CLINICAL STUDY REPORT SYNOPSIS

Study Title:	A Phase 2, Double-Blind, Randomized, Placebo-Controlled, 4-Arm Study to Investigate Symptoms, Function, Health-Related Quality of Life and Safety With Repeated Subcutaneous Administration of Ponsegromab Versus Placebo in Adult Participants With Heart Failure
Study Number:	C3651011
Study Phase:	2
Regulatory Agency or Public Disclosure Identifier Number:	ClinicalTrials.gov ID: NCT05492500 EU CT #: 2023-509747-27-00
Pediatric Investigational Plan Number:	Not Applicable
Study Intervention:	Ponsegromab (PF-06946860)
Study Sponsor:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
Study Initiation Date (FPFV):	26 Sep 2022
Primary Completion Date (PCD):	06 Jan 2025
Presentation of data in this CSR synopsis based on: **Study Completion (LPLV) Date:**	05 Mar 2025
Early Termination Status	As of 27 Nov 2024, this study was terminated by the sponsor in consultation with the independent external Data Monitoring Committee, based on a pre-specified unblinded review of interim efficacy and safety data.
CSR Version and Report Date:	**Document Version**: Final LPLV CSR Version 1.0 **Report Date**: 19 Dec 2025

GOOD CLINICAL PRACTICE STATEMENT

This study was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents.

CLINICAL STUDY REPORT SYNOPSIS

Number of Study Center(s) and Investigator(s):

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

None

Brief Description of the Trial Design and Methodology:

This was a Phase 2, parallel-group, randomized, double-blind, placebo-controlled study to evaluate the effect of ponsegromab on health-related quality of life (HRQL), physical activity, safety, and circulating biomarkers in adult participants with heart failure (HF) and elevated circulating growth differentiation factor 15 (GDF-15).

The study was terminated by Pfizer on 27 Nov 2024 in consultation with the independent external Data Monitoring Committee, based on a pre-specified unblinded review of interim efficacy and safety data. All results available for the Main Cohort (Cohort A) are reported in this clinical study report (CSR).

Following the 56-day screening period to confirm eligibility, the study included a 22-week treatment period (from Day 1 to Week 20, and Week 22 for primary endpoint collection), and a 10-week follow-up period for a total study duration of 32 weeks (not including the screening period).

Approximately 416 participants were to be enrolled into the Main Cohort (Cohort A) and randomized to one of 3 doses of ponsegromab (100 mg [n=18], 200 mg [n=18], or 300 mg [n=190]) or to matched placebo (n=190). Blinded study drug was administered subcutaneously (SC) every 4 weeks (Q4W) for a total of 6 doses during the 22-week treatment period.

This study was conducted in partnership with the TIMI Group, an Academic Research Organization (ARO). The study also used an unblinded External Data Monitoring Committee (E-DMC), a blinded Steering Committee, and a separate blinded adjudication committee for adjudication of all deaths, HF hospitalizations and urgent HF visits.

Number of Participants (planned and analyzed):

Table S1. Number of Participants (Planned and Analyzed) - Main Cohort (Cohort A)

Population	N	Definition
Planned	416	
Randomized	433	
Censored Analysis Set	433	All evaluable participants. For participants who discontinued study intervention or received a prohibited procedure, all observations post-discontinuation (ie, last dose of IP +31 days), or post-procedure, were censored and treated as missing data. For participants who missed a dose, or received an incomplete dose, all observations post-missed/incomplete dose were censored. If dosing resumed,

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Number of Participants (Planned and Analyzed) - Main Cohort (Cohort A)

		subsequent data were included immediately after administration of study intervention.
Safety Analysis Set	433	All participants randomly assigned to study intervention and who took at least 1 dose of study intervention (not including the open-label placebo administered in screening).

Diagnosis and Main Criteria for Inclusion and Exclusion:

The Main Cohort (Cohort A) enrolled adult participants with HF and reduced left ventricular ejection fraction [LVEF], elevated N-terminal pro-B type natriuretic peptide [NT-proBNP] and elevated circulating GDF-15 concentrations at screening. In addition, participants were required to have a reduced Kansas City Cardiomyopathy Questionnaire (KCCQ-23) Clinical Summary Score (CSS) and evidence of cachexia or fatigue or functional impairment at screening.

Study Intervention:

Study interventions in this study were ponsegromab (PF-06946860) and placebo. In the Main Cohort (Cohort A), ponsegromab was administered at dose levels of 100 mg, 200 mg, and 300 mg, subcutaneously every 4 weeks.

The manufacturing lot numbers for the study interventions dispensed in the Main Cohort are provided in Table S2.

Table S2. Study Intervention(s) Administered - Main Cohort (Cohort A)

Study Intervention Description	Vendor Lot No.	Pfizer Lot No.	Dosage Form
PF-06946860 Solution for Injection	N/A	22-DP-01303	Solution
PF-06946860 Solution for Injection	N/A	23-DP-01806	Solution
PF-06946860 Solution for Injection	1-FIN-3666	20-002056	Solution
PF-06946860 Solution for Injection	1-FIN-3807	21-DP-00435	Solution
Placebo Solution for Injection Containing: Histidine, Sucrose, PS80, EDTA	20-DP-00117	20-000247	Solution
Placebo for PF-06946860 Solution for Injection	1-FIN-5082	22-DP-01165	Solution

Global Substantial Modifications

Table S3. Global Substantial Modifications

Date of Protocol Amendment	Amendment
18 Jul 2024	To incorporate 2 optional study cohorts, add an adjudication committee and offer flexible language and clarifications.
06 Jun 2023	To incorporate an open-label, pharmacokinetic (PK) cohort, clarifications to eligibility criteria and other sections, remove the Heart Failure Daily Diary, and simplify the approach to activity monitoring.

Global Interruptions and Re-starts

Not applicable

CLINICAL STUDY REPORT SYNOPSIS

Endpoints And Statistical Methods:

Table S4. Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Primary					
• To compare the effect of ponsegromab 300 mg versus placebo, on HF disease-specific health status in participants with HF and elevated GDF-15	• Change from baseline in KCCQ-23 CSS at Week 22.	Primary analysis (efficacy)	Censored analysis set	Data collected after a participant discontinued study intervention, received a prohibited procedure, missed a dose or received an incomplete dose were censored and treated as missing. If dosing resumed, subsequent data were included immediately after IP administration. Missing values were not imputed.	MMRM
Secondary					
• To compare the effect of ponsegromab versus placebo on HF disease-specific overall health status in participants with HF and elevated GDF-15.	• Change from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22.	Secondary analysis (efficacy)	Censored analysis set	Data collected after a participant discontinued study intervention, received a prohibited procedure, missed a dose or received an incomplete dose were censored and treated as missing. If dosing resumed, subsequent data were included immediately after IP administration. Missing values were not imputed.	MMRM
• To compare the effect of ponsegromab versus placebo on HF disease-specific health status in participants with HF and elevated GDF-15.	• Responses as defined by a ≥5-point increase from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22.	Secondary analysis (efficacy)	Censored analysis set	Data collected after a participant discontinued study intervention, received a prohibited procedure, missed a dose or received an incomplete dose were censored and treated as missing. If dosing resumed, subsequent data were included immediately after IP administration. Missing values were imputed using a multiple imputation method for the statistical analysis.	Logistic regression model with multiple imputation

CLINICAL STUDY REPORT SYNOPSIS

Table S4. Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
• To compare the effect of ponsegromab versus placebo on the physical function of participants with HF and elevated GDF-15.	• Change from baseline in 6MWD at Week 22.	Secondary analysis (efficacy)	Censored analysis set	Data collected after a participant discontinued study intervention, received a prohibited procedure, missed a dose or received an incomplete dose were censored and treated as missing. If dosing resumed, subsequent data were included immediately after IP administration. Missing values were not imputed.	MMRM
• To compare the effect of ponsegromab versus placebo on fatigue reported by participants with HF and elevated GDF-15.	• Change from baseline in PROMIS Fatigue 7a at Week 22.	Secondary analysis (efficacy)	Censored analysis set	Data collected after a participant discontinued study intervention, received a prohibited procedure, missed a dose or received an incomplete dose were censored and treated as missing. If dosing resumed, subsequent data were included immediately after IP administration. Missing values were not imputed.	MMRM
• To describe the safety and tolerability of ponsegromab in participants with HF.	• Incidence of TEAEs, TESAEs, abnormal laboratory results, and vital signs.	Secondary analysis (safety)	Safety analysis set	All data collected were included. Missing values were not imputed.	Descriptive statistics

Abbreviations: 6MWD = 6-minute walk distance; IP = investigational product; MMRM = mixed models repeated measures; OSS = Overall Summary Score; PROMIS = Patient-Reported Outcomes Measurement Information System; TEAE = treatment-emergent adverse event; TESAE; TSS = Total Symptom Score.

CLINICAL STUDY REPORT SYNOPSIS

SUMMARY OF RESULTS:

Participant Disposition

A total of 433 participants were randomized and treated in the Main Cohort (Cohort A), of whom 198 were in the placebo group, 21 in ponsegromab 100 mg group, 17 in ponsegromab 200 mg group, and 197 in ponsegromab 300 mg group. Participants receiving any dose of ponsegromab were included in the 'ponsegromab combined' treatment group (n = 235).

A total of 348 (80.4%) participants completed the double-blind treatment phase. The overall discontinuation rate during the treatment phase (n = 85 [19.6%]) exceeded the projected rate of 15% due to study termination and was higher for placebo- (n = 44 [22.2%]) vs ponsegromab-treated (n = 41 [17.4%]) participants. The most common reasons for discontinuation from double-blind treatment were study termination by sponsor (n = 41 [9.5%]), death (n= 20 [4.6%]) and AE (n= 13 [3.0%]). Numerical differences in reasons for discontinuation were observed across treatment groups with no apparent adverse trends noted in the ponsegromab-combined group relative to placebo.

A total of 402 (92.8%) participants entered the follow-up (FU) phase and 383 (88.5%) participants completed the FU visit. Nineteen (4.4%) participants discontinued during FU and the discontinuation rate was higher for placebo- (n = 10 [5.1%]) versus ponsegromab-treated (n = 9 [3.8%]) participants. Reasons for discontinuation included death (n = 13 [3.0%]), AE, and withdrawal by participant (n = 3 [0.7%] each).

Demographic and Other Baseline Characteristics:

Overall, Cohort A is notable for several indicators of advanced HF, as evident from the older age, significantly elevated natriuretic peptide (NT-proBNP) and GDF-15 levels at screening, prevalent cachexia, high incidence of recent HF hospitalization, as well as a high symptom burden based on New York Heart Association (NYHA) classification and reduced KCCQ-23 CSS at screening.

Demographics and baseline characteristics were generally well balanced across treatment groups. Specifically, age, HF symptom burden (NYHA class and KCCQ-23 CSS at screening), baseline LVEF, GDF-15, NT-proBNP, eGFR, and prevalence of cachexia were generally similar across ponsegromab-combined and placebo groups.

- Median (range) age was 75.0 (21, 93) years. The majority of participants (73.0%) were between 65 to 84 years old, and 53.8% were aged ≥75 years.
- The majority of participants were male (75.3%), and the proportion of males was higher in ponsegromab-treated participants than in placebo-treated participants (77.9% vs 72.2%).
- Most participants were White (72.1%) or Asian (24.7%). Black or African Americans were under-represented (2.3%).

CLINICAL STUDY REPORT SYNOPSIS

- Median (range) body weight was 68.7 (34, 134), 62.0 (44, 104), 72.5 (43, 145), and 71.0 (37, 179) kg in placebo, and ponsegromab 100 mg, 200 mg, 300 mg groups, respectively.

Exposure:

All 433 participants received at least 1 dose of study intervention according to the assignment.

Summary of Efficacy/Safety Results

Due to the termination of the study and the small number of participants randomized to the ponsegromab 100 mg (n = 21) and 200 mg (n = 17) groups, inference for these 2 groups was not performed, with statistical analyses for efficacy endpoints performed on data from participants randomized to either placebo or ponsegromab 300 mg groups only. Thus efficacy results were reported for placebo and ponsegromab 300 mg groups only in Table S5 below.

Table S5. Study C3651011 Efficacy/Safety Results

Endpoints	Results
Primary:	
• Change from baseline in KCCQ-23 CSS at Week 22.	• An overall improvement (increase) in KCCQ-23 CSS was observed across treatment groups throughout the double-blind treatment period. At Week 22, mean (SD) increase from baseline was 7.21 (17.931) and 8.31 (19.277) in the placebo and ponsegromab 300 mg groups, respectively. There was no statistically significant improvement in participants treated with ponsegromab 300 mg relative to placebo at Week 22, with a placebo-adjusted LS mean CFB of 0.31 (90% CI: -2.91, 3.54; 1-sided p = 0.4360).
Secondary:	
• Change from baseline in KCCQ-23 OSS, TSS, and physical limitation at Week 22.	• An overall improvement (increase) in KCCQ-23 OSS was observed across treatment groups throughout the double-blind treatment period. At Week 22, mean (SD) increase from baseline was 7.91 (17.597) and 8.23 (20.355) in the placebo and ponsegromab 300 mg groups, respectively. There was no statistically significant improvement in participants treated with ponsegromab 300 mg relative to placebo at Week 22, with a placebo-adjusted LS mean CFB of -0.28 (90% CI: -3.50, 2.94; 1-sided p = 0.5572). • An overall improvement (increase) in KCCQ-23 TSS was observed across treatment groups during the double-blind treatment period. At Week 22, mean (SD) increase from baseline was 7.46 (18.042) and 8.79 (20.075) in the placebo and ponsegromab 300 mg groups, respectively. There was no statistically significant improvement in participants treated with ponsegromab 300 mg relative to placebo at Week 22, with a placebo-adjusted LS mean CFB of 0.90 (90% CI: -2.32, 4.11; 1-sided p = 0.3228).

CLINICAL STUDY REPORT SYNOPSIS

Table S5. Study C3651011 Efficacy/Safety Results

Endpoints	Results
	• An overall improvement (increase) in KCCQ-23 physical limitation score was observed across treatment groups throughout the double-blind treatment period. At Week 22, mean (SD) increase from baseline was 6.72 (22.116) and 7.63 (23.102) in the placebo and ponsegromab 300 mg groups, respectively. There was no statistically significant improvement in participants treated with ponsegromab 300 mg relative to placebo at Week 22, with a placebo-adjusted LS mean CFB of -0.16 (90% CI: -4.03, 3.71; 1-sided p = 0.5270).
• Responses as defined by a ≥5-point increase from baseline in KCCQ-23 CSS, OSS, TSS, and physical limitation at Week 22.	• At Week 22, 55.5% and 59.9% of participants in the placebo and ponsegromab 300 mg groups had a ≥5-point increase from baseline in KCCQ-23 CSS, respectively. There was no statistically significant improvement in the likelihood of participants demonstrating a ≥5-point increase in KCCQ-23 CSS if treated with ponsegromab 300 mg relative to placebo at Week 22. The modelled odds ratio was 1.06 (90% CI: 0.73, 1.54; 1-sided p = 0.3960). • At Week 22, 52.7% and 56.5% of participants in the placebo and ponsegromab 300 mg groups had a ≥5-point increase from baseline in KCCQ-23 OSS, respectively. There was no statistically significant improvement in participants treated with ponsegromab 300 mg relative to placebo at Week 22 (modelled odds ratio was 1.05 [90% CI: 0.72, 1.53; 1-sided p = 0.4114]). • At Week 22, 52.7% and 61.9% of participants in the placebo and ponsegromab 300 mg groups had a ≥5-point increase from baseline in KCCQ-23 TSS, respectively. There was no statistically significant improvement in participants treated with ponsegromab 300 mg relative to placebo at Week 22 (modelled odds ratio was 1.32 [90% CI: 0.90, 1.92; 1-sided p = 0.1162]). • At Week 22, 51.0% and 55.9% of participants in the placebo and ponsegromab 300 mg groups had a ≥5-point increase from baseline in KCCQ-23 physical limitation score, respectively. There was no statistically significant improvement in participants treated with ponsegromab 300 mg relative to placebo at Week 22 (modelled odds ratio was 1.06 [90% CI: 0.73, 1.53; 1-sided p = 0.3982]).
• Change from baseline in 6MWD at Week 22.	• The ponsegromab 300 mg and placebo groups both demonstrated an overall improvement (increase) in 6MWD over the double-blind treatment period, with an observed mean (SD) increase from baseline at Week 22 of 18.7 (72.13) meters and 11.3 (69.54) meters, respectively. There was no statistically significant improvement in participants treated with ponsegromab 300 mg relative to placebo at Week 22, with a placebo-adjusted LS mean CFB of 3.48 meters (90% CI: -9.41, 16.37; 1-sided p = 0.3282).
• Change from baseline in PROMIS Fatigue 7a at Week 22.	• An overall improvement (decrease) in PROMIS Fatigue 7a T-Score was observed across treatment groups over the double-blind treatment period. At Week 22, mean (SD) CFB was -1.66 (8.278) and -3.28 (8.407) in the placebo and ponsegromab 300 mg groups, respectively. There was no statistically significant improvement in

CLINICAL STUDY REPORT SYNOPSIS

Table S5. Study C3651011 Efficacy/Safety Results

Endpoints	Results
	participants treated with ponsegromab 300 mg relative to placebo at Week 22, with a placebo-adjusted LS mean CFB of -0.88 (90% CI: -2.32, 0.55; 1-sided p = 0.1551).
• Incidence of TEAEs, TESAEs, abnormal laboratory results, and vital signs.	• A higher proportion of ponsegromab-treated participants (including 100, 200 and 300 mg participants) had all-causality TEAEs (80.9% vs 75.3%), non-serious TEAEs (74.9% vs 69.7%), and TESAEs (35.3% vs 27.8%), compared to placebo-treated participants. o All-causality TEAEs within each of the narrow SMQs for Cardiac failure (33.2% vs 25.8%), Acute renal failure (11.5% vs 4.5%) and Infective pneumonia (8.1% vs 4.5%) were observed with higher frequency within the ponsegromab-treated vs placebo-treated participants. • A total of 111 (58.7%) placebo-treated participants and 168 (74.3%) ponsegromab-treated participants had laboratory test abnormalities. o In keeping with the higher frequency of acute renal failure-related TEAEs observed among ponsegromab-treated participants, a higher proportion of ponsegromab-treated participants had urea >1.3 × ULN (44.9% vs 33.3%), and creatinine >1.3 × ULN (29.8% vs 22.0%) than placebo-treated participants. o A higher proportion of ponsegromab-treated participants had liver function test abnormalities in bilirubin >1.5 × ULN (5.8% vs 1.1%), AST >3.0 × ULN (1.8% vs 0%), and ALT >3.0 × ULN (1.3% vs 0%) than placebo-treated participants. There were no Hy's law cases. o There were no clinically significant differences noted in other safety laboratory test abnormalities across treatment groups. • No meaningful trend in vital signs was observed for the ponsegromab 300 mg group vs placebo group.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CFB = change from baseline; CI = confidence interval; LS = least squares; SD = standard deviation; SMQ = Standardized MedDRA Queries; ULN = upper limit of normal.

CONCLUSIONS:

In conclusion, the study objectives of C3651011 were successfully evaluated in the Main Cohort (Cohort A). In this study in adult participants with heart failure, ponsegromab was associated with increased rates of the following: a) worsening heart failure, b) infective pneumonia, and c) acute renal failure, without any evidence of benefit for ponsegromab 300 mg Q4W through 20 weeks across primary and secondary efficacy endpoints at Week 22 (non-trough timepoint) compared to placebo.

- In this cohort of participants with high-risk HF and elevated GDF-15, there was no statistically significant improvement in either KCCQ-23 CSS or 6MWD at Week 22 between participants treated with ponsegromab 300 mg vs placebo. The placebo-adjusted LS mean CFB at Week 22 was 0.31 (90% CI: -2.91, 3.54; p = 0.4360) for KCCQ-23 CSS and 3.48 meters (90% CI: -9.41, 16.37; p = 0.3282) for 6MWD.

CLINICAL STUDY REPORT SYNOPSIS

- There was no statistically significant improvement in KCCQ-23 OSS, TSS, physical limitation score, and PROMIS Fatigue 7a T-Score at Week 22 in participants treated with ponsegromab 300 mg vs placebo.

- All-causality TEAEs (190 [80.9%] vs 149 [75.3%]) and TESAEs (83 [35.3%] vs 55 [27.8%]) were reported in a higher number of ponsegromab-treated vs placebo-treated participants.

- The number of deaths due to TEAEs was similar among placebo- and ponsegromab-treated participants (17 [8.6%] vs 16 [6.8%]).