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(71) Demandeur/Applicant:
GEMPHIRE THERAPEUTICS INC., US

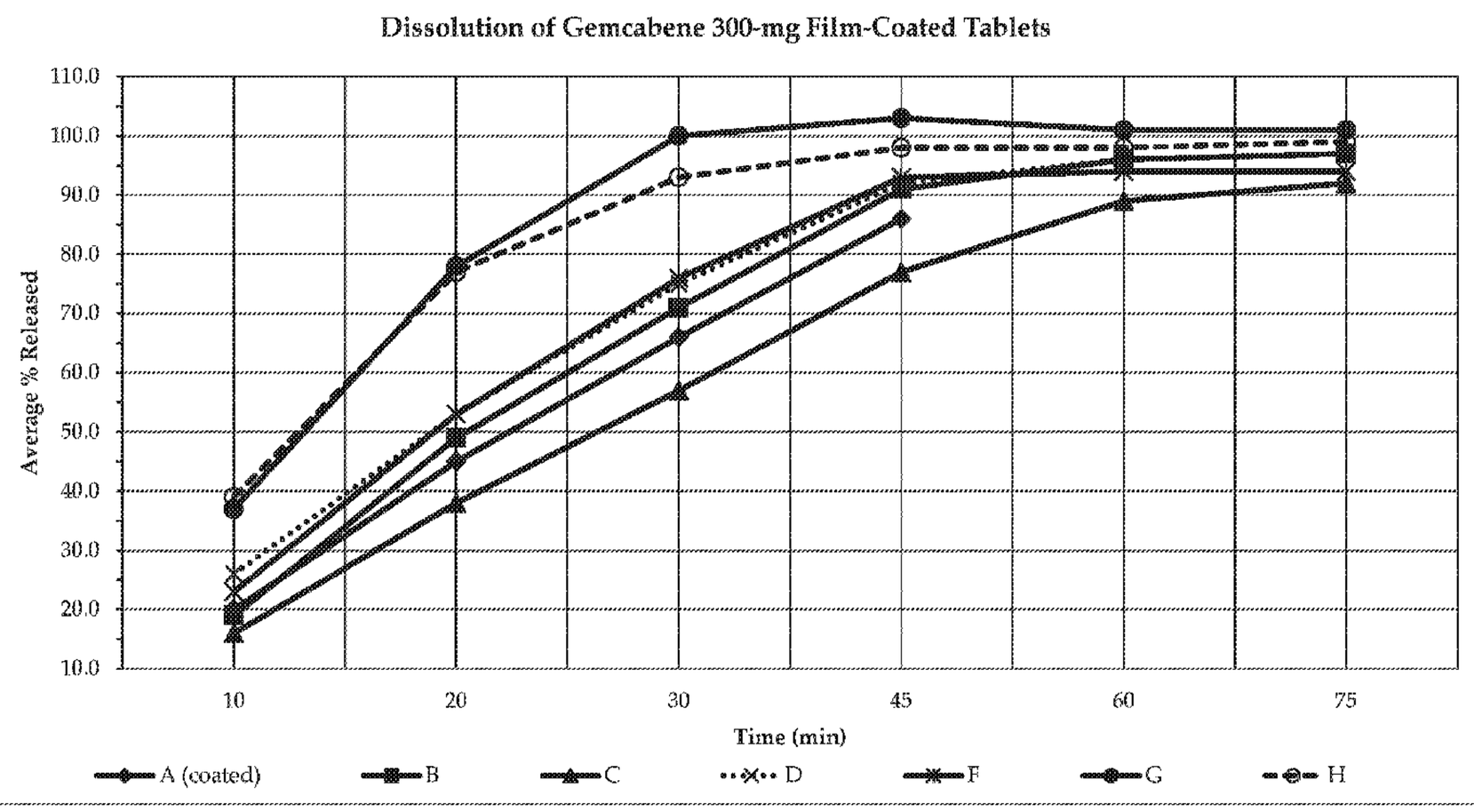
(72) Inventeurs/Inventors:
ONICIU, DANIELA CARMEN, US;
BISGAIER, CHARLES LARRY, US;
GOMES, JOSE RUI, CH;
HECKHOFF, STEFAN, DE

(74) Agent: OYEN WIGGS GREEN & MUTALA LLP

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(54) Title: GEMCABENE, PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF, COMPOSITIONS THEREOF AND METHODS OF USE THEREFOR

Fig. 1A



(57) Abrégé/Abstract:
This present invention provides gemcabene pharmaceutically acceptable salts having a PSD90 of 35 µm to about 90 µm, methods for purifying crude gemcabene, pharmaceutically acceptable salts of purified gemcabene, pharmaceutical compositions of a gemcabene pharmaceutically acceptable salt and therapeutic and prophylactic methods useful for various conditions, including dyslipidemia.

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(71) Applicant: **GEMPHIRE THERAPEUTICS INC.** [US/US]; 17199 North Laurel Park, Suite 401, Livonia, Michigan 48152 (US).

(72) Inventors: **ONICIU, Daniela Carmen**; 4148 NW 34th Drive, Gainesville, Florida 32505 (US). **BISGAIER, Charles Larry**; 3605 Tanglewood Dr., Ann Arbor, Michigan 48105 (US). **GOMES, José Rui**; Hasenmattstrasse 3, 4059 Basel (CH). **HECKHOFF, Stefan**; Schlossstrasse 51 A, 79541 Loerrach (DE).

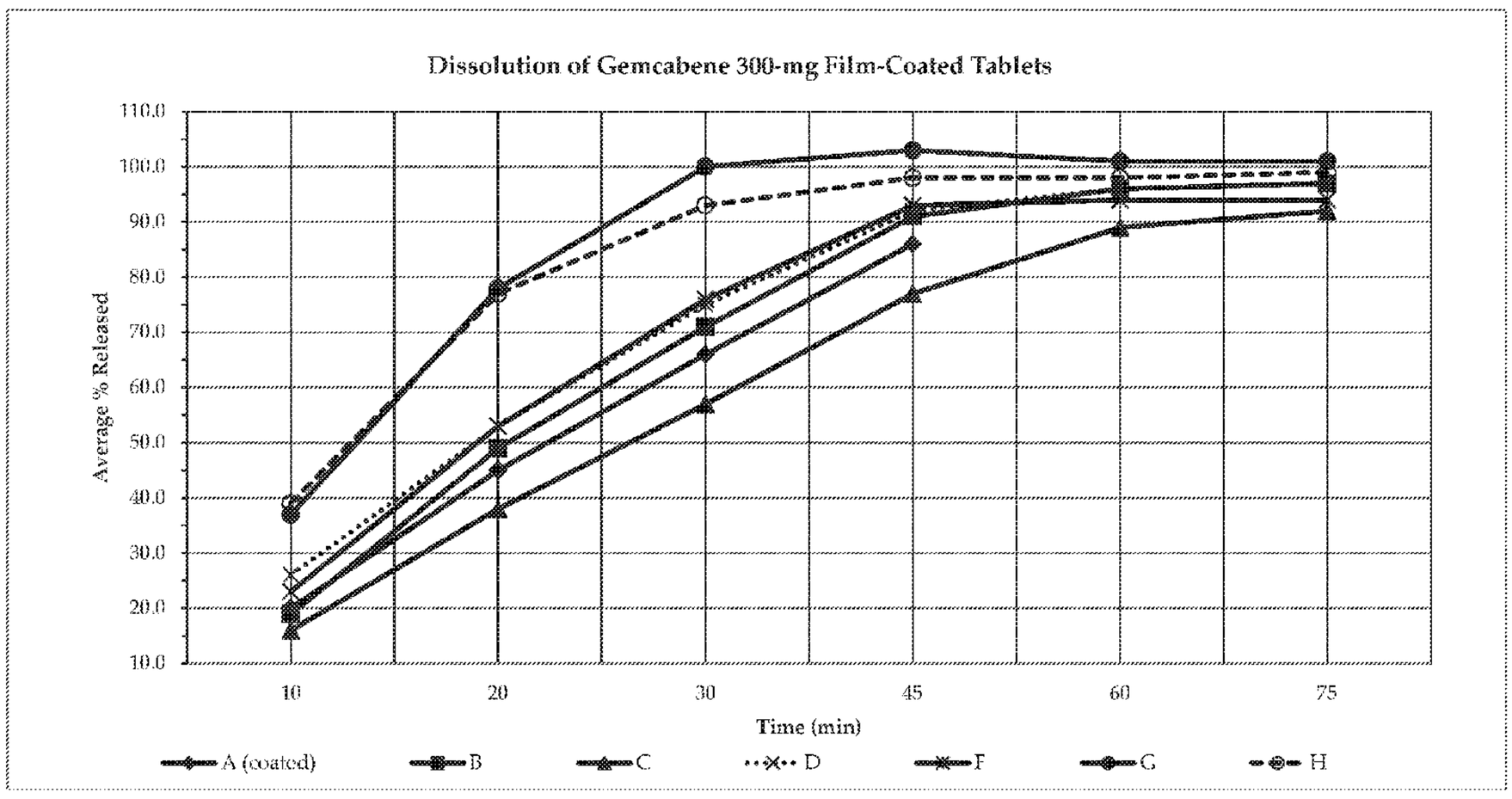
(74) Agent: **LANGER, Matthew E.** et al.; Cooley LLP, 1299 Pennsylvania Avenue, Suite 700, Washington, District of Columbia 20004 (US).

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(54) Title: GEMCABENE, PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF, COMPOSITIONS THEREOF AND METHODS OF USE THEREFOR

Fig. 1A



(57) Abstract: This present invention provides gemcabene pharmaceutically acceptable salts having a PSD90 of 35 μm to about 90 μm, methods for purifying crude gemcabene, pharmaceutically acceptable salts of purified gemcabene, pharmaceutical compositions of a gemcabene pharmaceutically acceptable salt and therapeutic and prophylactic methods useful for various conditions, including dyslipidemia.

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GEMCABENE, PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF, COMPOSITIONS THEREOF AND METHODS OF USE THEREFOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/486,728, filed April 18, 2017, U.S. Provisional Application No. 62/486,822, filed April 18, 2017, U.S. Provisional Application No. 62/569,358, filed October 6, 2017, and U.S. Provisional Application No. 62/584,576, filed November 10, 2017, the disclosure of each of which is incorporated by reference herein in its entirety.

DESCRIPTION OF THE TEXT FILE SUBMITTED ELECTRONICALLY

[0002] The contents of the text file submitted electronically herewith are incorporated herein by reference in their entirety: A computer readable format copy of the Sequence Listing (filename: GMPH_004_04WO_SeqList_ST25.txt; date recorded: April 18, 2018; file size 9,110 bytes).

FIELD OF THE INVENTION

[0003] This invention provides pharmaceutically acceptable salts of 6-(5-carboxy-5-methyl-hexyloxy)-2,2-dimethyl-hexanoic acid ("gemcabene"), wherein the pharmaceutically acceptable salts have a PSD90 ranging from 35 μm to about 90 μm as measured by laser light diffraction, and compositions comprising (i) an effective amount of a pharmaceutically acceptable salt of gemcabene, wherein the pharmaceutically acceptable salt has a PSD90 ranging from 35 μm to about 90 μm as measured by laser light diffraction, and (ii) a pharmaceutically acceptable carrier or vehicle. This invention further provides methods for purifying crude gemcabene, comprising dissolving the crude gemcabene in in heptane to provide a heptane solution of the crude gemcabene and cooling the heptane solution to a temperature ranging from 10 °C to 15 °C to precipitate gemcabene. The invention further provides pharmaceutically acceptable salts of gemcabene as synthesized or purified by the methods of the invention. The pharmaceutically acceptable salts of gemcabene and compositions thereof are useful for treating or preventing liver disease or an abnormal liver condition, a disorder of lipoprotein or glucose metabolism, a cardiovascular or related vascular disorder, a disease caused by fibrosis (such as liver fibrosis), or a disease associated with inflammation (such as liver inflammation).

BACKGROUND

[0004] Elevated levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides are associated with mixed dyslipidemia including type IIb hyperlipidemia. Type IIb is characterized

by elevation of apolipoprotein B, very low-density lipoprotein cholesterol (VLDL-C), intermediate density lipoprotein cholesterol (IDL), and small dense low-density lipoprotein (LDL) levels, in addition to elevation in LDL-C and triglyceride levels.

[0005] Individuals with mixed dyslipidemia including individuals with type IIb hyperlipidemia have an increased rate of developing a cardiovascular disease and those individual with familial combined hyperlipidemia (FCHL) have a high incidence of premature coronary artery disease. Familial hyperlipidemias can be classified according to the Fredrickson classification, which is based on the pattern of lipoprotein migration in electrophoresis or ultracentrifugation. In addition, type IIb patients have a high risk of developing non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatosis hepatitis (NASH), which are forms of fatty liver that can develop due to hepatic triglyceride overproduction and accumulation. NAFLD is strongly associated with features of metabolic syndrome, including obesity, insulin resistance, type-2 diabetes mellitus, and dyslipidemia. NASH can cause the liver to swell and become damaged. NASH tends to develop in people who are overweight or obese, or have diabetes, or mixed dyslipidemia, or high cholesterol or high triglycerides or an inflammatory condition. NASH is marked by hepatocyte ballooning and liver inflammation, which can lead to liver damage and progress to scarring and irreversible changes, similar to the damage caused by heavy alcohol use.

[0006] NAFLD, NASH or fatty liver can lead to metabolic complications including elevation of liver enzymes, fibrosis, cirrhosis, hepatocellular carcinoma, and liver failure. Liver failure is life-threatening and therefore there is a need to develop therapies to delay development, prevent formation or reverse the condition of a fatty liver, such as in type IIb patients and other patients at risk for, or present with fatty liver disease.

[0007] Current treatment options for type IIb hyperlipidemia are limited. While statins are very effective at lowering LDL-C, in general they are not very effective at also lowering triglyceride concentrations. Further, high dose statin therapy is often not well tolerated because it can cause muscle pain (myalgia) and increase patient's risk for serious muscle toxicity, such as rhabdomyolysis. Also, commonly used triglyceride lowering agents that are given in combination with statins are not well-tolerated. Fibrates when given with statins are known to have drug-drug interactions resulting in increased statin blood drug levels and present an increased safety risk. Indeed, the interaction of the statin, Baychol (Cerivastatin) with the fibrate, gemfibrozil resulted severe muscle toxicity and deaths, and raised safety concerns that resulted in the removal of Baychol from the market. Fibrates are associated with myalgia and an increased risk of muscle toxicity, fish oil needs to be taken multiple times daily, and is associated with a fish oil aftertaste, burping or regurgitation, and niacin causes flushing particularly when administered in combination with statins.

[0008] Thus, there is a need for a safe and efficacious treatment for type IIb hyperlipidemia which can lower one or both LDL-C concentrations and triglyceride concentrations, treatment or prevention of liver disease or an abnormal liver condition, a disorder of lipoprotein or glucose metabolism, a cardiovascular or related vascular disorder, a disease caused by increased levels of fibrosis, or a disease associated with increased inflammation, with minimal risks or side effects.

[0009] Further, a pharmaceutically acceptable salt of gemcabene having a PSD90 of less than 30 µm can be difficult to handle due to its low density and/or increased electrostatic properties. Without bound to any theory, particles having low density and/or high electrostatic properties render tableting these particles difficult, particularly in manufacturing processes.

SUMMARY OF THE INVENTION

[0010] The present invention provides pharmaceutically acceptable salts of gemcabene, the pharmaceutically acceptable salts having a particle size distribution characterized by a PSD90 ranging from 35 µm to about 90 µm as measured by laser light diffraction and providing a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 200 µg·hr/mL at steady state to about 6000 µg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[0011] The present invention still further provides pharmaceutically acceptable salts of gemcabene, the pharmaceutically acceptable salts having a PSD90 ranging from 35 µm to about 90 µm as measured by laser light diffraction and providing a plasma gemcabene AUC_{last} ranging from about 50 µg·hr/mL to about 7500 µg·hr/mL after a single dose administration of about 50 mg to about 900 mg to a human subject.

[0012] The present invention still further provides methods for purifying crude gemcabene, wherein the crude gemcabene comprises no more than 1% w/w of 2,2,7,7-tetramethyl-octane-1,8-dioic acid as determined by high-performance liquid chromatography, comprising: dissolving the crude gemcabene in heptane to provide a heptane solution of the crude gemcabene; and cooling the heptane solution to a temperature ranging from 10 °C to 15 °C to precipitate gemcabene, wherein the gemcabene comprises 0.5% w/w or less of 2,2,7,7-tetramethyl-octane-1,8-dioic acid by area as determined by high-performance liquid chromatography.

[0013] The present invention still further provides gemcabene purified by the methods of the present invention.

[0014] The present invention still further provides pharmaceutically acceptable salts of gemcabene prepared from the gemcabene purified by the methods of the present invention.

[0015] A gemcabene pharmaceutically acceptable salt disclosed herein is a "compound of the invention".

[0016] The present invention still further provides compositions comprising an effective amount of a compound of the invention, and a pharmaceutically acceptable carrier or vehicle (each composition being a "composition of the invention").

[0017] The present invention still further provides methods for treating or preventing a liver disease or an abnormal liver condition, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0018] The present invention still further provides methods for treating or preventing a disorder of lipoprotein metabolism, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0019] The present invention still further provides methods for reducing in a subject's blood plasma or blood serum the subject's total cholesterol concentration, low-density lipoprotein cholesterol concentration, low-density lipoprotein concentration, very low-density lipoprotein cholesterol concentration, very low-density lipoprotein concentration, non-HDL cholesterol concentration, non-HDL concentration, apolipoprotein B concentration, triglyceride concentration, apolipoprotein C-III concentration, C-reactive protein concentration, fibrinogen concentration, lipoprotein(a) concentration, interleukin-6 concentration, angiopoietin-like protein 3 concentration, angiopoietin-like protein 4 concentration, PCSK9 concentration, or serum amyloid A concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0020] The present invention still further provides methods for elevating in the subject's blood plasma or blood serum the subject's high-density lipoprotein cholesterol concentration, high-density lipoprotein concentration, high-density cholesterol triglyceride concentration, adiponectin concentration or apolipoprotein A-I concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0021] The present invention still further provides methods for treating or preventing thrombosis, a blood clot, a primary cardiovascular event, a secondary cardiovascular event, progression to nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, liver cirrhosis hepatocellular carcinoma, liver failure, pancreatitis, pulmonary fibrosis or hyperlipoproteinemia type IIB, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0022] The present invention still further provides methods for reducing a subject's risk of developing thrombosis, a blood clot, a primary cardiovascular event, a secondary cardiovascular event, progression to nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, liver cirrhosis, hepatocellular carcinoma, liver failure, pancreatitis, pulmonary fibrosis or hyperlipoproteinemia

type IIB, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0023] The present invention still further provides methods of reducing or inhibiting progression of fibrosis, steatosis, ballooning or inflammation in the liver of a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0024] The present invention still further provides methods for reducing post-prandial lipemia or preventing prolonged post-prandial lipemia, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0025] The present invention still further provides methods for reducing a fibrosis score or a nonalcoholic fatty liver disease activity score in a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0026] The present invention still further provides methods for stabilizing, regressing, or maintaining a fibrosis score or a nonalcoholic fatty liver disease activity score in a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0027] The present invention still further provides methods for slowing the progression of a fibrosis score or a nonalcoholic fatty liver disease activity score in a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0028] The present invention still further provides methods for reducing a fat content in a liver of a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0029] The present invention still further provides methods for treating or preventing a disorder of glucose metabolism, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0030] The present invention still further provides methods for treating or preventing a cardiovascular disorder or a related vascular disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0031] The present invention still further provides methods for treating or preventing inflammation, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0032] The present invention still further provides methods for preventing or reducing the risk of developing pancreatitis, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0033] The present invention still further provides methods for treating or preventing a pulmonary disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0034] The present invention still further provides methods for treating or preventing musculoskeletal discomfort, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0035] The present invention still further provides methods for lowering a subject's LDL-C concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

BRIEF DESCRIPTION OF THE FIGURES

[0036] Fig. 1A is a line graph showing a dissolution profile of gemcabene from a composition of the invention in the form of a film-coated tablet.

[0037] Fig. 1B is a line graph showing a dissolution profile of gemcabene from a composition of the invention in the form of a film-coated tablet.

[0038] Fig. 2 is a scanning electron micrograph of gemcabene calcium salt hydrate Crystal Form 1 having a particle size distribution characterized by a PSD90 of about 58 μm as measured by laser light diffraction.

[0039] Fig. 3 is a line graph showing LDL-C concentrations of three familial hypercholesterolemia patients (1F, 2M and 3M) as measured during the course of their treatment with gemcabene calcium salt hydrate Crystal Form 1 having a particle size distribution characterized by a PSD90 of 52 μm as measured by laser light diffraction (gemcabene calcium salt hydrate Crystal Form 1, 300-mg strength film-coated tablet, Tablet D).

[0040] Fig. 4 is a line graph showing values for percent change from baseline of LDL-C concentrations of the three familial hypercholesterolemia patients (1F, 2M and 3M) shown in Fig. 3 as measured during the course of their treatment with gemcabene calcium salt hydrate Crystal Form 1 having a particle size distribution characterized by a PSD90 of 52 μm as measured by laser light diffraction (gemcabene calcium salt hydrate Crystal Form 1 300-mg strength film-coated tablet, Tablet D).

[0041] Fig. 5A shows photomicrographs of hematoxylin and eosin-stained liver sections of STAM™ model mice treated with gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (ID: 306) or with vehicle (ID: 208) and photomicrographs of hematoxylin and eosin-stained liver sections of normal mice treated with vehicle (ID: 103).

[0042] Fig. 5B shows photomicrographs of hematoxylin and eosin-stained liver sections of STAM™ model mice treated with gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (ID: 402 and 508) and photomicrographs of hematoxylin and eosin-stained liver sections of STAM™ model mice treated with reference compound telmisartan.

[0043] Fig. 6 shows photomicrographs of Sirius red-stained liver sections of STAM™ model mice treated with vehicle (ID: 208), treated with gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (ID: 303, 403, 501), or treated with reference compound telmisartan (ID: 606) and photomicrographs of Sirius red-stained liver sections of normal mice treated with vehicle (ID: 102).

[0044] Fig. 7 shows graphs with components of the NAFLD Activity Score (NAS) of STAM™ model mice treated with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction or reference compound telmisartan and normal mice treated with vehicle.

[0045] Fig. 8A shows a graph of the NAS in STAM™ model mice treated with (a) vehicle, gemcabene calcium salt hydrate Crystal Form 1 with a PSD90 of 52 μm as measured by laser light diffraction or reference compound telmisartan. **Fig. 8B** shows a graph of the liver Sirius-red positive area (the fibrosis area) in STAM™ model mice treated with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction or reference compound telmisartan.

[0046] Fig. 9 is a graph showing non-fasting plasma triglyceride concentrations in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0047] Fig. 10 is a graph showing gene expression levels of hepatic sulfatase 2 (Sulf-2) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0048] Fig. 11 is a graph showing gene expression levels for hepatic apolipoprotein C-III (ApoC-III) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0049] Fig. 12 is a graph showing gene expression levels for hepatic sterol regulatory element binding transcription factor 1 (SREBP-1) in normal mice treated with vehicle and NASH-

induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0050] Fig. 13 is a graph showing gene expression levels for hepatic chemokine (C-C motif) ligand 4 (MIP-1β) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0051] Fig. 14 is a graph showing gene expression levels for hepatic chemokine (C-C motif) receptor 5 (CCR5) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0052] Fig. 15 is a graph showing gene expression levels for chemokine (C-C motif) receptor 2 (CCR2) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0053] Fig. 16 is a graph showing gene expression levels for hepatic nuclear factor of kappa light polypeptide gene enhancer in B cells 1 (NF-κB) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0054] Fig. 17 is a graph showing gene expression levels for hepatic C-reactive protein, pentraxin-related (CRP) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0055] Fig. 18 is a graph showing gene expression levels for hepatic low-density lipoprotein receptor (LDL-receptor) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0056] Fig. 19 is a graph showing gene expression levels for hepatic acetyl-coenzyme A carboxylase alpha (ACC1) in normal mice treated with vehicle and NASH-induced mice treated

for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0057] Fig. 20 is a graph showing gene expression levels for hepatic acetyl-coenzyme A carboxylase beta (ACC2) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0058] Fig. 21 is a graph showing gene expression levels for hepatic patatin-like phospholipase domain containing 3 (PNPLA3) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0059] Fig. 22 is a graph showing gene expression levels for hepatic matrix metalloproteinase 2 (MMP-2) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0060] Fig. 23 is a graph showing gene expression levels for hepatic alcohol dehydrogenase 4 (class II), pi polypeptide (ADH4) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0061] Fig. 24 is a graph showing hepatic gene expression levels for tumor necrosis factor alpha (TNF-α) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0062] Fig. 25 is a graph showing gene expression levels for hepatic chemokine (C-C motif) ligand 2 (MCP-1) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0063] Fig. 26 is a graph showing hepatic gene expression levels for actin, alpha smooth muscle actin (α-SMA) in normal mice treated with vehicle and NASH-induced mice treated for three

weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0064] Fig. 27 is a graph showing gene expression levels for hepatic tissue inhibitor of metalloproteinase 1 (TIMP-1) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0065] Fig. 28 is a powder X-ray diffractogram of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (Sample 4 in Table 2).

[0066] Fig. 29 is a powder X-ray diffractogram of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 62 μm as measured by laser light diffraction (Sample 7 in Table 2).

[0067] Fig. 30 shows measurements of amorphous gemcabene calcium particle size distribution.

[0068] Fig. 31 shows the effect of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction on the correlation between hepatic ApoC-III or hepatic Sulf-2 and plasma triglycerides in a diabetic mouse model.

[0069] Fig. 32 is a graph showing hepatic gene expression levels for interleukin 6 (IL-6) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0070] Fig. 33 is a graph showing hepatic gene expression levels for interleukin 1β (IL-1β) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0071] Fig. 34 is a graph showing hepatic gene expression levels for chemokine (C-X-C motif) ligand 1 (CXCL1/KC) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0072] Fig. 35 is a graph showing hepatic gene expression levels for stearoyl-coenzyme A desaturase (SCD) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0073] Fig. 36 is a graph showing hepatic gene expression levels for lipoprotein lipase (LPL) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0074] Fig. 37 is a graph showing hepatic gene expression levels for angiopoietin-like protein 3 (ANGPTL3) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0075] Fig. 38 is a graph showing hepatic gene expression levels for angiopoietin-like protein 4 (ANGPTL4) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0076] Fig. 39 is a graph showing hepatic gene expression levels for angiopoietin-like protein 8 (ANGPTL8) in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0077] Fig. 40 is a graph showing hepatic gene expression levels for fetuin-A in normal mice treated with vehicle and NASH-induced mice treated for three weeks with vehicle, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 52 μm as measured by laser light diffraction (30, 100 or 300 mg/kg) or reference compound telmisartan (10 mg/kg).

[0078] Fig. 41A shows arithmetic-mean concentration of gemcabene (±SD) versus time, overlaid by dose for the time points collected 0-24 h post-dose displayed on linear axes.

[0079] Fig. 41B shows arithmetic-mean concentration of gemcabene (±SD) versus time, overlaid by dose for the time points collected 0-24 h post-dose displayed on semi-log axes.

[0080] Fig. 42A shows arithmetic-mean predose (C_{trough}) concentration of gemcabene (±SD) versus time, overlaid by dose.

[0081] Fig. 42B shows arithmetic-mean predose (C_{trough}) concentration of gemcabene (±SD) versus time, overlaid by dose with the 900 mg Day 28 trough concentration from patient 006-003 excluded.

[0082] Fig. 43 is a line graph showing values for percent change from baseline of LDL-C concentrations of the eight familial hypercholesterolemia patients in Example 19 as measured during the course of their treatment with gemcabene calcium salt hydrate Crystal Form 1 having

a particle size distribution characterized by a PSD90 of 52 µm as measured by laser light diffraction (gemcabene calcium salt hydrate Crystal Form 1 300-mg strength film-coated tablet, Tablet D).

[0083] Fig. 44 is a line graph showing values for percent change from baseline of LDL-C concentrations of the three familial hypercholesterolemia patients, who were determined to have homozygous familial hypercholesterolemia (HoFH) genotype based on post-trial genetic assessment, as measured during the course of their treatment with gemcabene calcium salt hydrate Crystal Form 1 having a particle size distribution characterized by a PSD90 of 52 µm as measured by laser light diffraction (gemcabene calcium salt hydrate Crystal Form 1 300-mg strength film-coated tablet, Tablet D).

[0084] Fig. 45 is a line graph showing values for percent change from baseline of LDL-C concentrations of the three familial hypercholesterolemia patients, who were determined to have heterozygous familial hypercholesterolemia (HeFH) genotype based on post-trial genetic assessment, as measured during the course of their treatment with gemcabene calcium salt hydrate Crystal Form 1 having a particle size distribution characterized by a PSD90 of 52 µm as measured by laser light diffraction (gemcabene calcium salt hydrate Crystal Form 1 300-mg strength film-coated tablet, Tablet D).

[0085] Fig. 46 shows least square (LS) mean % change in atherogenic biomarkers from baseline in hypercholesterolemia subjects on stable moderate and high intensity statins receiving gemcabene calcium salt hydrate Crystal Form 1 (PSD90 = 52 µm).

[0086] Fig. 47 shows least square (LS) mean % change in atherogenic biomarkers from placebo in hypercholesterolemia subjects on stable moderate and high intensity statins receiving gemcabene calcium salt hydrate Crystal Form 1 (PSD90 = 52 µm).

[0087] Fig. 48 shows least square (LS) mean % change in atherogenic biomarkers from placebo in mixed dyslipidemia subjects (LDL-C ≥ 100 mg/dL and triglycerides ≥ 200 and < 500 mg/dL) on stable moderate and high intensity statins receiving gemcabene calcium salt hydrate Crystal Form 1 (PSD90 = 52 µm).

[0088] Fig. 49 shows least square (LS) mean % change in inflammatory markers from baseline in hypercholesterolemia subjects on stable moderate and high intensity statins receiving gemcabene calcium salt hydrate Crystal Form 1 (PSD90 = 52 µm).

[0089] Fig. 50 shows least square (LS) mean % change in an inflammatory marker from placebo in hypercholesterolemia subjects on stable moderate and high intensity statins receiving gemcabene calcium salt hydrate Crystal Form 1 (PSD90 = 52 µm).

[0090] Fig. 51 shows least square (LS) mean % change in inflammatory markers from placebo in mixed dyslipidemia subjects (LDL-C ≥ 100 mg/dL and triglycerides ≥ 200 and < 500 mg/dL) on

stable moderate and high intensity statins receiving gemcabene calcium salt hydrate Crystal Form 1 (PSD90 = 52 μm).

[0091] Fig. 52A is a X-ray powder diffractogram of amorphous gemcabene calcium salt.

[0092] Fig. 52B is an overlay of a thermogravimetric analysis (TGA) thermogram and differential thermal analysis (DTA) thermogram of amorphous gemcabene calcium salt.

[0093] Fig. 52C is a differential scanning calorimetry (DSC) thermogram of amorphous gemcabene calcium salt.

[0094] Fig. 53A is a X-ray powder diffractogram of gemcabene calcium salt Crystal Form 2.

[0095] Fig. 53B is an overlay of a thermogravimetric analysis (TGA) thermogram and differential thermal analysis (DTA) thermogram of gemcabene calcium salt Crystal Form 2.

[0096] Fig. 54A is a X-ray powder diffractogram of gemcabene calcium salt Crystal Form C3.

[0097] Fig. 54B is an overlay of a thermogravimetric analysis (TGA) thermogram and differential thermal analysis (DTA) thermogram of gemcabene calcium salt Crystal Form C3.

[0098] Fig. 54C is a differential scanning calorimetry (DSC) thermogram of gemcabene calcium salt Crystal Form C3.

[0099] Fig. 55A is a X-ray powder diffractogram of crystalline gemcabene calcium salt ethanol solvate.

[00100] Fig. 55B is an overlay of a thermogravimetric analysis (TGA) thermogram and differential thermal analysis (DTA) thermogram of crystalline gemcabene calcium salt ethanol solvate.

DETAILED DESCRIPTION OF THE INVENTION

[00101] The present invention provides compounds of the invention. In some embodiments, the compound of the invention is gemcabene calcium salt. In some embodiments, the compound of the invention is gemcabene calcium salt hydrate. In some embodiment, the compound of the invention is amorphous or crystalline pharmaceutically acceptable salt of gemcabene. Gemcabene has been previously described, e.g., in U.S. Patent No. 5,648,387, which is hereby incorporated by reference in its entirety. Various gemcabene calcium salt hydrates have been previously described, e.g., in U.S. Patent No. 6,861,555, which is hereby incorporated by reference in its entirety.

[00102] The present invention further provides compositions of the invention. In some embodiments, the compositions of the invention further comprise an additional pharmaceutically active agent. In other embodiments, the compositions of the invention further comprise two or more additional pharmaceutically active agents. The compositions of the invention are useful for treating or preventing various diseases including liver disease or an abnormal liver condition, a

disorder of lipoprotein or glucose metabolism, a cardiovascular or related vascular disorder, a disease caused by increased levels of fibrosis, or a disease associated with increased inflammation. The invention further provides methods for treating or preventing liver disease or an abnormal liver condition, a disorder of lipoprotein or glucose metabolism, a cardiovascular or related vascular disorder, a disease caused by increased levels of fibrosis, or a disease associated with increased inflammation, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00103] Each of the therapeutic or prophylactic methods disclosed herein is a "therapeutic or prophylactic method of the invention".

[00104] A compound of the invention has a PSD90 ranging from 35 μm to about 90 μm. In some embodiments, the compound of the invention has a PSD90 ranging from 35 μm to about 85 μm. In some embodiments, the compound of the invention has a PSD90 ranging from 35 μm to about 80 μm. In some embodiments, the compound of the invention has a PSD90 ranging from 35 μm to about 75 μm. In some embodiments, the compound of the invention has a PSD90 ranging from 40 μm to about 75 μm. In some embodiments, the compound of the invention has a PSD90 ranging from 45 μm to about 75 μm. In some embodiments, the compound of the invention has a PSD90 ranging from 50 μm to about 75 μm. In some embodiments, the compound of the invention has a PSD90 ranging from 45 μm to 75 μm. In some embodiments, the compound of the invention has a PSD90 ranging from 50 μm to 75 μm.

[00105] In some embodiments, the compounds of the invention have a dissolution profile having a value of at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm. In some embodiments, the compound of the invention has a dissolution profile having a value of at least 85% in no more than 45 minutes. In some embodiments, the compound of the invention has a dissolution profile having a value of at least 90% in no more than 45 minutes.

[00106] In some embodiments the compounds of the invention have a dissolution profile having a n value of at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm.

[00107] In some embodiments, the compound of the invention is a gemcabene calcium salt. In other embodiments, the compound of the invention is a gemcabene calcium salt hydrate. In some embodiments, the compound of the invention is an amorphous solid. In some embodiments, the compound of the invention is a crystalline polymorph. In some embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form 1. In other embodiments, the

compound of the invention is gemcabene calcium salt hydrate Crystal Form 2. In other embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form C1. In other embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form C2. In other embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form C3. In some embodiments, the compound of the invention is an amorphous gemcabene calcium salt. In some embodiments, the compound of the invention is an amorphous gemcabene calcium salt hydrate.

[00108] In some embodiments, the compound of the invention has a water content of about 2% w/w to about 5% w/w of the compound of the invention. In other embodiments, the compound of the invention has the water content of about 2% w/w to about 4% w/w. In some embodiments, the water content is about 3% w/w to about 5% w/w. In other embodiments, the water content is about 3% w/w to about 4% w/w.

[00109] In some embodiments, the compound of the invention is a gemcabene calcium salt solvate. In some embodiments, the compound of the invention is a gemcabene calcium salt alcohol solvate. In some embodiments, the compound of the invention is a gemcabene calcium salt ethanol solvate. In some embodiments, the compound of the invention is a gemcabene calcium salt *n*-propyl solvate. In some embodiments, the compound of the invention is a gemcabene calcium salt isopropyl solvate. In some embodiments, the compound of the invention is a gemcabene calcium salt methanol solvate. In some embodiments, the compound of the invention is a gemcabene calcium salt *n*-butyl solvate.

[00110] In some embodiments, the compound of the invention has an ethanol content of about 0% w/w to about 0.5% w/w of the compound of the invention. In some embodiments, the compound of the invention has an ethanol content of about 0.5% w/w to about 8% w/w of the compound of the invention.

[00111] In some embodiments, the composition of the invention is in a form of a tablet or a capsule. In some embodiments, the composition of the invention further comprises an effective amount of an additional pharmaceutically active agent. In other embodiments, the composition of the invention further comprises an effective amount of two or more additional pharmaceutically active agents.

[00112] In some embodiments, the additional pharmaceutically active agent is a statin. In some embodiments, the statin is atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin, mevastatin, dalvastatin, dihydrocompactin, or cerivastatin, or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutically acceptable salt of the statin is a calcium salt. In some embodiments, the statin is atorvastatin calcium.

[00113] Other illustrative additional pharmaceutically active agents include, but are not limited to, a lipid lowering agent, a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor, a cholesterol absorption inhibitor, an ACC (acetyl-CoA carboxylase) inhibitor, an ApoC-III (apolipoprotein C-III) inhibitor, an ApoB (apolipoprotein B) synthesis inhibitor, an ANGPTL 3 (angiopoietin-like protein 3) inhibitor, an ANGPTL 4 (angiopoietin-like protein 4) inhibitor, an ANGPTL 8 (angiopoietin-like protein 8) inhibitor, an ACL (adenosine triphosphate citrate lyase) inhibitor, a microsomal transfer protein inhibitor, a fenofibric acid, a fish oil, a fibrate, a thyroid hormone beta receptor agonist, a farnesoid X receptor (FXR), a CCR2/CCR5 (C-C chemokine receptor types 2 (CCR2) and 5 (CCR5)) inhibitor or antagonist, a caspase protease inhibitor, an ASK-1 (Apoptosis signal-regulating kinase 1) inhibitor, a galectin-3 protein, a NOX (Nicotinamide adenine dinucleotide phosphate oxidase) inhibitor, an ileal bile acid transporter, a PPAR (peroxisome proliferator-activated receptor) agonist, a PPAR dual agonist, a pan-PPAR agonist, a sodium-glucose co-transporter 1 or 2 (SGLT1 or SGLT2) inhibitor, a dipeptidyl peptidase 4 (DPP4) inhibitor, a fatty acid synthase (FAS) inhibitor, a toll-like receptor antagonist, a thyroid hormone receptor-beta (THR-β) agonist, a liver-directed, selective THR-β agonist, an ACO1 modulator, a 1-mieloperoxidase inhibitor, a 1-ketohexokinase (1-KHK) inhibitor, an oxidative stress inhibitor, a fibroblast growth factor 21 (FGF21) or 19 (FGF19) inhibitor, a transforming growth factor beta-1 (TGF-β1) agonist, a hepatic de novo lipogenesis (DNL) inhibitor, an enoyl CoA hydratase inhibitor, a cholesterol 7-alpha hydroxylase (Cyp7A1) agonist, a Collagen Type 3 inhibitor, and a CETP (cholesterylester transfer protein) inhibitor. In some embodiments, the additional pharmaceutically active agent is ezetimibe.

[00114] In some embodiments, the additional pharmaceutically active agent is a contraceptive agent. As used herein, a "contraceptive agent" refers to any pharmaceutically active agent that promotes the prevention of conception, impregnation, or implantation or prevents or reduces the likelihood of pregnancy. In some embodiments, the contraceptive agent is one or both of ethinyl estradiol and norethindrone. In some embodiments, the contraceptive agent is a combination of ethinyl estradiol and norethindrone. In some embodiments, the contraceptive agent is estrogen, an estrogen derivative, progestin or a progestin derivative.

[00115] The present invention provides methods for treating or preventing a liver disease or an abnormal liver condition, comprising administering to a subject in need thereof an effective amount of a compound of the invention. Illustrative liver diseases or abnormal liver conditions include, but are not limited to, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, alcoholic steatohepatitis, cirrhosis, inflammation, fibrosis, partial fibrosis, primary biliary cirrhosis, primary sclerosing cholangitis, liver failure, hepatocellular carcinoma, liver cancer, hepatic steatosis, hepatocyte ballooning, hepatic lobular inflammation, and hepatic triglyceride

accumulation. In some embodiments, the liver disease or liver condition is nonalcoholic fatty liver disease or nonalcoholic steatohepatitis.

[00116] The present invention provides methods for treating or preventing an abnormal fibrosis of an internal organ of a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the abnormal fibrosis of an internal organ is in a human subject.

[00117] The present invention provides methods for treating or preventing a disease or an abnormal condition generated by an inflammatory response of an organ in a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the inflammatory response is in an internal organ. In some embodiments, the subject is a human.

[00118] The present invention provides methods for treating or preventing a disorder of lipoprotein metabolism, comprising administering to a subject in need thereof an effective amount of a compound of the invention. Illustrative disorders of lipoprotein metabolism include, but are not limited to, dyslipidemia, dyslipoproteinemia, mixed dyslipidemia, atherosclerotic cardiovascular disease (ASCVD), type IIb hyperlipidemia, familial combined hyperlipidemia, familial hypercholesterolemia, familial chylomicronemia syndrome, hypertriglyceridemia, dysbetalipoproteinemia, lipoprotein overproduction, lipoprotein deficiency, elevation of total cholesterol, elevation of low-density lipoprotein cholesterol concentration, elevation of very low-density lipoprotein cholesterol concentration, elevation of non-HDL cholesterol concentration, elevation of apolipoprotein B concentration, elevation of apolipoprotein C-III concentration, elevation of C-reactive protein concentration, elevation of fibrinogen concentration, elevation of lipoprotein(a) concentration, elevation of interleukin-6 concentration, elevation of angiopoietin-like protein 3 concentration, elevation of angiopoietin-like protein 4 concentration, elevation of serum amyloid A concentration, elevation of PCSK9, increased risk of thrombosis, increased risk of a blood clot, low HDL-cholesterol concentration, elevation of low-density lipoprotein concentration, elevation of very low-density lipoprotein concentration, elevation of triglyceride concentration, prolonged post-prandial lipemia, lipid elimination in bile, a metabolic disorder, phospholipid elimination in bile, oxysterol elimination in bile, abnormal bile production, peroxisome proliferator activated receptor-associated disorder, hypercholesterolemia, hyperlipidemia and visceral obesity. In some embodiments, the disorder of lipoprotein metabolism is mixed dyslipidemia, atherosclerotic cardiovascular disease (ASCVD), type IIb hyperlipidemia, or familial combined hyperlipidemia. In some embodiments, the disorder of lipoprotein metabolism is familial hypercholesterolemia.

[00119] The present invention provides methods for reducing a subject's total cholesterol, low-density lipoprotein cholesterol concentration, very low-density lipoprotein cholesterol concentration, non-HDL cholesterol concentration, apolipoprotein B concentration, apolipoprotein C-III concentration, C-reactive protein concentration, fibrinogen concentration, lipoprotein(a) concentration, interleukin-6 concentration, angiopoietin-like protein 3 concentration, angiopoietin-like protein 4 concentration, serum amyloid A concentration, PCSK9 concentration, low-density lipoprotein concentration, very low-density lipoprotein concentration, or triglyceride concentration, comprising administering to a subject in need thereof, an effective amount of a compound of the invention. In some embodiments, the present invention provides methods for reducing a subject's triglyceride concentration or LDL-cholesterol, comprising administering to a subject in need thereof, an effective amount of a compound of the invention.

[00120] The present invention provides methods for reducing a subject's cholesterol-rich remnant ApoB-lipoprotein or triglyceride-rich remnant ApoB-lipoprotein concentration in the subject's blood serum or plasma, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the present invention provides methods for reducing a subject's cholesterol- and triglyceride-rich remnant ApoB-lipoporteins (C-TRLs) in the subject's plasma, comprising administering to a subject in need thereof, an effective amount of a compound of the invention.

[00121] The present invention provides methods for increasing hepatic clearance of cholesterol-rich remnant ApoB-lipoprotein or triglyceride-rich remnant ApoB-lipoprotein in a subject, comprising administering to a subject in need thereof, an effective amount of a compound of the invention. In some embodiments, the present invention provides methods for enhancing or increasing hepatic clearance of C-TRLs in a subject, comprising administering to a subject in need thereof, an effective amount of a compound of the invention. Without bound to any theory, fast hepatic clearance of C-TRLs lead to less cholesterol deposition (less plaque buildup) in arteries. Thus, increasing hepatic clearance of cholesterol-rich remnant ApoB-lipoprotein, triglyceride-rich remnant ApoB-lipoprotein, or C-TRLs can be useful in treating or preventing cardiovascular diseases including atherosclerosis.

[00122] The present invention provides methods for reducing a subject's risk of thrombosis or blood clot, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00123] The present invention provides methods for treating or preventing a disorder of glucose metabolism, comprising administering to a subject in need thereof an effective amount of a compound of the invention. Illustrative disorders of glucose metabolism include, but are not limited to, insulin resistance, impaired glucose tolerance, impaired fasting glucose (concentration

in blood), diabetes mellitus, familial partial lipodystrophy, lipodystrophy, obesity, peripheral lipoatrophy, diabetic nephropathy, diabetic retinopathy, renal disease, and septicemia. In some embodiments, obesity is central obesity.

[00124] The present invention provides methods for treating or preventing an atherometabolic syndrome, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the present invention provides methods for reducing a subject's risk of developing an atherometabolic syndrome, comprising administering to a subject in need thereof, an effective amount of a compound of the invention. Atherometabolic syndrome, like type 2 diabetes, increases plasma levels of cholesterol- and triglyceride-rich remnant ApoB-lipoproteins (C-TRLs). In some embodiments, atherometabolic syndrome includes metabolic syndrome, which can be defined by a cluster of symptoms that include abdominal obesity, impaired glucose tolerance, dyslipidemia, and raised blood pressure. In some embodiments, atherometabolic syndrome includes one or more conditions associated with increased risk of cardiovascular disease or one or more conditions associated with increased blood pressure, increased LDL-C, lowered HDL-C, and/or increased blood sugar level.

[00125] The present invention provides methods for treating or preventing a cardiovascular disorder or a related vascular disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. Illustrative cardiovascular disorders or related vascular disorders include, but are not limited to, arteriosclerosis, atherosclerosis, hypertension, coronary artery disease, myocardial infarction, arrhythmia, atrial fibrillation, heart valve disease, heart failure, cardiomyopathy, myopathy, pericarditis, impotence, and a thrombotic disorder.

[00126] The present invention provides methods for treating or preventing a C-reactive protein-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the C-reactive protein related disorder is inflammation, ischemic necrosis, or a thrombotic disorder.

[00127] The present invention provides methods for treating or preventing disorders related to modulating inflammation markers or C-reactive proteins, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the disorder related to modulating inflammation markers or C-reactive proteins is inflammation, ischemic necrosis, or a thrombotic disorder.

[00128] The present invention provides methods for treating or preventing Alzheimer's disease, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00129] The present invention provides methods for treating or preventing Parkinson's disease, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00130] The present invention provides methods for treating or preventing pancreatitis, comprising administering to a subject in need thereof an effective amount of a compound of the invention. The present invention provides methods for preventing or reducing the risk of developing pancreatitis, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00131] The present invention provides methods for treating or preventing pulmonary disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the pulmonary disorder is chronic obstructive pulmonary disease or an idiopathic pulmonary fibrosis.

[00132] The present invention provides methods for treating or preventing musculoskeletal discomfort, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the musculoskeletal discomfort is myalgia. In another embodiment, the musculoskeletal discomfort is myositis.

[00133] The present invention provides methods for treating or preventing a sulfatase-2-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the sulfatase-2-related disorder is a hepatic sulfatase-2-related disorder. In some embodiments, the sulfatase-2-related disorder is a disorder of lipogenesis or lipid modulation.

[00134] Examples of disorders of lipogenesis include, but are limited to, diabetes and related conditions, obesity, hepatic steatosis, non-alcoholic steatohepatitis, cancer, cardiovascular disease (hypertriglyceridemia), and skin disorders.

[00135] Examples of disorders of lipid modulation include, but are not limited to, elevated total cholesterol, elevated low-density lipoprotein cholesterol (LDL-C), elevated apolipoprotein B (Apo B), elevated triglyceride and elevated non-high-density lipoprotein cholesterol.

[00136] The present invention provides methods for downregulating hepatic sulfatase-2 expression in a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00137] The present invention provides methods for treating or preventing an ApoC-III related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the ApoC-III related disorder is a disorder of lipogenesis or lipid modulation, described herein.

[00138] The present invention provides methods for treating or preventing an ACC1-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the ACC1-related disorder is a disorder of lipogenesis or lipid modulation, described herein.

[00139] The present invention provides methods for treating or preventing an ADH-4-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the ADH-4-related disorder is a disorder of lipogenesis or lipid modulation, described herein.

[00140] The present invention provides methods for treating or preventing a TNF-α-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the TNF-α-related disorder is inflammation.

[00141] The present invention provides methods for treating or preventing a MCP-1-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the MCP-1-related disorder is inflammation.

[00142] The present invention provides methods for treating or preventing a MIP-1β-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the MIP-1β-related disorder is inflammation.

[00143] The present invention provides methods for treating or preventing a CCR5-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the CCR5-related disorder is inflammation.

[00144] The present invention provides methods for treating or preventing a CCR2-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the CCR2-related disorder is inflammation.

[00145] The present invention provides methods for treating or preventing a NF-κB-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the NF-κB-related disorder is inflammation.

[00146] The present invention provides methods for treating or preventing a TIMP-1-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the TIMP-1-related disorder is fibrosis. In some embodiments, the fibrosis is hepatic fibrosis.

[00147] The present invention provides methods for treating or preventing a MMP-2-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the MMP-2-related disorder is hepatic carcinogenesis or cancer.

[00148] In some embodiments, the therapeutic or prophylactic methods of the invention further comprise administering an effective amount of an additional pharmaceutically active agent. In some embodiments, the therapeutic or prophylactic methods of the invention further comprise administering an effective amount of two or more additional pharmaceutically active agent. In some embodiments, the additional pharmaceutically active agent is a statin. In some embodiments, the statin is atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin, mevastatin, dalvastatin, dihydrocompactin, or cerivastatin or a pharmaceutically acceptable salt thereof. In some embodiments, the statin is atorvastatin calcium.

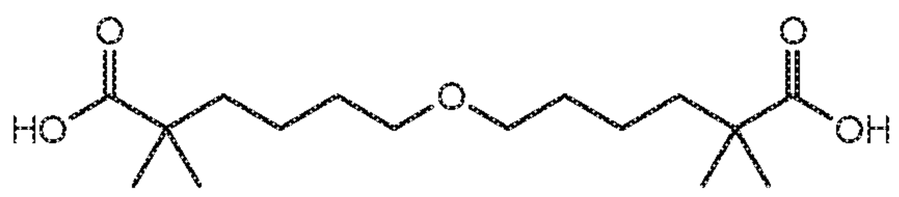
[00149] Illustrative additional pharmaceutically active agents are as disclosed herein. In some embodiments, the additional pharmaceutically active agent is a human hormone FGF19.

DEFINITIONS

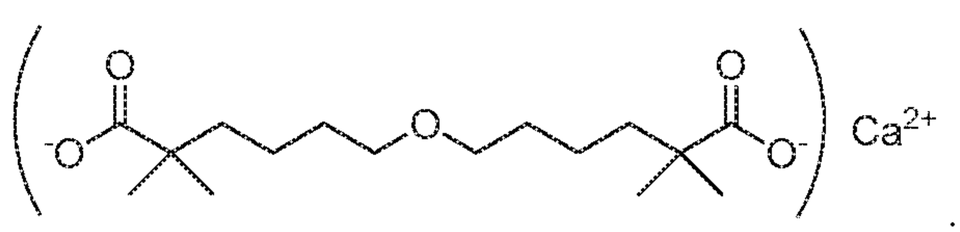
[00150] The term "about" when immediately preceding a numerical value means ± up to 20% of the numerical value. For example, "about" a numerical value means ± up to 20% of the numerical value, in some embodiments, ± up to 19%, ± up to 18%, ± up to 17%, ± up to 16%, ± up to 15%, ± up to 14%, ± up to 13%, ± up to 12%, ± up to 11%, ± up to 10%, ± up to 9%, ± up to 8%, ± up to 7%, ± up to 6%, ± up to 5%, ± up to 4%, ± up to 3%, ± up to 2%, ± up to 1%, ± up to less than 1%, or any other value or range of values therein.

[00151] A "subject" is a human or non-human mammal, e.g., a bovine, horse, feline, canine, rodent, or non-human primate. The human can be a male or female, child, adolescent or adult. The female can be premenarcheal or postmenarcheal.

[00152] As used herein, the "gemcabene" (United States Adopted Name) has the chemical name 6-(5-carboxy-5-methyl-hexyloxy)-2,2-dimethyl-hexanoic acid, which is also known as 6-(5-carboxy-5-methyl-hexyloxy)-2,2-dimethylhexanoic acid or 6,6'-oxybis(2,2-dimethylhexanoic acid), and has the structure:



[00153] As used herein, "gemcabene calcium salt" has the structure:



[00154] Illustrative pharmaceutically acceptable salts of a basic compound include those of an inorganic or organic acid, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, camphorsulfonic acid, oxalic acid, maleic acid, succinic acid, citric acid, formic acid, hydrobromic acid, benzoic acid, tartaric acid, fumaric acid, salicylic acid, mandelic

acid, or carbonic acid. In some embodiments, examples of inorganic or organic acids suitable to form an acid addition salt, include but are not limited to, hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, camphorsulfonic acid, oxalic acid, maleic acid, succinic acid, citric acid, formic acid, hydrobromic acid, benzoic acid, tartaric acid, fumaric acid, salicylic acid, mandelic acid, carbonic acid, etc.

[00155] Illustrative pharmaceutically acceptable salts of an acidic compound, e.g., gemcabene, include alkali metal salts, (e.g., lithium, sodium and potassium salts), alkaline earth metal salts (e.g., calcium and magnesium salts), aluminum salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol) and procaine. In some embodiments, a pharmaceutically acceptable salt derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Pharmaceutically acceptable salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like.

[00156] An "effective amount" when used in connection with a compound of the invention means an amount of the compound of the invention that, when administered to a subject for treating or preventing a disorder or abnormal condition, is effective to treat or prevent the disorder or abnormal condition, alone or in combination with an additional pharmaceutically active agent.

[00157] An "effective amount" when used in connection with an additional pharmaceutically active agent means an amount of the additional pharmaceutically active agent that, when administered to a subject for treating or preventing a disorder or abnormal condition, is effective to treat or prevent the disorder or abnormal condition, alone or in combination with a compound of the invention.

[00158] All weight percentages (i.e., "% by weight" and "wt. %" and w/w) referenced herein, unless otherwise indicated, are relative to the total weight of the mixture or composition, as the case can be.

[00159] As used herein, "D_{90}" or "PSD90", means that 90% of the particles of a compound of the invention have a diameter that is less than the indicated diameter. For example, a D_{90} or a PSD90 of 75 μm means that 90% of the cumulative volume of the particles of the indicated compound of the invention have a diameter that is less than 75 μm. Similarly, as used herein, "D_{50}" or "PSD50", means that 50% of the cumulative volume of the particles of a compound of the invention have a diameter that is less than the indicated diameter. Also, as used herein, "D_{10}" or "PSD10", means that 10% of the cumulative volume of the particles of a compound of the invention have a diameter that is less than the indicated diameter.

[00160] As used herein, an "immediate-release" composition refers to a composition of the invention that releases at least 75% (by weight) of a compound of the invention within one hour of administration to a subject. In some embodiments, an immediate-release composition of the invention releases at least 75% by weight, at least 80% by weight, at least 85% by weight, or at least 90% by weight of a compound of the invention within 45 minutes of administration to a subject.

[00161] As used herein, "$AUC_{(0\text{-}24)}$" refers to area under the plasma concentration-time curve from time 0 to 24 hours following a compound's administration.

[00162] As used herein, "AUC_{last}", which is synonymous with "$AUC_{(0\text{-}tldc)}$", "$AUC_{(0\text{-}tlqc)}$", "$AUC_{(0\text{-}tc)}$", and "$AUC_{(0\text{-}t)}$", refers to area under the plasma concentration-time curve from time 0 to the last detectable concentration of a compound following its administration. As used herein, "baseline plasma or blood serum LDL-C" refers to plasma or blood serum LDL-C of a subject as measured prior to administration of the compound of the invention.

[00163] As used herein, a subject "on a stable dose" of a lipid-lowering medication, drug or agent, such as a statin, refers to a subject that has been taking the same dose of lipid-lowering medication (e.g., statins) for a period of time in which the subject's blood serum or plasma concentration of LDL-C has stabilized. As used herein, "stabilized" means that a new steady state level of LDL-C in the subject's blood serum or plasma concentration has been achieved at a time after beginning the lipid-lowering medication and remains relatively constant from day today within reasonable margins (±15%) of the new steady state level.

[00164] As used herein, a "statin therapy" refers to a treatment where a subject is administered a statin. In some embodiment, the subject is "undergoing statin therapy", i.e., being administered with a statin. In some embodiments, the stain therapy is maximally tolerated statin therapy. In some embodiments, the statin therapy is ineffective to treat or prevent a disease or condition as disclosed herein. In some embodiments, the statin therapy is ineffective to lower the subject's LDL-C concentration, lower the subject's triglyceride concentration, or raise the subject's HDL-C concentration to a normal value or to the subject's goal value. As used herein, "maximally

tolerated statin therapy" refers to therapeutic regimen comprising the administration of daily dose of a statin that is the maximally tolerated dose for a particular subject. "Maximally tolerated dose" means the highest dose of statin that can be administered to a subject without causing unacceptable adverse side effects in the subject.

[00165] As used herein, "a subject with homozygous familial hypercholesterolemia (HoFH)" or "an HoFH subject" is a subject determined to have HoFH by genetic confirmation or clinical diagnosis. A subject with HoFH (1) has a genetic confirmation of two mutant alleles at the LDL-receptor, apolipoprotein B, PCSK9 or the LDL-RAP1 (LDL-receptor adaptor protein 1) gene locus. For example, the subject may have paired or same (homozygous) or two unpaired or dissimilar (compound homozygous or compound heterozygous) mutations at alleles on the LDL-receptor, apolipoprotein B, PCSK9, or the LDL-RAP1 gene locus; or (2) is clinically determined to have (a) untreated LDL-C > 500 mg/dL (12.92 mmol/L) or treated LDL-C ≥ 300 mg/dL (7.76 mmol/L) together with either appearance of cutaneous or tendinous xanthoma before 10 years of age, or evidence of heterozygous familial hypercholesterolemia in both parents, or (b) LDL-C > 300 mg/dL (7.76 mmol/L) on maximally tolerated lipid-lowering drug therapy. The clinically diagnosis (phenotypic) is only indicative of HoFH, but there are some subjects that does not meet the clinical LDL-C limitations (e.g., subjects have LDL-C ≤ 500 mg/dL or LDL-C < 300 mg/dL) yet have HoFH by genetic confirmation. Similarly, subjects can be clinically diagnosed as having HoFH but not by genetic confirmation.

[00166] As used herein, "a subject with heterozygous familial hypercholesterolemia (HeFH)" or "an HeFH subject" is a subject determined to have HeFH by genetic confirmation or clinical diagnosis. A subject with HeFH is clinically determined to have LDL-C ≥ 190 mg/dL.

[00167] Genotype analysis for each of four genes is not commonly conducted as the analysis is lengthy, expensive and interpretations of results are controversial. For example, polymorphic changes in DNA that result in a single amino acid or small changes may result in little or no functional change in the protein, but this genetic variation is considered a "mutation" or "varian" of the predominant gene in the population. The loose interpretation of functional activity does not allow precision in genetic classification. Furthermore, other genetic and environmental factors result in phenotypic variation. For the above reasons, in medical practice, the classification of familial hypercholesterolemia, and more specifically homozygous familial hypercholesterolemia, is generally based on clinical interpretation. The clinical interpretation is sometimes supported by follow-up gene sequence analysis for both alleles of the LDL-receptor, apolipoprotein B, PCSK9 and LDL-RAP1 for the subject and if feasible the parents, siblings, and other relatives.

[00168] **Table A**. Examples of Genetic Inheritance and Terminology of Familial Hypercholesterolemia

		Genes Inherited from Mother				
Genes Inherited from Father	Mutation	None	LDL-R (Position 1)	LDL-R (Position 2)	ApoB (Position 1)	LDL-R (Position 1) plus ApoB (Position 1)
	None	Normal	Heterozygous	Heterozygous	Heterozygous	Compound Heterozygous
	LDL-R (Position 1)	Heterozygous	Homozygous	Compound Homozygous	Compound Heterozygous	Homozygous
	LDL-R (Position 2)	Heterozygous	Compound Homozygous	Homozygous	Compound Heterozygous	Compound Homozygous
	ApoB (Position 1)	Heterozygous	Compound Heterozygous	Compound Heterozygous	Homozygous	Homozygous
	LDL-R (Position 1) plus ApoB (Position 1)	Compound Heterozygous	Homozygous	Compound Homozygous	Homozygous	Double Homozygous

PARTICLE SIZE DISTRIBUTION

[00169] In some embodiments, the PSD90 of the compounds of the invention is achieved by reducing the particles' size, e.g., by micronizing or milling. In some embodiments, the micronizing or milling is achieved using a pinmill. In some embodiments, the micronizing or milling is achieved using a Fitzmill.

[00170] In some embodiments, the compounds of the invention have a PSD90 ranging from 35 μm to about 90 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 36 μm to about 90 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 37 μm to about 90 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 38 μm to about 90 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 39 μm to about 90 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 40 μm to about 90 μm.

[00171] In some embodiments, the compounds of the invention have a PSD90 ranging from 35 μm to about 85 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 36 μm to about 85 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 37 μm to about 85 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 38 μm to about 85 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 39 μm to about 85 μm. In some

embodiments, the compounds of the invention have a PSD90 ranging from 40 μm to about 85 μm.

[00172] In some embodiments, the compounds of the invention have a PSD90 ranging from 35 μm to about 80 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 36 μm to about 80 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 37 μm to about 80 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 38 μm to about 80 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 39 μm to about 80 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 40 μm to about 80 μm.

[00173] In some embodiments, the compounds of the invention have a PSD90 ranging from 35 μm to about 75 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 36 μm to about 75 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 37 μm to about 75 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 38 μm to about 75 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 39 μm to about 75 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 40 μm to about 75 μm.

[00174] In other embodiments, the compounds of the invention have a PSD90 ranging from 45 μm to about 90 μm. In other embodiments, the compounds of the invention have a PSD90 ranging from 45 μm to about 85 μm. In other embodiments, the compounds of the invention have a PSD90 ranging from 45 μm to about 80 μm. In other embodiments, the compounds of the invention have a PSD90 ranging from 45 μm to about 75 μm.

[00175] In some embodiments, the compounds of the invention have a PSD90 ranging from 50 μm to about 90 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 50 μm to about 85 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 50 μm to about 80 μm. In some embodiments, the compounds of the invention have a PSD90 ranging from 50 μm to about 75 μm.

[00176] In some embodiments, the compounds of the invention have a PSD90 of 35 μm, 36 μm, 37 μm, 38 μm, 39 μm, 40 μm, 41 μm, 42 μm, 43 μm, 44 μm, 45 μm, 46 μm, 47 μm, 48 μm, 49 μm, 50 μm, 51 μm, 52 μm, 53 μm, 54 μm, 55 μm, 56 μm, 57 μm, 58 μm, 59 μm, 60 μm, 61 μm, 62 μm, 63 μm, 64 μm, 65 μm, 66 μm, 67 μm, 68 μm, 69 μm, 70 μm, 71 μm, 72 μm, 73 μm, 74 μm, 75 μm, 76 μm, 77 μm, 78 μm, 79 μm, 80 μm, 81 μm, 82 μm, 83 μm, 84 μm, 85 μm, 86 μm, 87 μm, 88 μm, 89 μm, 90 μm, or a value ranging from and to any of these diameters.

[00177] In some embodiments, the compounds of the invention have a PSD90 of about 44 μm, about 45 μm, about 46 μm, about 47 μm, about 48 μm, about 49 μm, about 50 μm, about 51 μm, about 52 μm, about 53 μm, about 54 μm, about 55 μm, about 56 μm, about 57 μm, about 58 μm, about 59 μm, about 60 μm, about 61 μm, about 62 μm, about 63 μm, about 64 μm, about 65 μm, about 66 μm, about 67 μm, about 68 μm, about 69 μm, about 70 μm, about 71 μm, about 72 μm, about 73 μm, about 74 μm, about 75 μm, about 76 μm, about 77 μm, about 78 μm, about 79 μm, about 80 μm, about 81 μm, about 82 μm, about 83 μm, about 84 μm, about 85 μm, about 86 μm, about 87 μm, about 88 μm, about 89 μm, about 90 μm, or a value ranging from and to any of these diameters.

[00178] Without being bound by theory, the compounds of the invention having a PSD90 of about 50 μm to about 62 μm particularly enable compressed tablet formulation with desired properties such as high drug loading, good compressibility, fast dissolution profile, and minimal to no cracking.

[00179] In some embodiments, the particle size distribution and the PSD90 of a compound of the invention is determined by the laser light diffraction particle size distribution analysis. The particle size distribution is determined in accordance with the Fraunhofer light diffraction method. In this method, a coherent laser beam passes through the sample and the resulting diffraction pattern is focused on a multi-element detector. Since the diffraction pattern depends, among other parameters, on particle size, the particle size distribution can be calculated based on the measured diffraction pattern of the sample. The method is described in more detail in USP38-NF33, <429> Light Diffraction Measurement of Particle Size.

DISSOLUTION PROFILES

[00180] In some embodiments, the compound of the invention has a dissolution profile characterized by its (% dissolution) over time. For example, the dissolution profile can have a (% dissolution) value of at least 80% in 45 minutes or less in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C as measured by high-performance liquid chromatography using a detection wavelength of 210 nm. In some embodiments, the compound of the invention is a calcium salt. In some embodiments, the calcium salt is a calcium salt hydrate. In some embodiments, the compound of the invention is an amorphous solid. In some embodiments, the compound of the invention is a crystalline polymorph. In some embodiments, the calcium salt hydrate is calcium salt hydrate Crystal Form 1. In some embodiments, the calcium salt hydrate is calcium salt hydrate Crystal Form 2. In other embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form C3. In other embodiments, the compound of the invention is gemcabene calcium

salt hydrate Crystal Form C2. In other embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form C1.

[00181] In some embodiments, the compound of the invention is a calcium salt solvate. In some embodiments, the calcium salt solvate is a calcium salt ethanol solvate.

[00182] In some embodiments, a compound of the invention has a dissolution profile characterized by % dissolution value of at least 85% gemcabene in 45 minutes or less in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C and as measured by high-performance liquid chromatography using a detection wavelength of 210 nm. In some embodiments, a compound of the invention has a dissolution profile characterized by % dissolution value of at least 90% gemcabene in 45 minutes or less in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C and as measured by high-performance liquid chromatography using a detection wavelength of 210 nm. *See* Example 13 for detailed method of determining % dissolution values.

[00183] In some embodiments, a compound of the invention has a dissolution profile characterized by % dissolution value of at least 80%, at least 81%, at least 82%, at least 83%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, or at least 95%, or any value ranging from these percentages (e.g., 85%-90% dissolution), in 45 minutes or less in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C and as measured by high-performance liquid chromatography using a detection wavelength of 210 nm.

[00184] In some embodiments, the compound of the invention has a dissolution profile characterized by % dissolution value of at least 70% in 30 minutes or less in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C as measured by high-performance liquid chromatography using a detection wavelength of 210 nm. In some embodiments, the pharmaceutically acceptable salt is a calcium salt. In some embodiments, the calcium salt is a calcium salt hydrate. In some embodiments, the compound of the invention is an amorphous solid. In some embodiments, the compound of the invention is a crystalline polymorph. In some embodiments, the calcium salt hydrate is calcium salt hydrate Crystal Form 1. In some embodiments, the calcium salt hydrate is calcium salt hydrate Crystal Form 2. In some embodiments, the calcium salt hydrate is calcium salt hydrate Crystal Form C3. In some embodiments, the calcium salt hydrate is calcium salt hydrate Crystal Form C2. In some embodiments, the calcium salt hydrate is calcium salt hydrate Crystal Form C1.

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[00185] **Table B**. Summary of illustrative polymorphic forms of gemcabene calcium

	Crystal Form 1	**Crystal Form 2**	**Crystal Form C3**	**Gemcabene calcium salt ethanol solvate**	**Amorphous**
Appearance	White solid	White solid	White solid	White solid	White solid
Thermal Analysis (TGA/DTA)	A weight loss of 3.6 % is noted in the TGA up to 180 °C. Single endothermic event at onset 133 °C (peak at 153 °C) by DTA.	A weight loss of 3.6 wt.% is noted in the TGA up to approximately 200 °C	A weight loss of 5.5 % in noted by TGA up to approximately 200 °C.	A weight loss of 4.8 % is noted by TGA up to approximately 160°C. Single endothermic event at onset 110 °C (peak at 137 °C) by DTA.	A weight loss of 3.1 wt. % is noted by TGA up to approximately 150°C.
Thermal Analysis (DSC)	N/A	A single exotherm at onset 49 °C (peak 62 °C), followed by a single endotherm at onset 176 °C (peak 194 °C) are observed by DSC.	A single endotherm at onset 31 ° C (peak 35 °C), followed by a single endotherm at onset 150 °C (peak 167 °C) are observed by DSC.	N/A	No thermal events are noted in the DSC.
Residual Solvent (GC)	Ethanol – 1100 ppm	Ethanol – 288 ppm	Ethanol – 76070 ppm	Ethanol - 28628 ppm t-Butyl methyl ether - 511 ppm	N/A
Moisture Content (KF)	Average 3.5% w/w	Average 3.1 % w/w	Average 2.1 % w/w	N/A	Average 2.6 % w/w
% Gemcabene[1] (HPLC/CAD)	87.52 % (w/w%)	89.57 % (w/w%)	83.98 % (w/w%)	90.51 % (w/w%)	88.85 % (w/w%)
Particle Size (PSD)	D10 = 8.9 µm D50 = 24.3 µm D90 = 44.1 µm	D10 = 5.0 µm D50 = 14.4 µm D90 = 38.2 µm	D10 = 8.8 µm D50 = 20.4 µm D90 = 44.3 µm	D10 = 3.3 µm D50 = 31.8 µm D90 = 85.0 µm	D10 = 5.2 µm D50 = 26.4 µm D90 = 60.3 µm

[1]% Gemcabene indicates percent by weight which is attributed to gemcabene conjugate base component, which excludes the weight of calcium or water content.

TGA = thermogravimetric analysis; DTA = differential thermal analysis; DSC = differential scanning calorimetry; GC = gas chromatography; KF = Karl-Fisher; HPLC/CAD = high –performance liquid chromatography with charged aerosol detector; PSD = particle size distribution

[00186] In some embodiments, a compound of the invention has a dissolution profile characterized by % dissolution value of at least 85% in 45 minutes or less in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C as measured by high-performance liquid chromatography using a detection wavelength of 210 nm. In some embodiments, a compound of the invention has a dissolution profile characterized by % dissolution value of at least 90% gemcabene in 45 minutes or less in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C as measured by high-performance liquid chromatography using a detection wavelength of 210 nm.

[00187] In some embodiments, a compound of the invention has a dissolution profile characterized by % dissolution value of, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, or at least 75%, or a value ranging from and to any of these percentages, in 30 minutes or less in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C as measured by high-performance liquid chromatography using a detection wavelength of 210 nm.

[00188] In some embodiments, a compound of the invention comprises an amorphous form or a crystalline form of gemcabene or a pharmaceutically acceptable salt thereof having a dissolution profile comprising a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm and (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm.

[00189] The present invention further provides a pharmaceutically acceptable salt of gemcabene, the pharmaceutically acceptable salt having (a) a PSD90 ranging from 40 µm to about 75 µm as measured by laser light diffraction and (b) a dissolution profile characterized by a % dissolution value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm.

[00190] In some embodiments, the dissolution profile is measured using the composition of the invention. In some embodiments, the dissolution profile of a compound of the invention is measured using a composition of the invention that is in the form of a tablet. In some embodiments, the tablet is a compressed tablet. In some embodiment, the compressed tablet is a film-coated compressed tablet.

[00191] In some embodiments, the dissolution profile of a compound of the invention is measured using a composition of the invention that is in the form of a capsule.

WATER AND ETHANOL CONTENTS

[00192] In some embodiments, the compound of the invention has a water content of about 1% w/w to about 6% w/w of the compound of the invention. In some embodiments, the compound of the invention has a water content of about 2% w/w to about 5% w/w of the compound of the invention. In some embodiments, the water content of the compound of the invention is about 2% w/w to about 5%, about 2% w/w to about 4% w/w, about 3% w/w to about 5% w/w, or about 3% w/w to about 4% w/w of the compound of the invention, or a value ranging from and to any of these percent by weight values. In some embodiments, the water content of the compound of the invention is about 2.0%, about 2.1%, about 2.2%, about 2.3%, about 2.4%, about 2.5%, about 2.6%, about 2.7%, about 2.8%, about 2.9%, about 3.0%, about 3.1%, about 3.2%, about 3.3%, about 3.4%, about 3.5%, about 3.6%, about 3.7%, about 3.8%, about 3.9%, about 4.0%, about 4.1%, about 4.2%, about 4.3%, about 4.4%, about 4.5%, about 4.6%, about 4.7%, about 4.8%, about 4.9%, or about 5.0% by weight of the compound of the invention. In other embodiments, the water content of the compound of the invention is about 3.4%, about 3.5%, about 3.6%, or about 3.7% by weight of the compound of the invention.

[00193] In some embodiments, the compound of the invention has an ethanol content of about 0% w/w to about 0.5% w/w of the compound of the invention. In some embodiments, the ethanol content of the compound of the invention is about 0.0%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, or about 0.5% by weight of the compound of the invention.

[00194] In some embodiments, a compound of the invention has an ethanol content that is less than about 5000 ppm of the compound of the invention. In some embodiments, a compound of the invention has an ethanol content that is less than about 4000 ppm of the compound of the invention. In some embodiments, a compound of the invention has an ethanol content that is less than about 3000 ppm of the compound of the invention. In some embodiments, a compound of the invention has an ethanol content that is less than about 2000 ppm of the compound of the invention. In some embodiments, the ethanol content is less than about 500 ppm, less than about 600 ppm, less than about 700 ppm, less than about 800 ppm, less than about 900 ppm, less than about 1000 ppm, less than about 1100 ppm, less than about 1200 ppm, less than about 1300 ppm, less than about 1400 ppm, less than about 1500 ppm, less than about 1600 ppm, less than about 1700 ppm, less than about 1800 ppm, less than about 1900 ppm, or less than about 2000 ppm, of the compound of the invention.

[00195] In some embodiments, the compound of the invention has an ethanol content of about 0.5% w/w to about 8% w/w of the compound of the invention. In some embodiment, the compound of the invention is an ethanol solvate having an ethanol content of about 0.5% w/w to about 8% w/w of the compound of the invention. In some embodiments, the ethanol content of

the compound of the invention is about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0% by, about 1.1%, about 1.2%, about 1.3%, about 1.4%, about 1.5%, about 1.6%, about 1.7%, about 1.8%, about 1.9%, 2.0%, about 2.1%, about 2.2%, about 2.3%, about 2.4%, about 2.5%, about 2.6%, about 2.7%, about 2.8%, about 2.9%, about 3.0%, about 3.1%, about 3.2%, about 3.3%, about 3.4%, about 3.5%, about 3.6%, about 3.7%, about 3.8%, about 3.9%, about 4.0%, about 4.1%, about 4.2%, about 4.3%, about 4.4%, about 4.5%, about 4.6%, about 4.7%, about 4.8%, about 4.9%, about 5.0%, about 5.1%, about 5.2%, about 5.3%, about 5.4%, about 5.5%, about 5.6%, about 5.7%, about 5.8%, about 5.9%, about 6.0%, about 6.1%, about 6.2%, about 6.3%, about 6.4%, about 6.5%, about 6.6%, about 6.7%, about 6.8%, about 6.9%, about 7.0%, about 7.1%, about 7.2%, about 7.3%, about 7.4%, about 7.5%, about 7.6%, about 7.7%, about 7.8%, about 7.9%, or about 8.0%, weight of the compound of the invention.

[00196] In some embodiments, a compound of the invention has an ethanol content is about 20,000 ppm to about 40,000 ppm of the compound of the invention. In some embodiments, a compound of the invention is an ethanol solvate having an ethanol content is about 20,000 ppm to about 40,000 ppm of the compound of the invention. In some embodiments, a compound of the invention has an ethanol content that is about 20,000 ppm, about 21,000 ppm, about 22,000 ppm, about 23,000 ppm, about 24,000 ppm, about 25,000 ppm, about 26,000 ppm, about 27,000 ppm, about 28,000 ppm, about 29,000 ppm, about 30,000 ppm, about 31,000 ppm, about 32,000 ppm, about 33,000 ppm, about 34,000 ppm, about 35,000 ppm, about 36,000 ppm, about 37,000 ppm, about 38,000 ppm, about 39,000 ppm, about 40,000 ppm of the compound of the invention. In some embodiments, a compound of the invention has an ethanol content that is about 28,000 ppm, about 28,100 ppm, about 28,200 ppm, about 28,300 ppm, about 28,400 ppm, about 28,500 ppm, about 28,600 ppm, about 28,700 ppm, about 28,800 ppm, or about 28,900 ppm of the compound of the invention.

PHARMACOKINETICS

[00197] In some embodiments, a steady state plasma concentration of gemcabene in a subject is achieved within about 5-20 days following the start of repeated dose administration of the compound of the invention or following increase in daily dosing of the compound of the invention. In some embodiments, a steady state plasma concentration of gemcabene in a subject is achieved within about 14 days following the start of repeated dose administration of the compound of the invention or following increase in daily dosing of the compound of the invention. In some embodiments, the steady state is achieved within 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 days following the start of daily administration of the compound of the invention at a

dose of about 50 mg/day to about 900 mg/day or following the increase in daily dose of the compound of the invention to a dose of about 50 mg/day to about 900 mg/day.

[00198] The present invention provides compounds of the invention having a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm, and providing a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 200 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00199] The present invention provides pharmaceutically acceptable salts of gemcabene, the pharmaceutically acceptable salts having (a) a particle size distribution characterized by a PSD90 ranging from 40 μm to about 75 μm as measured by laser light diffraction (b) a dissolution profile characterized by a % dissolution value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm; and providing a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 200 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg to about 900 mg.

[00200] In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 200 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 250 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 250 μg·hr/mL at steady state to about 5750 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 300 μg·hr/mL at steady state to about 5500 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00201] In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from 200 μg·hr/mL at steady state to 6000 μg·hr/mL at steady state when administered to a human subject in an amount that is molar equivalent to about 50 mg of

gemcabene per day to about 900 mg of gemcabene per day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from 250 μg·hr/mL at steady state to 6000 μg·hr/mL at steady state when administered to a human subject in an amount that is molar equivalent to about 50 mg of gemcabene per day to about 900 mg of gemcabene per day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from 250 μg·hr/mL at steady state to 5750 μg·hr/mL at steady state when administered to a human subject in an amount that is molar equivalent to about 50 mg of gemcabene per day to about 900 mg of gemcabene per day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from 300 μg·hr/mL at steady state to 5500 μg·hr/mL at steady state when administered to a human subject in an amount that is molar equivalent to about 50 mg of gemcabene per day to about 900 mg of gemcabene per day.

[00202] In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ of about 200 μg·hr/mL, about 250 μg·hr/mL, about 300 μg·hr/mL, about 350 μg·hr/mL, about 400 μg·hr/mL, about 450 μg·hr/mL, about 500 μg·hr/mL, about 550 μg·hr/mL, about 600 μg·hr/mL, about 650 μg·hr/mL, about 700 μg·hr/mL, about 750 μg·hr/mL, about 800 μg·hr/mL, about 850 μg·hr/mL, about 900 μg·hr/mL, about 950 μg·hr/mL, about 1000 μg·hr/mL, about 1100 μg·hr/mL, about 1200 μg·hr/mL, about 1300 μg·hr/mL, about 1400 μg·hr/mL, about 1500 μg·hr/mL, about 1600 μg·hr/mL, about 1700 μg·hr/mL, about 1800 μg·hr/mL, about 1900 μg·hr/mL, about 2000 μg·hr/mL, about 2100 μg·hr/mL, about 2200 μg·hr/mL, about 2300 μg·hr/mL, about 2400 μg·hr/mL, about 2500 μg·hr/mL, about 2600 μg·hr/mL, about 2700 μg·hr/mL, about 2800 μg·hr/mL, about 2900 μg·hr/mL, about 3000 μg·hr/mL, about 3100 μg·hr/mL, about 3200 μg·hr/mL, about 3300 μg·hr/mL, about 3400 μg·hr/mL, about 3500 μg·hr/mL, about 3600 μg·hr/mL, about 3700 μg·hr/mL, about 3800 μg·hr/mL, about 3900 μg·hr/mL, about 4000 μg·hr/mL, about 4100 μg·hr/mL, about 4200 μg·hr/mL, about 4300 μg·hr/mL, about 4400 μg·hr/mL, about 4500 μg·hr/mL, about 4600 μg·hr/mL, about 4700 μg·hr/mL, about 4800 μg·hr/mL, about 4900 μg·hr/mL, about 5000 μg·hr/mL, about 5100 μg·hr/mL, about 5200 μg·hr/mL, about 5300 μg·hr/mL, about 5400 μg·hr/mL, about 5500 μg·hr/mL, about 5600 μg·hr/mL, about 5700 μg·hr/mL, about 5800 μg·hr/mL, about 5900 μg·hr/mL, or about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day, or when administered to a human subject in an amount that is molar equivalent to about 50 mg of gemcabene per day to about 900 mg gemcabene per day.

[00203] In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 200 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady

state or from about 250 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day, about 60 mg/day, about 70 mg/day, about 80 mg/day, about 90 mg/day, about 100 mg/day, about 110 mg/day, about 120 mg/day, about 130 mg/day, about 140 mg/day, about 150 mg/day, about 160 mg/day, about 170 mg/day, about 180 mg/day, about 190 mg/day, about 200 mg/day, about 210 mg/day, about 220 mg/day, about 230 mg/day, about 240 mg/day, about 250 mg/day, about 260 mg/day, about 270 mg/day, about 280 mg/day, about 290 mg/day, 300 mg/day, about 310 mg/day, about 320 mg/day, about 330 mg/day, about 340 mg/day, about 350 mg/day, about 360 mg/day, about 370 mg/day, about 380 mg/day, about 390 mg/day, 400 mg/day, about 410 mg/day, about 420 mg/day, about 430 mg/day, about 440 mg/day, about 450 mg/day, about 460 mg/day, about 470 mg/day, about 480 mg/day, about 490 mg/day, 500 mg/day, about 510 mg/day, about 520 mg/day, about 530 mg/day, about 540 mg/day, about 550 mg/day, about 560 mg/day, about 570 mg/day, about 580 mg/day, about 590 mg/day, 600 mg/day, about 610 mg/day, about 620 mg/day, about 630 mg/day, about 640 mg/day, about 650 mg/day, about 660 mg/day, about 670 mg/day, about 680 mg/day, about 690 mg/day, 700 mg/day, about 710 mg/day, about 720 mg/day, about 730 mg/day, about 740 mg/day, about 750 mg/day, about 760 mg/day, about 770 mg/day, about 780 mg/day, about 790 mg/day, about 800 mg/day, about 810 mg/day, about 820 mg/day, about 830 mg/day, about 840 mg/day, about 850 mg/day, about 860 mg/day, about 870 mg/day, about 880 mg/day, about 890 mg/day, or about 900 mg/day.

[00204] In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from 200 μg·hr/mL at steady state to 6000 μg·hr/mL at steady state or from 250 μg·hr/mL at steady state to 6000 μg·hr/mL at steady state when administered to a human subject in an amount that is molar equivalent to about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg,

800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, or about 900 mg of gemcabene per day.

[00205] In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 200 μg·hr/mL at steady state to about 1000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day or in an amount that is molar equivalent to about 50 mg of gemcabene per day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 200 μg·hr/mL at steady state to about 500 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day or in an amount that is molar equivalent to about 50 mg of gemcabene per day.

[00206] In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 300 μg·hr/mL at steady state to about 1500 μg·hr/mL at steady state when administered to a human subject at a dose of about 150 mg/day or in an amount that is molar equivalent to about 150 mg of gemcabene per day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 500 μg·hr/mL at steady state to about 1200 μg·hr/mL at steady state when administered to a human subject at a dose of about 150 mg/day or in an amount that is molar equivalent to about 150 mg of gemcabene per day.

[00207] In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 500 μg·hr/mL at steady state to about 2500 μg·hr/mL at steady state when administered to a human subject at a dose of about 300 mg/day or in an amount that is molar equivalent to about 300 mg of gemcabene per day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 1000 μg·hr/mL at steady state to about 2000 μg·hr/mL at steady state when administered to a human subject at a dose of about 300 mg/day or in an amount that is molar equivalent to about 300 mg of gemcabene per day.

[00208] In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 750 μg·hr/mL at steady state to about 3250 μg·hr/mL at steady state when administered to a human subject at a dose of about 450 mg/day or in an amount that is molar equivalent to about 450 mg of gemcabene per day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 1250 μg·hr/mL at steady state to about 3000 μg·hr/mL at steady state when administered to a human subject at a dose of about 450 mg/day or in an amount that is molar equivalent to about 450 mg of gemcabene per day.

[00209] In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 1500 μg·hr/mL at steady state to about 5000 μg·hr/mL at steady state when administered to a human subject at a dose of about 600 mg/day or in an amount that is molar equivalent to about 600 mg of gemcabene per day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 1500 μg·hr/mL at steady state to about 4500 μg·hr/mL at steady state when administered to a human subject at a dose of about 600 mg/day or in an amount that is molar equivalent to about 600 mg of gemcabene per day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from 2000 μg·hr/mL at steady state to 4000 μg·hr/mL at steady state when administered to a human subject at a dose of about 600 mg/day or in an amount that is molar equivalent to about 600 mg of gemcabene per day.

[00210] In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 3000 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 900 mg/day or in an amount that is molar equivalent to about 900 mg of gemcabene per day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from 3250 μg·hr/mL at steady state to about 5750 μg·hr/mL at steady state when administered to a human subject at a dose of about 900 mg/day or in an amount that is molar equivalent to about 900 mg of gemcabene per day.

[00211] In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 500 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose ranging from about 300 mg/day to about 900 mg/day or in an amount that is molar equivalent in a range from about 300 mg to about 900 mg of gemcabene per day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 1500 μg·hr/mL at steady state to about 5250 μg·hr/mL at steady state when administered to a human subject at a dose ranging from about 450 mg/day to about 750 mg/day or in an amount that is molar equivalent in a range from about 450 mg to about 750 mg of gemcabene per day. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 1500 μg·hr/mL at steady state to about 5250 μg·hr/mL at steady state when administered to a human subject at a dose ranging from about 500 mg/day to about 700 mg/day or in an amount that is molar equivalent in a range from about 500 mg to about 700 mg of gemcabene per day.

[00212] The present invention provides compounds of the invention having a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a

detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm, and providing a plasma gemcabene AUC_{last} ranging from about 50 µg·hr/mL to about 7500 µg·hr/mL after a single dose administration of about 50 mg to about 900 mg to a human subject.

[00213] The present invention provides a pharmaceutically acceptable salt of gemcabene, the pharmaceutically acceptable salt having (a) a PSD90 ranging from 40 µm to about 75 µm as measured by laser light diffraction and (b) a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm, and providing a plasma gemcabene AUC_{last} ranging from about 50 µg·hr/mL to about 7500 µg·hr/mL after a single dose administration of about 50 mg to about 900 mg to a human subject.

[00214] In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 50 µg·hr/mL to about 7500 µg·hr/mL after a single dose administration of about 50 mg to about 900 mg. In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 150 µg·hr/mL to about 5750 µg·hr/mL after a single dose administration of about 50 mg to about 900 mg. In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 400 µg·hr/mL to about 5500 µg·hr/mL after a single dose administration of about 50 mg to about 900 mg. In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 500 µg·hr/mL to about 5250 µg·hr/mL after a single dose administration of about 50 mg to about 900 mg.

[00215] In another embodiment, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 50 µg·hr/mL to about 7500 µg·hr/mL after a single dose administration of the compound of the invention in an amount that is molar equivalent to about 50 mg of gemcabene to about 900 mg of gemcabene. In another embodiment, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 150 µg·hr/mL to about 5750 µg·hr/mL after a single dose administration of the compound of the invention in an amount that is molar equivalent to about 50 mg of gemcabene to about 900 mg of gemcabene. In another embodiment, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 400 µg·hr/mL to about 5500 µg·hr/mL after a single dose administration of the compound of the invention in an amount that is molar equivalent to about 50 mg of gemcabene to about 900 mg of gemcabene. In another embodiment, the compound of the invention provides a plasma

gemcabene AUC_{last} ranging from about 500 μg·hr/mL to about 5250 μg·hr/mL after a single dose administration of the compound of the invention in an amount that is molar equivalent to about 50 mg of gemcabene to about 900 mg of gemcabene. In another embodiment, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 500 μg·hr/mL to about 5500 μg·hr/mL after a single dose administration of the compound of the invention in an amount that is molar equivalent to about 50 mg of gemcabene to about 900 mg of gemcabene.

[00216] In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} of about 50 μg·hr/mL, about 100 μg·hr/mL, about 150 μg·hr/mL, about 200 μg·hr/mL, about 250 μg·hr/mL, about 300 μg·hr/mL, about 350 μg·hr/mL, about 400 μg·hr/mL, about 450 μg·hr/mL, about 500 μg·hr/mL, about 550 μg·hr/mL, about 600 μg·hr/mL, about 650 μg·hr/mL, about 700 μg·hr/mL, about 750 μg·hr/mL, about 800 μg·hr/mL, about 850 μg·hr/mL, about 900 μg·hr/mL, about 950 μg·hr/mL, about 1000 μg·hr/mL, about 1100 μg·hr/mL, about 1200 μg·hr/mL, about 1300 μg·hr/mL, about 1400 μg·hr/mL, about 1500 μg·hr/mL, about 1600 μg·hr/mL, about 1700 μg·hr/mL, about 1800 μg·hr/mL, about 1900 μg·hr/mL, about 2000 μg·hr/mL, about 2100 μg·hr/mL, about 2200 μg·hr/mL, about 2300 μg·hr/mL, about 2400 μg·hr/mL, about 2500 μg·hr/mL, about 2600 μg·hr/mL, about 2700 μg·hr/mL, about 2800 μg·hr/mL, about 2900 μg·hr/mL, about 3000 μg·hr/mL, about 3100 μg·hr/mL, about 3200 μg·hr/mL, about 3300 μg·hr/mL, about 3400 μg·hr/mL, about 3500 μg·hr/mL, about 3600 μg·hr/mL, about 3700 μg·hr/mL, about 3800 μg·hr/mL, about 3900 μg·hr/mL, about 4000 μg·hr/mL, about 4100 μg·hr/mL, about 4200 μg·hr/mL, about 4300 μg·hr/mL, about 4400 μg·hr/mL, about 4500 μg·hr/mL, about 4600 μg·hr/mL, about 4700 μg·hr/mL, about 4800 μg·hr/mL, about 4900 μg·hr/mL, about 5000 μg·hr/mL, about 5100 μg·hr/mL, about 5200 μg·hr/mL, about 5300 μg·hr/mL, about 5400 μg·hr/mL, about 5500 μg·hr/mL, about 5600 μg·hr/mL, about 5700 μg·hr/mL, about 5800 μg·hr/mL, about 5900 μg·hr/mL, about 6000 μg·hr/mL, about 6100 μg·hr/mL, about 6200 μg·hr/mL, about 6300 μg·hr/mL, about 6400 μg·hr/mL, about 6500 μg·hr/mL, about 6600 μg·hr/mL, about 6700 μg·hr/mL, about 6800 μg·hr/mL, about 8900 μg·hr/mL, about 7000 μg·hr/mL, about 7100 μg·hr/mL, about 7200 μg·hr/mL, about 7300 μg·hr/mL, about 7400 μg·hr/mL, about 7500 μg·hr/mL, after a single dose administration of about 50 mg to about 900 mg, or after single administration of the compound of the present invention in an amount that is molar equivalent to about 50 mg of gemcabene to about 900 mg gemcabene.

[00217] In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 50 μg·hr/mL to about 7500 μg·hr/mL after a single administration of about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110

mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, or about 900 mg.

[00218] In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 50 μg·hr/mL to about 7500 μg·hr/mL after a single administration of the compound of the invention in an amount that is molar equivalent to about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, or about 900 mg of gemcabene.

[00219] In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 50 μg·hr/mL to about 750 μg·hr/mL after single administration to a human subject at a dose of about 50 mg or in an amount that is molar equivalent to about 50 mg of gemcabene. In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 100 μg·hr/mL to about 500 μg·hr/mL after single

administration to a human subject at a dose of about 50 mg or in an amount that is molar equivalent to about 50 mg of gemcabene.

[00220] In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 100 μg·hr/mL to about 1250 μg·hr/mL after single dose administration to a human subject at a dose of about 150 mg or in an amount that is molar equivalent to about 150 mg of gemcabene. In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 200 μg·hr/mL to about 1000 μg·hr/mL after single dose administration to a human subject at a dose of about 150 mg or in an amount that is molar equivalent to about 150 mg of gemcabene.

[00221] In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 500 μg·hr/mL to about 2250 μg·hr/mL after single dose administration to a human subject at a dose of about 300 mg or in an amount that is molar equivalent to about 300 mg of gemcabene. In some embodiments, the compound of the invention provides a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 750 μg·hr/mL to about 2000 μg·hr/mL after single dose administration to a human subject at a dose of about 300 mg or in an amount that is molar equivalent to about 300 mg of gemcabene.

[00222] In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 1000 μg·hr/mL to about 4000 μg·hr/mL after single dose administration to a human subject at a dose of about 600 mg or in an amount that is molar equivalent to about 600 mg of gemcabene. In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 1500 μg·hr/mL to about 3500 μg·hr/mL after single dose administration to a human subject at a dose of about 600 mg or in an amount that is molar equivalent to about 600 mg of gemcabene. In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 1750 μg·hr/mL to about 3750 μg·hr/mL after single administration to a human subject at a dose of about 600 mg or in an amount that is molar equivalent to about 600 mg of gemcabene.

[00223] In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 2500 μg·hr/mL to about 6000 μg·hr/mL after single dose administration to a human subject at a dose of about 900 mg or in an amount that is molar equivalent to about 900 mg of gemcabene. In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 2750 μg·hr/mL to about 5500 μg·hr/mL after single dose administration to a human subject at a dose of about 900 mg or in an amount that is molar equivalent to about 900 mg of gemcabene.

[00224] In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 500 μg·hr/mL to about 5500 μg·hr/mL after single dose

administration to a human subject at a dose of about 300 mg to about 900 mg or in an amount that is molar equivalent to about 300 mg to about 900 mg of gemcabene. In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 750 μg·hr/mL to about 5000 μg·hr/mL after single dose administration to a human subject at a dose of about 450 mg to about 750 mg or in an amount that is molar equivalent to about 450 mg to about 750 mg of gemcabene. In some embodiments, the compound of the invention provides a plasma gemcabene AUC_{last} ranging from about 1000 μg·hr/mL to about 4500 μg·hr/mL after single dose administration to a human subject at a dose of about 500 mg to about 700 mg or in an amount that is molar equivalent to about 500 mg to about 700 mg of gemcabene.

[00225] In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum low-density lipoprotein cholesterol (LDL-C) by about 1% to about 80% when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day. In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum LDL-C by about 5% to about 75% when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day. In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum LDL-C by about 10% to about 75% when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day. In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum LDL-C by about 15% to about 70% when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day. In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum LDL-C by about 1%, about 2%,about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, or about 80% when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00226] In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum LDL-C by at least about 1%, at least about 2%,at least

about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 51%, at least about 52%, at least about 53%, at least about 54%, at least about 55%, at least about 56%, at least about 57%, at least about 58%, at least about 59%, at least about 60%, at least about 61%, at least about 62%, at least about 63%, at least about 64%, at least about 65%, at least about 66%, at least about 67%, at least about 68%, at least about 69%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, or at least about 80%, when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00227] In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum total cholesterol by about 1% to about 80%, including all subranges therein, when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00228] In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum LDL-C by about 1% to about 80% when administered to a human subject in an amount that is molar equivalent to about 50 mg to about 900 mg gemcabene per day. In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum LDL-C by about 5% to about 75%, about 10% to about 75%, or about 15% to about 70%, when administered to a human subject in an amount that is molar equivalent to about 50 mg to about 900 mg gemcabene per day. In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum LDL-C by about 1%, about 2%,about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%,

about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, or about 80% when administered to a human subject in an amount that is molar equivalent to about 50 mg to about 900 mg gemcabene per day.

[00229] In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum LDL-C by at least about 1%, at least about 2%,at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 51%, at least about 52%, at least about 53%, at least about 54%, at least about 55%, at least about 56%, at least about 57%, at least about 58%, at least about 59%, at least about 60%, at least about 61%, at least about 62%, at least about 63%, at least about 64%, at least about 65%, at least about 66%, at least about 67%, at least about 68%, at least about 69%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, or at least about 80%, when administered to a human subject in an amount that is molar equivalent to about 50 mg to about 900 mg gemcabene per day.

[00230] In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum total cholesterol by about 1% to about 80%, all subranges therein, when administered to a human subject in an amount that is molar equivalent to about 50 mg to about 900 mg gemcabene per day.

[00231] In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum LDL-C by about 1% to about 80% or by about 1% to about 75% when administered to a human subject in an amount that is molar equivalent to about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about

220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 980 mg, about 990 mg, or about 1000 mg of gemcabene per day.

[00232] In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum apolipoprotein B (Apo B) by about 1% to about 50% when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day. In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum Apo B by about 1% to about 40% when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day. In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum Apo B by about 1% to about 30% when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day. In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum Apo B by about 5% to about 30% when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day. In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum Apo B by about 1%, about 2%,about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, or about 60%, when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day. In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood

serum Apo B by at least about 1%, at least about 2%,at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 51%, at least about 52%, at least about 53%, at least about 54%, at least about 55%, at least about 56%, at least about 57%, at least about 58%, at least about 59%, or at least about 60%, when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00233] In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum Apo B by about 1% to about 50% when administered to a human subject in an amount that is molar equivalent to about 50 mg to about 900 mg gemcabene per day. In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum Apo B by about 1% to about 40%, about 1% to about 30%, or about 5% to about 30%, when administered to a human subject in an amount that is molar equivalent to about 50 mg to about 900 mg gemcabene per day. In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum Apo B by about 1%, about 2%,about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, or about 60%, when administered to a human subject in an amount that is molar equivalent to about 50 mg to about 900 mg gemcabene per day. In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum Apo B by at least about 1%, at least about 2%,at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at

least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 51%, at least about 52%, at least about 53%, at least about 54%, at least about 55%, at least about 56%, at least about 57%, at least about 58%, at least about 59%, or at least about 60%, when administered to a human subject in an amount that is molar equivalent to about 50 mg to about 900 mg gemcabene per day.

[00234] In some embodiments, the compound of the invention provides reduction in a human subject's baseline plasma or blood serum Apo B by about 1% to about 50% when administered to a human subject in an amount that is molar equivalent to about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, or about 900 mg of gemcabene per day.

[00235] In some embodiments, the present invention provides compounds of the invention having (a) an amorphous form or a crystalline form and (b) a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm and providing a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 250 μg·hr/mL at

steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00236] In some embodiments, the present invention provides pharmaceutical compositions comprising an amorphous form or a crystalline form of the compounds of the invention having a dissolution profile value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm and providing a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 250 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00237] In some embodiments, the present invention provides compounds of the invention having (a) an amorphous form or a crystalline form and (b) a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm and providing a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from 250 μg·hr/mL at steady state to 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00238] In some embodiments, the present invention provides pharmaceutical compositions comprising an amorphous form or a crystalline form of the compounds of the invention having a dissolution profile value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm and providing a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from 250 μg·hr/mL at steady state to 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00239] In some embodiments, the present invention provides compounds of the invention having an amorphous form or a crystalline form and providing a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 200 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day. In some embodiments, the present invention provides compounds of the invention having an amorphous form or a crystalline form and providing a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from 200

μg·hr/mL at steady state to 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00240] In some embodiments, the present invention provides pharmaceutical compositions comprising an amorphous form or a crystalline form of the compounds of the invention providing a plasma gemcabene $AUC_{(0-24)}$ ranging from about 200 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day. In some embodiments, the present invention provides pharmaceutical compositions comprising an amorphous form or a crystalline form of the compounds of the invention providing a plasma gemcabene $AUC_{(0-24)}$ ranging from 200 μg·hr/mL at steady state to 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00241] In some embodiments, the present invention provides compounds of the invention having an amorphous form or a crystalline form and providing a plasma gemcabene $AUC_{(0-24)}$ ranging from 250 μg·hr/mL at steady state to 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00242] In some embodiments, the present invention provides pharmaceutical compositions comprising an amorphous form or a crystalline form of the compounds of the invention providing a plasma gemcabene $AUC_{(0-24)}$ ranging from 250 μg·hr/mL at steady state to 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00243] In some embodiments, the present invention provides compounds of the invention having an amorphous form or a crystalline form and providing a plasma gemcabene $AUC_{(0-24)}$ ranging from about 250 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00244] In some embodiments, the present invention provides pharmaceutical compositions comprising an amorphous form or a crystalline form of the compounds of the invention providing a plasma gemcabene $AUC_{(0-24)}$ ranging from about 250 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00245] In some embodiments, the present invention provides amorphous or crystalline compounds of the invention having a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm and providing

a plasma gemcabene $AUC_{(0-24)}$ ranging from about 200 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00246] In some embodiments, the present invention provides pharmaceutical compositions comprising an amorphous form or a crystalline form of the compounds of the invention having a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm and providing a plasma gemcabene $AUC_{(0-24)}$ ranging from about 200 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00247] In some embodiments, the present invention provides amorphous or crystalline compounds of the invention having a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm and providing a plasma gemcabene $AUC_{(0-24)}$ ranging from 200 μg·hr/mL at steady state to 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00248] In some embodiments, the present invention provides pharmaceutical compositions comprising an amorphous form or a crystalline form of the compounds of the invention having a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm and providing a plasma gemcabene $AUC_{(0-24)}$ ranging from 200 μg·hr/mL at steady state to 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00249] In some embodiments, the present invention provides amorphous or crystalline compounds of the invention having a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by

high-performance liquid chromatography using a detection wavelength of 210 nm and providing a plasma gemcabene $AUC_{(0-24)}$ ranging from 250 μg·hr/mL at steady state to 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00250] In some embodiments, the present invention provides pharmaceutical compositions comprising an amorphous form or a crystalline form of the compounds of the invention having a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm and providing a plasma gemcabene $AUC_{(0-24)}$ ranging from 250 μg·hr/mL at steady state to 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00251] In some embodiments, the present invention provides amorphous or crystalline compounds of the invention having a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm and providing a plasma gemcabene $AUC_{(0-24)}$ ranging from about 250 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00252] In some embodiments, the present invention provides pharmaceutical compositions comprising an amorphous form or a crystalline form of the compounds of the invention having a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm and providing a plasma gemcabene $AUC_{(0-24)}$ ranging from about 250 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg/day to about 900 mg/day.

[00253] In some embodiments, the present invention provides compounds of the invention having (a) an amorphous form or a crystalline form and (b) a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210

nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm and proving a plasma gemcabene AUC_{last} ranging from about 50 μg·hr/mL to about 7500 μg·hr/mL after a single dose administration of about 50 mg to about 900 mg to a human subject.

[00254] In some embodiments, the present invention provides pharmaceutical compositions comprising an amorphous form or a crystalline form of the compounds of the invention having a dissolution profile having a value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm and proving a plasma gemcabene AUC_{last} ranging from about 50 μg·hr/mL to about 7500 μg·hr/mL after a single dose administration of about 50 mg to about 900 mg to a human subject.

[00255] In some embodiments, the present invention provides compounds of the invention having an amorphous form or a crystalline form and providing a plasma gemcabene AUC_{last} ranging from about 50 μg·hr/mL to about 7500 μg·hr/mL after a single dose administration of about 50 mg to about 900 mg to a human subject.

[00256] the present invention provides pharmaceutical compositions comprising an amorphous form or a crystalline form of the compounds of the invention providing a plasma gemcabene AUC_{last} ranging from about 50 μg·hr/mL to about 7500 μg·hr/mL after a single dose administration of about 50 mg to about 900 mg to a human subject.

[00257] In some embodiments, an effective dose of the compound of the invention can be a dose that achieves ≥ 10% mean reduction in low-density lipoprotein cholesterol (LDL-C) after 4 weeks of treatment. In some embodiments, an effective dose of the compound of the invention can be a dose that achieves ≥ 15% mean reduction in LDL-C after 4 weeks of treatment. In some embodiments, an effective dose of the compound of the invention can be a dose that achieves ≥ 5%, ≥ 6%, ≥ 7%, ≥ 8%, ≥ 9%, ≥ 10%, ≥ 11%, ≥ 12%, ≥ 13%, ≥ 14%, or 15% mean reduction in LDL-C after 4 weeks of treatment. In some embodiments, an effective dose of the compound of the invention can be a dose that achieves ≥ 5%, ≥ 6%, ≥ 7%, ≥ 8%, ≥ 9%, ≥ 10%, ≥ 11%, ≥ 12%, ≥ 13%, ≥ 14%, or 15% mean reduction in LDL-C after 4 weeks of daily administration of the compound of the invention in about 50 mg to about 900 mg per day.

[00258] In some embodiments, the pharmacokinetic values and properties of a compound of the invention is measured with a composition of the invention that is in the form of a tablet. In

some embodiments, the tablet is a compressed tablet. In some embodiment, the compressed tablet is a film-coated compressed tablet.

[00259] In some embodiments, the pharmacokinetic values and properties of a compound of the invention is measured using a composition of the invention that is in the form of a capsule.

[00260] In some embodiments, $AUC_{(0-24)}$ or AUC_{last} of a compound of the invention is measured with a composition of the invention that is in the form of a tablet. In some embodiments, the tablet is a compressed tablet. In some embodiment, the compressed tablet is a film-coated compressed tablet.

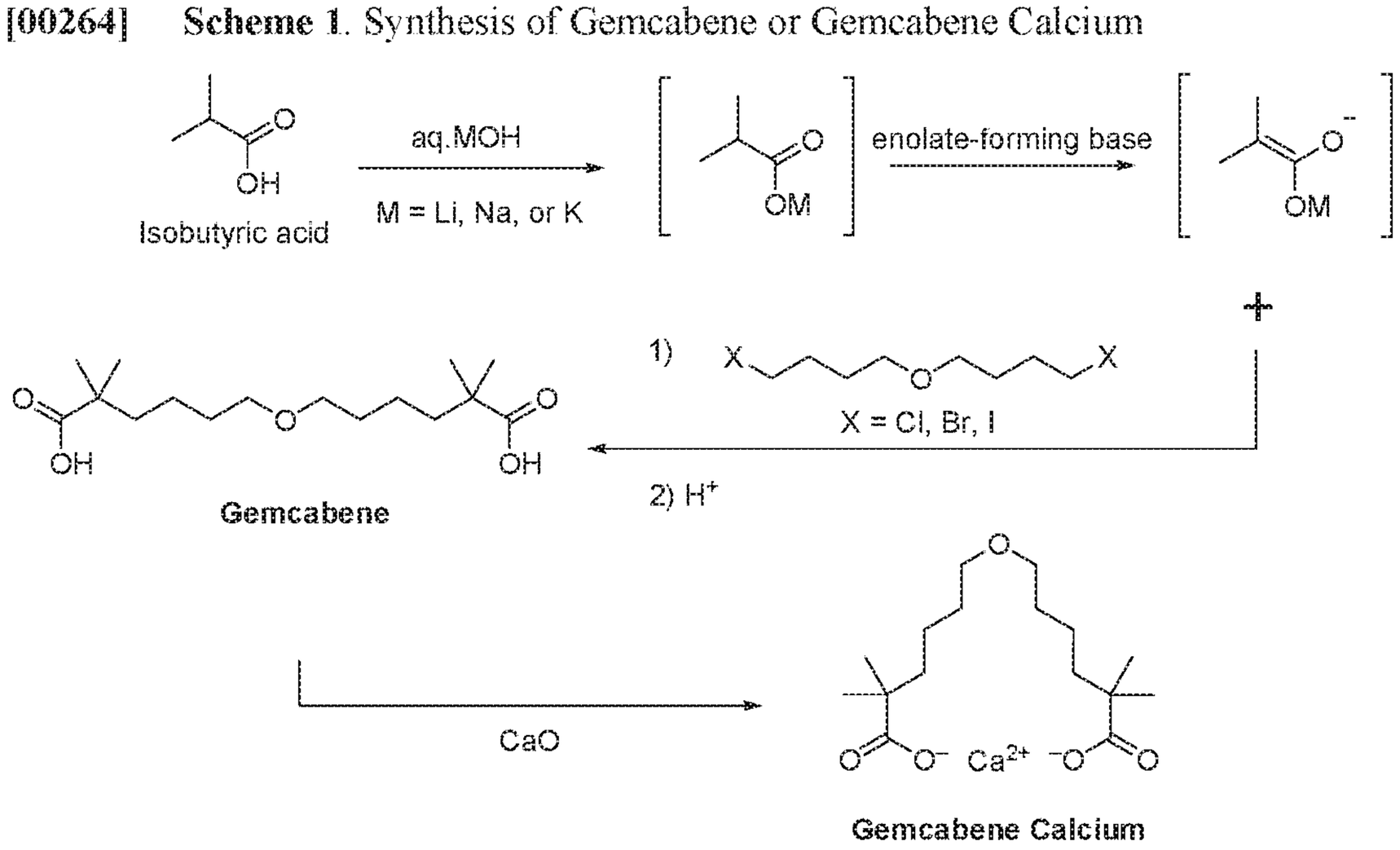
[00261] In some embodiments, $AUC_{(0-24)}$ or AUC_{last} of a compound of the invention is measured using a composition of the invention that is in the form of a capsule.

[00262] In some embodiments, the pharmacokinetic values and properties disclosed herein are in connection with a human subject.

METHODS FOR MAKING GEMCABENE

[00263] The present invention further provides methods for making gemcabene. Gemcabene is useful for making the compounds of the invention. Gemcabene or gemcabene calcium can be prepared by a synthetic process as shown in Scheme 1.

[00264] **Scheme 1**. Synthesis of Gemcabene or Gemcabene Calcium



[00265] Isobutyric acid is converted to an alkali metal salt. In some embodiments, isobutyric acid is converted to an alkali metal salt using an alkali metal hydroxide. In some embodiments, the alkali metal hydroxide is lithium hydroxide, sodium hydroxide or potassium hydroxide. In some embodiments, the alkali metal hydroxide is sodium hydroxide.

[00266] In some embodiments, the alkali metal hydroxide is lithium hydroxide, which converts isobutyric acid to lithium isobutyrate. In some embodiments, the alkali metal hydroxide is sodium hydroxide, which converts isobutyric acid to sodium isobutyrate. In some embodiments, the alkali metal hydroxide is potassium hydroxide, which converts isobutyric acid to potassium isobutyrate.

[00267] In some embodiments, the alkali metal hydroxide is present in an aqueous solution or suspension. In some embodiments, the alkali metal hydroxide is present in an about 30% (w/w) in aqueous solution.

[00268] In some embodiments, the alkali metal salt is sodium hydroxide. In some embodiments, the sodium hydroxide is present in an aqueous solution. In some embodiments, the aqueous solution of sodium hydroxide is 30% (w/w).

[00269] In some embodiments, isobutyric acid is converted to an alkali metal salt in the presence of an organic solvent. In some embodiments, the organic solvent is a hydrocarbon solvent. In some embodiments, the hydrocarbon solvent is benzene, toluene, xylene or an alkane. In some embodiments, the alkane is a C_5-C_{12} alkane. In some embodiments, the alkane is pentane, hexane or heptane. In some embodiments, the alkane is *n*-pentane, *n*-hexane or *n*-heptane. In some embodiments, the alkane is *n*-heptane.

[00270] It is important to eliminate substantially all water from the reaction mixture comprising the isobutyrate alkali metal salt prior to proceeding to adding the enolate-forming base because the enolate-forming base can react with residual water. In some embodiments, water is removed by heterogeneous azeotropic distillation (composition in azeotrope: 12.9% water and 87.1% heptane; b.p. 79.2 °C) prior to adding the enolate-forming base. In some embodiments, heterogeneous azeotropic distillation of water is performed at about 100 to about 110 °C. In some embodiments, heterogeneous azeotropic distillation of water is performed at about 105 °C. In some embodiments, heterogeneous azeotropic distillation of water is performed at about 900 mbar to about 1100 mbar. In some embodiments, heterogeneous azeotropic distillation of water is performed at about 1000 mbar.

[00271] Prior to adding the enolate-forming base, to effectively remove substantially all water from the reaction mixture, the removal of water, for example, by heterogeneous azeotropic distillation, can be measured by volume. In other embodiments, Karl-Fisher analysis can be performed. In some embodiments, water, if any, present in the reaction mixture prior to the addition of the enolate-forming base is ≤0.05% w/w of the reaction mixture as determined by Karl-Fisher analysis. In some embodiments, water, if any, present in the reaction mixture prior to the addition of the enolate-forming base is 0.05% w/w or less, 0.04% w/w or less, 0.03% w/w or less, 0.02% w/w or less, 0.015% w/w or less, 0.0125% w/w or less, or 0.01% w/w or less of the

reaction mixture as determined by Karl-Fisher analysis. In some embodiments, water, if any, present in the reaction mixture prior to the addition of the enolate-forming base is less than 0.05% w/w, less than 0.04% w/w, less than 0.03% w/w, less than 0.02% w/w, less than 0.015% w/w, less than 0.0125% w/w, or less than 0.01% w/w of the reaction mixture as determined by Karl-Fisher analysis.

[00272] In some embodiments, the alkali metal salt of isobutyric acid is converted to an enolate using an enolate-forming base. In some embodiments, the enolate-forming base is lithium hexamethyldisilazide, lithium diisopropylamide (LDA), lithium tetramethylpiperidide (LiTMP), or lithium diethylamide ($LiNEt_2$). In some embodiments, the enolate-forming base is LDA and is prepared *in situ* using diisopropylamine and an organolithium reagent, such as *n*-butyllithium, *n*-hexyllithium or *n*-heptyllithium. In some embodiments, the enolate-forming base is generated in an aprotic solvent. In some embodiments, the enolate-forming base is obtained commercially and is present in an aprotic solvent. In some embodiments, the enolate-forming base is generated in THF or solvent mixture comprising THF. In some embodiments, the enolate-forming base is in THF or solvent mixture comprising THF.

[00273] In some embodiments, the LDA is pre-made and obtained commercially, particularly in view of organolithium reagents' highly pyrogenic properties. In some embodiments, the LDA is pre-made. In some embodiments, the pre-made LDA is present in solution. In some embodiments, the pre-made LDA solution is about 25% w/w to about 30% w/w LDA. In some embodiments, the LDA is 28% w/w in heptane/THF/ethylbenzene. In some embodiments, the pre-made LDA is present in solution. In some embodiments, the pre-made LDA solution is about 1.5M to about 2.5M. In some embodiments, the LDA is 2.0M to 2.2M in heptane/THF/ethylbenzene. In some embodiments, the addition of the enolate-forming base is performed under anhydrous conditions. In some embodiments, the addition of the enolate-forming base is performed under substantially anhydrous conditions. In some embodiments, the addition of the enolate-forming base is performed under conditions where the water content is $\leq$0.05% w/w of the reaction mixture as determined by Karl-Fisher analysis.

[00274] In some embodiments, the enolate-forming base is admixed with the alkali metal salt of isobutyric acid to provide an enolate of the alkali metal salt of isobutyric acid. The enolate-forming base can be added to the alkali metal salt of isobutyric acid, or vice versa. In some embodiments, the enolate-forming base is LDA, the alkali metal salt of isobutyric acid is sodium isobutyrate and the LDA is added to the sodium isobutyrate. In some embodiments, the enolate-forming base and the alkali metal salt of isobutyric acid are admixed at a temperature ranging from about 10 °C to about 15 °C. In some embodiments, after the enolate-forming base and the alkali metal salt of isobutyric acid are admixed, the reaction mixture is heated at 42 °C ± 2 °C. In

some embodiments, the reaction mixture is heated at 42 °C ± 2 °C for about 30 minutes to 2 hours. In some embodiments, the reaction mixture is heated at 42 °C ± 2 °C for about 1 hour. In some embodiments, the enolate-forming base and the alkali metal salt of isobutyric acid are admixed in the presence of heptane, tetrahydrofuran (THF), or combination thereof. In some embodiments, the enolate-forming base and the alkali metal salt of isobutyric acid are admixed in the presence of *n*-heptane, tetrahydrofuran (THF), or combination thereof.

[00275] The enolate of the alkali metal salt of isobutyric acid is admixed with a bis-(4-halobutyl)ether. The enolate can be added to the bis-(4-halobutyl)ether, or vice versa. In some embodiments, the bis-(4-halobutyl)ether is bis-(4-chlorobutyl)ether; in some embodiments, the bis-(4-halobutyl)ether is bis-(4-bromobutyl)ether; and in some embodiments, the bis-(4-halobutyl)ether is bis-(4-iodobutyl)ether.

[00276] In some embodiments, about two equivalents of the enolate of the alkali metal salt of isobutyric acid are admixed with a bis-(4-halobutyl)ether. In some embodiments, about two to about three equivalents of the enolate of the alkali metal salt of isobutyric acid are admixed with a bis-(4-halobutyl)ether. In some embodiments, 2.2 to 2.5 equivalents of the enolate of the alkali metal salt of isobutyric acid are admixed with a bis-(4-halobutyl)ether.

[00277] In some embodiments, the bis-(4-halobutyl)ether is added to the enolate dropwise. In some embodiments, the bis-(4-halobutyl)ether is added to the enolate dropwise over about 1 hour to about 5 hours. In some embodiments, the bis-(4-halobutyl)ether is added to the enolate dropwise over about 1 hour to about 4 hours. In some embodiments, the bis-(4-halobutyl)ether is added to the enolate at a temperature ranging from about 40 °C to about 45 °C. In some embodiments, the bis-(4-halobutyl)ether is added to the enolate at a temperature ranging from 40 °C to 44 °C. In some embodiments, the bis-(4-halobutyl)ether is added to the enolate as a solution in THF. In some embodiments, the bis-(4-halobutyl)ether is bis-(4-chlorobutyl)ether, the enolate is a lithium enolate of sodium isobutyrate, the bis-(4-chlorobutyl)ether is added as a solution in THF to the lithium enolate of sodium isobutyrate at a temperature ranging from 40 °C to 44 °C.

[00278] In some embodiments, after the addition of the bis-(4-halobutyl)ether, the reaction mixture is allowed to stir a temperature ranging from about 40 °C to about 45 °C. In some embodiments, after the addition of the bis-(4-halobutyl)ether, the reaction mixture is allowed to stir at a temperature ranging from 40 °C to 44 °C. In some embodiments, after the addition of the bis-(4-halobutyl)ether, the reaction mixture is allowed to stir for about 8 hours to about 30 hours. In some embodiments, after the addition of the bis-(4-halobutyl)ether, the reaction mixture is allowed to stir for at least 10 hours. In some embodiments, after the addition of the bis-(4-halobutyl)ether, the reaction mixture is allowed to stir for about 10 hours to about 24 hours. In

some embodiments, after the addition of the bis-(4-halobutyl)ether, the reaction mixture is allowed to stir for about 14 hours to about 24 hours.

[00279] In some embodiments, after the addition of the bis-(4-halobutyl)ether, the reaction mixture is allowed to stir at a temperature ranging from 40 °C to 44 °C and until quantitative ^{1}H NMR analysis indicates ≤5% bis-(4-halobutyl)ether in the reaction mixture (e.g., ≥95% conversion of bis-(4-halobutyl)ether). In some embodiments, after the addition of bis-(4-halobutyl)ether, the reaction mixture is allowed to stir at a temperature ranging from 40 °C to 44 °C and until ^{1}H NMR analysis indicates 5% or less, 4% or less, 3% or less, 2% or less, or 1.5% or less bis-(4-halobutyl)ether in the reaction mixture. In some embodiments, after the addition of bis-(4-halobutyl)ether, the reaction mixture is allowed to stir at a temperature ranging from 40 °C to 44 °C and until ^{1}H NMR analysis indicates less than 5%, less than 4%, less than 3%, less than 2%, or less than 1.5% bis-(4-halobutyl)ether in the reaction mixture.

[00280] Once bis-(4-halobutyl)ether reaction is substantially complete (e.g., quantitative ^{1}H NMR analysis indicates ≤5% bis-(4-halobutyl)ether), an aqueous work-up can be performed to extract the gemcabene salt product into an aqueous phase. Once the gemcabene salt is contained in the aqueous phase, the aqueous phase can be acidified, for example, with a mineral acid, such as hydrochloric acid. Once the aqueous phase is acidified, and the gemcabene salt converted to gemcabene, the gemcabene can be extracted with an organic solvent. Useful organic solvents include heptane, hexane, methyl tetrahydrofuran, toluene, ethyl acetate, butyl acetate, cyclohexane, 2-butanone, and diisopropyl ether. In some embodiments, the organic solvent is heptane. In some embodiments, the organic solvent is *n*-heptane. In some embodiments, the aqueous phase is extracted multiple times with the organic solvent. In some embodiments, the organic solvent used in the extractions after the bis-(4-halobutyl)ether reaction is complete or substantially complete has a temperature ranging from about 40 °C to about 60 °C. In some embodiments, the organic solvent used in the extractions after the bis-(4-halobutyl)ether reaction is complete or substantially complete has a temperature ranging from about 48 °C to about 54 °C. In some embodiments, the extractions are performed at a temperature ranging from about 40 °C to about 60 °C (temperature indicates the temperature of the solvents used in extractions).

[00281] The organic layer containing gemcabene can be evaporated to substantial dryness. The resultant crude gemcabene can be admixed with water, which can be subsequently evaporated. In some embodiments, the water is evaporated at ≤ 60 °C. The further resultant crude gemcabene can be dissolved in an organic solvent, such as heptane, and the organic solution can be washed with water and evaporated to substantial dryness. This process can be repeated one or more times. In some embodiments, the process is performed twice. In some embodiments, the process is performed at least twice.

[00282] In some embodiments, isobutyric acid impurity, resulting from, for example, use of more than two equivalents of the enolate of the alkali metal salt of isobutyric acid per equivalent of bis-(4-halobutyl)ether, can be removed by co-distillation with water. Without being bound by theory, it is believed that the isobutyric acid is removed as an azeotrope with water. The presence of isobutyric acid impurity in the crude gemcabene can adversely affect its crystallization and the purity of crystallized gemcabene.

[00283] In some embodiments, co-distillation of water is performed at a temperature ranging from about 100 °C to about 110 °C. In some embodiments, co-distillation of water is performed at a temperature ranging from about 100 °C to about 105 °C. In some embodiments, co-distillation of water is performed at ambient pressure. In some embodiments, co-distillation of water is performed at reduced pressure. In some embodiments, co-distillation of water is performed at reduced pressure such that co-distillation of water is performed at a temperature in ranging from about 35 °C to about 70 °C. In some embodiments, co-distillation of water is performed at reduced pressure such that co-distillation of water is performed at a temperature ranging from about 40 °C to about 60 °C. In some embodiments, co-distillation of water is performed at about 10 mbar to about 100 mbar.

[00284] In some embodiments, a first co-distillation with water provides crude gemcabene comprising isobutyric acid impurity in 5% w/w or less of the crude gemcabene as determined by ion chromatography. In some embodiments, a first co-distillation with water provides the crude gemcabene comprising isobutyric acid impurity in 5% w/w or less, 4% w/w or less, 3% w/w or less, 2% w/w or less, or 1% w/w or less of the crude gemcabene as determined by ion chromatography. In some embodiments, a first co-distillation with water provides the crude gemcabene comprising isobutyric acid impurity in less than 5% w/w, less than 4% w/w, less than 3% w/w, less than 2% w/w, or less than 1% w/w of the crude gemcabene as determined by ion chromatography. In some embodiments, a first co-distillation with water provides the crude gemcabene comprising isobutyric acid impurity in 0.9% w/w or less, 0.8% w/w or less, 0.7% w/w or less, 0.6% w/w or less, or 0.5% w/w or less of the crude gemcabene as determined by ion chromatography. In some embodiments, a first co-distillation with water provides the crude gemcabene comprising isobutyric acid impurity in less than 0.9% w/w, less than 0.8% w/w, less than 0.7% w/w, less than 0.6% w/w, or less than 0.5% w/w of the crude gemcabene as determined by ion chromatography. In some embodiments, a first co-distillation with water provides the crude gemcabene comprising isobutyric acid impurity in 0.8% w/w or less of the crude gemcabene as determined by ion chromatography.

[00285] In some embodiments, a second co-distillation with water provides the crude gemcabene comprising isobutyric acid impurity in 1% w/w or less of the crude gemcabene as

determined by ion chromatography. In some embodiments, a second co-distillation with water provides the crude gemcabene comprising isobutyric acid impurity in 1.0% w/w or less, 0.9% w/w or less, 0.8% w/w or less, 0.7% w/w or less, 0.6% w/w or less, 0.5% w/w or less, 0.4% w/w or less, 0.3% w/w or less, or 0.2% w/w or less of the crude gemcabene as determined by ion chromatography. In some embodiments, a second co-distillation with water provides the crude gemcabene comprising isobutyric acid impurity in less than 1.0% w/w, less than 0.9% w/w, less than 0.8% w/w, less than 0.7% w/w, less than 0.6% w/w, less than 0.5% w/w, less than 0.4% w/w, less than 0.3% w/w, or less than 0.2% w/w of the crude gemcabene as determined by ion chromatography. In some embodiments, a second co-distillation with water provides the crude gemcabene comprising isobutyric acid impurity in 0.5% w/w or less, 0.4% w/w or less, 0.3% w/w or less, or 0.2% w/w or less of the crude gemcabene as determined by ion chromatography. In some embodiments, a second co-distillation with water provides the crude gemcabene comprising isobutyric acid impurity in 0.3% w/w or less of the crude gemcabene as determined by ion chromatography.

[00286] After distillation and/or evaporation of water and removal of isobutyric acid impurity, a water/heptane heterogeneous azeotropic distillation can be performed in order to remove substantially all water content as determined by Karl-Fisher analysis. In some embodiments, the water content, if any, is ≤0.05% w/w of the reaction mixture as determined by Karl-Fisher analysis. In some embodiments, the water content, if any, is 0.05% w/w or less, or 0.04% w/w or less of the reaction mixture as determined by Karl-Fisher analysis. In some embodiments, the water content, if any, is less than 0.05% w/w, or less than 0.04% w/w of the reaction mixture as determined by Karl-Fisher analysis.

[00287] In some embodiments, before crystallization of gemcabene, the crude gemcabene is passed through silica gel to remove impurities, such as any colored or polar impurities. In some embodiments, silica gel filtration is performed using 5% (v/v) THF in heptane as an eluent. In some embodiments, subsequent to the silica gel filtration, the silica gel is washed with only heptane. In some embodiments, heptane is *n*-heptane.

[00288] The gemcabene-containing fractions from silica gel filtration can be evaporated to substantial dryness and the resultant residue can be crystallized from an organic solvent or mixture of organic solvents. In some embodiments, the organic solvent is heptane or a mixture of heptane and THF. In some embodiments, the organic solvent is heptane in the absence of THF. In some embodiments, heptane is *n*-heptane.

[00289] In some embodiments, crude gemcabene is dissolved in the organic solvent at a temperature ranging from about 20 °C to about 50 °C. In some embodiments, the crude gemcabene is dissolved in the organic solvent at a temperature ranging from 35 °C to 50 °C.

[00290] In some embodiments, once the crude gemcabene is dissolved in the organic solvent, the organic solution is cooled to 15 °C ± 2 °C. In some embodiments, the organic solution is cooled to 15 °C ± 2 °C and subsequently seeded with one or more gemcabene crystals. In some embodiments, the organic solvent is heptane. In some embodiments, the organic solvent is *n*-heptane.

[00291] In some embodiments, the gemcabene is allowed to crystallize at a temperature ranging from 9 °C to 16 °C. In some embodiments, the gemcabene is allowed to crystallize at a temperature ranging from 10 °C to 15 °C. In some embodiments, the gemcabene is allowed to crystallize at a temperature ranging from 10 °C to 14 °C. In some embodiments, the gemcabene is allowed to crystallize at a temperature of 10 °C, 11°C, 12°C, 13°C, 14°C, or 15 °C. In some embodiments, the gemcabene is allowed to crystallize at a temperature of 12 °C.

[00292] In some embodiments, the crude gemcabene before recrystallization comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid impurity. Allowing gemcabene to crystallize from heptane at a temperature ranging from 10 °C to 15 °C yields gemcabene containing substantially less 2,2,7,7-tetramethyl-octane-1,8-dioic acid impurity than gemcabene that is allowed to crystallize from heptane at a temperature below 10 °C. Moreover, as shown in Table C, the gemcabene of Entry 4, which was allowed to crystallize from heptane maintained at 12-14 °C without further cooling contained significantly less 2,2,7,7-tetramethyl-octane-1,8-dioic acid than that contained in the gemcabene of the other Entries. In some embodiments, heptane is *n*-heptane.

[00293] **Table C**. Summary of crystallization experiment with varying temperature and time

Entry	1st Temp. Time	Ramp time from 1st Temp. to 2nd Temp.	2nd Temp. Time	Total stirring time (≤15 °C)	Yield of Gemcabene	Amount of TMODA by HPLC-CAD
1	15 °C 4 h	2.5 h 5 °C/h	5-6 °C 20.5 h	27 h	85%	0.41% w/w
2	15 °C 2.8 h	1.2 h ~10.7 °C/h	5-8 °C 2.8 h	6.5 h	76%	0.10% w/w
3	15 °C 18.5 h	2.4 h 5 °C/h	5-6 °C 4 h	26 h	85%	0.32% w/w
4	12-14 °C 20.5 h	-	-	21.5 h	83%	0.03% w/w
5	15-16 °C 1.8 h	1.2 h 10 °C/h	5-8 °C 2.2 h	5.3 h	85%	0.13% w/w

TMODA = 2,2,7,7-Tetramethyl-octane-1,8-dioic acid; HPLC-CAD = high-performance liquid chromatography equipped with a charged aerosol detector; % w/w of the crystalized gemcabene

[00294] In some embodiments, a first gemcabene crystallization from heptane at a temperature ranging from 9 °C to 16 °C yields gemcabene comprising2,2,7,7-tetramethyl-octane-1,8-dioic acid impurity in ≤0.5% w/w of the crystallized gemcabene as determined by high-performance liquid chromatography (HPLC). In some embodiments, a second gemcabene crystallization from heptane at a temperature ranging from 10 °C to 15 °C once yields gemcabene comprising 2,2,7,7-tetramethyl-octane-1,8-dioic acid impurity in ≤0.5% w/w of the crystallized gemcabene as determined by high-performance liquid chromatography (HPLC). In some embodiments, a first gemcabene crystallization from *n*-heptane at a temperature ranging from 10 °C to 15 °C yields gemcabene comprising 2,2,7,7-tetramethyl-octane-1,8-dioic acid impurity, if any, in 0.5% w/wor less, 0.4% w/wor less, 0.3% w/wor less, 0.2% w/w or less, 0.15% w/w or less, 0.1% w/w or less, or 0.05% w/w or less of the crystallized gemcabene as determined by HPLC. In some embodiments, a first gemcabene crystallization from heptane at a temperature ranging from 10 °C to 15 °C yields gemcabene comprising 2,2,7,7-tetramethyl-octane-1,8-dioic acid impurity in less than 0.5% w/w, less than 0.4% w/w, less than 0.3% w/w, less than 0.2% w/w, less than 0.15% w/w, less than 0.1% w/w, or less than 0.05% w/w of the crystallized gemcabene as determined by HPLC. In some embodiments, a first gemcabene crystallization from heptane at a temperature of 12 °C yields gemcabene comprising 2,2,7,7-tetramethyl-octane-1,8-dioic acid impurity in less than 0.2% w/w, less than 0.15% w/w, less than 0.1% w/w, or less than 0.05% w/w of the crystallized gemcabene as determined by HPLC. In some embodiments, HPLC is equipped with charged aerosol detector (CAD). In some embodiments, HPLC is equipped with ultraviolet detector (UV). In some embodiments, heptane is *n*-heptane.

[00295] In some embodiments, a first gemcabene crystallization from heptane at a temperature ranging between 10 °C to 14 °C yields gemcabene containing 2,2,7,7-tetramethyl-octane-1,8-dioic acid in a range of 0.5% w/w to 0.1% w/w, 0.4% w/w to 0.1% w/w, 0.3% w/w to 0.1% w/w, or 0.2% w/w to 0.1% w/w of the crystallized gemcabene as determined by HPLC. In some embodiments, a first gemcabene crystallization from heptane at a temperature ranging between 10 °C to 14 °C yields gemcabene comprising 2,2,7,7-tetramethyl-octane-1,8-dioic acid in a range of 0.5% w/w to 0.01% w/w, 0.4% w/w to 0.01% w/w, 0.3% w/w to 0.01% w/w, or 0.2% w/w to 0.01% w/w of the crystallized gemcabene as determined by HPLC. In some embodiments, a first gemcabene crystallization from heptane at a temperature ranging between 10 °C to 14 °C yields gemcabene comprising 2,2,7,7-tetramethyl-octane-1,8-dioic acid in a range of 0.5% w/w to 0.001% w/w, 0.4% w/w to 0.001% w/w, 0.3% w/w to 0.001% w/w, or 0.2% w/w to 0.001% w/w of the crystallized gemcabene as determined by HPLC. In some embodiments, heptane is *n*-heptane.

[00296] In some embodiments, the concentration of the crystallization solution affects the recovery of gemcabene. In some embodiments, the crystallization solution has a concentration greater than 0.3 g/mL crude gemcabene in the organic solvent or mixtures of organic solvent. In some embodiments, the crystallization solution has a concentration of ≥0.4 g/mL, ≥0.5 g/mL, or ≥0.6 g/mL crude gemcabene in the organic solvent or mixtures of organic solvent. In some embodiments, the crystallization solution has a concentration ranging from 0.3 g of crude gemcabene /mL of heptane to 0.9 g of crude gemcabene /mL of heptane. In some embodiments, crystallization solution has a concentration ranging from 0.5 g of crude gemcabene /mL of heptane to 0.8 g of crude gemcabene /mL of heptane. In some embodiments, the crystallization solution has a concentration ranging from 0.5 g of crude gemcabene /mL of heptane to 0.7 g of crude gemcabene /mL of heptane. In some embodiments, crystallization solution has a concentration of 0.6 g crude gemcabene /mL of heptane. In some embodiments, heptane is *n*-heptane.

[00297] The yield of gemcabene can be affected by the number of equivalents of isobutyric acid, alkali metal hydroxide or enolate-forming base in relation to bis-(4-halobutyl)ether. In some embodiments, molar equivalents ranging from 2.05 to 3.00 of each of isobutyric acid, alkali metal hydroxide, and enolate-forming base are used compared to 1.00 molar equivalent of bis-(4-halobutyl)ether. In some embodiments, molar equivalents ranging from 2.15 to 2.50 of each of isobutyric acid, alkali metal hydroxide, and enolate-forming base are used compared to 1.0 molar equivalent of bis-(4-halobutyl)ether. In some embodiments, molar equivalents ranging from 2.20 to 2.40 of each of isobutyric acid, alkali metal hydroxide, and enolate-forming base are used compared to 1.0 molar equivalent of bis-(4-halobutyl)ether. In some embodiments, 2.20 equivalents of each of isobutyric acid, alkali metal hydroxide, and enolate-forming are used compared to 1.0 molar equivalent of bis-(4-chlorobutyl)ether. In some embodiments, the alkali metal hydroxide is sodium hydroxide and the enolate-forming base is LDA. In some embodiments, the alkali metal hydroxide is sodium hydroxide, the enolate-forming base is LDA and the bis-(4-halobutyl)ether is bis-(4-iodobutyl)ether.

[00298] In some embodiments, gemcabene made according to any one of the methods disclosed herein has a purity ranging from about 85% w/w to 100% w/w as determined by high-performance liquid chromatography (HPLC). In some embodiments, gemcabene has a purity ranging from about 90% w/w to100% w/w as determined by HPLC. In some embodiments, gemcabene has a purity ranging from about 95% w/w to 100% w/w as determined by HPLC. In some embodiments, gemcabene has a purity ranging from about 98% w/w to 100% w/w as determined by HPLC. In some embodiments, gemcabene has a purity ranging from about 99% w/w to 100% w/w as determined by HPLC. In some embodiments, gemcabene has a purity

ranging from 99.0% to 100% as determined by HPLC. In some embodiments, gemcabene has a purity ranging from about 99.5% w/w to 100% w/w as determined by HPLC. In some embodiments, HPLC is equipped with a charged aerosol detector (CAD) or with an ultraviolet detector (UV).

[00299] In some embodiments, gemcabene made according to any one of the methods disclosed herein comprises isobutyric acid impurity in ≤0.5% w/w of the gemcabene as determined by ion chromatography (IC). In some embodiments, gemcabene comprises isobutyric acid impurity, if any, in 0.5% w/w or less, 0.4% w/w or less, 0.3% w/w or less, 0.2% w/w or less, 0.15% w/w or less, 0.1% w/w or less, or 0.05% w/w or less of the gemcabene as determined by IC. In some embodiments, gemcabene comprises isobutyric acid impurity in less than 0.5%, less than 0.4% w/w, less than 0.3% w/w, less than 0.2% w/w, less than 0.15% w/w, less than 0.1% w/w, or less than 0.05% w/w of the gemcabene as determined by IC. In some embodiments, gemcabene comprises isobutyric acid impurity in 0.05% w/w or less of the gemcabene as determined by IC. In some embodiments, gemcabene is substantially free of isobutyric acid impurity. In some embodiments, isobutyric acid impurity in gemcabene is below the quantification limit of the IC. In some embodiments, the quantification limit of isobutyric acid using an IC is 0.05% w/w.

[00300] In some embodiments, gemcabene made according to any one of the methods disclosed herein comprises 6-(4-hydroxybutoxy)-2,2-dimethylhexanoic acid impurity in ≤0.5% w/w of the gemcabene as determined by high-performance liquid chromatography (HPLC). In some embodiments, gemcabene comprises 6-(4-hydroxybutoxy)-2,2-dimethylhexanoic acid impurity in 0.5% w/w or less, 0.4% w/w or less, 0.3% w/w or less, 0.2% w/w or less, 0.15% w/w or less, 0.1% w/w or less, or 0.05% w/w or less of the gemcabene as determined by HPLC. In some embodiments, gemcabene comprises 6-(4-hydroxybutoxy)-2,2-dimethylhexanoic acid impurity, if any, in less than 0.5% w/w, less than 0.4% w/w, less than 0.3% w/w, less than 0.2% w/w, less than 0.15% w/w, less than 0.1% w/w, or less than 0.05% w/w of the gemcabene as determined by HPLC. In some embodiments, HPLC is equipped with a charged aerosol detector (CAD) or with an ultraviolet detector (UV).

[00301] In some embodiments, gemcabene made according to any one of the methods disclosed herein comprises (*Z*)-2,2-dimethyl-hex-4-enoic acid impurity in ≤0.5% w/w of the gemcabene as determined by high-performance liquid chromatography (HPLC). In some embodiments, gemcabene comprises (*Z*)-2,2-dimethyl-hex-4-enoic acid impurity in less than 0.5% w/w, less than 0.4% w/w, less than 0.3% w/w, less than 0.2% w/w, less than 0.15% w/w, less than 0.1% w/w, or less than 0.05% w/w of the gemcabene as determined by HPLC. In some embodiments, gemcabene comprises (*Z*)-2,2-dimethyl-hex-4-enoic acid impurity, if any, in 0.5%

w/w or less, 0.4% w/w or less, 0.3% w/w or less, 0.2% w/w or less, 0.15% w/w or less, 0.1% w/w or less, or 0.05% w/w or less of the gemcabene as determined by HPLC. In some embodiments, HPLC is equipped with a charged aerosol detector (CAD) or with an ultraviolet detector (UV).

[00302] In some embodiments, gemcabene made according to any one of the methods disclosed herein comprises (*E*)-2,2-dimethyl-hex-4-enoic acid impurity in ≤1.0% w/w of the gemcabene as determined by high-performance liquid chromatography (HPLC). In some embodiments, gemcabene comprises (*E*)-2,2-dimethyl-hex-4-enoic acid impurity in ≤0.5% of the gemcabene as determined by HPLC. In some embodiments, gemcabene comprises (*E*)-2,2-dimethyl-hex-4-enoic acid impurity in less than 1.0% w/w, less than 0.9% w/w, less than 0.8% w/w, less than 0.7% w/w, less than 0.6% w/w, less than 0.5% w/w, less than 0.4% w/w, less than 0.3% w/w, less than 0.2% w/w, less than 0.15% w/w, less than 0.1% w/w, or less than 0.05% w/w of the gemcabene as determined by HPLC. In some embodiments, gemcabene comprises (*E*)-2,2-dimethyl-hex-4-enoic acid impurity, if any, in 1.0% w/w or less, 0.9% w/w or less, 0.8% w/w or less, 0.7% w/w or less, 0.6% w/w or less, 0.5% w/w or less, 0.4% w/w or less, 0.3% w/w or less, 0.2% w/w or less, 0.15% w/w or less, 0.1% w/w or less, or 0.05% w/w or less as determined by HPLC. In some embodiments, HPLC is equipped with a charged aerosol detector (CAD) or with an ultraviolet detector (UV).

[00303] The present invention further provides gemcabene made according to any one of the methods disclosed herein. The present invention further provides gemcabene purified according to any one of the methods disclosed herein. The present invention further provides gemcabene purified by dissolving the crude gemcabene in heptane and cooling the heptane solution to a temperature ranging from 10 °C to 15 °C to precipitate gemcabene. In some embodiments, heptane is *n*-heptane.

[00304] The present invention further provides a pharmaceutically acceptable salt of gemcabene, wherein gemcabene is synthesized according to any one of the methods disclosed herein. The present invention further provides a pharmaceutically acceptable salt of gemcabene, wherein gemcabene is purified according to any one of the methods disclosed herein. The present invention further provides a pharmaceutically acceptable salt of gemcabene, wherein gemcabene is purified by dissolving the crude gemcabene in heptane and cooling the heptane solution to a temperature ranging from 10 °C to 15 °C to precipitate gemcabene. In some embodiments, heptane is *n*-heptane.

[00305] In some embodiments, gemcabene synthesized according to any one of the methods disclosed herein can be converted into gemcabene calcium. In some embodiment, gemcabene is allowed to react with calcium oxide. In some embodiment, gemcabene is allowed to react with

calcium oxide in ethanol. In some embodiment, gemcabene is allowed to react with calcium oxide in ethanol under refluxing conditions. After gemcabene was allowed to react with calcium oxide, the reaction mixture can be stirred at 22 °C ± 2 °C for about one hour and then can be filtered. The filtered product can then be dried under vacuum. In some embodiments, the drying is performed under stream of nitrogen under vacuum.

[00306] In some embodiments, purified water is added to the dried gemcabene calcium and heated. In some embodiments, purified water is added to the dried gemcabene calcium at atmospheric pressure and heated to a temperature range of about 80 to about 110 °C. In some embodiments, purified water is added to the dried gemcabene calcium at atmospheric pressure and heated to a temperature range of about 85 °C to about 95 °C for about 5 hours to about 10 hours. In some embodiments, purified water is added to the dried gemcabene calcium at atmospheric pressure and heated to 90 °C for about 6 hours. Heating gemcabene calcium with purified water provides gemcabene calcium salt hydrate.

[00307] In some embodiments, gemcabene calcium salt hydrate is dried under vacuum. In some embodiments, gemcabene calcium salt hydrate is dried under vacuum at a temperature range of about 80 °C to about 110 °C. In some embodiments, gemcabene calcium salt hydrate is dried under vacuum at a temperature range of about 85 °C to about 95 °C for at least 5 hours, at least 10 hours, or at least 15 hours. In some embodiments, gemcabene calcium salt hydrate is dried under vacuum at a temperature of 90 °C for at least 16 hours to yield gemcabene calcium salt hydrate Crystal Form 1. Similarly, gemcabene calcium salt solvate can be obtained with alcohol solvents, such as ethanol.

[00308] In some embodiments, gemcabene calcium salt hydrate or solvate prepared from gemcabene synthesized according to any one of the methods disclosed herein has a purity ranging from about 85% w/w to 100% w/w as determined by high-performance liquid chromatography (HPLC). In some embodiments, gemcabene calcium salt hydrate or solvate has a purity ranging from about 90% w/w to 100% w/w as determined by HPLC. In some embodiments, gemcabene calcium salt hydrate or solvate has a purity ranging from about 95% w/w to 100% w/w as determined by HPLC. In some embodiments, gemcabene calcium salt hydrate or solvate has a purity ranging from about 98% w/w to 100% w/w as determined by HPLC. In some embodiments, gemcabene calcium salt hydrate or solvate has a purity ranging from about 99% w/w to 100% w/w as determined by HPLC. In some embodiments, gemcabene calcium salt hydrate or solvate has a purity ranging from about 99.5% w/w to 100% w/w as determined by HPLC. In some embodiments, gemcabene calcium salt hydrate or solvate has a purity ranging from 99.5% w/w to 100% w/w as determined by HPLC. In some embodiments, gemcabene calcium salt hydrate or solvate has a purity ranging from 99.7% w/w to 100% w/w as

determined by HPLC. In some embodiments, HPLC is equipped with a charged aerosol detector (CAD) or with an ultraviolet detector (UV).

[00309] In some embodiments, gemcabene calcium salt hydrate or solvate prepared from gemcabene synthesized according to any one of the methods disclosed herein comprises 6-(4-hydroxybutoxy)-2,2-dimethylhexanoic acid impurity in ≤0.5% w/w of the gemcabene calcium salt hydrate or solvate as determined by high-performance liquid chromatography (HPLC). In some embodiments, gemcabene calcium salt hydrate or solvate comprises 6-(4-hydroxybutoxy)-2,2-dimethylhexanoic acid impurity, if any, in less than 0.5%, less than 0.4% w/w, less than 0.3% w/w, less than 0.2% w/w, less than 0.15% w/w, less than 0.1% w/w, or less than 0.05% w/w of the gemcabene calcium salt hydrate or solvate as determined by HPLC. In some embodiments, gemcabene calcium salt hydrate or solvate comprises 6-(4-hydroxybutoxy)-2,2-dimethylhexanoic acid impurity in 0.5% w/w or less, 0.4% w/w or less, 0.3% w/w or less, 0.2% w/w or less, 0.15% w/w or less, 0.1% w/w or less, or 0.05% w/w or less of the gemcabene calcium salt hydrate or solvate as determined by HPLC. In some embodiments, HPLC is equipped with a charged aerosol detector (CAD) or with an ultraviolet detector (UV).

[00310] In some embodiments, gemcabene calcium salt hydrate or solvate prepared from gemcabene synthesized according to any one of the methods disclosed herein comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid impurity in ≤0.5% w/w of the gemcabene calcium salt hydrate or solvate as determined by high-performance liquid chromatography (HPLC). In some embodiments, gemcabene calcium salt hydrate or solvate comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid impurity in less than 0.5% w/w, less than 0.4% w/w, less than 0.3% w/w, less than 0.2% w/w, less than 0.15% w/w, less than 0.1% w/w, or less than 0.05% w/w of the gemcabene calcium salt hydrate or solvate as determined by HPLC. In some embodiments, gemcabene calcium salt hydrate or solvate comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid impurity, if any, in 0.5% w/w or less, 0.4% w/w or less, 0.3% w/w or less, 0.2% w/w or less, 0.15% w/w or less, 0.1% w/w or less, or 0.05% w/w or less of the gemcabene calcium salt hydrate or solvate as determined by HPLC. In some embodiments, gemcabene calcium salt hydrate or solvate comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid impurity in less than 0.2% w/w, less than 0.15% w/w, less than 0.1% w/w, or less than 0.05% w/w of the gemcabene calcium salt hydrate or solvate as determined by HPLC. In some embodiments, HPLC is equipped with a charged aerosol detector (CAD) or with an ultraviolet detector (UV).

[00311] In some embodiments, gemcabene calcium salt hydrate or solvate prepared from gemcabene synthesized according to any one of the methods disclosed herein comprises isobutyric acid impurity in ≤0.5% w/w of the gemcabene calcium salt hydrate or solvate as determined by ion chromatography (IC). In some embodiments, gemcabene calcium salt hydrate

or solvate comprises isobutyric acid impurity in less than 0.5% w/w, less than 0.4% w/w, less than 0.3% w/w, less than 0.2% w/w, less than 0.15% w/w, less than 0.1% w/w, or less than 0.05% w/w of the gemcabene calcium salt hydrate or solvate as determined by IC. In some embodiments, gemcabene calcium salt hydrate or solvate comprises isobutyric acid impurity, if any, in 0.5% w/w or less, 0.4% w/w or less, 0.3% w/w or less, 0.2% w/w or less, 0.15% w/w or less, 0.1% w/w or less, or 0.05% w/w or less of the gemcabene calcium salt hydrate or solvate as determined by IC. In some embodiments, gemcabene calcium salt hydrate or solvate comprises isobutyric acid impurity in 0.07% w/w or less of the gemcabene calcium salt hydrate or solvate as determined by IC. In some embodiments, gemcabene calcium salt hydrate or solvate comprises isobutyric acid impurity in 0.05% w/w or less of the gemcabene calcium salt hydrate or solvate as determined by IC. In some embodiments, gemcabene calcium salt hydrate or solvate is substantially free of isobutyric acid impurity. In some embodiments, isobutyric acid impurity in gemcabene calcium salt hydrate or solvate is below the quantification limit of the IC. In one embodiment, the quantification limit of isobutyric acid using an IC is 0.05% w/w.

[00312] In some embodiments, gemcabene calcium salt hydrate or solvate made from gemcabene synthesized according to any one of the methods disclosed herein comprises (*Z*)-2,2-dimethyl-hex-4-enoic acid impurity in ≤0.5% w/w of the gemcabene calcium salt hydrate or solvate as determined by high-performance liquid chromatography (HPLC). In some embodiments, gemcabene calcium salt hydrate or solvate comprises (*Z*)-2,2-dimethyl-hex-4-enoic acid impurity in less than 0.5% w/w, less than 0.4% w/w, less than 0.3% w/w, less than 0.2% w/w, less than 0.15% w/w, less than 0.1% w/w, or less than 0.05% w/w of the gemcabene calcium salt hydrate or solvate as determined by HPLC. In some embodiments, gemcabene calcium salt hydrate or solvate comprises (*Z*)-2,2-dimethyl-hex-4-enoic acid impurity, if any, in 0.5% w/w or less, 0.4% w/w or less, 0.3% w/w or less, 0.2% w/w or less, 0.15% w/w or less, 0.1% w/w or less, or 0.05% w/w or less of the gemcabene calcium salt hydrate or solvate as determined by HPLC. In some embodiments, HPLC is equipped with a charged aerosol detector (CAD) or with an ultraviolet detector (UV).

[00313] In some embodiments, gemcabene calcium salt hydrate or solvate made from gemcabene synthesized according to any one of the method disclosed herein comprises *E*)-2,2-dimethyl-hex-4-enoic acid impurity in ≤0.5% w/w (of the gemcabene calcium salt hydrate or solvate as determined by HPLC. In some embodiments, gemcabene calcium salt hydrate or solvate comprises (*E*)-2,2-dimethyl-hex-4-enoic acid impurity in less than 0.5% w/w, less than 0.4% w/w, less than 0.3% w/w, less than 0.2% w/w, less than 0.15% w/w, less than 0.1% w/w, or less than 0.05% w/w of the gemcabene calcium salt hydrate or solvate as determined by HPLC. In some embodiments, gemcabene calcium salt hydrate or solvate comprises (*E*)-2,2-dimethyl-

hex-4-enoic acid impurity, if any, in 0.5% w/w or less, 0.4% w/w or less, 0.3% w/w or less, 0.2% w/w or less, 0.15% w/w or less, 0.1% w/w or less, or 0.05% w/w or less of the gemcabene calcium salt hydrate or solvate as determined by HPLC. In some embodiments, HPLC is equipped with a charged aerosol detector (CAD) or with an ultraviolet detector (UV).

[00314] In some embodiments, gemcabene calcium salt hydrate or solvate made from gemcabene synthesized according to any one of the methods disclosed herein comprises ≤2.5 ppm (bis-(4-chlorobutyl)ether impurity as determined by gas chromatography (GC). In some embodiments, gemcabene calcium salt hydrate or solvate comprises less than 2.5 ppm, less than 2.0 ppm, less than 1.5 ppm or less than 1.0 ppm (bis-(4-chlorobutyl)ether impurity as determined by GC. In some embodiments, gemcabene calcium salt hydrate or solvate comprises 2.5 ppm or less, 2.0 ppm or less, 1.5 ppm or less, or 1.0 ppm or less (bis-(4-chlorobutyl)ether impurity as determined by GC.

[00315] In some embodiments, gemcabene calcium salt hydrate or solvate prepared from gemcabene synthesized according to any one of the method disclosed herein contains ≤2.5 ppm 6-(4-chlorobutoxy)-2,2-dimethyl-hexanoic acid impurity as determined by gas chromatography (GC). In some embodiments, gemcabene calcium salt hydrate or solvate contains less than 2.5 ppm, less than 2.0 ppm, less than 1.5 ppm or less than 1.0 ppm 6-(4-chlorobutoxy)-2,2-dimethyl-hexanoic acid impurity as determined by GC. In some embodiments, gemcabene calcium salt hydrate or solvate contains 2.5 ppm or less, 2.0 ppm or less, 1.5 ppm or less, or 1.0 ppm or less 6-(4-chlorobutoxy)-2,2-dimethyl-hexanoic acid impurity as determined by GC.

[00316] In some embodiments, gemcabene calcium salt hydrate or solvate prepared from gemcabene synthesized according to any one of the method disclosed herein contains ≤2.5 ppm 1-chloro-4-hydroxybutane impurity as determined by gas chromatography (GC). In some embodiments, gemcabene calcium salt hydrate or solvate contains less than 2.5 ppm, less than 2.0 ppm, less than 1.5 ppm or less than 1.0 ppm 1-chloro-4-hydroxybutane impurity as determined by GC. In some embodiments, gemcabene calcium salt hydrate or solvate contains 2.5 ppm or less, 2.0 ppm or less, 1.5 ppm or less, or 1.0 ppm or less 1-chloro-4-hydroxybutane impurity as determined by GC.

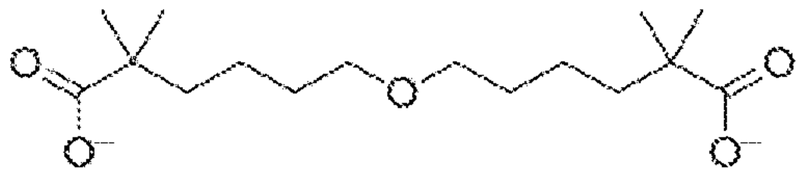
[00317] In some embodiments, gemcabene calcium salt hydrate or solvate prepared from gemcabene synthesized according to any one of the method disclosed herein contains ≤8 ppm collectively the sum of 1-chloro-4-hydroxybutane, 6-(4-chlorobutoxy)-2,2-dimethyl-hexanoic acid and (bis-(4-chlorobutyl)ether impurities as determined by gas chromatography (GC). In some embodiments, gemcabene calcium salt hydrate or solvate contains less than 8 ppm, less than 7.0 ppm, less than 6 ppm or less than 5.0 ppm collectively the sum of 1-chloro-4-

hydroxybutane, 6-(4-chlorobutoxy)-2,2-dimethyl-hexanoic acid and (bis-(4-chlorobutyl)ether impurities as determined by GC. In some embodiments, gemcabene calcium salt hydrate or solvate contains 8 ppm or less, 7.5 ppm or less, 7.0 ppm or less, or 6.5 ppm or less 1-chloro-4-hydroxybutane impurity as determined by GC.

[00318] In some embodiments, gemcabene calcium salt hydrate made from gemcabene synthesized according to any one of the methods disclosed herein comprises water in the range of about 2.0% w/w to about 5.0% w/w of the gemcabene calcium salt hydrate as determined by Karl-Fisher analysis. In some embodiments, gemcabene calcium salt hydrate prepared from gemcabene synthesized according to any one of the methods disclosed herein comprises water in the range of 2.0% w/w to 5.0% w/w of the gemcabene calcium salt hydrate as determined by Karl-Fisher analysis.

[00319] In some embodiments, gemcabene calcium salt hydrate or solvate made from gemcabene synthesized according to any one of the methods disclosed herein comprises calcium in a range from about 10% m/m to about 15 % m/m of the gemcabene calcium salt hydrate or solvate as determined by inductively coupled plasma optical emission spectrometry (ICP-OES). In some embodiments, gemcabene calcium salt hydrate or solvate prepared from gemcabene synthesized according to any one of the methods disclosed herein comprises calcium in a range from about 10% m/m to about 14% m/m of the gemcabene calcium salt hydrate or solvate as determined by ICP-OES. In some embodiments, gemcabene calcium salt hydrate or solvate prepared from gemcabene synthesized according to any one of the methods disclosed herein comprises calcium in a range from 9.8% m/m to 13.8% m/m of the gemcabene calcium salt hydrate or solvate as determined by ICP-OES. In some embodiments, gemcabene calcium salt hydrate or solvate prepared from gemcabene synthesized according to any one of the methods disclosed herein comprises calcium in a range from 11.5% m/m to 12.5% m/m of the gemcabene calcium salt hydrate or solvate as determined by ICP-OES. In some embodiments, gemcabene calcium salt hydrate or solvate prepared from gemcabene synthesized according to any one of the methods disclosed herein comprises calcium in about 11.77% m/m of the gemcabene calcium salt hydrate or solvate as determined by ICP-OES.

[00320] In some embodiments, gemcabene calcium salt hydrate or solvate made from gemcabene synthesized according to any one of the methods disclosed herein comprises a gemcabene conjugate base component ranging from about 82% w/w to about 92% w/w of the gemcabene calcium salt hydrate or solvate as determined by high-performance liquid chromatography (HPLC), wherein the gemcabene conjugate base has the structure:



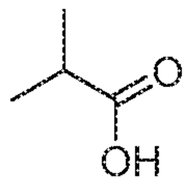
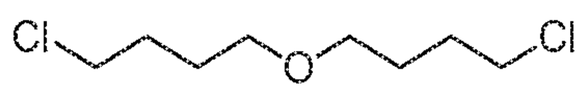
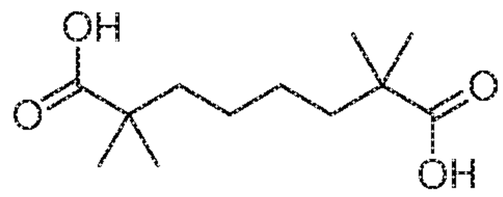
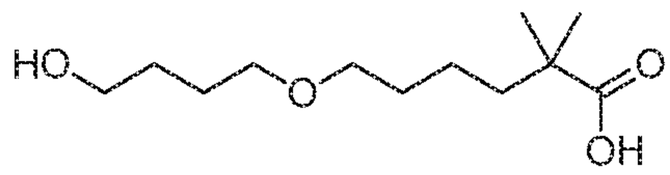
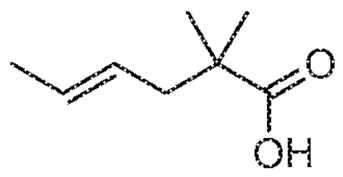
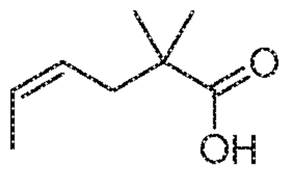
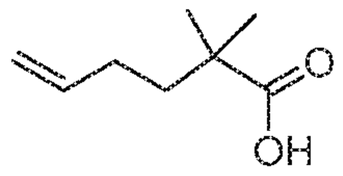
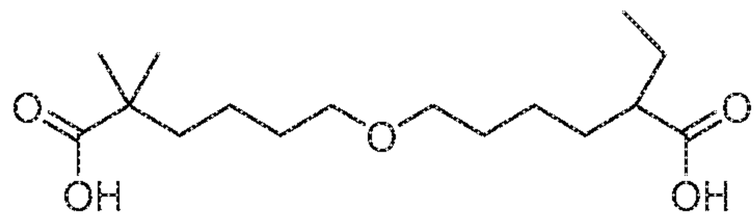
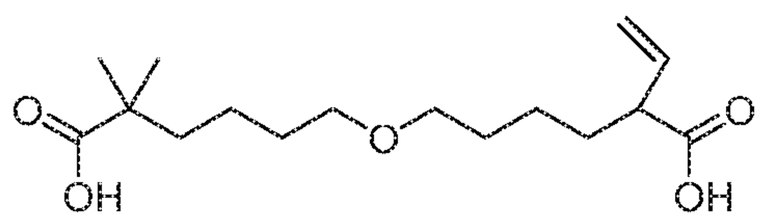
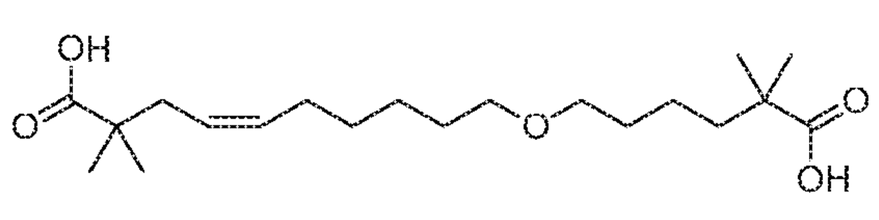
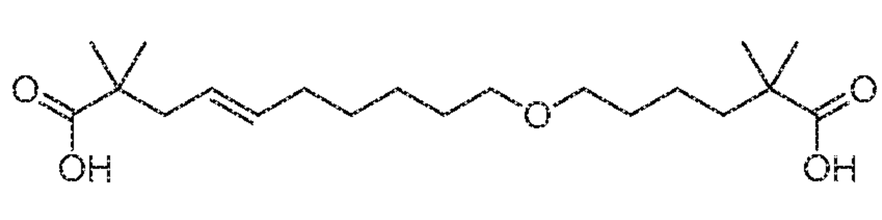
. In some embodiments, gemcabene calcium salt hydrate or solvate made from gemcabene made according to any one of the methods disclosed herein comprises a gemcabene conjugate base component ranging from 82% w/w to 92% w/w of the gemcabene calcium salt hydrate or solvate as determined by high-performance liquid chromatography (HPLC). The gemcabene conjugate base component is percentage of the gemcabene calcium salt hydrate or solvate without accounting for water, solvent, and calcium content. In some embodiments, HPLC is equipped with an ultraviolet detector (UV).

[00321] In some embodiments, gemcabene calcium salt hydrate or solvate made from gemcabene made according to any one of the methods disclosed herein has an anhydrous gemcabene calcium content from about 98% w/w to about 105% w/w of the gemcabene calcium salt hydrate or solvate as determined by high-performance liquid chromatography (HPLC). In some embodiments, gemcabene calcium salt hydrate or solvate made from gemcabene made according to any one of the methods disclosed herein has an anhydrous gemcabene calcium content from 98% w/w to 105% w/w of the gemcabene calcium salt hydrate or solvate as determined by high-performance liquid chromatography (HPLC).

- anhydrous gemcabene calcium content = (% gemcabene calcium as-is)/(100% - % water by Karl-Fisher analysis)
- gemcabene calcium as-is = (% gemcabene) *[(molecular weight of gemcabene calcium)/(molecular weight of gemcabene)]

[00322] In some embodiments, gemcabene calcium salt hydrate or solvate made from gemcabene made according to any one of the methods disclosed herein comprises 2.0% or less of total impurities as determined by high-performance liquid chromatography. In some embodiments, gemcabene calcium salt hydrate or solvate prepared from gemcabene synthesized according to any one of the methods disclosed herein comprises total impurities in less than 2.0% w/w of the gemcabene calcium salt hydrate or solvate as determined by high-performance liquid chromatography (HPLC). In some embodiments, HPLC is equipped with a charged aerosol detector (CAD) or with an ultraviolet detector (UV). Different HPLC instrument's impurity analyses can be added to provide the sum of impurities. As used herein, an "impurities" refers to any organic compounds that are not gemcabene or a pharmaceutically acceptable salt of gemcabene that is detectable by HPLC. For example, isobutyric acid and bis-(4-halobutyl)ether are examples of impurities. Other examples of related substances are presented in Table D.

[00323] **Table D**. Examples of Related Substances

Impurity	Chemical structure
Isobutyric acid $C_4H_8O_2$ MW 88.11	
Bis-(4-chlorobutyl)ether $C_4H_{16}C_{12}O$ MW 199.12	
2,2,7,7-Tetramethyl-octane-1,8-dioic acid $C_{12}H_{22}O_4$ MW 230.30	
6-(4-Hydroxybutoxy)-2,2-dimethylhexanoic acid $C_{12}H_{24}O_4$ MW 232.32	
(*E*)-2,2-Dimethyl-hex-4-enoic acid $C_8H_{14}O_2$ MW 142.20	
(*Z*)-2,2-Dimethyl-hex-4-enoic acid $C_8H_{14}O_2$ MW 142.20	
2,2-Dimethyl-hex-5-enoic acid $C_8H_{14}O_2$ MW 142.20	
6-((5-Carboxyheptyl)oxy)-2,2-dimethylhexanoic acid $C_{16}H_{30}O$ MW 302.41	
6-(7-Carboxy-7-methyl-5-ethenyl-octyloxy)-2,2-dimethyl-hexanoic acid $C_{20}H_{36}O_5$ MW 356.50	
(*Z*)-6-(9-Carboxy-9-methyl-dec-6-enyloxy)-2,2-dimethyl-hexanoic acid $C_{20}H_{36}O_5$ MW 356.50	
(*E*)-6-(9-Carboxy-9-methyl-dec-6-enyloxy)-2,2-dimethyl-hexanoic acid $C_{20}H_{36}O_5$ MW 356.50	

[00324] The present invention further provides methods for purifying crude gemcabene, wherein the crude gemcabene comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid in no more than 5% w/w of the crude gemcabene as determined by high-performance liquid chromatography (HPLC), comprising: dissolving the crude gemcabene in heptane to provide a heptane solution of the crude gemcabene; and cooling the heptane solution to a temperature ranging from 10 °C to 15

°C to precipitate gemcabene, wherein the gemcabene comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid in 0.5% w/w or less of the gemcabene of as determined by high-performance liquid chromatography.

[00325] The present invention further provides methods for purifying crude gemcabene, wherein the crude gemcabene comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid in no more than 3% w/w of the crude gemcabene as determined by high-performance liquid chromatography (HPLC), comprising: dissolving the crude gemcabene in heptane to provide a heptane solution of the crude gemcabene; and cooling the heptane solution to a temperature ranging from 10 °C to 15 °C to precipitate gemcabene, wherein the gemcabene comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid in 0.5% w/w or less of the gemcabene of as determined by high-performance liquid chromatography. In some embodiments, the crude gemcabene comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid in no more than 2.5% w/w of the crude gemcabene as determined by HPLC. In some embodiments, the crude gemcabene comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid in no more than 2% w/w of the crude gemcabene as determined by HPLC. In some embodiments, the crude gemcabene comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid in no more than 1.5% w/w of the crude gemcabene as determined by HPLC. In some embodiments, the crude gemcabene comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid in no more than 1% w/w of the crude gemcabene as determined by HPLC.

[00326] The present invention further provides methods for purifying crude gemcabene, wherein the crude gemcabene comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid in no more than 1% w/w of the crude gemcabene as determined by high-performance liquid chromatography, comprising: dissolving the crude gemcabene in heptane to provide a heptane solution of the crude gemcabene; and cooling the heptane solution to a temperature ranging from 10 °C to 15 °C to precipitate gemcabene, wherein the gemcabene comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid in 0.5% w/w or less of the gemcabene of as determined by high-performance liquid chromatography.

[00327] In some embodiments, the crude gemcabene prior to purification comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid impurity in greater than 0.7% w/w and no more than 1% w/w of the crude gemcabene as determined by high-performance liquid chromatography (HPLC). In some embodiments, the crude gemcabene prior to purification comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid impurity in greater than 0.5% w/w and no more than 1% w/w of the crude gemcabene as determined by HPLC. In some embodiments, the crude gemcabene prior to purification comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid impurity in a range of 1.0% w/w to 0.5% w/w of the crude gemcabene as determined by HPLC.

[00328] In some embodiments, the gemcabene after purification comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid from 0.01% w/w to 0.5% w/w of the gemcabene as determined by high-performance liquid chromatography.

[00329] In some embodiments, the temperature of the heptane solution for purification ranges from 10 °C to 14 °C. In some embodiments, the temperature of the heptane solution for purification is 12 °C. In some embodiments, the temperature of the heptane solution during crystallization ranges from 10 °C to 14 °C. In some embodiments, the temperature of the heptane solution during crystallization is 12 °C.

[00330] In some embodiments, the crude gemcabene further comprises isobutyric acid in 0.5% w/w or less of the crude gemcabene as determined by ion chromatography. In some embodiments, the crude gemcabene comprises isobutyric acid in 0.3% or less of the crude gemcabene as determined by ion chromatography.

[00331] In some embodiments, the concentration of crude gemcabene in the heptane solution ranges from 0.3 g of crude gemcabene/mL of heptane to 0.8 g of crude gemcabene/mL of heptane. In some embodiments, the concentration of crude gemcabene in the heptane solution ranges from 0.5 g of crude gemcabene/mL of heptane to 0.7 g of crude gemcabene/mL of heptane. In some embodiments, the concentration of crude gemcabene in the heptane solution is 0.6 g of crude gemcabene/mL of heptane.

[00332] In some embodiments, the method of purifying crude gemcabene further comprises: dissolving the gemcabene in heptane to provide a heptane solution of the gemcabene; and cooling the heptane solution to a temperature ranging from 10 °C to 15 °C to precipitate recrystallized gemcabene.

[00333] In some embodiments of the method of purification of the crude gemcabene, heptane is *n*-heptane.

[00334] In some embodiments, the method of purifying crude gemcabene further comprises: allowing an enolate of an alkali metal salt of isobutyric acid to react with a bis-(4-halobutyl)ether to provide crude gemcabene salt and acidifying the crude gemcabene salt to provide the crude gemcabene. In some embodiments, the enolate of an alkali metal salt of isobutyric acid to react is allowed to react with the bis-(4-halobutyl)ether under conditions essentially free of water. In some embodiments, the method further comprising allowing sodium isobutyrate to react with an enolate-forming base to provide the enolate of sodium isobutyrate. In some embodiments, the method further comprising allowing isobutyric acid to react with sodium hydroxide to provide the sodium isobutyrate.

[00335] In some embodiments, the bis-(4-halobutyl)ether is bis-(4-chlorobutyl)ether.

[00336] In some embodiments, the enolate of the alkali metal salt of isobutyric acid is an enolate of sodium isobutyrate.

[00337] In some embodiments, the enolate-forming base is lithium hexamethyldisilazide, lithium diisopropylamide, lithium tetramethylpiperidide, or lithium diethylamide.

[00338] In some embodiments, the sodium hydroxide is in a water solution, and further comprising removing the water via evaporation after allowing the isobutyric acid to react with sodium hydroxide and before allowing the sodium isobutyrate to react with the enolate-forming base. In some embodiments, the sodium isobutyrate has a water content of 0.05% w/w or less of the reaction mixture comprising sodium isobutyrate as determined by Karl-Fisher analysis. In some embodiments, the sodium isobutyrate has a water content of about 0.05% w/w or less of the reaction mixture comprising sodium isobutyrate as determined by Karl-Fisher analysis.

[00339] In some embodiments, the enolate of the alkali metal salt of isobutyric acid is present in an amount of two or more molar equivalents and the bis-(4-halobutyl)ether present in an amount of one molar equivalent. In some embodiments, the enolate of an alkali metal salt of isobutyric acid is present in an amount of 2.1 to 2.4 molar equivalents and the bis-(4-halobutyl)ether present in an amount of one molar equivalent.

[00340] In some embodiments, the crude gemcabene further comprises isobutyric acid.

[00341] In some embodiments, at least some of the isobutyric acid is removed from the crude gemcabene via distillation after acidifying the crude gemcabene salt and before precipitating gemcabene from the heptane solution at a temperature ranging from 10 °C to 15 °C. In some embodiments, the removal of isobutyric acid further comprising admixing the crude gemcabene and water prior to removing at least some of the isobutyric acid. In some embodiments, the distillation removes water and isobutyric acid. In some embodiments, the admixing the crude gemcabene and water and removing the water and at least some of the isobutyric acid is performed at least two times.

[00342] In some embodiments, the crude gemcabene after distillation comprises isobutyric acid in 0.5% w/w or less of the distilled crude gemcabene as determined by ion chromatography. In some embodiments, the crude gemcabene after distillation comprises isobutyric acid in 0.3% or less of the distilled crude gemcabene as determined by ion chromatography.

[00343] The present invention further provides gemcabene made by or purified by any one of the methods disclosed herein. In some embodiments, gemcabene comprises isobutyric acid in 0.10% w/w or less of the gemcabene as determined by ion chromatography. In some embodiments, gemcabene comprises isobutyric acid in 0.05% w/w or less of the gemcabene as determined by ion chromatography.

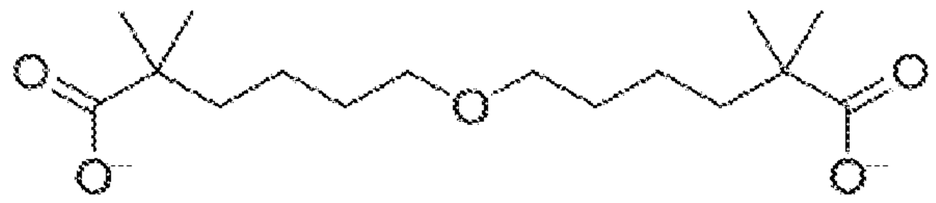
[00344] The present invention further provides a pharmaceutically acceptable salt of gemcabene made by or purified by any one of the methods disclosed herein. In some embodiments, the pharmaceutically acceptable salt is a calcium salt. In some embodiments, the calcium salt is a hydrate. In some embodiments, the calcium salt hydrate is Crystal Form 1. In some embodiments, the calcium salt hydrate is Crystal Form 2. In some embodiments, the calcium salt hydrate is Crystal Form C3. In some embodiments, the calcium salt is an ethanol solvate.

[00345] In some embodiments, the pharmaceutically acceptable salt of gemcabene comprises 2,2,7,7-tetramethyl-octane-1,8-dioic acid in 0.5% w/w or less of the pharmaceutically acceptable salt of gemcabene as determined by high-performance liquid chromatography. In some embodiments, the pharmaceutically acceptable salt gemcabene comprises water in 2% w/w to 5% w/w of the pharmaceutically acceptable salt of gemcabene as determined by Karl-Fisher analysis. In some embodiments, the pharmaceutically acceptable salt of gemcabene comprises isobutyric acid in 0.5% w/w or less of the pharmaceutically acceptable salt of gemcabene as determined by ion chromatography. In some embodiments, the pharmaceutically acceptable salt gemcabene comprises isobutyric acid in 0.10% w/w or less of the pharmaceutically acceptable salt of gemcabene as determined by ion chromatography. In some embodiments, the pharmaceutically acceptable salt gemcabene comprises isobutyric acid in 0.05% w/w or less of the pharmaceutically acceptable salt of gemcabene as determined by ion chromatography.

[00346] In some embodiments, the pharmaceutically acceptable salt gemcabene comprises 2.5 ppm or less of bis-(4-chlorobutyl)ether as determined by gas chromatography. In some embodiments, the pharmaceutically acceptable salt gemcabene comprises 2.5 ppm or less of.6-(4-chlorobutoxy)-2,2-dimethyl-hexanoic acid as determined by gas chromatography. In some embodiments, the pharmaceutically acceptable salt gemcabene comprises 2.5 ppm or less of 1-chloro-4-hydroxybutane as determined by gas chromatography. In some embodiments, the pharmaceutically acceptable salt gemcabene comprises 8 ppm or less of sum of all genotoxic impurities, including but not limited to, bis-(4-chlorobutyl)ether, 1-chloro-4-hydroxybutane and 6-(4-chlorobutoxy)-2,2-dimethyl-hexanoic acid as determined by gas chromatography.

[00347] In some embodiments, the pharmaceutically acceptable salt gemcabene comprises total impurities in 2.0% w/w or less of the pharmaceutically acceptable salt of gemcabene as determined by high-performance liquid chromatography.

[00348] In some embodiments, the pharmaceutically acceptable salt gemcabene comprises a gemcabene conjugate base component in a range of 82% w/w to 92% w/w of the pharmaceutically acceptable salt of gemcabene as determined by high-performance liquid chromatography, wherein the gemcabene conjugate base component has the structure:



[00349] In some embodiments, the pharmaceutically acceptable salt gemcabene comprises calcium in about 10% m/m to about 14 % m/m of the pharmaceutically acceptable salt of gemcabene as determined by inductively coupled plasma optical emission spectrometry. In some embodiments, the pharmaceutically acceptable salt gemcabene comprises calcium in about 9.8% m/m to 13.8% m/m of the pharmaceutically acceptable salt of gemcabene as determined by inductively coupled plasma optical emission spectrometry.

[00350] The present invention further provides pharmaceutical compositions comprising a pharmaceutically acceptable salt of gemcabene and a pharmaceutically acceptable carrier or vehicle, wherein gemcabene is synthesized according to any one of the methods disclosed herein. The present invention further provides pharmaceutical compositions comprising a pharmaceutically acceptable salt of gemcabene and a pharmaceutically acceptable carrier or vehicle, wherein gemcabene is purified according to any one of the methods disclosed herein. The present invention further provides pharmaceutical compositions comprising a pharmaceutically acceptable salt of gemcabene and a pharmaceutically acceptable carrier or vehicle, wherein gemcabene is purified according to any one of the methods disclosed by dissolving the crude gemcabene in heptane and cooling the heptane solution to a temperature ranging from 10 °C to 15 °C to precipitate gemcabene. In some embodiments, heptane is *n*-heptane.

METHODS FOR TREATMENT OR PREVENTION

[00351] The present invention provides methods for treating or preventing various diseases and conditions as disclosed herein, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject is human.

[00352] The present invention provides methods for treating or preventing liver disease or an abnormal liver condition, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00353] Examples of liver disease or liver conditions include, but are not limited to, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis, cirrhosis, inflammation, liver fibrosis, partial fibrosis, primary biliary cirrhosis, primary sclerosing cholangitis, liver failure, hepatocellular carcinoma (HCC), liver cancer, hepatic steatosis, hepatocyte ballooning (also known as hepatocellular ballooning), hepatic lobular inflammation, and hepatic triglyceride accumulation. In some embodiments, the liver

disease or the liver condition is NAFLD or NASH. In some embodiments, the liver disease or the liver condition is NAFLD. In other embodiments, the liver disease or the liver condition is NASH. In some embodiments, the liver disease or the liver condition is hepatic steatosis. In some embodiments, the liver disease or the liver condition is liver fibrosis.

[00354] In some embodiments, treating or preventing liver fibrosis, NAFLD, or NASH includes regressing, stabilizing, or inhibiting progression of liver fibrosis, NAFLD, or NASH.

[00355] The present invention further provides methods for reducing liver fat (fat content of the liver), stabilizing the amount of liver fat, or reducing the accumulation of liver fat, comprising administering to a subject in need thereof an effective amount of a compound of the invention. The present invention further provides methods for reducing liver steatosis (fat content of the liver), stabilizing the amount of liver triglycerides, or reducing the accumulation of liver triglycerides, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00356] The present invention further provides methods for treating or preventing lobular inflammation or hepatocyte ballooning, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiment, treating or preventing lobular inflammation or hepatocyte ballooning is slowing the progression of, stabilizing, or reducing the lobular inflammation or hepatocyte ballooning.

[00357] The present invention further provides methods for treating or preventing a disorder of lipoprotein metabolism, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00358] Examples of disorders of lipoprotein metabolism include, but are not limited to, dyslipidemia, dyslipoproteinemia, mixed dyslipidemia, atherosclerotic cardiovascular disease (ASCVD), type IIb hyperlipidemia or familial combined hyperlipidemia, familial hypercholesterolemia, familial chylomicronemia syndrome, hypertriglyceridemia, dysbetalipoproteinemia, lipoprotein overproduction or deficiency, elevation of total cholesterol, elevation of low-density lipoprotein cholesterol concentration, elevation of very low-density lipoprotein cholesterol concentration, elevation of non-high-density lipoprotein (non-HDL) cholesterol concentration, elevation of apolipoprotein B concentration, elevation of apolipoprotein C-III concentration, elevation of C-reactive protein concentration, elevation of fibrinogen concentration, elevation of lipoprotein(a) concentration, elevation of interleukin-6 concentration, elevation of angiopoietin-like protein 3 concentration, elevation of angiopoietin-like protein 4 concentration, elevation of serum amyloid A concentration, elevation of PCSK9, increased risk of thrombosis, increased risk of a blood clot, low high-density lipoprotein (HDL)-cholesterol concentration, elevation of low-density lipoprotein concentration, elevation of very

low-density lipoprotein concentration, elevation of triglyceride concentration, prolonged post-prandial lipemia, lipid elimination in bile, metabolic disorder, phospholipid elimination in bile, oxysterol elimination in bile, abnormal bile production, peroxisome proliferator activated receptor-associated disorder, hypercholesterolemia, hyperlipidemia and visceral obesity.

[00359] In some embodiments, the disorder of lipoprotein metabolism is dyslipidemia, dyslipoproteinemia, mixed dyslipidemia, atherosclerotic cardiovascular disease (ASCVD), type IIb hyperlipidemia, familial combined hyperlipidemia, familial hypercholesterolemia, familial chylomicronemia syndrome, hypertriglyceridemia, dysbetalipoproteinemia, metabolic syndrome, lipoprotein overproduction, lipoprotein deficiency, non-insulin dependent diabetes, abnormal lipid elimination in bile, a metabolic disorder, abnormal phospholipid elimination in bile, an abnormal oxysterol elimination in bile, an abnormal bile production, hypercholesterolemia, hyperlipidemia or visceral obesity. In other embodiments, the disorder of lipoprotein metabolism is mixed dyslipidemia, atherosclerotic cardiovascular disease (ASCVD), type IIb hyperlipidemia, familial combined hyperlipidemia, or familial hypercholesterolemia. In some embodiments, the disorder of lipoprotein metabolism is hypertriglyceridemia. In some embodiments, the disorder of lipoprotein metabolism is hypercholesterolemia. In other embodiments, the hypertriglyceridemia is a severe hypertriglyceridemia. "Severe hypertriglyceridemia" is where a subject has a baseline plasma triglyceride concentration of greater than or equal to 500 mg/dl. In some embodiments, familial hypercholesterolemia (FH) is homozygous FH (HoFH) or heterozygous FH (HeFH).

[00360] The present invention further provides methods for treating or preventing a peroxisome proliferator activated receptor-associated disorder.

[00361] The present invention further provides methods for reducing a subject's plasma or blood serum triglyceride concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00362] The present invention further provides methods for reducing in a subject's blood plasma or blood serum, the subject's total cholesterol concentration, low-density lipoprotein cholesterol concentration, low-density lipoprotein concentration, very low-density lipoprotein cholesterol concentration, very low-density lipoprotein concentration, non-HDL cholesterol concentration, non-HDL concentration, apolipoprotein B concentration, triglyceride concentration, apolipoprotein C-III concentration, C-reactive protein concentration, fibrinogen concentration, lipoprotein(a) concentration, interleukin-6 concentration, angiopoietin-like protein 3 concentration, angiopoietin-like protein 4 concentration, PCSK9 concentration, or serum amyloid A concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, a method for reducing a subject's

blood plasma or blood serum total cholesterol concentration and reducing a subject's blood plasma or blood serum low-density lipoprotein cholesterol concentration, low-density lipoprotein concentration, very low-density lipoprotein cholesterol concentration, very low-density lipoprotein concentration, non-HDL cholesterol concentration, non-HDL concentration, apolipoprotein B concentration, triglyceride concentration, apolipoprotein C-III concentration, C-reactive protein concentration, fibrinogen concentration, lipoprotein(a) concentration, interleukin-6 concentration, angiopoietin-like protein 3 concentration, angiopoietin-like protein 4 concentration, PCSK9 concentration, or serum amyloid A concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention is provided. In some embodiments, the present invention provides methods for reducing in the subject's blood plasma or blood serum, the subject's triglyceride concentration or low-density lipoprotein cholesterol concentrations, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00363] The present invention further provides methods for lowering in a subject's blood plasma or blood serum, the subject's low-density lipoprotein cholesterol (LDL-C) concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention, wherein the subject is on a stable dose of a statin.

[00364] The present invention provides methods for elevating in a subject's blood plasma or blood serum, the subject's high-density lipoprotein cholesterol concentration, high-density lipoprotein concentration, high-density cholesterol triglyceride concentration, adiponectin concentration or apolipoprotein A-I concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00365] The present invention provides methods for cholesterol or triglyceride mobilization from a subject's endothelial and epithelial cells to the subject's blood plasma or blood serum and transport for clearance and excretion, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00366] The present invention provides methods for reducing a subject's risk of developing a thrombosis, a blood clot, a primary cardiovascular event, a secondary cardiovascular event, progression to nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, liver cirrhosis, hepatocellular carcinoma, liver failure, pancreatitis, pulmonary fibrosis, or hyperlipoproteinemia type IIB, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the present invention provides methods for reducing a subject's risk of developing pancreatitis.

[00367] The present invention provides methods for reducing a subject's risk of developing an ApoC-II deficiency.

[00368] The present invention provides methods for treating or preventing fibrosis, steatosis, ballooning or inflammation in the liver of a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, treating or preventing ballooning or inflammation in the liver of a subject is reducing ballooning or inflammation in the liver of a subject. The present invention further provides reducing or inhibiting progression of fibrosis, steatosis, ballooning or inflammation in the liver of a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00369] The present invention provides methods for reducing post-prandial lipemia or preventing prolonged post-prandial lipemia, comprising administering to a subject in need thereof an effective amount of a compound of the invention. The present invention provides methods for decreasing the extent and duration of post-prandial lipemia, comprising administering to a subject in need thereof an effective amount of a compound of the invention. The present invention provides methods for decreasing the extent and duration of post-prandial lipemia, comprising administering to a subject in need thereof a composition of the invention.

[00370] The present invention provides methods for treating or preventing hypoalphalipoproteinemia.

[00371] The present invention provides methods for reducing a magnitude or duration of post-prandial lipemia, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00372] The present invention provides methods for reducing a fat content of the liver of a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention. The present invention provides methods for reducing a steatosis of the liver of a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00373] The present invention further provides methods for reducing a subject's risk of thrombosis or blood clot, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00374] In some embodiments, the therapeutic or prophylactic methods of the invention are effective to reduce a subject's plasma or blood serum triglyceride concentration to below about 200 mg/dl or to below about 150 mg/dl. In some embodiments, the therapeutic or prophylactic methods of the invention are effective to reduce a subject's plasma or blood serum triglyceride concentration to below about 200 mg/dl or to below about 150 mg/dl within about 8 to about 12 weeks after administering a compound of the invention.

[00375] In some embodiments, the therapeutic or prophylactic methods of the invention are effective to reduce the subject's plasma or blood serum triglyceride concentration by at least 10% in a subject whose baseline plasma or blood serum triglyceride concentration is 500 mg/dl or higher, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the therapeutic or prophylactic methods of the invention are effective to reduce the subject's plasma or blood serum triglyceride concentration by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, or any range between any of these values, of the baseline plasma or blood serum triglyceride concentration where the subject has a baseline plasma or blood serum triglyceride concentration of 500 mg/dl or higher. In some embodiments, the therapeutic or prophylactic methods of the invention are effective to reduce the subject's plasma or blood serum triglyceride concentration by up to about 60% of the baseline plasma or blood serum triglyceride concentration in a subject whose baseline plasma or blood serum triglyceride concentration is 500 mg/dl or higher, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00376] In some embodiments, the therapeutic or prophylactic methods of the invention are effective to reduce the subject's plasma or blood serum triglyceride concentration by at least 10% in a subject whose baseline plasma or blood serum triglyceride concentration is 200 mg/dl or higher, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the therapeutic or prophylactic methods of the invention are effective to reduce the subject's plasma or blood serum triglyceride concentration by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, or any range between any of these values, of the baseline plasma or blood serum triglyceride concentration where the subject has a baseline plasma or blood serum triglyceride concentration is 200 mg/dl or higher. In some embodiments, the therapeutic or prophylactic methods of the invention are effective to reduce the subject's plasma or blood serum triglyceride concentration by up to about 35%, by up to about 36%, by up to about 37%, by up to about 38%, by up to about 39%, or by up to about 40% of the baseline plasma or blood serum triglyceride concentration in a subject whose baseline plasma or blood serum triglyceride concentration is 200 mg/dl or higher, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00377] The present invention further provides methods for reducing a subject's plasma or blood serum LDL cholesterol concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00378] In some embodiments, the present methods are effective to reduce the subject's plasma or blood serum LDL cholesterol concentration to below about 130 mg/dl. In some embodiments, the present methods are effective to reduce the subject's plasma or blood serum LDL cholesterol concentration to below about 130 mg/dl within about 8 to about 12 weeks of administering a compound of the invention.

[00379] The present invention further provides methods for reducing a subject's ApoB concentration, comprising administering to a subject in need thereof an effective amount a compound of the invention. In some embodiments, the methods are effective to reduce the subject's ApoB concentration to below about 120 mg/dl. In some embodiments, the methods are effective to reduce the subject's ApoB concentration to below about 120 mg/dl within about 8 to about 12 weeks following administering a compound of the invention.

[00380] In some embodiments, the subject has atherometabolic syndrome, metabolic syndrome, type-2 diabetes, impaired glucose tolerance, obesity, dyslipidemia, hepatitis B, hepatitis C, a human immunodeficiency virus (HIV) infection, or a metabolic disorder such as Wilson's disease, a glycogen storage disorder, galactosemia, an inflammatory condition or an elevated body mass index above what is normal for the subject's gender, age or height. Without being bound by theory, metabolic syndrome, type-2 diabetes, impaired glucose tolerance, obesity, dyslipidemia, hepatitis B, hepatitis C, an HIV infection, or a metabolic disorder such as Wilson's disease, a glycogen storage disorder or galactosemia is believed to be a risk factor for developing fatty liver (steatosis).

[00381] In some embodiments, the subject has an HIV infection. In some embodiments, the subject has an HIV infection and the subject is being administered with a highly active antiretroviral therapy (HAART) agent such as an antiretroviral inhibitor. Without being bound by theory, a compound of the invention is believed to be catabolized to a much lesser extent by the same P450 enzymes that metabolize antiretroviral inhibitors when treating an HIV subject undergoing an antiretroviral inhibitor treatment.

[00382] In some embodiments, the present invention further provides methods for treating or preventing an HIV-associated the liver disease or the liver condition. In some embodiments, the present invention further provides methods for treating or preventing an HIV-associated NAFLD. In some embodiments, the present invention further provides methods for treating or preventing an HIV-associated lipodystrophy. In some embodiments, the present invention further provides methods for treating or preventing a liver disease or the liver condition, comprising administering an effective amount of a compound of the invention to a subject who has an HIV infection. In some embodiments, the present invention further provides methods for treating or

preventing NAFLD, comprising administering an effective amount of a compound of the invention to a subject who has an HIV infection.

[00383] The present invention further provides methods for treating or preventing a disorder of glucose metabolism, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00384] Examples of disorders of glucose metabolism include, but are not limited to, is insulin resistance, impaired glucose tolerance, impaired fasting glucose (concentrations in blood), diabetes mellitus, lipodystrophy, familial partial lipodystrophy, obesity, peripheral lipoatrophy, diabetic nephropathy, diabetic retinopathy, renal disease, and septicemia. In some embodiments, obesity is central obesity.

[00385] In some embodiments, the present invention further provides methods for treating or preventing a disorder of glucose metabolism, comprising administering an effective amount of a compound of the invention to a subject who has an HIV infection, In some embodiments, the present invention further provides methods for treating or preventing lipodystrophy, comprising administering an effective amount of a compound of the invention to a subject who has an HIV infection.

[00386] The present invention further provides methods for treating or preventing a cardiovascular disorder or a related vascular disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00387] Examples of cardiovascular disorders and related vascular disorders include, but are not limited to, arteriosclerosis, atherosclerosis, hypertension, coronary artery disease, myocardial infarction, arrhythmia, atrial fibrillation, heart valve disease, heart failure, cardiomyopathy, myopathy, pericarditis, impotence, and a thrombotic disorder.

[00388] The present invention further provides methods for reducing a subject's risk of having a cardiovascular or vascular event, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00389] In some embodiments, the cardiovascular or vascular event is primary cardiovascular event. In other embodiments, the cardiovascular event is secondary cardiovascular event. Examples of cardiovascular events include, but are not limited to, myocardial infarction, stroke, angina, acute coronary syndrome, coronary artery bypass graft surgery and cardiovascular death. A primary cardiovascular event is the first cardiovascular event that a subject experiences. If the same subject experiences a second cardiovascular event, then the second cardiovascular event is a secondary cardiovascular event.

[00390] The present invention further provides methods for treating or preventing a disease caused by an increased level of fibrosis, comprising administering to a subject in need thereof an

effective amount of a compound of the invention. In some embodiments, the disease caused by an increased level of fibrosis is a lung disease. In some embodiments, the disease caused by an increased level of fibrosis is a heart disease. In some embodiments, the disease caused by an increased level of fibrosis is a skin disease. Examples of diseases caused by an increased level of fibrosis include, but are not limited to, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, emphysema, nephrogenic fibrosis, endometrial fibrosis, perineural fibrosis, hepatic fibrosis, myocardial fibrosis, acute lung injury, radiation-induced lung injury following treatment for cancer, progressive massive fibrosis, a complication of coal workers' pneumoconiosis (lungs), cirrhosis (liver), atrial fibrosis, endomyocardial fibrosis, old myocardial infarction, arterial stiffness (heart), glial scar (brain), arthrofibrosis (knee, shoulder, other joints), Crohn's Disease (intestine), Dupuytren's contracture (hands, fingers), keloid (skin), mediastinal fibrosis (soft tissue of the mediastinum), myelofibrosis (bone marrow), Peyronie's disease (penis), nephrogenic systemic fibrosis (skin), retroperitoneal fibrosis (soft tissue of the retroperitoneum), scleroderma/systemic sclerosis (skin, lungs), and some forms of adhesive capsulitis (shoulder). In some embodiments, the disease caused by increased levels of fibrosis is a chronic obstructive pulmonary disease or an idiopathic pulmonary fibrosis.

[00391] The present invention further provides methods for treating or preventing a disease associated with increased inflammation, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the disease associated with increased inflammation is an autoimmune disease.

[00392] Examples of diseases associated with increased inflammation include, but are not limited to, multiple sclerosis, inflammatory bowel disease, celiac disease, Crohn’s disease, antiphospholipid syndrome, atherosclerosis, autoimmune encephalomyelitis, autoimmune hepatitis, Graves' disease, ulcerative colitis, multiple sclerosis, myasthenia gravis, myositis, polymyositis, Raynaud's phenomenon, rheumatoid arthritis, scleroderma, Sjogren's syndrome, systemic lupus, type 1 diabetes and uveitis. In some embodiments, the disease associated with increased inflammation is multiple sclerosis, inflammatory bowel disease, celiac disease, or Crohn’s disease.

[00393] The present invention further provides methods for preventing death from or increasing survival from a disease associated with increased inflammation, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the disease associated with increased inflammation is influenza, sepsis, or a viral disease.

[00394] Examples of viral diseases include, but are not limited to, influenza, human immunodeficiency virus infection, hepatitis B, and hepatitis C.

[00395] The present invention further provides methods for treating or preventing a inflammation, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the inflammation is indicated by an increased concentration of C-reactive protein in a patient's plasma or serum.

[00396] Examples of C-reactive protein related disorders include, but are not limited to, inflammation, ischemic necrosis, and a thrombotic disorder.

[00397] The present invention further provides methods for treating or preventing a sulfatase-2-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. Examples of sulfatase-2-related disorders include, but are not limited to, disorders of lipogenesis or lipid modulation, elevated plasma or blood serum triglycerides or hyperlipidemia, hypercholesterolemia, diabetes, fatty liver disease, obesity, atherosclerosis, and/or cardiovascular diseases.

[00398] The present invention further provides methods for treating or preventing an apolipoprotein C-III-related disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. Examples of apolipoprotein C-III-related disorders include, but are not limited to, disorders of lipogenesis or lipid modulation, elevated plasma or blood serum triglycerides or hyperlipidemia, hypercholesterolemia, diabetes, fatty liver disease, obesity, atherosclerosis, and/or cardiovascular diseases.

[00399] The present invention further provides methods for treating or preventing Alzheimer's disease, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00400] The present invention further provides methods for treating or preventing Parkinson's disease, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00401] The present invention further provides methods for treating or preventing pancreatitis, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00402] The present invention further provides methods for treating or preventing the risk of developing pancreatitis, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00403] The present invention further provides methods for treating or preventing a pulmonary disorder, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the pulmonary disorder is a chronic obstructive pulmonary disease or an idiopathic pulmonary fibrosis.

[00404] The present invention further provides methods for treating or preventing musculoskeletal discomfort, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00405] The present invention further provides methods for reducing a subject's plasma or blood serum fibrinogen concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[00406] In some embodiments, the subject's plasma or blood serum fibrinogen concentration is greater than 300 mg/dl. In some embodiments, the subject's plasma or blood serum fibrinogen concentration is greater than 400 mg/dl.

[00407] The present invention further provides methods for reducing a fibrosis score or a nonalcoholic fatty liver disease activity score in a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention. The nonalcoholic fatty liver disease activity score (NAS or NAFLD score) is a composite score that measures changes in NAFLD during therapeutic trials. NAS is a composite score comprised of three components that includes scores for steatosis, lobular inflammation and hepatocyte ballooning (Table 15). NAS is the unweighted sum of the scores for steatosis, lobular inflammation and hepatocyte ballooning. Steatosis grade is quantified as the percentage of hepatocytes that contain fat droplets. The fibrosis stage of the liver is evaluated separately from NAS by histological evaluation of the intensity of Sirius red staining of collagen in the pericentral region of liver lobules.

[00408] The present invention provides methods for slowing the progression of a component of NAS, comprising administering to a subject in need thereof a compound of the invention. The present invention provides methods for slowing the progression of a component of NAS, comprising administering to a subject in need thereof a composition of the invention.

[00409] The present invention provides methods for slowing the progression of steatosis, lobular inflammation, or hepatocyte ballooning, comprising administering to a subject in need thereof a compound of the invention. The present invention provides methods for slowing the progression of steatosis, lobular inflammation, or hepatocyte ballooning, comprising administering to a subject in need thereof a composition of the invention.

[00410] The present invention provides methods for slowing the progression of steatosis, comprising administering to a subject in need thereof a compound of the invention or a composition of the invention. The present invention provides methods for slowing the progression of lobular inflammation, comprising administering to a subject in need thereof a compound of the invention or a composition of the invention. The present invention provides methods for slowing the progression of hepatocyte ballooning, comprising administering to a subject in need thereof a compound of the invention or a composition of the invention.

[00411] The present invention further provides methods for reducing elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglyceride or non-high-density lipoprotein cholesterol in a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention. The present invention further provides methods for increasing high-density lipoprotein cholesterol in a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has primary hyperlipidemia. In some embodiments, the primary hyperlipidemia is heterozygous familial. In some embodiments, the primary hyperlipidemia is homozygous familial. In some embodiments, the primary hyperlipidemia isnon-familial. In some embodiments, the subject has mixed hyperlipidemia.

[00412] The present invention further provides methods for treating or preventing a condition or disease associated with hepatic overexpression of sulfatase-2 (Sulf-2) mRNA, comprising administering to a subject in need thereof an effect amount of a compound of the invention. Without bound to any theory, it is believed that Sulf-2 inhibits hepatic disposal of C-TRLs, thereby increasing plasma or blood serum triglyceride concentration in a subject. Conditions or diseases associated with hepatic overexpression of Sulf-2 include but are not limited to, elevated plasma or blood serum triglycerides or hyperlipidemia, hypercholesterolemia, diabetes, fatty liver disease, obesity, atherosclerosis, and/or cardiovascular diseases.

[00413] The present invention further provides methods for treating or preventing a condition or disease associated with hepatic overexpression of ApoC-III mRNA, comprising administering to a subject in need thereof an effect amount of a compound of the invention. Without bound to any theory, it is believed that overexpression of ApoC-III mRNA leads to increased plasma or blood serum triglyceride concentration in a subject. Conditions or diseases associated with hepatic overexpression of ApoC-III include, but are not limited to, elevated blood serum triglycerides or hyperlipidemia, hypercholesterolemia, diabetes, fatty liver disease, obesity, atherosclerosis, and/or cardiovascular diseases.

[00414] The present invention further provides methods for treating or preventing a condition or disease associated with hepatic overexpression of ANGPTL3 mRNA, comprising administering to a subject in need thereof an effect amount of a compound of the invention. Without bound to any theory, it is believed that overexpression of ANGPTL3 mRNA leads to blockage of lipoprotein lipase activity and elevated plasma or blood serum triglyceride concentration in a subject. Conditions or diseases associated with hepatic overexpression of ANGPTL3 include, but are not limited to, elevated blood serum triglycerides or hyperlipidemia, hypercholesterolemia, diabetes, fatty liver disease, obesity, atherosclerosis, and/or cardiovascular diseases.

[00415] The present invention further provides methods for treating or preventing a condition or disease associated with hepatic overexpression of ANGPTL4 mRNA, comprising administering to a subject in need thereof an effect amount of a compound of the invention. Without bound to any theory, it is believed that overexpression of ANGPTL4 mRNA leads to blockage of lipoprotein lipase activity and elevated plasma or blood serum triglyceride concentration in a subject. Conditions or diseases associated with hepatic overexpression of ANGPTL4 include, but are not limited to, elevated blood serum triglycerides or hyperlipidemia, hypercholesterolemia, diabetes, fatty liver disease, obesity, atherosclerosis, and/or cardiovascular diseases.

[00416] The present invention further provides methods for treating or preventing a condition or disease associated with hepatic overexpression of ANGPTL8 mRNA, comprising administering to a subject in need thereof an effect amount of a compound of the invention. Without bound to any theory, it is believed that overexpression of ANGPTL8 mRNA leads to blockage of lipoprotein lipase activity and elevated plasma or blood serum triglyceride concentration in a subject. Conditions or diseases associated with hepatic overexpression of ANGPTL8 include, but are not limited to, elevated blood serum triglycerides or hyperlipidemia, hypercholesterolemia, diabetes, fatty liver disease, obesity, atherosclerosis, and/or cardiovascular diseases.

[00417] The present invention provides methods for lowering a subject's blood plasma or blood serum LDL-C concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention or a composition of the invention. The present invention further provides methods for reducing a subject's blood plasma or blood serum elevated total cholesterol or elevated LDL-C, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has homozygous familial hypercholesterolemia (HoFH). In some embodiment, the subject is known to have HoFH. In some embodiments, the subject has heterozygous familial hypercholesterolemia (HeFH). In some embodiments, the subject is known to have HeFH. The therapeutic or prophylactic methods of the invention can further comprise administering an additional pharmaceutically active agent to a subject. The therapeutic or prophylactic methods of the invention can further comprise administering two or more additional pharmaceutically active agents to a subject. In some embodiments, the subject is on a stable dose of statin.

[00418] The present invention provides methods for lowering a subject's LDL-C concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention, wherein the subject is on a stable dose of a statin.

[00419] In some embodiments, the additional pharmaceutically active agent is a statin, lipid lowering agent, a PCSK9 inhibitor, Vitamin E, an ANGPTL3 inhibitor, an ANGPTL4 inhibitor, an ANGPTL8 inhibitor, a cholesterol absorption inhibitor, a ACC inhibitor, an ApoC-III inhibitor, an ACL inhibitor, a fish oil, a fibrate, a thyroid hormone beta receptor agonist, a famesoid X receptor (FXR), a CCR2/CCR5 (C-C chemokine receptor types 2 (CCR2) and 5 (CCR5)) inhibitor or antagonist, a caspase protease inhibitor, an ASK-1 (Apoptosis signal-regulating kinase 1) inhibitor, a galectin-3 protein, a NOX (Nicotinamide adenine dinucleotide phosphate oxidase) inhibitor, an ileal bile acid transporter, a PPAR (peroxisome proliferator-activated receptor) agonist, a PPAR dual agonist, a pan-PPAR agonist, a sodium-glucose co-transporter 1 or 2 (SGLT1 or SGLT2) inhibitor, a dipeptidyl peptidase 4 (DPP4) inhibitor, a fatty acid synthase (FAS) inhibitor, a toll-like receptor antagonist, a thyroid hormone receptor-beta (THR-β) agonist, a liver-directed, selective THR-β agonist, an ACO1 modulator, a 1-mieloperoxidase inhibitor, a 1-ketohexokinase (1-KHK) inhibitor, an oxidative stress inhibitor, a fibroblast growth factor 21 (FGF21) or 19 (FGF19) inhibitor, a transforming growth factor beta-1 (TGF-β1) agonist, a hepatic de novo lipogenesis (DNL) inhibitor, an enoyl CoA hydratase inhibitor, a cholesterol 7-alpha hydroxylase (Cyp7A1) agonist, a Collagen Type 3 inhibitor, or a CETP inhibitor. The additional therapeutic agent can be a lipid-lowering treatment or agent. The lipid-lowering treatment or agent can be ezetimibe.

[00420] The therapeutic or prophylactic methods of the invention can further comprise administering a statin and ezetimibe.

[00421] In some embodiments, the subject is undergoing gastric bypass surgery.

[00422] The present invention further provides methods for treating or preventing heterozygous familial hypercholesterolemia (HeFH), comprising administering to a subject in need thereof an effective amount of a compound of the invention. The present invention further provides methods for treating or preventing atherosclerotic cardiovascular disease (ASCVD), comprising administering to a subject in need thereof an effective amount of a compound of the invention. In further embodiments, the atherosclerotic cardiovascular disease is a clinical atherosclerotic cardiovascular disease. In some embodiments, the subject is an adult. In some embodiments, the subject is on statin therapy. In some embodiments, the statin therapy is maximally tolerated statin therapy. In some embodiments, the methods further comprise administering a statin to the subject. In some embodiments, the subject has abnormally high plasma or blood serum LDL-C. In some embodiments, the maximally tolerated statin therapy is insufficient to lower the subject's plasma or blood serum LDL-C. In some embodiment, the maximally tolerated statin therapy is insufficient to lower the subject's plasma or blood serum LDL-C to the subject's goal plasma or blood serum LDL-C concentration.

[00423] A subject's goal plasma or blood serum LDL-C concentration varies with the subject's risk factor or factors, pre-existing conditions, and/or health status. For example, LDL-C goal concentration for all human subjects, including human subjects with CHD (coronary heart disease) and other clinical forms of atherosclerotic disease should be less than 100 mg/dL. In addition, a reasonable or a desirable LDL-C goal concentration for all human subject with CHD and other clinical forms of atherosclerotic disease can be less than 70 mg/dL (Smith et al. *Circulation.* 2006;113:2363-2372).

[00424] The present invention further provides methods for treating or preventing HoFH, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject is on one or more other low-density lipoprotein (LDL) lowering therapies. In some embodiments, the methods further comprise administering an LDL-lowering therapy to the subject. Non-limiting examples of LDL-lowering therapies include statins, ezetimibe and LDL apheresis. In some embodiments, the subject has abnormally high LDL-C. In some embodiments, the other LDL-lowering therapy is insufficient to lower the subject's LDL-C. In some embodiments, the other LDL-lowering therapy is insufficient to lower the subject's LDL-C to the subject's goal concentration. In some embodiments, the methods further comprise administering one or more additional pharmaceutically active agents, as disclosed herein.

[00425] The present invention further provides methods for reducing risk of a cardiovascular event, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has coronary heart disease (CHD). In some embodiments, the subject has a history of acute coronary syndrome (ACS). In some embodiments, the subject has been previously treated with a statin. In other embodiments, the subject has not been previously treated with a statin.

[00426] The present invention further provides methods for treating or preventing primary hypercholesterolemia, comprising administering to a subject in need thereof an effective amount of a compound of the invention. The primary hypercholesterolemia can be HeFH or non-familial hypercholesterolemia. In some embodiments, the present invention further provides methods for treating or preventing mixed hyperlipidemia in a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject or the subject's symptoms are not effectively treated with statin therapy alone. As used herein, "not effectively treated with statin therapy alone" means that the subject's plasma or blood serum LDL-C is not lowered to the subject's goal concentration with a given treatment. In some embodiments, the subject had been administered with a statin and/or ezetimibe prior to administration of a compound of the invention. In some embodiments, the subject was treated

with a statin and/or ezetimibe previously, prior to administration of a compound of the invention. In some embodiments, the methods further comprise administering a one or both of a statin and ezetimibe to the subject.

[00427] The present invention further provides methods for treating or preventing HoFH, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the method further comprises administering an adjunctive treatment. The adjunctive treatment can be one or more of a statin, ezetimibe and LDL apheresis. In some embodiments, the adjunctive treatment is LDL-lowering therapy. In some embodiments, the adjunctive treatment can be one or more of a statin, ezetimibe, LDL apheresis, PCSK9 inhibitor, and bile acid sequestrant. In some embodiments, the adjunctive treatment can be one or more of a statin, ezetimibe, LDL apheresis, PCSK9 inhibitor, bile acid sequestrant, lomitapide (Juxtapid®) and mipomersen (Kynamro®). In some embodiments, the adjunctive treatment can be one or more additional pharmaceutically active agents, as disclosed herein.

[00428] The present invention further provides methods for reducing risk of having myocardial infarction, having a stroke, needing a revascularization procedure or having angina, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject does not have coronary heart disease (CHD). In some embodiments, the subject has one or more risk factors for CHD. Examples of risk factors for CHD include, but are not limited to, high plasma or blood serum cholesterol, high plasma or blood serum triglyceride, high blood pressure, diabetes, prediabetes, overweight or obesity, smoking, lack of physical activity, unhealthy diets, stress. In addition, age, gender, and family history of early CHD can be a risk factor for CHD.

[00429] The present invention further provides methods for reducing a subject's risk of myocardial infarction or stroke, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has type 2 diabetes. In some embodiments, the subject has type 2 diabetes and does not have CHD. In some embodiments, the subject has one or more risk factors for CHD.

[00430] The present invention further provides methods for reducing a subject's risk of non-fatal myocardial infarction, risk of fatal stroke or non-fatal stroke, need for a revascularization procedure, risk of congestive heart failure (CHF) or risk of angina, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has CHD.

[00431] The present invention further provides methods for reducing in a subject's blood plasma or blood serum elevated total cholesterol, LDL-C, Apo B or triglyceride concentration, comprising administering to a subject in need thereof an effective amount of a compound of the

invention. The present invention further provides methods for increasing high-density lipoprotein cholesterol in a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject is an adult. In some embodiments, the subject has primary hyperlipidemia. Primary hyperlipidemia can be heterozygous familial or non-familial. In some embodiments, the subject has mixed dyslipidemia.

[00432] The present invention further provides methods for reducing in a subject's blood plasma or blood serum elevated triglyceride concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has hypertriglyceridemia. In some embodiments, the subject has primary dysbetalipoproteinemia. In yet some other embodiment, the subject has hypoalphalipoproteinemia.

[00433] The present invention further provides methods for reducing in a subject's blood plasma or blood serum total cholesterol or LDL-C concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has HoFH.

[00434] The present invention further provides methods for reducing in a subject's blood plasma or blood serum elevated total cholesterol, LDL-C or Apo B concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject is a human male or a human female (e.g., postmenarcheal female) who is 10-17 years of age. In some embodiments, the subject has HeFH. In some embodiments, the subject's diet is insufficient to reduce the subject's elevated total cholesterol, LDL-C or Apo B. In some embodiments, the subject's life-style or diet and life-style is insufficient to reduce the subject's elevated total cholesterol, LDL-C or Apo B.

[00435] The present invention further provides methods for reducing a subject's risk of mortality, CHD death, non-fatal myocardial infarction, stroke or need for a revascularization procedure, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject is at high risk of a coronary event.

[00436] The present invention further provides methods for reducing in a subject's blood plasma or blood serum elevated total cholesterol, LDL-C, Apo B or triglyceride concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention. The present invention further provides methods for increasing in a subject's blood plasma or blood serum high-density lipoprotein cholesterol, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has primary hyperlipidemia. In some embodiments, the primary

hyperlipidemia is HeFH. In some embodiments, the primary hyperlipidemia is non-familial hyperlipidemia. In some embodiments, the subject has mixed dyslipidemia.

[00437] The present invention further provides methods for reducing in a subject's blood plasma or blood serum elevated triglyceride concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has hypertriglyceridemia. The present invention further provides methods for reducing in a subject's blood plasma or blood serum triglyceride or very-low-density lipoprotein cholesterol (VLDL-C), comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has primary dysbetalipoproteinemia.

[00438] The present invention further provides methods for reducing in a subject's blood plasma or blood serum elevated total cholesterol or LDL-C concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject is an adult. In some embodiments, the subject has HoFH.

[00439] The present invention further provides methods for treating or preventing hypertriglyceridemia, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the method further comprises adjusting the subject's diet. In some embodiments, the method further comprises placing the subject on a low-fat diet.

[00440] The present invention further provides methods for treating or preventing primary dysbetalipoproteinemia, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the primary dysbetalipoproteinemia is Type III hyperlipoproteinemia. In some embodiments, the method further comprises adjusting the subject's diet. In some embodiments, the method further comprises placing the subject on a low-fat diet.

[00441] The present invention further provides methods for reducing in a subject's blood plasma or blood serum total cholesterol, LDL-C or Apo B concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has HoFH.

[00442] The present invention further provides methods for reducing in a subject's blood plasma or blood serum elevated LDL-C, total cholesterol, Apo B or triglyceride concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention. The present invention further provides methods for increasing in a subject's blood plasma or blood serum high-density lipoprotein cholesterol concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In

some embodiments, the subject is an adult. In some embodiments, the subject has primary hypercholesterolemia. In some embodiments, the subject has mixed dyslipidemia.

[00443] The present invention further provides methods for treating or preventing severe hypertriglyceridemia, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject is an adult.

[00444] The present invention further provides methods for reducing the rate or incidence of myocardial infarction or stroke, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has acute coronary syndrome (ACS). In some embodiments, the subject has non-ST-segment elevation ACS (unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)). In some embodiments, the subject has ST-elevation myocardial infarction (STEMI). In electrocardiography, the ST segment connects the QRS complex and the T wave. In some embodiments, the subject has had a previous myocardial infarction, previous stroke or established peripheral arterial disease. In some embodiments, the subject has had a recent myocardial infarction or recent stroke. In some embodiments, recent myocardial infarction or a recent stroke took event within one year. In some embodiments, ecent myocardial infarction or a recent stroke took event within three months.

[00445] The present invention further provides methods for reducing in a subject's blood plasma or blood serum total cholesterol, LDL-C or Apo B concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has primary hypercholesterolemia. Primary hypercholesterolemia can be heterozygous familial or non-familial. In some embodiments, the method further comprises administering an HMG-CoA reductase inhibitor to the subject.

[00446] The present invention further provides methods for reducing in a subject's blood plasma or blood serum total cholesterol or LDL-C concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has HoFH. In some embodiments, the method further comprises administering an additional lipid-lowering treatment to the subject. In some embodiments, the additional lipid-lowering treatment may be a statin (e.g., atorvastatin or simvastatin) or LDL apheresis.

[00447] The present invention further provides methods for reducing in a subject's blood plasma or blood serum elevated sitosterol or campesterol concentration, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has homozygous familial sitosterolemia.

[00448] The present invention further provides methods for treating or preventing Type IV or Type V hyperlipidemia, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has a risk of pancreatitis. In some embodiments, a change in the subject's diet does not adequately lower the subject's plasma or blood serum triglyceride concentrations. In some embodiments, a normal blood serum triglyceride concentration is less than 150 mg/dL according to ATP III Classification of serum triglycerides (National Institute of Health Publication No. 01-3305; May 2001; Cholesterol Guidelines). In some embodiments, the subject has an abnormally high serum triglyceride concentration. In some embodiments, the subject has a blood serum triglyceride concentration of over 2000 mg/dL and optionally has an elevation of VLDL-cholesterol or has fasting chylomicronemia. In some embodiments, the subject has a triglyceride of from 1000 to 2000 mg/dL and optionally has a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis.

[00449] The present invention further provides methods for reducing risk of developing coronary heart disease, comprising administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, the subject has Type IIb hyperlipidemia. In some embodiments, the subject does not have history of or symptoms of existing coronary heart disease. In some embodiments, the subject has had weight loss, dietary therapy, exercise, or was administered another pharmacologic agent (e.g., a bile acid sequestrant or nicotinic acid) that was ineffective to treat the subject's hyperlipidemia. In some embodiments, the subject has in a subject's blood plasma or blood serum, one or more of an abnormally low HDL-cholesterol concentration, an abnormally high LDL-cholesterol concentration and an abnormally high triglyceride concentration.

[00450] In some embodiments, the therapeutic or prophylactic methods of the invention further comprise administering an effective amount of an additional pharmaceutically active agent. In some embodiments, the therapeutic or prophylactic methods of the invention further comprise administering an effective amount of two or more additional pharmaceutically active agent.

[00451] In some embodiments, the additional pharmaceutically active agent is a statin. In some embodiments, statin is atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin, mevastatin, dalvastatin, dihydrocompactin, or cerivastatin, or a pharmaceutically acceptable salt thereof. In some embodiments, the statin is atorvastatin calcium.

[00452] In some embodiments, the additional pharmaceutically active agent is a statin. In some embodiments, the additional pharmaceutically active agent is an HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitor.

[00453] In some embodiments, the additional pharmaceutically active agent is a lipid modifying agent, lipid lowering agent, anti-fibrolytic agent, or an anti-inflammatory agent. In some embodiments, the additional pharmaceutically active agent is a cholesterol lowering agent. In other embodiments, the additional pharmaceutically active agent is a cholesterol absorption inhibitor. In other embodiments, the cholesterol absorption inhibitor is ezetimibe.

[00454] In some embodiments, the additional pharmaceutically active agent is a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor, Vitamin E, an ANGPTL3 inhibitor, an ANGPTL4 inhibitor, an ANGPTL8 inhibitor, a cholesterol absorption inhibitor, an ACC (acetyl-CoA carboxylase) inhibitor, an ApoC-III (apolipoprotein C-III) inhibitor, an ApoB (apolipoprotein B) synthesis inhibitor, an ACL (adenosine triphosphate citrate lyase) inhibitor, a microsomal transfer protein inhibitor, a fenofibric acid, a fish oil, a fibrate, a thyroid hormone beta receptor agonist, a farnesoid X receptor (FXR), a CCR2/CCR5 (C-C chemokine receptor types 2 (CCR2) and 5 (CCR5)) inhibitor or antagonist, a caspase protease inhibitor, an ASK-1 (Apoptosis signal-regulating kinase 1) inhibitor, a galectin-3 protein, a NOX (Nicotinamide adenine dinucleotide phosphate oxidase) inhibitor, an ileal bile acid transporter, a PPAR (peroxisome proliferator-activated receptor) agonist, a PPAR dual agonist, a pan-PPAR agonist, a sodium-glucose co-transporter 1 or 2 (SGLT1 or SGLT2) inhibitor, a dipeptidyl peptidase 4 (DPP4) inhibitor, a fatty acid synthase (FAS) inhibitor, a toll-like receptor antagonist, a thyroid hormone receptor-beta (THR-β) agonist, a liver-directed, selective THR-β agonist, an ACO1 modulator, a 1-mieloperoxidase inhibitor, a 1-ketohexokinase (1-KHK) inhibitor, an oxidative stress inhibitor, a fibroblast growth factor 21 (FGF21) or 19 (FGF19) inhibitor, a transforming growth factor beta-1 (TGF-β1) agonist, a hepatic de novo lipogenesis (DNL) inhibitor, an enoyl CoA hydratase inhibitor, a cholesterol 7-alpha hydroxylase (Cyp7A1) agonist, a Collagen Type 3 inhibitor, or a CETP (cholesterylester transfer protein) inhibitor. In other embodiments, the additional lipid lowering agent is PCSK9 inhibitor. In some embodiments, the additional lipid lowering agent is bempedoic acid, nicotinic acid, gemfibrozil, niacin, a bile-acid resin, a fibric acid derivative, or a cholesterol absorption inhibitor. In some embodiments, the additional lipid lowering agent is bempedoic acid, nicotinic acid, or gemfibrozil. In some embodiments the lipid-reducing agent is gemfibrozil. In some embodiments, the one or more pharmaceutically active agent is bempedoic acid.

[00455] Examples of fish oils include, but are not limited to, salmon oil, sardine oil, cod liver oil, tuna oil, herring oil, menhaden oil, mackerel oil, refined fish oils, and mixtures thereof. Fish oils comprise omega-3 fatty acids: eicosapentaenoic acid and docosahexaenoic acid. In some embodiments, the fish oil is prescription fish oil. In some embodiments, the eicosapentaenoic

acid is enriched or esterified, such as, but not limited to an ethyl ester. In some embodiments, the eicosapentaenoic acid is enriched and esterified.

[00456] In some embodiments, the CETP inhibitor is dalcetrapib (CAS 211513-37-0), torcetrapib (CAS 262352-17-0), anacetrapib (CAS 875446-37-0), evacetrapib (CAS 1186486-62-3), BAY 60-5521 (CAS 893409-49-9), obicetrapib (866399-87-3), ATH-03 (Affris), DRL-17822 (Dr. Reddy's), DLBS-1449 (Dexa Medica), *S*-[2-[1-(2-ethylbutyl)cyclohexylcarbonylamino]phenyl]-2-methylthiopropionate, 1-(2-ethyl-butyl)-cyclohexanecarboxylic acid (2-mercapto-phenyl)-amide or bis[2-[1-(2-ethylbutyl) cyclohexylcarbonylamino]phenyl] disulfide, or pharmaceutically acceptable salt thereof.

[00457] In some embodiments, the additional pharmaceutically active agent is an antibody to CETP. In some embodiments, the antibody to CETP is a monoclonal antibody. In other embodiments, the antibody to CETP is a monoclonal antibody (Mab, TP1) to CETP.

[00458] In some embodiments, the additional pharmaceutically active agent is an antibody against CETP. In some embodiments, the additional pharmaceutically active agent induces antibodies against CETP and is a vaccine. In some embodiments, the vaccine is TT/CETP (Rittershaus, C. W. *et al.*, Arteriosclerosis, Thrombosis, and Vascular Biology. 2000;20:2106-2112). In other embodiments, the additional pharmaceutically active agent induces antibodies against CETP and is CETi-1 (Celldex Therapeutics).

[00459] In some embodiments, the additional pharmaceutically active agent immunizes a subject with CETP or CETP protein fragment.

[00460] In some embodiments, the additional pharmaceutically active agent reduces CETP by inhibition with an SiRNA to CETP mRNA.

[00461] In some embodiments, the additional pharmaceutically active agent targets CETP transcription by administration of DNAi to the CETP gene. In other embodiments, the additional pharmaceutically active agent targets CETP transcription by administration of DNAi in an appropriate deliver vehicle such as a Smarticle™.

[00462] In some embodiments, the additional pharmaceutically active agent is an anti-coagulation agent or a lipid regulating agent. In some embodiments the anti-coagulation agent is aspirin, dabigatran, rivaroxaban, apixaban clopidogrel, clopNPT (conjugate of clopidogrel with 3-nitropyridine-2-thiol), prasugrel, ticagrelor, cangrelor, a platelet $P2Y_{12}$ receptor inhibitor, thienopyridine, warfarin (Coumadin) acenocoumarol, phenprocoumon, atromentin, phenindione, edoxaban betrixaban, letaxaban eribaxaban hirudin, lepirudin, bivalirudin, argatroban, dabigatran. ximelagatran, batroxobin, hementin, a heparin or vitamin E.

[00463] In some embodiments, the additional pharmaceutically active agent is simtuzumab (CAS 1318075-13-6), selonsertib (CAS 1448428-04-3), GS-9674 (Gilead Sciences), GS-0976

(Gliead Sciences), obeticholic acid (CAS 459789-99-2; Intercept), or cenicriviroc (CAS 497223-25-3; Allergan-Takeda), or pharmaceutically acceptable salt thereof. In some embodiments, the additional pharmaceutically active agent is, but is not limited to, elafibranor (Genfit), seladelpar (Cymabay), or EDP-305 (Enanta Pharmaceuticals).

[00464] In some embodiments, the additional pharmaceutically active agent is an anti-inflammatory agent, an anti-hypertensive agent, an anti-diabetic agent, an anti-obesity, an anti-fibrotic or an anti-coagulation agent. In some embodiments, the additional pharmaceutically active agent disclosed herein can be a pharmaceutically acceptable salt thereof. The pharmaceutically acceptable salt can be an acid addition salt where the pharmaceutically active agent is basic, e.g., includes a basic nitrogen atom, and can be a cationic salt. The pharmaceutically acceptable salt can be a base addition salt where the pharmaceutically active agent is acidic.

[00465] In some embodiments, the therapeutic or prophylactic methods of the invention do not induce hepatotoxicity or a musculoskeletal disorder.

[00466] In some embodiments, a subject to which a compound of the invention or composition of the invention is administered is on statin therapy. In some embodiments, the statin is atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin, mevastatin, dalvastatin, dihydrocompactin, or cerivastatin, or a pharmaceutically acceptable salt thereof. In some embodiments, the statin is atorvastatin calcium.

[00467] In some embodiments, the therapeutic or prophylactic methods of the invention comprises administering to a subject in need thereof an effective amount of a compound of the invention. In some embodiments, any one of the therapeutic or prophylactic methods as disclosed herein can comprise administering to a subject in need thereof an effective amount of a composition of the invention in place of an effective amount of a compound of the invention. In some embodiments, any one of the therapeutic or prophylactic methods as disclosed herein can comprise administering to a subject in need thereof an effective amount of a composition of the invention.

COMPOSITIONS OF THE INVENTION

[00468] The compositions of the invention comprise (i) an effective amount of a compound of the invention and (ii) a pharmaceutically acceptable carrier or vehicle.

[00469] In some embodiments, the compositions of the invention further comprise an effective amount of an additional pharmaceutically active agent, such as disclosed herein. In other embodiments, the compositions of the invention further comprise an effective amount of two or more additional pharmaceutically active agent as disclosed herein.

[00470] In some embodiments, the pharmaceutically acceptable carrier or vehicle, includes, but is not limited to, a binder, filler, diluent, disintegrant, wetting agent, lubricant, glidant, coloring agent, dye-migration inhibitor, sweetening agent or flavoring agent.

[00471] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, Panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof.

[00472] Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. In some embodiments, the binder is hydroxypropylcellulose.

[00473] The binder or filler can be present from about 2% to about 49% by weight of the compositions of the invention provided herein or any range within these values. In some embodiments, the binder or filler is present in the composition of the invention from about 5% to about 15% by weight. In some embodiments, the binder or filler is present in the composition of the invention at about 5%, 6%, 7%, 8%, 9%, 8%, 10%, 11%, 12%, 13%, 14%, or 15% by weight or any range within any of these values.

[00474] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. In some embodiments, the diluent is lactose monohydrate. In another embodiment, the diluent is lactose monohydrate Fast-Flo 316 NF.

[00475] The compositions of the invention can comprise from about 5% to about 49% of a diluent by weight of composition or any range between any of these values. In some embodiments, the diluent is present in the compositions of the invention from about 15% to about 30% by weight. In some embodiments, the diluent is present in the composition of the

invention at about 15%, 16%, 17%, 18%, 19%, 18%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, or 30% by weight or any range within any of these values.

[00476] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of disintegrant in the compositions of the invention can vary. In some embodiments, the disintegrant is croscarmellose sodium. In some embodiments, the disintegrant is croscarmellose sodium NF (Ac-Di-Sol).

[00477] The compositions of the invention can comprise from about 0.5% to about 15% or from about 1% to about 10% by weight of a disintegrant. In some embodiments, the compositions of the invention comprise a disintegrant in an amount of about 5%, 6%, 7%, 8%, 9%, 8%, 10%, 11%, 12%, 13%, 14%, or 15% by weight of the composition or in any range within any of these values.

[00478] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. In some embodiments, the lubricant is magnesium stearate.

[00479] The compositions can of the invention can comprise about 0.1 to about 5% by weight of a lubricant. In some embodiments, the compositions of the invention comprise a lubricant in an amount of about 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 0.8%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, or 3.0%, by weight of the composition or in any range within any of these values.

[00480] Suitable glidants include colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and talc, including asbestos-free talc.

[00481] Coloring agents include any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof.

[00482] Flavoring agents include natural flavors extracted from plants, such as fruits, and synthetic blends of compounds that provide a pleasant taste sensation, such as peppermint and methyl salicylate.

[00483] Sweetening agents include sucrose, lactose, mannitol, syrups, glycerin, sucralose, and artificial sweeteners, such as saccharin and aspartame.

[00484] Suitable emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suspending and dispersing agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrolidone. Preservatives include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether.

[00485] Solvents include glycerin, sorbitol, ethyl alcohol, and syrup.

[00486] Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate.

[00487] It should be understood that many carriers and excipients can serve several functions, even within the same formulation.

[00488] The compounds of the invention and the compositions of the invention can be formulated for administration by a variety of means including orally, parenterally, by inhalation spray, topically, or rectally in formulations containing pharmaceutically acceptable carriers, adjuvants and vehicles. The term "parenteral" as used here includes subcutaneous, intravenous, intramuscular, and intraarterial injections with a variety of infusion techniques. Intraarterial and intravenous injection as used herein includes administration through catheters.

[00489] The compounds of the invention and the compositions of the invention can be formulated in accordance with the routine procedures adapted for desired administration route. Accordingly, the compositions of the invention can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The compounds of the invention and the compositions of the invention can be formulated as a preparation suitable for implantation or injection. Thus, for example, pharmaceutically acceptable salt of gemcabene and the compositions of the invention can be formulated with suitable polymeric or hydrophobic materials (e.g., as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives (e.g., as a sparingly soluble salt). The compounds of the invention and the compositions of the invention can be in

powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. Suitable formulations for each of these methods of administration can be found, for example, in Remington: The Science and Practice of Pharmacy, A. Gennaro, ed., 20th edition, Lippincott, Williams & Wilkins, Philadelphia, PA.

[00490] In some embodiments, the compositions of the invention are suitable for oral administration. These compositions can comprise solid, semisolid, gelmatrix or liquid dosage forms suitable for oral administration. As used herein, oral administration includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, without limitation, tablets, capsules, pills, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, granules, bulk powders, effervescent or non-effervescent powders or granules, solutions, emulsions, suspensions, solutions, wafers, sprinkles, elixirs, syrups or any combination thereof. In some embodiments, compositions of the invention suitable for oral administration are in the form of a tablet or a capsule. In some embodiments, the composition of the invention is in a form of a tablet. In some embodiments, the composition of the invention is in a form of a capsule. In some embodiments, the compound of the invention is contained in a capsule.

[00491] In some embodiments, capsules are immediate release capsules. Non-limiting example of a capsule is a coni-snap® hard gelatin capsule.

[00492] The compositions of the invention can be in the form of compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenylsalicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which can be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. A film coating can impart the same general characteristics as a sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[00493] In some embodiments, the coating is a film coating. In some embodiments, the film coating comprises Opadry White and simethicone emulsion 30% USP.

[00494] In some embodiments, the compound of the invention is contained in a tablet. In some embodiments, the compound of the invention is contained in a compressed tablet. In some

embodiments, the compound of the invention is contained in a film-coated compressed tablet. In some embodiments, the compositions of the invention are in the form of film-coated compressed tablets.

[00495] In some embodiments, the compositions of the invention is prepared by fluid bed granulation of the compound of the invention with one or more pharmaceutically acceptable carrier, vehicle, or excipients. In some embodiments, the compositions of the invention prepared by fluid bed granulation process can provide tablet formulation with good flowability, good compressibility, fast dissolution, good stability, and/or minimal to no cracking. In some embodiments, the fluid bed granulation process allows preparation of formulations having high drug loading, such as over 70% or over 75% of a compound of the invention.

[00496] The compositions of the invention can be in the form of soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), can comprise of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells can contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein can be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules can also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[00497] The compositions of the invention can be in liquid or semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion can be a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions can include a pharmaceutically acceptable non-aqueous liquids or solvent, emulsifying agent, and preservative. Suspensions can include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions can include a pharmaceutically acceptable acetal, such as a di-(lower alkyl)acetal of a lower alkyl aldehyde (the term "lower" means an alkyl having between 1 and 6 carbon atoms), e.g., acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs can be clear, sweetened, and hydroalcoholic solutions. Syrups can be concentrated aqueous solutions of a sugar, for example, sucrose, and can comprise a preservative. For a liquid dosage form, for example, a solution in a polyethylene

glycol can be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be measured conveniently for administration.

[00498] The compositions of the invention for oral administration can be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Miccellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00499] The compositions of the invention can be provided as non- effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders can include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders can include organic acids and a source of carbon dioxide.

[00500] Coloring and flavoring agents can be used in all of the above dosage forms. And, flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[00501] The compositions of the invention can be formulated as immediate or modified release dosage forms, including delayed-, extended, pulsed-, controlled, targeted-, and programmed-release forms.

[00502] In some embodiments, the compositions of the invention comprise a film-coating.

[00503] The compositions of the invention can comprise another active ingredient that does not impair the composition's therapeutic or prophylactic efficacy or can comprise a substance that augments or supplements the composition's efficacy.

[00504] The tablet dosage forms can comprise a pharmaceutically acceptable salt of gemcabene in powdered, crystalline, or granular form, and can further comprise a carrier or vehicle described herein, including binder, disintegrant, controlled-release polymer, lubricant, diluent, or colorant.

[00505] In some embodiments, the compositions of the invention comprise from about 50 mg to about 900 mg, about 150 mg to about 600 mg, or about 150 mg to about 300 mg of a compound of the invention. In some embodiments, the compositions of the invention comprise a compound of the invention in an amount of about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460

mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, about 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, or an amount ranging from and to any of these values. In some embodiments, the compositions of the invention comprise about 50 mg of a compound of the invention. In some embodiments, the compositions of the invention comprise about 150 mg of a compound of the invention. In some embodiments, the compositions of the invention comprise about 300 mg of a compound of the invention. In some embodiments, the compositions of the invention comprise about 600 mg of a compound of the invention.

[00506] In some embodiments, the compositions of the invention comprise a compound of the invention in an amount that is a molar equivalent to 50 mg to about 900 mg, about 150 mg to about 600 mg, or about 150 mg to about 300 mg of gemcabene. In some embodiments, the compositions of the invention comprise a compound of the invention in an amount that is a molar equivalent to about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, about 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, or about 900 mg gemcabene or an amount ranging from and to any of these values. In some embodiments, the compositions of the invention comprise a pharmaceutically acceptable salt of gemcabene in an amount that is a molar equivalent to about 50 mg. In some embodiments, the compositions of the invention comprise a compound of the invention in an amount that is a molar equivalent to about 150 mg of

gemcabene. In some embodiments, the compositions of the invention comprise a compound of the invention in an amount that is a molar equivalent to about 300 mg. In some embodiments, the compositions of the invention comprise a compound of the invention in an amount that is a molar equivalent to about 600 mg.

[00507] In other embodiments, the compositions of the invention comprise a compound of the invention in an amount of about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, or any amount ranging from and to these values. In some embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form 1. In some embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form 2. In other embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form C1. In other embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form C2. In other embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form C3. In some embodiments, the compound of the invention is an amorphous gemcabene calcium salt hydrate.

[00508] In other embodiments, the compositions of the invention comprise a compound of the invention in an amount that is a molar equivalent to about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, or about 900 mg gemcabene, or any amount ranging from and to these values. In some embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form 1. In some embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form 2. In other embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form C1. In other embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form C2. In other embodiments, the compound of the invention is gemcabene calcium salt hydrate Crystal Form C3. In some embodiments, the compound of the invention is an amorphous gemcabene calcium salt hydrate.

[00509] In some embodiments, the compositions of the invention are in the form of a tablet or a capsule. In some embodiments, the compositions of the invention comprise a compound of the invention having a PSD90 ranging from 45 μm to about 75 μm and are in the form of a tablet or a capsule. In some embodiments, the compositions of the invention comprise a compound of the invention having a PSD90 ranging from 50 μm to about 75 μm and are in the form of a tablet or a capsule.

[00510] In one aspect, the tablet or the capsule comprises about 50 mg of a compound of the invention having a PSD90 ranging from 40 μm to about 75 μm. In one aspect, the tablet or the capsule comprises about 50 mg of a compound of the invention having a PSD90 ranging from 45 μm to about 75 μm. In one aspect, the tablet or the capsule comprises about 50 mg of a compound of the invention having a PSD90 ranging from 50 μm to about 75 μm.

[00511] In some embodiments, the tablet or the capsule comprises a compound of the invention having a PSD90 ranging from 40 μm to about 75 μm in an amount that is a molar equivalent to about 50 mg of gemcabene. In some embodiments, the tablet or the capsule comprises a compound of the invention having a PSD90 ranging from 45 μm to about 75 μm in an amount that is a molar equivalent to about 50 mg of gemcabene. In some embodiments, the tablet or the capsule comprises a compound of the invention having a PSD90 ranging from 50 μm to about 75 μm in an amount that is a molar equivalent to about 50 mg of gemcabene.

[00512] In one aspect, the tablet or the capsule comprises about 150 mg of a compound of the invention having a PSD90 ranging from 40 μm to about 75 μm. In one aspect, the tablet or the capsule comprises about 150 mg of a compound of the invention having a PSD90 ranging from 45 μm to about 75 μm. In one aspect, the tablet or the capsule comprises about 150 mg of a compound of the invention having a PSD90 ranging from 50 μm to about 75 μm.

[00513] In some embodiments, the tablet or the capsule comprises a compound of the invention having a PSD90 ranging from 40 μm to about 75 μm in an amount that is a molar equivalent to about 150 mg of gemcabene. In some embodiments, the tablet or the capsule comprises a compound of the invention having a PSD90 ranging from 45 μm to about 75 μm in an amount that is a molar equivalent to about 150 mg of gemcabene. In some embodiments, the tablet or the capsule comprises a compound of the invention having a PSD90 ranging from 50 μm to about 75 μm in an amount that is a molar equivalent to about 150 mg of gemcabene.

[00514] In some embodiments, the tablet or the capsule comprises about 300 mg of a compound of the invention having a PSD90 ranging from 40 μm to about 75 μm In some embodiments, the tablet or the capsule comprises about 300 mg of a compound of the invention having a PSD90 ranging from 45 μm to about 75 μm In some embodiments, the tablet or the

capsule comprises about 300 mg of a compound of the invention having a PSD90 ranging from 50 µm to about 75 µm.

[00515] In some embodiments, the tablet or the capsule comprises a compound of the invention having a PSD90 ranging from 40 µm to about 75 µm in an amount that is a molar equivalent to about 300 mg of gemcabene. In some embodiments, the tablet or the capsule comprises a compound of the invention having a PSD90 ranging from 45 µm to about 75 µm in an amount that is a molar equivalent to about 300 mg of gemcabene. In some embodiments, the tablet or the capsule comprises a compound of the invention having a PSD90 ranging from 50 µm to about 75 µm in an amount that is a molar equivalent to about 300 mg of gemcabene.

[00516] In some embodiments, the tablet or the capsule comprises about 600 mg of a compound of the invention having a PSD90 ranging from 40 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises about 600 mg of a compound of the invention having a PSD90 ranging from 45 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises about 600 mg of a compound of the invention having a PSD90 ranging from 50 µm to about 75 µm.

[00517] In some embodiments, the tablet or the capsule comprises a compound of the invention having a PSD90 ranging from 40 µm to about 75 µm in an amount that is a molar equivalent to about 600 mg of gemcabene. In some embodiments, the tablet or the capsule comprises a compound of the invention having a PSD90 ranging from 45 µm to about 75 µm in an amount that is a molar equivalent to about 600 mg of gemcabene. In some embodiments, the tablet or the capsule comprises a compound of the invention having a PSD90 ranging from 50 µm to about 75 µm in an amount that is a molar equivalent to about 600 mg of gemcabene.

[00518] In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 40 µm to about 75 µm and are in the form of a tablet or a capsule. In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 45 µm to about 75 µm and are in the form of a tablet or a capsule. In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 50 µm to about 75 µm and are in the form of a tablet or a capsule.

[00519] In some embodiments, the tablet or the capsule comprises about 150 mg of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 40 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises about 150 mg of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 45 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises about 150 mg of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 50 µm to about 75 µm. In some

embodiments, the tablet or the capsule comprises gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 40 μm to about 75 μm, from 45 μm to about 75 μm, or from 50 μm to about 75 μm, in an amount that is molar equivalent to about 150 mg of gemcabene.

[00520] In some embodiments, the tablet or the capsule comprises about 300 mg of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 40 μm to about 75 μm. In some embodiments, the tablet or the capsule comprises about 300 mg of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 45 μm to about 75 μm. In some embodiments, the tablet or the capsule comprises about 300 mg of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 50 μm to about 75 μm. In some embodiments, the tablet or the capsule comprises gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 40 μm to about 75 μm, from 45 μm to about 75 μm, or from 50 μm to about 75 μm, in an amount that is molar equivalent to about 300 mg of gemcabene.

[00521] In some embodiments, the tablet or the capsule comprises about 600 mg of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 40 μm to about 75 μm. In some embodiments, the tablet or the capsule comprises about 600 mg of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 45 μm to about 75 μm. In some embodiments, the tablet or the capsule comprises about 600 mg of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 50 μm to about 75 μm. In some embodiments, the tablet or the capsule comprises gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 40 μm to about 75 μm, from 45 μm to about 75 μm, or from 50 μm to about 75 μm, in an amount that is molar equivalent to about 600 mg of gemcabene.

[00522] In other embodiments, the tablet or the capsule comprises about 900 mg of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 40 μm to about 75 μm. In other embodiments, the tablet or the capsule comprises about 900 mg of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 45 μm to about 75 μm. In other embodiments, the tablet or the capsule comprises about 900 mg of gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 50 μm to about 75 μm. In some embodiments, the tablet or the capsule comprises gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 ranging from 40 μm to about 75 μm, from 45 μm to about 75 μm, or from 50 μm to about 75 μm, in an amount that is molar equivalent to about 900 mg of gemcabene.

[00523] In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 40 μm to about 75 μm and are in the form of a tablet or a capsule. In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 45 μm to about 75 μm and are in the form of a tablet or a capsule. In some embodiments, the

compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 50 µm to about 75 µm and are in the form of a tablet or a capsule.

[00524] In some embodiments, the tablet or the capsule comprises about 150 mg of gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 40 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises about 150 mg of gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 45 µm to about 75 µm or from 50 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 40 µm to about 75 µm, from 45 µm to about 75 µm, or from 50 µm to about 75 µm, in an amount that is molar equivalent to about 150 mg of gemcabene.

[00525] In some embodiments, the tablet or the capsule comprises about 300 mg of gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 40 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises about 300 mg of gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 45 µm to about 75 µm or from 50 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 40 µm to about 75 µm, from 45 µm to about 75 µm, or from 50 µm to about 75 µm, in an amount that is molar equivalent to about 300 mg of gemcabene.

[00526] In some embodiments, the tablet or the capsule comprises about 600 mg of gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 40 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises about 600 mg of gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 45 µm to about 75 µm or from 50 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 40 µm to about 75 µm, from 45 µm to about 75 µm, or from 50 µm to about 75 µm, in an amount that is molar equivalent to about 600 mg of gemcabene.

[00527] In some embodiments, the tablet or the capsule comprises about 900 mg of gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 40 µm to about 75 µm.

[00528] In some embodiments, the tablet or the capsule comprises about 900 mg of gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 45 µm to about 75 µm or from 50 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises gemcabene calcium salt hydrate Crystal Form 2 having a PSD90 ranging from 40 µm to about 75 µm, from 45 µm to about 75 µm, or from 50 µm to about 75 µm, in an amount that is molar equivalent to about 900 mg of gemcabene.

[00529] In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 40 µm to about 75 µm and are in the form of a tablet or a capsule. In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 45 µm to about 75 µm and are in the form of a tablet or a capsule. In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 50 µm to about 75 µm and are in the form of a tablet or a capsule.

[00530] In some embodiments, the tablet or the capsule comprises about 150 mg of gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 40 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises about 150 mg of gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 45 µm to about 75 µm or from 50 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 40 µm to about 75 µm, from 45 µm to about 75 µm, or from 50 µm to about 75 µm, in an amount that is molar equivalent to about 150 mg of gemcabene.

[00531] In some embodiments, the tablet or the capsule comprises about 300 mg of gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 40 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises about 300 mg of gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 45 µm to about 75 µm or from 50 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 40 µm to about 75 µm, from 45 µm to about 75 µm, or from 50 µm to about 75 µm, in an amount that is molar equivalent to about 300 mg of gemcabene.

[00532] In some embodiments, the tablet or the capsule comprises about 600 mg of gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 40 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises about 600 mg of gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 45 µm to about 75 µm or from 50 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 40 µm to about 75 µm, from 45 µm to about 75 µm, or from 50 µm to about 75 µm, in an amount that is molar equivalent to about 600 mg of gemcabene.

[00533] In some embodiments, the tablet or the capsule comprises about 900 mg of gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 40 µm to about 75 µm. In some embodiments, the tablet or the capsule comprises about 900 mg of gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 45 µm to about 75 µm or

from 50 μm to about 75 μm In some embodiments, the tablet or the capsule comprises gemcabene calcium salt hydrate Crystal Form C3 having a PSD90 ranging from 40 μm to about 75 μm, from 45 μm to about 75 μm, or from 50 μm to about 75 μm, in an amount that is molar equivalent to about 900 mg of gemcabene.

[00534] In some embodiments, the compositions of the invention comprise a compound of the invention in an amount of about 38.5 wt% to about 99.9 wt%, about 79 wt% to about 98 wt%, about 65% to about 98 wt%, or about 50 wt% to about 70 wt% of the total weight of the pharmaceutical composition. In some embodiments, the compositions of the invention comprise a compound of the invention in an amount of about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or about 99.9% by weight of the composition, or an amount ranging from and to any of these values.

[00535] In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form 1 in an amount of about 38.5 wt% to about 99.9 wt%, about 79 wt% to about 98 wt%, about 65% to about 98 wt%, or about 50 wt% to about 70 wt% of the total weight of the pharmaceutical composition. In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form 2 in an amount of about 38.5 wt% to about 99.9 wt%, about 79 wt% to about 98 wt%, about 65% to about 98 wt%, or about 50 wt% to about 70 wt% of the total weight of the pharmaceutical composition. In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form C3 in an amount of about 38.5 wt% to about 99.9 wt%, about 79 wt% to about 98 wt%, about 65% to about 98 wt%, or about 50 wt% to about 70 wt% of the total weight of the pharmaceutical composition. In some embodiments, the compositions of the invention comprise amorphous gemcabene calcium salt hydrate in an amount of about 38.5 wt% to about 99.9 wt%, about 79 wt% to about 98 wt%, about 65% to about 98 wt%, or about 50 wt% to about 70 wt% of the total weight of the pharmaceutical composition.

[00536] In some embodiments, the compositions of the invention further comprise another pharmaceutically active agent. In some embodiments, the compositions of the invention further comprise about 0.1 mg to about 100 mg, about 5 mg to about 80 mg, about 10 mg to about 60 mg

or about 10 mg to about 40 mg of a statin or a pharmaceutically acceptable salt thereof. In other embodiments, the compositions of the invention comprise a statin or a pharmaceutically acceptable salt thereof in an amount of about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, 51 mg, about 52 mg, about 53 mg, about 54 mg, about 55 mg, about 56 mg, about 57 mg, about 58 mg, about 59 mg, about 60 mg, 61 mg, about 62 mg, about 63 mg, about 64 mg, about 65 mg, about 66 mg, about 67 mg, about 68 mg, about 69 mg, about 70 mg, 71 mg, about 72 mg, about 73 mg, about 74 mg, about 75 mg, about 76 mg, about 77 mg, about 78 mg, about 79 mg, about 80 mg, 81 mg, about 82 mg, about 83 mg, about 84 mg, about 85 mg, about 86 mg, about 87 mg, about 88 mg, about 89 mg, about 90 mg, 91 mg, about 92 mg, about 93 mg, about 94 mg, about 95 mg, about 96 mg, about 97 mg, about 98 mg, about 99 mg, about 100 mg, or an amount ranging from and to these values. In some embodiments, the statin is an atorvastatin calcium.

[00537] In some embodiments, a composition of the invention comprising a compound of the invention further comprises a statin or a pharmaceutically acceptable salt thereof in an amount of about 0.001 wt% to about 75 wt%, about 0.005 wt% to about 61.5 wt%, about 2 wt% to about 35 wt%, or about 2 wt% to about 21 wt% of the composition. In some embodiments of the present disclosure, the compositions of the invention comprise a statin or a pharmaceutically acceptable salt thereof in an amount of about 0.001%, about 0.002%, about 0.003%, about 0.004%, about 0.005%, about 0.006%, about 0.007%, about 0.008%, about 0.009%, about 0.01%, about 0.02%, about 0.03%, about 0.04%, about 0.05%, about 0.06%, about 0.07%, about 0.08%, about 0.09%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%,

about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, or about 75%, by weight of the composition, or an amount ranging from and to these values. In some embodiments of the present disclosure, the compositions of the invention comprise a statin or a pharmaceutically acceptable salt thereof in an amount of about 61%, about 61.1%, about 61.2%, about 61.3%, about 61.4%, about 61.5%, about 61.6%, about 61.7%, about 61.8%, about 61.9%, or about 62.0%, by weight of the composition, or an amount ranging from and to these values.

[00538] In some embodiments, the compositions of the invention further comprise about 0.1 mg to about 50 mg, about 1 mg to about 30 mg, about 5 mg to about 20 mg or about 10 mg of ezetimibe or a pharmaceutically acceptable salt thereof. In other embodiments, the compositions of the invention comprise ezetimibe or a pharmaceutically acceptable salt thereof in an amount of about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, or about 50 mg, or an amount ranging from and to these values. In some embodiments, the compositions of the invention further comprise two pharmaceutically active agents. In some embodiments, the compositions of the invention further comprise a) about 0.1 mg to about 50 mg, about 1 mg to about 30 mg, about 5 mg to about 20 mg or about 10 mg of ezetimibe or a pharmaceutically acceptable salt thereof and b) about 0.1 mg to about 100 mg, about 5 mg to about 80 mg, about 10 mg to about 60 mg or about 10 mg to about 40 mg of a statin or a pharmaceutically acceptable salt thereof. In other embodiments, the compositions of the invention comprise a) ezetimibe or a pharmaceutically acceptable salt thereof in an amount of about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, 41 mg, about 42 mg,

about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, or about 50 mg, or an amount ranging from and to these values, and b) a statin or a pharmaceutically acceptable salt thereof in an amount of about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, 51 mg, about 52 mg, about 53 mg, about 54 mg, about 55 mg, about 56 mg, about 57 mg, about 58 mg, about 59 mg, about 60 mg, 61 mg, about 62 mg, about 63 mg, about 64 mg, about 65 mg, about 66 mg, about 67 mg, about 68 mg, about 69 mg, about 70 mg, 71 mg, about 72 mg, about 73 mg, about 74 mg, about 75 mg, about 76 mg, about 77 mg, about 78 mg, about 79 mg, about 80 mg, 81 mg, about 82 mg, about 83 mg, about 84 mg, about 85 mg, about 86 mg, about 87 mg, about 88 mg, about 89 mg, about 90 mg, 91 mg, about 92 mg, about 93 mg, about 94 mg, about 95 mg, about 96 mg, about 97 mg, about 98 mg, about 99 mg, about 100 mg, or an amount ranging from and to these values. In some embodiments, the statin is an atorvastatin calcium.

[00539] In some embodiments, a composition of the invention comprising gemcabene calcium salt hydrate Crystal Form 1, gemcabene calcium salt hydrate Crystal Form 2 or gemcabene calcium salt hydrate Crystal Form C3 further comprises a statin or a pharmaceutically acceptable salt thereof in an amount of about 0.001 wt% to about 75 wt%, about 0.005 wt% to about 61.5 wt%, about 2 wt% to about 35 wt%, or about 2 wt% to about 21 wt% of the composition.

[00540] In some embodiments, the compositions of the invention comprise a compound of the invention in an amount of about 50 mg to about 900 mg and statin or a pharmaceutically acceptable salt thereof in an amount of about 1 mg to about 80 mg. In some embodiments, the compositions of the invention comprise a compound of the invention in an amount of about 150 mg to about 600 mg and statin or a pharmaceutically acceptable salt thereof in an amount of about 10 mg to about 40 mg. In some embodiments, the compositions of the invention a compound of the invention in an amount of about 150 mg to about 300 mg and statin or a pharmaceutically acceptable salt thereof in an amount of about 10 mg to about 40 mg. In some embodiments, the compositions of the invention a compound of the invention in an amount of about 150 mg to about 900 mg and statin or a pharmaceutically acceptable salt thereof in an amount of about 10 mg to about 60 mg.

[00541] In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form 1 in an amount of about 50 mg to about 900 mg and statin or a pharmaceutically acceptable salt thereof in an amount of about 1 mg to about 80 mg. In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form 1 in an amount of about 150 mg to about 600 mg and statin or a pharmaceutically acceptable salt thereof in an amount of about 10 mg to about 40 mg. In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form 1 in an amount of about 150 mg to about 300 mg and statin or a pharmaceutically acceptable salt thereof in an amount of about 10 mg to about 40 mg. In some embodiments, the compositions of the invention comprise gemcabene calcium salt hydrate Crystal Form 1 in an amount of about 150 mg to about 900 mg and statin or a pharmaceutically acceptable salt thereof in an amount of about 10 mg to about 60 mg.

[00542] In some embodiments, the compositions of the invention comprise a compound of the invention in an amount of about 38.5 wt% to about 99.9 wt% and a statin or a pharmaceutically acceptable salt thereof in an amount of about 0.1 wt% to about 61.5 wt% of the composition. In other embodiments, the compositions of the invention comprise a compound of the invention in an amount of about 65 wt% to about 98 wt% and a statin or a pharmaceutically acceptable salt thereof in an amount of about 2 wt% to about 35 wt% of the composition. In some embodiments, the compositions of the invention comprise a compound of the invention in an amount of about 79 wt% to about 98 wt% and a statin or a pharmaceutically acceptable salt thereof in an amount of about 2 wt% to about 21 wt% of the composition. In some embodiments, the pharmaceutically acceptable salt is a calcium salt. In some embodiments, the calcium salt is a calcium salt hydrate. In some embodiments, the calcium salt hydrate is calcium salt hydrate Crystal Form 1.

[00543] In some embodiments, the additional pharmaceutically active agent is present in an amount of about 10 mg to 100 mg or about 5 mg to 50 mg in the compositions of the invention. In some embodiments, the additional pharmaceutically active agent is present in an amount of about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, or any range between any of these values in the compositions of the invention.

[00544] In some embodiments, the compositions of the invention can further comprise an excipient such as a diluent, a disintegrant, a wetting agent, a binder, a glidant, a lubricant, or any combination thereof. In some embodiments, a tablet comprises a binder. And, in some embodiments, the binder comprises microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn starch, polyvinylpyrridone, hydroxypropyl cellulose, hydroxymethyl cellulose, or any combination thereof. In other embodiments, the tablet comprises a disintegrant. In other

embodiments, the disintegrant comprises sodium croscarmellose, sodium starch glycolate, or any combination thereof. In other embodiments, the tablet comprises a lubricant. And, in some embodiments, the lubricant comprises magnesium stearate stearic acid, hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

[00545] In some embodiments, the compositions of the invention are in the form of a tablet that comprises a binder such as any of the binders described herein.

[00546] In some embodiments, the compositions of the invention are in the form of a tablet that comprises a disintegrant such as any of the disintegrants described herein.

[00547] In some embodiments, the compositions of the invention are in the form of a tablet that comprises a lubricant such as any of the lubricants described herein.

[00548] In some embodiments, the compositions of the invention can be in a modified release or a controlled release dosage form. In some embodiments, the compositions of the invention can comprise particles exhibiting a particular release profile. For example, the composition of the invention can comprise a compound of the invention in an immediate release form while also comprising a statin or a pharmaceutically acceptable salt thereof in a modified release form, both compressed into a single tablet. Other combination and modification of release profile can be achieved as understood by one skilled in the art. Examples of modified release dosage forms suited for pharmaceutical compositions of the instant invention are described, without limitation, in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500.

[00549] In some embodiments, the compositions of the invention are a matrix-controlled release dosage form. For example, the compositions of the invention can comprise about 300 mg to about 600 mg of a compound of the invention provided as a matrix-controlled release form. In some embodiments, a matrix-controlled release form can further comprise an additional pharmaceutically active agent. In some embodiments, the release profile of the compound of the invention and of the additional pharmaceutically active agent is the same or different. Suitable matrix-controlled release dosage forms are described, for example, in Takada et al in "Encyclopedia of Controlled Drug Delivery," Vol. 2, Mathiowitz ed., Wiley, 1999.

[00550] In some embodiments, the compositions of the invention comprise from about 10 mg to about 40 mg of the statin and from about 300 mg to about 600 mg of a compound of the invention, wherein the composition is in a matrix-controlled modified release dosage form.

[00551] In some embodiments, the matrix-controlled release form comprises an erodible matrix comprising water-swellable, erodible, or soluble polymers, including synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00552] In some embodiments, the erodible matrix of the matrix-controlled release form comprises chitin, chitosan, dextran, or pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum, or scleroglucan; starches, such as dextrin or maltodextrin; hydrophilic colloids, such as pectin; phosphatides, such as lecithin; alginates; propylene glycol alginate; gelatin; collagen; cellulosics, such as ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), carrrboxymethyl ethyl cellulose (CMEC,) hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), or ethylhydroxy ethylcellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®, Rohm America, Inc., Piscataway, NJ); poly(2-hydroxyethyl-methacrylate); polylactides; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-glycolic acid copolymers; poly-D-(-)-3-hydroxybutyric acid; or other acrylic acid derivatives, such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, or (trimethylaminoethyl)methacrylate chloride; or any combination thereof.

[00553] In other embodiments, the compositions of the invention are in a matrix-controlled modified release form comprising a non-erodible matrix. In some embodiments, the statin, the compound of the invention is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. In some embodiments, the non-erodible matrix of the matrix-controlled release form comprises an insoluble polymer, such as polyethylene, polypropylene, polyisoprene, polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene, polyvinylchloride, a methyl acrylate-methyl methacrylate copolymer, an ethylene-vinylacetate copolymer, an ethylene/propylene copolymer, an ethylene/ethyl acrylate copolymer, a vinylchloride copolymer with vinyl acetate, a vinylidene chloride, an ethylene or a propylene, an ionomer polyethylene terephthalate, a butyl rubber epichlorohydrin rubber, an ethylene/vinyl alcohol copolymer, an ethylene/vinyl acetate/vinyl alcohol terpolymer, an ethylene/vinyloxyethanol copolymer, a polyvinyl chloride, a plasticized nylon, a plasticized polyethyleneterephthalate, a natural rubber,

a silicone rubber, a polydimethylsiloxane, a silicone carbonate copolymer, or a hydrophilic polymer, such as an ethyl cellulose, a cellulose acetate, a crospovidone, or a cross-linked partially hydrolyzed polyvinyl acetate; a fatty compound, such as a carnauba wax, a microcrystalline wax, or a triglyceride; or any combination thereof.

[00554] The compositions of the invention that are in a modified release dosage form can be prepared by methods known to those skilled in the art, including direct compression, dry or wet granulation followed by compression, melt-granulation followed by compression.

[00555] In some embodiments, the compositions of the invention comprise a tablets-in-capsule system, which can be a multifunctional and multiple unit system comprising versatile mini-tablets in a hard gelatin capsule. The mini-tablets can be rapid-release, extended-release, pulsatile, delayed-onset extended-release minitablets, or any combination thereof. In some embodiments, combinations of mini-tablets or combinations of mini-tablets and minibeads comprising multiple active pharmaceutical agents can each have specific lag times, of release multiplied pulsatile drug delivery system (DDS), site-specific DDS, slow-quick DDS, quick/slow DDS and zero-order DDS.

[00556] In some embodiments, the compositions of the invention are in an osmotic-controlled release dosage form.

[00557] In some embodiments, the osmotic-controlled release device comprises a one-chamber system, a two-chamber system, asymmetric membrane technology (AMT), an extruding core system (ECS), or any combination thereof. In some embodiments, such devices comprise at least two components: (a) the core which contains the active pharmaceutical agent(s); and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

[00558] In some embodiments, the core of the osmotic device optionally comprises an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic agents useful in the present invention comprises water-swellable hydrophilic polymers, which are also referred to as "osmopolymers" or "hydrogels," including, but not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), cross-linked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC),

hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00559] Another class of osmotic agents comprises osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-toluenesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00560] Osmotic agents of different dissolution rates can be employed to influence how rapidly the compound of the invention dissolves following administration. For example, an amorphous sugar, such as Mannogeme EZ (SPI Pharma, Lewes, DE) can be included to provide faster delivery during the first couple of hours (e.g., about 1 to about 5 hrs) to promptly produce prophylactic or therapeutic efficacy, and gradually and continually release of the remaining amount to maintain the desired level of therapeutic or prophylactic effect over an extended period of time. In some embodiments, the gemcabene or pharmaceutically acceptable salt thereof is released from the compositions of the invention at such a rate to replace the amount of the compound of the invention metabolized or excreted by the subject.

[00561] The core can also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing.

[00562] Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating, include plasticized, unplasticized, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxlated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP,

HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00563] The semipermeable membranes can also be a hydrophobic microporous membrane, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Pat. No. 5,798,119. Such hydrophobic but water-vapor permeable membrane are typically composed of hydrophobic polymers such as polyalkenes, polyethylene, polypropylene, polytetrafluoroethylene, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00564] The delivery port(s) on the semipermeable membrane can be formed post-coating by mechanical or laser drilling. Delivery port(s) can also be formed in situ by erosion of a plug of water-soluble material or by rupture of a thinner portion of the membrane over an indentation in the core. In addition, delivery ports can be formed during coating process, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220.

[00565] The total amount of the compound of the invention released and the release rate can substantially be modulated via the thickness and porosity of the semipermeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

[00566] In some embodiments, the pharmaceutical composition in an osmotic controlled-release dosage form can further comprise additional conventional excipients as described herein to promote performance or processing of the formulation.

[00567] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; Santus and Baker, *J. Controlled Release* **1995**, *35*, 1-21; Verma et al., *Drug Development and Industrial Pharmacy* **2000**, *26*, 695-708; Verma et al., *J. Controlled Release* **2002**, *79*, 7-27).

[00568] In some embodiments, the pharmaceutical composition provided herein is formulated as asymmetric membrane technology (AMT) controlled-release dosage form that comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipients. *See*, U.S. Pat. No. 5,612,059 and WO 2002/17918. The AMT controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art, including direct compression, dry granulation, wet granulation, and a dip-coating method.

[00569] In some embodiments, the pharmaceutical composition provided herein is formulated as ESC controlled-release dosage form that comprises an osmotic membrane that coats a core comprising the compound of the invention, hydroxylethyl cellulose, and other pharmaceutically acceptable excipients.

[00570] In some embodiments, the compositions of the invention are a modified release dosage form that is fabricated as a multiparticulate-controlled release dosage form that comprises a plurality of particles, granules, or pellets, microparticulates, beads, microcapsules and microtablets, ranging from about 10 μm to about 3 mm, about 50 μm to about 2.5 mm, or from about 100 μm to 1 mm in diameter.

[00571] The multiparticulate-controlled release dosage forms can provide a prolonged release dosage form with an improved bioavailability. Suitable carriers to sustain the release rate of the compound of the invention include, without limitation, ethyl cellulose, HPMC, HPMC-phtalate, colloidal silicondioxide and Eudragit-RSPM.

[00572] Pellets suitable to be used in the compositions and therapeutic or prophylactic methods of the invention comprise 50-80% (w/w) of a drug and 20-50% (w/w) of microcrystalline cellulose or other polymers. Suitable polymers include, but are not limited to, microcrystalline wax, pregelatinized starch and maltose dextrin.

[00573] Beads can be prepared in capsule and tablet dosage forms. Beads in tablet dosage form can demonstrate a slower dissolution profile than microparticles in capsule form. Microparticle fillers suitable for compositions and therapeutic or prophylactic methods of the invention include, without limitation, sorbitan monooleate (Span 80), HPMC, or any combination thereof. Suitable dispersions for controlled release latex include, for example, ethyl-acrylate and methyl-acrylate.

[00574] In some embodiments, the compositions of the invention are in the form or microcapsules and/or microtablets. In some embodiments, microcapsules comprise extended release polymer microcapsules containing a statin and a compound of the invention with various solubility characteristics. Extended release polymer microcapsules can be prepared with colloidal polymer dispersion in an aqueous environment. In other embodiments, microcapsules suitable for the compositions and methods provided herein can be prepared using conventional microencapsulating techniques (Bodmeier & Wang, 1993).

[00575] Such multiparticulates can be made by the processes known to those skilled in the art, including wet-and dry-granulation, extrusion/spheronization, roller-compaction, melt-congealing, and by spray-coating seed cores. *See,* for example, *Multiparticulate Oral Drug Delivery*; Marcel Dekker: 1994; and *Pharmaceutical Pelletization Technology*; Marcel Dekker: 1989. Excipients for such technologies are commercially available and described in US Pharmacopeia, and

gemcabene salts are prepared as described in U.S. Patent No. 6,861,555 or in International Application Publication WO 2016/077832 as, for example, gemcabene calcium salt single polymorph.

[00576] Other excipients as described herein can be blended with the compositions of the invention to aid in processing and forming the multiparticulates. The resulting particles can themselves constitute the multiparticulate dosage form or can be coated by various film-forming materials, such as enteric polymers, water-swellable, or water-soluble polymers. The multiparticulates can be further processed as a capsule or a tablet.

[00577] In other embodiments, the compositions of the invention are in a dosage form that has an instant releasing component and at least one delayed releasing component, and is capable of giving a discontinuous release of the compound in the form of at least two consecutive pulses separated in time from 0.1 hrs to 24 hrs.

[00578] The invention further provides a kit comprising a composition of the invention and instructions for its use. The kit can further comprise a composition comprising an additional pharmaceutically active agent. In some embodiments the kit comprises a composition of the invention comprising from about 50 mg to about 900 mg of a compound of the invention and another composition comprising from about 0.1 mg to about 80 mg of a statin; and instructions for the use thereof. In some embodiments the kit comprises a composition of the invention comprising from about 50 mg to about 900 mg of a compound of the invention and another composition comprising from about 10 mg to about 80 mg of a statin; and instructions for the use thereof. In some embodiments, the kit comprises a composition of the invention comprising from about 150 mg to about 600 mg of a compound of the invention and from about 10 mg to about 40 mg of a statin; and instructions for the use thereof.

[00579] In some embodiments the kit comprises a composition of the invention comprising from about 50 mg to about 900 mg of a compound of the invention and another composition comprising from about 5 mg to about 80 mg of an atorvastatin or a pharmaceutically acceptable salt thereof; and instructions for the use thereof. In some embodiments the kit comprises a composition of the invention comprising from about 50 mg to about 900 mg of a compound of the invention and another composition comprising from about 10 mg to about 80 mg of an atorvastatin or a pharmaceutically acceptable salt thereof; and instructions for the use thereof. In some embodiments, the kit comprises a composition of the invention comprising from about 150 mg to about 600 mg of a compound of the invention and from about 10 mg to about 40 mg of an atorvastatin or a pharmaceutically acceptable salt thereof; and instructions for the use thereof.

[00580] In some embodiments, the kit comprises a composition of the invention comprising from about 50 mg to about 900 mg of a compound of the invention and another composition

comprising from about 5 mg to about 20 mg of ezetimibe or a pharmaceutically acceptable salt thereof; and instructions for the use thereof. In some embodiments, the kit comprises a composition of the invention comprising from about 50 mg to about 900 mg of a compound of the invention and another composition comprising from about 10 mg of ezetimibe or a pharmaceutically acceptable salt thereof; and instructions for the use thereof. In some embodiments, the kit comprises a composition of the invention comprising from about 150 mg to about 600 mg of a compound of the invention and another composition comprising from about 10 mg of ezetimibe or a pharmaceutically acceptable salt thereof; and instructions for the use thereof.

[00581] In some embodiments the kit comprises a) a composition of the invention comprising from about 50 mg to about 900 mg of a compound of the invention, b) a composition comprising from about 5 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof, c) a composition comprising from about 5 mg to about 20 mg of ezetimibe or a pharmaceutically acceptable salt thereof, and d) instructions for the use thereof. In some embodiments the kit comprises a) a composition of the invention comprising from about 50 mg to about 900 mg of a compound of the invention, b) a composition comprising from about 10 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof, c) a composition comprising about 10 mg of ezetimibe or a pharmaceutically acceptable salt thereof, and d) instructions for the use thereof. In some embodiments the kit comprises a) a composition of the invention comprising from about 150 mg to about 600 mg of a compound of the invention, b) a composition comprising from about 10 mg to about 40 mg of a statin or a pharmaceutically acceptable salt thereof, c) a composition comprising about 10 mg of ezetimibe or a pharmaceutically acceptable salt thereof, and d) instructions for the use thereof.

[00582] In some embodiments the kit comprises a) a composition of the invention comprising from about 50 mg to about 900 mg of a compound of the invention, b) a composition comprising from about 5 mg to about 80 mg of an atorvastatin or a pharmaceutically acceptable salt thereof, c) a composition comprising from about 5 mg to about 20 mg of ezetimibe or a pharmaceutically acceptable salt thereof, and d) instructions for the use thereof. In some embodiments the kit comprises a) a composition of the invention comprising from about 50 mg to about 900 mg of a compound of the invention, b) a composition comprising from about 10 mg to about 80 mg of an atorvastatin or a pharmaceutically acceptable salt thereof, c) a composition comprising about 10 mg of ezetimibe or a pharmaceutically acceptable salt thereof, and d) instructions for the use thereof. In some embodiments the kit comprises a) a composition of the invention comprising from about 150 mg to about 600 mg of a compound of the invention, b) a composition comprising from about 10 mg to about 40 mg of an atorvastatin or a pharmaceutically acceptable

salt thereof, c) a composition comprising about 10 mg of ezetimibe or a pharmaceutically acceptable salt thereof, and d) instructions for the use thereof.

[00583] In some embodiments, the composition of the invention and the other composition are contained in separate containers. In some embodiments, the composition of the invention and the other composition are contained in the same container.

[00584] In some embodiments, the container is a bottle, vial, blister pack, or any combination thereof. In some embodiments, the container is a bottle, vial, blister pack, or any combination thereof with a closure (e.g., a cap, a top, or a sealed package to provide the composition of the invention in a closed system).

[00585] In some embodiments, the statin is atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin, mevastatin, dalvastatin, dihydrocompactin, or cerivastatin, or any pharmaceutically acceptable salt thereof. In some embodiments, the statin is atorvastatin or a pharmaceutically acceptable salt thereof.

[00586] In some embodiments, the composition of the invention or the other composition is in the form of a tablet.

[00587] In some embodiments, the tablet comprises one or more excipients selected from a diluent, a disintegrant, a wetting agent, a binder, a glidant, a lubricant, or any combination thereof.

[00588] In some embodiments, the compositions of the invention are administered to a subject in need thereof. In some embodiments, the composition of the invention is in a unit dose form. In some embodiments as used herein, "unit dose" or "unit-dose" refers to a specific formulation containing a specific amount of a compound of the invention. In a non-limiting example, a unit dose of can be a tablet comprising about 300 mg of a compound of the invention. In some embodiments, a unit dose comprises about 50 mg, about 150 mg, about 300 mg, or about 600 mg of a compound of the invention. In another embodiment, a unit dose comprises a compound of the invention in an amount that is molar equivalent to about 150 mg, about 300 mg, or about 600 mg gemcabene.

[00589] In some embodiments, the compositions of the invention are administered to a subject in need thereof, once, twice, three times, or four times a day. In some embodiments, the compositions of the invention are administered to a subject in need thereof in ways that allows a daily dose of about 600 mg to about 900 mg of a compound of the invention. In some embodiments, the compositions of the invention are administered to a subject in need thereof in ways that allows a daily dose in an amount that is molar equivalent to about 600 mg to about 900 mg of gemcabene. In some embodiments, the daily dose is about 600 mg of a compound of the

invention. In another embodiment, the daily dose is an amount that is molar equivalent to 600 mg of gemcabene.

[00590] In some embodiments, the compositions of the invention comprise about 300 mg of a compound of the invention and are administered to a subject in need thereof once a day. In some embodiments, the compositions of the invention comprise about 300 mg of a compound of the invention and are administered to a subject in need thereof twice a day. In some embodiments, the compositions of the invention comprise about 300 mg of a compound of the invention and are administered to a subject in need thereof three times a day.

[00591] In some embodiments, the compositions of the invention comprise a compound of the invention in an amount that is molar equivalent to about 300 mg of gemcabene and are administered to a subject in need thereof once a day. In some embodiments, the compositions of the invention comprise a compound of the invention in an amount that is molar equivalent to about 300 mg of gemcabene and are administered to a subject in need thereof twice a day. In some embodiments, the compositions of the invention comprise a compound of the invention in an amount that is molar equivalent to about 300 mg of gemcabene and are administered to a subject in need thereof three times a day.

[00592] In some embodiments, the compositions of the invention comprise about 600 mg of a compound of the invention and are administered to a subject in need thereof once a day. In some embodiments, the compositions of the invention comprise a compound of the invention in an amount that is molar equivalent to about 600 mg of gemcabene and are administered to a subject in need thereof once a day.

[00593] In some embodiments, the compositions of the invention comprise about 150 mg of a compound of the invention and are administered to a subject in need thereof once a day. In some embodiments, the compositions of the invention comprise about 150 mg of a compound of the invention and are administered to a subject in need thereof twice a day. In some embodiments, the compositions of the invention comprise about 150 mg of a compound of the invention and are administered to a subject in need thereof three times a day. In some embodiments, the compositions of the invention comprise about 150 mg of a compound of the invention and are administered to a subject in need thereof four times a day.

[00594] In some embodiments, two separate unit doses, each comprising about 150 mg of a compound of the invention, are administered to a subject in need thereof once a day. In some embodiments, two separate unit doses, each comprising about 150 mg of a compound of the invention, are administered to a subject in need thereof twice a day (total 600 mg/day). In some embodiments, two separate unit doses, each comprising about 150 mg of a compound of the invention, are administered to a subject in need thereof three times a day (total 900 mg/day).

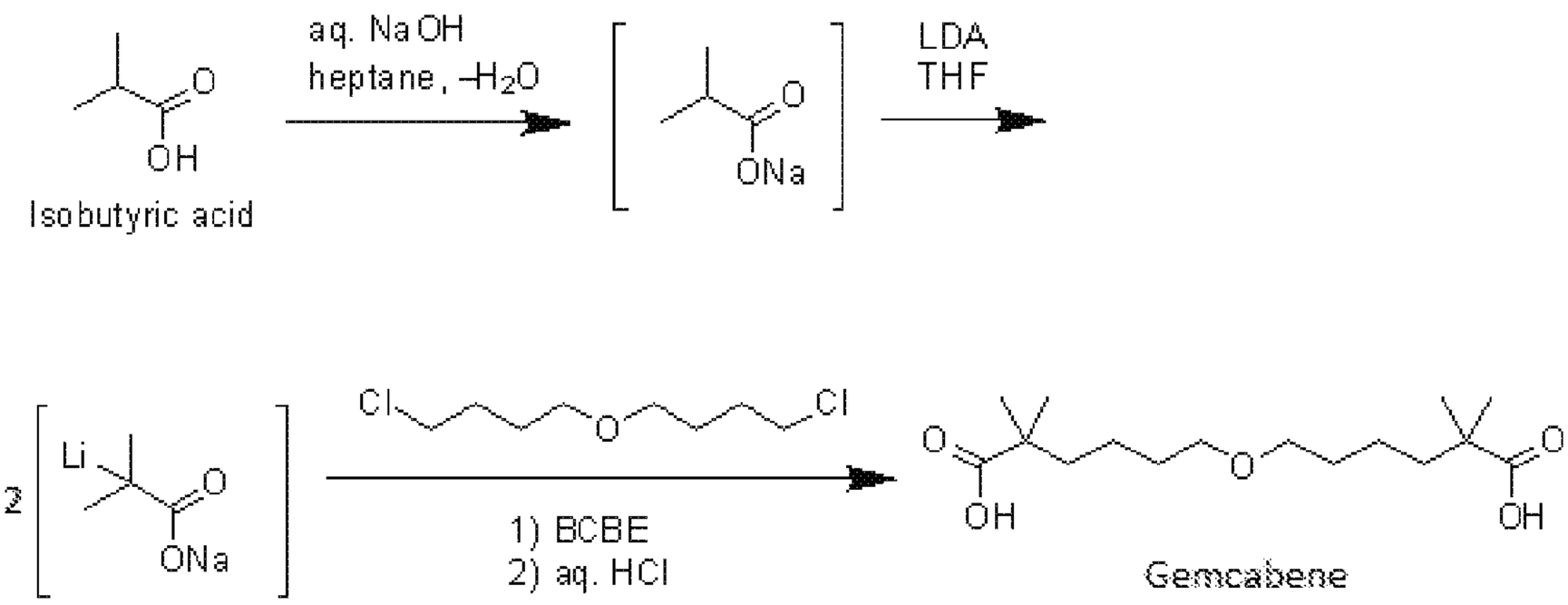
[00595] In some embodiments, the compositions of the invention comprising a compound of the invention in an amount that is molar equivalent to about 150 mg of gemcabene is administered to a subject in need thereof once a day. In some embodiments, the compositions of the invention comprising a compound of the invention in an amount that is molar equivalent to about 150 mg of gemcabene is administered to a subject in need thereof twice a day. In some embodiments, the compositions of the invention comprising a compound of the invention in an amount that is molar equivalent to about 150 mg of gemcabene is administered to a subject in need thereof three times a day. In some embodiments, the compositions of the invention comprising a compound of the invention in an amount that is molar equivalent to about 150 mg of gemcabene is administered to a subject in need thereof four times a day.

[00596] In some embodiments, two separate unit doses, each comprising a compound of the invention in an amount that is molar equivalent to about 150 mg of gemcabene, are administered to a subject in need thereof once a day. In some embodiments, two separate unit doses, each comprising a compound of the invention in an amount that is molar equivalent to about 150 mg of gemcabene, are administered to a subject in need thereof twice a day (total 600 mg/day = two separate unit doses (150 mg x 2) x 2 (twice a day)). In some embodiments, two separate unit doses, each comprising a compound of the invention in an amount that is molar equivalent to about 150 mg of gemcabene, are administered to a subject in need thereof three times a day (total 900 mg/day).

EXAMPLES

[00597] **Example 1: Chemical Synthesis of Gemcabene Calcium Salt Hydrate Crystal Form 1**

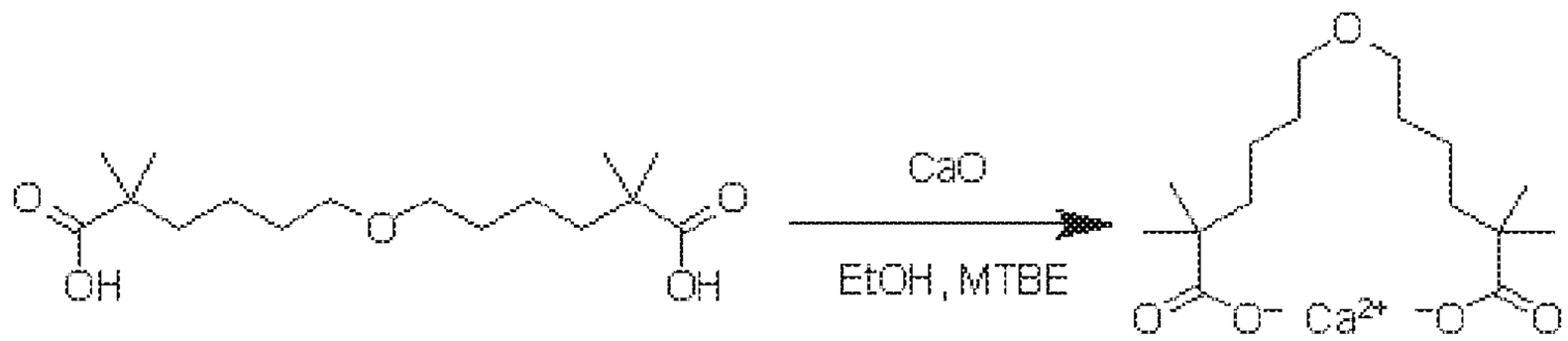
[00598] Scheme 2: Synthesis of 6-(5-carboxy-5-methyl-hexyloxy)-2,2-dimethylhexanoic acid (Gemcabene)



[00599] Step 1. 6-(5-carboxy-5-methyl-hexyloxy)-2,2-dimethylhexanoic acid (Gemcabene): In a reactor (ST-1005, glass-lined, 1600 l), isobutyric acid (41.0 kg, 466 mol, 2.2 equiv) and heptane (276 kg) were combined and a molar equivalent of 30% sodium hydroxide was charged (62.1 kg), followed by water (1.1 kg) and heptane (126 kg) under stirring. The mixture was refluxed with water removal until the rate of water removal effectively stopped. Then, a Karl-Fisher analysis of the water content was performed to confirm removal of water (water content measured 0.012%). Tetrahydrofuran (THF) (279 kg) was added followed by a lithium diisopropylamide solution (lithium diisopropylamide 28% w/w in heptane/THF/ethylbenzene, 174.6 kg, 2.2 equiv) at 10 °C – 15 °C. After flushing with THF (33.8 kg) the mixture was heated at 42 °C ± 2 °C for about 1 hour. Bis-(4-chlorobutyl)ether (42.0 kg, 211 mol, 1.0 equiv, BCBE) diluted with THF (11.6 kg) was added at 40 °C – 45 °C in four hours. After flushing with THF (11.4 kg) the mixture was heated at 42 °C ± 2 °C for 14 – 24 hours. Water (159 kg) was added and the resultant precipitate was dissolved at 52 °C ± 2 °C. The aqueous layer was then separated. Additional water was added (159 kg) to the upper organic layer at 50 °C ± 2 °C and the layers were separated. The aqueous layer was combined with the first aqueous layer and the organic layer was discarded. The aqueous layer was combined with heptane (177 kg) and an excess of concentrated hydrochloric acid was added (299 kg) at 25 °C – 50 °C. The product-containing organic layer was separated, and the aqueous layer was extracted with heptane (106 kg) at 50 °C ± 2 °C. The aqueous layer was then discarded. The combined product-containing heptane layer was washed twice with water (64 kg) at 50 °C ± 2 °C and the aqueous layers were discarded. The heptane layer was evaporated to dryness at ≤ 60 °C. The resultant residue was mixed twice with water (320 kg each wash) and evaporated to dryness at ≤ 60 °C. The remaining material was dissolved in heptane (286 kg) at 22 °C ± 2 °C and washed with water (193 kg) and the aqueous layer was discarded. The heptane layer was evaporated to dryness at ≤ 60 °C and co-evaporated three-times with heptane (each 109 kg). Karl-Fisher analysis indicated water content was 0.04%. The resultant residue was dissolved in heptane (130 kg) and THF (1.4 kg) at 22 °C ± 2 °C, filtered through silica gel (64.0 kg) and the silica gel was washed first with heptane (246 kg)/THF (16.0 kg) mixture and then only with heptane (492 kg). The collected filtrate was concentrated to a volume of about 150 L at ≤ 60 °C. The solution was transferred to a smaller vessel (ST-164, glass-lined, 160 l) with heptane (44 kg), followed by evaporation to dryness at ≤ 60 °C. ^{1}H NMR analysis of the crude indicated 96.7% purity. The crude gemcabene was dissolved in heptane (55.0 kg) at 40 °C ± 5 °C and the heptane solution was cooled to 15 °C ± 2 °C. After seeding with gemcabene crystals (30 g), the solution was cooled to 12 °C. After crystallization for 18 hours, the product was isolated on a filter drier (FT-1001, stainless steel, 1000 l), washed in three portions with cold heptane (3 x 9.6 kg) and dried in

vacuum at 35 °C ± 2 °C for 15 hours, to give 50.7 kg (167 mol). The resulting yield was about 79%. The purified gemcabene contained 0.4% 2,2,7,7-Tetramethyl-octane-1,8-dioic acid.

[00600] Scheme 3. Synthesis of 6-(5-carboxy-5-methyl-hexyloxy)-2,2-dimethylhexanoic acid calcium (gemcabene calcium salt) hydrate Crystal Form 1



[00601] Step 2. 6-(5-Carboxy-5-methyl-hexyloxy)-2.2-dimethylhexanoic acid calcium (gemcabene calcium salt) hydrate Crystal Form 1: Gemcabene (50.5 kg; 167 mol, 1.00 equiv, from Step 1) was dissolved in ethanol (347 kg, denatured with 1% cyclohexane) and filtered through a 1.2 µm filter in the reaction vessel (ST-1005, glass-lined, 1600 l). The equipment was flushed with additional ethanol (38 kg). Calcium oxide (9.35 kg, 167 mol, 1.00 equiv) was added at 22 °C under stirring, and the mixture is heated at reflux for 20 - 25 hours. The resulting mixture was cooled to 52 °C ± 2 °C and *tert*-butyl methyl ether (125 kg, filtered through a 1.2 µm filter) was charged. After cooling to 22 °C ± 2 °C, the mixture was stirred for an additional hour. The crystalline ethyl alcohol solvate was isolated by filtration in an agitated filter dryer (FT-1001, stainless steel, 1000 l) and washed with *tert*-butyl methyl ether in three portions (3 x 37 kg, filtered through a 1.2 µm filter). The crystalline ethyl alcohol solvate was dried with interval agitation (3 minutes stirring, 15 minutes not stirring) at a jacket temperature of 30 °C for 66 minutes, 50 °C for 30 minutes, 70 °C for 30 minutes, and 90 °C for at least 12 hours in vacuum with a stream of 20L/h nitrogen. Vacuum was broken with nitrogen and purified water (6.29 kg, 349 mol, 2.09 equiv) was added with agitation and stirring was continued at atmospheric pressure at 90 °C for 6 hours. Vacuum was re-established, and the crystalline hydrate was dried at 90 °C for at least 16 hours to yield gemcabene calcium salt hydrate Crystal Form 1 (53.2 kg, 157 moles). The resulting amount was about 94% yield and this sample is referred to as "neat" or a sample "obtained as neat" (pre-milling).

[00602] Step 3. Milling of 6-(5-Carboxy-5-methyl-hexyloxy)-2.2-dimethylhexanoic acid calcium (gemcabene calcium salt) hydrate Crystal Form 1: The gemcabene calcium salt hydrate Crystal Form 1 obtained in Step 2 (53.2 kg, 157 mol) was milled using a pinmill (MP160) with a dedicated rotor and stator equipped with 4 pin rows (n. 699), under nitrogen flow. An amount of 49.3 kg of gemcabene calcium Crystal Form 1 with a PSD90 ranging from 40 µm to 75 µm was obtained in 93% yield.

[00603] **Methods**

[00604] Unless otherwise noted, following methods were used to determine purities and impurities of gemcabene and pharmaceutically acceptable salt of gemcabene.

[00605] **High-performance liquid chromatography (HPLC) - Impurities**

[00606] Operating Parameters:

Instrument Type:	Agilent 1200 Series or ThermoScientific Ultimate 3000 UHPLC (QC-HPLC-26), or equivalent
Column:	Ace Excel 3 C4, 150 mm x 2.1 mm, 3 µm (CPS 164/x), or suitable equivalent
Flow Rate:	0.4 mL/min
Run Time:	60 minutes
Mobile Phase A:	Water + 0.1% v/v formic acid
Mobile Phase B:	Acetonitrile + 0.1% v/v formic acid
Column Temperature:	40 °C
Injection Volume:	5 µL (for sample and blank)
Detection:	UV at 205 nm Charged aerosol detector (CAD) (nebulizer: 30°C, gain range: 200 pA, filter: 4 or corona)
Acquisition Time	43 min
Sample Concentration	10 mg/mL
Sample Solvent, Blank, Flush solution	Acetonitrile / Water / Formic acid 430:570:1 v/v/v

[00607] *Gradient*:

Time (min)	**Mobile Phase A (%)**	**Mobile Phase B (%)**
0.0	90	10
1.0	90	10
30.0	5	95
35.0	5	95
35.1	90	10
43.0	90	10

[00608] *Sample Solution (10 mg/mL)*: 100 mg (± 5 mg) sample was added to a 10 mL-flask and Sample Solvent was added to the mark.

[00609] *Reference Mix Stock Solutions (0.5 mg/mL for gemcabene and 0.25 mg/L for other substances)*: 10 mg (± 1 mg) gemcabene + 5 mg (± 1 mg) 2,2,7,7-tetramethyl-octane-1,8-dioic acid + 5 mg (± 1 mg) 6-(4-hydroxybutoxy)-2,2-dimethylhexanoic acid + 5 mg (± 1 mg) 2,2-dimethyl-hex-4-enoic acid (E/Z ratio approximately 5:1) were added in a 20 mL-flask and the Sample Solvent was added to the mark (Reference Mix Stock). 2.0 mL of Reference Mix Stock was added to a 20 mL-flask and the Sample Solvent was added to the mark (Diluted Reference Stock).

[00610] Illustrative Injection Sequence

Injection No.	**Injection Volume**	**Sample**	**Detection Method Relied On for References**
1	5.0 µL	Blank	

Injection No.	Injection Volume	Sample	Detection Method Relied On for References
2	5.0 µL	Blank	
3	0.5 µL	Diluted Reference Stock	CAD
4	1.0 µL	Diluted Reference Stock	CAD
5	2.0 µL	Diluted Reference Stock	CAD + UV
6	5.0 µL	Diluted Reference Stock	CAD + UV
7	1.0 µL	Reference Mix Stock	CAD + UV
8	2.0 µL	Reference Mix Stock	UV
9	5.0 µL	Reference Mix Stock	UV
10	10.0 µL	Reference Mix Stock	UV
11	5.0 µL	Blank	
12	5.0 µL	Sample 1	
13	5.0 µL	Sample 1 repeat	
14	5.0 µL	Blank	
15	5.0 µL	Sample 2	
16	5.0 µL	Sample 2 repeat	
17	5.0 µL	Blank	

[00611] *System Suitability Test Criteria*:

- No interfering peaks in the Blank
- Calibration criteria: $R^2 \geq 0.98$

[00612] *Evaluation*:

[00613] UV: Reporting threshold: 0.05% w/w

- Impurity content of (*E*)-2,2-dimethyl-hex-4-enoic acid was evaluated against calibration of reference material.
- Impurity content of (*Z*)-2,2-dimethyl-hex-4-enoic acid was evaluated against calibration of reference material.
- All known impurities not detected with CAD are calibrated with the standard 2,2-dimethyl-hex-4-enoic acid (E/Z mixture).

[00614] CAD: Reporting threshold: 0.05% w/w

- Impurity content of 6-(4-hydroxybutoxy)-2,2-dimethylhexanoic acid was evaluated against calibration of reference material.
- Impurity content of 2,2,7,7-tetramethyl-octane-1,8-dioic acid was evaluated against calibration of reference material.
- Any unknown impurities were evaluated against calibration of 2,2,7,7-tetramethyl-octane-1,8-dioic acid.

[00615] Total HPLC impurities (% w/w) = Sum of impurities by UV and sum of impurities by CAD.

[00616] High-performance liquid chromatography (HPLC) – gemcabene calcium purity and conjugate base of gemcabene component analysis

[00617] Operating Parameters:

Instrument Type:	Agilent 1200 Series or ThermoScientific Ultimate 3000 UHPLC (QC-HPLC-26), or equivalent
Column:	Ace Excel 3 C4, 150 mm x 2.1 mm, 3 µm (CPS 164/x), or suitable equivalent
Flow Rate:	0.4 mL/min
Run Time:	60 minutes
Mobile Phase A:	Water + 0.1% v/v formic acid
Mobile Phase B:	Acetonitrile + 0.1% v/v formic acid
Column Temperature:	40 °C
Injection Volume:	2.0 µL (for sample and blank)
Detection:	UV at 210 nm
Acquisition Time	43 min
Sample Concentration	10 mg/mL
Sample Solvent, Blank, Rinsing solution	Acetonitrile / Water / Formic acid 430:570:1 v/v/v

[00618] *Gradient*:

Time (min)	Mobile Phase A (%)	Mobile Phase B (%)
0.0	90	10
1.0	90	10
30.0	5	95
35.0	5	95
35.1	90	10
43.0	90	10

[00619] *Sample Solution (10 mg/mL)*: 100 mg (± 5 mg) sample was added to a 10 mL-flask and Sample Solvent was added to the mark.

[00620] *Reference Gemcabene Solutions (10 mg/mL)*: 100 mg (± 5 mg) gemcabene was added in a 10 mL-flask and the Sample Solvent was added to the mark (Reference).

[00621] Illustrative Injection Sequence

Injection No.	Injection Volume	Sample
1	2.0 µL	Blank
2	2.0 µL	Blank
3	2.0 µL	Reference 1
4	2.0 µL	Reference 2
5	2.0 µL	Reference 3
6	2.0 µL	Reference 4
7	2.0 µL	Reference 5
8	2.0 µL	Reference 6
9	2.0 µL	Reference Drift Check
10	2.0 µL	Blank
11	2.0 µL	Sample 1
12	2.0 µL	Sample 1 repeat
13	2.0 µL	Blank

Injection No.	Injection Volume	Sample
14	2.0 µL	Sample 2
15	2.0 µL	Sample 2 repeat
16	2.0 µL	Blank
17	2.0 µL	Reference Drift Check
18	2.0 µL	Blank

[00622] *System Suitability Test Criteria*:

- No interfering peaks in the Blank
- Relative Standard Deviation (6 Reference injections) ≤ 2.0%
- Recovery (of each Reference injection) 98.0-102.0% w/w

[00623] *Evaluation*:

[00624] UV: Gemcabene purity evaluated against calibration of Reference material.

[00625] **Ion chromatography (IC)**

[00626] Operating Parameters:

Instrument Type:	Dionex ICS-5000+ SP, ICS-5000+ EG, Dionex ICS-5000+DC, Autosampler AS, or equivalent
IC Column:	Dionex ion pac AS11-HC (147/xx) or equivalent
Flow Rate:	0.4 mL/min
Run Time:	60 minutes
Mobile Phase	Water (IC quality) Eluent Generator KOH (e.g., Dionex EGC III KOH Eluent Generator Cartridge – Product no. 074532)
Suppressor set	112mA
Cell Temperature:	35 °C
Injection Volume:	10 µL
Oven temperature	30 °C
Flow rate	1.5 mL/min
Sample Concentration	5 mg/mL
Blank for Sample Solvent and Standard solutions	Standard solutions: Water (IC quality) Sample solutions: Water/acetonitrile (IC quality) 1:1 + 0.05% trifluoroacetic acid (HPLC grade)

[00627] *Gradient*:

Time (min)	KOH Gradient (mM)	Flow Rate (mL/min)
0.0	1	1.5
5.0	1	1.5
14.0	15	1.5
23.0	30	1.5
23.1	1	1.5
30.0	1	1.5

[00628] *Sample Solution (5 mg/mL)*: 25 mg (± 1.0 mg) sample was added to a 5 mL-flask and dissolved with water/acetonitrile 1:1 + 0.05% trifluoroacetic acid and filled to the mark. The flask was placed in an ultrasound bath for 10 min and then left to cool for approx. 1 hr. Then the solution was observed to make sure it was clear and had no particles (no deposit). If there were particles, sample was filtered into a vial via the syringe filter (e.g. filter 0.45 um – for organic PTFE solutions) (discarded 2-3 ml filtrate in advance to saturate the filter). If no particles were present, the sample can be analyzed without filtration.

[00629] *Standard Stock Solutions (1000 µg/mL)*: 50 µL isobutyric acid was added to a 50 mL-flask and water was added to the mark (Reference Stock).

[00630] *Standard Stock Solutions (100 µg/mL)*: 1.0 mL of Reference Stock was diluted to 10 mL with water. Other standard solutions were prepared as shown below.

Concentration of Standard Solution (µg/mL)	**Volume of 100 µg/mL Stock Solution**	**Volume of water added**
25	250 µL	750 µL
15	150 µL	850 µL
10	100 µL	900 µL
5	50 µL	950 µL
2.5	100 µL of 25 µL Stock Solution	900 µL

[00631] Illustrative Injection Sequence

Injection No.	**Sample**
1	Blank – water (3 injections)
2	Standard 2.5 µg/mL
3	Standard 5.0 µg/mL
4	Standard 10.0 µg/mL
5	Standard 15.0 µg/mL
6	Standard 25.0 µg/mL
7	Standard 2.5 µg/mL
8	Blank - water
9	Blank – water/acetonitrile 1:1 + 0.05% trifluoroacetic acid
10	Sample 1
11	Sample 2
12	Blank – water (3 injections)
13	Check Standard 25.0 µg/mL
14	Blank – water (2 injections)

[00632] *System Suitability Test Criteria*:

- $R^2 \geq 0.99$
- % Drift agreement: 97%-103%

- Bottom count Standard 25.0 µg/mL ≥ 2500
- Asymmetry (Target) Standard 25.0 µg/mL ≤ 2.0
- S/N (signal-to-noise ratio) Standard 25.0 µg/mL ≥ 10

[00633] *Evaluation*: Limit of quantification was 2.50 µg/mL which corresponds to 0.05% w/w.

[00634] **Gas chromatography (GC) – bis-(4-chlorobutyl)ether and residual solvents**

[00635] Operating Parameters:

Instrument Type:	Agilent 68900N or equivalent
Detector:	FID (flame ionization detector)
Data System:	Dionex-Chromeleon
Flow Split:	16 mL/min
Split Ratio:	1:10
Column:	Capillary, fused silica, 30 m x 0.25 mm x 0.5 µm
Stationary Phase:	RTX-5 Amine
Carrier Gas (Flow)	He 4.6 (0.6 mL/min; constant flow)
Pressure	117 Kpa
Make-up Gas (Flow)	N_2 (35 mL/min)
Synthetic Air	450 mL/min
Hydrogen Gas	35 mL/min
Injector Temp. /Detector Temp.	220 °C/220 °C
Injection volume	100 µL

[00636] *Temperature Program*:

Temp (°C)	Time (min)	Rate (°C/min)
45	9	20
205	3.1	--

[00637] *Stock bis-(4-chlorobutyl)ether*: Exactly 125 mg (5 ppm*) of bis-(4-chlorobutyl)ether was added to a 20 mL volumetric flask containing 10 ml of *N*-methyl-2-pyrrolidone (NMP). The volumetric flask was filled to the mark with NMP. *The value in ppm refers to 100 µl of stock uplift and 125 mg nominal weight.

[00638] *Stock Solution*: 125 mg (1000ppm*) *n*-hexane, 250 mg (2000ppm*) THF, 125 mg (1000ppm*) diisopropylamine, 250 mg (2000ppm*) ethylbenzene and 125 mg (1000ppm*) of cyclohexane were accurately measured into a 20 mL volumetric flask containing approximately 10 mL of NMP. The volumetric flask was filled to the mark with NMP and solution was mixed until it became homogeneous. *The value in ppm refers to 100 µl of stock uplift and 125 mg nominal weight.

[00639] *Spiking Solution*: Exactly 250 mg (10000 ppm*) of each of n-heptane, t-butyl methyl ether, and ethanol were weighed into a 20 mL volumetric flask containing approximately 10 mL

NMP. 20 µL of Stock bis-(4-chlorobutyl)ether and 4 mL of Stock Solution was added to the volumetric flask. Then, the volumetric flask was filled to the mark with NMP and solution was mixed until it became homogeneous. *The value in ppm refers to 100 µl of stock uplift and 125 mg nominal weight.

[00640] *Sample Preparation*: Approximately 110-140 mg of finely powdered gemcabene calcium was weighed into a GCHS vial and exact mass was recorded. 3 mL of water was added with a pipette and 100 µL NMP was added with a microliter syringe and the vial was closed immediately. The sample solution was mixed via ultrasonication for approximately 5 min.

[00641] *Spiked Sample Preparation*: Approximately 110-140 mg of finely powdered gemcabene calcium was weighed into a GCHS vial and exact mass was recorded. 3 mL of water was added with a pipette. Then, an appropriate amount of Spiking Solution (10 µL, 20 µL, 30 µL, 40 µL, 50 µL, etc.) and NMP (together with Spiking Solution should be 100 µL) were added. The vial was closed immediately. The sample solution was mixed via ultrasonication for approximately 5 min.

[00642] **Inductively coupled plasma optical emission spectrometry (ICP-OES)**

[00643] Method is based on Ph. Eur., chapter 2.2.57 "Inductively Coupled Plasma-Atomic Emission Spectrometry" and USP-NF, chapter <730> "Plasma Spectrochemistry".

[00644] Operating Parameters and Reagents:

Instrument:	ICP – Optical Emission spectrometer (Vista-PRO, Agilent or suitable equivalent)
Emission wavelength	317.93 nm
Plasma observation	Axial
Plasma power	1200 W
Plasma gas flow	16.5 L/min Ar
Auxiliary gas flow	1.5 L/min Ar
Nebulizer	Concentric
Spray chamber	Cyclon spray chamber
Nebulizer gas flow	0.75 L/min
Pump rate	20 rpm
Reagents:	
Water	Deionized or higher purity
Nitric Acid	Conc. (min 65% m/m), for analysis or higher purity, e.g., suprapur®
Hydrochloric acid	30%, for analysis or higher purity, e.g., suprapur®
Ca Standard solution (1000 mg/L)	Single Element Standards for ICP (e.g., AccuTrace, ICP-09N-1)
Quality control material	A reference substance containing the analyte other than the one used for preparation of calibration solutions, e.g. Calcium D-Gluconate Monohydrate

[00645] *System Suitability Test*:

Quality Control:	Analyzed the quality control sample at least once. The relative deviation from the expected analyte concentration must not exceed ± 10 % for the analyte
Linearity Check:	Evaluated data from linear regression calculation. Correlation coefficients must be ≥0.999
Blank Solutions:	The blank solutions were analyzed. For Bach determination, the Ca concentration of the blank solution must not be more than 1% of the lowest concentration of the test solutions

[00646] *Solutions*:

Calibration solutions	Laboratory prepared mixtures with known and suitable element concentrations. Prepared at least 4 calibration solutions (including zero solution) from the stock standard solution by appropriate dilution with water and addition of 2 mL of conc. HNO_3 per 100 mL; selected the calibration range according to the expected analyte concentration. E.g. for an element content of 11.8 % m/m (8.0, 12.0 and 16.0) mg/L would be suitable concentrations.
Zero solution	Prepared as described for the calibration solutions, but without addition of any standard solution.
Test solutions	Test solutions were prepared in duplicate. Weighed approx. 25 mg of the test substance accurately (to within 0.01 mg) into a digestion vessel. Added 2.0 mL of nitric acid and 0.2 mL of hydrochloric acid to the test substance. Capped the digestion vessel. Allowed the mixture to react for approximately 15 minutes in an ultrasonic bath at room temperature. Placed the loosely capped vessel into the digestion autoclave. Operated the digestion autoclave according to the manufacturer's instructions. After completion of the digestion procedure and after cooling the digestion vessel down to ambient temperature added 3.0 mL of nitric acid and diluted to 250 mL with deionized water using volumetric flasks. Volumes may be adapted as long as the ratio remains the same.
Blank solutions	Prepared in duplicate analogously to the test solutions but without any test substance.
Quality control sample solution	The quality control solution was prepared from the quality control material after corresponding digestion (see test solution) by appropriate dilution with water. The analyte concentration must be within the calibrated range.

[00647] Measurement: The emission of the zero solution and the calibration solutions were measured using suitable Instrument parameters (see above). The emission of blank solution, quality control solution and test solutions were measured. If necessary, the test solutions were diluted with zero solution (dilution factor f) to obtain a reading within the calibration range. Alternatively, new calibration solutions were prepared in order to adapt the calibration range.

[00648] Calculation: The calibration function was determined using the corresponding readings. The analyte element concentration was calculated in the test solutions from the

measured emission with this calibration function subtracting the reading of the zero solution. The analyte element concentration was calculated in the test substance using the equation below. These calculations were done by the Instrument software.

[00649] $$c = \frac{a \times V \times f}{m \times 10000}$$

- c = concentration of analyte element in the Lest substance (% m/m)
- a = analyte concentration in the test solution (mg/L)
- V = volume of the test solution (mL)
- f = dilution factor, e.g. f = 1.0 if the test solution is not diluted
- m = mass of test substance (g)
- 10000 is a conversion factor (mg/kg to % m/m).

[00650] Both, values of the duplicate determination (with 2 decimals) and the mean value (1 decimal) were reported.

[00651] **Karl-Fisher Analysis**

[00652] Karl-Fisher analysis was performed according to Ph. Eur. 2.5.32. For Karl-Fisher Analysis, limit of quantification was 0.05% w/w.

[00653] **Example 2: Solubility Studies of Gemcabene Calcium Salt Crystal Form 1**

[00654] Approximately 20 mg of gemcabene calcium Crystal Form 1 was added to 5 x 2 mL vials. The solubility in 5 solvents was tested using a solvent addition method. Solvents included acetone, ethanol, ethyl acetate, *t*-butyl methyl ether (*t*-BME) and water. Solvent was added in 5 volume (100 µL) aliquots until either dissolution or 2 mL in total had been added. Between each addition, samples were heated to 60 °C (40 °C for acetone and *t*-BME). Any solids remaining after 24 hours at ambient were analyzed by X-ray powder diffraction (XRPD). Water sample dissolved and did not precipitate even after 48 hours at < 5 °C. Table 1 shows the result of the solubility studies.

[00655] Table 1. Solubility of gemcabene calcium salt Crystal Form 1

Solvent	Solubility (mg/mL)	Crystalline Form
Acetone	<10	Form 1
Ethanol	<10	Form 1
Ethyl Acetate	<10	Form 1
t-Butyl Methyl Ether (*t*-BME)	<10	Form 1
Water	33	N/A

[00656] Example 3: Amorphous Gemcabene Calcium Salt

[00657] Gemcabene calcium salt Crystal Form 1 was prepared as described in Example 1. Approximately 40 g of gemcabene calcium salt Crystal Form 1 was weighed. To this, approximately 800 mL of water was added and mixed at ambient temperature for dissolution. After approximately 4 hours, the solid was found to have dissolved and the solution was transferred to a 2 L round bottom flask. The solution was then frozen before being placed on a freeze dryer for approximately 72 hours. X-ray powder diffraction (XRPD) analysis of a combined lot of material showed that the diffractogram is consistent with reference amorphous data (Fig. 52A). Polarized light microscope (PLM) images showed glass-like particles with limited birefringence. Thermogravimetric analysis (TGA) showed a weight loss of 3.1 % up to 150 °C (Fig. 52B). No thermal events were noted in the differential thermal analysis (DTA) or in the differential scanning calorimetry (DSC) (Figs. 52B and 52C). The moisture content of the material was determined to be 2.62 % by Karl-Fisher titration. The amorphous gemcabene calcium salt was determined to have a gemcabene content (% gemcabene) of 88.85 % on a % w/w basis by high-performance liquid chromatography equipped with charged aerosol detector (HPLC-CAD). Particle size distribution (PSD) analysis returned a D10 value of 5.2 µm, a D50 value of 26.4 µm and a D90 value of 60.3 µm.

[00658] On large scale (greater than 1 kg scale), the amorphous form was obtained by drying gemcabene calcium ethanol solvate. The amorphous solid was difficult to handle due to electrostatic properties and a relatively low bulk density of < 0.3 g/mL (tapped).

[00659] Example 4: Gemcabene Calcium Salt Crystal Form 2

[00660] Gemcabene calcium salt Crystal Form 1 was prepared as described in Example 1. To a 5 L glass reactor held at 70 °C, approximately 160 g of gemcabene calcium salt Crystal Form 1 was added, along with approximately 2.4 L of an ethanol:water (90:10 v/v%) solution. The slurry was then mixed at 120 RPM using a 4 pitch-blade PTFE impeller for approximately 2 hours. After 2 hours, a further 824 mL water was added to the slurry (new solvent ratio of ethanol:water (67:33 v/v%)) and the material was then left to slurry for approximately 18 hours. The crystallization was then cooled to 40 °C and the stirring rate decreased to 100 RPM. The crystallization was held for 2 hours then separated by filtration. The solid was then dried at 80 °C for 48 hours. An isolated yield of approximately 69 % was recovered. Samples of the wet and dried material were analyzed by X-ray powder diffraction (XRPD) spectroscopy (Fig. 53A) and were confirmed to be gemcabene calcium salt Crystal Form 2. Polarized light microscope (PLM) images of the dried solid showed agglomerated particles with limited birefringence. Theremogravimetric analysis showed a weight loss of 4.1 % up to 200 °C, associated with

solvent loss (Fig. 53B). A single endothermic event is noted in the differential thermal analysis (DTA) at onset 141 °C and a peak at 154 °C, likely associated with solvent loss 9Fig. 53B). The mother liquor was determined to have a concentration of 18.47 mg/mL by high-performance liquid chromatography (HPLC). The gemcabene calcium salt Crystal Form 2 was determined to have a gemcabene content (% gemcabene) of 86.91 %w/w. Gas chromatography analysis of the material showed a residual ethanol content of 61 ppm. Particle size distribution (PSD) analysis was carried out and gave a D10 value of 5.0 µm, a D50 of 14.4 µm and a D90 of 38.2 µm.

[00661] Example 5: Gemcabene Calcium Salt Crystal Form C3

[00662] Amorphous form of gemcabene calcium salt was prepared as described in Example 3. To a large crystallization dish, approximately 50 g of amorphous gemcabene calcium salt was added. To the crystallization dish, 250 mL ethanol was added in 50 mL aliquots, with the material mixed between additions to ensure even solvent distribution. The mixture was mixed several times during drying to minimize large aggregate formation. The material was then dried at ambient under vacuum for approximately 72 hours. X-ray powder diffraction (XRPD) spectroscopy analysis showed that the dried material was consistent with gemcabene calcium salt Crystal Form C3. Polarized light microscope (PLM) images showed agglomerated particles with limited birefringence. Thermogravimetric analysis showed a weight loss of 5.5 % up to 160 °C (Fig. 54B). A single endothermic event was noted in the differential thermal analysis (DTA) at onset 121 °C, with a peak at 129 °C (Fig. 54B). Differential scanning calorimetry (DSC) analysis showed an exothermic event at onset 31 °C, with a peak 35 °C, followed by a single endothermic event at onset 150 °C, with a peak at 167 °C (Fig. 53C). The moisture content of the material was determined to be 2.1 % by Karl-Fisher titration. The gemcabene calcium salt Crystal Form C3 was determined to have a gemcabene content (% gemcabene) of 83.98 % on a % w/w basis was determined by high-performance liquid chromatography equipped with charged aerosol detector (HPLC-CAD). Gas chromatography analysis showed a residual ethanol content of 76070 ppm. Particle size distribution (PSD) analysis returned a D10 value of 8.8 µm, a D50 value of 20.4 µm and a D90 value of 44.3 µm.

[00663] Example 6: Gemcabene Calcium Salt Ethanol Solvate

[00664] To a 5 L glass reactor at 70 °C, approximately 266 g of gemcabene was dissolved in 1 L of ethanol. To the solution, approximately 1 equivalent calcium oxide (approximately 49.3 g) and additional 1.5 L ethanol were added. The slurry was then mixed at 150 RPM, using a 4 pitch-blade PTFE impeller for approximately 18 hours. The solution was then cooled to 25 °C and held for 1 hour. A total of 840 mL *t*-butyl methyl ether (*t*-BME) was then added as anti-solvent. After

addition, the mixing rate was lowered to 120 RPM and the vessel held at these conditions for 2 hours, then the precipitate was filtered. *t*-BME was used to rinse the vessel prior to washing the solid. The solid was then left to dry on the filter for approximately 10 minutes. The damp solid was then placed in a crystallization dish and dried at ambient temperature for 90 hours. An isolated yield of approximately 63 % was recovered from the scale up. Samples of the wet and dried material were analyzed by -ray powder diffraction (XRPD) spectroscopy (Fig. 55A), and were confirmed to be crystalline gemcabene calcium salt ethanol solvate. Polarized light microscope (PLM) images of the dried solid show agglomerated particles with limited birefringence. Thermogravimetric analysis showed a weight loss of 4.9 % up to 200 °C, associated with solvent loss (Fig. 55B). A single endothermic event was noted in the differential thermal analysis (DTA) at onset 110 °C and a peak at 137 °C, likely associated with solvent loss (Fig. 55B). The mother liquor was determined to have a concentration of 21.59 mg/mL by high-performance liquid chromatography (HPLC). The crystalline gemcabene calcium salt ethanol solvate was determined to have a gemcabene content (% gemcabene) of 90.51 %w/w. Gas chromatography analysis of the material showed a residual ethanol content of 28628 ppm and a residual *t*-BME content of 511 ppm. Particle size distribution (PSD) analysis was performed and gave a D10 value of 3.3 µm, a D50 of 31.8 µm and a D90 of 85 µm.

[00665] Example 7: Gemcabene Calcium Salt Hydrate Crystal Forms C1, C2 and C3 (Collectively, Gemcabene Calcium Salt Hydrate Crystal Form C)

[00666] Gemcabene calcium salt hydrate Crystal Forms C1-C3 were obtained by way of prolonged drying by charging the wet amorphous form of gemcabene calcium salt hydrate product to an agitated pan dryer at temperatures of 80 °C for at least 24 hours then at higher temperature up to 100 °C for 24 hours or more. Depending on the temperature of drying and the duration of drying, various forms of Crystal Form C were obtained, including Crystal Form C1, Crystal Form C2, and Crystal Form C3.

[00667] Example 8: Determination of particle size distribution by laser light diffraction

[00668] Material and Methods

[00669] *Particle Size Distribution by Laser Light Diffraction*: The particle size distribution was determined in accordance with the Fraunhofer light diffraction method. A coherent laser beam was passed through the sample and the resulting diffraction pattern was focused on a multi-element detector. Because the diffraction pattern depends, among other parameters, on particle size, the particle size distribution (PSD) was calculated based on the measured diffraction patter of the sample.

[00670] Stock dispersion solution was prepared by adding a few drops of the dispersing aid (e.g., 1% w/w solution of a detergent in white spirit such as Span 80, Fluka (85548-250 ml)) to an appropriate amount of substance and mixed carefully. The dispersion was then slowly diluted to a final volume of about 10 ml while vortexing. The suspension cell of the instrument (Malvern Mastersizer 2000 equipped with Hydro 2000S sample dispersion unit) was filled with dispersion medium and a background measurement was taken. The stock dispersion was added to the suspension cell until an optical concentration of 5% to 15% was reached. Once the measurement was initialized, the final optical concentration increased following the internal ultrasonication step and did not exceed 25%. The cumulative volume distribution was determined in accordance with the instrument's instruction manual.

[00671] The PSD10, PSD50, and PSD90 values were determined from the cumulative volume distribution of each measurement. Values smaller than 10 μm were reported to one decimal place. Results larger than 10 μm were reported as single digit values. Sample parameters used in analysis are shown below:

Analysis Model:	General Purpose	Sensitivity:	Normal
Dispersion accessory:	Hydro 2000S	Re-circulation Rate:	1500 RPM
Particle RI:	0	Absorption	0
Dispersant RI:	1.430	Sample Mass:	Approx. 100 mg
Sonication Time:	60 seconds	Internal Sonication Power:	100%
Obscuration:	5-20%	Pre-measurement Delay:	300 seconds
Dispersant:	0.2% Span-80 in Stoddard Solvent, with 5 minutes of equilibration prior to the background measurement		

[00672] *Scanning Electron Microscopy*: Scanning electron micrographs were obtained using a FEI Phenom SEM using 5kV of accelerating voltage. The samples were prepared for imaging by mounting a small quantity (about 1 mg - 10 mg) of sample to an aluminum sample stub using a piece of two-sided carbon tape. A conductive gold/palladium coating was applied to the sample to prevent charging effects from interfering with the imaging process. Electron micrographs were then collected. Magnification, image height, and a graduated micron bar can be found at the bottom of each micrograph.

[00673] Gemcabene calcium salt hydrate Crystal Form 1 having various particle sizes were prepared by use of different milling techniques. Total of nine Samples (Samples 1-9, Table 2) of gemcabene calcium salt hydrate Crystal Form 1 were subjected to the laser light diffraction particle size analysis. The PSD90 of each Sample determined by laser light diffraction is shown in Table 2.

[00674] *Samples 1-3 (Table 2)*: These samples were prepared by milling *Sample 5* (Table 2) under different conditions. Sample 1 was prepared by milling Sample 5 using Fitzpatrick Comminuting Machine model L1A at high speed (8946 RPM) through an 80-mesh screen. The resulting particle size after milling had PSD90 of about 150 µm. Sample 2 was prepared by further milling Sample 1 using a pinmill. The PSD90 of Sample 2 was about 75 µm. Sample 3 was prepared by further milling Sample 1 using a Fitzpatrick Comminuting Machine model L1A at high speed. The PSD90 of Sample 3 was about 110 µm.

[00675] *Samples 4, 5, 6, and 9 (Table 2)*: These samples were prepared by direct recrystallization (neat). Samples 4 and 6 each had a PSD90 of 52 µm. Samples *5* and *9* were also prepared by direct recrystallization; however, these samples had a PSD90 of 431 µm and 996 µm, respectively. The unusually high PSD90 compared to the other two neat samples may be explained by their higher content of specific impurities (e.g., 2,2,7,7-tetramethyl-octane-1,8-dioic acid) and larger amounts of residual solvents (e.g., ethanol).

[00676] *Samples 7 and 8:* These samples were prepared from various batches of gemcabene calcium salt hydrate Crystal Form 1 crystallized by precipitating it neat, then milled with a pinmill.

[00677] **Table 2:** PSD90 of Batches of Gemcabene Calcium Salt Hydrate Crystal Form 1

Sample	PSD90 (µm)
1	151
2	76
3	110
4	52
5	431
6	52
7	62
8	48
9	996

[00678] Scanning electron micrograph of *Sample 4* (Table 2) is as shown in Fig. 2.

[00679] As described in Examples 6 and 7 below, Gemcabene calcium salt hydrate Crystal Form 1 of *Samples 1-4 and 6-8* (Table 2) was used to produce drug product tablets by wet granulation in fluidized bed. Tablets could not be manufactured from *Samples 5 and 9* (Table 2) because the particle size distribution was too large and the particles did not fluidize in the fluidized bed granulation. Further, gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 less than about 30 µm showed difficulties in the formulation process due to electrostatic properties and low loose density.

[00680] Example 9: Powder Diffraction Study of Gemcabene Calcium Salt Hydrate Crystal Form 1 and Water and Ethanol Content

[00681] Powder X-ray diffraction (PXRD) was performed using a Panalytical X'Pert Powder diffractometer using CuKα radiation (λ = 1.54056 Å). Samples were mounted onto a flat sample support. Data were collected with a scan step size of 0.004178° and a time per step of 5.08 s in the 5 - 45° 2θ range under ambient conditions. A background was collected under the same conditions and subtracted, leaving primarily the diffraction of the sample.

[00682] Each PXRD pattern was analyzed using the GSAS II crystallography data analysis software program, utilizing the peak fit function. Peaks were selected and peak position, intensity, and full width at half maximum ("FWHM") were allowed to refine freely. The small residual background was fit using a 5-term polynomial function which was allowed to refine freely.

[00683] The PXRD results for Samples 4 and 7 (Table 2) demonstrated that both samples are gemcabene calcium salt hydrate Crystal Form 1 (Figs. 28 and 29). Thus, the particle size minimally affects the diffraction pattern, and the Crystal Form 1 is preserved during the milling process. The water content indicates that Samples 4 and 6-8 (Table 2) are a monohydrate, with a water content of about 3.5% w/w, corresponding to about 0.78 equivalents of water per a mole of gemcabene calcium salt (Table 3). The water content specification is between 2% w/w to 5% w/w to correspond to a monohydrate. The water contents of two other gemcabene calcium salt hydrate Crystal Form 1 samples having PSD90 of 55 µm (Sample 10) and PSD90 of 47 µm (Sample 11) were determined to be about 3.7% w/w in each sample, which corresponds to about 0.82 equivalents of water per a mole of gemcabene calcium salt. Thus, the water content of gemcabene calcium salt hydrate Crystal Form 1 with PDS90 ranging from 47 µm to 62 µm had a water content of about 3.5% w/w to about 3.7% w/w, corresponding to about 0.78 to about 0.82 equivalents of water per a mole of gemcabene calcium salt.

[00684] The ethanol content specification is less than 5000 ppm. For example, the ethanol content in Samples 4 and 6-10 was determined to range from 710 ppm to 1840 ppm.

[00685] The loose bulk densities of Samples 4 and 6-10 ranged from 0.25 g/mL to 0.30 g/mL and the tapped bulk densities of Samples 4 and 6-10 ranged from 0.33 g/mL to 0.49 g/mL (Table 3).

[00686] Table 3: Water and Ethanol Contents and Bulk Density

	Sample 4	**Sample 6**	**Sample 7**	**Sample 8**	**Sample 10**	**Sample 11**
PSD90	52 µm	52 µm	62 µm	48 µm	55 µm	47 µm
Water content	3.5% w/w	3.5% w/w	3.5% w/w	3.5% w/w	3.7% w/w	3.7% w/w

Ethanol content	1100 ppm	1480 ppm	1620 ppm	1781 ppm	710 ppm	1840 ppm
Loose Bulk Density	0.25 g/mL	0.25 g/mL	0.30 g/mL	0.26 g/mL	0.27 g/mL	0.26 g/mL
Tapped Bulk Density	0.39 g/mL	0.41 g/mL	0.49 g/mL	0.39 g/mL	0.33 g/mL	0.36 g/mL

[00687] Example 10: Gemcabene Calcium Salt Hydrate Crystal Form 1 Granulation

[00688] Gemcabene calcium salt hydrate Crystal Form 1 from each of Samples 1-4 and 6-8 of Table 2 was granulated with excipients using a fluid bed granulation process. A sample batch formula for gemcabene calcium salt hydrate Crystal Form 1 granulation is shown in Table 4.

[00689] *Blend Formulation-Intragranular*

[00690] The binding solution was prepared by weighing 41.06 kg of purified water and adding to a stainless-steel mixer and mixed. The mixing took about 1.5-2.5 hours. Hydroxylpropyl cellulose was slowly added to the water while mixing. The mixer speed was maintained to sufficiently mix the hydroxypropyl cellulose without generating foam. The mixing was continued until the hydroxypropyl cellulose was completely dissolved and a clear homogeneous solution was obtained.

[00691] The spray pump was verified to deliver a rate of 100 to 350 g/minute of the hydroxypropyl cellulose solution.

[00692] The Glatt 30 fluid bed granulator was set with a process air volume of 500 m^3 per hour, an inlet air temperature of 70 °C, and exhaust temperature of 45 °C ± 10 °C.

[00693] Gemcabene calcium salt hydrate Crystal Form 1 and lactose monohydrate were milled with a 45R mesh screen, for example with Quadro Comil 197 Ultra equipped with a Round Impeller (45R screen; 0.045" opening size; round), to de-lump and the material was captured in a container double lined with polyethylene bags.

[00694] After pre-heating, the fluid bed granulator was charged with de-lumped gemcabene calcium salt hydrate Crystal Form 1and lactose monohydrate. Once the powder fluidization began, the binding solution was sprayed over the powder. After the powder was wet, the spray rate was reduced and the air volume was adjusted until all binder solution was sprayed. The inlet air volume was adjusted to ensure fluidization of granules and the target temperature was kept at about 28 °C. After all binder solution was applied, granulation was continued with water to achieve acceptable visual granulation endpoint. The granulation was dried to a loss on drying (LOD) value of not more than 2.0%.

[00695] The rate of spraying the binding solution can vary depending on the scale of the granulation, etc. For example, for 22L granulator/drying bowl size scale, the spray rate of the binder can be at 75 -90 g/min for first 30 - 45 minutes then 50-65 g/min for the remaining time

until theoretical amount is sprayed on. Further, if required, purified water can be added to continue granulation until visually acceptable granulation is achieved before drying.

[00696] The bulk dried granulated samples prepared from Samples 1-4 and 6-8 from Example 8, Table 2, are referred to as Samples 1G, 2G, 3G, 4G, 6G, 7G, and 8G, respectively.

[00697] Bulk-dried granulation Samples 1G, 2G, 3G, 4G, 6G, 7G and 8G were each milled through a 39R mesh screen and collected in a container double-lined with polyethylene bags (e.g., Quadro Comil 197 Ultra equipped with a round bar impeller) to provide Samples 1M, 2M, 3M, 4M, 6M, 7M, and 8M, respectively.

[00698] **Table 4**: Gemcabene Calcium Salt Hydrate Crystal Form 1 Granulation Sample Formulation

Components	**% w/w**
Intragranular	
Gemcabene Calcium Salt Hydrate Crystal Form 1	63.8
Lactose Monohydrate Fast-Flo 316 NF	23.4
Hydroxypropyl Cellulose (Klucel EF)	8.0
Extragranular	
Croscarmellose Sodium NF	4.0
Magnesium Stearate NF	0.8
	Total: 100

[00699] *Blend Formulation-Extragranular*

[00700] A V-blender was charged with the milled Samples 1M-4M and 6M-8M. Croscarmellose Sodium was passed through a 20 mesh hand screen and charged into the V-blender with the granulation and blended for 10 minutes. A bag containing the magnesium stearate component was rinsed with the granulation blend. The mixture was filtered through a 20 mesh screen, added to the V-blender and blended for about 3 minutes. The final granulation blend was discharged into drums which are double lined with polyethylene bags and sealed.

[00701] The completed final blends were discharged and weighed prior to proceeding to the compression process. The discharged final blends based on Samples 1M-4M and 6M-8M are referred to as Samples 1FB, 2FB, 3FB, 4FB, 6FB, 7FB, and 8FB, respectively.

[00702] **Example 11: Gemcabene Calcium Salt Hydrate Crystal Form 1 Film-Coated Tablet Formulation**

[00703] Samples 1FB-4FB and 6FB-8FB were compressed 300-mg film-coated tablets. A sample tablet formula is shown in Table 5.

[00704] **Table 5:** Gemcabene Calcium Salt Hydrate Crystal Form 1 Film-Coated Tablet Formulation

Components	% w/w
Core Ingredients	
Gemcabene Calcium Salt Hydrate Crystal Form 1 Samples 1FB-4FB and 6FB-8FB, Example 10	100.00
Coating Ingredients	
Opadry White YS 1-7040	2.98
Simethicone Emulsion 30% USP	0.02
	Total: 103.0

[00705] Each of Samples 1FB-4FB was added, separately, to a tablet press equipped with a force feeder. Samples 1FB-4FB were respectively compressed per specified parameters in Table 6. The tablet weight and hardness were adjusted to target tablet weight and hardness, and were passed through a metal detector and tablet de-duster and collected into double lined polyethylene bags.

[00706] Samples 1FB, 2FB, 3FB, 4FB, 6FB, 7FB, and 8FB were compressed on a rotary tablet press using 0.2759" X 0.6285" oval tooling to a theoretical fill weight of 470 mg. See Table 6 below for compression parameters, batch weight variation and tablet properties. All tablets compressed well and had a low relative standard deviation (RSD) for tablet weight variation. Tablets prepared from Samples 1FB, 2FB, 3FB, 4FB, 6FB, 7FB, and 8FB are referred to as Tablets A, B, C, D, F, G, and H, respectively.

[00707] **Table 6:** Compression Parameters and Tablet Properties of Gemcabene Calcium Salt Hydrate Crystal Form 1 300 mg Film-Coated Tablets

	Tablet A	**Tablet B**	**Tablet C**	**Tablet D**
Final Blend Sample	Sample 1FB	Sample 2FB	Sample 3FB	Sample 4FB
D_{90} of gemcabene calcium salt hydrate Crystal Form 1 in each Sample	151 µm	76 µm	110 µm	52 µm
Compression				
Tablet Tooling Size	0.2759" X 0.6285" oval			
Tablet Press	MiniPress	MiniPress	MiniPress	Stokes GEM
Pre-Compression Force (kN)	n/a	n/a	n/a	8
Compression Force (kN)	n/a	n/a	n/a	7
Turret Speed	32 Dial Setting	13 RPM	17 RPM	41.1 RPM
Hopper Type	Gravity Feeder	Gravity Feeder	Gravity Feeder	Force Feeder
Feeder Speed (RPM)	n/a	n/a	n/a	39.9
Tablet Weight Variation				
Target Weight of 10 tablets (g)	4.700			
Target Weight Range of 10 tablets (±5%) (g)	4.465 - 4.935			
In-Process Average Weight (g)	4.7809	4.6845	4.7293	4.715
In-Process Weight Variance	0.554	0.532	1.482	1.466

	Tablet A	Tablet B	Tablet C	Tablet D
(%RSD)				
In-Process Weight Variance Range (g)	± 0.053	± 0.089	± 0.137	± 0.152
Target Individual Tablet Weight (g)	0.470			
Target Individual Tablet Weight Range (±10%) (g)	0.423 - 0.517			
End of Run Average Weight (g)	0.4718	0.4696	0.4645	0.469
End of Run Weight Variance (%RSD)	1.312	1.036	3.275	2.586
End of Run Weight Variance Range (g)	± 0.022	± 0.014	± 0.058	± 0.045
Tablet Properties				
Average Tablet Hardness (kp)	17.5	16.2	14.9	16.2
Average Tablet Thickness (mm)	6.08	6.02	5.74	6.21
End of Run Friability (%)	0.0	0.0	0.2	0.0

[00708] Each batch was film-coated in either the experimental Vector Coater LDCS instrument (Tablets A-C, Table 6) or the GMP Compu-Lab 24 (Tablet D, Table 6). The film-coating suspension consisted of Opadry White YS 1-7040 and Simethicone Emulsion 30% USP.

[00709] Purified water was weighed into a stainless-steel container and mixed to create a vortex. Simethicone emulsion and Opadry White YS 1-7040 were added to the purified water and mixed for a minimum of 50 minutes or until the suspension was visually uniform. Tablets A-D were, separately, divided into two batches and are weighed out for coating. The Tablets were charged into a coating pan heated to an outlet temperature of 42 °C (± 2 °C). The Tablets were film-coated to a 3.0 % weight gain (± 1.0%). After 90% of theoretical amount of film-coating suspension for each batch were sprayed, the average weight was checked and spraying continued to achieve a weight gain of 2.0% to 4.0%. Tablets were allowed to dry and cool down. The Tablets were packaged in tared containers double lined with polyethylene bags.

[00710] Film-coated Tablets F-H were prepared by the same process used for making Tablet D.

[00711] Example 12: Granulation of Gemcabene Calcium Salt Amorphous Form

[00712] An amorphous form of the gemcabene calcium salt was utilized in the preparation of a laboratory scale granulation batch. The laboratory scale fluid-bed granulation equipment was a Freund-Vector MFL-01 laboratory fluid-bed processor configured for a top-spray process,

which is a scaled-down Glatt equipment used for the granulation of the clinical batches. Table 7A gives the quantitative theoretical composition of the tablet formulation and the laboratory scale batch size.

[00713] Table 7A. Composition of Gemcabene Tablets (300 mg)

Ingredient	Concentration % w/w	mg/Tablet	Amount/ Batch (g)
Intra-Granular Materials			
Gemcabene Calcium, Amorphous	63.83	300.0[1]	75.0[1]
Lactose Monohydrate, NF (316 Fast-Flo)	23.37	109.84[1]	27.46[1]
Hydroxypropyl Cellulose, NF (Klucel EF)	8.0	37.6	9.4
Water, Purified[2]	N/A[2]	N/A[2]	178.6[2]
Extra-Granular Materials			
Croscarmellose Sodium, NF (Ac-Di-Sol)	4.0	18.8	4.7[3]
Magnesium stearate	0.80	3.76	0.94[3]
Total	100.0	470.0	117.5

[1]Gemcabene calcium and lactose were adjusted for each Tablet to provide the amorphous form of gemcabene calcium salt in an amount that is a molar equivalent to 300 mg gemcabene.
[2]Water is removed during processing and not accounted for in the batch weight or Tablet weight.
[3]Extra-granular component quantities are adjusted based on expected granulation yield.

[00714] High-performance liquid chromatography (HPLC) indicated that the amorphous gemcabene calcium contained 80.9% (w/w) molar equivalent of gemcabene. Thus, the amount of the amorphous gemcabene calcium charged to the batch was adjusted by this factor, resulting in 92.71g of amorphous gemcabene calcium being dispensed with a commensurate decrease in the lactose monohydrate quantity to 9.75g. The amorphous gemcabene calcium was screened to form a uniform powder for use in the granulation process using a #40 mesh (425 μm) sieve and 92.72 g of the screened material was dispensed into the granulator. Bulk and tapped density testing and particle size analysis by laser diffraction were performed using excess screened material. Bulk and tapped density testing was performed per USP <616> using a 100 mL graduated cylinder. Laser diffraction particle size analysis was performed using a Cilas 1180LD laser diffraction particle size analyzer with a dry powder dispersion method as described in Example 8 for gemcabene calcium salt Crystal Form 1 (see also Table 7B for laser diffraction particle size analysis conditions). Table 7C reports the physical testing results. Particle size results are reported as the average of three replicate measurements in terms of a volume distribution and Fig. 30 displays an overlay of the particle size distributions obtained from these three measurements.

[00715] **Table 7B**. Particle size analysis conditions using Cilas 1180LD

Analysis Parameter	**Value**
Analysis Mode	Dry Powder
Optical Model	Fraunhofer
Dispersion Media	Air
Dispersion Media RI	1.000
Powder Distributor Frequency (Hz)	50
Powder Distributor Power (%)	90
Hopper Gap Setting	2
Dispersion Air Pressure (mb)	3000
Background measurement (sec.)	10
Sample Measurement (sec.)	10
Sample Size (mg)	500

[00716] **Table 7C**. Particle size and density of amorphous gemcabene calcium

Average Particle Size in µm (%RSD)	
D_{10}	2.833 (2.3)
D_{50}	17.006 (0.9)
D_{90}	54.580 (2.1)
Powder Density	
Bulk Density (g/mL)	0.11
Tapped Density (g/mL)	0.25
Carr's Index	56.0%

[00717] Amorphous gemcabene calcium and Lactose Monohydrate were charged into the fluid-bed's expansion chamber and were allowed to mix for 2 minutes using a process air flow of 50 L per minute (LPM). The fluid bed charge was then granulated by the addition of a granulation solution, consisting of water and Hydroxypropyl Cellulose (Klucel® EF). This solution was dispensed into the granulator as an atomized spray from the fluid-bed's air atomized spray nozzle. Target granulation process parameters were scaled for the MFL-01 fluid-bed from the large-scale granulation process. Table 7D reports the target processing parameters.

[00718] **Table 7D**. Target Granulation Parameters for Freund-Vector MFL-01 Fluid-Bed

Parameter	**Target Value**
Inlet Temperature	70°C
Product Temperature	<37°C
Air Flow	50 LPM
Solution Flow Rate	5 g/min
Atomization pressure	10 psi

[00719] Addition of the granulating fluid to the amorphous gemcabene calcium resulted in heavy agglomeration of the amorphous gemcabene calcium particles. Granulating fluid addition rates of 50%, 37%, and 24% of the original 5 g/min target rate were evaluated in an attempt to prevent the agglomeration. However, the agglomeration continued and worsened with the addition of any amount of granulating fluid. As the amount of agglomeration increased, the process air volume was continually increased to maintain fluidization of the powder bed. Higher process air volume with a slower granulating fluid addition rate also did not seem to reduce the agglomeration issue. The continued agglomeration at higher air flow and lower spray rate could have resulted from the large amounts of large agglomerates which were already present in the powder bed or could be an indication that any amount of aqueous granulating fluid will cause excessive agglomeration, even if dried off of the powder bed rapidly. Typically, the combination of low spray rate and high air flow results in quick drying of the granulating fluid, decreasing the time the powder surface is exposed to the solvent and affecting rapid deposition of the polymer binder. These conditions reduce the potential for agglomeration, however, due to the very low density of the amorphous gemcabene calcium, it would not be possible to start the fluid-bed granulation process with a high process air volume without forcing all of the drug substance particles out of the spray zone and into the filters. It was concluded that the solubility and density characteristics of the amorphous gemcabene calcium evaluated in this study are not conducive to granulation using the current formulation and process

[00720] Example 13: Dissolution Profiles of Gemcabene Film-Coated Tablets (300 mg) Prepared from Gemcabene Calcium Salt Crystal Form 1 having various PSD90 values

[00721] *Dissolution*: The dissolution profiles for 300-mg film-coated Tablets A-D and F-H of gemcabene Calcium Salt Hydrate Crystal Form 1 were measured in 900 mL pH 5.0 potassium acetate (50 mM) buffer using USP Apparatus 2 (paddles) set to 50 rpm. Each % dissolution time point was quantified by HPLC using a detection wavelength of 210 nm (Fig. 1A, Fig. 1B and Table 8). Figs. 1A and 1B, showing mean dissolution, demonstrates that the particle size

distribution of the gemcabene calcium salt hydrate Crystal Form 1 does influence the dissolution profiles of the immediate release tablets. The tablets made from gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 151 μm and 110 μm, Tablets A and C, respectively, showed significantly lower release profiles than Tablets B and D, prepared with gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 76 μm and 52 μm, respectively. Specifically, the average % release values at 20, 30 and 45 minutes are lower with Tablets A and C when compared with % dissolution of Tablets B and D. For example, the amount of gemcabene detected at 45 minutes was about 8% to 15% lower for Tablets A and C than that of the Tablets made from gemcabene calcium salt hydrate Crystal Form 1 having a smaller particle size (Tablets B and D). Tablets G and H, made from gemcabene calcium salt hydrate Crystal Form 1 having a PSD90 of 62 μm and 48 μm, respectively, show a more favorable dissolution profile with almost 40 % average release at 10 min and essentially 100 % average release at 30 min. Meanwhile, when drug substance gemcabene Calcium Salt Hydrate Crystal Form 1 is used neat (recrystallized only), the dissolution profiles show lower release profiles.

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[00722] **Table 8.** PSD90 for Gemcabene Calcium Crystal Form 1 and Dissolution Profiles of Their Corresponding Immediate Release 300-mg Strength Tablets

Gemcabene Calcium Sample No. (Example 8, Table 2)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Milling Condition	Milled - Fitzmill	Milled - Pinmill	Milled - Fitzmill	Neat	Neat	Neat	Milled - Pinmill	Milled - Pinmill	Neat - recrystallized
D_{10}	6.3 µm	4.8 µm	5.3 µm	5.8 µm	7.8 µm	7.8 µm	5.4 µm	8.2 µm	17 µm
D_{50}	50.4 µm	22.9 µm	32.2 µm	22 µm	101 µm	25 µm	20 µm	24 µm	386 µm
D_{90}	151 µm	76 µm	110 µm	52 µm	431 µm	52 µm	62 µm	48 µm	996 µm
	Tablet Dissolution (average % released)								
Tablet (Example 11)	**A**	**B**	**C**	**D**		**F**	**G**	**H**	
10 min	20	19	16	26		23	37	39	
20 min	45	49	38	53		53	78	77	
30 min	66	71	57	75		76	100	93	
45 min	86	91	77	92		93	103	98	
60 min	N/A	96	89	96		94	101	98	
75 min	N/A	97	92	97		94	101	99	

[00723] *Dissolution medium* (50 mM potassium acetate): Prepared by dissolving 245 g of potassium acetate into an aliquot of deionized water. The aliquot was transferred to a 50 L carboy and diluted to volume. The pH was adjusted to 5.0±0.05 using glacial acetic acid. The dissolution medium was deaerated using helium sparge or other appropriate means.

[00724] *Standard*: In duplicate, 39 mg gemcabene was accurately weighed and transferred to a 100 mL volumetric flask, then dissolved in about 10 mL of acetonitrile (ACN). If necessary, sonication can be used to dissolve gemcabene. The gemcabene solution was diluted to volume with the dissolution medium.

[00725] Dissolution Parameters:

Dissolution Medium:	50 mM Potassium Acetate in water, adjusted to pH 5.0 with glacial acetic acid
Dissolution Apparatus:	USP Type 2, Paddles
Rotation Speed:	50 rpm
Sample:	Gemcabene Calcium Salt Hydrate Crystal Form 1 300 mg; n = 6 tablets; 1 tablet per vessel in a basket sinker
Solution volume:	900 mL
Solution temperature:	37 °C ± 5 °C
Sampling times:	10, 20, 30, 45, 60, and/or 75 minutes
Sampling technique:	Withdraw 2 mL sample with a syringe and stainless-steel cannula with a 45 µm filter tip into an HPLC vial

[00726] *Operating Parameters:*

a) Die paddles were set to a rotation speed of 50 rpm.

b) Each vessel was filled with 900 mL of dissolution medium.

c) Randomly 6 tablets were selected and the weight of each was recorded.

d) Each tablet was placed inside a Japanese basket sinker.

e) The temperature was measured in one of the center vessels using a calibrated thermometer as the paddle is rotating midway between the top of the paddle and top of the fluid and midway between the shaft and the side of the vessel. The temperature should be 37 °C ± 5 °C.

f) One tablet was placed within a sinker at precisely timed intervals to allow for adequate sampling time.

g) 2 mL sample aliquot was withdrawn using an appropriate syringe and stainless-steel cannula equipped with a 45 µm filter tip into an HPLC vial. Samples were

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME	1	DE	2
CONTENANT LES PAGES	1	À	155

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JUMBO APPLICATIONS/PATENTS

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THIS IS VOLUME	1	OF	2
CONTAINING PAGES	1	TO	155

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

WHAT IS CLAIMED IS:

1. A pharmaceutically acceptable salt of gemcabene, the pharmaceutically acceptable salt having a PSD90 ranging from 40 μm to about 75 μm as measured by laser light diffraction and providing a plasma gemcabene $AUC_{(0\text{-}24)}$ ranging from about 200 μg·hr/mL at steady state to about 6000 μg·hr/mL at steady state when administered to a human subject at a dose of about 50 mg to about 900 mg.

2. A pharmaceutically acceptable salt of gemcabene, the pharmaceutically acceptable salt having a PSD90 ranging from 40 μm to about 75 μm as measured by laser light diffraction and providing a plasma gemcabene AUC_{last} ranging from about 50 μg·hr/mL to about 7500 μg·hr/mL after a single dose administration of about 50 mg to about 900 mg to a human subject.

3. The pharmaceutically acceptable salt of claim 1 or 2, wherein the pharmaceutically acceptable salt has a dissolution profile characterized by a % dissolution value of (1) at least 80% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 45 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm or (2) at least 70% in pH 5.0 potassium acetate buffer at 37 °C ± 5 °C in no more than 30 minutes as measured by high-performance liquid chromatography using a detection wavelength of 210 nm.

4. The pharmaceutically acceptable salt of claim 1 or 2, wherein the pharmaceutically acceptable salt is a calcium salt.

5. A method for purifying crude gemcabene, wherein the crude gemcabene comprises no more than 3% w/w of 2,2,7,7-tetramethyl-octane-1,8-dioic acid as determined by high-performance liquid chromatography, comprising:

dissolving the crude gemcabene in heptane to provide a heptane solution of the crude gemcabene; and

cooling the heptane solution to a temperature ranging from 10 °C to 15 °C to precipitate gemcabene, wherein the gemcabene comprises 0.5% w/w or less of 2,2,7,7-tetramethyl-octane-1,8-dioic acid as determined by high-performance liquid chromatography.

6. The method of claim 5, further comprising:

dissolving the gemcabene in heptane to provide a heptane solution of the gemcabene; and

cooling the heptane solution to a temperature ranging from 10 °C to 15 °C to precipitate recrystallized gemcabene.

7. The method of claim 5, further comprising:

allowing two or more molar equivalents of an enolate of an alkali metal salt of isobutyric acid to react with one molar equivalent of a bis-(4-halobutyl)ether to provide crude gemcabene salt and

acidifying the crude gemcabene salt to provide the crude gemcabene.

8. Gemcabene made by the method of any one of claims 5-7.

9. A pharmaceutically acceptable salt of gemcabene of claim 8.

10. The pharmaceutically acceptable salt of claim 9, wherein the pharmaceutically acceptable salt is a calcium salt.

11. The pharmaceutically acceptable salt of claim 9, wherein the pharmaceutically acceptable salt comprises water in 3% w/w to 5% w/w of the pharmaceutically acceptable salt as determined by Karl-Fisher analysis.

12. The pharmaceutically acceptable salt of claim 9, wherein the pharmaceutically acceptable salt comprises isobutyric acid in 0.07% w/w or less of the pharmaceutically acceptable salt as determined by ion chromatography.

13. The pharmaceutically acceptable salt of claim 9, wherein the pharmaceutically acceptable salt comprises 2.5 ppm or less of bis-(4-chlorobutyl)ether as determined by gas chromatography.

14. The pharmaceutically acceptable salt of claim 9, wherein the pharmaceutically acceptable salt comprises 2.5 ppm or less of 6-(4-chlorobutoxy)-2,2-dimethyl-hexanoic acid as determined by gas chromatography.

15. The pharmaceutically acceptable salt of claim 9, wherein the pharmaceutically acceptable salt comprises 2.5 ppm or less of 1-chloro-4-hydroxybutane as determined by gas chromatography.

16. A composition comprising an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15 and a pharmaceutically acceptable carrier or vehicle.

17. A method for treating or preventing a liver disease or an abnormal liver condition, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

18. A method for treating or preventing a disorder of lipoprotein metabolism, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

19. The method of claim 18, wherein the disorder of lipoprotein metabolism is dyslipidemia, dyslipoproteinemia, mixed dyslipidemia, atherosclerotic cardiovascular disease (ASCVD), type IIb hyperlipidemia, familial combined hyperlipidemia, familial hypercholesterolemia, familial chylomicronemia syndrome, hypertriglyceridemia, dysbetalipoproteinemia, metabolic syndrome, lipoprotein overproduction, lipoprotein deficiency, non-insulin dependent diabetes, abnormal lipid elimination in bile, a metabolic disorder, abnormal phospholipid elimination in bile, an abnormal oxysterol elimination in bile, an abnormal bile production, hypercholesterolemia, hyperlipidemia or visceral obesity.

20. A method for reducing a subject's total cholesterol concentration, low-density lipoprotein cholesterol concentration, low-density lipoprotein concentration, very low-density lipoprotein cholesterol concentration, very low-density lipoprotein concentration, non-HDL cholesterol concentration, non-HDL concentration, apolipoprotein B concentration, triglyceride concentration, apolipoprotein C-III concentration, C-reactive protein concentration, fibrinogen concentration, lipoprotein(a) concentration, interleukin-6 concentration, angiopoietin-like protein 3 concentration, angiopoietin-like protein 4 concentration, PCSK9 concentration, or serum amyloid A concentration, in the subject's blood serum or plasma, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

21. A method for treating or preventing a disorder or a condition, comprising administering to a subject in need thereof an effective of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15, wherein the disorder or the condition is thrombosis, blood clot, primary cardiovascular event, secondary cardiovascular event, progression to nonalcoholic fatty liver

disease, nonalcoholic steatohepatitis, liver cirrhosis hepatocellular carcinoma, liver failure, pancreatitis, pulmonary fibrosis or hyperlipoproteinemia type IIB.

22. A method for reducing a subject's risk of thrombosis, blood clot, primary cardiovascular event, secondary cardiovascular event, progression to nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, liver cirrhosis hepatocellular carcinoma, liver failure, pancreatitis, pulmonary fibrosis or hyperlipoproteinemia type IIB, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

23. A method of reducing or inhibiting progression of fibrosis, steatosis, ballooning or inflammation in a liver of a subject, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

24. A method of reducing post-prandial lipemia or preventing prolonged post-prandial lipemia, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

25. A method of reducing a fibrosis score or a nonalcoholic fatty liver disease activity score in a subject, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

26. A method of stabilizing, regressing or maintaining a fibrosis score or a nonalcoholic fatty liver disease activity score in a subject, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

27. A method of slowing the progression of a fibrosis score or a nonalcoholic fatty liver disease activity score in a subject, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

28. A method of reducing a fat content in a liver of a subject, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

29. A method for treating or preventing a disorder of glucose metabolism, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

30. A method for treating or preventing a cardiovascular disorder or a related vascular disorder, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

31. A method for treating or preventing inflammation, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

32. The method of claim 31, wherein the inflammation is indicated by an increased concentration of C-reactive protein in a patient's plasma or serum.

33. A method for preventing or reducing the risk for developing pancreatitis, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

34. A method for treating or preventing a pulmonary disorder, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

35. The method of claim 34, wherein the pulmonary disorder is chronic obstructive pulmonary disease or an idiopathic pulmonary fibrosis.

36. A method for treating or preventing musculoskeletal discomfort, comprising administering to a subject in need thereof an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

37. A method for lowering a subject's LDL-C concentration comprising administering to a subject in need thereof, an effective amount of the pharmaceutically acceptable salt of any one of claims 1, 2 and 9-15.

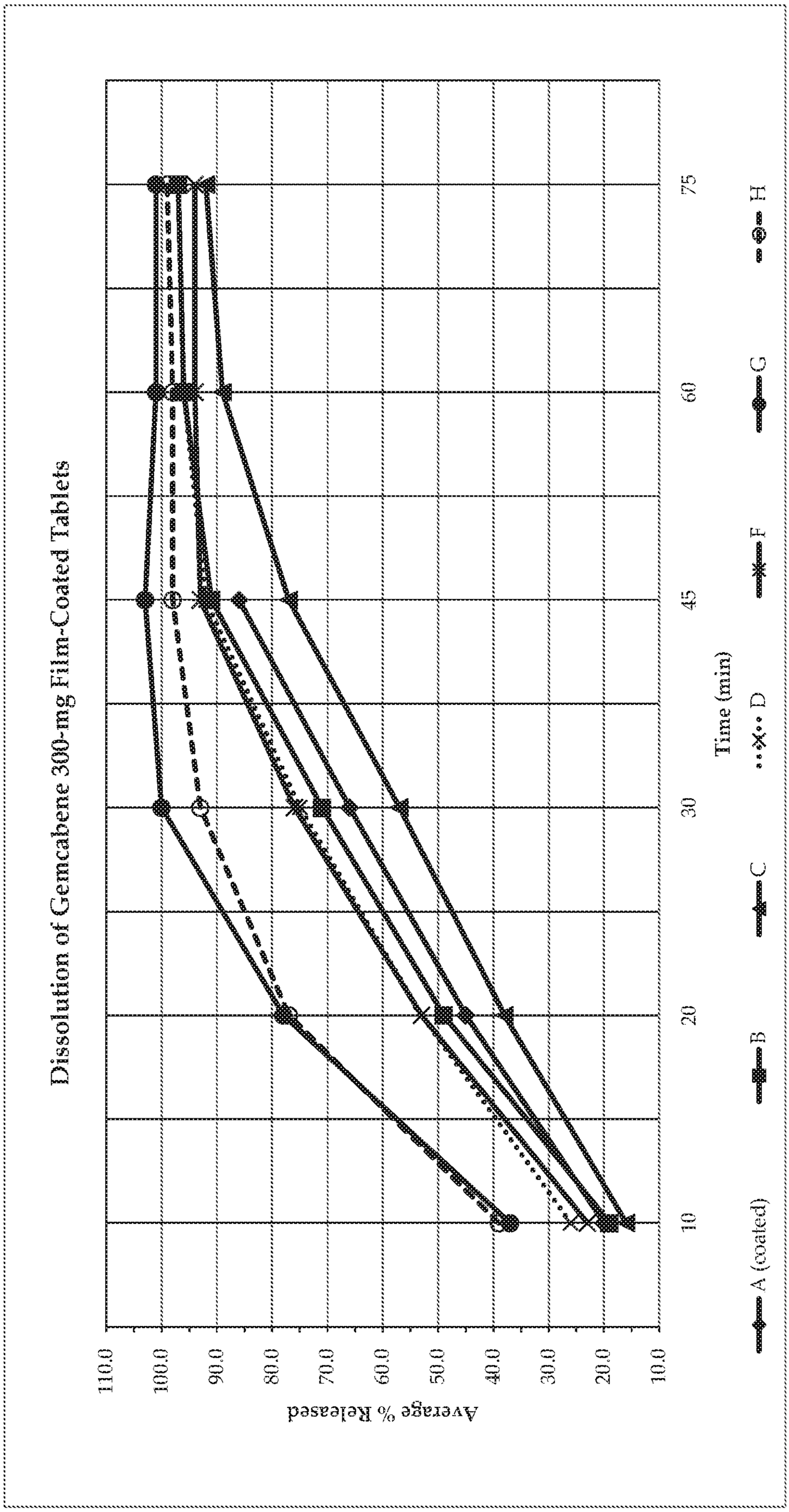

Dissolution of Gemcabene 300-mg Film-Coated Tablets
Average % Released
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
Time (min)
10
20
30
45
60
75
A (coated)
B
C
D
F
G
H

Fig. 1A

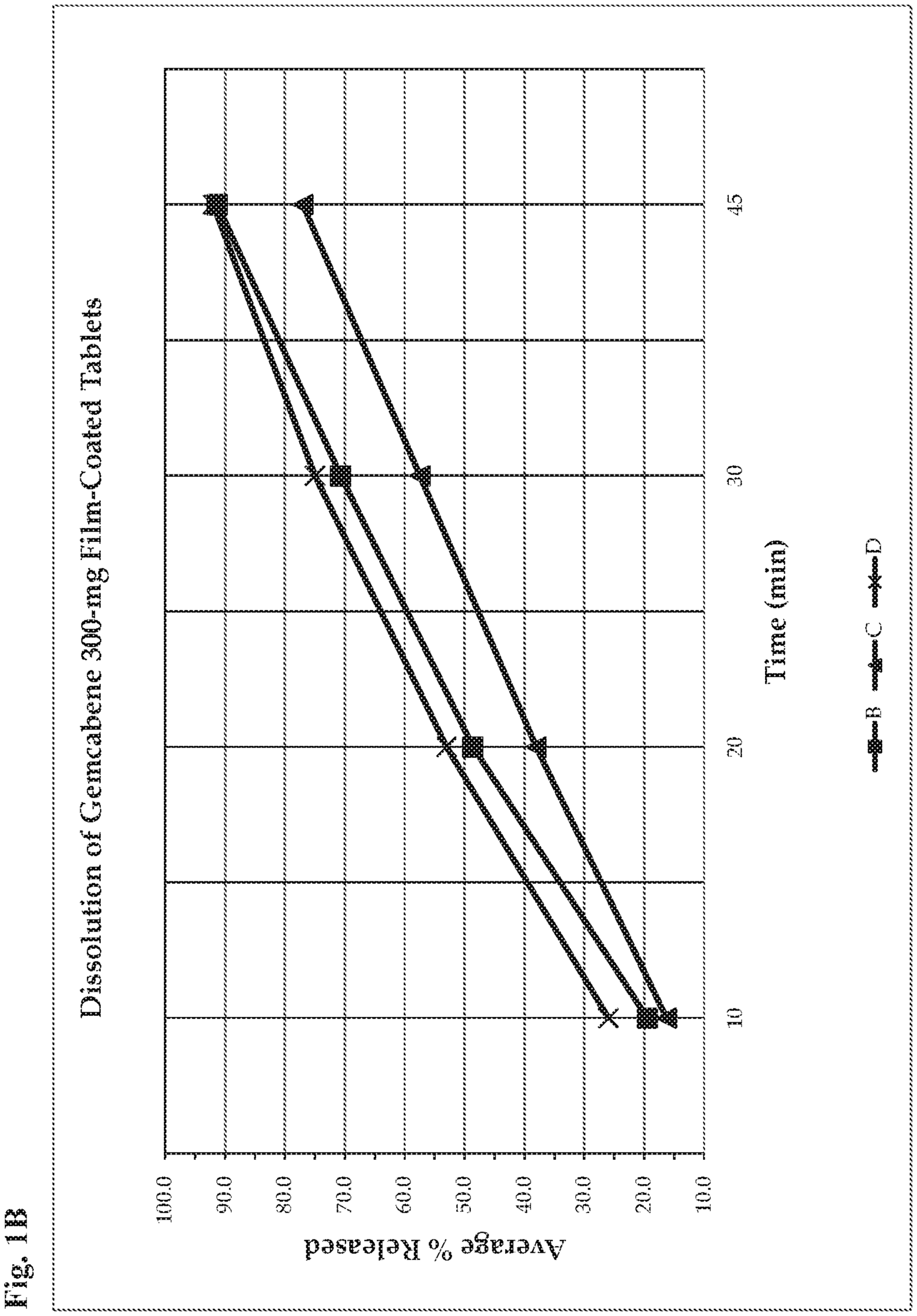

Dissolution of Gemcabene 300-mg Film-Coated Tablets
Average % Released
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
10
20
30
45
Time (min)
B
C
D

Fig. 1B

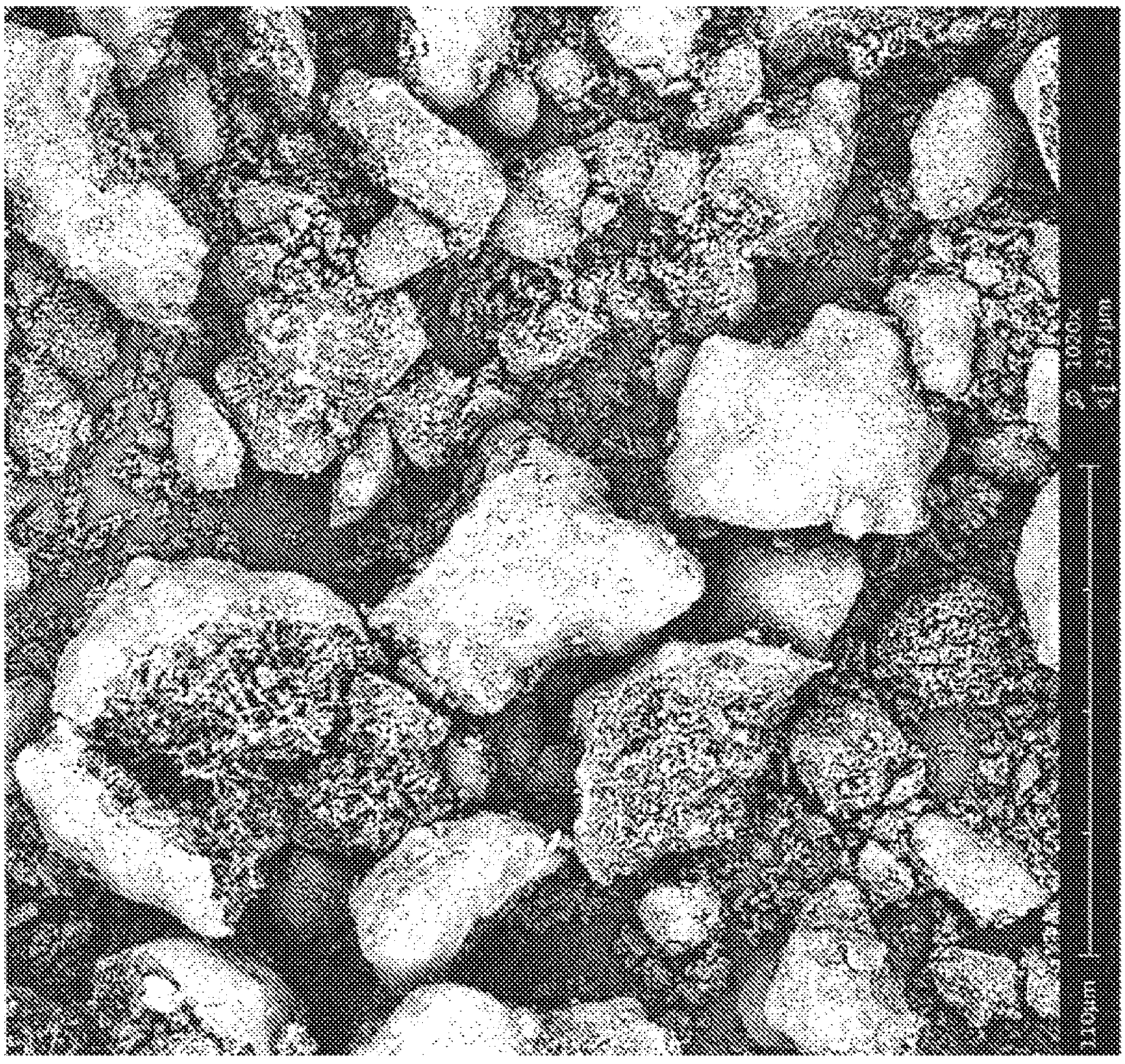


Fig. 2

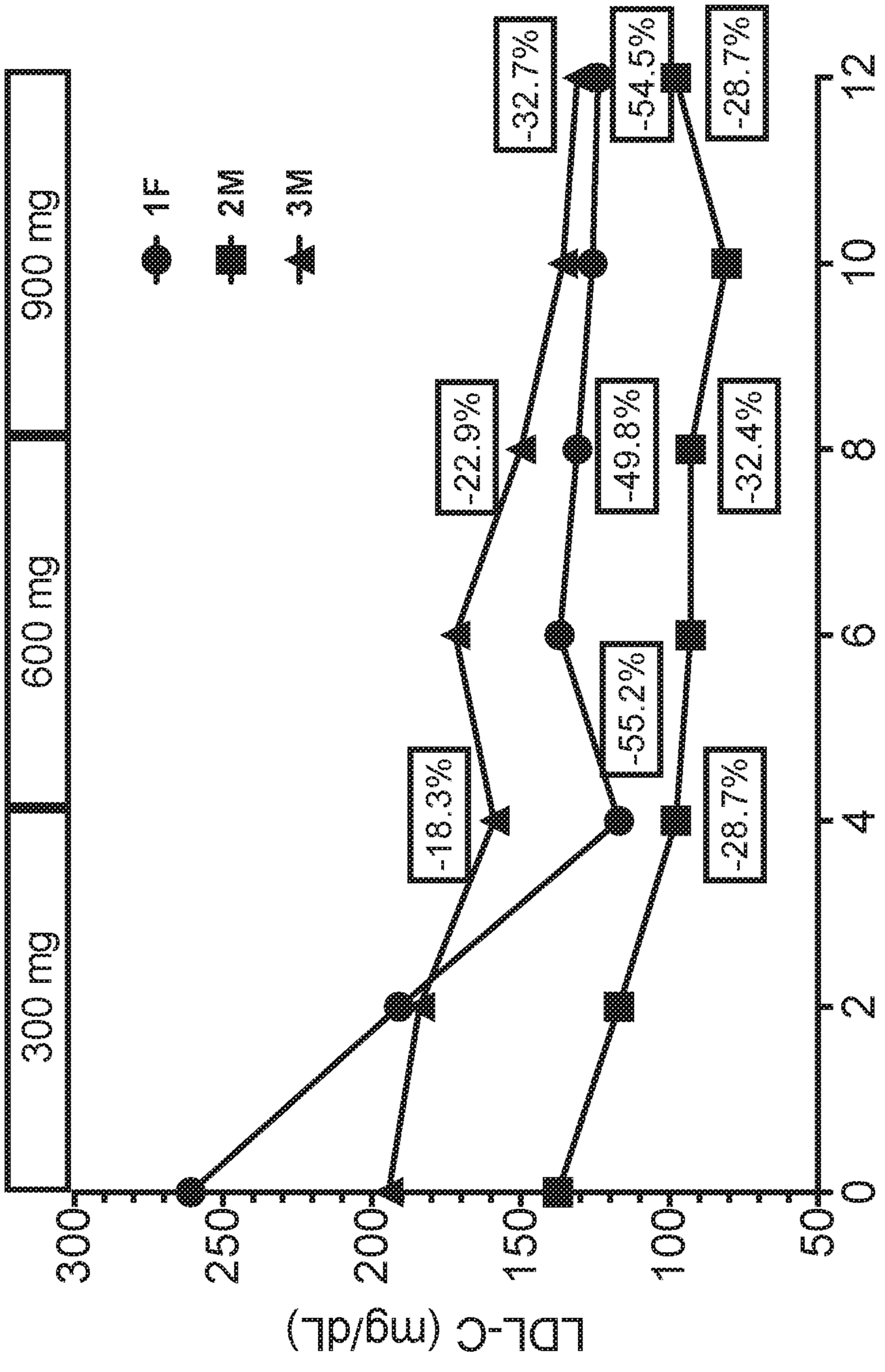

900 mg
600 mg
300 mg
1F
2M
3M
-32.7%
-54.5%
-28.7%
-22.9%
-49.8%
-32.4%
-18.3%
-55.2%
-28.7%
12
10
8
6
4
2
0
Time (weeks)
300
250
200
150
100
50
LDL-C (mg/dL)

Fig. 3

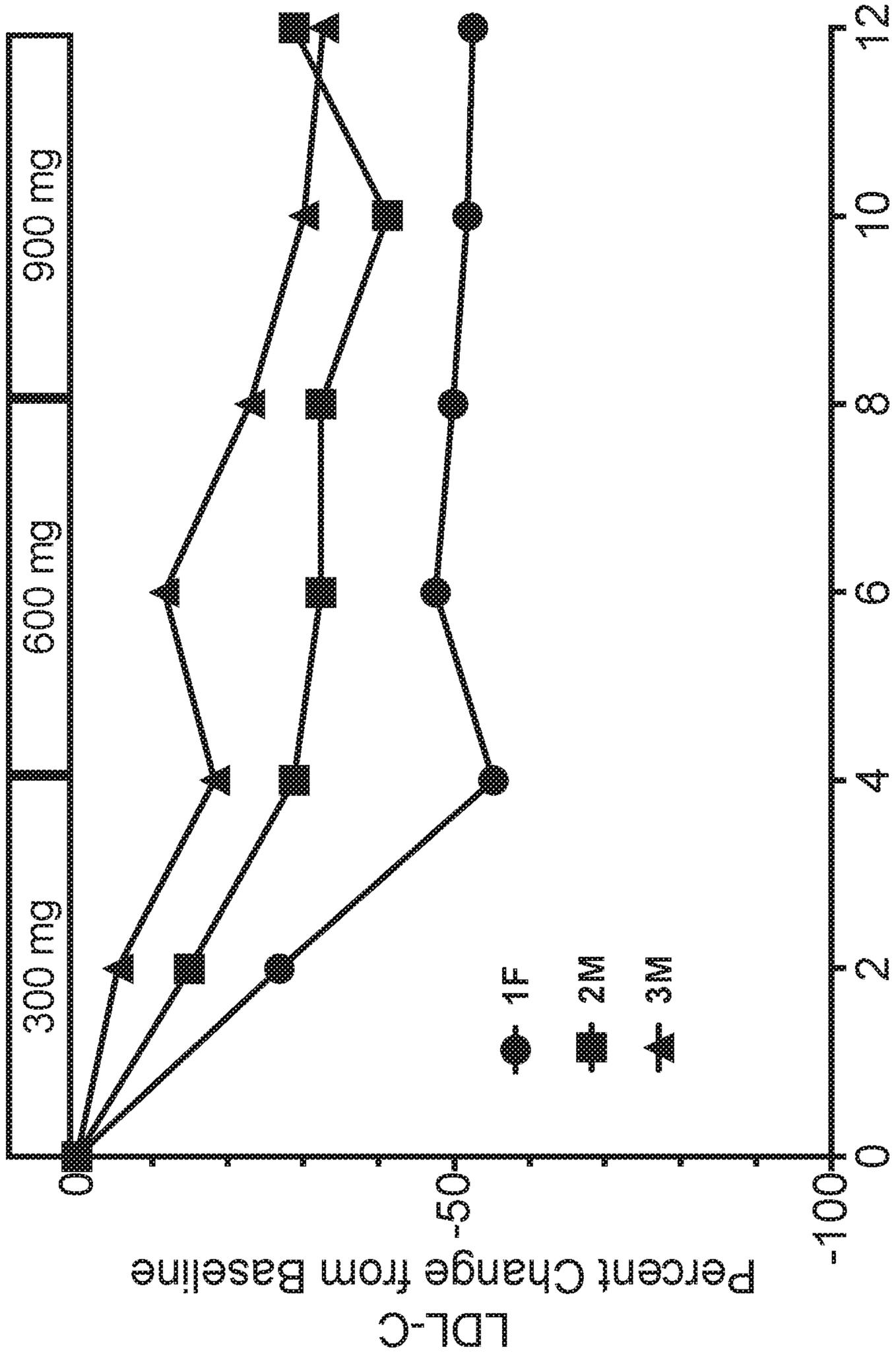
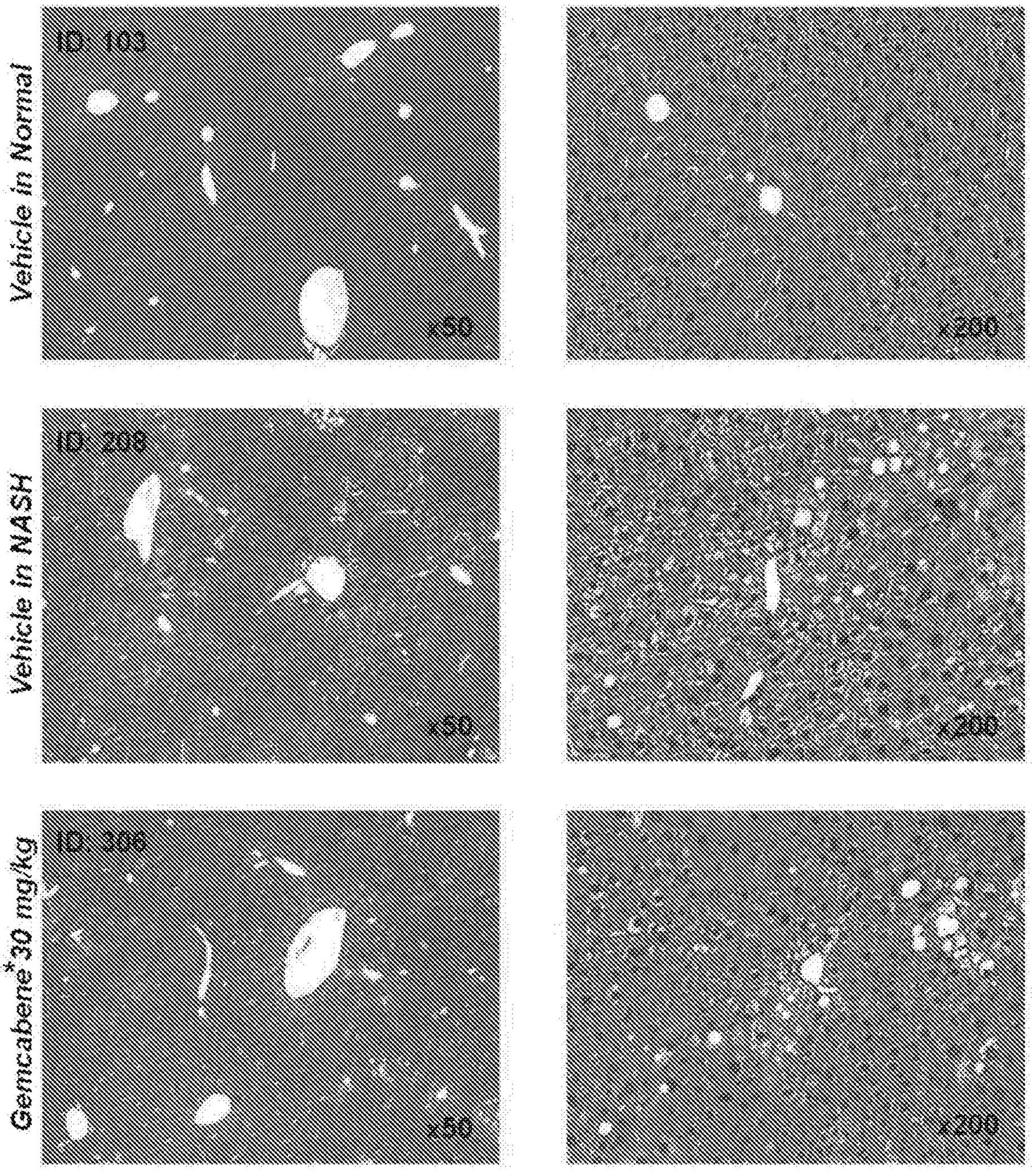

LDL-C
Percent Change from Baseline
0
-50
-100
2
4
6
8
10
12
Time (weeks)
1F
2M
3M
900 mg
600 mg
300 mg

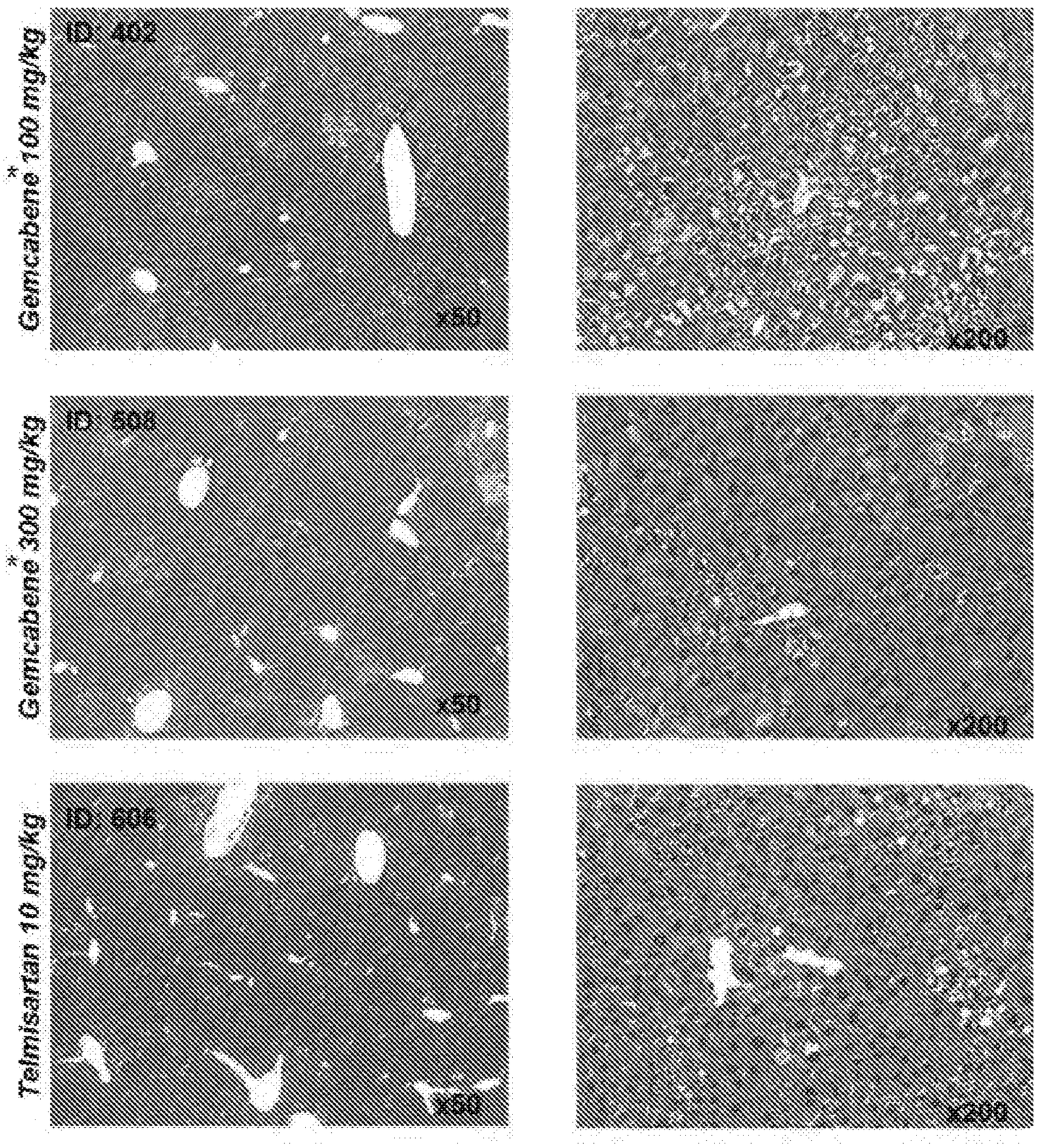
Fig. 4

Fig. 5A



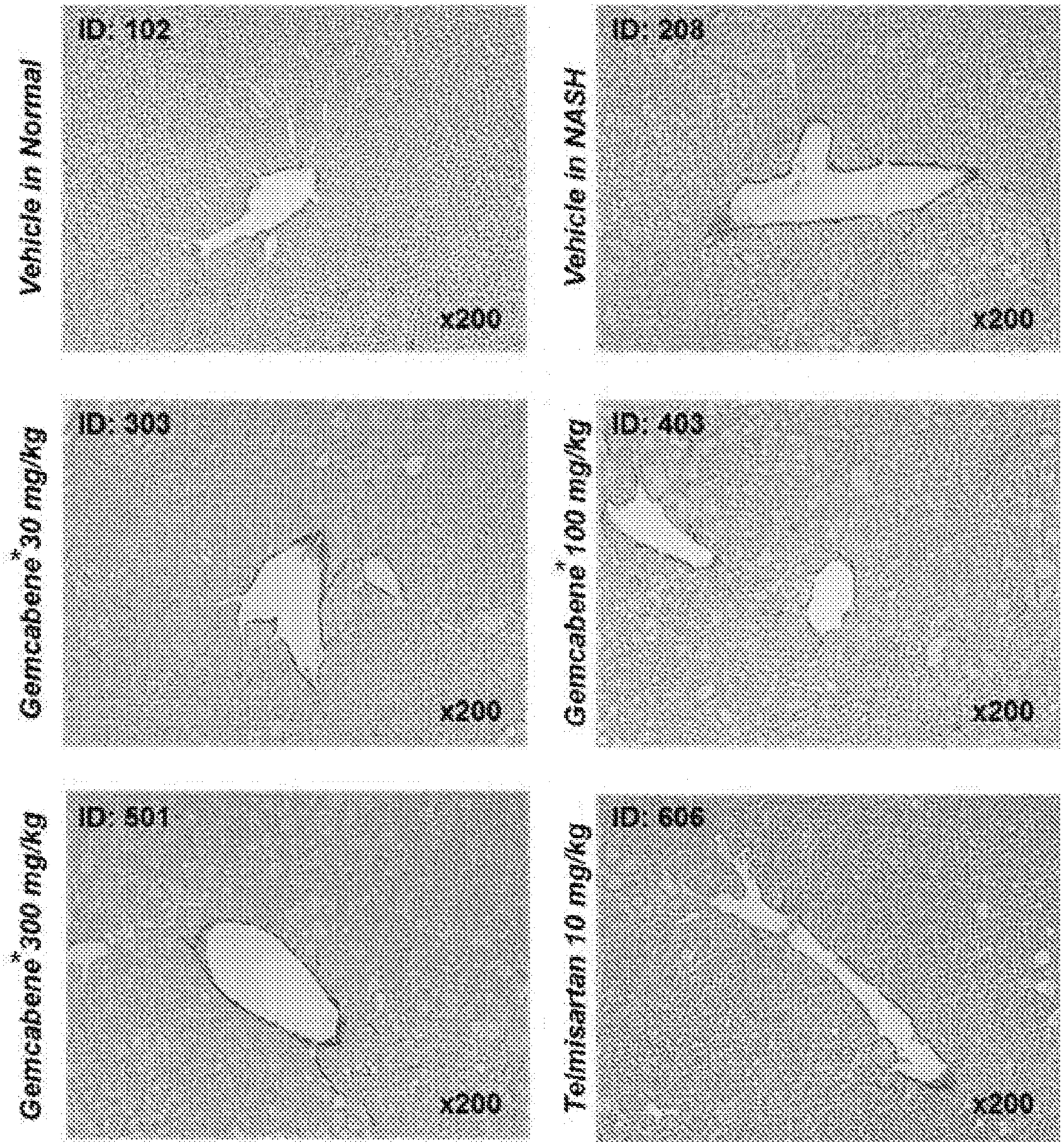
*Gemcabene calcium salt hydrate Crystal Form 1 (PSD90 = 52 μm)

Fig. 5B



*Gemcabene calcium salt hydrate Crystal Form 1 (PSD90 = 52 μm)

Fig. 6



Parameter (mean ± SD)	Vehicle in Normal (n=8)	Vehicle in NASH (n=8)	Gemcabene* 30 mg/kg (n=8)	Gemcabene* 100 mg/kg (n=8)	Gemcabene* 300 mg/kg (n=8)	Telmisartan 10 mg/kg (n=7)
Sirius red-positive area (%)	0.19 ± 0.03	0.84 ± 0.12	0.56 ± 0.18	0.53 ± 0.18	0.59 ± 0.16	0.48 ± 0.09

*Gemcabene calcium salt hydrate Crystal Form 1 (PSD90 = 52 µm)

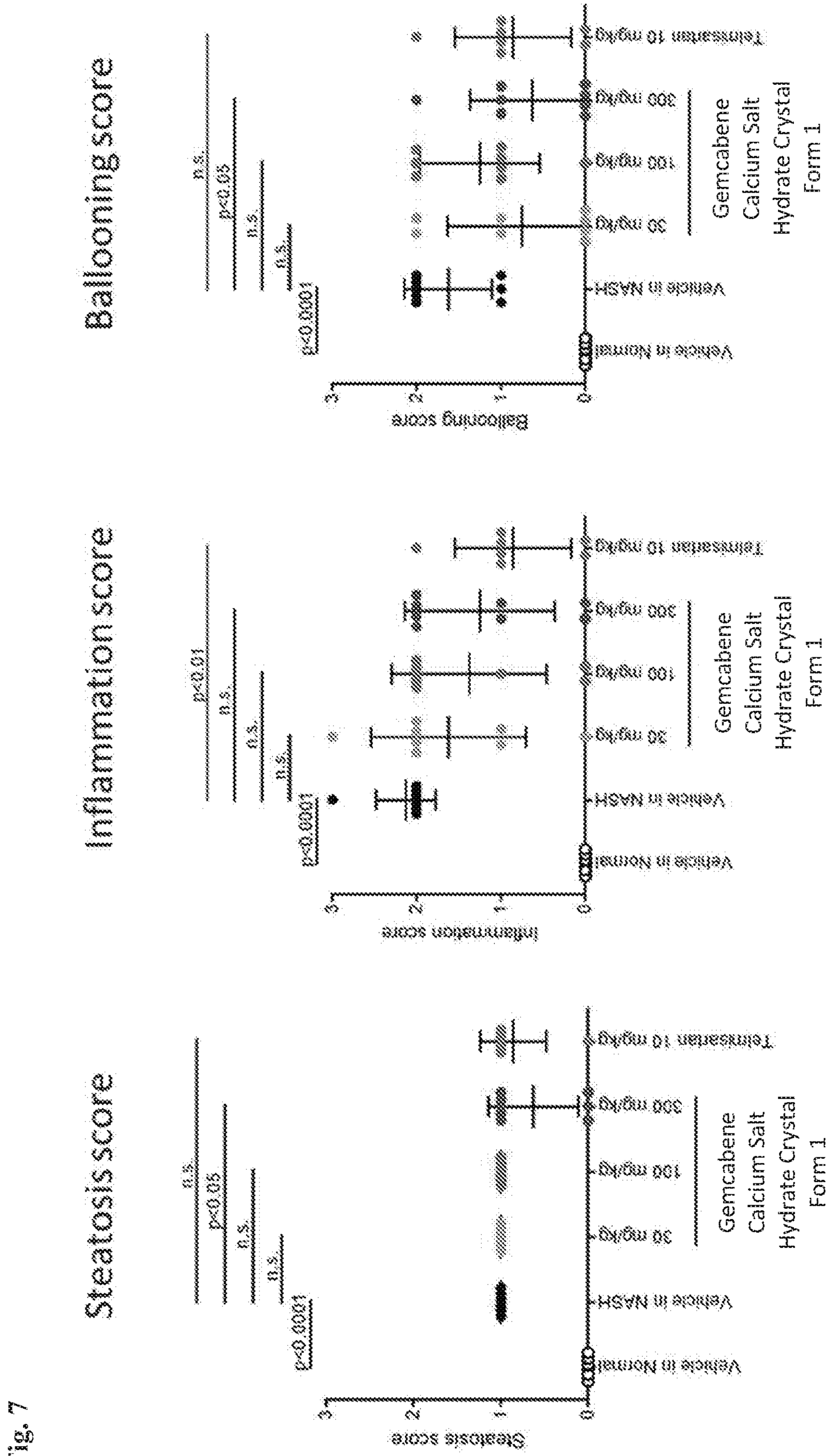

Ballooning score
n.s.
p<0.05
n.s.
n.s.
p<0.001
Telmisartan 10 mg/kg
300 mg/kg
100 mg/kg
30 mg/kg
Gemcabene
Calcium Salt
Hydrate Crystal
Form 1
Vehicle in NASH
Vehicle in Normal
Ballooning score
Inflammation score
p<0.01
n.s.
n.s.
n.s.
p<0.0001
Telmisartan 10 mg/kg
300 mg/kg
100 mg/kg
30 mg/kg
Gemcabene
Calcium Salt
Hydrate Crystal
Form 1
Vehicle in NASH
Vehicle in Normal
Inflammation score
Steatosis score
n.s.
p<0.05
n.s.
n.s.
p<0.0001
Telmisartan 10 mg/kg
300 mg/kg
100 mg/kg
30 mg/kg
Gemcabene
Calcium Salt
Hydrate Crystal
Form 1
Vehicle in NASH
Vehicle in Normal
Steatosis score

Fig. 7

Fig. 8A

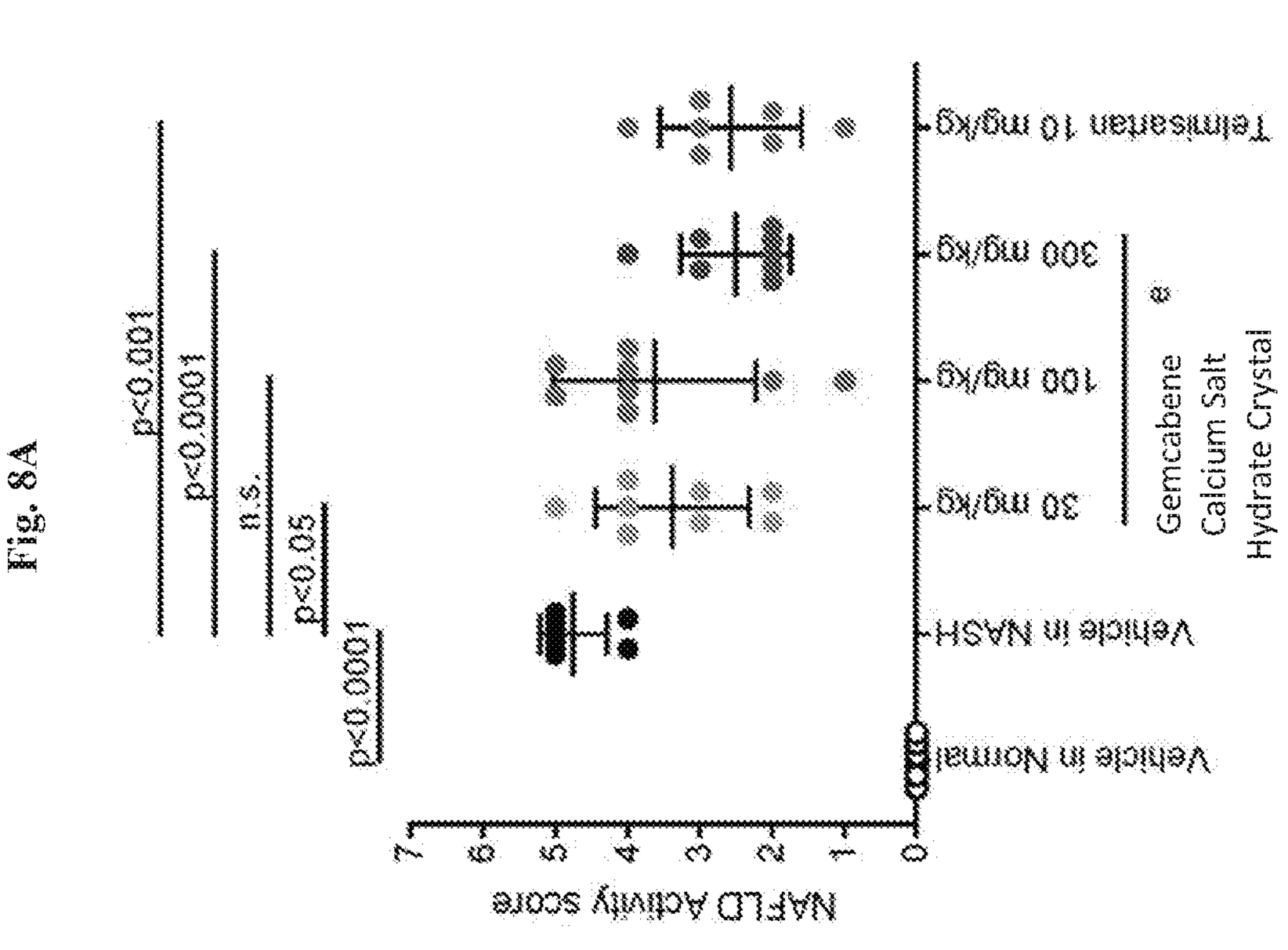

p<0.001
p<0.0001
n.s.
p<0.05
p<0.0001
NAFLD Activity score
0
1
2
3
4
5
6
7
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

Fig. 8B

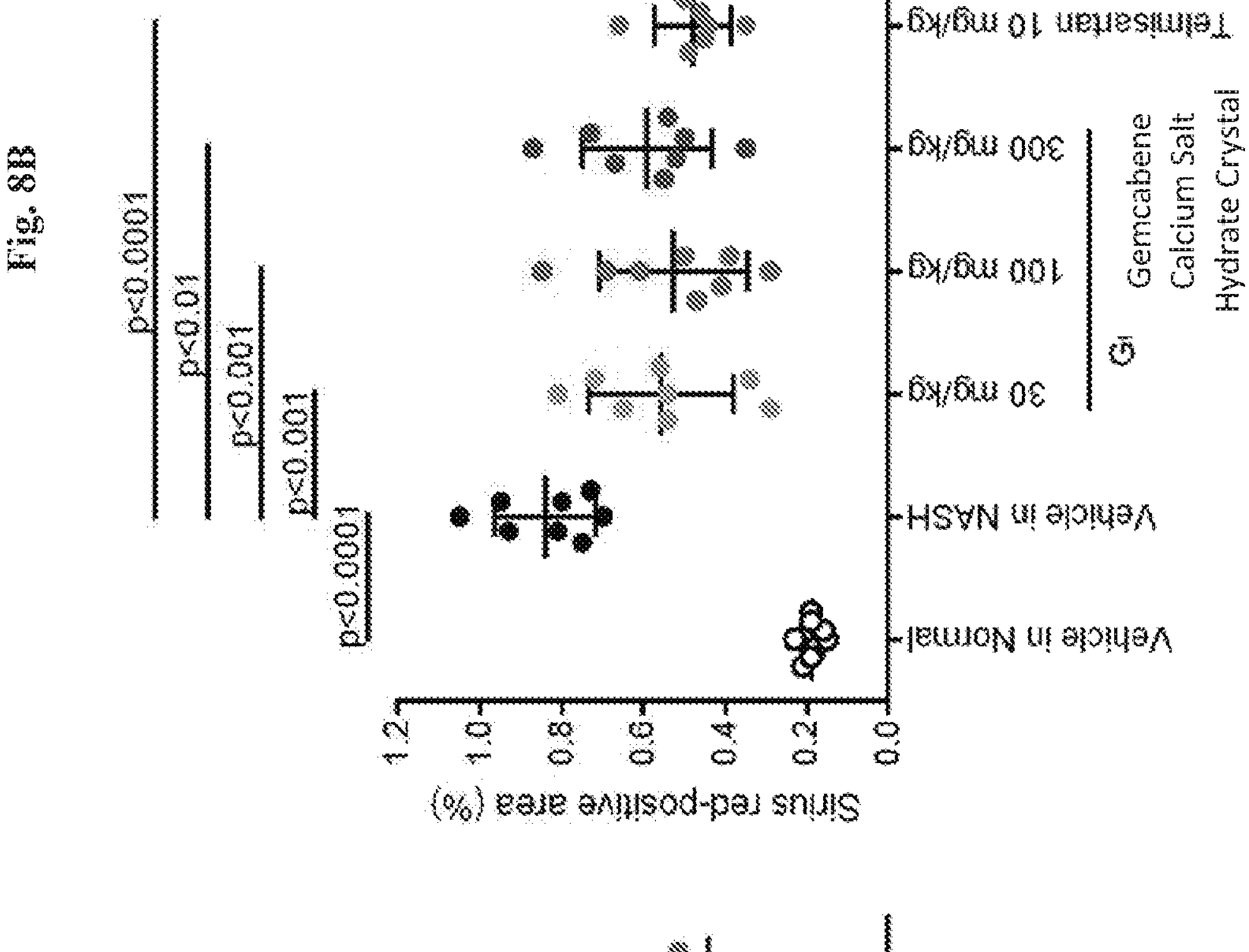

p<0.0001
p<0.01
p<0.001
p<0.001
p<0.0001
Sirius red-positive area (%)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

Fig. 9

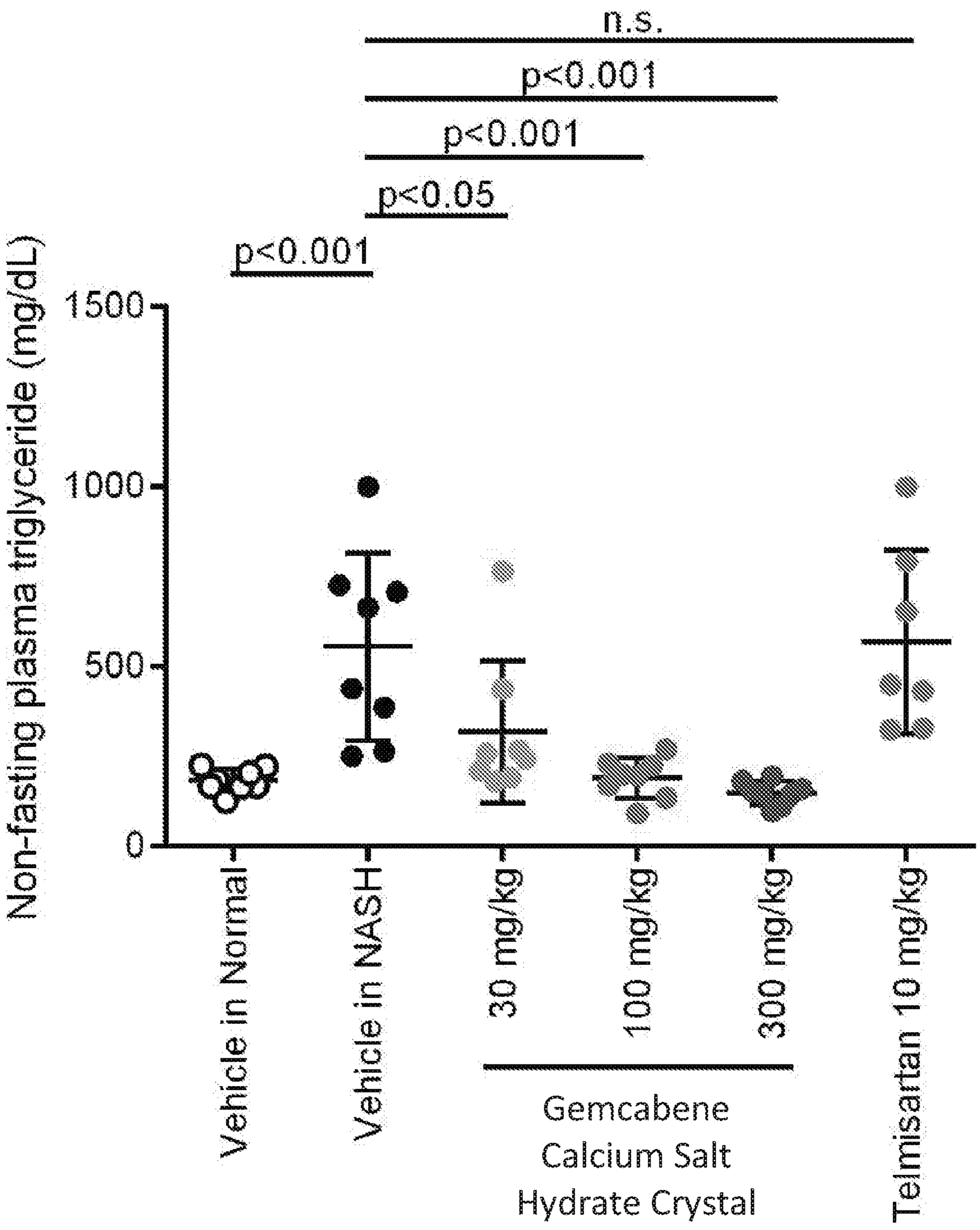

n.s.
p<0.001
p<0.001
p<0.05
p<0.001
Non-fasting plasma triglyceride (mg/dL)
1500
1000
500
0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1
Olmisartan 10 mg/kg

Fig. 10

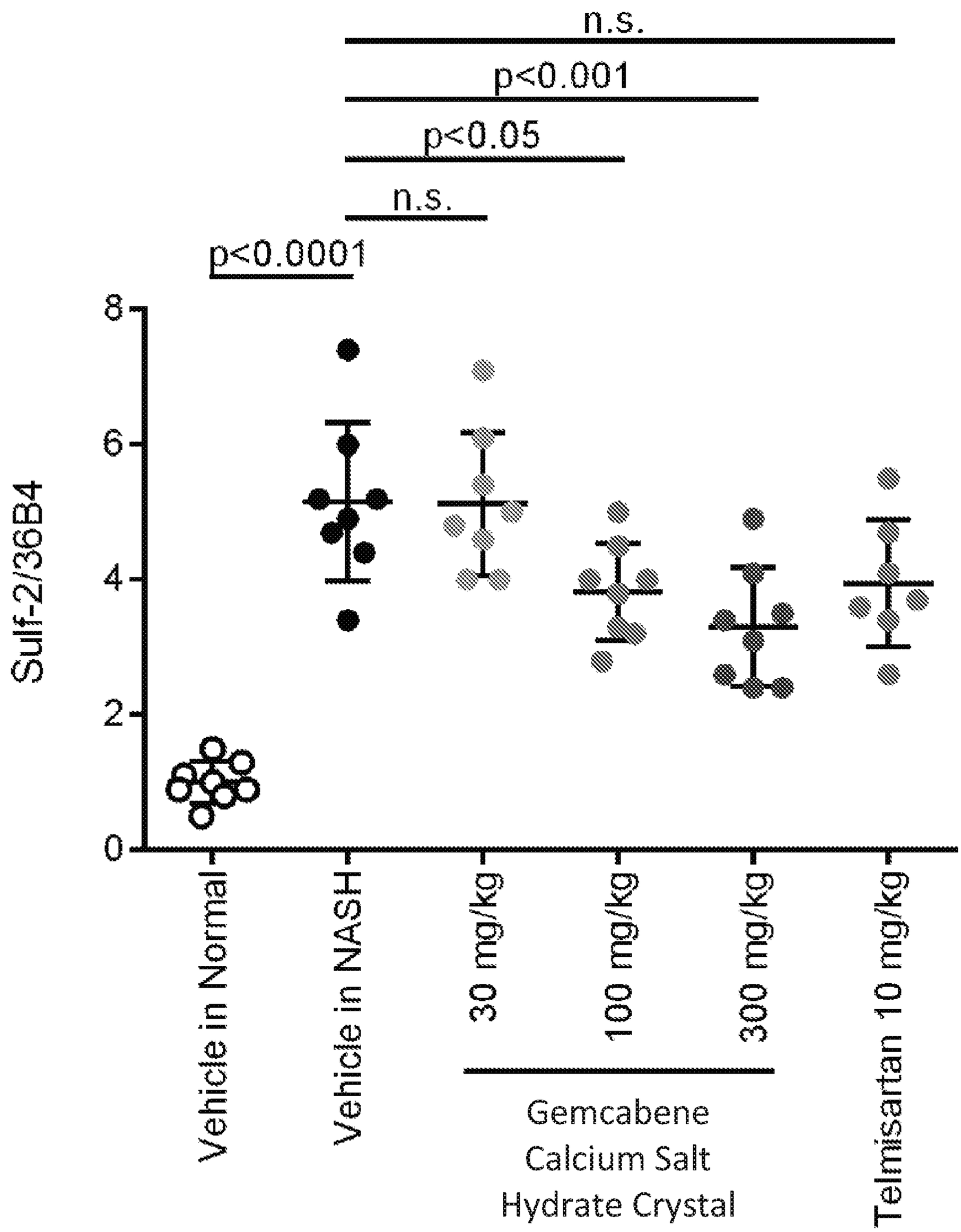

n.s.
p<0.001
p<0.05
n.s.
p<0.0001
Sulf-2/36B4
8
6
4
2
0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene
Calcium Salt
Hydrate Crystal
Form 1

Fig. 11

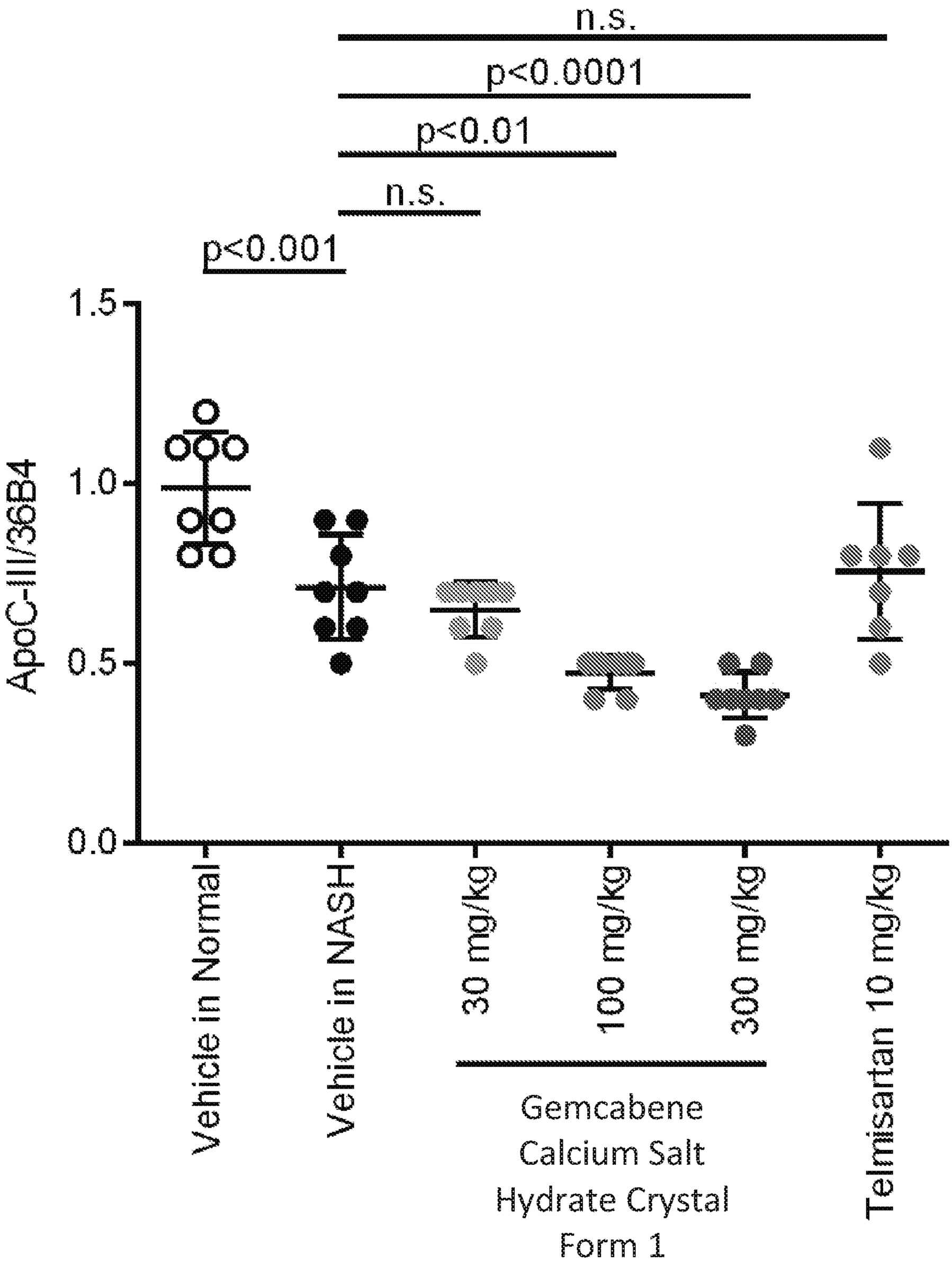

n.s.
p<0.0001
p<0.01
n.s.
p<0.001
ApoC-III/36B4
1.5
1.0
0.5
0.0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1
Telmisartan 10 mg/kg

Fig. 12

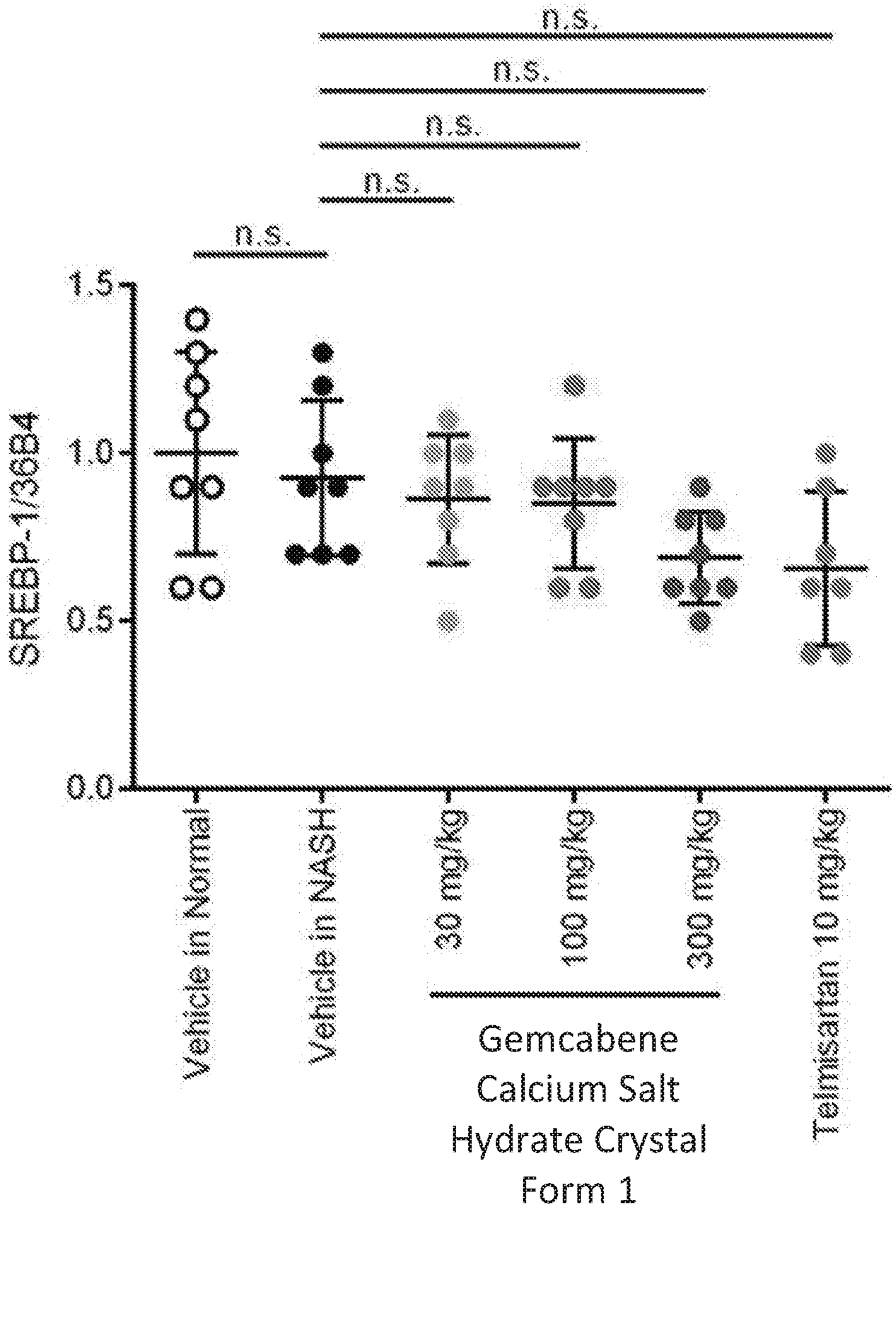

n.s.
n.s.
n.s.
n.s.
n.s.
SREBP-1/36B4
1.5
1.0
0.5
0.0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene
Calcium Salt
Hydrate Crystal
Form 1

Fig. 13

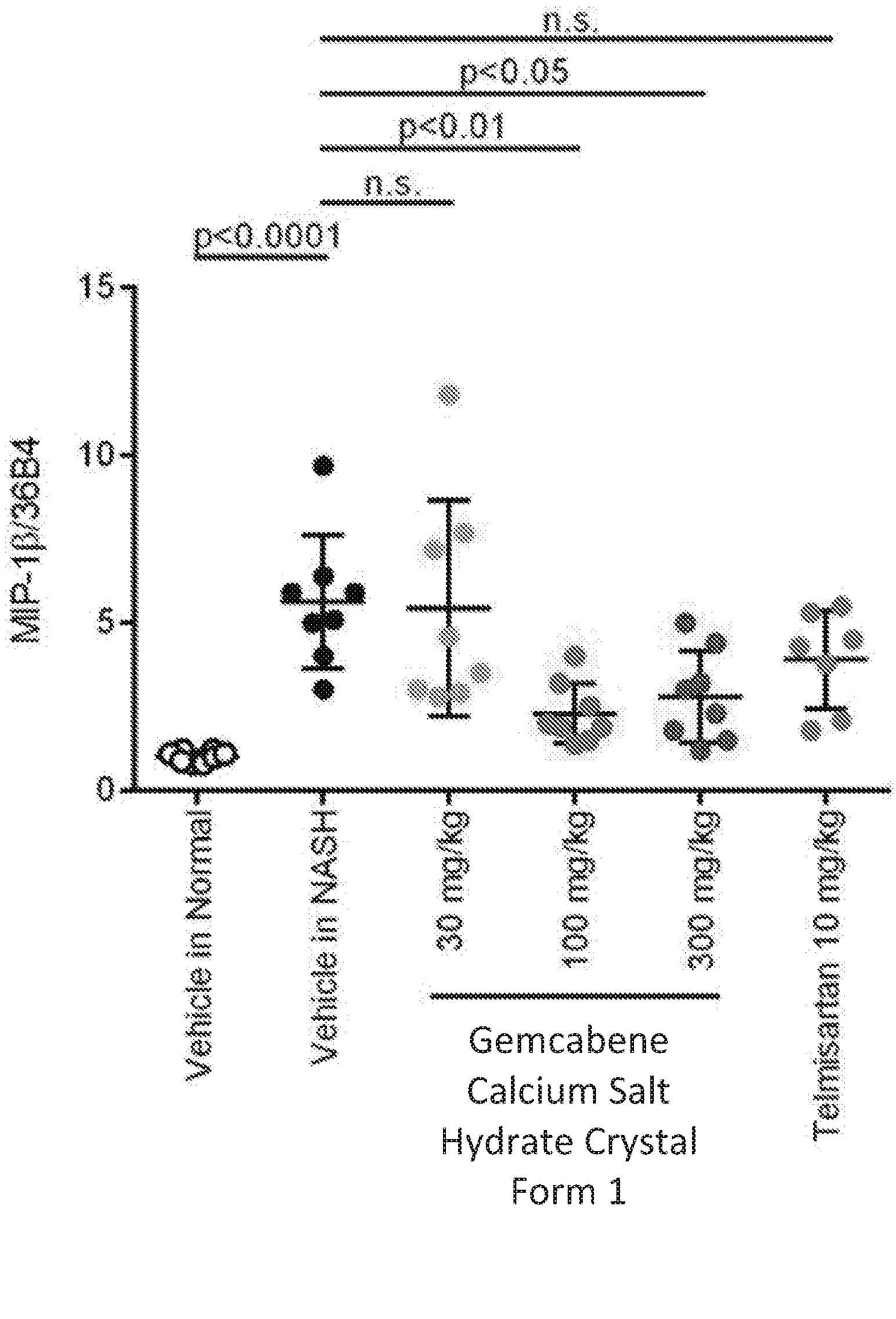

n.s.
p<0.05
p<0.01
n.s.
p<0.0001
MIP-1β/3684
15
10
5
0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1
Telmisartan 10 mg/kg

Fig. 14

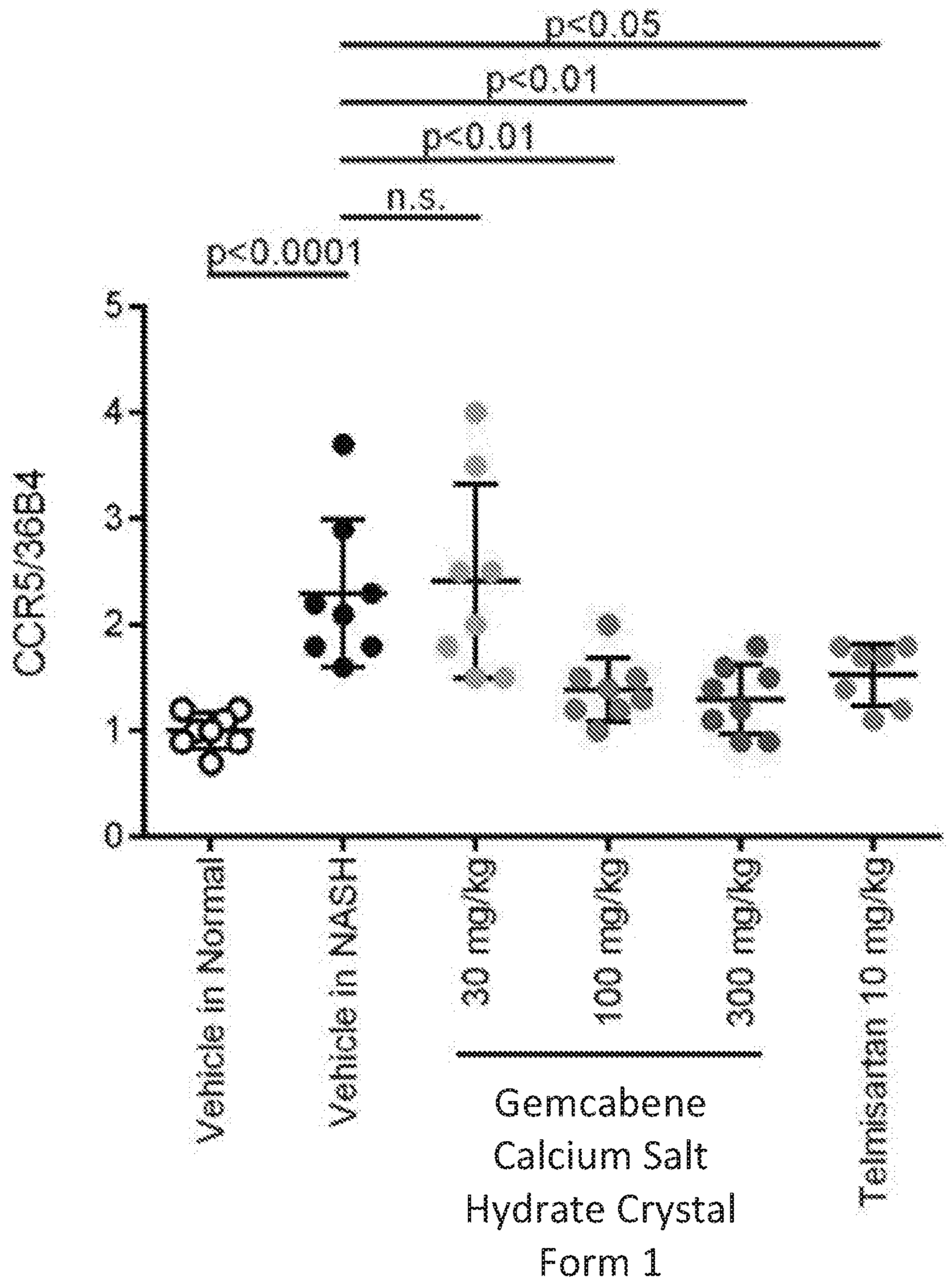

p<0.05
p<0.01
p<0.01
n.s.
p<0.0001
CCR5/36B4
0
1
2
3
4
5
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene
Calcium Salt
Hydrate Crystal
Form 1

Fig. 15

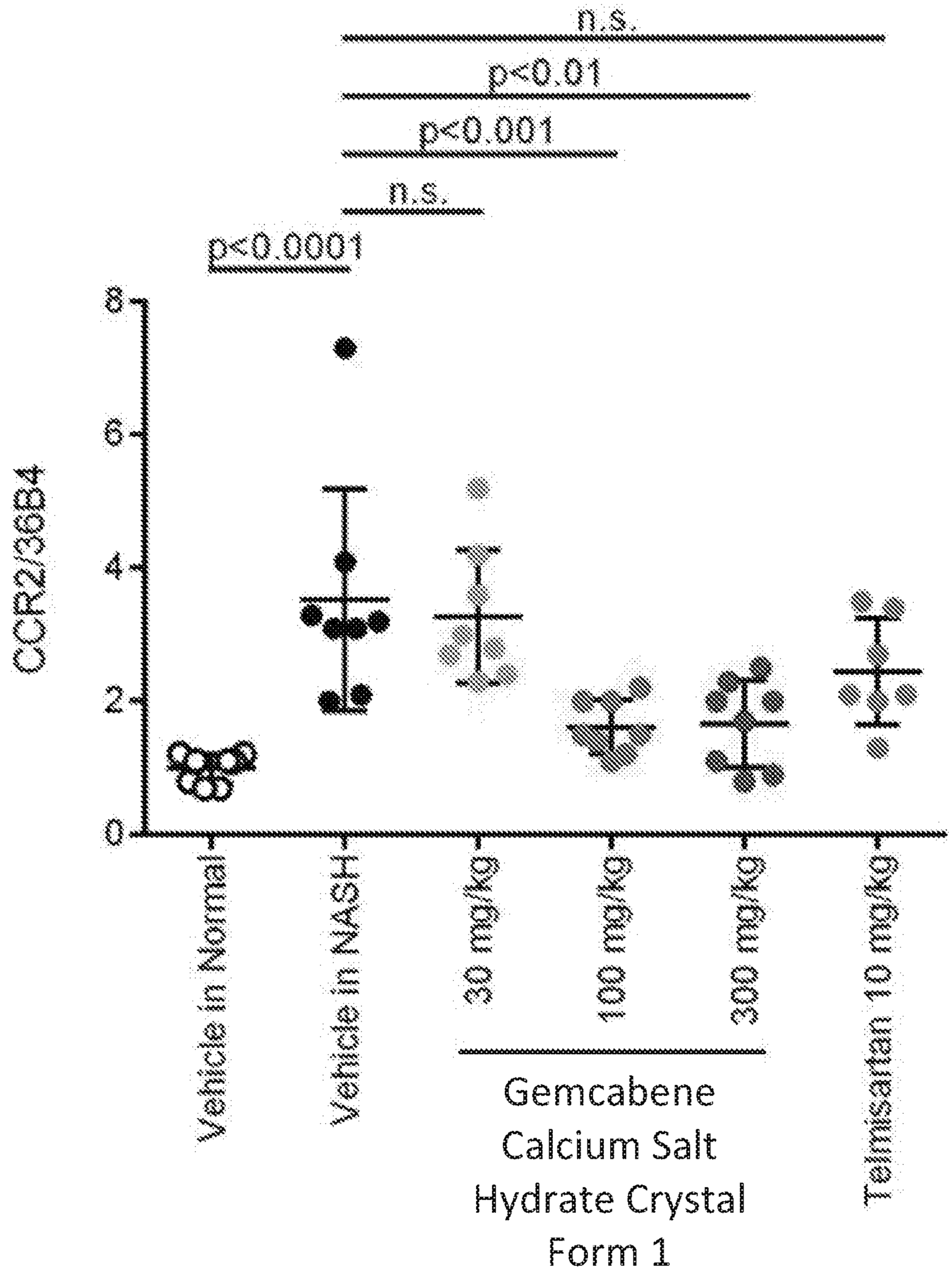

n.s.
p<0.01
p<0.001
n.s.
p<0.0001
CCR2/36B4
0
2
4
6
8
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

Fig. 16

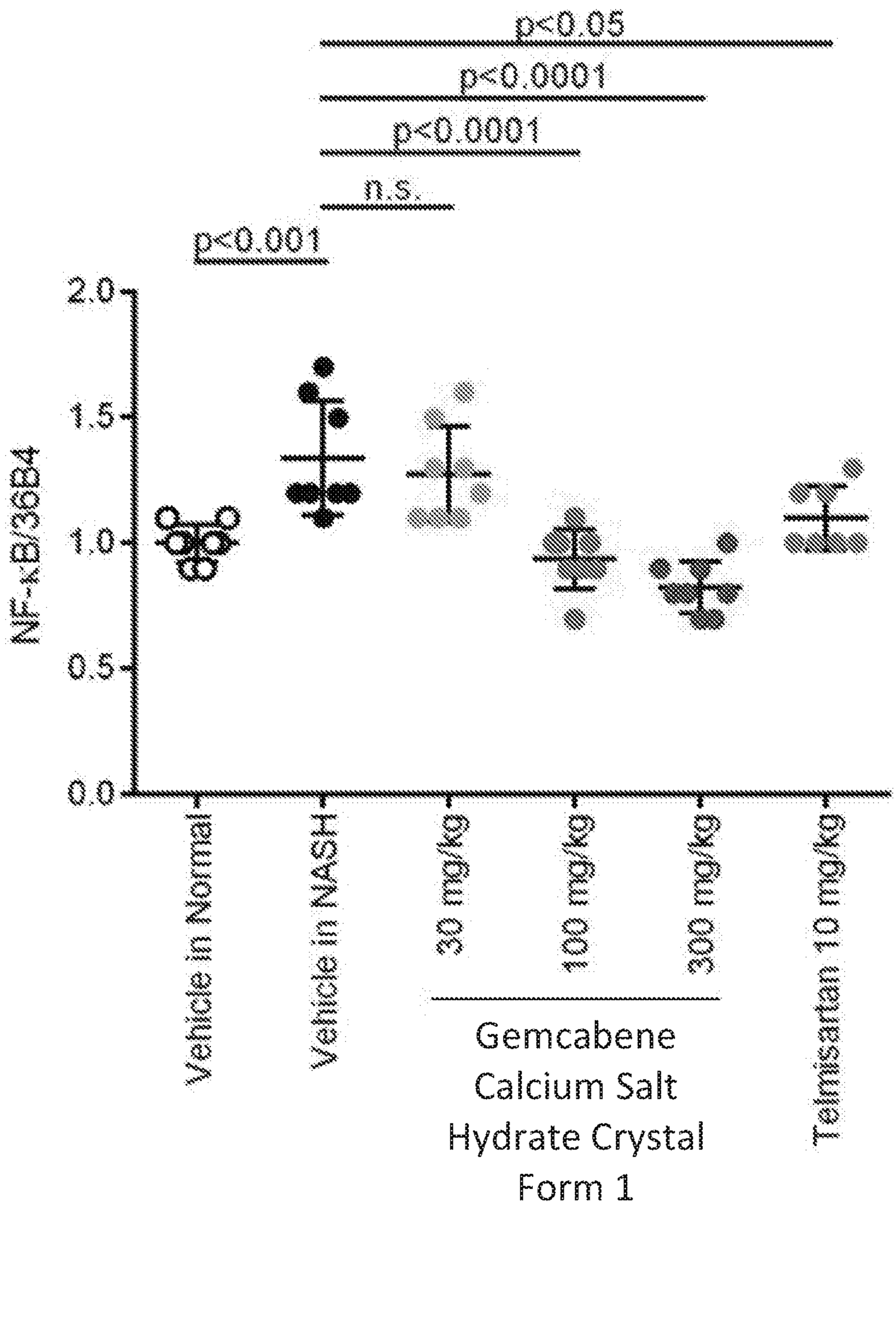

p<0.05
p<0.0001
p<0.0001
n.s.
p<0.001
NF-κB/36B4
2.0
1.5
1.0
0.5
0.0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1
Telmisartan 10 mg/kg

FIG. 17

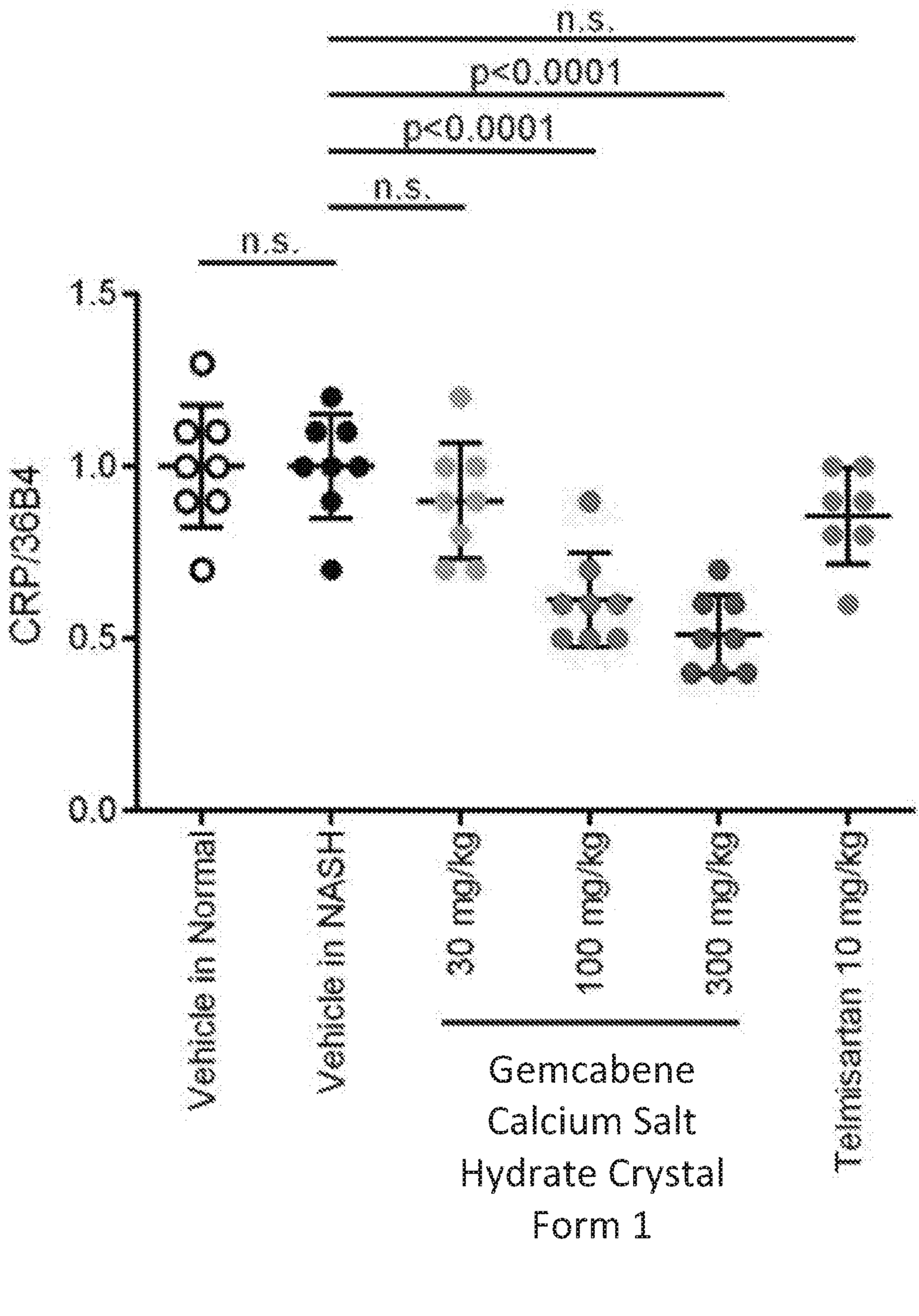

n.s.
p<0.0001
p<0.0001
n.s.
n.s.
CRP/36B4
1.5
1.0
0.5
0.0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene
Calcium Salt
Hydrate Crystal
Form 1

FIG. 18

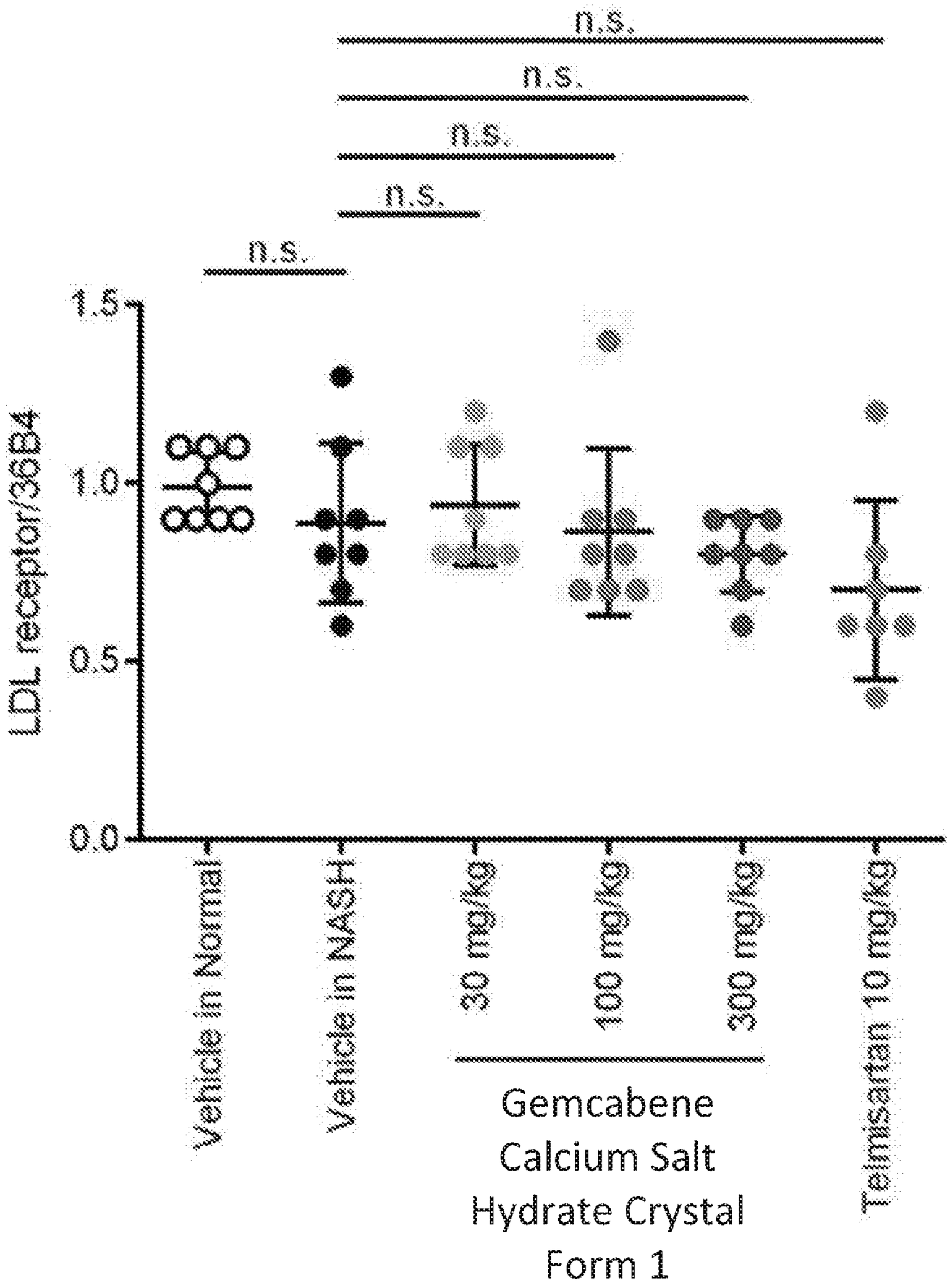

n.s.
n.s.
n.s.
n.s.
n.s.
LDL receptor/36B4
1.5
1.0
0.5
0.0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

FIG. 19

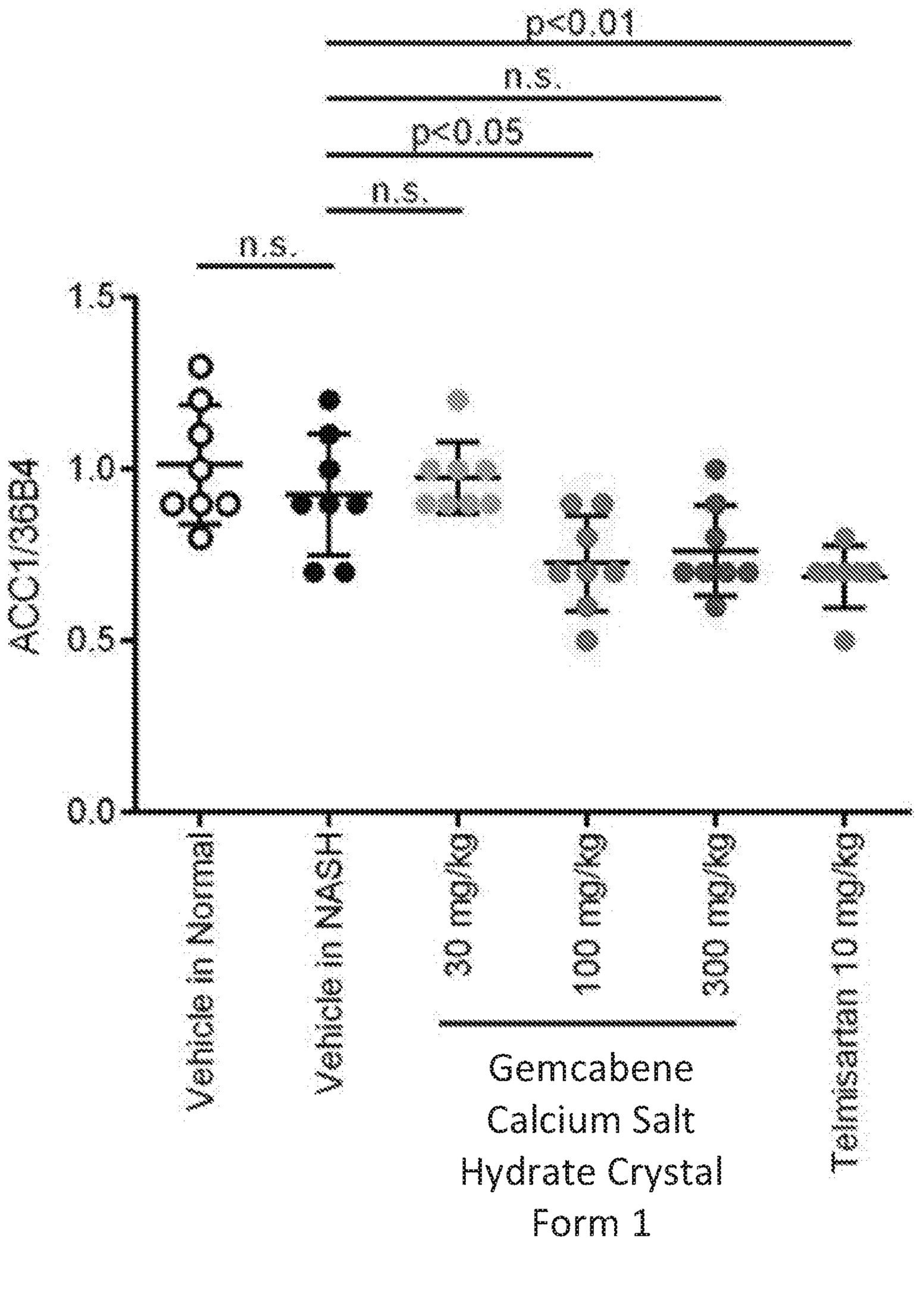

p<0.01
n.s.
p<0.05
n.s.
n.s.
ACC1/36B4
1.5
1.0
0.5
0.0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1
Telmisartan 10 mg/kg

FIG. 20

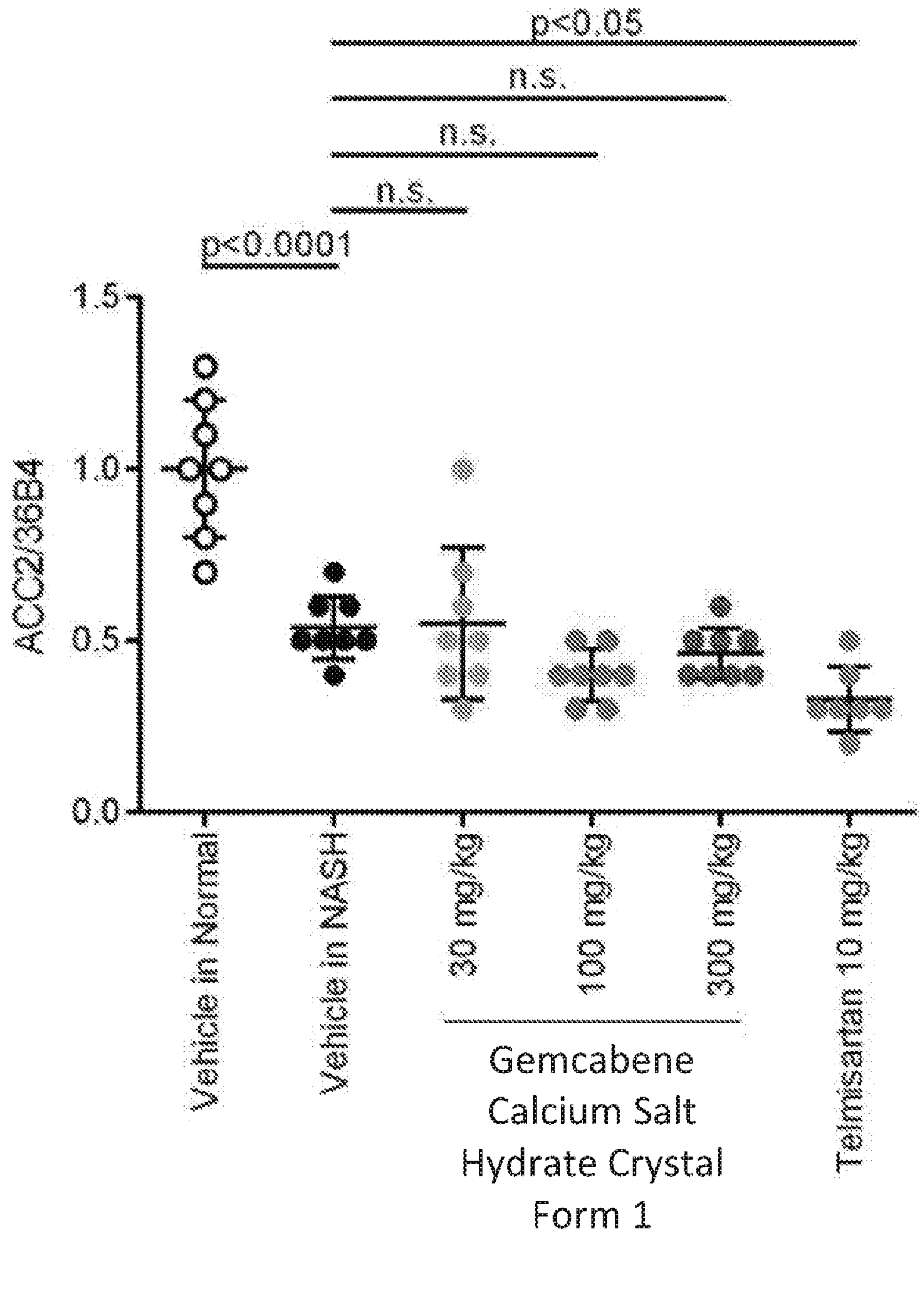

p<0.05
n.s.
n.s.
n.s.
p<0.0001
1.5
1.0
0.5
0.0
AOC2/36B4
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene
Calcium Salt
Hydrate Crystal
Form 1

FIG. 21

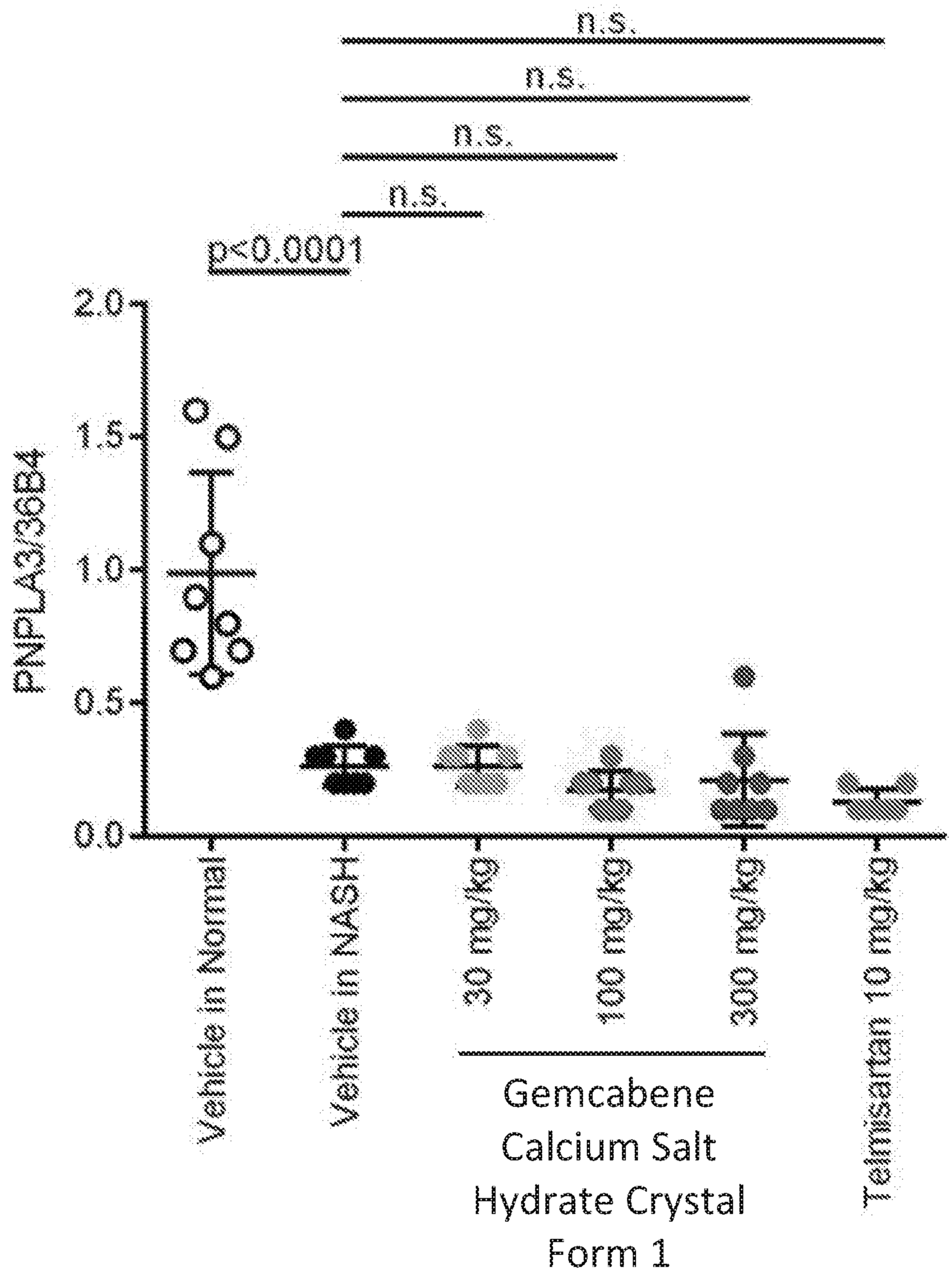

n.s.
n.s.
n.s.
n.s.
p<0.0001
PNPLA3/SBB4
2.0
1.5
1.0
0.5
0.0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

FIG. 22

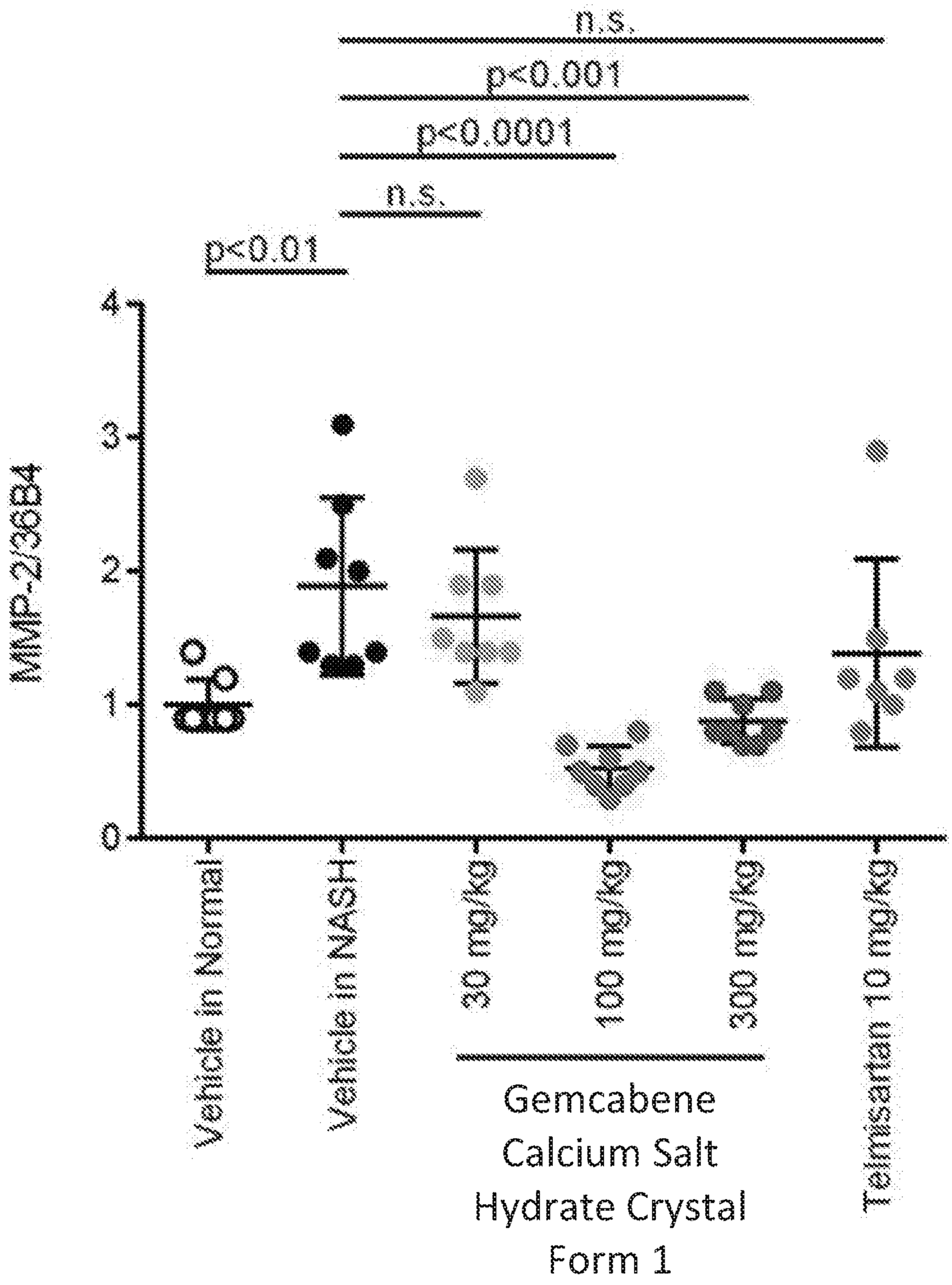

n.s.
p<0.001
p<0.0001
n.s.
p<0.01
MMP-2/36B4
0
1
2
3
4
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

FIG. 23

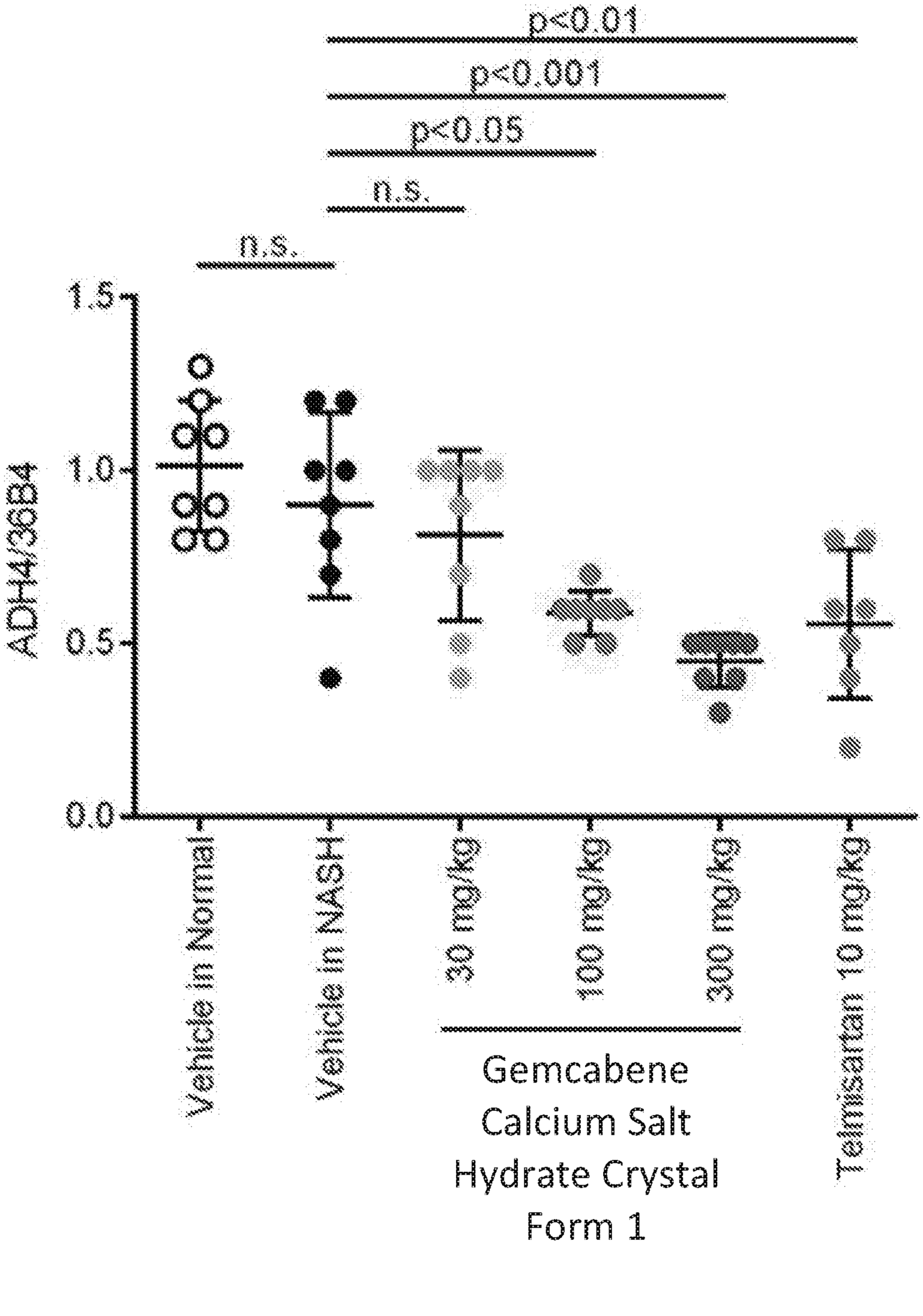

p<0.01
p<0.001
p<0.05
n.s.
n.s.
ADH4/36B4
1.5
1.0
0.5
0.0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene
Calcium Salt
Hydrate Crystal
Form 1

FIG. 24

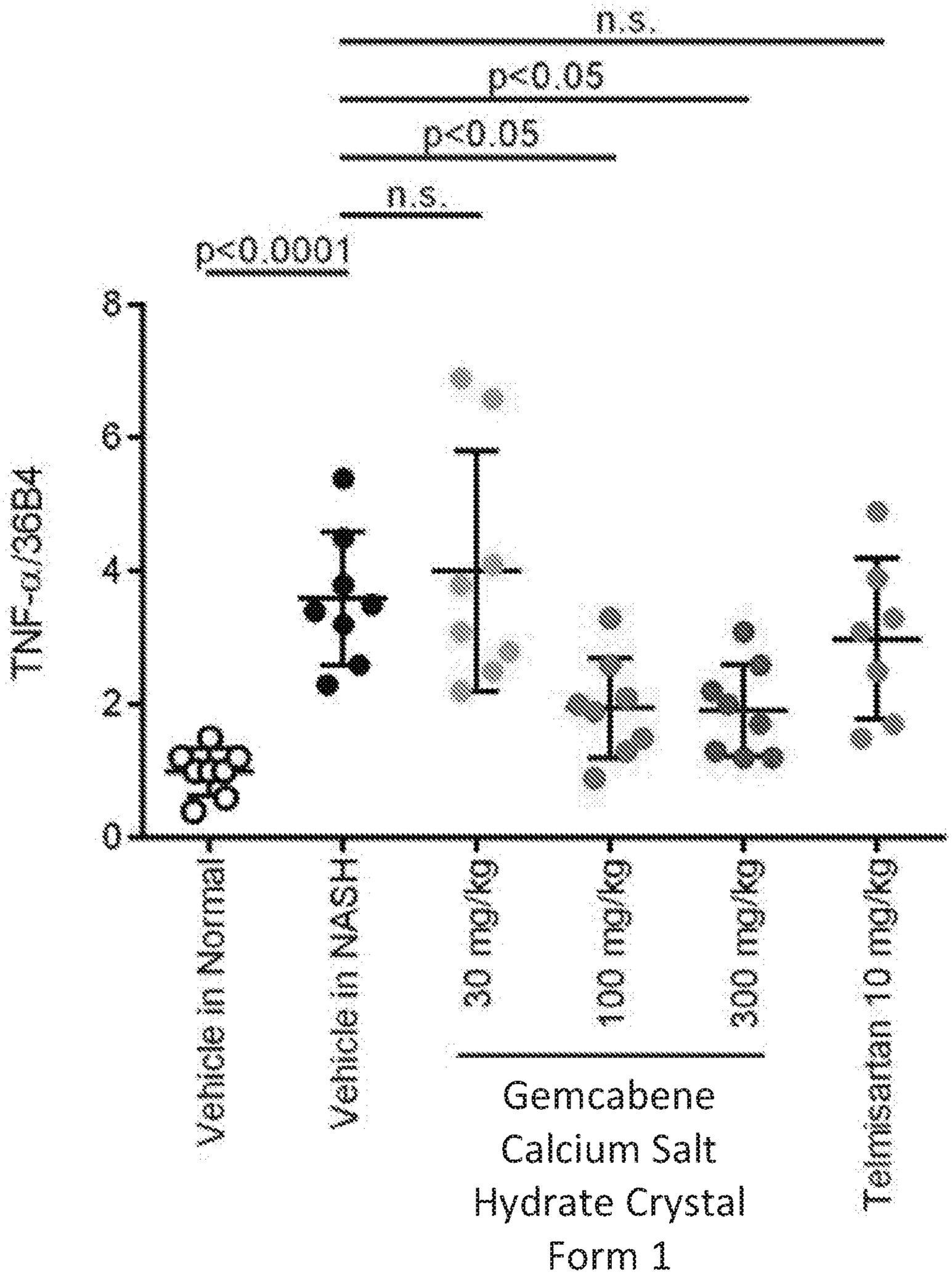

n.s.
p<0.05
p<0.05
n.s.
p<0.0001
TNF-α/36B4
0
2
4
6
8
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

FIG. 25

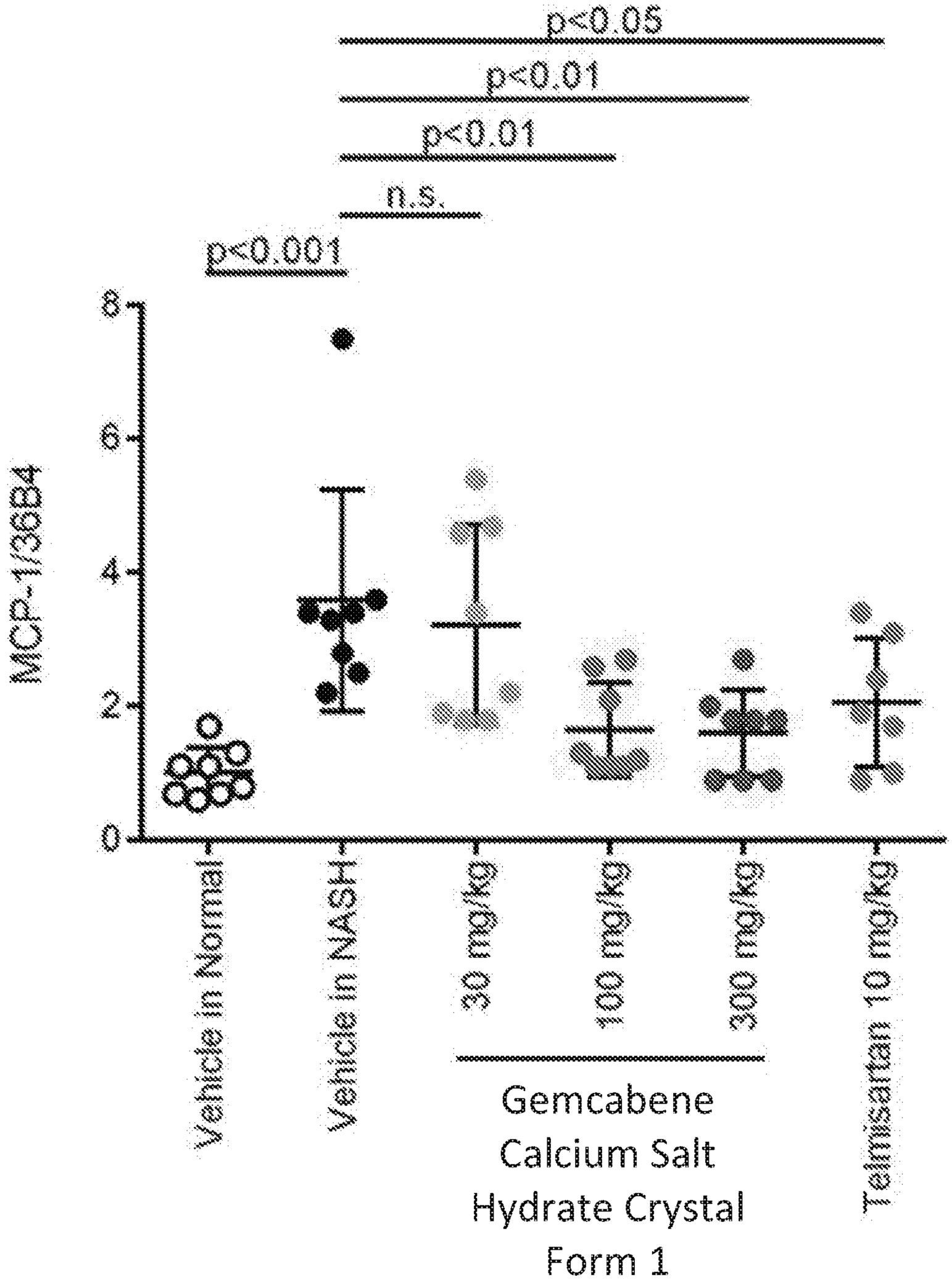

p<0.05
p<0.01
p<0.01
n.s.
p<0.001
MCP-1/36B4
8
6
4
2
0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

FIG. 26

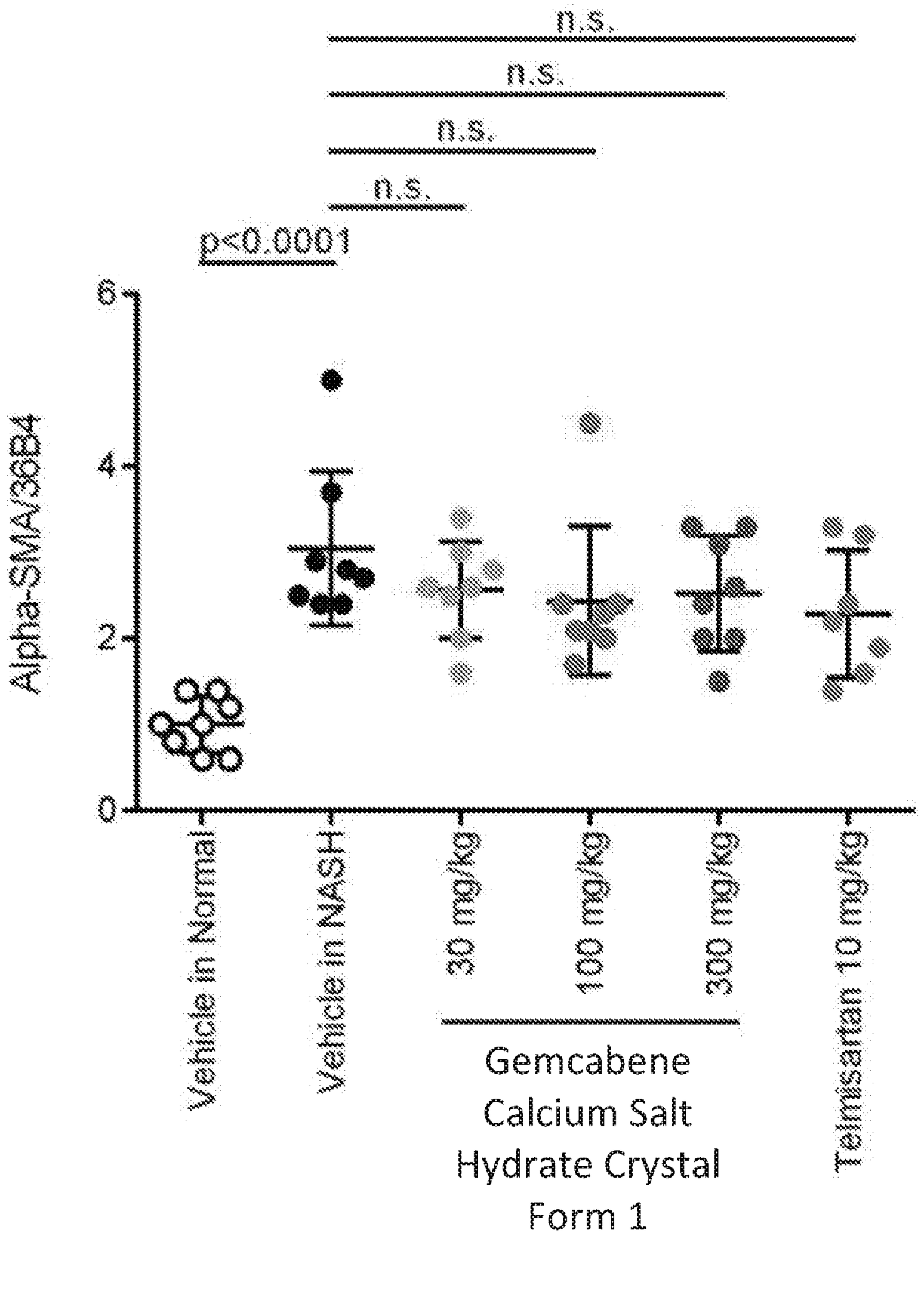

n.s.
n.s.
n.s.
n.s.
p<0.0001
Alpha-SMA/36B4
6
4
2
0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene
Calcium Salt
Hydrate Crystal
Form 1

FIG. 27

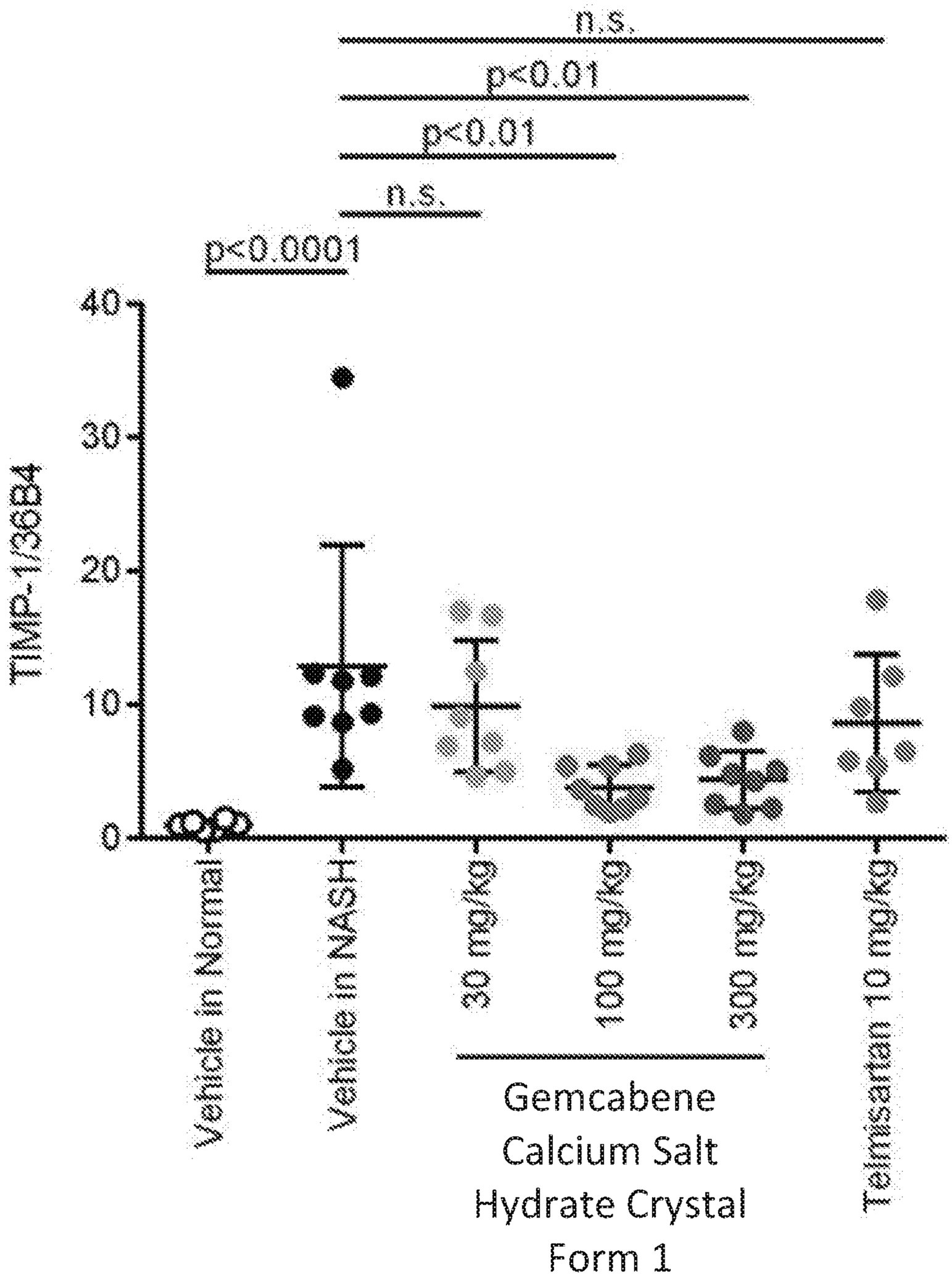

n.s.
p<0.01
p<0.01
n.s.
p<0.0001
TIMP-1/36B4
40
30
20
10
0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

Fig. 28

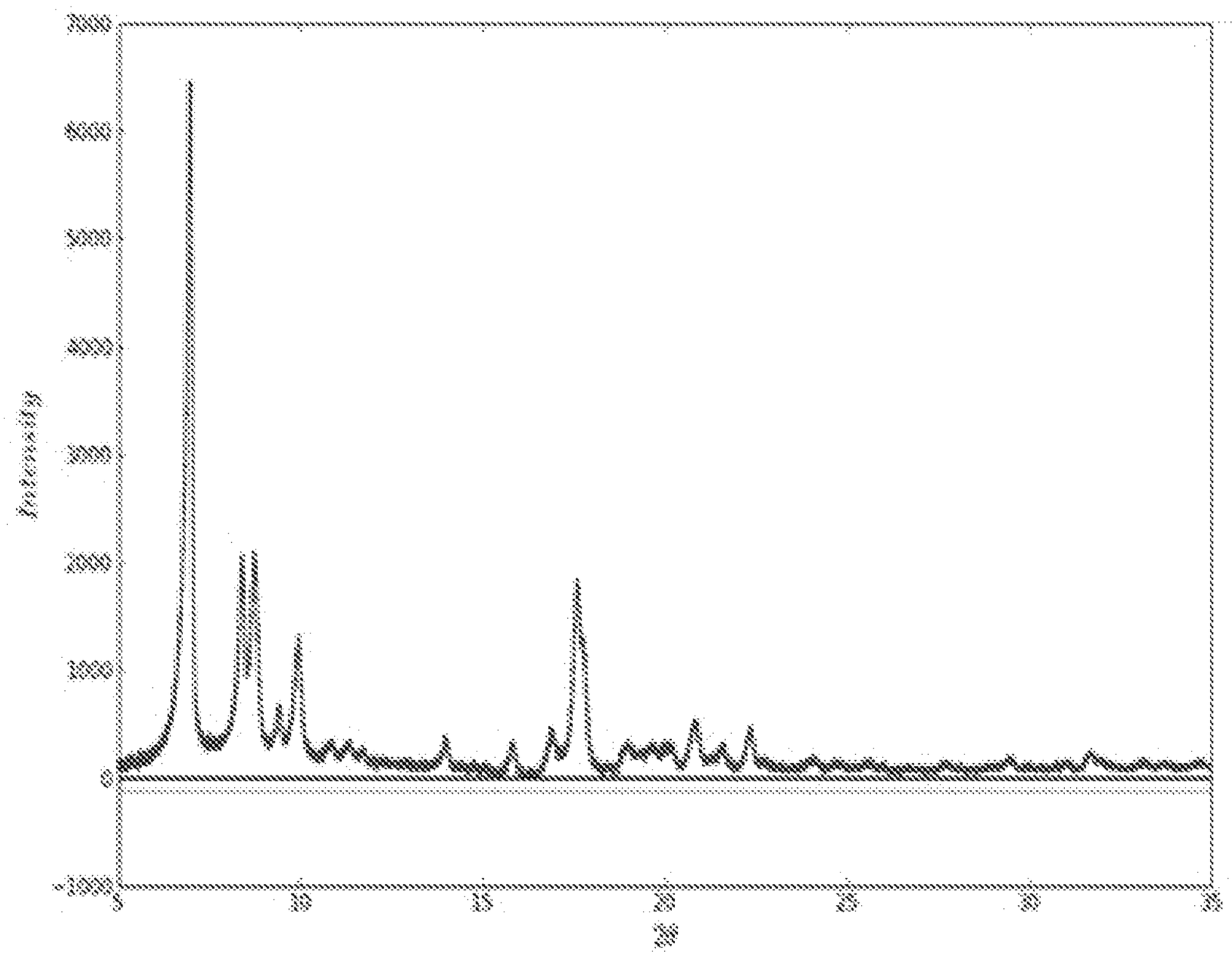

Intensity
3000
2000
1000
0
-1000
5
10
15
20
25
30
35
2θ

Fig. 29

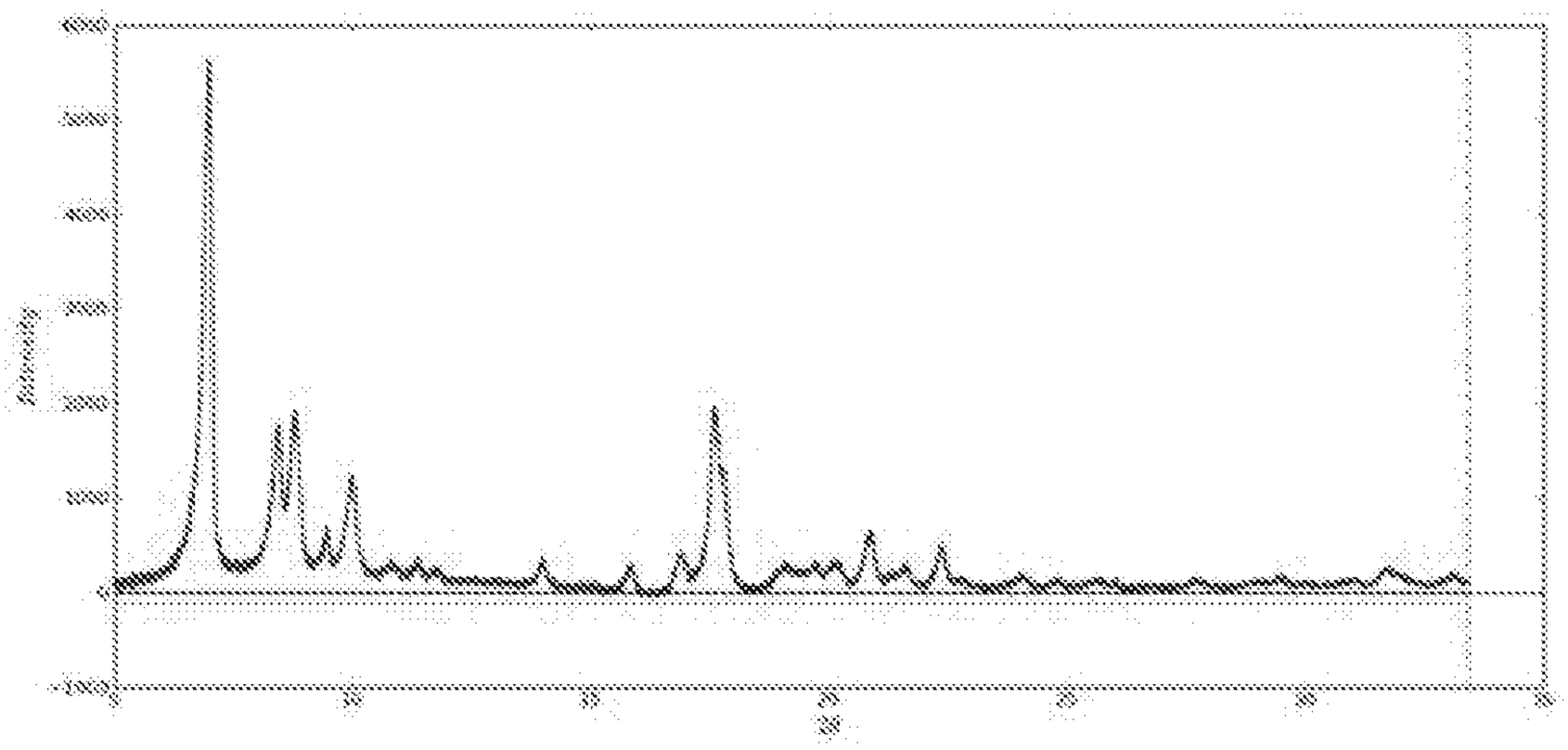
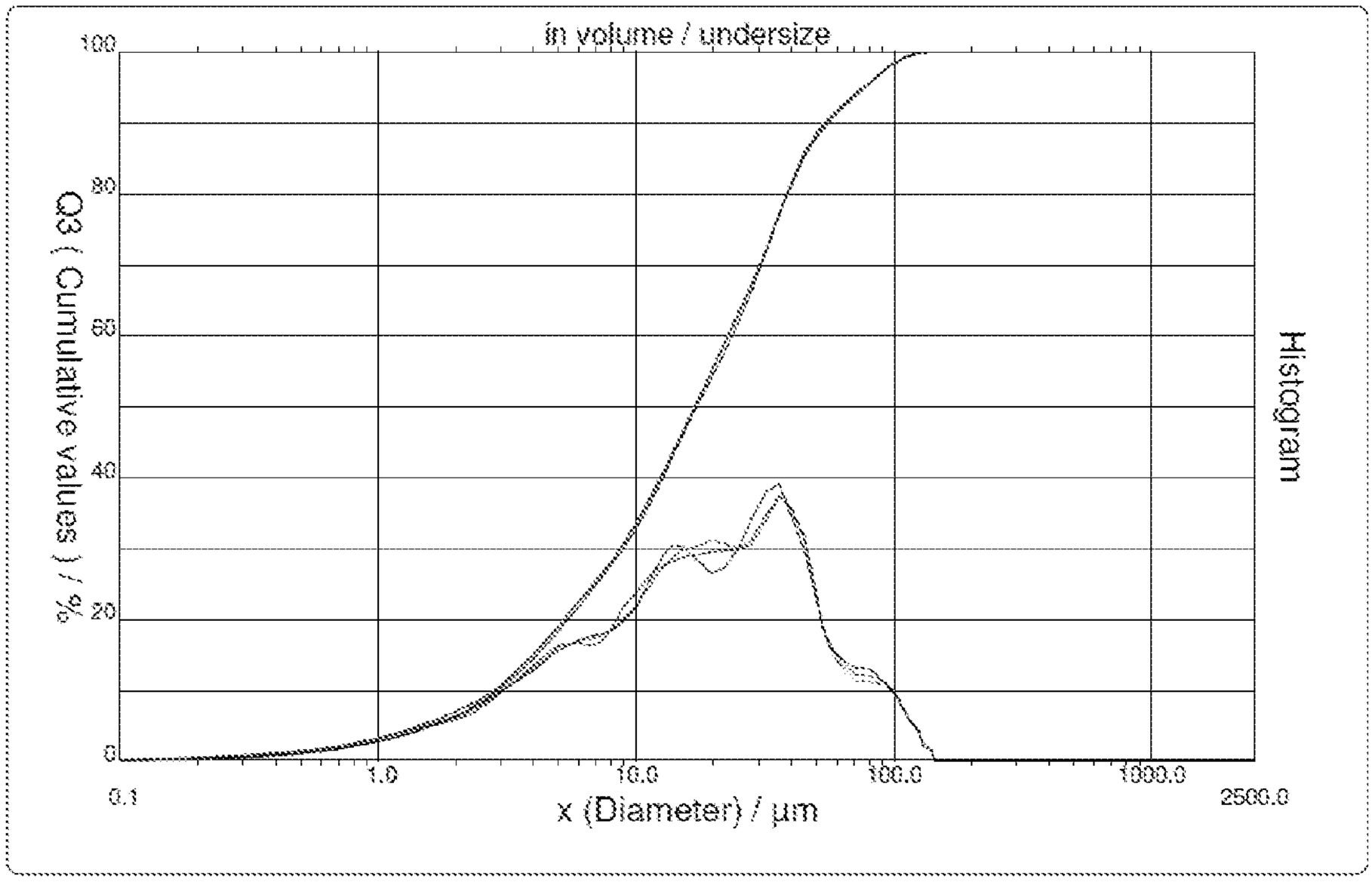
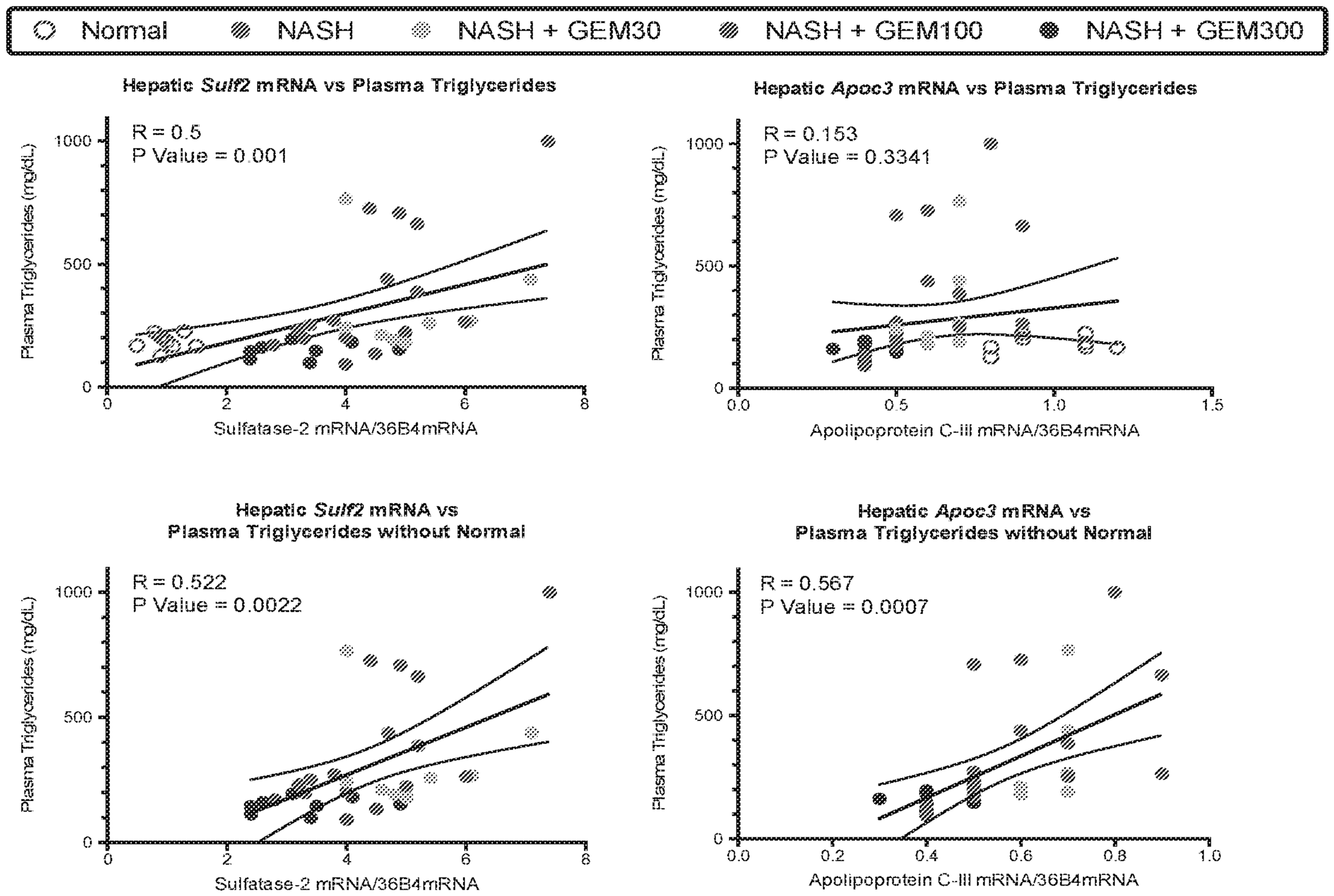

Intensity
4000
3000
2000
1000
0
10
15
20
25
30
35
2θ

Fig. 30


in volume / undersize
100
80
60
40
20
0
Q3 (Cumulative values) / %
0.1
1.0
10.0
100.0
1000.0
2500.0
x (Diameter) / µm
Histogram

CA 03059073 2019-10-03

Fig. 31



GEM = gemcabene calcium salt hydrate Crystal Form 1 (PSD90 = 52 μm); GEM 30 indicates 30 mg/kg of gemcabene calcium salt hydrate Crystal Form 1 (PSD90 = 52 μm)

FIG. 32

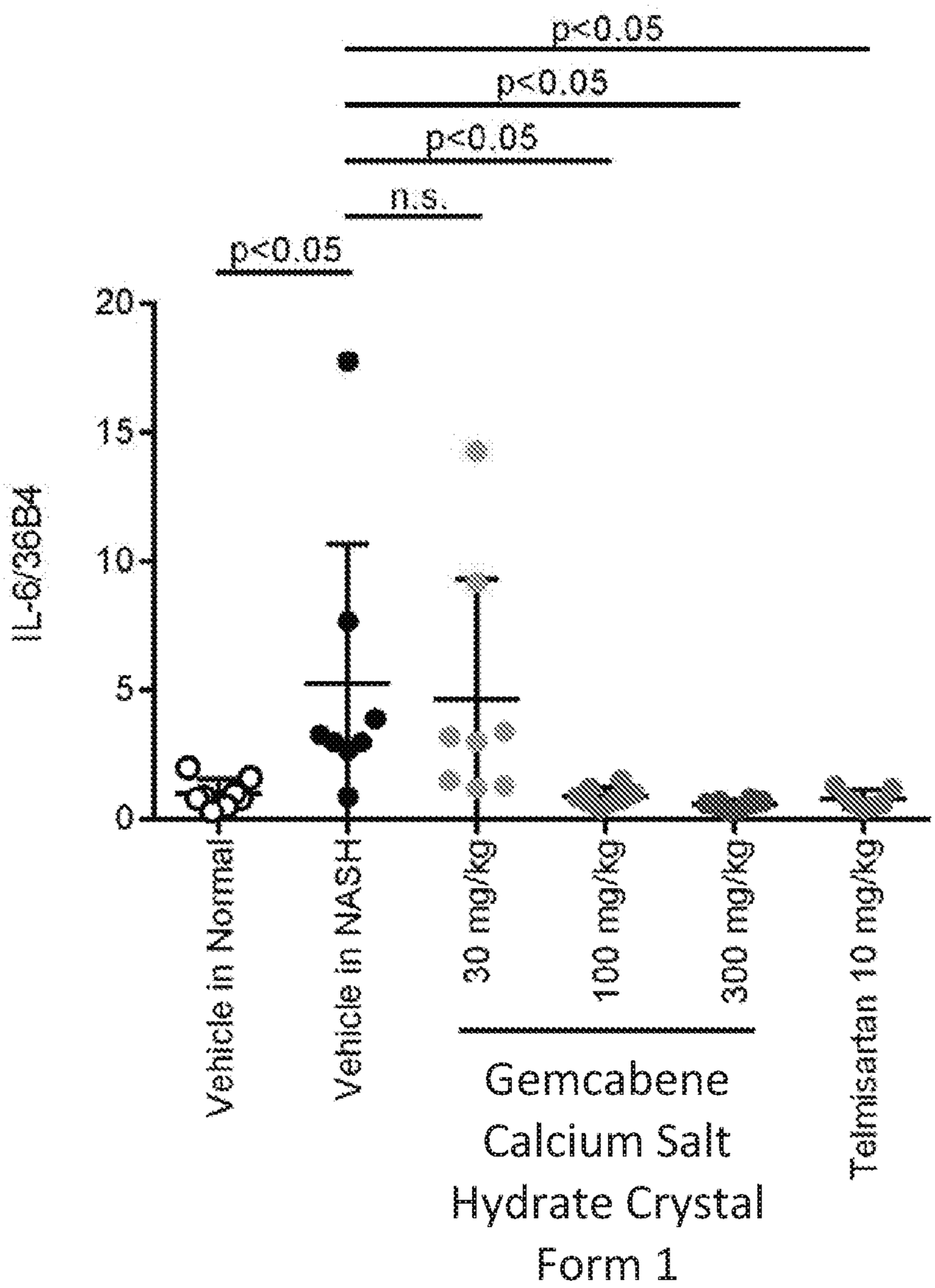

p<0.05
p<0.05
p<0.05
n.s.
p<0.05
IL-6/36B4
20
15
10
5
0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

FIG. 33

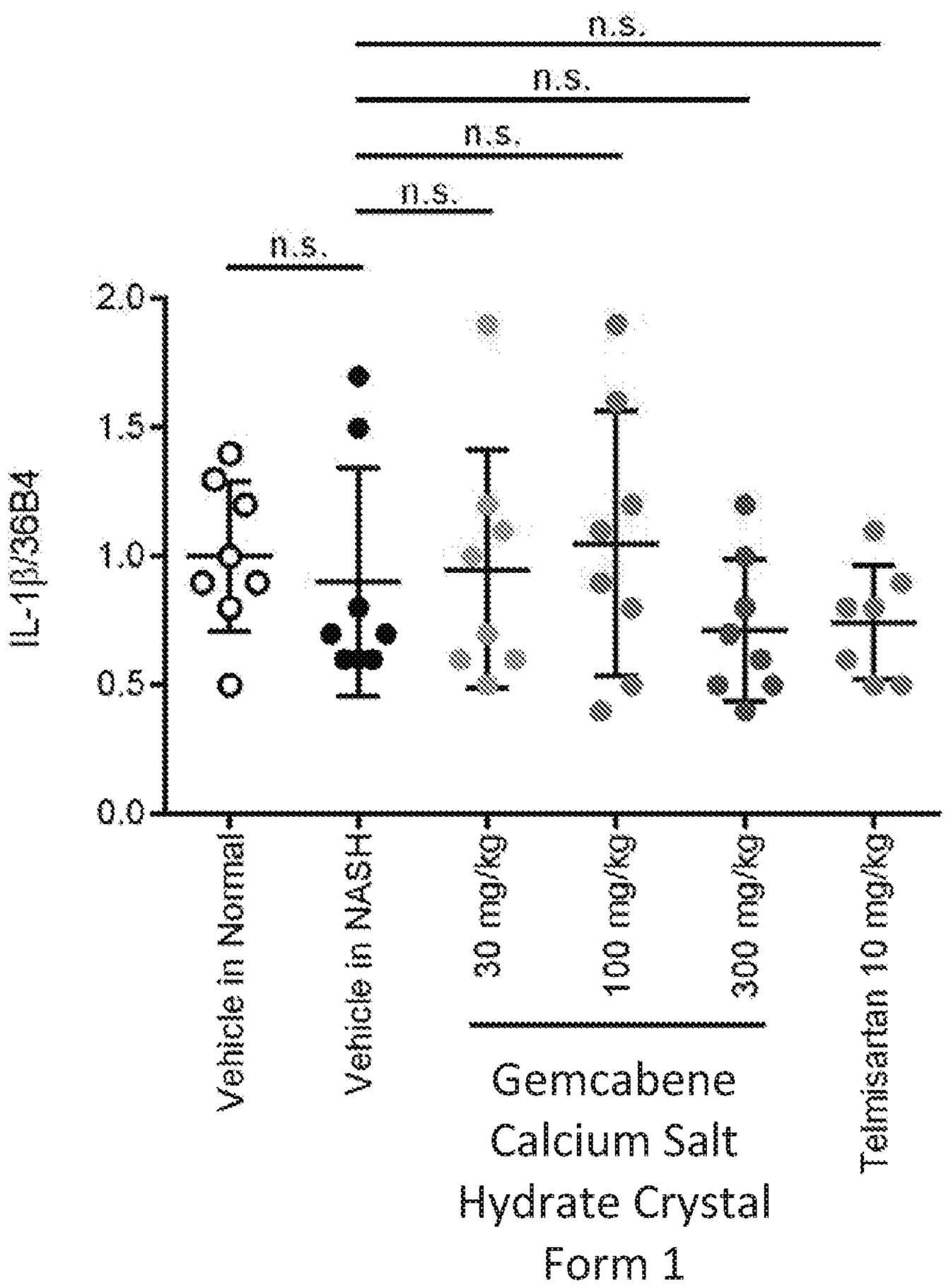

n.s.
n.s.
n.s.
n.s.
n.s.
2.0
1.5
1.0
0.5
0.0
IL-1β/36B4
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

FIG. 34

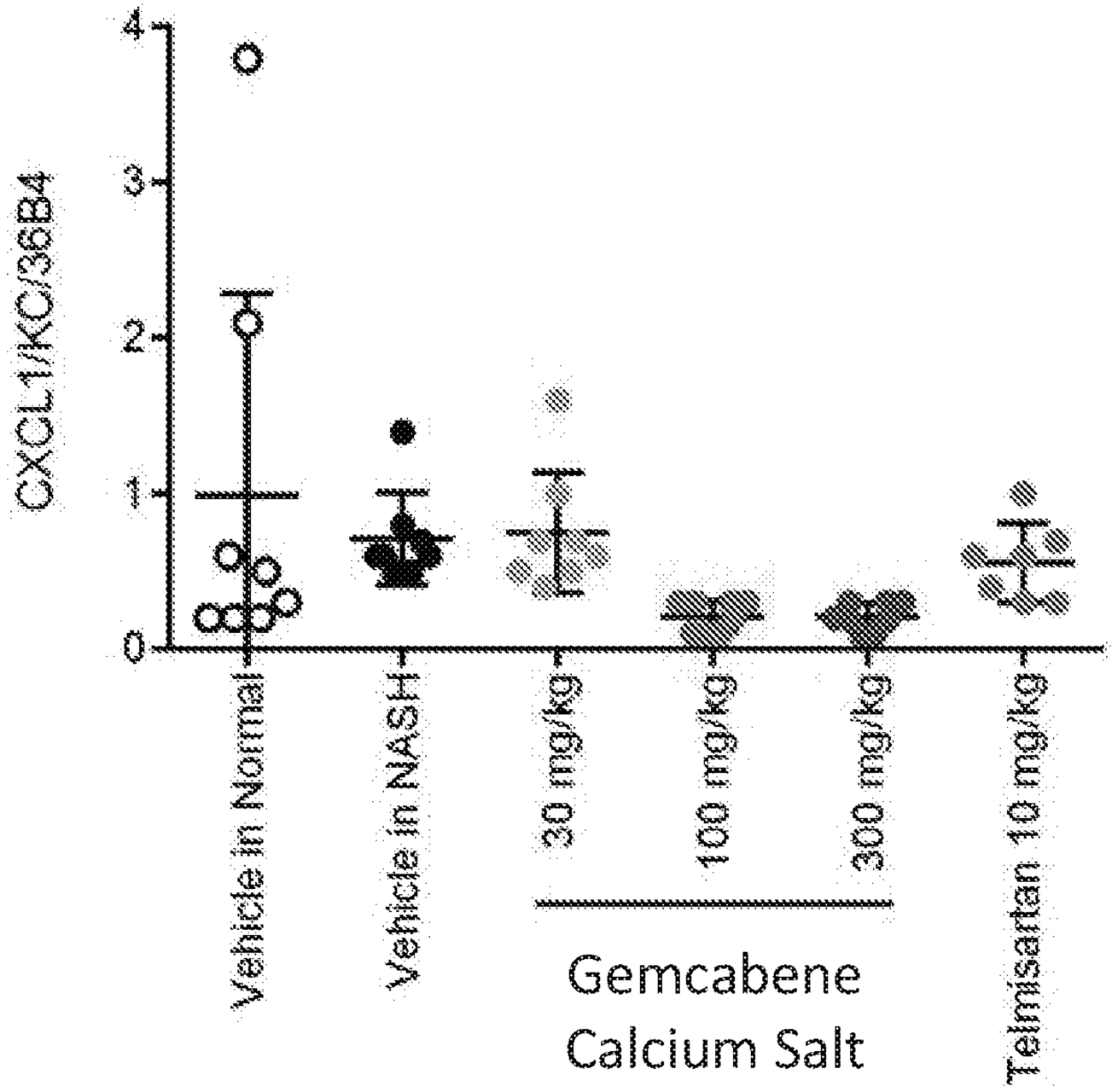

CXCL1/KC/36B4
0
1
2
3
4
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

FIG. 35

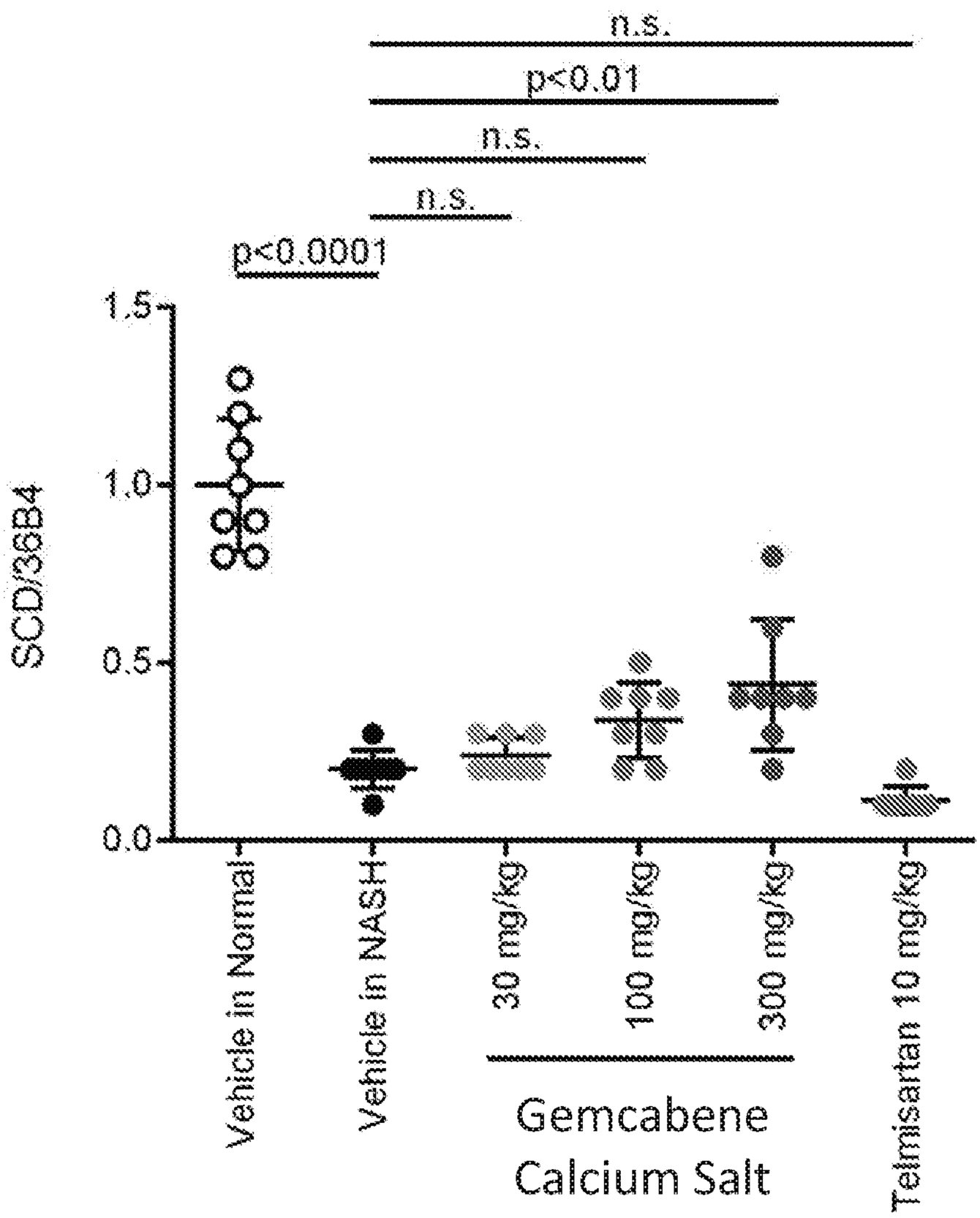

n.s.
p<0.01
n.s.
n.s.
p<0.0001
SCD/36B4
1.5
1.0
0.5
0.0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

FIG. 36

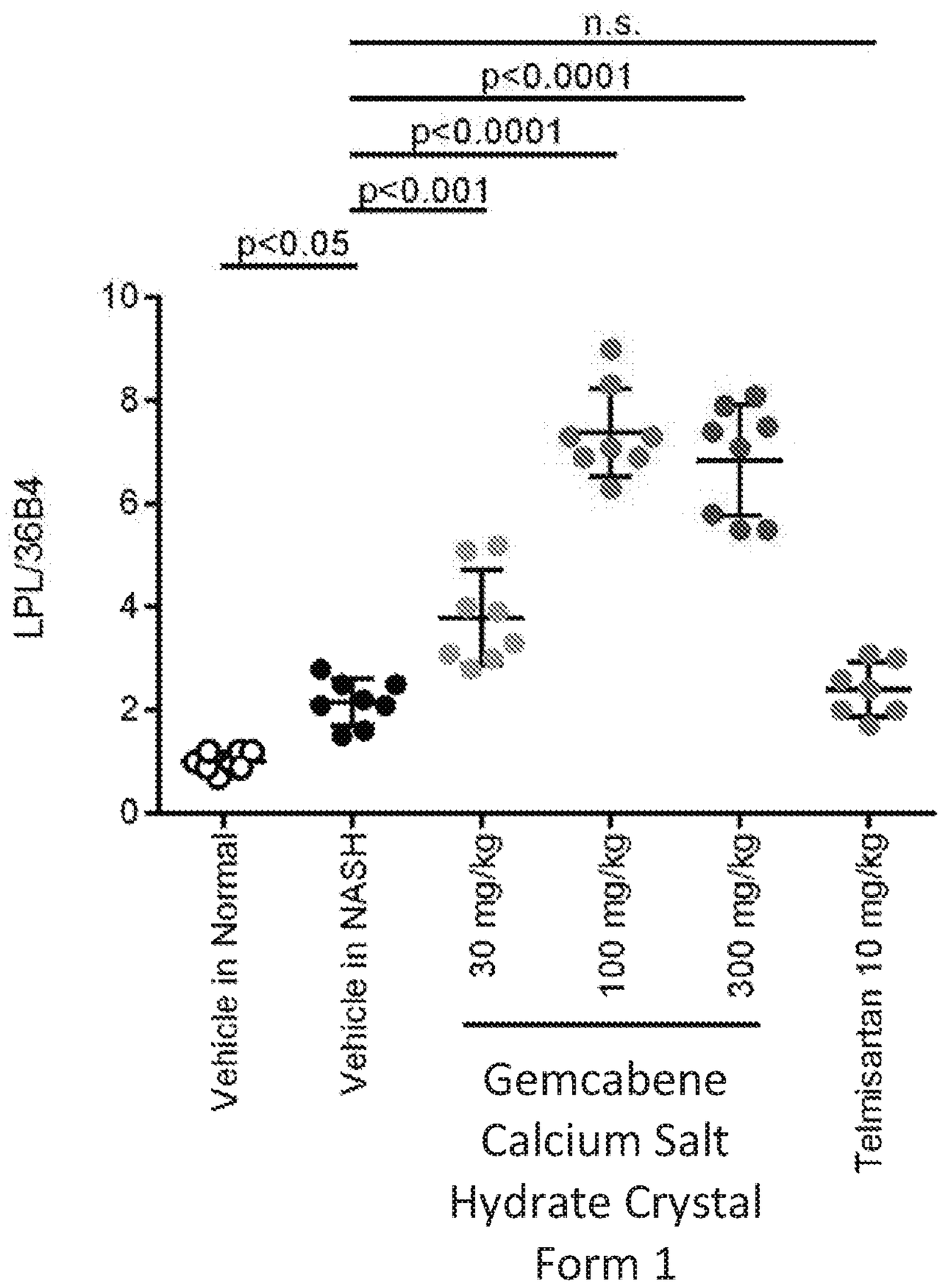

n.s.
p<0.0001
p<0.0001
p<0.001
p<0.05
LPL/36B4
0
2
4
6
8
10
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

FIG. 37

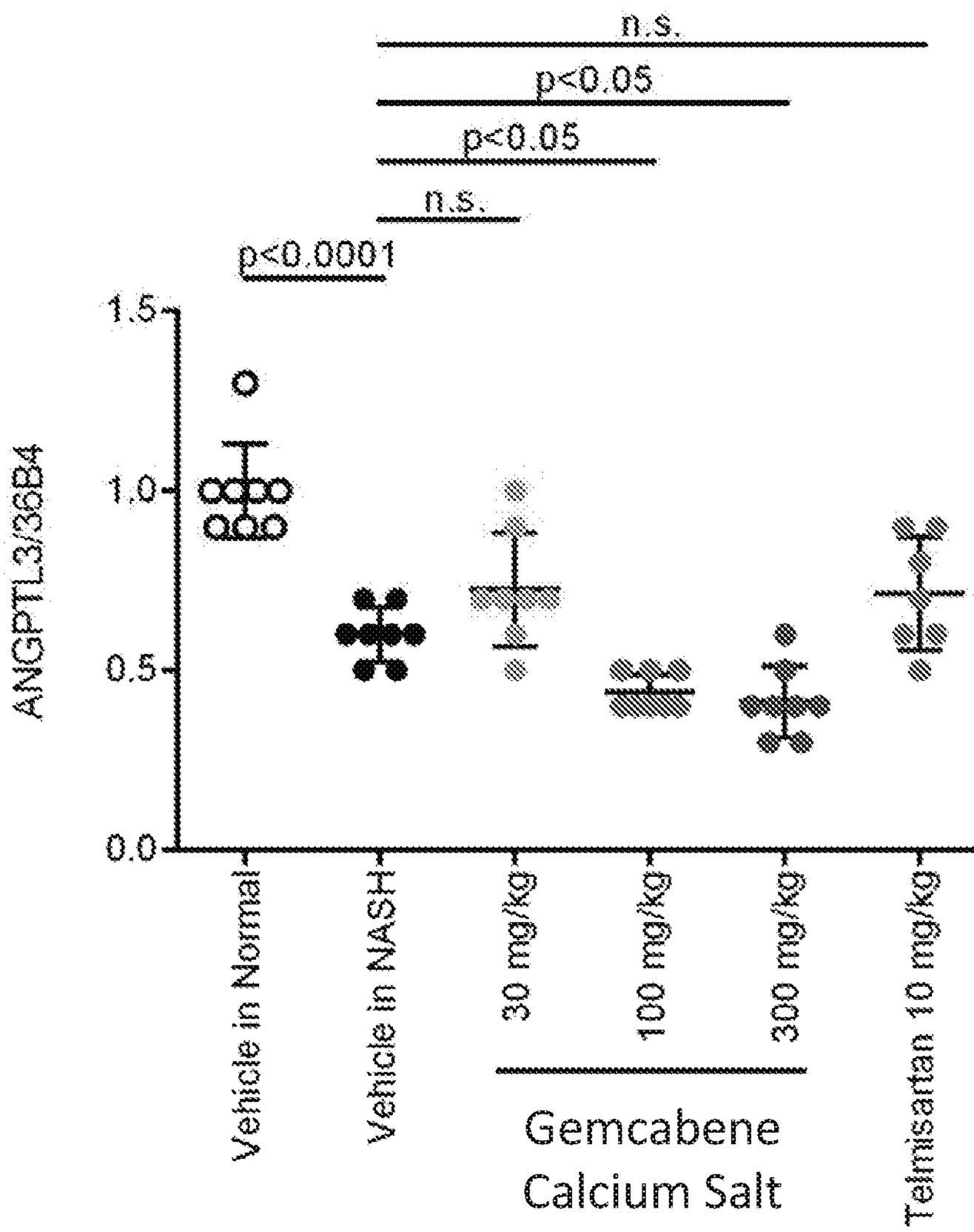

n.s.
p<0.05
p<0.05
n.s.
p<0.0001
ANGPTL3/36B4
1.5
1.0
0.5
0.0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene
Calcium Salt
Hydrate Crystal
Form 1

Fig. 38

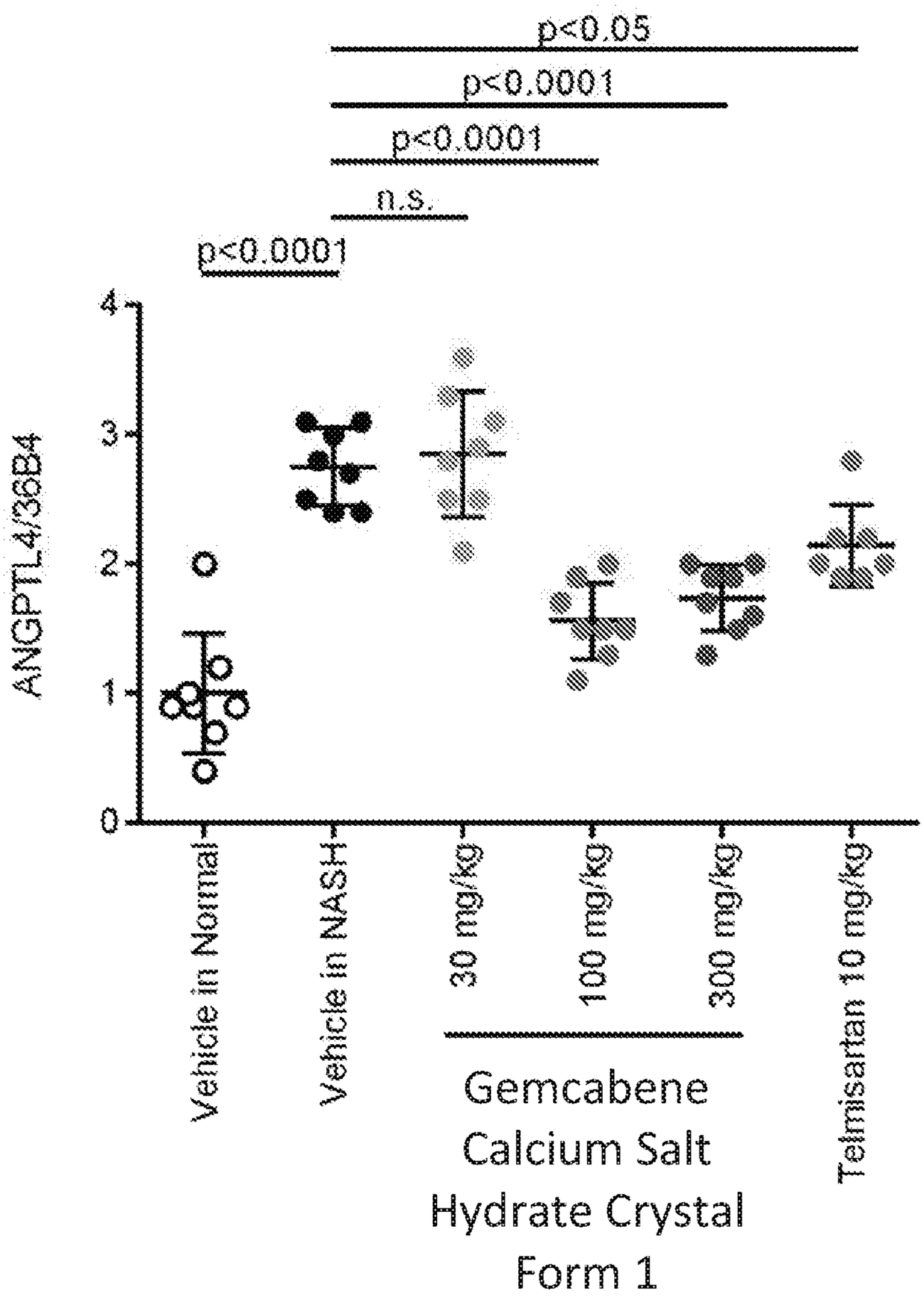

p<0.05
p<0.0001
p<0.0001
n.s.
p<0.0001
ANGPTL4/36B4
0
1
2
3
4
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

FIG. 39

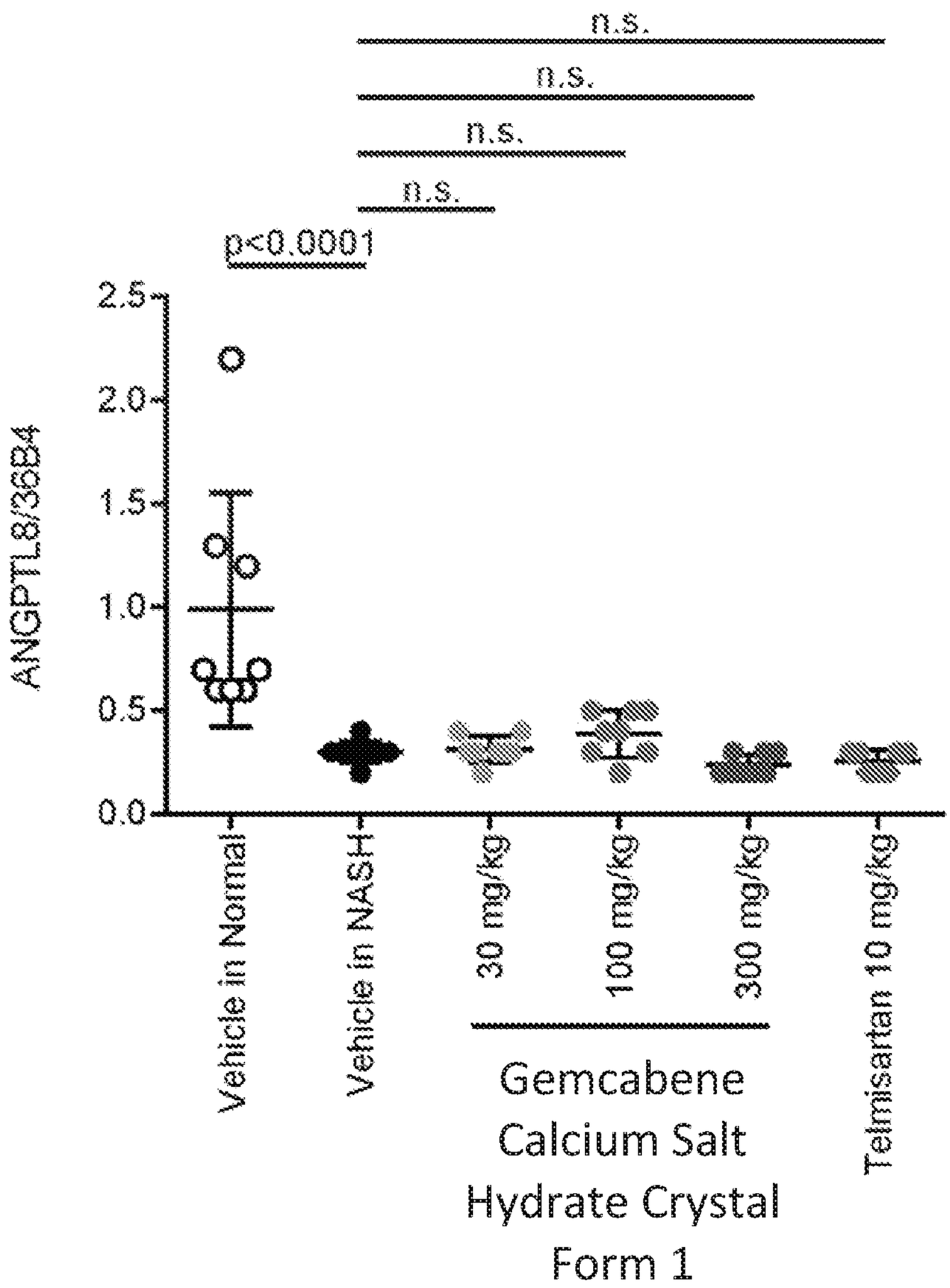

n.s.
n.s.
n.s.
n.s.
p<0.0001
ANGPTL8/36B4
2.5
2.0
1.5
1.0
0.5
0.0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

FIG. 40

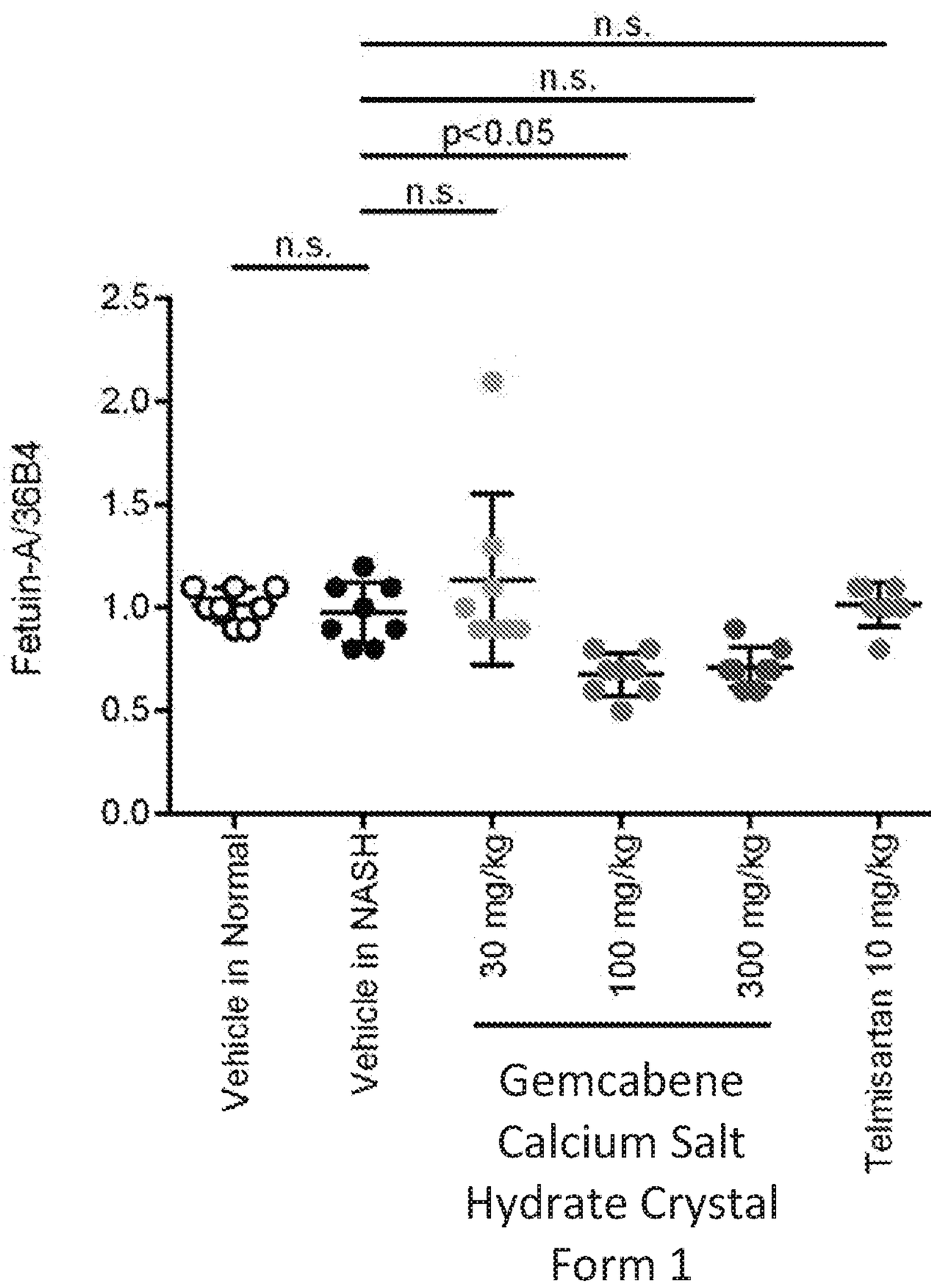

n.s.
n.s.
p<0.05
n.s.
n.s.
Fetuin-A/36B4
2.5
2.0
1.5
1.0
0.5
0.0
Vehicle in Normal
Vehicle in NASH
30 mg/kg
100 mg/kg
300 mg/kg
Telmisartan 10 mg/kg
Gemcabene Calcium Salt Hydrate Crystal Form 1

FIG. 41A

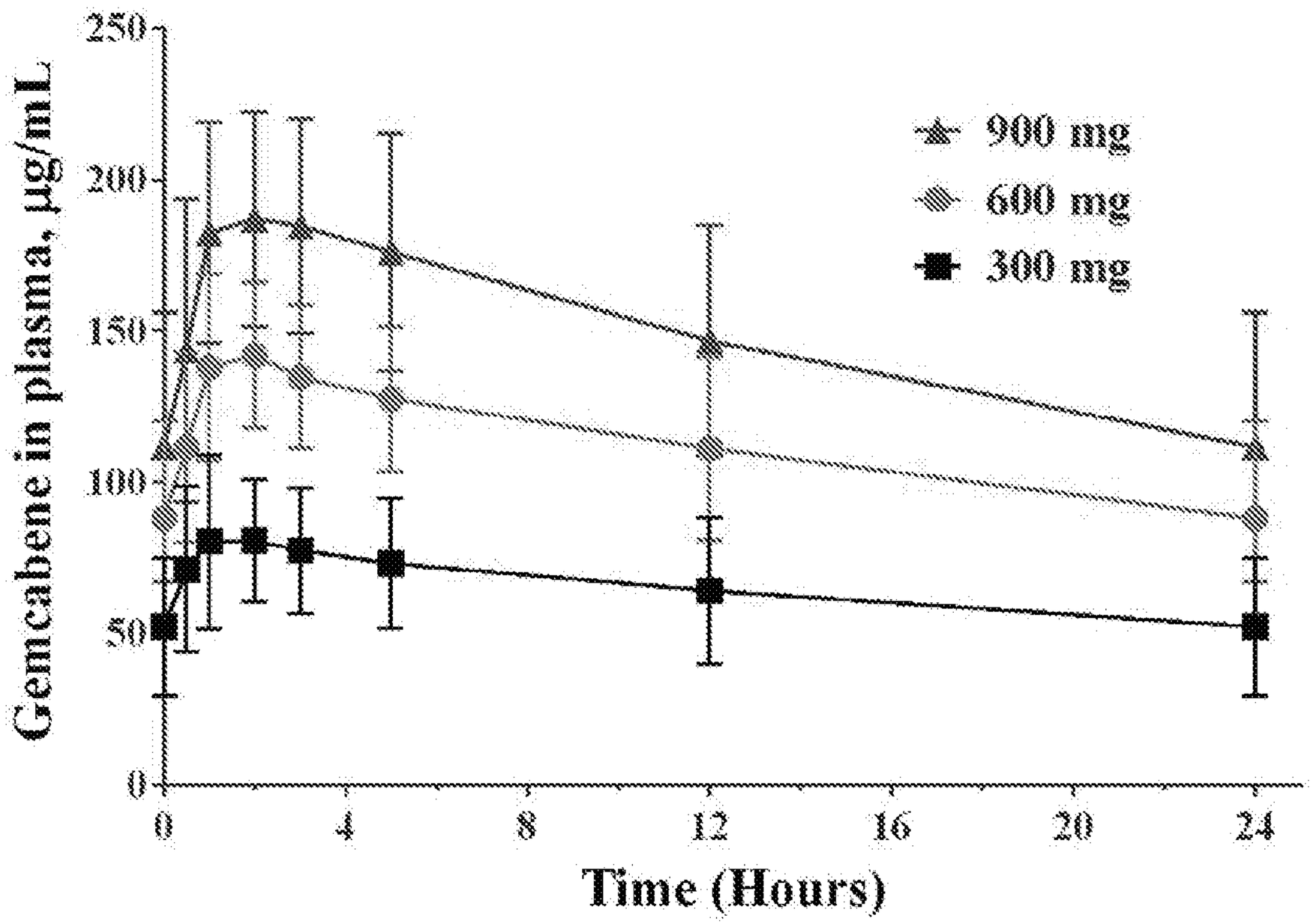


FIG. 41B

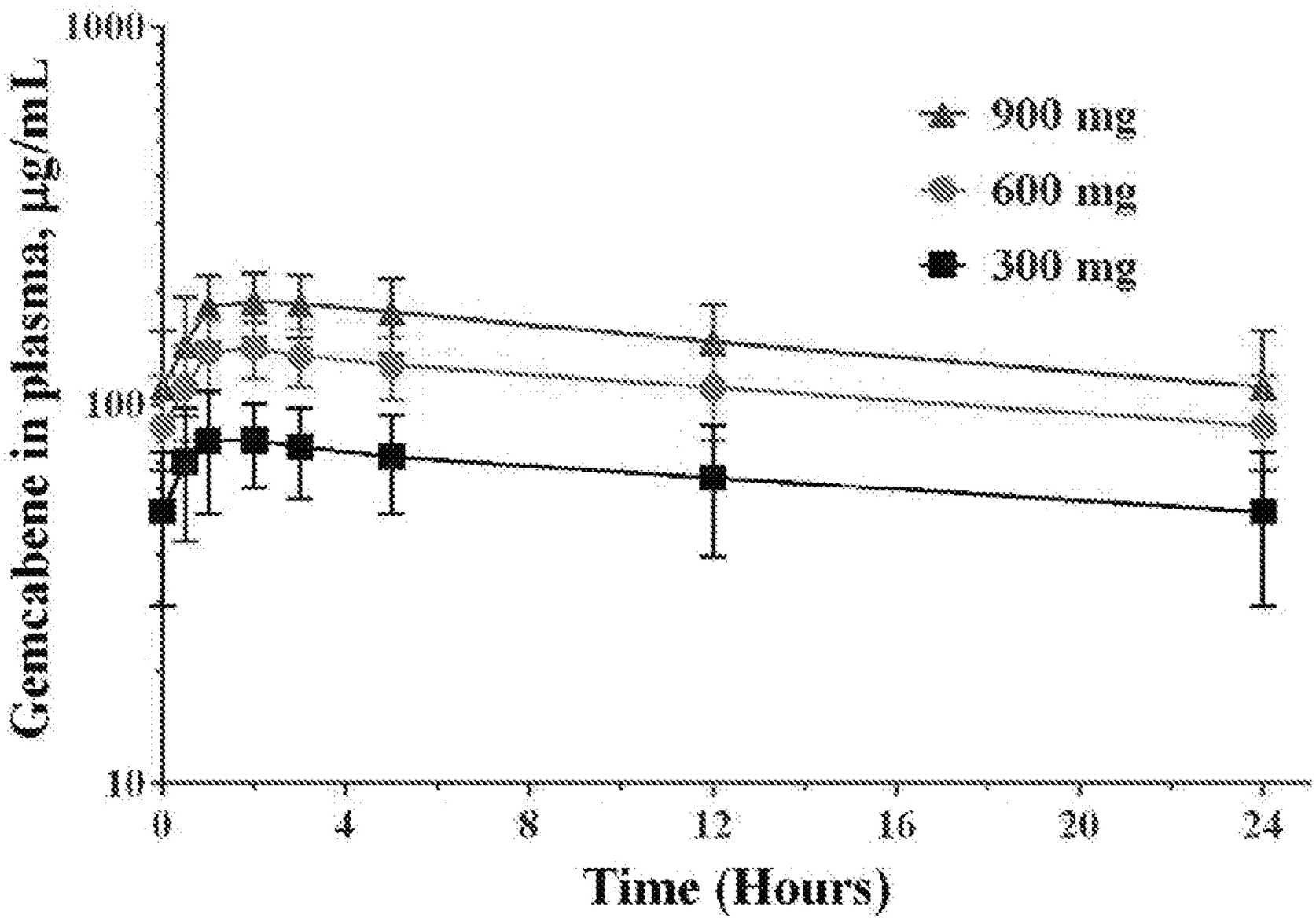


FIG. 42A

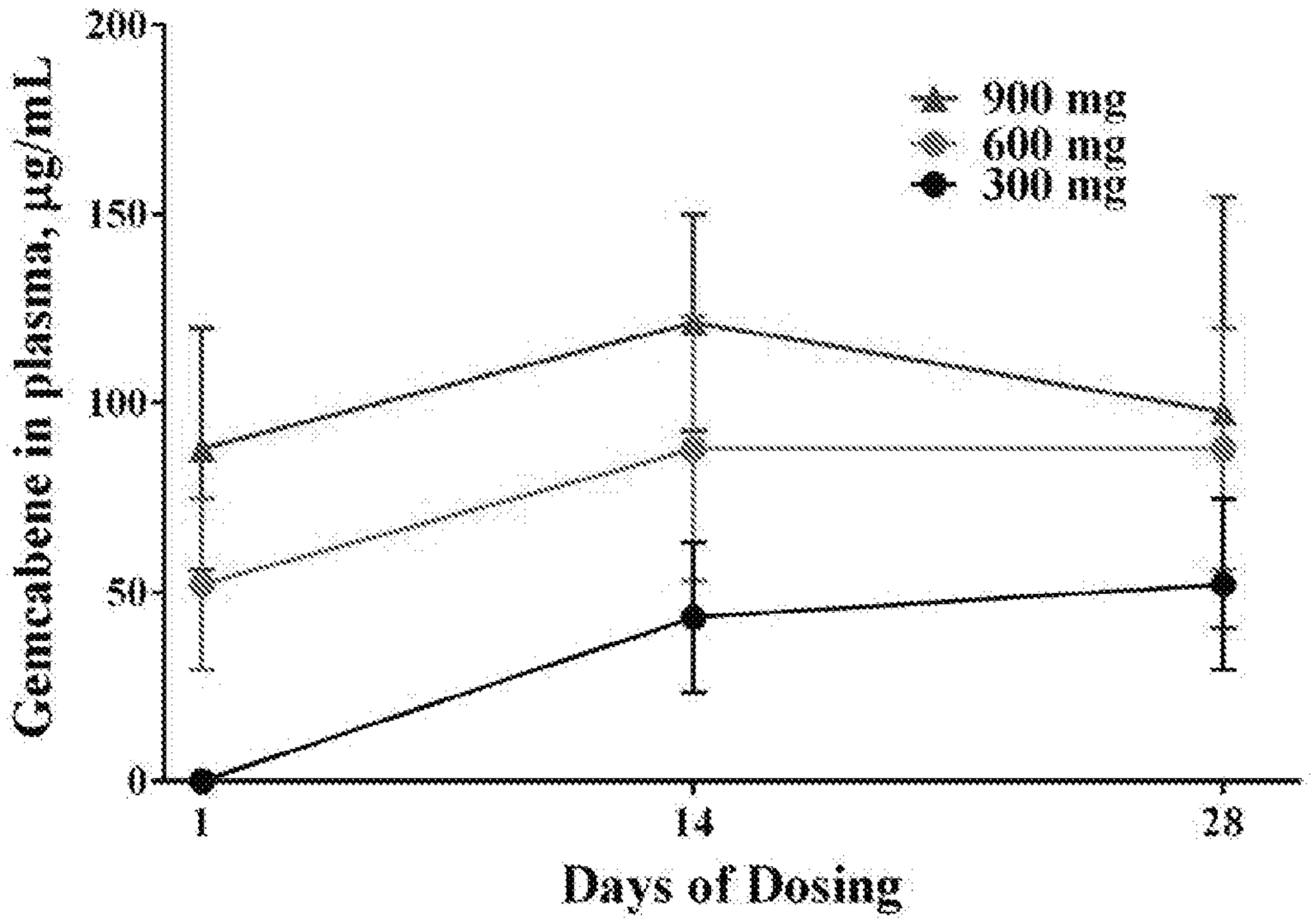


FIG. 42B

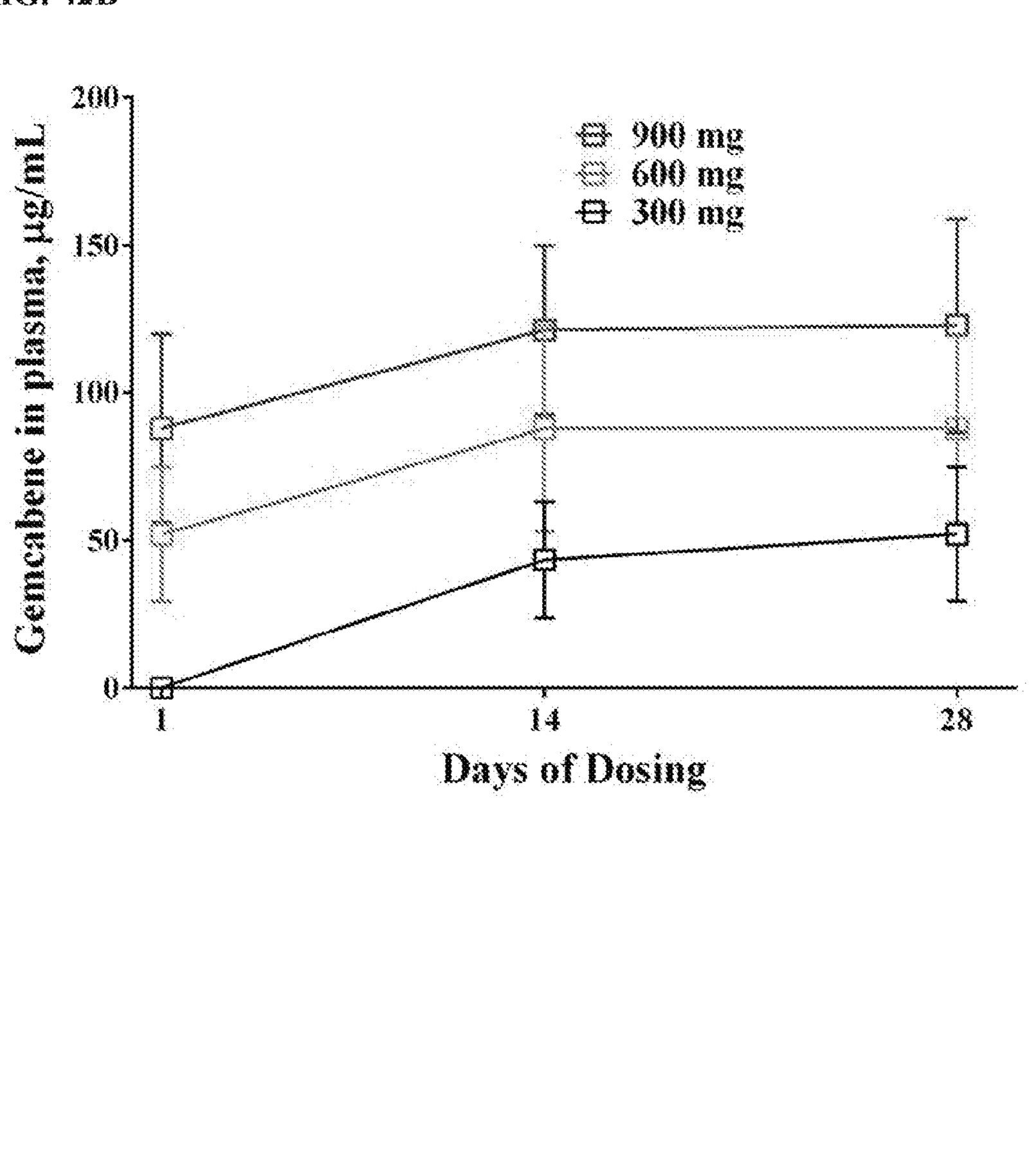


FIG. 43

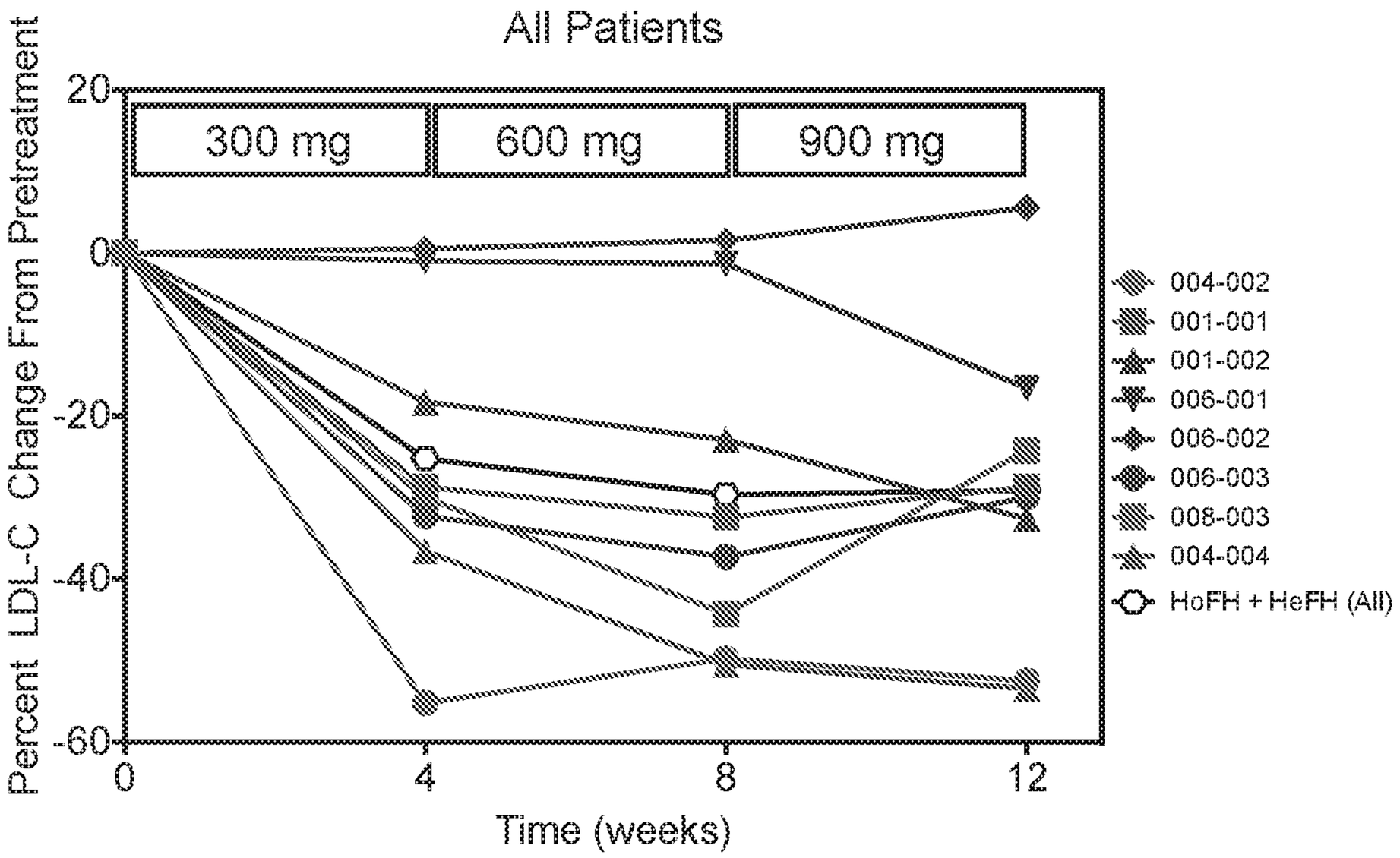

All Patients
300 mg
600 mg
900 mg
Percent LDL-C Change From Pretreatment
20
0
-20
-40
-60
0
4
8
12
Time (weeks)
004-002
001-001
001-002
006-001
006-002
006-003
008-003
004-004
HoFH + HeFH (All)

FIG. 44

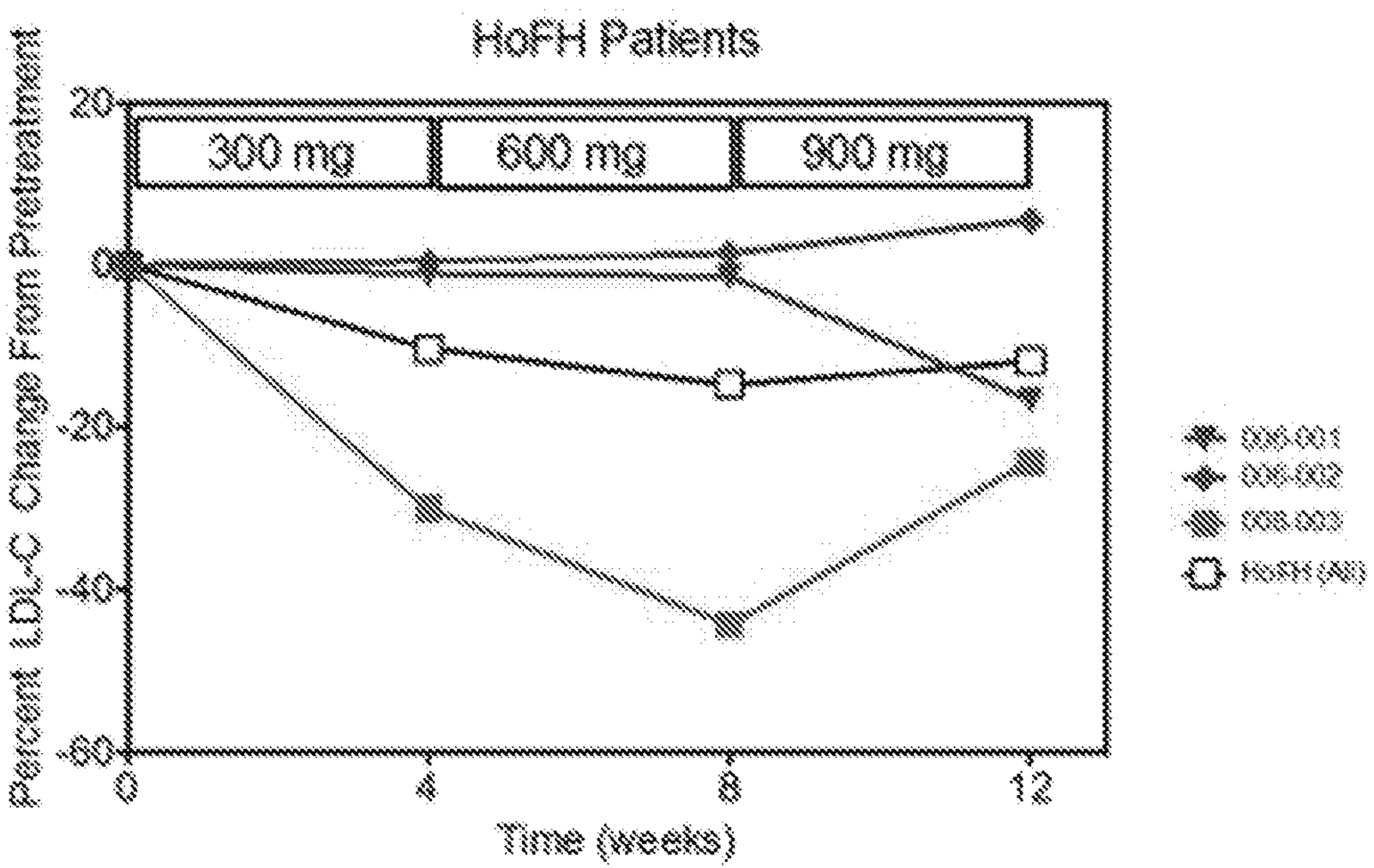

HoFH Patients
300 mg
600 mg
900 mg
20
0
-20
-40
-60
0
4
8
12
Time (weeks)

FIG. 45

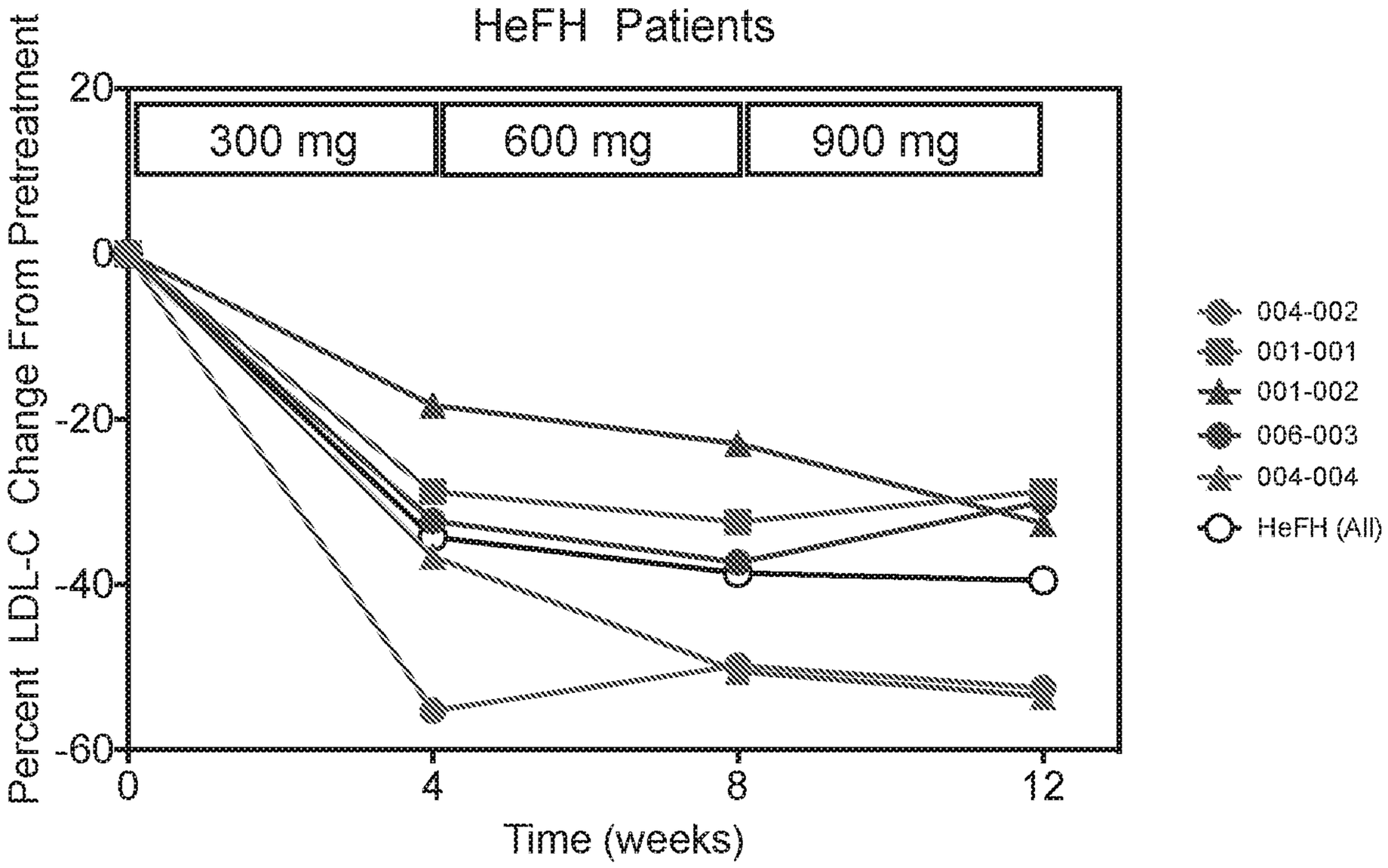

HeFH Patients
300 mg
600 mg
900 mg
Percent LDL-C Change From Pretreatment
20
0
-20
-40
-60
0
4
8
12
Time (weeks)
004-002
001-001
001-002
006-003
004-004
HeFH (All)

FIG. 46

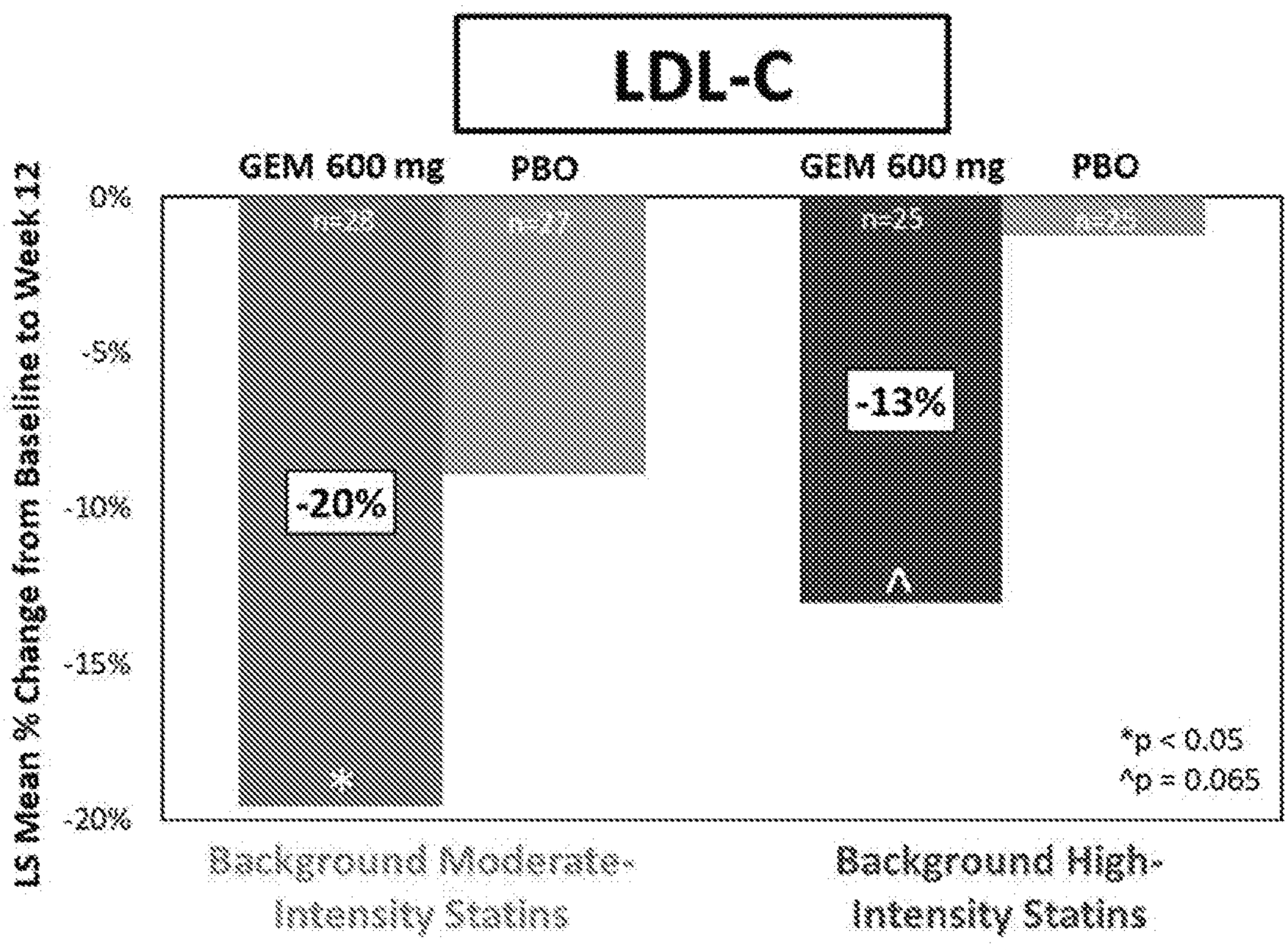

LDL-C
GEM 600 mg
PBO
GEM 600 mg
PBO
n=28
n=27
n=26
n=27
LS Mean % Change from Baseline to Week 12
0%
-5%
-10%
-15%
-20%
-20%
-13%
*
^
*p < 0.05
^p = 0.065
Background Moderate-Intensity Statins
Background High-Intensity Statins

FIG. 47

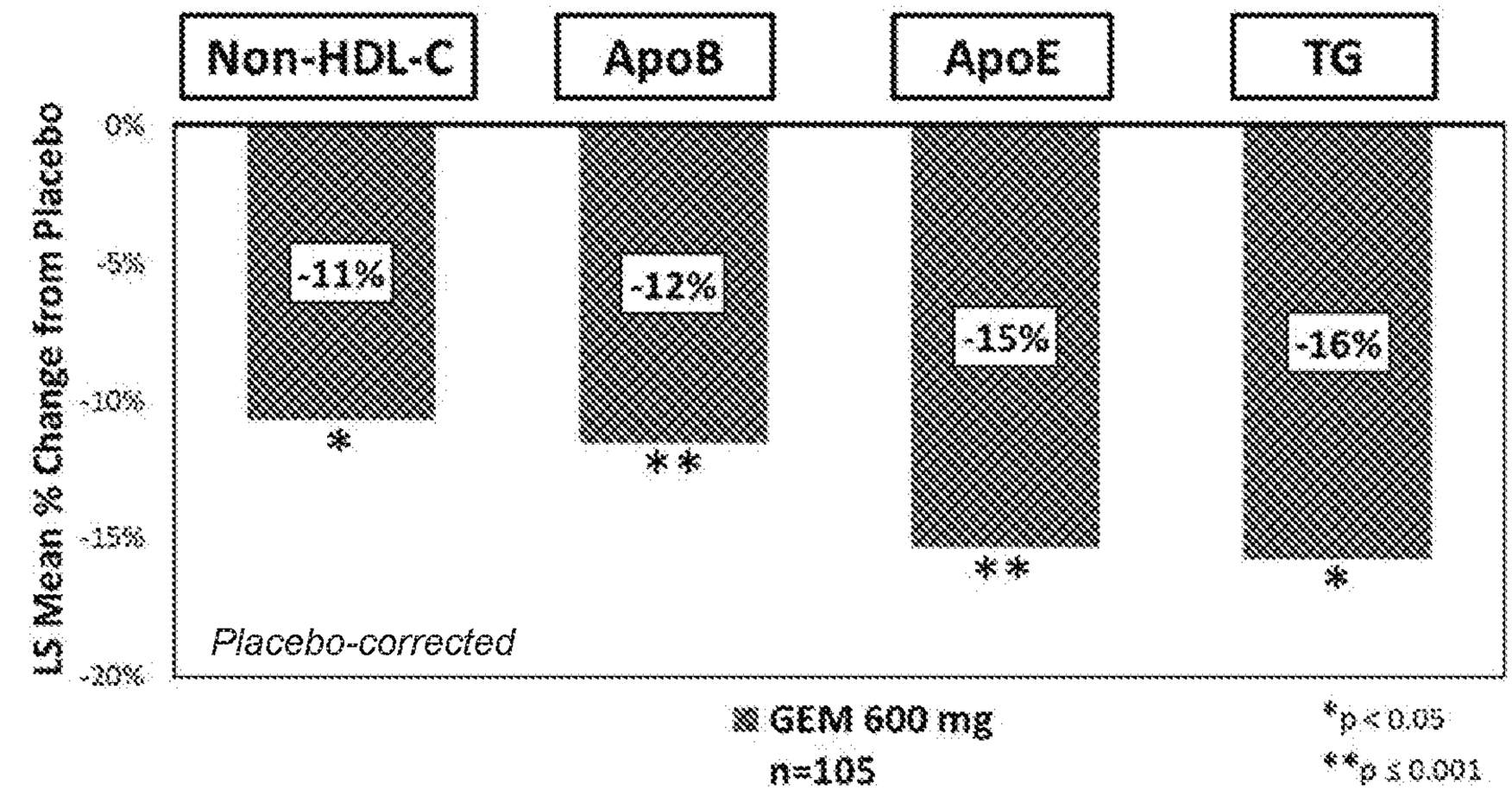

Non-HDL-C
ApoB
ApoE
TG
LS Mean % Change from Placebo
0%
-5%
-10%
-15%
-20%
-11%
-12%
-15%
-16%
*
**
**
*
Placebo-corrected
GEM 600 mg
n=105
*p < 0.05
**p ≤ 0.001

FIG. 48

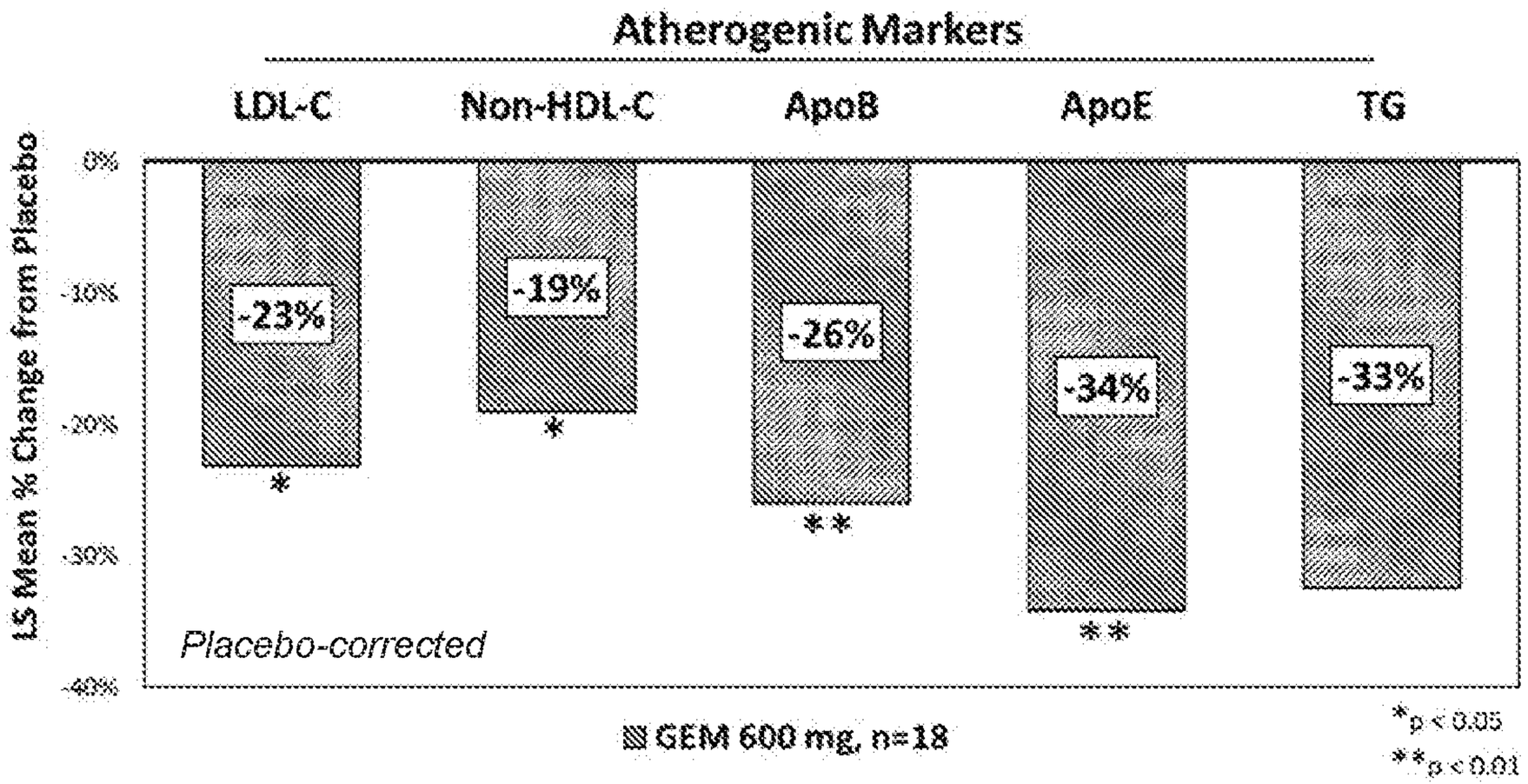

Atherogenic Markers
LDL-C
Non-HDL-C
ApoB
ApoE
TG
LS Mean % Change from Placebo
0%
-10%
-20%
-30%
-40%
-23%
-19%
-26%
-34%
-33%
*
*
**
**
Placebo-corrected
GEM 600 mg, n=18
*p < 0.05
**p < 0.01

FIG. 49

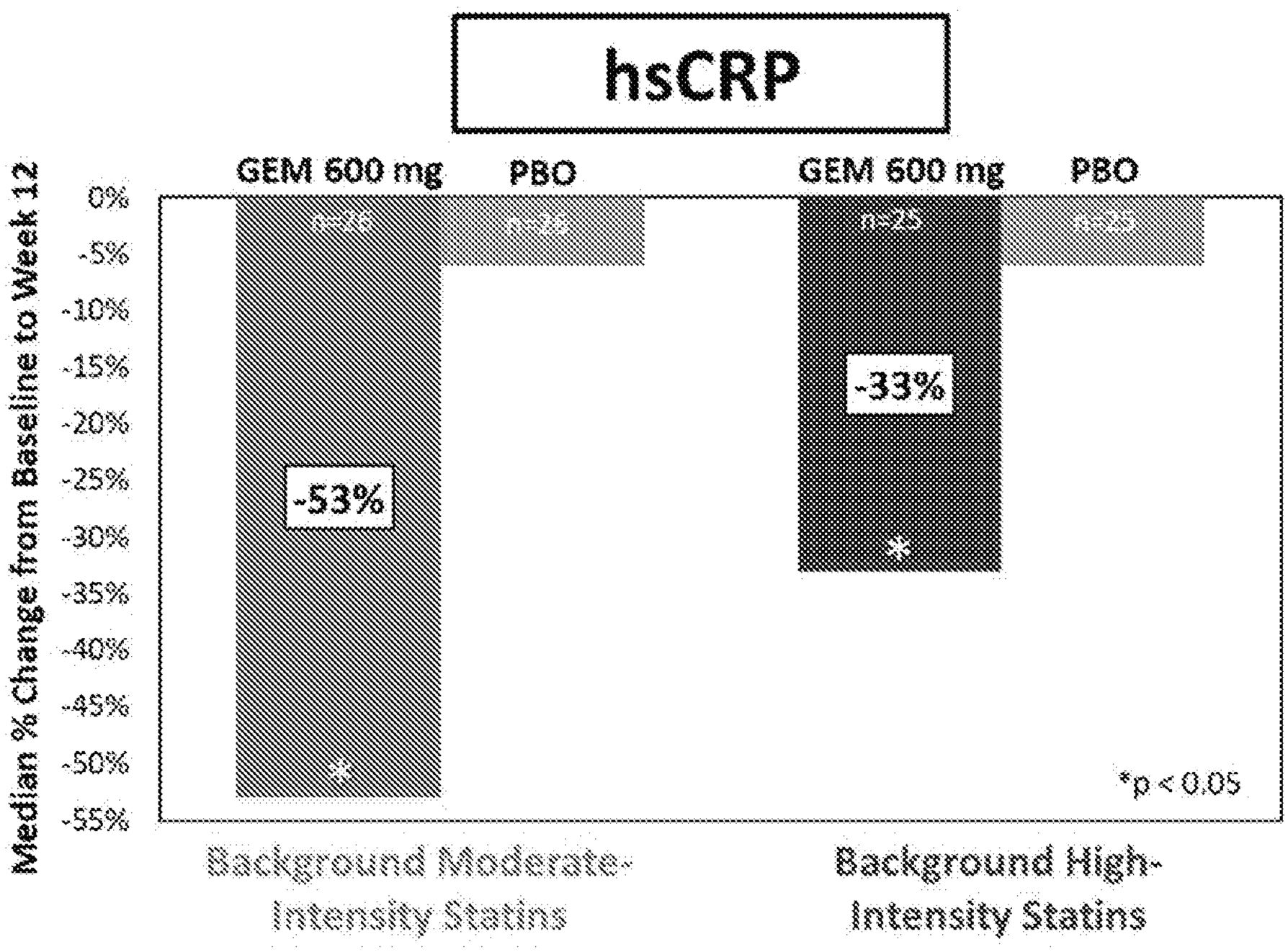

hsCRP
GEM 600 mg
PBO
GEM 600 mg
PBO
n=24
n=23
n=23
n=23
Median % Change from Baseline to Week 12
0%
-5%
-10%
-15%
-20%
-25%
-30%
-35%
-40%
-45%
-50%
-55%
-53%
-33%
*
*
*p < 0.05
Background Moderate-Intensity Statins
Background High-Intensity Statins

FIG. 50

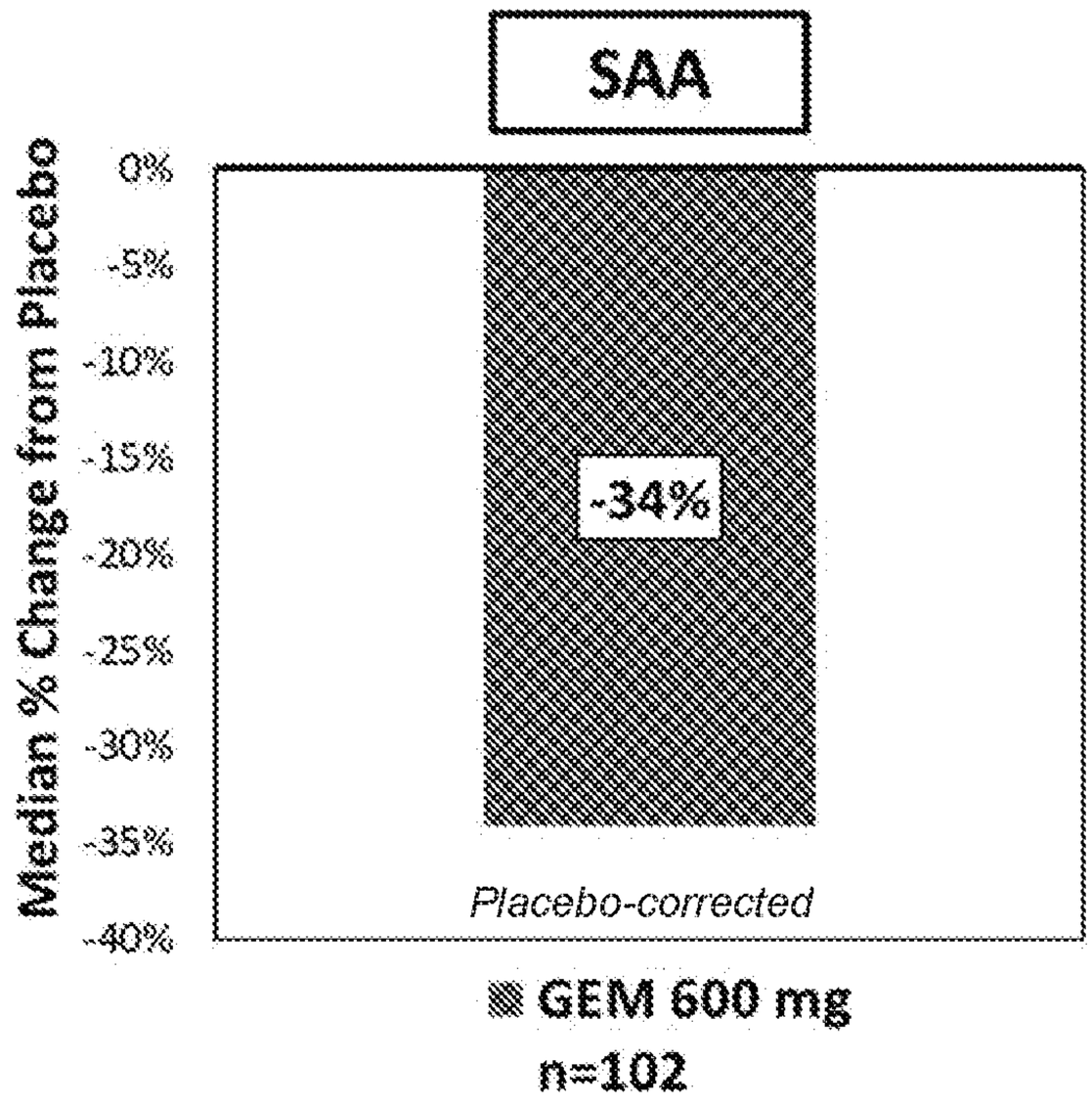
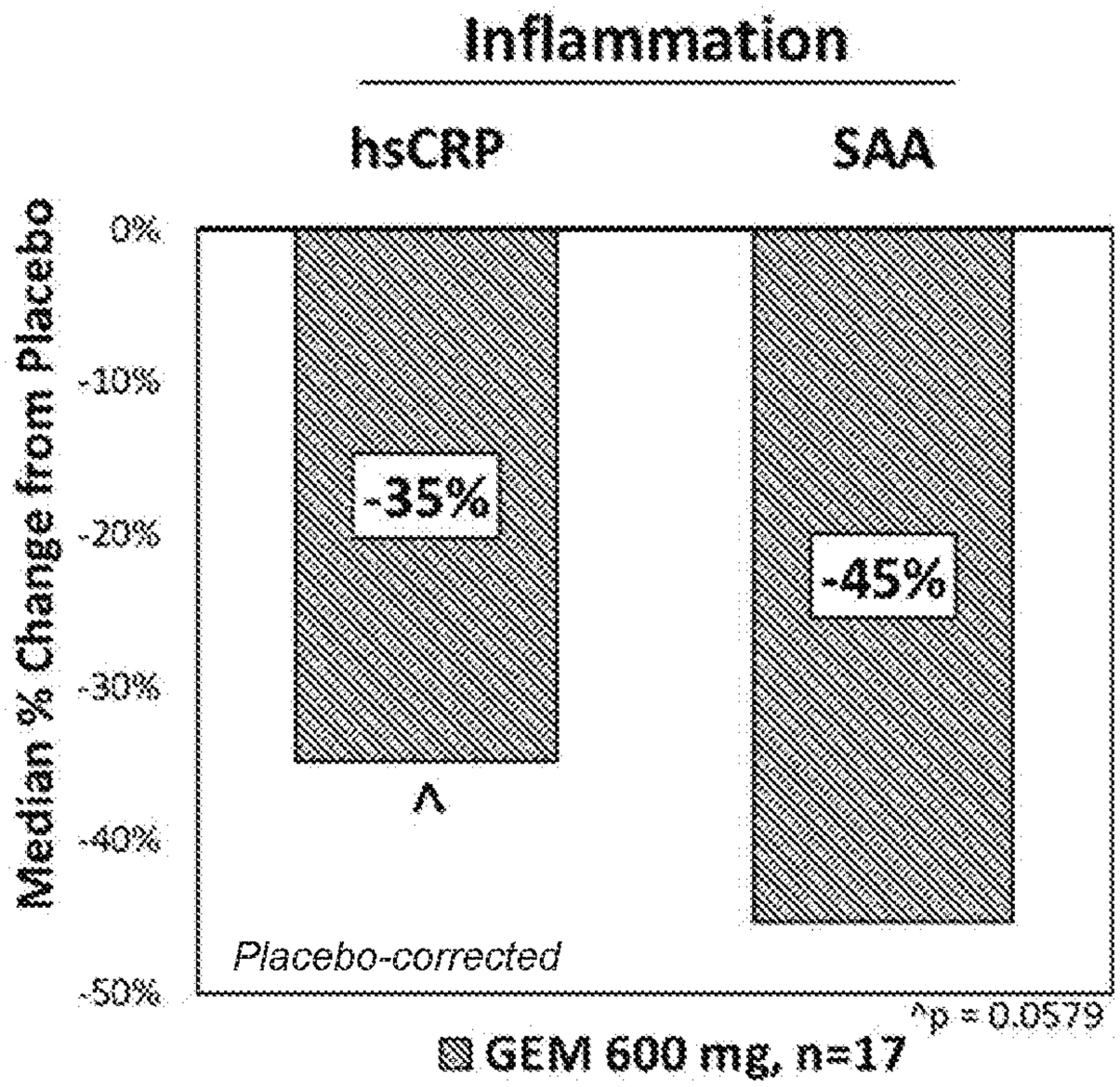

SAA
Median % Change from Placebo
0%
-5%
-10%
-15%
-20%
-25%
-30%
-35%
-40%
-34%
Placebo-corrected
GEM 600 mg
n=102

FIG. 51


Inflammation
hsCRP
SAA
Median % Change from Placebo
0%
-10%
-20%
-30%
-40%
-50%
-35%
-45%
^
Placebo-corrected
^p = 0.0579
GEM 600 mg, n=17

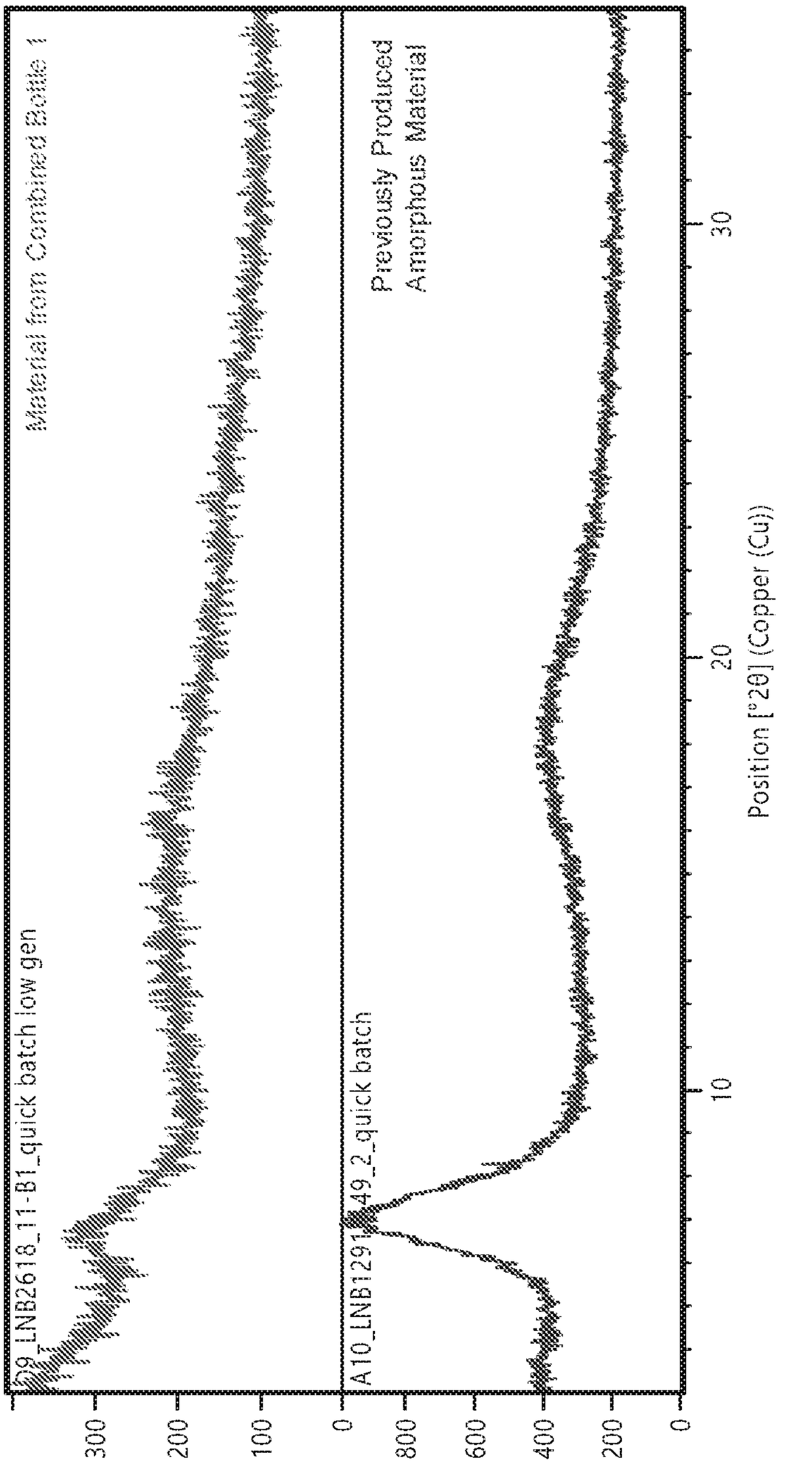

Material from Combined Bottle 1
LNB2618_11-B1_quick batch low gen
Previously Produced
Amorphous Material
LNB1291_49_2_quick batch
A10_LNB1
D9_LNB26
Counts
300
200
100
0
800
600
400
200
0
10
20
30
Position [°2θ] (Copper (Cu))

FIG. 52A

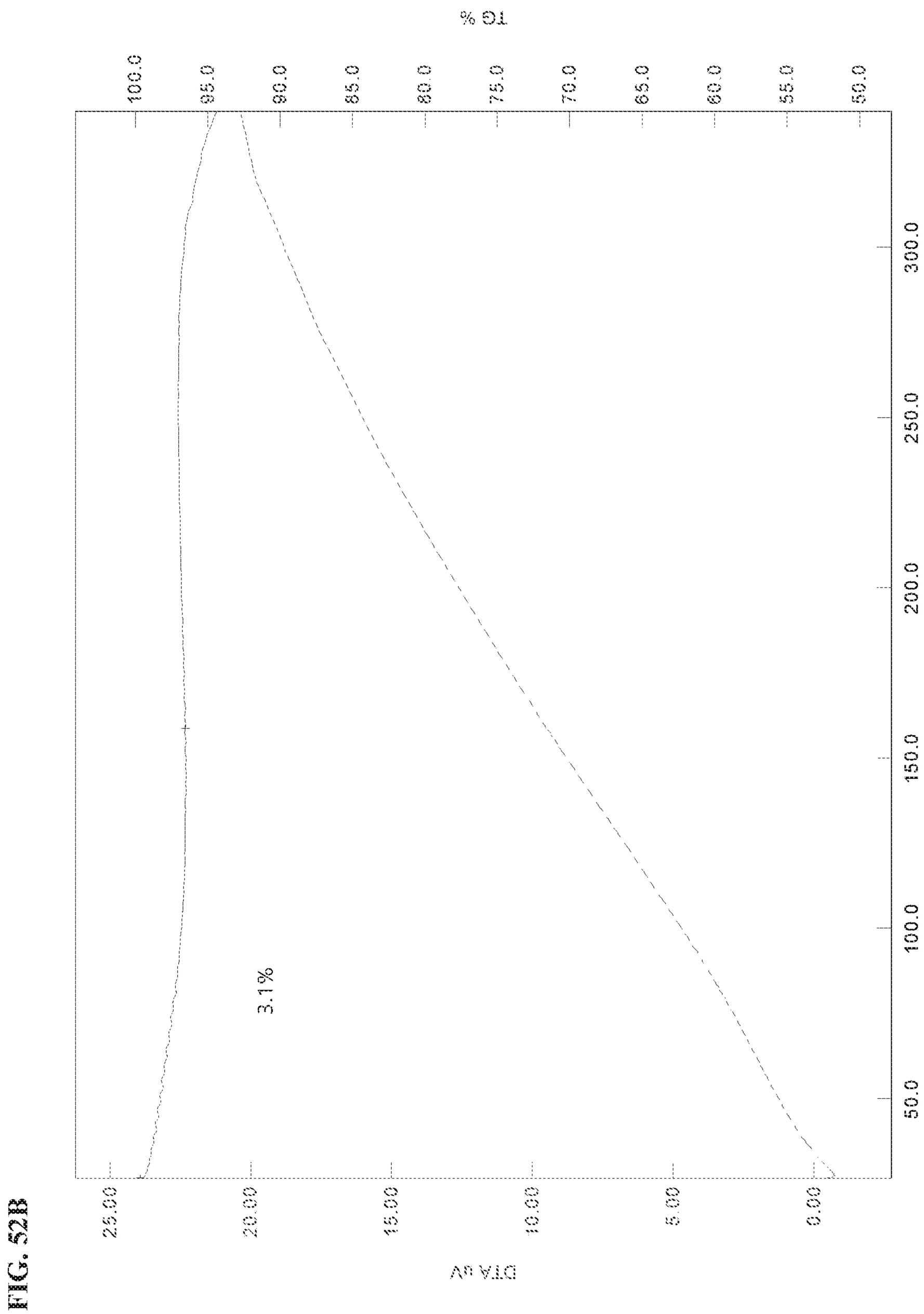

% Cl
100.0
95
90
85
80
75
70
65
60
55
50
300.0
250.0
200.0
Temp Cel
150.0
100.0
50.0
3.1%
25.00
20.00
15.00
10.00
5.00
0.00
DTA uV

FIG. 52B

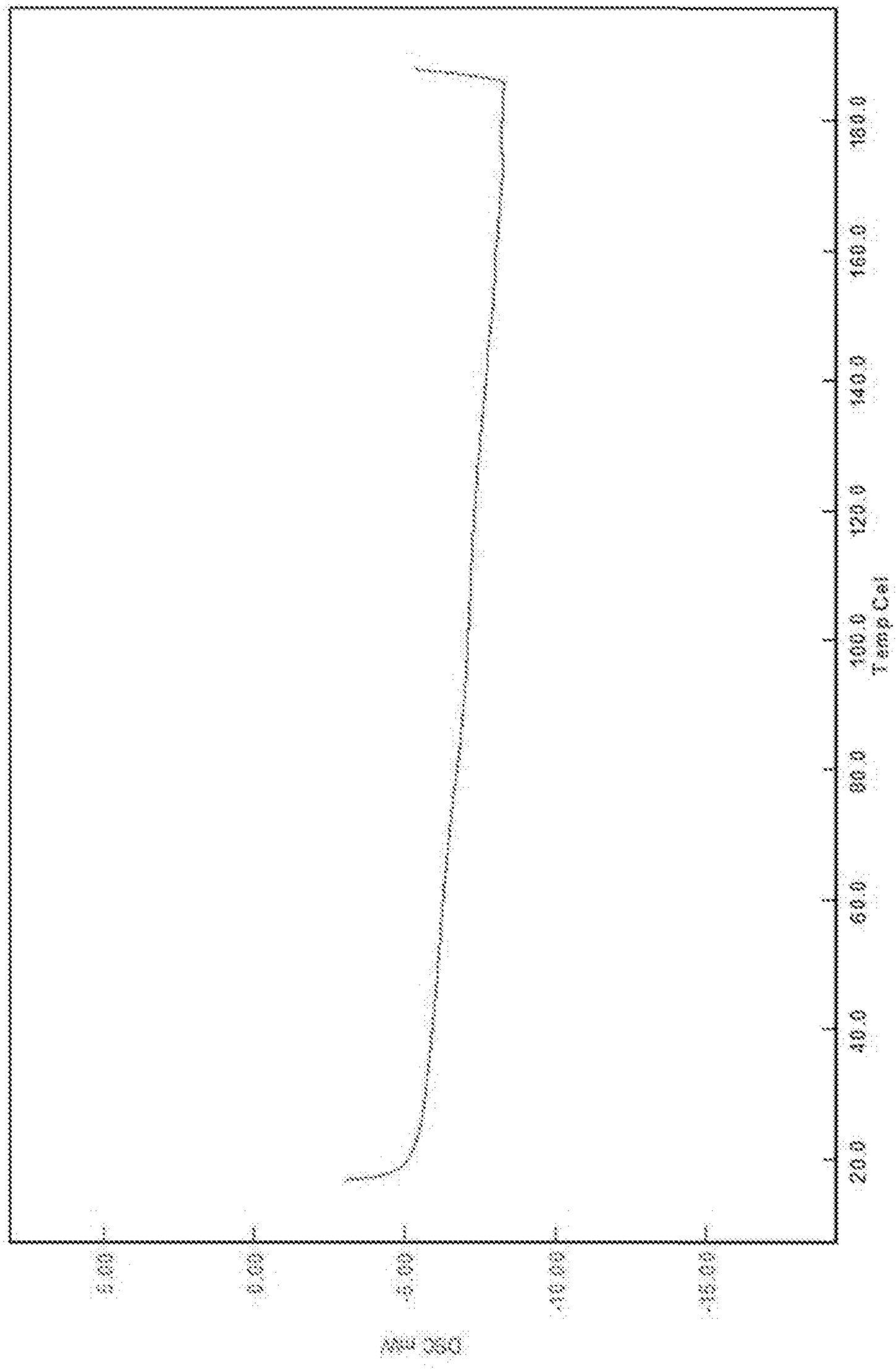

-5.00
0.00
5.00
10.00
15.00
mW/mg
60.0
80.0
100.0
120.0
140.0
160.0
180.0
Temp Cel
20.0
40.0

FIG. 52C

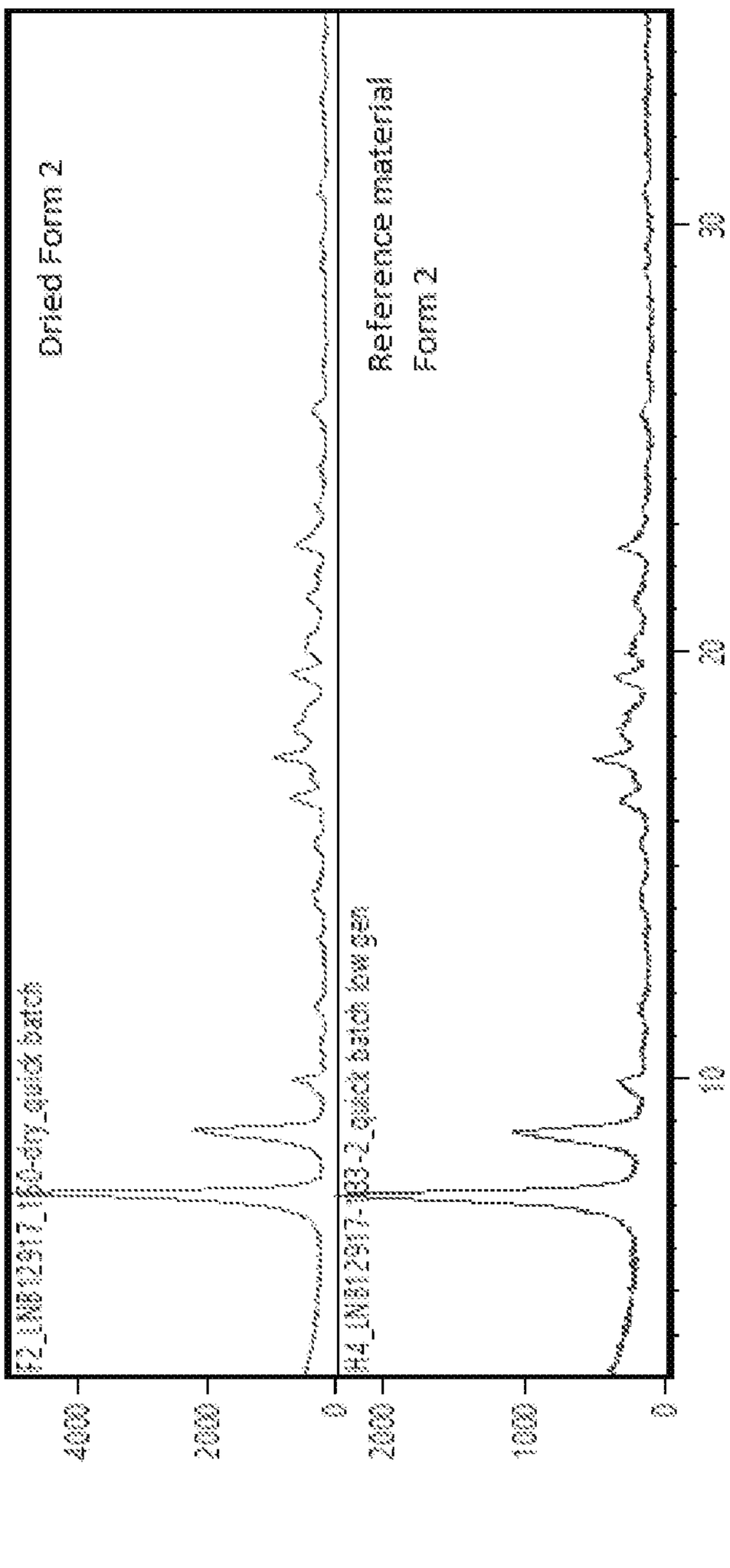

Dried Form 2
Reference material
Form 2
#2_INB123117_160-dry_quick batch
#4_INB123117-103-2_quick batch low gen
4000
2000
0
2000
1000
0
20
10
Counts

FIG. 53A

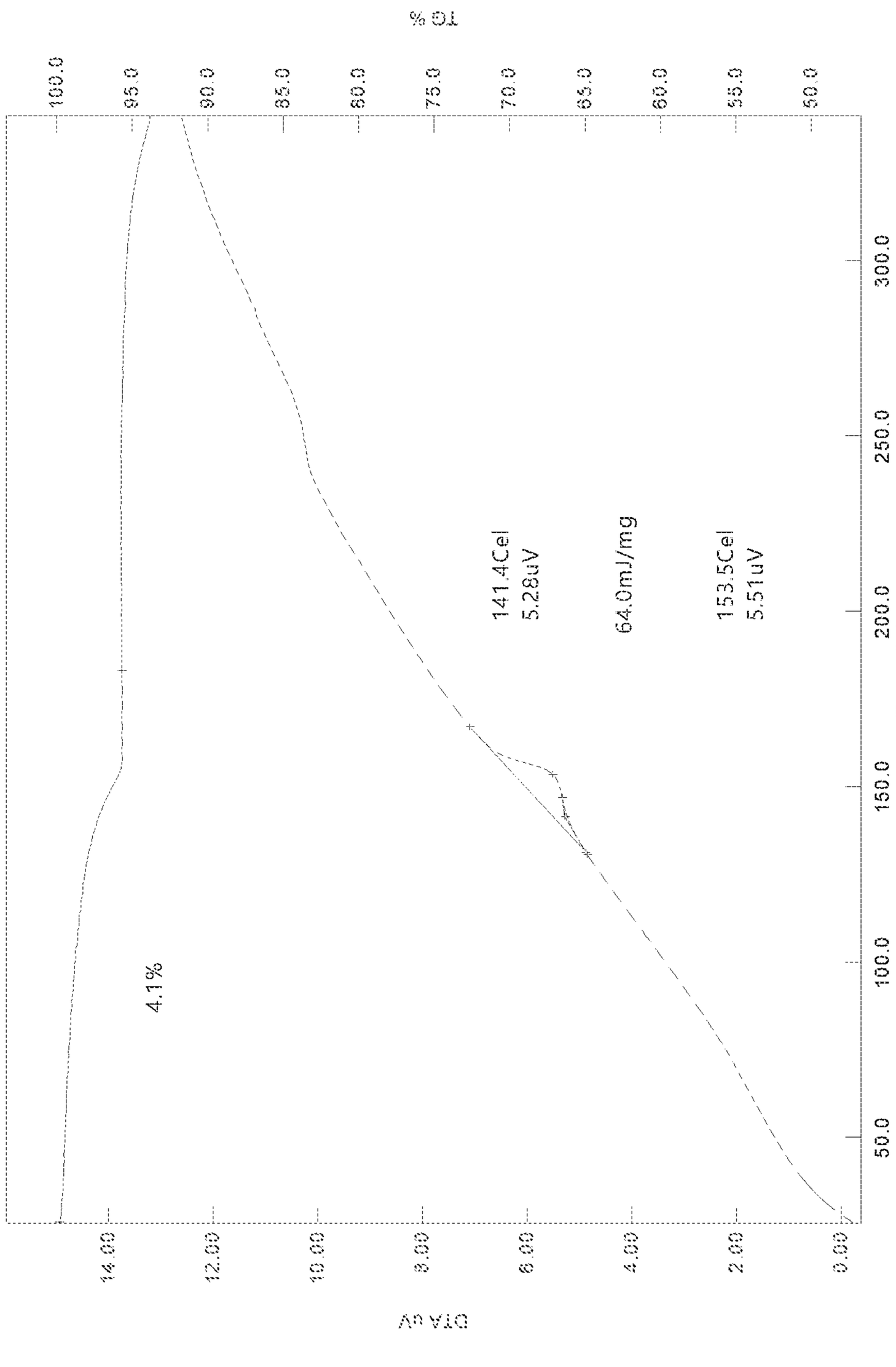

%
100.0
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
55.0
50.0
300.0
250.0
200.0
150.0
100.0
Temp Cel
4.1%
141.4Cel
5.28uV
64.0mJ/mg
153.5Cel
5.51uV
DTA uV
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
50.0

FIG. 53B

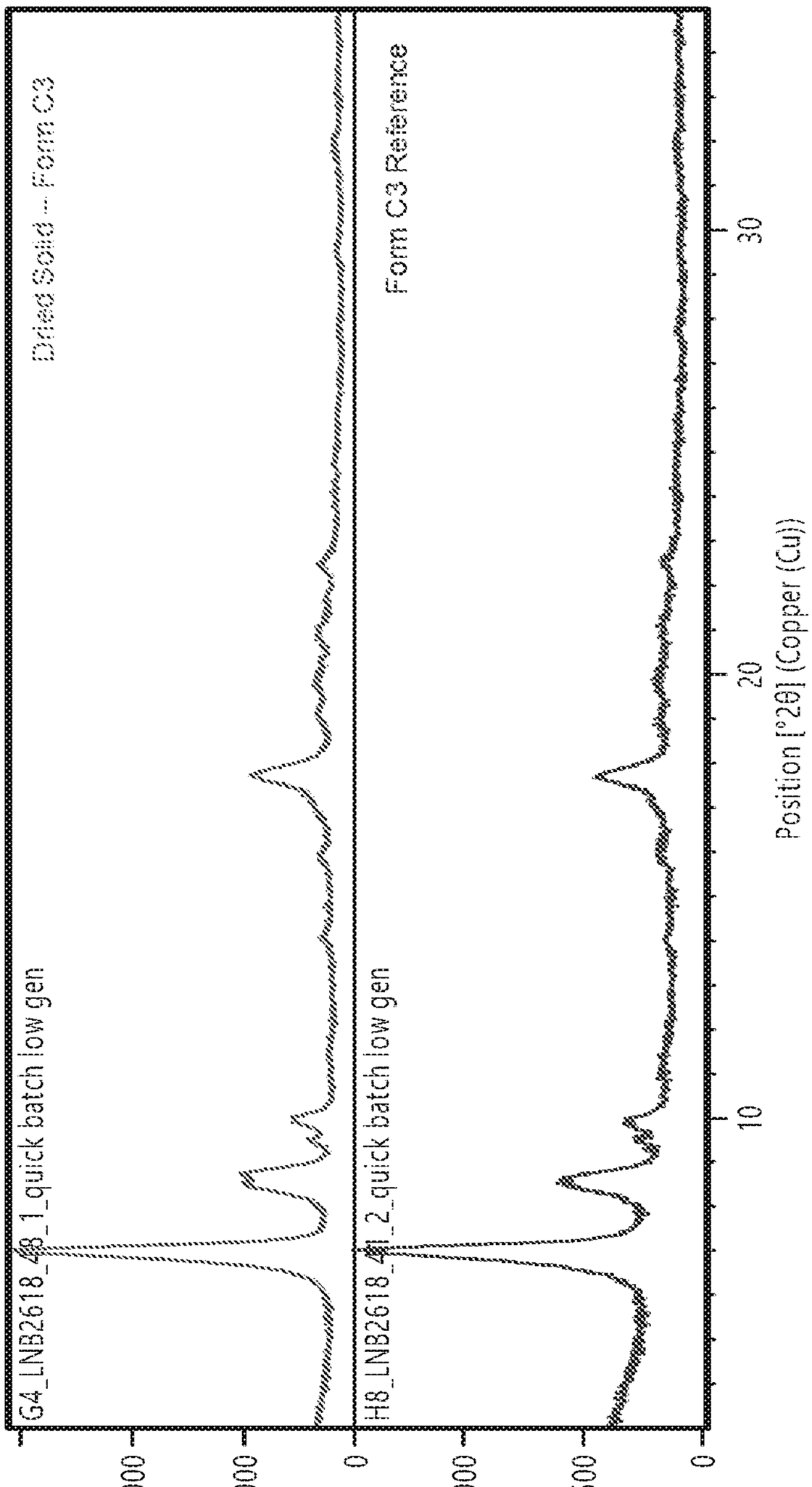

Dried Solid – Form C3
Form C3 Reference
G4_LNB2618_48_1_quick batch low gen
H8_LNB2618_41_2_quick batch low gen
Counts
2000
1000
0
1000
500
0
10
20
30
Position [°2θ] (Copper (Cu))

FIG. 54A

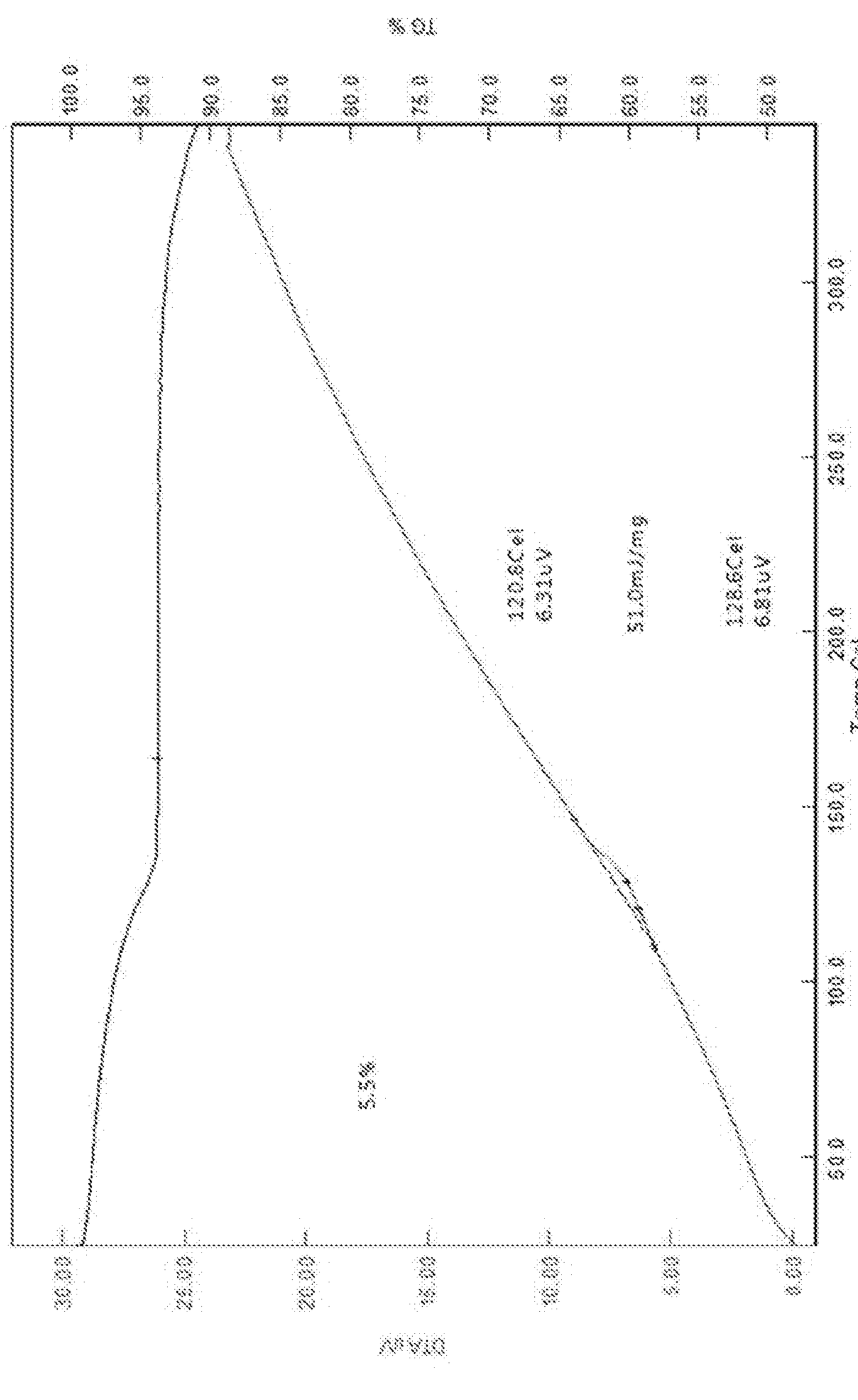

100.0
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
55.0
50.0
%
300.0
250.0
200.0
150.0
100.0
Temp Cel
120.8Cel
6.31uV
51.0mJ/mg
128.6Cel
6.81uV
5.5%
30.00
25.00
20.00
15.00
10.00
5.00
0.00
DTA uV
50.0

FIG. 54B

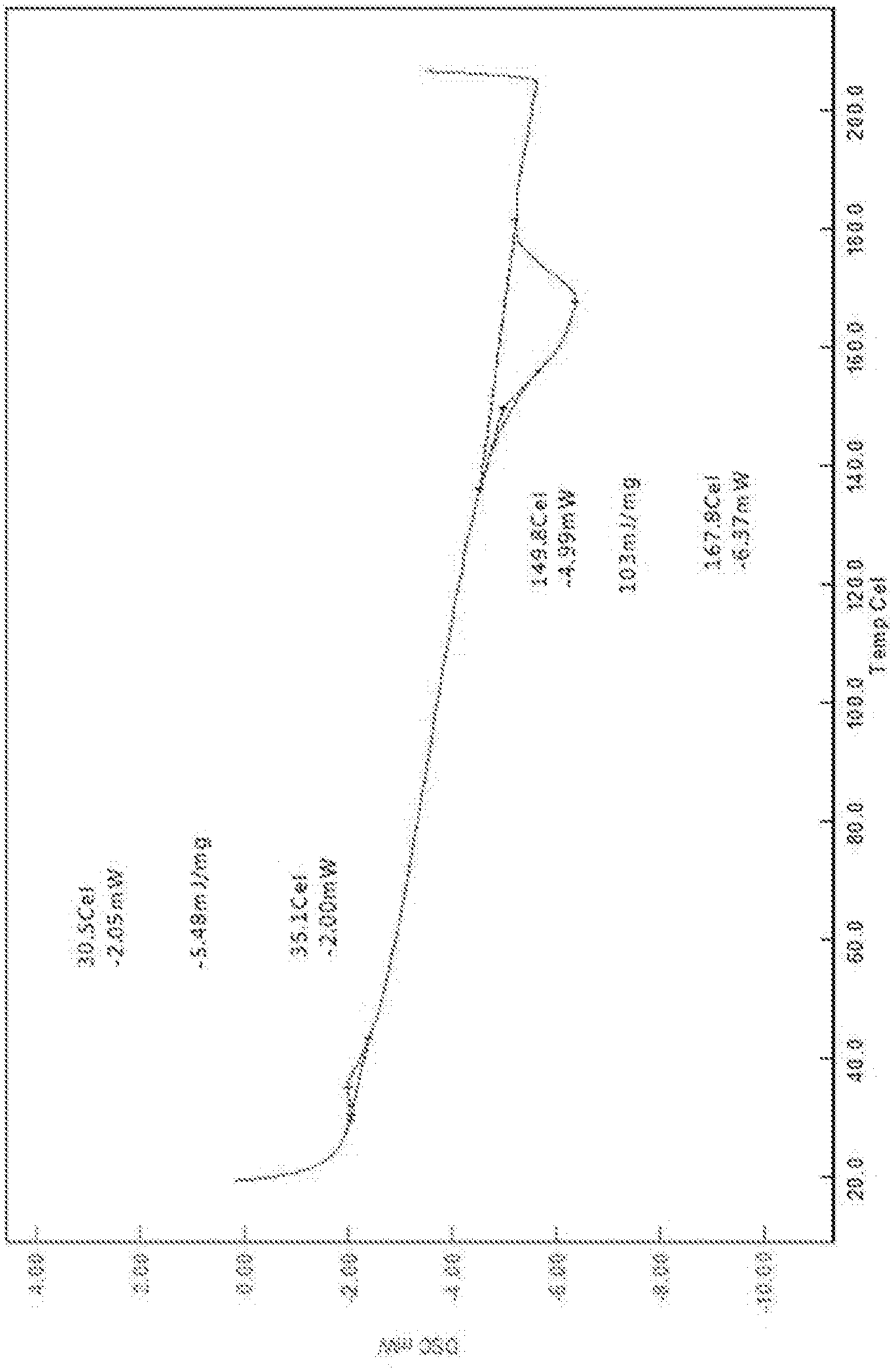

30.5Cel
-2.05mW
-5.49mJ/mg
35.1Cel
-2.00mW
149.8Cel
-4.99mW
103mJ/mg
167.8Cel
-6.37mW
Temp Cel
Exo Down
60.0
80.0
100.0
120.0
140.0
160.0
180.0
200.0
20.0
40.0
-1.00
0.00
1.00
2.00
3.00
4.00
5.00
6.00

FIG. 54C

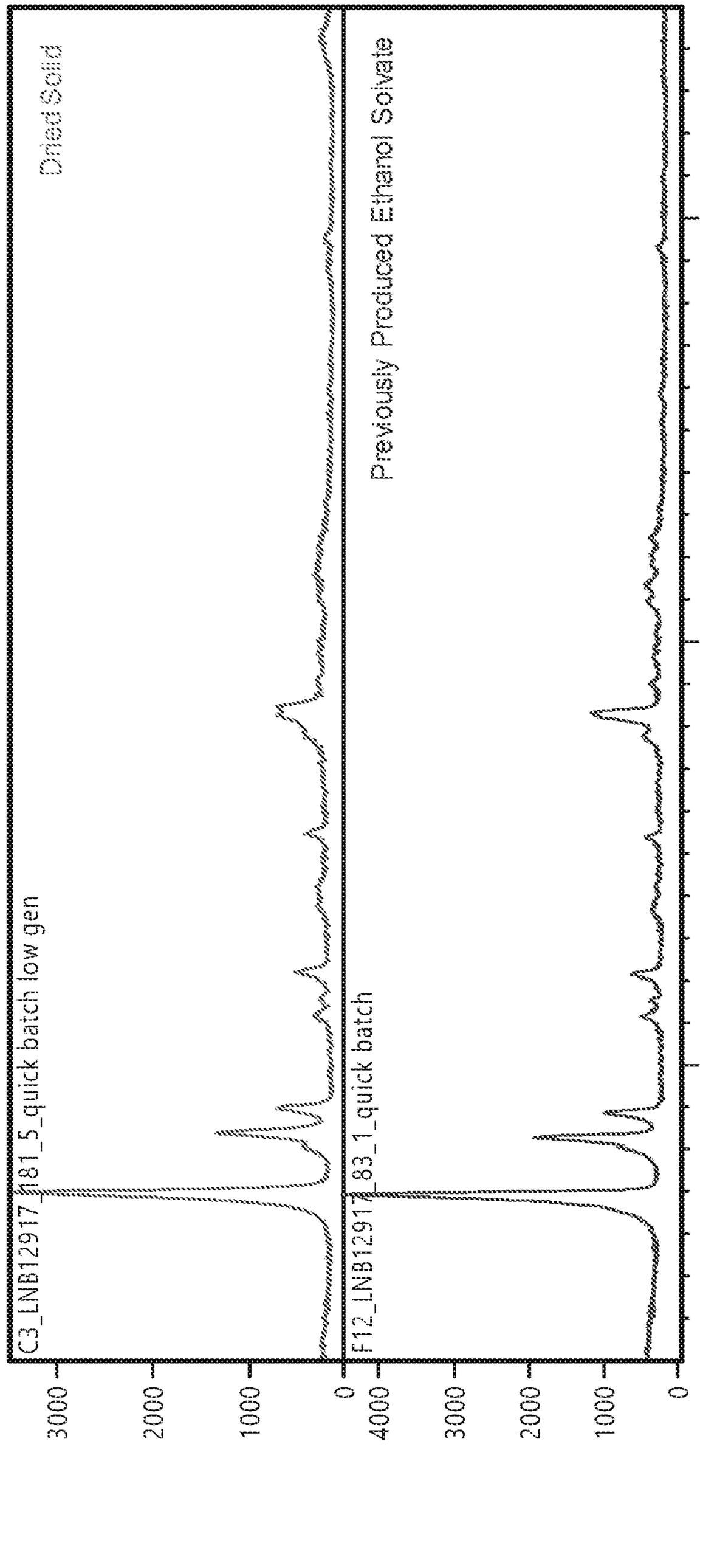

Dried Wet Solid
Previously Produced Ethanol Solvate
C3_LNB12917_181_5_quick batch low gen
F12_LNB12917_83_1_quick batch
Counts
3000
2000
1000
0
4000
3000
2000
1000
0
10
20
30
Position [°2θ] (Copper (Cu))

FIG. 55A

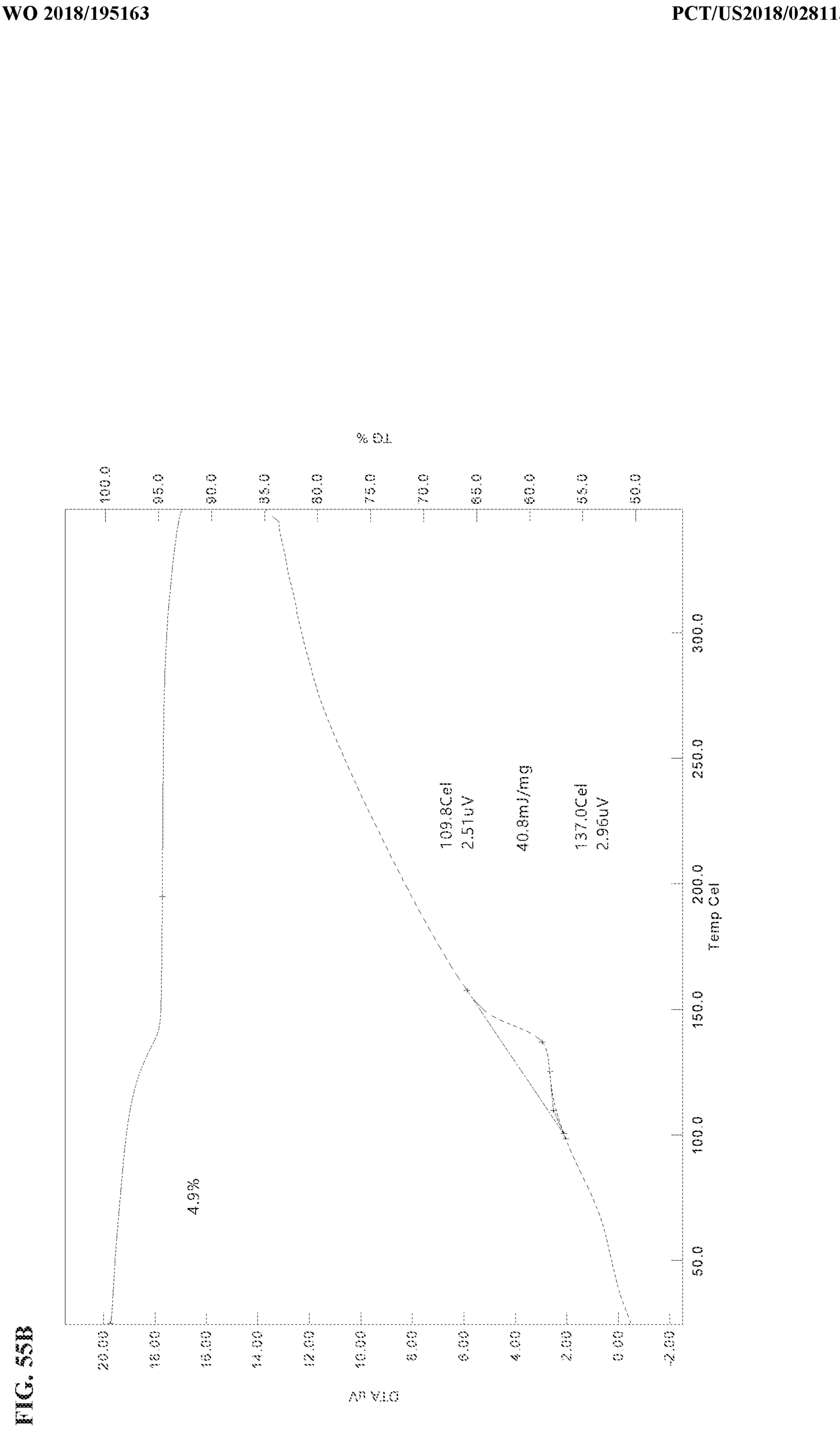
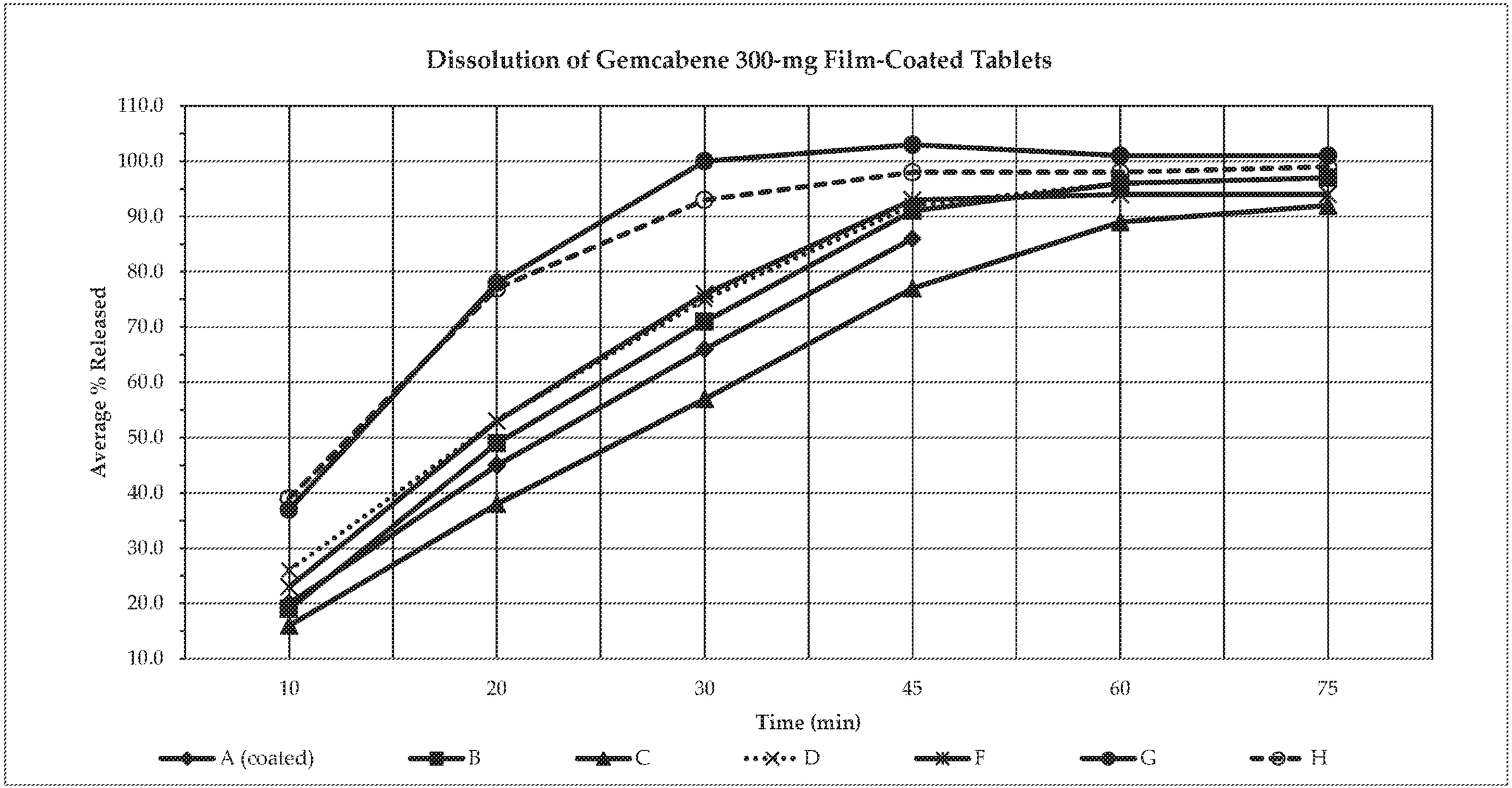

TG %
100.0
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
55.0
50.0
109.8Cel
2.51uV
40.8mJ/mg
137.0Cel
2.96uV
4.9%
DTA uV
20.00
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
-2.00
100.0
150.0
200.0
250.0
300.0
Temp Cel

FIG. 55B

Fig. 1A


Dissolution of Gemcabene 300-mg Film-Coated Tablets
Average % Released
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
10
20
30
45
60
75
Time (min)
A (coated)
B
C
D
F
G
H