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Study Title:	A Phase 2, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Dose-Ranging, Dose-Finding, Parallel Group Study to Assess Efficacy and Safety of PF-06865571 (DGAT2i) Alone and When Coadministered With PF-05221304 (ACCi) in Adult Participants With Biopsy-Confirmed Nonalcoholic Steatohepatitis and Fibrosis Stage 2 or 3
Study Number:	C2541013
Study Phase:	II
Regulatory Agency or Public Disclosure Identifier Number:	ClinicalTrials.gov ID (NCT): NCT04321031 EudraCT Number: 2019-004775-39
Pediatric Investigational Plan Number:	Not Applicable
Study Intervention:	PF-06865571 (Ervogastat), PF-05221304 (Clesacostat)
Indication:	Nonalcoholic Steatohepatitis (NASH) with Fibrosis Stage 2 or 3
Study Sponsor:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
Study Initiation Date (FPFV):	15 June 2020
Primary Completion Date (PCD):	23 January 2024
Presentation of Data in this CSR Synopsis Based on: **Study Completion (LPLV) Date:**	21 February 2024
Early Termination Status	This study was not terminated early and was completed as per protocol.
CSR Version and Report Date:	**Document Version** | **Report Date**

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	Final LPLV CSR (amendment to 04 November 2024) Version 2.0	22 January 2025
	Final CSR (LPLV) Version 1.0	04 November 2024

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.

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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:

Amin NB, Darekar A, Anstee QM et al., Efficacy and safety of an orally administered DGAT2 inhibitor alone or coadministered with a liver-targeted ACC inhibitor in adults with non-alcoholic steatohepatitis (NASH): rationale and design of the phase II, dose-ranging, dose-finding, randomised, placebo-controlled MIRNA (Metabolic Interventions to Resolve NASH with fibrosis) study. BMJ Open.2022;12(3):e056159.

Rationale:

This was the first clinical study specifically designed to evaluate the effect of ervogastat and ervogastat + clesacostat on resolution of nonalcoholic steatohepatitis (NASH) or improvement in liver fibrosis as assessed histologically (via liver biopsy). Additional exploratory assessment of non-invasive imaging-based and blood-based collections was also conducted to enable potential identification of non-invasive markers of disease and/or treatment response in the target adult population.

In this study, primary pharmacology of the study drugs was assessed via magnetic resonance imaging using proton density fat fraction acquisition (MRI-PDFF) in participants at selected sites in North America (described as the imaging substudy).

In this report, PF-06865571, a diacylglycerol acyltransferase 2 inhibitor [DGAT2i]) is referred to as ervogastat, and PF-05221304, an acetyl-CoA carboxylase inhibitor [ACCi]) is referred to as clesacostat.

Objectives, Endpoints, and Statistical Methods:

Table 1. Objectives and Endpoints

Type	Objectives	Endpoints
Primary:		
Efficacy	To evaluate the effect of a range of ervogastat doses administered alone, and coadministration of ervogastat + clesacostat, compared to placebo, and the coadministration of ervogastat + clesacostat relative to ervogastat alone, in participants with biopsy-confirmed NASH and fibrosis, on resolution of NASH without worsening of fibrosis or improvement in fibrosis by ≥1 stage without worsening of NASH, or both	Proportion of participants achieving resolution of NASH without worsening of fibrosis or improvement in fibrosis by ≥1 stage without worsening of NASH or both, based on assessment by sponsor-identified central pathologist(s), at Week 48

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Table 1. Objectives and Endpoints

Type	Objectives	Endpoints
Secondary:		
Efficacy	To evaluate the effect of a range of ervogastat doses administered alone, and coadministration of ervogastat + clesacostat, compared to placebo, and the coadministration of ervogastat + clesacostat relative to ervogastat alone, on liver fat	Percent change in liver fat (assessed via MRI-PDFF in substudy population), at Week 48
Efficacy	To evaluate the effect of a range of ervogastat doses administered alone, and coadministration of ervogastat + clesacostat, compared to placebo, and the coadministration of ervogastat + clesacostat relative to ervogastat alone, in participants achieving improvement in different responder definitions	Proportion of participants achieving improvement in different responder definitions based on assessment by sponsor-identified central pathologist(s) at Week 48 – • Resolution of NASH, without worsening of fibrosis • Improvement in fibrosis by ≥1 stage, without worsening of NASH • Improvement in fibrosis by ≥2 stages, without worsening of NASH • Improvement of ≥2 points in Total NAFLD Activity Score (NAS) without worsening
Safety	To assess the safety and tolerability with a range of ervogastat doses administered alone, and coadministration of ervogastat + clesacostat, compared to placebo, and the coadministration of ervogastat + clesacostat relative to ervogastat alone	Assessment of treatment-emergent adverse events (TEAEs), safety-related clinical laboratory tests, vital signs, and 12-lead electrocardiograms (ECGs), over time up to Week 48

For all endpoints, baseline is defined as the evaluable result closest prior to dosing on Day 1/Visit 5

The planned analyses, analysis populations, comparisons, and statistical tests are described in the final version of the SAP V3.0 issued prior to unblinding the study database.

Methodology:

This was a multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled, dose-ranging/finding, parallel group, evaluation of ervogastat monotherapy and coadministration of ervogastat + clesacostat, in participants with biopsy-proven NASH with fibrosis stage F2 (defined as significant fibrosis with scarring extending from hepatocytes to endothelial cells) or F3 (defined as bridging fibrosis extending to portal tracts) as assessed by the Sponsor-identified central pathologist(s). Study intervention was administered orally, twice daily (BID) for up to 48 weeks, with the participants randomized to 1 of 9 (Original

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Protocol) or 1 of 7 (Protocol Amendment 1) treatment arms. Participants were assigned double-blind, double-dummy administration of placebo, 1 of up to 4 doses/dosing regimens of ervogastat monotherapy, or 1 of 2 dose-levels of ervogastat + clesacostat.

Number of Participants (Planned and Analyzed):

This study planned to randomize approximately 350 participants (50/arm) to ensure approximately 40/arm offer evaluable data for the primary objective. However, the COVID-19 pandemic resulted in slower recruitment and less than planned number of participants being randomized.

A total of 2327 participants entered prequalification (PreQ) with 1173 (50.4%) entering the main study (ie, SCR1 [screening 1]). A total of 256 were randomized into the study; of these, 255 participants were treated. A total of 229 participants completed the 48-week double-blind treatment phase, and 230 participants completed the 4-week safety follow-up phase. Data from 3 randomized participants – 2 from a site that was closed for GCP non-compliance and 1 who was randomized but not dosed/treated – were excluded. The number of participants (both planned and analyzed) in the study is shown in Table 2:

Table 2. Number of Participants (Planned and Analyzed)

Population	N	Definition
Planned	~350	
Enrolled	1173	Participants who sign the Main study ICD and entered the Main study
Randomized	256	Randomly assigned to investigational product
Randomized and Dosed	255	All randomized participants who had taken at least 1 dose of investigational product
FAS	255	All randomized participants who had taken at least 1 dose of investigational product who had provided baseline data for the primary endpoint (i.e. evaluable baseline biopsy data). Participants were analyzed according to the treatment group they were randomized to. • The only exception to this was for participants randomized before Protocol Amendment 1 was enacted who were randomized to either of the 2 QD (once daily) dosing regimens of ervogastat alone, were analyzed under the corresponding ervogastat BID treatment group.
SAS	255	All participants who had taken at least 1 dose of investigational product. Participants were analyzed according to the treatment they actually received. • The only exception to this was for participants randomized before Protocol Amendment 1 was enacted who were randomized to either of the 2 QD dosing regimens of ervogastat alone, were analyzed under the corresponding ervogastat BID treatment group.

FAS=full analysis set; SAS=safety analysis set

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The number of participants included in each analysis population was well balanced across treatment groups except in the ervogastat 75 mg BID and 150 mg BID monotherapy dose groups. The proportion of participants was higher in these groups due to the pooling of participants randomized to ervogastat monotherapy 150 mg QD and 300 mg QD with 75 mg BID and 150 mg BID, respectively, while retaining the same total daily dose.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were participants with biopsy-confirmed NASH with F2 or F3 fibrosis as assessed centrally by 2, Sponsor-identified, independent, NASH-CRN central pathologist(s).

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

The following tablet strengths were provided centrally by the sponsor for use as study intervention:

- Ervogastat: 25 mg, 50 mg and 150 mg PF-06865571 tablets and matching placebo;
- Clesacostat: 5 mg and 10 mg PF-05221304 tablets and matching placebo.

Table 3. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength /Potency	Dosage Form
PF-05221304-82 Trihydrate 10 mg Tablet	20-DP-00208	20-002600	10 mg	Tablet
PF-05221304-82 Trihydrate 10 mg Tablet	19-DP-00067	19-003391	10 mg	Tablet
PF-05221304-82 Trihydrate 10 mg Tablet	N/A	21-DP-00470	10 mg	Tablet
PF-05221304-82 Trihydrate 5 mg Tablet	20-DP-00207	20-002597	5 mg	Tablet
PF-05221304-82 Trihydrate 5 mg Tablet	19-DP-00065	19-003390	5 mg	Tablet
PF-05221304-82 Trihydrate 5 mg Tablet	N/A	21-DP 00469	5 mg	Tablet
PF-06865571 150 mg Tablet	20-DP-00155	20-001288	150 mg	Tablet
PF-06865571 150 mg Tablet	20-DP-00156	20-001289	150 mg	Tablet
PF-06865571 150 mg Tablet	19-DP-00086	19-004342	150 mg	Tablet
PF-06865571 150 mg Tablet	20-005081	20-DP-00306	150 mg	Tablet
PF-06865571 150 mg Tablet	20-DP-00309	20-DP-00309	150 mg	Tablet
PF-06865571 150 mg Tablet	20-005084	20-DP-00309	150 mg	Tablet
PF-06865571 150 mg Tablet	20-005085	20-DP-00310	150 mg	Tablet
PF-06865571 150 mg Tablet	N/A	21-DP-00396	150 mg	Tablet
PF-06865571 150 mg Tablet	N/A	21-DP-00398	150 mg	Tablet
PF-06865571 150 mg Tablet	20-DP-00157	20-001290	150 mg	Tablet
PF-06865571 150 mg Tablet	20-DP-00265	20-003903	150 mg	Tablet
PF-06865571 150 mg Tablet	N/A	21-DP-00399	150 mg	Tablet
PF-06865571 150 mg Tablet	N/A	21-DP-00455	150 mg	Tablet
PF-06865571 150 mg Tablet	N/A	21-DP-00456	150 mg	Tablet
PF-06865571 150 mg Tablet	N/A	21-DP-00457	150 mg	Tablet
PF-06865571 150 mg Tablet	20-005081	21-DP-00536	150 mg	Tablet
PF-06865571 25 mg Tablet	20-DP-00141	20-000776	25 mg	Tablet

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Table 3. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength /Potency	Dosage Form
PF-06865571 25 mg Tablet	20-DP-00263	20-003901	25 mg	Tablet
PF-06865571 25 mg Tablet	19-DP-00084	19-004341	25 mg	Tablet
PF-06865571 25 mg Tablet	20-005028	20-DP-00303	25 mg	Tablet
PF-06865571 25 mg Tablet	N/A	21-DP-00449	25 mg	Tablet
PF-06865571 50 mg Oval White to Off-White Tablet	20-DP-00142	20-000777	50 mg	Tablet
PF-06865571 50 mg Oval White to Off-White Tablet	20-DP-00264	20-003902	50 mg	Tablet
PF-06865571 50 mg Oval White to Off-White Tablet	19-DP-00085	19-004338	50 mg	Tablet
PF-06865571 50 mg Oval White to Off-White Tablet	N/A	21-DP-00494	50 mg	Tablet
Placebo 8 mm Tablet	20-DP-00266	20-003900	0 mg	Tablet
Placebo 8 mm Tablet	19-DP-00072	19-003741	0 mg	Tablet
Placebo 8 mm Tablet	N/A	21-DP-00536	0 mg	Tablet
Placebo 8 mm Tablet	20-003900	21-DP-00558	0 mg	Tablet
Placebo Oval Tablet [redacted]	19-DP-00061	19-003191	0 mg	Tablet
Placebo Oval Tablet [redacted]	19-DP-00073	19-003756	0 mg	Tablet
Placebo Oval Tablet [redacted]	19-DP-00062	19-003192	0 mg	Tablet
Placebo Oval Tablet [redacted]	19-DP-00099	20-000029	0 mg	Tablet
Placebo Oval Tablet [redacted]	20-000030	20-000030	0 mg	Tablet

PF-06865571 = ervogastat; PF-05221304 = clesacostat; N/A = Not Applicable [redacted]

Duration of Study Intervention:

The study interventions were packaged together in blister cards for oral dosing. Each dose consisted of 3 tablets, ie, 2 large tablets (ervogastat/matching placebo) and 1 small tablet (clesacostat /matching placebo) and was identical between AM and PM dosing - thus maintaining the blind across all arms.

The overall planned duration of treatment with study intervention was 48 weeks ± 4 days though study drug dispensed permitted dosing for 48 weeks ± 7 days.

Global Substantial Modifications:

The substantial amendment to protocol v1.0 was a result of a strategic decision to reprioritize the number of scientific questions being addressed by this study after accounting for the totality of data generated across multiple studies. These substantial modifications were not prompted by the safety data in Study C2541013 or other ongoing studies in the program (Table 4).

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Table 4. Global Substantial Modifications

Date of Protocol Amendment	Key Revisions
30 August 2021	Participants initially assigned to QD treatment groups were switched, in a blinded manner at their next visit after protocol approval, to the corresponding BID regimen with the same total dose (150 mg/day or 300 mg/day) and analyzed as part of that BID regimen (75 mg BID and 150 mg BID). Thus, the sample size was reduced from 450 (50/arm) to around 350 (still retaining 50/arm) participants, with an intent to ensure about 40 per arm provide evaluable primary endpoint data.
	Other changes included – • Revisions to eligibility criteria which permitted the use of FibroScan® criteria instead of FAST™ scores for some inclusion criteria, increasing the upper BMI (body mass index) limit from 40 kg/m² to 45 kg/m², and permitting re-screening of previously excluded participants under the revised criteria. • Permitting use of alternative imaging techniques for liver biopsies, where allowed, in cases of excessive abdominal girth. • Providing clarifying detail surrounding the reporting of AE/SAEs related to pregnancy, breastfeeding, and occupational exposure.

Global Interruptions and Restarts: Not Applicable.

Summary Of Results:

Demographic and Other Baseline Characteristics:

Demographic and baseline characteristics for the Safety Analysis Set (SAS) were representative of the target population and were balanced across treatment groups.

Across all treatment groups, the median age of participants was 58 years (range 23 to 76 years) and 58.8% were White (27.8% Hispanic or Latino) while 34.1% were Asian. Female participants represented 60.4% of the population randomized and dosed. The median weight of participants (85.91 kg), the median BMI (31.9 kg/m^2), and the median waist circumference (106.00 cm), aligned with the population having traits of metabolic syndrome, and being overweight/having obesity.

Overall, 155 (60.8%) participants had T2DM (type 2 diabetes mellitus) with pharmacological management achieved with the use of up to 3 agents and use of metformin in 122 participants (47.84%) at baseline.

Participants were randomized and dosed across 107 sites, globally (North America=68 sites [n=170 participants], Asia=32 sites [n=77 participants], and Europe=7 sites [n=8

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participants]). Of the 255 participants, 113 participants (44.3%) with baseline MRI data were included in the MRI substudy.

Across the pre-defined stratification factors, 35.3% participants had liver fibrosis stage F2 and 64.7% had liver fibrosis stage F3, as determined on SCR2 biopsy, by central pathologists (as part of determination of eligibility), with 54.9% of the population having a NAS (NAFLD activity score) score ≥5 at baseline.

Exposure:

The planned duration of study intervention was up to 48 weeks (336±4 days). The median (range) duration of study intervention (from the first day up to, and including, the last day of study intervention), in the 255 participants randomized and dosed, was 337.0 (14, 360) days and was similar across treatment groups. Overall, most participants (n=214 [83.9%]) received between 253 and 343 days (i.e., 36.1 to 49 weeks) of study intervention.

Efficacy Results:

Evaluation of Primary and Secondary Endpoints using logistic regression model: For the primary endpoint of proportion of participants achieving resolution of NASH without worsening of fibrosis or improvement in fibrosis by ≥1 stage without worsening of NASH or both, all active doses had a greater response than placebo with both doses-levels of ervogastat + clesacostat significantly outperforming placebo. However, the 12-fold dose range of ervogastat monotherapy evaluated did not separated from placebo, with ≥95% certainty (one-sided) – see figure below.

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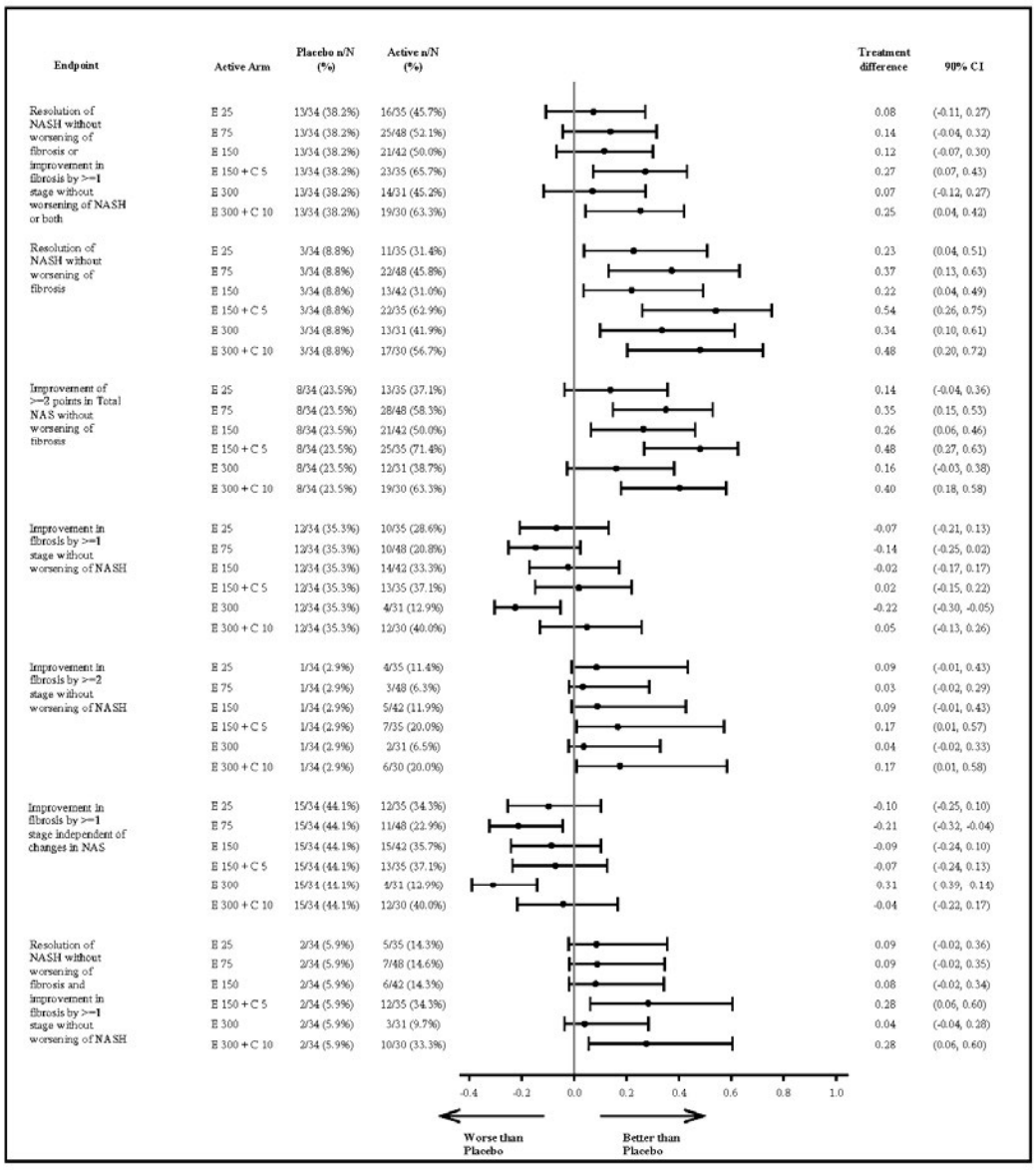

E = PF5571 = Ervogastat and E+C = PF5571+PF1304 = Ervogastat+Clesacostat; N=Number of participants in Full Analysis Set.
Improvement/Resolution endpoints, participants with missing or non-evaluable results are considered not to have improved/resolved.
Logistic Regression model is used with treatment and baseline fibrosis stage (F2/F3) as factors.
Risk difference and 2-sided 90% confidence interval for risk difference were calculated by using the observed placebo rate and estimated odds ratio from the logistic regression model.
PFIZER CONFIDENTIAL SDTM Creation: 14MAY2024 (05:55) Source Data: adbiop Table Generation: 17SEP2024 (06:49)
Output File: /nda_nash/C2541013/adbiop_rtf001

All doses of ervogastat and both dose-levels of ervogastat + clesacostat separated from placebo for the NASH component of the primary endpoint (ie, resolution of NASH without worsening in fibrosis) while none of the ervogastat monotherapy or ervogastat + clesacostat dose-level demonstrated separation from placebo for effect on the fibrosis component of the primary endpoint (ie, improvement in fibrosis by ≥1 stage without worsening in NASH). It

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is noteworthy, that ervogastat+clesacostat separated from placebo for the more stringent endpoints of:

- Improvement in fibrosis by ≥2 stages without worsening of NASH,
- Resolution of NASH without worsening of fibrosis and improvement in fibrosis by ≥1 stage without worsening of NASH.

Across the histological endpoints, the lowest dose of ervogastat monotherapy (ie, 25 mg BID) was identified as the minimally efficacious dose, with the top 2 doses studied (ie, ervogastat 150 mg BID and 300 mg BID) yielding comparable maximum efficacy. Both dose-levels of ervogastat + clesacostat demonstrated comparable efficacy across the histological endpoints.

Secondary Endpoint: Percent Change from Baseline in Liver Fat at Week 48 Assessed via MRI-PDFF

The primary pharmacology was demonstrated with a decrease in liver fat (via MRI-PDFF), which clearly separated from placebo, observed across all doses of ervogastat monotherapy and both dose-levels of ervogastat + clesacostat. A greater reduction in liver fat was observed with both dose-levels of ervogastat + clesacostat compared to ervogastat monotherapy with ≥75% certainty (one-sided).

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Table 5. Statistical Analysis of Percent Change From Baseline in Liver Fat (MRI-PDFF) at Week 48 - Pairwise Comparisons With ANCOVA Model (FAS,MRI Substudy, Hypothetical Estimand) (Protocol C2541013)

		Percent Change From Baseline		Difference vs Placebo		Difference of Combination vs corresponding BID		
Treatment	N	LSM (SE)	90% CI	LSM	90% CI	LSM	50% CI	90% CI
Placebo	9	1.41 (22.11)	(-27.32, 41.49)					
PF-5571 25 mg BID	12	-41.00 (18.89)	(-55.79, -21.28)	-41.82	(-62.57, -9.57)			
PF-5571 75 mg BID	18	-42.53 (15.66)	(-54.90, -26.75)	-43.33	(-62.37, -14.64)			
PF-5571 150 mg BID	12	-58.77 (19.44)	(-69.34, -44.56)	-59.35	(-73.95, -36.55)			
PF-5571 150 mg BID + PF-1304 5 mg BID	11	-67.76 (19.93)	(-76.19, -56.36)	-68.21	(-79.72, -50.15)	-21.80	(-34.02, -7.32)	(-48.51, 18.76)
PF-5571 300 mg BID	8	-49.76 (23.70)	(-64.76, -28.38)	-50.46	(-69.53, -19.44)			
PF-5571 300 mg BID + PF-1304 10 mg BID	8	-68.83 (23.72)	(-78.14, -55.56)	-69.27	(-81.08, -50.07)	-37.97	(-49.40, -23.95)	(-62.41, 2.37)

PF5571 = Ervogastat and PF1304 = Clesacostat.
N = number of participants in Full Analysis Set based on Hypothetical Estimand.
For difference of combination vs corresponding BID, comparison is done between PF5571 150 mg BID+ PF1304 5 mg BID vs PF5571 150 mg BID and PF5571 300 mg BID+ PF1304 10 mg BID vs PF5571 300 mg BID.
Log-transformed relative changes from baseline are modelled using an ANCOVA model with treatment and baseline fibrosis stage (F2/F3) as factors, and log-transformed baseline liver fat as a covariate.
Values have been back-transformed from the log scale. Relative change From baseline (RC) was converted to percent change from baseline as follows: Percent change = 100*(RC-1).
PFIZER CONFIDENTIAL SDTM Creation: 14MAY2024 (05:44) Source Data: adgimr Table Generation: 28AUG2024 (02:57)
(Snapshot date : 10MAY2024) Output File: ./nda_nash/C2541013/adgimr_ns002_ancova
Table 14.2.2.3 PF5571 (+PF1304) is for Pfizer internal use.

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Safety Results:

There were no fatal events reported in the study across all the treatment groups. All doses of ervogastat monotherapy and ervogastat + clesacostat combination therapy treatment groups were well tolerated.

SAEs (Serious Adverse Events):

The number of participants with treatment-emergent SAEs was low (n=19) divided across the four ervogastat monotherapy (n=11/156, 7.1%) treatment groups, two ervogastat + clesacostat treatment groups (n=7/65, 10.8%), and placebo (n=1/34; 2.9%).

A total of 4 participants discontinued study intervention due to AEs/SAEs (1 for each of the TEAEs: diabetes mellitus inadequate control, haemangioma, hypertriglyceridemia, and acute kidney injury**)** but continued in the study without taking the study drug and another 6 participants discontinued the study due to AEs/SAEs (1 for each of the TEAEs: COVID-19, breast cancer, abdominal pain, mucoepidermoid carcinoma, post-acute COVID-19 syndrome, and anxiety).

TEAEs (Treatment-Emergent Adverse Events):

The number of participants reporting all-causality TEAEs was similar across all the ervogastat monotherapy treatment groups (76.3%) compared with placebo (76.5%). The number of participants reporting all-causality TEAEs were similar between ervogastat 150 mg BID + clesacostat 5 mg BID (71.4%) and its corresponding ervogastat monotherapy dose at 150 mg BID (71.4%) and lower at ervogastat 300 mg BID + clesacostat 10 mg BID (76.7%) compared with its corresponding ervogastat monotherapy dose at 300 mg BID (83.9%).

Of the 255 participants randomized and dosed, 62 (24%) participants did not report any TEAEs; 104 participants (41%) reported TEAEs of mild intensity, 69 participants (27%) reported TEAEs of moderate intensity, and 20 participants (8%) reported TEAEs of severe intensity. The 20 TEAEs of severe intensity were reported in 2/34 (5.9%) participants receiving placebo, 11/156 (7.1%) receiving ervogastat monotherapy, and 7/65 (10.8%) receiving ervogastat + clesacostat.

There were 32 participants (12.5% of population randomized and dosed) with at least 1 TEAE, which were assessed to be treatment-related by the Investigator. Of these, 30 participants had mild to moderate treatment-related TEAEs across all treatment groups and 2 participants (both in ervogastat 300 mg BID treatment group) had severe treatment-related TEAEs (PTs: acute kidney injury and rash).

Although there was a lack of increasing frequency (or severity) of treatment-related TEAEs with increasing doses of ervogastat monotherapy, there was a numerically higher proportion of participants with treatment-related TEAEs observed with the top 2 doses (ie, ervogastat

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300 mg BID and ervogastat 300 mg BID + clesacostat 10 mg BID dose groups) – 22.6% and 23.3%, respectively, relative to 8.8% on placebo.

AESIs (Adverse Events of Special Interest):

The AESIs for this study were limited to the identified adverse drug reaction of hypertriglyceridemia and thrombocytopenia with clesacostat monotherapy which were applicable to the 2 dose-levels of ervogastat + clesacostat, and COVID-19 (given that study was ongoing during the pandemic). There were no identified adverse drug reactions with ervogastat monotherapy.

The overall number of participants with fasting serum triglyceride result ≥800 mg/dL (≥9 mmol/L) was low (n=2, 5.7% in ervogastat 150 mg BID + clesacostat 5 mg BID and n=1, 3.3% in ervogastat 300 mg BID + clesacostat 10 mg BID) vs. ervogastat monotherapy (n=1, 2.1% in ervogastat 75 mg BID), compared to none of the participants in the placebo group.

None of the participants had platelet count <100,000/mm^3 or clinically meaningful bleeding events.

In this study, 2 participants discontinued their participation due to COVID-19.

Clinical Laboratory Evaluation:

There were 2 participants in whom study intervention was prematurely stopped due to abnormalities in laboratory test results. Sustained elevation in fasting serum triglycerides (TEAE of hypertriglyceridaemia) in 1 participant in ervogastat 150 mg BID + clesacostat 5 mg BID treatment group, required discontinuation of study drug when multiple attempts to reduce fasting triglyceride levels via pharmacological intervention failed though this this participant did complete the study. In another participant receiving ervogastat 300 mg BID, study drug was discontinued due to reduction in eGFR (TEAE of acute kidney injury), with subsequent withdrawal of consent by the participant.

Other Safety Evaluations:

No clinically meaningful findings in the vital signs measurements or ECGs were observed in this study. The observations were comparable across intervention groups.

Conclusions:

The pre-defined primary endpoint on liver histology was met by both dose-levels of ervogastat + clesacostat though not ervogastat alone - this was likely due to the limited sample size and a large placebo response on the improvement in fibrosis by ≥1 stage component of the primary endpoint, observed in this study.

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Both ervogastat alone and ervogastat + clesacostat demonstrated a robust effect on resolution of NASH without worsening fibrosis with clear separation from placebo; and ervogastat + clesacostat also demonstrated separation from placebo in improvement in fibrosis by ≥2 stages without worsening NASH.

Primary pharmacology (reduction in liver fat assessed via MRI-PDFF) was demonstrated by all active doses evaluated, with the effect of ervogastat + clesacostat vs placebo greater than that of ervogastat monotherapy.

The 12-fold dose-range of ervogastat monotherapy along with the 2 dose-levels of ervogastat + clesacostat were well tolerated; however, the observed changes in serum triglycerides and accompanying effect on other lipid parameters with both dose-levels of ervogastat + clesacostat (a known effect associated with clesacostat), are undesirable due to their potential implications for long term cardiometabolic health.