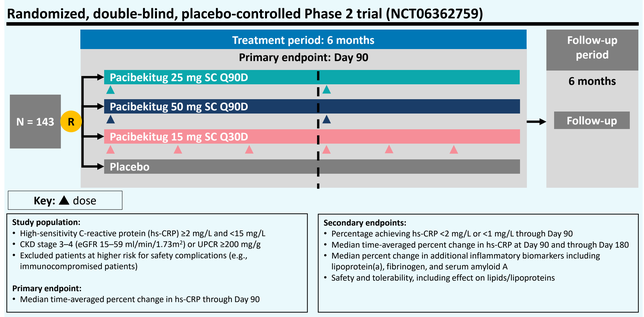

Figure 1. TRANQUILITY trial design.
CKD, chronic kidney disease; **eGFR**, estimated glomerular filtration rate; **Q30D**, monthly; **Q90D**, quarterly; **SC**, subcutaneous; **UPCR**, urine protein-creatinine ratio.

- The prespecified primary analysis used a modified intention-to-treat (mITT) population (N = 126), defined as: baseline hs-CRP ≥1.9 mg/L, ≥1 post-baseline hs-CRP value, and received all planned study drug doses during primary evaluation period.
- Baseline characteristics were consistent with other studies in patients with CKD and were generally balanced across treatment arms (**Table 1**).

	Placebo N = 31	Pacibekitug 25 mg Q90D N = 31	Pacibekitug 50 mg Q90D N = 30	Pacibekitug 15 mg Q30D N = 34
Age, years, median (IQR)	72 (62, 77)	73 (66, 76)	70 (61, 78)	65 (60, 73)
Female	21 (68)	17 (55)	19 (63)	21 (62)
Body mass index, kg/m², median (IQR)	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	15 (48)	16 (52)	20 (67)	7 (21)
Diabetes[a]	21 (68)	16 (52)	20 (67)	19 (56)
Statin use	¡19 (61)	22 (71)	22 (73)	22 (65)
Incretin use	12 (38.7)	5 (16.1)	7 (23.3)	10 (29.4)
LDL cholesterol, mg/dL, median (IQR)	88 (61, 118)	105 (80, 123)	80 (70, 114)	101 (81, 120)
eGFR, ml/min/1.73m², median (IQR)[b]	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, median (IQR)	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, median (IQR)[b]	3.60 (2.70, 5.10)	3.90 (2.35, 5.55)	5.18 (3.60, 7.35)	4.73 (3.80, 7.40)

Table 1. Key baseline characteristics of the primary analysis population.
Data provided are presented as N (%) unless otherwise indicated. [a]Includes patients with screening hemoglobin A1c ≥6.5% and those with a history of diabetes or on medications for diabetes at baseline. [b]Baseline values were calculated as the average of the Screening and Day 1 values. **A1c**, glycated hemoglobin; **ASCVD**, atherosclerotic cardiovascular disease; **eGFR**, estimated glomerular filtration rate; **hs-CRP**, high-sensitivity C-reactive protein; **IL-6**, interleukin-6; **LDL**, low-density lipoprotein; **Q30D**, monthly; **Q90D**, quarterly.

RESULTS

- Pacibekitug demonstrated statistically significant reductions in hs-CRP across all pacibekitug dosing arms (**Figure 2**).

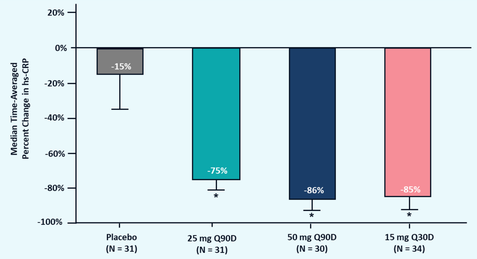

Figure 2. Median time-averaged percent change in hs-CRP through Day 90 in the mITT population.
Through the primary evaluation period, the Q90D dosing groups received a single dose of pacibekitug on Day 1, and the Q30D dosing group received three doses on Day 1, Day 30, and day 60.*p <0.0001 for all comparisons vs placebo. Error bars indicate IQR. **hs-CRP**, high-sensitivity C-reactive protein; **mITT**, modified intention-to-treat; **Q30D**, monthly; **Q90D**, quarterly.

- Rapid and durable suppression of hs-CRP was observed, with significant reductions at the earliest post-dose timepoint, Day 30, and throughout the primary evaluation period (Day 90; **Figure 3**).

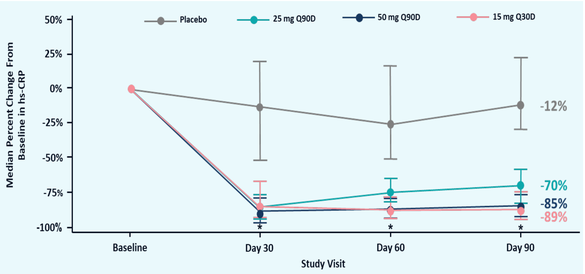

Figure 3. Median (IQR) time-averaged percent change in hs-CRP from baseline by visit through Day 90 in the mITT population.
*p <0.0001 for all comparisons vs placebo. Error bars indicate IQR. **hs-CRP**, high-sensitivity C-reactive protein; **mITT**, modified intention-to-treat; **Q30D**, monthly; **Q90D**, quarterly.

- A significant percentage of participants across all pacibekitug dosing arms achieved an hs-CRP of <2 mg/L and a more aggressive target of <1 mg/L at Day 90 (**Figure 4**).

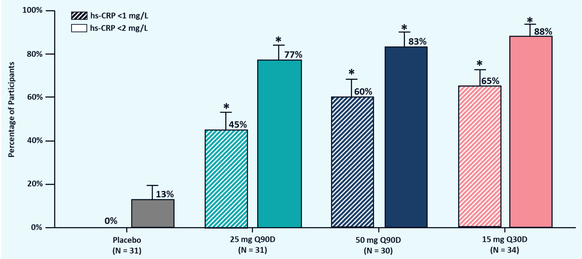

Figure 4. Percentage of participants achieving hs-CRP <2 mg/L and <1 mg/L at Day 90 in the mITT population.
*p <0.0001 for all comparisons vs placebo. Error bars indicate IQR. **hs-CRP**, high-sensitivity C-reactive protein; **mITT**, modified intention-to-treat; **Q30D**, monthly; **Q90D**, quarterly.

- Consistent, large reductions in hs-CRP were observed across clinically relevant subgroup analyses including sex, baseline diabetes status, and baseline use of statin or incretin therapy (**Figure 5**).

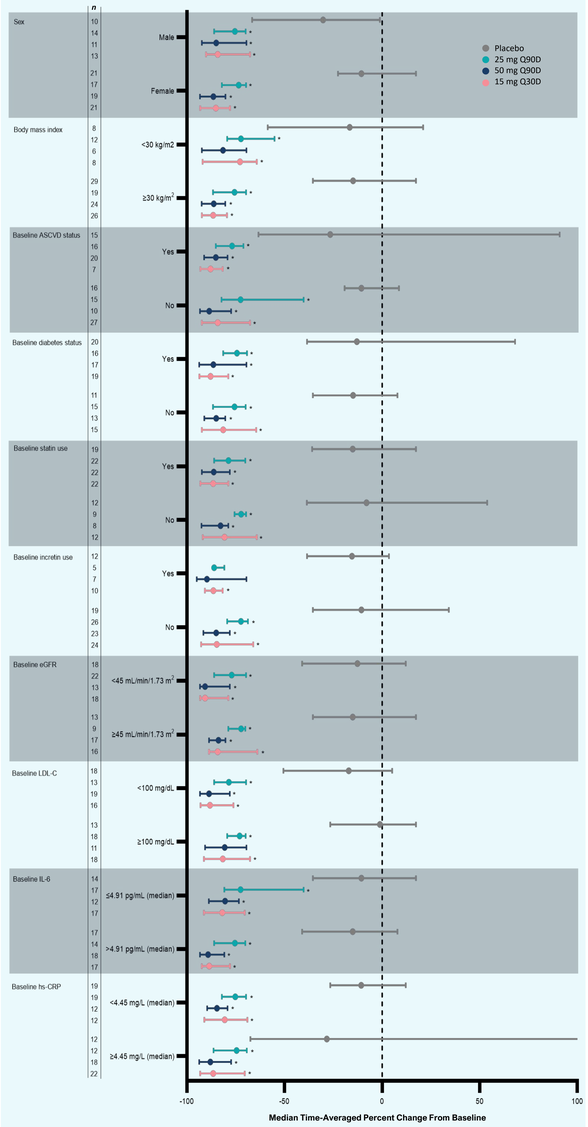

Figure 5. Reductions in hs-CRP stratified by baseline characteristics.
*p <0.05 vs placebo. Data are presented as median (IQR). **ASCVD**, atherosclerotic cardiovascular disease; **eGFR**, estimated glomerular filtration rate; **hs-CRP**, high-sensitivity C-reactive protein; **IL-6**, interleukin-6; **LDL-C**, low-density lipoprotein cholesterol; **Q30D**, monthly; **Q90D**, quarterly.

RESULTS

- Concordant reductions were observed with other markers of IL-6 pathway activity, including lipoprotein(a), fibrinogen, and serum amyloid A (**Figure 6**).

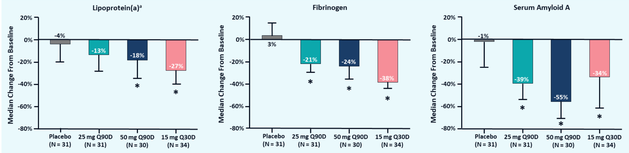

Figure 6. Median percent change in lipoprotein(a), fibrinogen, and serum amyloid A at Day 90.
Error bars indicate IQR. [a]Similar results were observed in the subgroup with baseline lipoprotein(a) ≥75 nmol/L: placebo, -4%; 25 mg Q90D, -13%; 50 mg Q90D, -20%; and 15 mg Q30D -27%.*p <0.05 for all comparisons vs placebo. **Q30D**, monthly; **Q90D**, quarterly.

- Overall, pacibekitug demonstrated comparable incidence rates of adverse events vs placebo in the safety population (N = 141; **Table 2**).
- No clinically meaningful increases in atherogenic lipids or lipoproteins were observed in the pacibekitug arms vs placebo, including when stratified by baseline statin use.

	Placebo N = 36	Pacibekitug Pooled N = 105	Pacibekitug 25 mg Q90D N = 35	Pacibekitug 50 mg Q90D N = 35	Pacibekitug 15 mg Q30D N = 35
Adverse events	20 (56)	54 (51)	19 (54)	17 (49)	18 (51)
Serious adverse events	3 (8)	8 (8)	5 (14)	1 (3)	2 (6)
AEs leading to discontinuation	0	2 (2%)	0	1 (3)	1 (3)
Infection	8 (22)	23 (22)	9 (26)	8 (23)	6 (17)
Serious infection	1 (3)	3 (3)	3 (9)	0	0
Death	0	1 (1)[a]	1 (3)[a]	0	0
Injection site reaction Grade 2+	0	0	0	0	0
Neutropenia Grade 2[b]	1 (3)	2 (2)	1 (3)	0	1 (3)
Neutropenia Grade 3+[b]	0	0	0	0	0
Thrombocytopenia Grade 2+[b]	0	0	0	0	0
ALT or AST >3x ULN	1 (3)	0	0	0	0

Table 2. Cumulative safety through the primary data extraction date.
Data presented as N (%). [a]Fatal case of COVID-19 in a 71-year-old man with baseline hs-CRP 11.1 mg/L, CKD stage 3, hypertension, and no booster vaccination (last vaccinated in 2020). COVID-19 onset occurred 84 days after a single 25-mg dose. [b]Laboratory abnormalities defined as confirmed low values on 2 consecutive assessments. **AE**, adverse event; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **CKD**, chronic kidney disease; **hs-CRP**, high-sensitivity C-reactive protein; **Q30D**, monthly; **Q90D**, quarterly; **ULN**, upper limit of normal.

CONCLUSIONS

- Pacibekitug 50 mg Q90D and 15 mg Q30D demonstrated 86% and 85% median time-averaged reductions in hs-CRP through Day 90, respectively.
- Consistent, large reductions in hs-CRP were observed across subgroups.
- Among participants receiving pacibekitug, 77%–88% and 45%–65% achieved an hs-CRP of <2 mg/L and <1 mg/L, respectively.
- Concordant reductions in additional IL-6–related pharmacodynamic biomarkers were observed (lipoprotein(a), fibrinogen, serum amyloid A).
- No safety signals were observed as of the primary data extraction date.
- Topline data from TRANQUILITY support quarterly dosing of pacibekitug in future studies in high-risk patients with cardiovascular disease.
- IL-6 inhibition, achieving the observed reductions in hs-CRP with pacibekitug in TRANQUILITY, has the potential to improve outcomes in patients with established atherosclerotic cardiovascular disease (ASCVD) or ASCVD risk factors.

DECLARATION OF INTEREST

ED, **FH**, **HZ**, and **JW** are employees of Tourmaline Bio, Inc.; **PP** is a TRANQUILITY trial investigator; **PMR** has received institutional research grant support from Kowa, Novartis, Amarin, Pfizer, Esperion, NovoNordisk, and the NHLBI; during the past 3 years has served as a consultant to Novartis, Agepha, Arbelos, Arrowhead, AstraZeneca, CSL Behring, Janssen, Civi Biopharm, Glaxo Smith Kline, SOCAR, Novo Nordisk, Eli Lilly, New Amsterdam, Boehringer-Ingelheim, Cytokinetics, Nodthera, Tourmaline Bio and Cardio Therapeutics; has minority shareholder equity positions in Uppton, Bitterroot Bio, and Angiowave; and receives compensation for service on the Peter Munk Advisory Board (University of Toronto), the Leducq Foundation, Paris FR, and the Baim Institute (Boston, MA); **MS** reports receives salary support from CPC, a non-profit academic research organization affiliated with the University of Colorado, that receives or has received research grant/consulting funding between July 2021 and July 2025 from the following organizations: 35Pharma, Inc, Abbott Labratories, Agios Pharmaceuticals, Inc., Alexion Pharma Gode Kaisha, American Heart Association, American Journal Managed Care, Amgen Inc., Amgen USA, Inc., Anthos Therapeutics, Inc., Arrowhead Pharmaceuticals, AstraZeneca Pharma India, AstraZeneca Pharmaceuticals LP, AstraZeneca UK Ltd, Autonomy Bio, Inc, Bayer, Bayer Aktiengesellschaft, Beth Israel Deaconess Medical Center, Better Therapeutics, Boston Clinical Research Institute, LLC, Bristol-Myers Squibb, Cleerly, Inc., Clergy United for the Transformation of Sandtown, Colorado Dept of Public Health and Environment, Congress Inc, Cook Regentec LLC, Eidos Therapeutics, Inc., Eluralbio, Inc, Esperion Therapeutics, Inc, Faraday Pharmaceuticals, Inc., Gocherbrum Bio Inc, Inomed, IsoneAb Limited, JanOne Biotech Holdings, Inc., Janssen Global Services, Janssen Pharmaceuticals, Inc., Janssen Scientific Affairs LLC, Las Animas and Huerfano Counties, District Health Dept, Lexicon Pharmaceuticals, Inc., Lilly USA, LLC, Medison Pharma, Medpace, Inc., Merck Sharp & Dohme Corp., Nectero Medical, Inc, NewAmsterdam Pharma, Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Pfizer, Piper Sandler & Co, PPD Development, L.P., Prothena Biosciences Limited, Regeneron, Regents of the University of Colorado (aka UCD), Sanofi Therapeutics S.A., Sanofi, Silence Therapeutics PLC, Stanford University, Stealth BioTherapeutics Inc., The Brigham and Women's Hospital, Thrombosis Research Institute, Tourmaline Bio, Inc, University of Colorado, University of Pittsburgh, VarmX, Verve Therapeutics, WraSer, LLC. MS also reports serving as a consultant or research support (or both) from Amarin, Lexicon, NewAmsterdam, Novartis, Regeneron, Sanofi, Silence, and Tourmaline; **DB** is a member of a scientific advisory board with Tourmaline Bio, Inc.

ACKNOWLEDGEMENTS: Medical writing and graphics support were provided by Talisa Silzer, PhD and Cassandra Uchida, PhD, of Sixsense Strategy Group, Inc., a Herspiegel Company, and were funded by Tourmaline Bio, Inc.

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