LIPID BINDING PROTEIN MOLECULE THERAPY

1. CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority benefit of U.S. provisional application nos. 63/479,912, filed January 13, 2023, 63/488,835, filed March 7, 2023, and 63/594,680, filed October 31, 2023, the contents of each which are incorporated herein in their entireties by reference thereto.

2. SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on December 18, 2023 is named CRN-051WO_SL.xml and is 4322 bytes in size.

3. BACKGROUND

[0003] Current treatments for sepsis and its sequelae conditions are inadequate. Thus, new treatments for these conditions are needed.

4. SUMMARY

[0004] The present disclosure provides methods for treating subjects having or at risk of various conditions. In various aspects, the condition is a gram-positive bacterial infection, a gram-negative bacterial infection, a viral infection, such as a SARS-CoV-2 (COVID-19) infection or an influenza virus infection, acute myocardial infarction (AMI), Alzheimer's disease, chronic inflammatory bowel disease (IBD), a cardiovascular disease (CVD), stroke, transient ischemic attack, cytokine release syndrome (CRS, cytokine storm), organ transplant, such as heart transplant rejection, ischemia reperfusion-induced tissue injury, post-operative inflammation, psoriasis, sepsis (*e.g.*, septic shock), including but not limited to sepsis wherein the subject has an abnormal level of at least two of TNFα, IL-6, IL-8, TREM-1, and a kynurenine pathway biomarker, such as an abnormal level of TREM-1 and at least one of quinolinic acid, kynurenic acid, kynurenine, tryptophan, and kynurenine/tryptophan ratio, sepsis-induced acute kidney injury (AKI), hypoalbuminemia, attention-deficit/hyperactivity disorder (ADHD), a central nervous system (CNS) disease, COVID-19 cognitive decline, depression or major depressive disorder, epilepsy, HIV-associated neurocognitive disorder, Huntington's disease, inflammatory bowel disease (IBD), long-term cognitive decline ("brain fog"), such as can occur after sepsis, mortality or neurological deficit following cardiac arrest, multiple sclerosis (MS), Parkinson's disease, schizophrenia, or vascular endothelial disorder.

[0005] The methods of the disclosure comprise treating a subject with a lipid binding protein molecule, for example an apolipoprotein such as ApoA-I, or an apolipoprotein mimetic. The lipid binding protein molecule can be administered at a high dose, which is typically an aggregate of two or more individual doses administered over one or more days, particularly where the indication is an acute indication such as sepsis. The high dose is typically higher than a dose that would be used to treat a chronic condition, such as familial hypercholesterolemia. For treatment of acute conditions, the high dose is typically administered over a relatively short period of time, for example, over a period of one day to two weeks or one day to three weeks, and typically comprises multiple administrations of the lipid binding protein

molecule, for example two to 20 individual doses. The individual doses can be separated by less than one day (*e.g.*, twice daily administration), or one day or more (*e.g.*, once daily administration).

[0006] In some embodiments of the methods of the disclosure, the lipid binding protein molecule is a component of a lipid binding protein-based complex. Lipid binding protein-based complexes can comprise amphipathic molecules such as lipids, for example a sphingomyelin and/or a negatively charged lipid. An exemplary lipid binding protein-based complex that can be used in the methods of the disclosure is CER-001. CER-001 is a negatively charged lipoprotein complex, and comprises recombinant human ApoA-I, sphingomyelin (SM), and 1, 2-dihexadecanoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (Dipalmitoylphosphatidyl-glycerol; DPPG).

[0007] As reported in Section 7 of the disclosure, CER-001 therapy was observed to have broad pleiotropic effects in an LPS-induced acute kidney injury animal model and in a clinical trial with septic human patients at high risk of acute kidney injury (AKI). In these studies, CER-001 therapy resulted in, *inter alia*, a reduction in levels of various inflammatory cytokines such as IL-6 and a reduction in levels of markers of the kynurenine pathway. The studied markers are associated with various conditions in addition to sepsis. Without being bound by theory, it is believed that the pleiotropic effects of CER-001 can be extended beyond septic patients to provide a clinical benefit to subjects having other conditions, for example the conditions described herein.

[0008] In one aspect, the disclosure provides a method of treating a subject with or at risk of a gram-positive bacterial infection, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0009] In one aspect, the disclosure provides a method of treating a subject with or at risk of a gram-negative bacterial infection, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0010] In one aspect, the disclosure provides a method of treating a subject with or at risk of a viral infection, such as a SARS-CoV-2 (COVID-19) infection or an influenza virus infection, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0011] In one aspect, the disclosure provides a method of treating a subject with or at risk of acute myocardial infarction (AMI), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0012] In one aspect, the disclosure provides a method of treating a subject with or at risk of Alzheimer's disease, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0013] In one aspect, the disclosure provides a method of treating a subject with or at risk of chronic inflammatory bowel disease (IBD), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0014] In one aspect, the disclosure provides a method of treating a subject with or at risk of a cardiovascular disease (CVD), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0015] In one aspect, the disclosure provides a method of treating a subject having or at risk of a stroke, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0016] In one aspect, the disclosure provides a method of treating a subject having or at risk of a transient ischemic attack, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0017] In one aspect, the disclosure provides a method of treating a subject with or at risk of cytokine release syndrome (CRS, cytokine storm), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0018] In one aspect, the disclosure provides a method of treating a subject with or at risk of organ transplant, such as heart transplant rejection, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0019] In one aspect, the disclosure provides a method of treating a subject with or at risk of ischemia reperfusion-induced tissue injury, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0020] In one aspect, the disclosure provides a method of treating a subject with or at risk of post-operative inflammation, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0021] In one aspect, the disclosure provides a method of treating a subject with or at risk of psoriasis, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0022] In one aspect, the disclosure provides a method of treating a subject with or at risk of sepsis (*e.g.*, septic shock), including but not limited to sepsis wherein the subject has an abnormal level of at least two (*e.g.,* two, three, four, or five) of TNFα, IL-6, IL-8, TREM-1, and a kynurenine pathway biomarker, such as an abnormal level of TREM-1 and at least one of quinolinic acid, kynurenic acid, kynurenine, tryptophan, and kynurenine/tryptophan ratio, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0023] In one aspect, the disclosure provides a method of treating a subject with or at risk of sepsis-induced acute kidney injury (AKI), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0024] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0025] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with a vitamin deficiency, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0026] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with inflammatory bowel disease (IBD), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0027] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with kidney disease, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0028] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with infections, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0029] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with stress, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0030] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with thyroid disease, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0031] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with diabetes, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0032] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with nephrotic syndrome, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0033] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with lupus, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0034] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with cirrhosis, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0035] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with liver disease, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0036] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with heart failure, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0037] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with malnutrition, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0038] In one aspect, the disclosure provides a method of treating a subject with or at risk of attention-deficit/hyperactivity disorder (ADHD), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0039] In one aspect, the disclosure provides a method of treating a subject with or at risk of a central nervous system (CNS) disease, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0040] In one aspect, the disclosure provides a method of treating a subject with or at risk of COVID-19 cognitive decline, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0041] In one aspect, the disclosure provides a method of treating a subject with or at risk of depression or major depressive disorder, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0042] In one aspect, the disclosure provides a method of treating a subject with or at risk of epilepsy, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0043] In one aspect, the disclosure provides a method of treating a subject with or at risk of HIV-associated neurocognitive disorder, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0044] In one aspect, the disclosure provides a method of treating a subject with or at risk of Huntington's disease, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0045] In one aspect, the disclosure provides a method of treating a subject with or at risk of inflammatory bowel disease (IBD), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0046] In one aspect, the disclosure provides a method of treating a subject with or at risk of long-term cognitive decline ("brain fog"), such as can occur after sepsis, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0047] In one aspect, the disclosure provides a method of treating a subject with or at risk of mortality or neurological deficit following cardiac arrest, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0048] In one aspect, the disclosure provides a method of treating a subject with or at risk of multiple sclerosis (MS), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0049] In one aspect, the disclosure provides a method of treating a subject with or at risk of Parkinson's disease, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0050] In one aspect, the disclosure provides a method of treating a subject with or at risk of schizophrenia, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0051] In one aspect, the disclosure provides a method of treating a subject with or at risk of vascular endothelial disorder, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0052] In one aspect, the disclosure provides a method of treating a subject with or at risk of a urinary tract infection, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0053] In one aspect, the disclosure provides a method of treating a subject with or at risk of a blood infection, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0054] In one aspect, the disclosure provides a method of treating a subject with or at risk of a post-surgical infection, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0055] In one aspect, the disclosure provides a method of treating a subject with or at risk of gastrointestinal perforation, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0056] In one aspect, the disclosure provides a method of treating a subject with or at risk of a perforated duodenal ulcer, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0057] In one aspect, the disclosure provides a method of treating a subject with or at risk of a perforated bowel, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0058] In one aspect, the disclosure provides a method of treating a subject with or at risk of septic shock (*e.g.*, a subject with sepsis who has not yet progressed to the stage of septic shock), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0059] In one aspect, the disclosure provides a method of treating a subject with or at risk of septic shock following trauma, for example abdominal trauma.

[0060] In some embodiments, a subject having septic shock has hypotension (*e.g.*, systolic arterial pressure < 90 mm Hg or mean arterial pressure (MAP) < 65 mm Hg) requiring the use of vasopressors despite intravenous fluid resuscitation.

[0061] In one aspect, the disclosure provides a method of treating a subject with or at risk of pneumonia, *e.g.*, hospital acquired pneumonia, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0062] In one aspect, the disclosure provides a method of treating a subject with or at risk of a pancreatitis, *e.g.*, necrotizing pancreatitis, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0063] In some aspects, the present disclosure provides dosing regimens for lipid binding protein molecule-based therapy (*e.g.*, ApoA-I therapy) for subjects described herein.

[0064] The dosing regimens of the disclosure typically entail multiple administrations of ApoA-I to a subject (*e.g.*, administered daily or twice in one day). The ApoA-I therapy can be continued for a pre-determined period, *e.g.*, for one week or less (*e.g.*, one day, two days, three days, four days, five days, six days, or seven days) or a period longer than one week (*e.g.*, two weeks or three weeks). Alternatively, administration of ApoA-I to a subject can be continued until one or more symptoms of a condition are reduced or continued until the levels (*e.g.*, serum levels) of one or more relevant biomarkers are reduced, for example reduced to a normal level or reduced relative to a baseline measurement taken prior to the start of ApoA-I therapy. For subjects having an infection (*e.g.*, a bacterial or viral infection), the therapy can in some embodiments be continued until the subject has recovered from the infection.

[0065] The dosing regimens of the disclosure can entail administering a lipid binding protein molecule (*e.g.*, ApoA-I) to a subject according to an initial "induction" regimen, optionally followed by administering the lipid binding protein molecule to the subject according to a "consolidation" regimen.

[0066] The induction regimen typically comprises administering multiple doses of the lipid binding protein molecule (*e.g.*, ApoA-I) to the subject, for example six doses over three days, eight doses over four days, 10 doses over five days, 12 doses over six days, or 14 doses over seven days.

[0067] The consolidation regimen typically comprises administering one or more doses of a lipid binding protein molecule (*e.g.*, ApoA-I) to the subject following the final dose of the induction regimen, for example one or more days after the final dose of the induction regimen. In some embodiments, the first dose of the consolidation regimen is administered on the third day after the final dose of the induction regimen. For example, a dosing regimen can comprise administration of a lipid binding protein molecule (*e.g.*, ApoA-I) to a subject according to an induction regimen on days 1, 2, and 3, and administration of the lipid binding protein molecule to the subject according to a consolidation regimen on day 6. In some embodiments, the consolidation regimen comprises two doses of the lipid binding protein molecule.

[0068] In certain aspects, a lipid binding protein molecule (*e.g.*, ApoA-I) is administered in combination with a standard of care therapy for the subject's disease or condition.

[0069] In certain aspects, an antihistamine (*e.g.*, dexchlorpheniramine, hydroxyzine, diphenhydramine, cetirizine, fexofenadine, or loratadine) can be administered before administration of a lipid binding protein molecule (*e.g.*, ApoA-I). The antihistamine can reduce the likelihood of allergic reactions.

[0070] Further features of exemplary lipid binding protein molecules and lipid binding protein-based complexes that can be used in methods and dosing regimens of the disclosure are described in Section 6.1 and specific embodiments 382 to 407 and 678 to 698, *infra*.

[0071] Further features of subjects who can be treated according to the methods and dosing regimens of the disclosure are described in Section 6.2 and specific embodiments 1 to 201, 332 to 381, 651 to 672, and 700 to 707, *infra*.

[0072] Further features of exemplary dosing regimens of the disclosure are described in Section 6.3 and specific embodiments 202 to 331, 408 to 636, 673 to 677, 699, and 709 to 717, *infra*.

[0073] Exemplary combination therapies are described in Section 6.4 and specific embodiments 637 to 650, *infra*.

5. BRIEF DESCRIPTION OF THE FIGURES

[0074] **FIG. 1A** shows quinolinic acid levels for individual endotoxemic pigs ("LPS") and individual endotoxemic pigs treated with one dose of CER-001 at 20 mg/kg ("20 mg"), in a study described in Example 1.

[0075] **FIG. 1B** shows quinolinic acid levels for individual endotoxemic pigs ("LPS") and individual endotoxemic pigs treated with two doses of CER-001 at 20 mg/kg, total 40 mg/kg ("40 mg"), in a study described in Example 1.

[0076] **FIG. 1C** shows quinolinic acid levels for all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg, in a study described in Example 1.

[0077] **FIG. 2A** shows kynurenic acid levels for individual endotoxemic pigs ("LPS") and individual endotoxemic pigs treated with one dose of CER-001 at 20 mg/kg ("20 mg"), in a study described in Example 1.

[0078] **FIG. 2B** shows kynurenic acid levels for individual endotoxemic pigs ("LPS") and individual endotoxemic pigs treated with two doses of CER-001 at 20 mg/kg each ("40 mg"), in a study described in Example 1.

[0079] **FIG. 2C** shows kynurenic acid levels for all three groups of endotoxemic pigs: LPS, 20mg, and 40 mg, in a study described in Example 1.

[0080] **FIG. 3A** shows tryptophan levels for individual endotoxemic pigs ("LPS") and individual endotoxemic pigs treated with one dose of CER-001 at 20 mg/kg ("20 mg"), in a study described in Example 1.

[0081] **FIG. 3B** shows tryptophan levels for individual endotoxemic pigs ("LPS") and individual endotoxemic pigs treated with two doses of CER-001 at 20 mg/kg each ("40 mg"), in a study described in Example 1.

[0082] **FIG. 3C** shows tryptophan levels for all three groups of endotoxemic pigs: LPS, 20mg, and 40 mg, in a study described in Example 1.

[0083] **FIG. 4A** shows kynurenine levels for individual endotoxemic pigs ("LPS") and individual endotoxemic pigs treated with one dose of CER-001 at 20 mg/kg ("20 mg"), in a study described in Example 1.

[0084] **FIG. 4B** shows kynurenine levels for individual endotoxemic pigs ("LPS") and individual endotoxemic pigs treated with two doses of CER-001 at 20 mg/kg each ("40 mg"), in a study described in Example 1.

[0085] **FIG. 4C** shows kynurenine levels for all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg, in a study described in Example 1.

[0086] **FIG. 5A** shows kynurenine/tryptophan ratios for first cohorts from all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg, in a study described in Example 1.

[0087] **FIG. 5B** shows kynurenine/tryptophan ratios for second cohorts from all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg, in a study described in Example 1.

[0088] **FIG. 6A** shows relative fold gene expression of indoleamine 2,3-dioxygenase 1 (IDO1) in brain tissue as determined by qPCR for cohorts from all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg, in a study described in Example 1.

[0089] **FIG. 6B** shows relative fold gene expression of aromatic-L-amino-acid/L-tryptophan decarboxylase (DDC) in brain tissue as determined by qPCR for cohorts from all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg, in a study described in Example 1.

[0090] **FIG. 6C** shows relative fold gene expression of kynurenine formamidase isoform X1 (AFMID) in brain tissue as determined by qPCR for cohorts from all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg, in a study described in Example 1.

[0091] **FIG. 6D** shows relative fold gene expression of kynurenine 3-monooxygenase (KMO) in brain tissue as determined by qPCR for cohorts from all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg, in a study described in Example 1.

[0092] **FIG. 6E** shows relative fold gene expression of kynurenine--oxoglutarate transaminase 3 (KYAT3) in brain tissue as determined by qPCR for cohorts from all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg, in a study described in Example 1.

[0093] **FIG. 6F** shows relative fold gene expression of interleukin-6 (IL-6) in brain tissue as determined by qPCR for cohorts from all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg, in a study described in Example 1.

[0094] **FIG. 7** shows a schematic of the clinical study of Example 2.

[0095] **FIG. 8A** shows lipopolysaccharide (LPS) changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0096] **FIG. 8B** shows LPS changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0097] **FIG. 8C** shows LPS changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0098] **FIG. 8D** shows LPS changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0099] **FIG. 8E** shows lipopolysaccharide (LPS) changes from baseline for each subject in the standard of care (SOC) group and the three experimental groups (CER-001) in the clinical study of Example 2.

[0100] **FIG. 8F** shows lipopolysaccharide (LPS) changes from baseline for each subject in the standard of care (SOC) group and each of the three experimental groups (CER-001) in the clinical study of Example 2.

[0101] **FIG. 9A** shows endotoxin activity assay (EAA) changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0102] **FIG. 9B** shows EAA changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0103] **FIG. 9C** shows EAA changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0104] **FIG. 9D** shows EAA changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0105] **FIG. 9E** shows endotoxin activity assay (EAA) changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0106] **FIG. 10A** shows TNF-alpha changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0107] **FIG. 10B** shows TNF-alpha changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0108] **FIG. 10C** shows TNF-alpha changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0109] **FIG. 10D** shows TNF-alpha changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0110] **FIG. 10E** shows TNF-alpha changes from baseline for each subject in the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0111] **FIG. 10F** shows TNF-alpha changes from baseline for each subject in each of the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0112] **FIG. 11A** shows MCP-1 changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0113] **FIG. 11B** shows MCP-1 changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0114] **FIG. 11C** shows MCP-1 changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0115] **FIG. 11D** shows MCP-1 changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0116] **FIG. 11E** shows MCP-1 changes from baseline for each subject in the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0117] **FIG. 11F** shows MCP-1 changes from baseline for each subject in each of the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0118] **FIG. 12A** shows IL-6 changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0119] **FIG. 12B** shows IL-6 changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0120] **FIG. 12C** shows IL-6 changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0121] **FIG. 12D** shows IL-6 changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0122] **FIG. 12E** shows IL-6 changes from baseline for each subject in the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0123] **FIG. 12F** shows IL-6 changes from baseline for each subject in each of the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0124] **FIG. 13A** shows IL-8 changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0125] **FIG. 13B** shows IL-8 changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0126] **FIG. 13C** shows IL-8 changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0127] **FIG. 13D** shows IL-8 changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0128] **FIG. 13E** shows IL-8 changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0129] **FIG. 13F** shows IL-8 changes from baseline for the standard of care (SOC) group (Group A) and each of the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0130] **FIG. 14A** shows IL-10 changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0131] **FIG. 14B** shows IL-10 changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0132] **FIG. 14C** shows IL-10 changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0133] **FIG. 14D** shows IL-10 changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0134] **FIG. 15A** shows TREM-1 changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0135] **FIG. 15B** shows TREM-1 changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0136] **FIG. 15C** shows TREM-1 changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0137] **FIG. 15D** shows TREM-1 changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0138] **FIG. 15E** shows TREM-1 changes from baseline for each subject in the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0139] **FIG. 15F** shows TREM-1 changes from baseline for each subject in each of the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0140] **FIG. 16A** shows VCAM changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0141] **FIG. 16B** shows VCAM changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0142] **FIG. 16C** shows VCAM changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0143] **FIG. 16D** shows VCAM changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0144] **FIG. 16E** shows VCAM changes from baseline for each subject in the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0145] **FIG. 16F** shows VCAM changes from baseline for each subject in each of the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0146] **FIG. 17A** shows ICAM changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0147] **FIG. 17B** shows ICAM changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0148] **FIG. 17C** shows ICAM changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0149] **FIG. 17D** shows ICAM changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0150] **FIG. 17E** shows ICAM changes from baseline for each subject in the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0151] **FIG. 17F** shows ICAM changes from baseline for each subject in each of the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0152] **FIG. 18A** shows ferritin changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0153] **FIG. 18B** shows ferritin changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0154] **FIG. 18C** shows ferritin changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0155] **FIG. 18D** shows ferritin changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0156] **FIG. 19A** shows white blood cell count changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0157] **FIG. 19B** shows white blood cell count changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0158] **FIG. 19C** shows white blood cell count changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0159] **FIG. 19D** shows white blood cell count changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0160] **FIG. 20A** shows C-reactive protein (CRP) changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0161] **FIG. 20B** shows CRP changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0162] **FIG. 20C** shows CRP changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0163] **FIG. 20D** shows CRP changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0164] **FIG. 20E** shows C-reactive protein (CRP) changes from baseline for each subject in the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0165] **FIG. 20F** shows C-reactive protein (CRP) changes from baseline for each subject in the standard of care (SOC) group (Group A) and each of the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0166] **FIG. 21A** shows KIM-1 changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0167] **FIG. 21B** shows KIM-1 changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0168] **FIG. 21C** shows KIM-1 changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0169] **FIG. 21D** shows KIM-1 changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0170] **FIG. 22A** shows serum albumin changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0171] **FIG. 22B** shows serum albumin changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0172] **FIG. 22C** shows serum albumin changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0173] **FIG. 22D** shows serum albumin changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0174] **FIG. 22E** shows serum albumin changes from baseline for each subject in the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0175] **FIG. 23A** shows serum creatinine changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0176] **FIG. 23B** shows serum creatinine changes from baseline for each of Groups A-D in the clinical study of Example 2.

[0177] **FIG. 23C** shows serum creatinine changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0178] **FIG. 23D** shows serum creatinine changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, in the clinical study of Example 2.

[0179] **FIG. 23E** shows the AUC for serum creatinine (mean ± SEM) for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0180] **FIG. 23F** shows the AUC for serum creatinine (95% confidence interval) for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0181] **FIG. 24A** shows estimated glomerular filtration rate (eGFR) changes from baseline for all subjects in the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0182] **FIG. 24B** shows eGFR changes from baseline for all subjects in each of Groups A-D in the clinical study of Example 2.

[0183] **FIG. 24C** shows eGFR changes from baseline only for subjects in the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) who entered the clinical study of Example 2 with AKI.

[0184] **FIG. 24D** shows eGFR changes from baseline for r the same subjects as in **FIG. 24C**.

[0185] **FIG. 24E** shows eGFR changes as a percentage of peak for all subjects in the standard of care (SOC) group (Group A) and aggregated Groups B-D in the clinical study of Example 2.

[0186] **FIG. 24F** shows eGFR changes as a percentage of peak only for subjects entering the study with AKI, in the standard of care (SOC) group (Group A) and aggregated Groups B-D in the clinical study of Example 2.

[0187] **FIG. 25** shows P/F changes from baseline for all subjects in the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 2.

[0188] **FIG. 26** shows survival proportions for all subjects after days in ICU for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 2.

[0189] **FIG. 27A** shows survival proportions over 30 days for all subjects for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 2.

[0190] **FIG. 27B** shows survival proportions over 30 days for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 2.

[0191] **FIG. 28A** shows the evolution of AKI staging for the standard of care group (Group A, "SOC") in the clinical study of Example 2.

[0192] **FIG. 28B** shows the evolution of AKI staging for aggregated Groups B-D ("CER-001") in the clinical study of Example 2.

[0193] **FIG. 29** shows days on mechanical ventilation for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 2.

[0194] **FIG. 30** shows days on vasopressor therapy for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 2.

[0195] **FIG. 31A** shows days on dialysis for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 2.

[0196] **FIG. 31B** shows days on dialysis for all subjects who entered the study for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 2.

[0197] **FIG. 32** shows days alive without organ support for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 2.

[0198] **FIG. 33A** shows changes in daily average mean arterial pressure (MAP) for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 2.

[0199] **FIG. 33B** shows changes in daily average mean arterial pressure (MAP) for each subject who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 2.

[0200] **FIG. 34** shows change in daily average heart rate (HR) for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 2.

[0201] **FIG. 35** shows change in daily average P/F ratio for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 2.

[0202] **FIG. 36** shows the survival curve of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0203] **FIG. 37** shows serum VCAM levels of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0204] **FIG. 38** shows serum ICAM levels of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0205] **FIG. 39** shows serum TNF-α levels of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0206] **FIG. 40** shows serum MCP-1 levels of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0207] **FIG. 41** shows serum Il-6 levels of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0208] **FIG. 42** shows systemic classical pathway complement activation in pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0209] **FIG. 43** shows systemic alternative pathway complement activation in pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0210] **FIG. 44** shows systemic lectin pathway complement activation in pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0211] **FIG. 45A** shows representative hematoxylin and eosin (HE) staining of hepatic tissue of pigs upon challenge with LPS, as described in Example 3.

[0212] **FIG. 45B** shows representative HE staining of hepatic tissue of pigs upon challenge with LPS and CER-001 treatment (20 mg/kg), as described in Example 3.

[0213] **FIG. 45C** shows representative HE staining of hepatic tissue of pigs upon challenge with LPS and CER-001 treatment (20 mg/kg x 2), as described in Example 3.

[0214] **FIG. 45D** shows liver injury quantified from images of stained liver of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0215] **FIG. 45E** shows serum levels of ALT enzyme of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0216] **FIG. 46A** shows representative HE staining of renal tissue of pigs upon challenge with LPS, as described in Example 3.

[0217] **FIG. 46B** shows representative HE staining of renal tissue of pigs upon challenge with LPS and CER-001 treatment (20 mg/kg), as described in Example 3.

[0218] **FIG. 46C** shows representative HE staining of renal tissue of pigs upon challenge with LPS and CER-001 treatment (20 mg/kg x 2), as described in Example 3.

[0219] **FIG. 46D** shows tubular pathological score quantified from images of stained kidney of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0220] **FIG. 46E** shows glomerular pathological score quantified from images of stained kidney of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0221] **FIG. 47** shows serum levels of creatinine of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0222] **FIG. 48** shows urinary output of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0223] **FIG. 49A** shows serum Cystatin C levels of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0224] **FIG. 49B** shows urinary Cystatin C levels of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0225] **FIG. 50A** shows serum KIM-1 levels of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0226] **FIG. 50B** shows urinary KIM-1 levels of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0227] **FIG. 51** shows serum LPS levels of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0228] **FIG. 52A** shows a western blot of LPS and β-actin protein expression in livers of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0229] **FIG. 52B** shows a densitometric analysis of LPS and β-actin protein expression in livers of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0230] **FIG. 53** shows endotoxin levels in bile of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0231] **FIG. 54** shows serum levels of human ApoA-I of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0232] **FIG. 55** shows levels of human ApoA-I in bile of pigs upon challenge with LPS and CER-001 infusions, as described in Example 3.

[0233] **FIG. 56A** shows mean ApoA-I levels for the control group and the aggregated study groups in the clinical study of Example 2.

[0234] **FIG. 56B** shows ApoA-I levels for each subject broken out by study group in the clinical study of Example 2.

[0235] **FIG. 56C** shows changes from baseline of ApoA-I levels for each subject in the clinical study of Example 2.

[0236] **FIG. 56D** shows changes from baseline of ApoA-I levels for each subject broken out by study group in the clinical study of Example 2.

[0237] **FIG. 57A** shows changes from baseline of aspartate transaminase (AST) levels for each subject in the clinical study of Example 2.

[0238] **FIG. 57B** shows changes from baseline of alanine transaminase (ALT) levels for each subject in the clinical study of Example 2.

[0239] **FIG. 58** shows MTT cell viability assay results for cultured endothelial cells upon challenge with LPS and CER-001 infusions, as described in Example 4.

[0240] **FIG. 59** summarizes endothelial nitric oxide synthase (eNOS)-based (eNOS(phosphoS1177)) FACS results for cultured endothelial cells upon challenge with LPS and CER-001 infusions, as described in Example 4.

[0241] **FIG. 60** shows eNOS(phosphoS1177)-based FACS results for cultured endothelial cells upon challenge with LPS and CER-001 infusions in one representative of three independent experiments, compared to basal and VEFG (positive control) cells, as described in Example 4.

[0242] **FIG. 61** shows MTT cell viability assay results for PBMCs from healthy donors upon challenge with LPS and CER-001 infusions, as described in Example 4.

[0243] **FIG. 62** shows TNF-α synthesis for PBMCs from healthy donors upon challenge with LPS and CER-001 infusions, as described in Example 4.

[0244] **FIG. 63** shows CD14-based FACS results for PBMCs from healthy donors upon challenge with LPS and CER-001 infusions in one representative of three independent experiments, as described in Example 4.

[0245] **FIG. 64** summarizes CD14-based FACS results for PBMCs from healthy donors upon challenge with LPS and CER-001 infusions, as described in Example 4.

[0246] **FIG. 65** shows days until ICU discharge for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 2.

[0247] **FIG. 66** shows changes in serum quinolinic acid (QA) levels from baseline (day 1) for subjects in the standard of care (SOC) group (Group A) and aggregated Groups B-D in the clinical study of Example 2.

[0248] **FIG. 67** shows changes in serum kynurenine/tryptophan ratios (Kyn/Trp) levels from baseline (day 1) for subjects in the standard of care (SOC) group (Group A) and aggregated Groups B-D in the clinical study of Example 2.

[0249] **FIG. 68** shows changes in serum serotonin levels from baseline (day 1) for subjects in the standard of care (SOC) group (Group A) and aggregated Groups B-D in the clinical study of Example 2.

[0250] **FIG. 69** shows the overall trial design of Example 5.

[0251] **FIG. 70** shows the study participation for an individual subject of Example 5.

6. DETAILED DESCRIPTION

[0252] The present disclosure provides methods for treating subjects having or at risk of various conditions with lipid binding protein molecules. In various aspects, the condition is a gram-positive bacterial infection, a gram-negative bacterial infection, a viral infection, such as a SARS-CoV-2 (COVID-19) infection or an influenza virus infection, acute myocardial infarction (AMI), Alzheimer's disease, chronic inflammatory bowel disease (IBD), a cardiovascular disease (CVD), stroke, transient ischemic attack, cytokine release syndrome (CRS, cytokine storm), organ transplant, such as heart transplant rejection, ischemia reperfusion-induced tissue injury, post-operative inflammation, psoriasis, sepsis (*e.g.*, septic shock), including but not limited to sepsis wherein the subject has an abnormal level of at least two of TNFα, IL-6, IL-8, TREM-1, and a kynurenine pathway biomarker, such as an abnormal level of TREM-1 and at least one of quinolinic acid, kynurenic acid, kynurenine, tryptophan, and kynurenine/tryptophan ratio, sepsis-induced acute kidney injury (AKI), hypoalbuminemia, hypoalbuminemia associated with a vitamin deficiency, hypoalbuminemia associated with inflammatory bowel disease (IBD), hypoalbuminemia associated with kidney disease, hypoalbuminemia associated with infections, hypoalbuminemia associated with stress, hypoalbuminemia associated with thyroid disease, hypoalbuminemia associated with diabetes, hypoalbuminemia associated with nephrotic syndrome, hypoalbuminemia associated with lupus, hypoalbuminemia associated with cirrhosis, hypoalbuminemia associated with liver disease, hypoalbuminemia associated with heart failure, hypoalbuminemia associated with malnutrition, attention-deficit/hyperactivity disorder (ADHD), a central nervous system (CNS) disease, COVID-19 cognitive decline, depression or major depressive disorder, epilepsy, HIV-associated neurocognitive disorder, Huntington's disease, inflammatory bowel disease (IBD), long-term cognitive decline ("brain fog"), such as can occur after sepsis, mortality or neurological deficit following cardiac arrest, multiple sclerosis (MS), Parkinson's disease, schizophrenia, or vascular endothelial disorder.

[0253] In some embodiments, the methods comprise administering a high dose of a lipid binding protein molecule.

[0254] In one aspect, the disclosure provides a method of treating a subject with or at risk of a gram-positive bacterial infection, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0255] In one aspect, the disclosure provides a method of treating a subject with or at risk of a gram-negative bacterial infection, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0256] In one aspect, the disclosure provides a method of treating a subject with or at risk of a viral infection, such as a SARS-CoV-2 (COVID-19) infection or an influenza virus infection, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0257] In one aspect, the disclosure provides a method of treating a subject with or at risk of acute myocardial infarction (AMI), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0258] In one aspect, the disclosure provides a method of treating a subject with or at risk of Alzheimer's disease, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0259] In one aspect, the disclosure provides a method of treating a subject with or at risk of chronic inflammatory bowel disease (IBD), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0260] In one aspect, the disclosure provides a method of treating a subject with or at risk of a cardiovascular disease (CVD), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0261] In one aspect, the disclosure provides a method of treating a subject having or at risk of a stroke, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0262] In one aspect, the disclosure provides a method of treating a subject having or at risk of a transient ischemic attack, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0263] In one aspect, the disclosure provides a method of treating a subject with or at risk of cytokine release syndrome (CRS, cytokine storm), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0264] In one aspect, the disclosure provides a method of treating a subject with or at risk of organ transplant, such as heart transplant rejection, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0265] In one aspect, the disclosure provides a method of treating a subject with or at risk of ischemia reperfusion-induced tissue injury, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0266] In one aspect, the disclosure provides a method of treating a subject with or at risk of post-operative inflammation, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0267] In one aspect, the disclosure provides a method of treating a subject with or at risk of psoriasis, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0268] In one aspect, the disclosure provides a method of treating a subject with or at risk of sepsis (*e.g.*, septic shock), including but not limited to sepsis wherein the subject has an abnormal level of at least two of TNFα, IL-6, IL-8, TREM-1, and a kynurenine pathway biomarker, such as an abnormal level

of TREM-1 and at least one of quinolinic acid, kynurenic acid, kynurenine, tryptophan, and kynurenine/tryptophan ratio, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0269] In one aspect, the disclosure provides a method of treating a subject with or at risk of sepsis-induced acute kidney injury (AKI), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0270] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0271] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with a vitamin deficiency, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0272] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with inflammatory bowel disease (IBD), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0273] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with kidney disease, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0274] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with infections, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0275] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with stress, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0276] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with thyroid disease, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0277] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with diabetes, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0278] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with nephrotic syndrome, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0279] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with lupus, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0280] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with cirrhosis, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0281] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with liver disease, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0282] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with heart failure, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0283] In one aspect, the disclosure provides a method of treating a subject with or at risk of hypoalbuminemia associated with malnutrition, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0284] In one aspect, the disclosure provides a method of treating a subject with or at risk of attention-deficit/hyperactivity disorder (ADHD), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0285] In one aspect, the disclosure provides a method of treating a subject with or at risk of a central nervous system (CNS) disease, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0286] In one aspect, the disclosure provides a method of treating a subject with or at risk of COVID-19 cognitive decline, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0287] In one aspect, the disclosure provides a method of treating a subject with or at risk of depression or major depressive disorder, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0288] In one aspect, the disclosure provides a method of treating a subject with or at risk of epilepsy, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0289] In one aspect, the disclosure provides a method of treating a subject with or at risk of HIV-associated neurocognitive disorder, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0290] In one aspect, the disclosure provides a method of treating a subject with or at risk of Huntington's disease, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0291] In one aspect, the disclosure provides a method of treating a subject with or at risk of inflammatory bowel disease (IBD), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0292] In one aspect, the disclosure provides a method of treating a subject with or at risk of long-term cognitive decline ("brain fog"), such as can occur after sepsis, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0293] In one aspect, the disclosure provides a method of treating a subject with or at risk of mortality or neurological deficit following cardiac arrest, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0294] In one aspect, the disclosure provides a method of treating a subject with or at risk of multiple sclerosis (MS), comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0295] In one aspect, the disclosure provides a method of treating a subject with or at risk of Parkinson's disease, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0296] In one aspect, the disclosure provides a method of treating a subject with or at risk of schizophrenia, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0297] In one aspect, the disclosure provides a method of treating a subject with or at risk of vascular endothelial disorder, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I).

[0298] In some embodiments, the condition is associated with abnormal levels of one or more of TREM-1, albumin, interleukin 10 (IL-10), a kynurenine pathway biomarker (such as tryptophan, serotonin, formylkynurenine, kynurenine, kynurenic acid, 2-amino-3-carboxymuconate-semialdehyde, 3-hydroxykynurenine, xanthurenic acid, anthralinic acid, 3-hydroxyanthralinic acid, quinolinic acid, picolinic acid, quinaldic acid, or kynurenine/tryptophan ratio), TNF-α, MCP-1, IL-6, IL-8, IL-10, VCAM-1, or ICAM-1.

[0299] In some embodiments, the condition is associated with an abnormal level of 2-amino-3-carboxymuconate-semialdehyde.

[0300] In some embodiments, the condition is associated with an abnormal level of 3-hydroxyanthranilic acid.

[0301] In some embodiments, the condition is associated with an abnormal level of 3-hydroxykynurenine.

[0302] In some embodiments, the condition is associated with an abnormal level of albumin.

[0303] In some embodiments, the condition is associated with an abnormal level of anthranilic acid.

[0304] In some embodiments, the condition is associated with an abnormal level of formylkynurenine.

[0305] In some embodiments, the condition is associated with an abnormal level of ICAM-1.

[0306] In some embodiments, the condition is associated with an abnormal level of IL-6.

[0307] In some embodiments, the condition is associated with an abnormal level of IL-8.

[0308] In some embodiments, the condition is associated with an abnormal level of kynurenic acid.

[0309] In some embodiments, the condition is associated with an abnormal level of kynurenine.

[0310] In some embodiments, the condition is associated with an abnormal level of kynurenine/tryptophan ratio.

[0311] In some embodiments, the condition is associated with an abnormal level of MCP-1.

[0312] In some embodiments, the condition is associated with an abnormal level of picolinic acid.

[0313] In some embodiments, the condition is associated with an abnormal level of quinaldic acid.

[0314] In some embodiments, the condition is associated with an abnormal level of quinolinic acid.

[0315] In some embodiments, the condition is associated with an abnormal level of serotonin.

[0316] In some embodiments, the condition is associated with an abnormal level of TNFα.

[0317] In some embodiments, the condition is associated with an abnormal level of TREM-1.

[0318] In some embodiments, the condition is associated with an abnormal level of tryptophan.

[0319] In some embodiments, the condition is associated with an abnormal level of VCAM-1.

[0320] In some embodiments, the condition is associated with an abnormal level of xanthurenic acid.

[0321] In some embodiments, the lipid binding protein molecule is provided as a component of a lipid binding protein-based complex. In some embodiments, the lipid binding protein-based complex is an Apomer, a Cargomer, a HDL based complex, or a HDL mimetic-based complex. In specific embodiments, the lipid binding protein-based complex is CER-001.

[0322] Exemplary features of lipid binding protein molecules and lipid binding protein-based complexes comprising the lipid binding protein molecules that can be used in the methods and compositions of the

disclosure are described in Section 6.1. Exemplary subject populations who can be treated by the methods of the disclosure and with the compositions of the disclosure are described in Section 6.2.

[0323] In some embodiments, methods of the disclosure comprise administering a lipid binding protein molecule (*e.g.*, ApoA-I) to a subject in two phases. First, the lipid binding protein molecule (*e.g.*, ApoA-I) is administered in an initial, intense "induction" regimen. The induction regimen is followed by a less intense "consolidation" regimen. Alternatively, a lipid binding protein molecule (*e.g.*, ApoA-I) can be administered to a subject in a single phase, for example according to an administration regimen corresponding to the dose and administration frequency of an induction or consolidation regimen described herein.

[0324] Induction regimens that can be used in the methods of the disclosure are described in Section 6.3.1 and consolidation regimens that can be used in the methods of the disclosure are described in Section 6.3.2. The dosing regimens of the disclosure comprise administering a lipid binding protein molecule (*e.g.*, ApoA-I) as monotherapy or as part of a combination therapy with one or more medications, for example in combination with a standard of care therapy for the subject's disease or condition. Combination therapies are described in Section 6.4.

6.1. Lipid binding protein molecules and lipid binding protein-based complexes

6.1.1. Lipid Binding Protein Molecules

[0325] Lipid binding protein molecules that can be used, either directly or in a lipid binding protein-based complexes described herein, include apolipoproteins such as those described in Section 6.1.1.1 and apolipoprotein mimetic peptides such as those described in Section 6.1.1.2. In some embodiments, a mixture of lipid binding protein molecules can be used, optionally as members of a complex. In some embodiments, the mixture of lipid binding protein molecules can comprise one or more apolipoproteins. In some embodiments, the mixture of lipid binding protein molecules can comprise one or more apolipoprotein mimetic peptides. In some embodiments, the mixture of lipid binding protein molecules can comprise one or more apolipoproteins and one or more apolipoprotein mimetic peptides.

6.1.1.1. Apolipoproteins

[0326] Suitable apolipoproteins from which the lipid binding protein molecule can be chosen, and that can be included in lipid binding protein-based complexes disclosed herein, include apolipoproteins ApoA-I, ApoA-II, ApoA-IV, ApoA-V, ApoB, ApoC-I, ApoC-II, ApoC-III, ApoD, ApoE, ApoJ, ApoH, and any combination of two or more of the foregoing. Polymorphic forms, isoforms, variants and mutants as well as truncated forms of the foregoing apolipoproteins, the most common of which are Apolipoprotein A-I_{Milano} (ApoA-I_M), Apolipoprotein A-I_{Paris} (ApoA-I_P), and Apolipoprotein A-$I_{Zaragoza}$ (ApoA-I_Z), can also be used. Apolipoproteins mutants containing cysteine residues are also known, and can also be used (see, *e.g.*, U.S. Publication No. 2003/0181372). The apolipoproteins may be in the form of monomers or dimers, which may be homodimers or heterodimers. For example, homo- and heterodimers (where feasible) of ApoA-I (Duverger et al., 1996, Arterioscler. Thromb. Vasc. Biol. 16(12):1424-29), ApoA-I_M (Franceschini et al., 1985, J. Biol. Chem. 260:1632-35), ApoA-I_P (Daum et al., 1999, J. Mol. Med. 77:614-22), ApoA-II (Shelness et al., 1985, J. Biol. Chem. 260(14):8637-46; Shelness et al., 1984, J. Biol. Chem. 259(15):9929-35), ApoA-IV (Duverger et al., 1991, Euro. J. Biochem. 201(2):373-83), ApoE (McLean et al., 1983, J. Biol. Chem. 258(14):8993-9000), ApoJ and ApoH may be used.

[0327] The apolipoproteins can be modified in their primary sequence to render them less susceptible to oxidations, for example, as described in U.S. Publication Nos. 2008/0234192 and 2013/0137628, and U.S. Patent Nos. 8,143,224 and 8,541,236. The apolipoproteins can include residues corresponding to elements that facilitate their isolation, such as His tags, or other elements designed for other purposes. Preferably, the apolipoprotein or apolipoprotein containing complex is soluble in a biological fluid (*e.g.*, lymph, cerebrospinal fluid, vitreous humor, aqueous humor, blood, or a blood fraction (*e.g.*, serum or plasma).

[0328] In some embodiments, the lipid binding protein molecule comprises covalently bound lipid-binding protein monomers, *e.g.*, dimeric apolipoprotein A-I_{Milano}, which is a mutated form of ApoA-I containing a cysteine. The cysteine allows the formation of a disulfide bridge which can lead to the formation of homodimers or heterodimers (*e.g.*, ApoA-I_{Milano}-ApoA-II).

[0329] In some embodiments, the apolipoprotein molecules comprise ApoA-I, ApoA-II, ApoA-IV, ApoA-V, ApoB, ApoC-I, ApoC-II, ApoC-III, ApoD, ApoE, ApoJ, or ApoH molecules or a combination thereof.

[0330] In some embodiments, the apolipoprotein molecules comprise or consist of ApoA-I molecules. In some embodiments, said ApoA-I molecules are human ApoA-I molecules. In some embodiments, said ApoA-I molecules are recombinant. In some embodiments, the ApoA-I molecules are not ApoA-I_{Milano}.

[0331] In some embodiments, the ApoA-I molecules are Apolipoprotein A-I_{Milano} (ApoA-I_M), Apolipoprotein A-I_{Paris} (ApoA-I_P), or Apolipoprotein A-$I_{Zaragoza}$ (ApoA-I_Z) molecules.

[0332] Apolipoproteins can be purified from animal sources (and in particular from human sources) or produced recombinantly as is well-known in the art, see, *e.g.*, Chung et al., 1980, J. Lipid Res. 21(3):284-91; Cheung et al., 1987, J. Lipid Res. 28(8):913-29. See also U.S. Patent Nos. 5,059,528, 5,128,318, 6,617,134; U.S. Publication Nos. 2002/0156007, 2004/0067873, 2004/0077541, and 2004/0266660; and PCT Publications Nos. WO 2008/104890 and WO 2007/023476. Other methods of purification are also possible, for example as described in PCT Publication No. WO 2012/109162, the disclosure of which is incorporated herein by reference in its entirety.

[0333] In particular embodiments, the ApoA-I is recombinant ApoA-I produced by a mammalian host cell. The host cell can be from any mammalian cell line. Polynucleotides encoding the ApoA-I can be codon optimized for expression in recombinant host cells. In some embodiments, host cells are mammalian host cells, including, but not limited to, Chinese hamster ovary cells (*e.g.* CHO-K1; ATCC No. CCL 61; CHO-S (*e.g.*, GIBCO Life Technologies Inc., Rockville, MD, Catalog #11619012)), VERO cells, BHK (ATCC No. CRL 1632), BHK 570 (ATCC No. CRL 10314), HeLa cells, COS-1 (ATCC No. CRL 1650), COS-7 (ATCC No. CRL 1651), MDCK cells, 293 cells (ATCC No. CRL 1573; Graham *et al.*, J. Gen. Virol. 36:59-72, 1977), 3T3 cells, myeloma cells (especially murine), PC12 cells and W138 cells. In certain embodiments, the mammalian cells, such as CHO-S cells, are adapted for growth in serum-free medium. Additional suitable cell lines are known in the art and available from public depositories such as the American Type Culture Collection, Manassas, Va.

[0334] In some embodiments, the recombinant ApoA-I is produced by a CHO cell, for example a CHO-S cell. As the person of ordinary skill in the art will be aware, recombinant polypeptides (*e.g.*, recombinant ApoA-I) expressed by a mammalian host cell, such as a CHO cell, may undergo post-translational processing (*e.g.*, glycosylation, etc.). The resulting recombinant ApoA-I can have one or more structural features (*e.g.*, glycosylation pattern) that are different from ApoA-I purified from human plasma.

[0335] The apolipoprotein can be in prepro- form, pro- form, or mature form. For example, the apolipoprotein can comprise ApoA-I (*e.g.*, human ApoA-I) in which the ApoA-I is preproApoA-I, proApoA-I, or mature ApoA-I. In some embodiments, the ApoA-I has at least 90% sequence identity to SEQ ID NO:1:

PPQSPWDRVKDLATVYVDVLKDSGRDYVSQFEGSALGKQLNLKLLDNWDSVTSTFSKLREQLGPVTQE FWDNLEKETEGLRQEMSKDLEEVKAKVQPYLDDFQKKWQEEMELYRQKVEPLRAELQEGARQKLHEL QEKLSPLGEEMRDRARAHVDALRTHLAPYSDELRQRLAARLEALKENGGARLAEYHAKATEHLSTLSEK AKPALEDLRQGLLPVLESFKVSFLSALEEYTKKLNTQ (SEQ ID NO:1)

[0336] In other embodiments, the ApoA-I has at least 95% sequence identity to SEQ ID NO:1. In other embodiments, the ApoA-I has at least 98% sequence identity to SEQ ID NO:1. In other embodiments, the ApoA-I has at least 99% sequence identity to SEQ ID NO:1. In other embodiments, the ApoA-I has 100% sequence identity to SEQ ID NO:1.

[0337] In some embodiments, the ApoA-I has at least 95% sequence identity to amino acids 25 to 267 of SEQ ID NO:2:

MKAAVLTLAVLFLTGSQARHFWQQDEPPQSPWDRVKDLATVYVDVLKDSGRDYVSQFEGSALGKQLNL KLLDNWDSVTSTFSKLREQLGPVTQEFWDNLEKETEGLRQEMSKDLEEVKAKVQPYLDDFQKKWQEE MELYRQKVEPLRAELQEGARQKLHELQEKLSPLGEEMRDRARAHVDALRTHLAPYSDELRQRLAARLE ALKENGGARLAEYHAKATEHLSTLSEKAKPALEDLRQGLLPVLESFKVSFLSALEEYTKKLNTQ (SEQ ID NO:2)

[0338] In other embodiments, the ApoA-I has at least 98% sequence identity to amino acids 25 to 267 of SEQ ID NO:2. In other embodiments, the ApoA-I has at least 99% sequence identity to amino acids 25 to 267 of SEQ ID NO:2. In other embodiments, the ApoA-I has 100% sequence identity to amino acids 25 to 267 of SEQ ID NO:2. Amino acids 25 to 267 of SEQ ID NO:2 are also identified herein as SEQ ID NO:3:

DEPPQSPWDRVKDLATVYVDVLKDSGRDYVSQFEGSALGKQLNLKLLDNWDSVTSTFSKLREQLGPVT QEFWDNLEKETEGLRQEMSKDLEEVKAKVQPYLDDFQKKWQEEMELYRQKVEPLRAELQEGARQKLH ELQEKLSPLGEEMRDRARAHVDALRTHLAPYSDELRQRLAARLEALKENGGARLAEYHAKATEHLSTLS EKAKPALEDLRQGLLPVLESFKVSFLSALEEYTKKLNTQ (SEQ ID NO:3).

[0339] In certain embodiments wherein the ApoA-I is recombinantly expressed by a host cell, the host cell comprises a nucleotide sequence encoding the amino acid sequence of a mature ApoA-I protein, which can be operably linked to a signal sequence for secretion of the ApoA-I from the host cell and/or to a proprotein sequence. In some embodiments, the nucleotide sequence encodes an amino acid sequence having at least 90% sequence identity (*e.g.*, at least 95%, at least 97% or 100%) to SEQ ID NO:2 (human prepro-ApoA-I), which comprises a signal sequence (amino acids 1-18 of SEQ ID NO:2) and a propeptide sequence (amino acids 19-24 of SEQ ID NO:2). Other signal sequences suitable for directed secretion of ApoA-I can be either heterologous to ApoA-I, *e.g.*, a human albumin signal peptide or a human IL-2 signal peptide, or homologous to ApoA-I.

[0340] In some embodiments, the nucleotide sequence encodes an amino acid sequence having at least 95% sequence identity to SEQ ID NO:2. In some embodiments, the nucleotide sequence encodes an amino acid sequence having at least 98% sequence identity to SEQ ID NO:2. In some embodiments, the nucleotide sequence encodes an amino acid sequence having at least 99% sequence identity to SEQ ID NO:2. In some embodiments, the nucleotide sequence encodes an amino acid sequence having 100% sequence identity to SEQ ID NO:2.

[0341] In some embodiments, ApoA-I is produced by a CHO cell (*e.g.*, CHO-S cell) engineered to express the amino acid sequence of SEQ ID NO:2. The engineered cell can comprise a nucleotide sequence encoding SEQ ID NO:2 operably linked to a promoter, for example a constitutive promoter. In some embodiments, the engineered cell comprises a nucleotide sequence encoding SEQ ID NO:2 operably linked to a simian cytomegalovirus immediate early promoter.

[0342] In some embodiments, recombinant ApoA-I can be produced by culturing any of the mammalian host cells described herein under conditions in which ApoA-I is expressed and secreted. The ApoA-I can be recovered from the supernatant of a cultured mammalian host cell, and optionally purified to yield mature, biologically active ApoA-I.

[0343] Further methods for recombinant expression and purification of ApoA-I are described in detail in WO 2012/109162, the contents of which are incorporated herein by reference in their entirety. See, for example, Sections 6.1.2-6.1.4 and Examples 1-2 of PCT Publication No. WO 2012/109162, the contents of which are incorporated herein by reference in their entireties.

[0344] The apolipoprotein molecule(s) can comprise a chimeric apolipoprotein comprising an apolipoprotein and one or more attached functional moieties, such as for example, one or more CRN-001 complex(es), one or more targeting moieties, a moiety having a desired biological activity, an affinity tag to assist with purification, and/or a reporter molecule for characterization or localization studies. An attached moiety with biological activity may have an activity that is capable of augmenting and/or synergizing with the biological activity of a compound incorporated into a complex of the disclosure. For example, a moiety with biological activity may have antimicrobial (for example, antifungal, antibacterial, anti-protozoal, bacteriostatic, fungistatic, or antiviral) activity. In one embodiment, an attached functional moiety of a chimeric apolipoprotein is not in contact with hydrophobic surfaces of the complex. In another embodiment, an attached functional moiety is in contact with hydrophobic surfaces of the complex. In some embodiments, a functional moiety of a chimeric apolipoprotein may be intrinsic to a natural protein. In some embodiments, a chimeric apolipoprotein includes a ligand or sequence recognized by or capable of interaction with a cell surface receptor or other cell surface moiety.

[0345] In one embodiment, a chimeric apolipoprotein includes a targeting moiety that is not intrinsic to the native apolipoprotein, such as for example, S. cerevisiae α-mating factor peptide, folic acid, transferrin, or lactoferrin. In another embodiment, a chimeric apolipoprotein includes a moiety with a desired biological activity that augments and/or synergizes with the activity of a compound incorporated into a complex of the disclosure. In one embodiment, a chimeric apolipoprotein may include a functional moiety intrinsic to an apolipoprotein. One example of an apolipoprotein intrinsic functional moiety is the intrinsic targeting moiety formed approximately by amino acids 130-150 of human ApoE, which comprises the receptor binding region recognized by members of the low density lipoprotein receptor family. Other examples of apolipoprotein intrinsic functional moieties include the region of ApoB-100 that interacts with the low density lipoprotein receptor and the region of ApoA-I that interacts with scavenger receptor type B 1. In other embodiments, a functional moiety may be added synthetically or recombinantly to produce a chimeric apolipoprotein. Another example is an apolipoprotein with the prepro or pro sequence from another preproapolipoprotein (*e.g.*, prepro sequence from preproapoA-II substituted for the prepro sequence of preproapoA-I). Another example is an apolipoprotein for which some of the amphipathic sequence segments have been substituted by other amphipathic sequence segments from another apolipoprotein.

[0346] As used herein, "chimeric" refers to two or more molecules that are capable of existing separately and are joined together to form a single molecule having the desired functionality of all of its constituent molecules. The constituent molecules of a chimeric molecule may be joined synthetically by chemical conjugation or, where the constituent molecules are all polypeptides or analogs thereof, polynucleotides encoding the polypeptides may be fused together recombinantly such that a single continuous polypeptide is expressed. Such a chimeric molecule is termed a fusion protein. A "fusion protein" is a chimeric molecule in which the constituent molecules are all polypeptides and are attached (fused) to each other such that the chimeric molecule forms a continuous single chain. The various constituents can be directly attached to each other or can be coupled through one or more linkers. One or more segments of various constituents can be, for example, inserted in the sequence of an apolipoprotein, or, as another example, can be added N-terminal or C-terminal to the sequence of an apolipoprotein. For example, a fusion protein can comprise an antibody light chain, an antibody fragment, a heavy-chain antibody, or a single-domain antibody.

[0347] In some embodiments, a chimeric apolipoprotein is prepared by chemically conjugating the apolipoprotein and the functional moiety to be attached. Means of chemically conjugating molecules are well known to those of skill in the art. Such means will vary according to the structure of the moiety to be attached, but will be readily ascertainable to those of skill in the art. Polypeptides typically contain a variety of functional groups, *e.g.*, carboxylic acid (--COOH), free amino (--NH2), or sulfhydryl (--SH) groups, that are available for reaction with a suitable functional group on the functional moiety or on a linker to bind the moiety thereto. A functional moiety may be attached at the N-terminus, the C-terminus, or to a functional group on an interior residue (i.e., a residue at a position intermediate between the N- and C-termini) of an apolipoprotein molecule. Alternatively, the apolipoprotein and/or the moiety to be tagged can be derivatized to expose or attach additional reactive functional groups.

[0348] In some embodiments, fusion proteins that include a polypeptide functional moiety are synthesized using recombinant expression systems. Typically, this involves creating a nucleic acid (*e.g.*, DNA) sequence that encodes the apolipoprotein and the functional moiety such that the two polypeptides will be in frame when expressed, placing the DNA under the control of a promoter, expressing the protein in a host cell, and isolating the expressed protein.

[0349] A nucleic acid encoding a chimeric apolipoprotein can be incorporated into a recombinant expression vector in a form suitable for expression in a host cell. As used herein, an "expression vector" is a nucleic acid which, when introduced into an appropriate host cell, can be transcribed and translated into a polypeptide. The vector may also include regulatory sequences such as promoters, enhancers, or other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are known to those skilled in the art (see, *e.g.*, Goeddel, 1990, Gene Expression Technology: Meth. Enzymol. 185, Academic Press, San Diego, Calif.; Berger and Kimmel, Guide to Molecular Cloning Techniques, Methods in Enzymology 152 Academic Press, Inc., San Diego, Calif.; Sambrook et al., 1989, Molecular Cloning--A Laboratory Manual (2nd ed.) Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, NY, etc.).

[0350] In some embodiments, an apolipoprotein has been modified such that when the apolipoprotein is incorporated into a complex of the disclosure, the modification will increase stability of the complex, confer targeting ability or increase capacity. In one embodiment, the modification includes introduction of cysteine residues into apolipoprotein molecules to permit formation of intramolecular or intermolecular

disulfide bonds, *e.g.*, by site-directed mutagenesis. In another embodiment, a chemical crosslinking agent is used to form intermolecular links between apolipoprotein molecules to enhance stability of the complex. Intermolecular crosslinking prevents or reduces dissociation of apolipoprotein molecules from the complex and/or prevents displacement by endogenous apolipoprotein molecules within an individual to whom the complexes are administered. In other embodiments, an apolipoprotein is modified either by chemical derivatization of one or more amino acid residues or by site directed mutagenesis, to confer targeting ability to or recognition by a cell surface receptor.

[0351] Lipid binding protein molecules and complexes comprising lipid binding protein molecules can be targeted to a specific cell surface receptor by engineering receptor recognition properties into an apolipoprotein. For example, lipid binding protein molecules or complexes may be targeted to a particular cell type known to harbor a particular type of infectious agent, for example by modifying a apolipoprotein of other lipid binding protein molecule to render it capable of interacting with a receptor on the surface of the cell type being targeted. For example, lipid binding protein molecules or complexes may be targeted to macrophages by altering a apolipoprotein or other lipid binding protein molecule to confer recognition by the macrophage endocytic class A scavenger receptor (SR-A). SR-A binding ability can be conferred to a lipid binding protein molecule or complex by modifying a apolipoprotein or other lipid binding protein molecule by site directed mutagenesis to replace one or more positively charged amino acids with a neutral or negatively charged amino acid. SR-A recognition can also be conferred by preparing a chimeric apolipoprotein that includes an N- or C-terminal extension having a ligand recognized by SR-A or an amino acid sequence with a high concentration of negatively charged residues. Lipid binding protein molecules and complexes comprising lipid binding protein molecules (*e.g.*, apolipoproteins) can also interact with apolipoprotein receptors such as, but not limited to, ABCA1 receptors, ABCG1 receptors, Megalin, Cubulin and HDL receptors such as SR-B1.

6.1.1.2. Apolipoprotein mimetics

[0352] Peptides, peptide analogs, and agonists that mimic the activity of an apolipoprotein (collectively referred to herein as "apolipoprotein peptide mimetics") can also be used as the lipid binding protein molecule or in the complexes described herein, either alone, in combination with one or more other lipid binding proteins. Non-limiting examples of peptides and peptide analogs that correspond to apolipoproteins, as well as agonists that mimic the activity of ApoA-I, ApoA-I_M, ApoA-II, ApoA-IV, and ApoE, that are useful as lipid binding protein molecules and/or are suitable for inclusion in the complexes and compositions described herein are disclosed in U.S. Pat. Nos. 6,004,925, 6,037,323 and 6,046,166 (issued to Dasseux *et al.*), U.S. Pat. No. 5,840,688 (issued to Tso), U.S. Pat. No. 6,743,778 (issued to Kohno), U.S. Publication Nos. 2004/0266671, 2004/0254120, 2003/0171277 and 2003/0045460 (to Fogelman), U.S. Publication No. 2006/0069030 (to Bachovchin), U.S. Publication No. 2003/0087819 (to Bielicki), U.S. Publication No. 2009/0081293 (to Murase *et al.*), and PCT Publication No. WO/2010/093918 (to Dasseux *et al.*), the disclosures of which are incorporated herein by reference in their entireties. These peptides and peptide analogues can be composed of L-amino acid or D-amino acids or mixture of L- and D-amino acids. They may also include one or more non-peptide or amide linkages, such as one or more well-known peptide/amide isosteres. Such apolipoprotein peptide mimetic can be synthesized or manufactured using any technique for peptide synthesis known in the art, including, *e.g.*, the techniques described in U.S. Pat. Nos. 6,004,925, 6,037,323 and 6,046,166.

[0353] In some embodiments, the lipid binding protein molecules comprise apolipoprotein peptide mimetic molecules and optionally one or more apolipoprotein molecules such as those described above.

[0354] In some embodiments, the apolipoprotein peptide mimetic molecules comprise an ApoA-I peptide mimetic, ApoA-II peptide mimetic, ApoA-IV peptide mimetic, or ApoE peptide mimetic or a combination thereof.

6.1.2. Lipid binding protein-based complexes

[0355] In some aspects, a lipid binding protein is a component of (*e.g.*, formulated as) a lipid binding protein-based complex, for example complexed with one or more amphipathic molecules such as lipids. Lipid binding protein-based complexes that can be used include HDL and HDL mimetic-based complexes.

[0356] In some aspects, lipid binding protein-based complexes can comprise a lipoprotein complex as described in U.S. Patent No. 8,206,750, PCT publication WO 2012/109162, PCT publication WO 2015/173633 A2 (*e.g.*, CER-001) or US 2004/0229794 A1, the contents of each of which are incorporated herein by reference in their entireties. The terms "lipoproteins" and "apolipoproteins" are used interchangeably herein, and unless required otherwise by context, the term "lipoprotein" encompasses lipoprotein mimetics. The terms "lipid binding protein" and "lipid binding polypeptide" are also used interchangeably herein, and unless required otherwise by context, the terms do not connote an amino acid sequence of particular length.

[0357] Lipoprotein complexes can comprise a protein fraction (*e.g.*, an apolipoprotein fraction) and a lipid fraction (*e.g.*, a phospholipid fraction). The protein fraction includes one or more lipid-binding protein molecules, such as apolipoproteins, peptides, or apolipoprotein peptide analogs or mimetics, for example one or more lipid binding protein molecules described in Section 6.1.1.

[0358] The lipid fraction typically includes one or more phospholipids which can be neutral, negatively charged, positively charged, or a combination thereof. Exemplary phospholipids and other amphipathic molecules which can be included in the lipid fraction are described in Section 6.1.3.

[0359] In certain embodiments, the lipid fraction contains at least one neutral phospholipid (*e.g.*, a sphingomyelin (SM)) and, optionally, one or more negatively charged phospholipids. In lipoprotein complexes that include both neutral and negatively charged phospholipids, the neutral and negatively charged phospholipids can have fatty acid chains with the same or different number of carbons and the same or different degree of saturation. In some instances, the neutral and negatively charged phospholipids will have the same acyl tail, for example a C16:0, or palmitoyl, acyl chain. In specific embodiments, particularly those in which egg SM is used as the neutral lipid, the weight ratio of the apolipoprotein fraction: lipid fraction ranges from about 1:2.7 to about 1:3 (*e.g.*, 1:2.7).

[0360] Any phospholipid that bears at least a partial negative charge at physiological pH can be used as the negatively charged phospholipid. Non-limiting examples include negatively charged forms, *e.g.*, salts, of phosphatidylinositol, a phosphatidylserine, a phosphatidylglycerol and a phosphatidic acid. In a specific embodiment, the negatively charged phospholipid is 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol)], or DPPG, a phosphatidylglycerol. Preferred salts include potassium and sodium salts.

[0361] In some embodiments, a lipoprotein complex used in the methods of the disclosure is a lipoprotein complex as described in U.S. Patent No. 8,206,750 or WO 2012/109162 (and its U.S. counterpart, US 2012/0232005), the contents of each of which are incorporated herein in its entirety by

reference. In particular embodiments, the lipid binding protein molecule component of the lipoprotein complex is as described in Section 6.1 and preferably in Section 6.1.1 of WO 2012/109162 (and US 2012/0232005), the lipid component is as described in Section 6.2 of WO 2012/109162 (and US 2012/0232005), which can optionally be complexed together in the amounts described in Section 6.3 of WO 2012/109162 (and US 2012/0232005). The contents of each of these sections are incorporated by reference herein. In certain aspects, a lipoprotein complex of the disclosure is in a population of complexes that is at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% homogeneous, as described in Section 6.4 of WO 2012/109162 (and US 2012/0232005), the contents of which are incorporated by reference herein.

[0362] In some embodiments, a lipid binding protein-based complex comprises 1 to 8 apolipoprotein molecules (*e.g.*, 1 to 6, 1 to 4, 1 to 2, 2 to 8, 2 to 6, 2 to 4, 4 to 8, 4 to 6, or 6 to 8 apolipoprotein molecules). In some embodiments, the complex comprises 1 apolipoprotein molecule. In some embodiments, the complex comprises 2 apolipoprotein molecules. In some embodiments, the complex comprises 3 apolipoprotein molecules. In some embodiments, the complex comprises 4 apolipoprotein molecules. In some embodiments, the complex comprises 5 apolipoprotein molecules. In some embodiments, the complex comprises 6 apolipoprotein molecules. In some embodiments, the complex comprises 7 apolipoprotein molecules. In some embodiments, the complex comprises 8 apolipoprotein molecules.

[0363] In some embodiments, the complex comprises 1 to 8 ApoA-I equivalents (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 8, 2 to 6, 2 to 4, 4 to 6, or 4 to 8 ApoA-I equivalents). Lipid binding proteins can be expressed in terms of ApoA-I equivalents based upon the number of amphipathic helices they contain. For example, ApoA-I_M, which typically exists as a disulfide-bridged dimer, can be expressed as 2 ApoA-I equivalents, because each molecule of ApoA-I_M contains twice as many amphipathic helices as a molecule of ApoA-I. Conversely, a peptide mimetic that contains a single amphipathic helix can be expressed as a 1/10-1/6 ApoA-I equivalent, because each molecule contains 1/10-1/6 as many amphipathic helices as a molecule of ApoA-I.

[0364] In a specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 50-80 molecules of lecithin and 20-50 molecules of SM.

[0365] In another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 50 molecules of lecithin and 50 molecules of SM.

[0366] In yet another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 80 molecules of lecithin and 20 molecules of SM.

[0367] In yet another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 70 molecules of lecithin and 30 molecules of SM.

[0368] In yet another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 60 molecules of lecithin and 40 molecules of SM.

[0369] In a specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure consists essentially of 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 50-80 molecules of lecithin and 20-50 molecules of SM.

[0370] In another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure consists essentially of 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 50 molecules of lecithin and 50 molecules of SM.

[0371] In yet another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure consists essentially of 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 80 molecules of lecithin and 20 molecules of SM.

[0372] In yet another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure consists essentially of 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 70 molecules of lecithin and 30 molecules of SM.

[0373] In yet another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure consists essentially of 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 60 molecules of lecithin and 40 molecules of SM.

[0374] In a specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises a lipid component that comprises about 90 to 99.8 wt % SM and about 0.2 to 10 wt % negatively charged phospholipid, for example, about 0.2-1 wt %, 0.2-2 wt %, 0.2-3 wt %, 0.2-4 wt %, 0.2-5 wt %, 0.2-6 wt %, 0.2-7 wt %, 0.2-8 wt %, 0.2-9 wt %, or 0.2-10 wt % total negatively charged phospholipid(s). In another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises about 90 to 99.8 wt % lecithin and about 0.2 to 10 wt % negatively charged phospholipid, for example, about 0.2-1 wt %, 0.2-2 wt %, 0.2-3 wt %, 0.2-4 wt %, 0.2-5 wt %, 0.2-6 wt %, 0.2-7 wt %, 0.2-8 wt %, 0.2-9 wt % or 0.2-10 wt % total negatively charged phospholipid(s).

[0375] In a specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises a lipid component that consists essentially of about 90 to 99.8 wt % SM and about 0.2 to 10 wt % negatively charged phospholipid, for example, about 0.2-1 wt %, 0.2-2 wt %, 0.2-3 wt %, 0.2-4 wt %, 0.2-5 wt %, 0.2-6 wt %, 0.2-7 wt %, 0.2-8 wt %, 0.2-9 wt %, or 0.2-10 wt % total negatively charged phospholipid(s). In another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure consists essentially of about 90 to 99.8 wt % lecithin and about 0.2 to 10 wt % negatively charged phospholipid, for example, about 0.2-1 wt %, 0.2-2 wt %, 0.2-3 wt %, 0.2-4 wt %, 0.2-5 wt %, 0.2-6 wt %, 0.2-7 wt %, 0.2-8 wt %, 0.2-9 wt % or 0.2-10 wt % total negatively charged phospholipid(s).

[0376] In still another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises a lipid fraction that comprises about 9.8 to 90 wt % SM, about 9.8 to 90 wt % lecithin and about 0.2-10 wt % negatively charged phospholipid, for example, from about 0.2-1 wt %, 0.2-2 wt %, 0.2-3 wt %, 0.2-4 wt %, 0.2-5 wt %, 0.2-6 wt %, 0.2-7 wt %, 0.2-8 wt %, 0.2-9 wt %, to 0.2-10 wt % total negatively charged phospholipid(s).

[0377] In still another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises a lipid fraction that consists essentially of about 9.8 to 90 wt % SM, about 9.8 to 90 wt % lecithin and about 0.2-10 wt % negatively charged phospholipid, for example, from about 0.2-1 wt %, 0.2-2 wt %, 0.2-3 wt %, 0.2-4 wt %, 0.2-5 wt %, 0.2-6 wt %, 0.2-7 wt %, 0.2-8 wt %, 0.2-9 wt %, to 0.2-10 wt % total negatively charged phospholipid(s).

[0378] In another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises an ApoA-I apolipoprotein and a lipid fraction, wherein the lipid fraction comprises sphingomyelin and about 3 wt% of a negatively charged phospholipid, wherein the molar ratio of the lipid fraction to the ApoA-I apolipoprotein is about 2:1 to 200:1, and wherein said complex is a small or large discoidal particle containing 2-4 ApoA-I equivalents.

[0379] In another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises an ApoA-I apolipoprotein and a lipid fraction, wherein the lipid fraction consists essentially of sphingomyelin and about 3 wt% of a negatively charged phospholipid, wherein the molar ratio of the lipid fraction to the ApoA-I apolipoprotein is about 2:1 to 200:1, and wherein said complex is a small or large discoidal particle containing 2-4 ApoA-I equivalents.

[0380] HDL-based or HDL mimetic-based complexes can include a single type of lipid-binding protein, or mixtures of two or more different lipid-binding proteins, which may be derived from the same or different species. Although not required, the complexes will preferably comprise lipid-binding proteins that are derived from, or correspond in amino acid sequence to, the animal species being treated, in order to avoid inducing an immune response to the therapy. Thus, for treatment of human patients, lipid-binding proteins of human origin are preferably used. The use of peptide mimetic apolipoproteins may also reduce or avoid an immune response.

[0381] In some embodiments, the lipid component includes two types of phospholipids: a sphingomyelin (SM) and a negatively charged phospholipid. Exemplary SMs and negatively charged lipids are described in Section 6.1.3.1.

[0382] Lipid components including SM can optionally include small quantities of additional lipids. Virtually any type of lipids may be used, including, but not limited to, lysophospholipids, galactocerebroside, gangliosides, cerebrosides, glycerides, triglycerides, and cholesterol and its derivatives.

[0383] When included, such optional lipids will typically comprise less than about 15 wt% of the lipid fraction, although in some instances more optional lipids could be included. In some embodiments, the optional lipids comprise less than about 10 wt%, less than about 5 wt%, or less than about 2 wt%. In some embodiments, the lipid fraction does not include optional lipids.

[0384] In a specific embodiment, the phospholipid fraction contains egg SM or palmitoyl SM or phytosphingomyelin and DPPG in a weight ratio (SM: negatively charged phospholipid) ranging from 90:10 to 99:1, more preferably ranging from 95:5 to 98:2. In one embodiment, the weight ratio is 97:3.

[0385] The molar ratio of the lipid component to the protein component of complexes of the disclosure can vary, and will depend upon, among other factors, the identity(ies) of the apolipoprotein comprising the protein component, the identities and quantities of the lipids comprising the lipid component, and the desired size of the complex. Because the biological activity of apolipoproteins such as ApoA-I are thought to be mediated by the amphipathic helices comprising the apolipoprotein, it is convenient to express the apolipoprotein fraction of the lipid:apolipoprotein molar ratio using ApoA-I protein equivalents. It is generally accepted that ApoA-I contains 6-10 amphipathic helices, depending upon the method used to calculate the helices. Other apolipoproteins can be expressed in terms of ApoA-I equivalents based upon the number of amphipathic helices they contain. For example, ApoA-I_M, which typically exists as a disulfide-bridged dimer, can be expressed as 2 ApoA-I equivalents, because each molecule of ApoA-I_M contains twice as many amphipathic helices as a molecule of ApoA-I. Conversely, a peptide

apolipoprotein that contains a single amphipathic helix can be expressed as a 1/10-1/6 ApoA-I equivalent, because each molecule contains 1/10-1/6 as many amphipathic helices as a molecule of ApoA-I. In general, the lipid:ApoA-I equivalent molar ratio of the lipoprotein complexes (defined herein as "Ri") will range from about 105:1 to 110:1. In some embodiments, the Ri is about 108:1. Ratios in weight can be obtained using a MW of approximately 650-800 for phospholipids.

[0386] In some embodiments, the molar ratio of lipid : ApoA-I equivalents ("RSM") ranges from about 80:1 to about 110:1, *e.g.*, about 80:1 to about 100:1. In a specific example, the RSM for complexes can be about 82:1.

[0387] In some embodiments, lipoprotein complexes used in the methods of the disclosure are negatively charged complexes which comprise a protein fraction which is preferably mature, full-length ApoA-I, and a lipid fraction comprising a neutral phospholipid, sphingomyelin (SM), and negatively charged phospholipid.

[0388] In a specific embodiment, the lipid component contains SM (*e.g.*, egg SM, palmitoyl SM, phytoSM, or a combination thereof) and negatively charged phospholipid (*e.g.*, DPPG) in a weight ratio (SM : negatively charged phospholipid) ranging from 90:10 to 99:1, more preferably ranging from 95:5 to 98:2, *e.g.*, 97:3.

[0389] In specific embodiments, the ratio of the protein component to lipid component can range from about 1:2.7 to about 1:3, with 1:2.7 being preferred. This corresponds to molar ratios of ApoA-I protein to lipid ranging from approximately 1:90 to 1:140. In some embodiments, the molar ratio of protein to lipid in the complex is about 1:90 to about 1:120, about 1:100 to about 1:140, or about 1:95 to about 1:125.

[0390] In particular embodiments, the complex comprises CER-001, CSL-111, CSL-112, CER-522, ETC-216, or ETC-642. In a preferred embodiment, the complex is CER-001.

[0391] CER-001 as used in the literature and in the Examples below refers to a complex described in Example 4 of WO 2012/109162. WO 2012/109162 refers to CER-001 as a complex having a 1:2.7 lipoprotein weight:total phospholipid weight ratio with a SM:DPPG weight:weight ratio of 97:3. Example 4 of WO 2012/109162 also describes a method of its manufacture.

[0392] When used in the context of a method and/or CER-001 dosing regimen of the disclosure, CER-001 refers to a lipoprotein complex whose individual constituents can vary from CER-001 as described in Example 4 of WO 2012/109162 by up to 20%. In certain embodiments, the constituents of the lipoprotein complex vary from CER-001 as described in Example 4 of WO 2012/109162 by up to 10%. Preferably, the constituents of the lipoprotein complex are those described in Example 4 of WO 2012/109162 (plus/minus acceptable manufacturing tolerance variations). The SM in CER-001 can be natural or synthetic. In some embodiments, the SM is a natural SM, for example a natural SM described in WO 2012/109162, *e.g.*, chicken egg SM or plant SM. In some embodiments, the SM is a synthetic SM, for example a synthetic SM described in WO 2012/109162, *e.g.*, synthetic palmitoylsphingomyelin, for example as described in WO 2012/109162. Methods for synthesizing palmitoylsphingomyelin are known in the art, for example as described in WO 2014/140787 and WO 2024/003612, the contents of which are incorporated herein by reference in their entireties. The lipoprotein in CER-001, apolipoprotein A-I (ApoA-I), preferably has an amino acid sequence corresponding to amino acids 25 to 267 of SEQ ID NO:1 of WO 2012/109162. ApoA-I can be purified by animal sources (and in particular from human sources) or produced recombinantly. In preferred embodiments, the ApoA-I in CER-001 is recombinant ApoA-I. CER-001 used in a dosing regimen of the disclosure is preferably highly homogeneous, for example at least

80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, or at least 99% homogeneous, as reflected by a single peak in gel permeation chromatography. See, *e.g.*, Section 6.4 of WO 2012/109162.

[0393] SEQ ID NO:1 of WO 2012/109162 is identified herein as SEQ ID NO:2. Amino acids 25 to 267 of SEQ ID NO:1 of WO 2012/109162 are identified herein as SEQ ID NO:3.

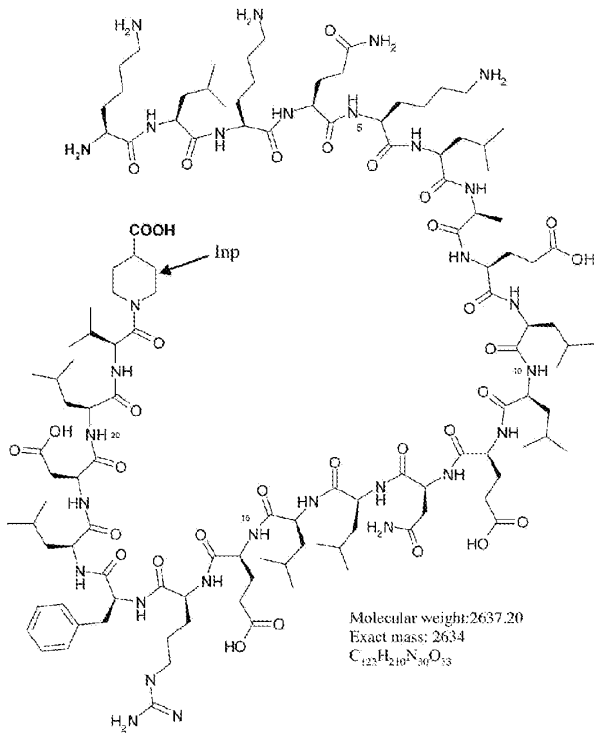
[0394] CSL-111 is a reconstituted human ApoA-I purified from plasma complexed with soybean phosphatidylcholine (SBPC) (Tardif *et al.*, 2007, JAMA 297:1675-1682).

[0395] CSL-112 is a formulation of ApoA-I purified from plasma and reconstituted to form HDL suitable for intravenous infusion (Diditchenko *et al.*, 2013, DOI 10.1161/ATVBAHA.113.301981).

[0396] ETC-216 (also known as MDCO-216) is a lipid-depleted form of HDL containing recombinant ApoA-I_{Milano}(Nicholls *et al.*, 2011, Expert Opin Biol Ther. 11(3):387-94. doi: 10.1517/14712598.2011.557061).

[0397] ETC-642 is complex of a 22-amino acid amphipathic peptide (ESP-2418) complexed with sphingomyelin and 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (Dipalmitoylphosphatidylcholine, DPPC (Di Bartolo et al., 2011, Atherosclerosis 217:395-400).

[0398] In another embodiment, a complex that can be used in the methods of the disclosure is CER-522. CER-522 is a lipoprotein complex comprising a combination of three phospholipids and a 22 amino acid peptide, CT80522:



CT80522

[0399] The phospholipid component of CER-522 consists of egg sphingomyelin,1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (Dipalmitoylphosphatidylcholine, DPPC) and 1,2–dipalmitoyl-*sn*-glycero-3-[phospho-*rac*-(1-glycerol)] (Dipalmitoylphosphatidyl- glycerol, DPPG) in a 48.5:48.5:3 weight ratio. The ratio of peptide to total phospholipids in the CER-522 complex is 1:2.5 (w/w).

[0400] In some embodiments, the lipoprotein complex is delipidated HDL. Most HDL in plasma is cholesterol-rich. The lipids in HDL can be depleted, for example partially and/or selectively depleted, *e.g.*, to reduce its cholesterol content. In some embodiments, the delipidated HDL can resemble small α, preβ-1, and other preβ forms of HDL. A process for selective depletion of HDL is described in Sacks *et al.*, 2009, J Lipid Res. 50(5): 894–907.

[0401] In certain embodiments, a lipoprotein complex comprises a bioactive agent delivery particle as described in US 2004/0229794.

[0402] A bioactive agent delivery particle can comprise a lipid binding polypeptide (*e.g.*, an apolipoprotein as described previously in this Section or in Section 6.1.1), a lipid bilayer (*e.g.*, comprising one or more phospholipids as described previously in this Section or in Section 6.1.3.1), and a bioactive agent (*e.g.*, an anti-cancer agent), wherein the interior of the lipid bilayer comprises a hydrophobic region, and wherein the bioactive agent is associated with the hydrophobic region of the lipid bilayer. In some embodiments, a bioactive agent delivery particle as described in US 2004/0229794.

[0403] In some embodiments, a bioactive agent delivery particle does not comprise a hydrophilic core.

[0404] In some embodiments, a bioactive agent delivery particle is disc shaped (*e.g.*, having a diameter from about 7 to about 29 nm).

[0405] Bioactive agent delivery particles include bilayer-forming lipids, for example phospholipids (*e.g.*, as described previously in this Section or in Section 6.1.3.1). In some embodiments, a bioactive agent delivery particle includes both bilayer-forming and non-bilayer-forming lipids. In some embodiments, the lipid bilayer of a bioactive agent delivery particle includes phospholipids. In one embodiment, the phospholipids incorporated into a delivery particle include dimyristoylphosphatidylcholine (DMPC) and dimyristoylphosphatidylglycerol (DMPG). In one embodiment, the lipid bilayer includes DMPC and DMPG in a 7:3 molar ratio.

[0406] In some embodiments, the lipid binding polypeptide is an apolipoprotein (*e.g.*, as described previously in this Section or in Section 6.1.1). The predominant interaction between lipid binding polypeptides, *e.g.*, apolipoprotein molecules, and the lipid bilayer is generally a hydrophobic interaction between residues on a hydrophobic face of an amphipathic structure, *e.g.*, an α-helix of the lipid binding polypeptide and fatty acyl chains of lipids on an exterior surface at the perimeter of the particle. Bioactive agent delivery particles may include exchangeable and/or non-exchangeable apolipoproteins. In one embodiment, the lipid binding polypeptide is ApoA-I.

[0407] In some embodiments, bioactive agent delivery particles include lipid binding polypeptide molecules, *e.g.*, apolipoprotein molecules, that have been modified to increase stability of the particle. In one embodiment, the modification includes introduction of cysteine residues to form intramolecular and/or intermolecular disulfide bonds.

[0408] In another embodiment, bioactive agent delivery particles include a chimeric lipid binding polypeptide molecule, *e.g.*, a chimeric apolipoprotein molecule, with one or more bound functional moieties, for example one or more targeting moieties and/or one or more moieties having a desired

biological activity, *e.g.*, antimicrobial activity, which may augment or work in synergy with the activity of a bioactive agent incorporated into the delivery particle.

6.1.3. Amphipathic molecules

[0409] An amphipathic molecule is a molecule that possesses both hydrophobic (apolar) and hydrophilic (polar) elements. Amphipathic molecules that can be used in complexes described herein include lipids (*e.g.*, as described in Section 6.1.3.1), detergents (*e.g.*, as described in Section 6.1.3.2), fatty acids (*e.g.*, as described in Section 6.1.3.3), and apolar molecules and sterols covalently attached to polar molecules such as, but not limited to, sugars or nucleic acids (*e.g.*, as described in Section 6.1.3.4).

[0410] The complexes can include a single class of amphipathic molecule (*e.g.*, a single species of phospholipids or a mixture of phospholipids) or can contain a combination of classes of amphipathic molecules (*e.g.*, phospholipids and detergents). The complex can contain one species of amphipathic molecules or a combination of amphipathic molecules configured to facilitate solubilization of the lipid binding protein molecule(s).

[0411] In some embodiments, the amphipathic molecules included in comprise a phospholipid, a detergent, a fatty acid, an apolar moiety or sterol covalently attached to a sugar, or a combination thereof (*e.g.*, selected from the types of amphipathic molecules discussed above).

[0412] In some embodiments, the amphipathic molecules comprise or consist of phospholipid molecules. In some embodiments, the phospholipid molecules comprise negatively charged phospholipids, neutral phospholipids, positively charged phospholipids or a combination thereof. In some embodiments, the phospholipid molecules contribute a net charge of 1-3 per apolipoprotein molecule in the complex. In some embodiments, the net charge is a negative net charge. In some embodiments, the net charge is a positive net charge. In some embodiments, the phospholipid molecules consist of a combination of negatively charged and neutral phospholipids. In some embodiments, the molar ratio of negatively charge phospholipid to neutral phospholipid ranges from 1:1 to 1:3. In some embodiments, the molar ratio of negatively charged phospholipid to neutral phospholipid is about 1:1 or about 1:2.

[0413] In some embodiments, the amphipathic molecules comprise neutral phospholipids and negatively charged phospholipids in a weight ratio of 95:5 to 99:1.

6.1.3.1. Lipids

[0414] Lipid binding protein-based complexes can include one or more lipids. In various embodiments, one or more lipids can be saturated and/or unsaturated, natural and/or synthetic, charged or not charged, zwitterionic or not. In some embodiments, the lipid molecules (*e.g.*, phospholipid molecules) can together contribute a net charge of 1-3 (*e.g.*, 1-3, 1-2, 2-3, 1, 2, or 3) per lipid binding protein molecule in the complex. In some embodiments, the net charge is negative. In other embodiments, the net charge is positive.

[0415] In some embodiments, the lipid comprises a phospholipid. Phospholipids can have two acyl chains that are the same or different (for example, chains having a different number of carbon atoms, a different degree of saturation between the acyl chains, different branching of the acyl chains, or a combination thereof). The lipid can also be modified to contain a fluorescent probe (*e.g.*, as described at avantilipids.com/product-category/products/fluorescent-lipids/). Preferably, the lipid comprises at least one phospholipid.

[0416] Phospholipids can have unsaturated or saturated acyl chains ranging from about 6 to about 24 carbon atoms (*e.g.*, 6-20, 6-16, 6-12, 12-24, 12-20, 12-16, 16-24, 16-20, or 20-24). In some embodiments, a phospholipid used in a complex of the disclosure has one or two acyl chains of 12, 14, 16, 18, 20, 22, or 24 carbons (*e.g.*, two acyl chains of the same length or two acyl chains of different length).

[0417] Non-limiting examples of acyl chains present in commonly occurring fatty acids that can be included in phospholipids are provided in Table 1, below:

Table 1

Length:Number of Unsaturations	Common Name
14:0	myristic acid
16:0	palmitic acid
18:0	stearic acid
18:1 cisΔ^{9}	oleic acid
18:2 cis$\Delta^{9,12}$	linoleic acid
18:3 cis$\Delta^{9,12,15}$	linonenic acid
20:4 cis$\Delta^{5,8,11,14}$	arachidonic acid
20:5 cis$\Delta^{5,8,11,14,17}$	eicosapentaenoic acid (an omega-3 fatty acid)

[0418] Lipids that can be present in the complexes of the disclosure include, but are not limited to, small alkyl chain phospholipids, egg phosphatidylcholine, soybean phosphatidylcholine, dipalmitoylphosphatidylcholine, dimyristoylphosphatidylcholine, distearoylphosphatidylcholine 1-myristoyl-2-palmitoylphosphatidylcholine, 1-palmitoyl-2-myristoylphosphatidylcholine, 1-palmitoyl-2-stearoylphosphatidylcholine, 1-stearoyl-2-palmitoylphosphatidylcholine, dioleoylphosphatidylcholine dioleophosphatidylethanolamine, dilauroylphosphatidylglycerol phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylglycerols, diphosphatidylglycerols such as dimyristoylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, distearoylphosphatidylglycerol, dioleoylphosphatidylglycerol, dimyristoylphosphatidic acid, dipalmitoylphosphatidic acid, dimyristoylphosphatidylethanolamine, dipalmitoylphosphatidylethanolamine, dimyristoylphosphatidylserine, dipalmitoylphosphatidylserine, brain phosphatidylserine, brain sphingomyelin, palmitoylsphingomyelin, dipalmitoylsphingomyelin, egg sphingomyelin, milk sphingomyelin, phytosphingomyelin, distearoylsphingomyelin, dipalmitoylphosphatidylglycerol salt, phosphatidic acid, galactocerebroside, gangliosides, cerebrosides, dilaurylphosphatidylcholine, (1,3)-D-mannosyl-(1,3)diglyceride, aminophenylglycoside, 3-cholesteryl-6'-(glycosylthio)hexyl ether glycolipids, and cholesterol and its derivatives. Synthetic lipids, such as synthetic palmitoylsphingomyelin or N-palmitoyl-4-hydroxysphinganine-1-phosphocholine (a form of phytosphingomyelin) can be used to minimize lipid oxidation.

[0419] In some embodiments, a lipid binding protein-based complex includes two types of phospholipids: a neutral lipid, *e.g.*, lecithin and/or sphingomyelin (abbreviated SM), and a charged phospholipid (*e.g.*, a negatively charged phospholipid). A "neutral" phospholipid has a net charge of about zero at physiological pH. In many embodiments, neutral phospholipids are zwitterions, although

other types of net neutral phospholipids are known and can be used. In some embodiments, the molar ratio of the charged phospholipid (*e.g.*, negatively charged phospholipid) to neutral phospholipid ranges from 1:1 to 1:3, for example, about 1:1, about 1:2, or about 1:3.

[0420] The neutral phospholipid can comprise, for example, one or both of the lecithin and/or SM, and can optionally include other neutral phospholipids. In some embodiments, the neutral phospholipid comprises lecithin, but not SM. In other embodiments, the neutral phospholipid comprises SM, but not lecithin. In still other embodiments, the neutral phospholipid comprises both lecithin and SM. All of these specific exemplary embodiments can include neutral phospholipids in addition to the lecithin and/or SM, but in many embodiments do not include such additional neutral phospholipids.

[0421] As used herein, the expression "SM" includes sphingomyelins derived or obtained from natural sources, as well as analogs and derivatives of naturally occurring SMs that are impervious to hydrolysis by LCAT, as is naturally occurring SM. SM is a phospholipid very similar in structure to lecithin, but, unlike lecithin, it does not have a glycerol backbone, and hence does not have ester linkages attaching the acyl chains. Rather, SM has a ceramide backbone, with amide linkages connecting the acyl chains. SM can be obtained, for example, from milk, egg or brain. SM analogues or derivatives can also be used. Non-limiting examples of useful SM analogues and derivatives include, but are not limited to, palmitoylsphingomyelin, N-palmitoyl-4-hydroxysphinganine-1-phosphocholine (a form of phytosphingomyelin), palmitoylsphingomyelin, stearoylsphingomyelin, D-erythro-N-16:0-sphingomyelin and its dihydro isomer, D-erythro-N-16:0-dihydro-sphingomyelin. Synthetic SM such as synthetic palmitoylsphingomyelin or N-palmitoyl-4-hydroxysphinganine-1-phosphocholine (phytosphingomyelin) can be used in order to produce more homogeneous complexes and with fewer contaminants and/or oxidation products than sphingolipids of animal origin. Methods for synthesizing SM are described in U.S. Publication No. 2016/0075634.

[0422] Sphingomyelins isolated from natural sources can be artificially enriched in one particular saturated or unsaturated acyl chain. For example, milk sphingomyelin (Avanti Phospholipid, Alabaster, Ala.) is characterized by long saturated acyl chains (*i.e.*, acyl chains having 20 or more carbon atoms). In contrast, egg sphingomyelin is characterized by short saturated acyl chains (i.e., acyl chains having fewer than 20 carbon atoms). For example, whereas only about 20% of milk sphingomyelin comprises C16:0 (16 carbon, saturated) acyl chains, about 80% of egg sphingomyelin comprises C16:0 acyl chains. Using solvent extraction, the composition of milk sphingomyelin can be enriched to have an acyl chain composition comparable to that of egg sphingomyelin, or vice versa.

[0423] The SM can be semi-synthetic such that it has particular acyl chains. For example, milk sphingomyelin can be first purified from milk, then one particular acyl chain, *e.g.*, the C16:0 acyl chain, can be cleaved and replaced by another acyl chain. The SM can also be entirely synthesized, by *e.g.*, large-scale synthesis. See, *e.g.*, Dong *et al.*, U.S. Pat. No. 5,220,043, entitled Synthesis of D-erythro-sphingomyelins, issued Jun. 15, 1993; Weis, 1999, Chem. Phys. Lipids 102 (1-2):3-12. SM can be fully synthetic, *e.g.*, as described in U.S. Publication No. 2014/0275590.

[0424] The lengths and saturation levels of the acyl chains comprising a semi-synthetic or a synthetic SM can be selectively varied. The acyl chains can be saturated or unsaturated, and can contain from about 6 to about 24 carbon atoms. Each chain can contain the same number of carbon atoms or, alternatively each chain can contain different numbers of carbon atoms. In some embodiments, the semi-synthetic or synthetic SM comprises mixed acyl chains such that one chain is saturated and one chain is

unsaturated. In such mixed acyl chain SMs, the chain lengths can be the same or different. In other embodiments, the acyl chains of the semi-synthetic or synthetic SM are either both saturated or both unsaturated. Again, the chains can contain the same or different numbers of carbon atoms. In some embodiments, both acyl chains comprising the semi-synthetic or synthetic SM are identical. In a specific embodiment, the chains correspond to the acyl chains of a naturally-occurring fatty acid, such as for example oleic, palmitic or stearic acid. In another embodiment, SM with saturated or unsaturated functionalized chains is used. In another specific embodiment, both acyl chains are saturated and contain from 6 to 24 carbon atoms. Non-limiting examples of acyl chains present in commonly occurring fatty acids that can be included in semi-synthetic and synthetic SMs are provided in Table 1, above.

[0425] In some embodiments, the SM is palmitoyl SM, such as synthetic palmitoyl SM, which has C16:0 acyl chains, or is egg SM, which includes as a principal component palmitoyl SM.

[0426] In a specific embodiment, functionalized SM, such as phytosphingomyelin, is used.

[0427] Lecithin can be derived or isolated from natural sources, or it can be obtained synthetically. Examples of suitable lecithins isolated from natural sources include, but are not limited to, egg phosphatidylcholine and soybean phosphatidylcholine. Additional non-limiting examples of suitable lecithins include, dipalmitoylphosphatidylcholine, dimyristoylphosphatidylcholine, distearoylphosphatidylcholine 1-myristoy1-2-palmitoylphosphatidylcholine, 1-palmitoy1-2-myristoylphosphatidylcholine, 1-palmitoy1-2-stearoylphosphatidylcholine, 1-stearoy1-2-palmitoylphosphatidylcholine, 1-palmitoy1-2-oleoylphosphatidylcholine, 1-oleoy1-2-palmitylphosphatidylcholine, dioleoylphosphatidylcholine and the ether derivatives or analogs thereof.

[0428] Lecithins derived or isolated from natural sources can be enriched to include specified acyl chains. In embodiments employing semi-synthetic or synthetic lecithins, the identity(ies) of the acyl chains can be selectively varied, as discussed above in connection with SM. In some embodiments of the complexes described herein, both acyl chains on the lecithin are identical. In some embodiments of complexes that include both SM and lecithin, the acyl chains of the SM and lecithin are all identical. In a specific embodiment, the acyl chains correspond to the acyl chains of myristitic, palmitic, oleic or stearic acid.

[0429] The complexes of the disclosure can include one or more negatively charged phospholipids (*e.g.*, alone or in combination with one or more neutral phospholipids). As used herein, "negatively charged phospholipids" are phospholipids that have a net negative charge at physiological pH. The negatively charged phospholipid can comprise a single type of negatively charged phospholipid, or a mixture of two or more different, negatively charged, phospholipids. In some embodiments, the charged phospholipids are negatively charged glycerophospholipids. Specific examples of suitable negatively charged phospholipids include, but are not limited to, a 1,2-dipalmitoyl-*sn*-glycero-3-[phospho-*rac*-(1-glycerol)], a phosphatidylglycerol, a phospatidylinositol, a phosphatidylserine, a phosphatidic acid, and salts thereof (*e.g.*, sodium salts or potassium salts). In some embodiments, the negatively charged phospholipid comprises one or more of phosphatidylinositol, phosphatidylserine, phosphatidylglycerol and/or phosphatidic acid. In a specific embodiment, the negatively charged phospholipid comprises or consists of a salt of a phosphatidylglycerol or a salt of a phosphatidylinositol. In another specific embodiment, the negatively charged phospholipid comprises or consists of 1,2-dipalmitoyl-*sn*-glycero-3-[phospho-*rac*-(1-glycerol)], or DPPG, or a salt thereof.

[0430] The negatively charged phospholipids can be obtained from natural sources or prepared by chemical synthesis. In embodiments employing synthetic negatively charged phospholipids, the identities of the acyl chains can be selectively varied, as discussed above in connection with SM. In some embodiments of the complexes of the disclosure, both acyl chains on the negatively charged phospholipids are identical. In some embodiments, the acyl chains all types of phospholipids included in a complex of the disclosure are all identical. In a specific embodiment, the complex comprises negatively charged phospholipid(s), and/or SM all having C16:0 or C16:1 acyl chains. In a specific embodiment the fatty acid moiety of the SM is predominantly C16:1 palmitoyl. In one specific embodiment, the acyl chains of the charged phospholipid(s), lecithin and/or SM correspond to the acyl chain of palmitic acid. In yet another specific embodiment, the acyl chains of the charged phospholipid(s), lecithin and/or SM correspond to the acyl chain of oleic acid.

[0431] Examples of positively charged phospholipids that can be included in the complexes of the disclosure include N1-[2-((1S)-1-[(3-aminopropyl)amino]-4-[di(3-amino-propyl)amino]butylcarboxamido)ethyl]-3,4-di[oleyloxy]-benzamide, 1,2-di-O-octadecenyl-3-trimethylammonium propane, 1,2-dimyristoleoyl-sn-glycero-3-ethylphosphocholine, 1-palmitoyl-2-oleoyl-sn-glycero-3-ethylphosphocholine, 1,2-dioleoyl-sn-glycero-3-ethylphosphocholine, 1,2-distearoyl-sn-glycero-3-ethylphosphocholine, 1,2-dipalmitoyl-sn-glycero-3-ethylphosphocholine, 1,2-dimyristoyl-sn-glycero-3-ethylphosphocholine, 1,2-dilauroyl-sn-glycero-3-ethylphosphocholine, 1,2-dilauroyl-sn-glycero-3-ethylphosphocholine, 1,2-dioleoyl-3-dimethylammonium-propane1,2-dimyristoyl-3-dimethylammonium-propane, 1,2-dipalmitoyl-3-dimethylammonium-propane, N-(4-carboxybenzyl)-N,N-dimethyl-2,3-bis(oleoyloxy)propan-1-aminium, 1,2-dioleoyl-3-trimethylammonium-propane, 1,2-dioleoyl-3-trimethylammonium-propane, 1,2-stearoyl-3-trimethylammonium-propane, 1,2-dipalmitoyl-3-trimethylammonium-propane, 1,2-dimyristoyl-3-trimethylammonium-propane, N-[1-(2,3-dimyristyloxy)propyl]-N, N-dimethyl-N-(2-hydroxyethyl) ammonium bromide, N,N,N-trimethyl-2-bis[(1-oxo-9-octadecenyl)oxy]-(Z,Z)- 1propanaminium methyl sulfate, and salts thereof (*e.g.*, chloride or bromide salts).

[0432] The lipids used are preferably at least 95% pure, and/or have reduced levels of oxidative agents (such as but not limited to peroxides). Lipids obtained from natural sources preferably have fewer polyunsaturated fatty acid moieties and/or fatty acid moieties that are not susceptible to oxidation. The level of oxidation in a sample can be determined using an iodometric method, which provides a peroxide value, expressed in milli-equivalent number of isolated iodines per kg of sample, abbreviated meq O/kg. *See, e.g.*, Gray, 1978, , *Journal of the American Oil Chemists Society* 55:539-545; Heaton *et al.*, , 1958, *Journal of the Science of Food and Agriculture* 9:781-786. Preferably, the level of oxidation, or peroxide level, is low, *e.g.*, less than 5 meq O/kg, less than 4 meq O/kg, less than 3 meq O/kg, or less than 2 meq O/kg.

[0433] Complexes can in some embodiments include small quantities of additional lipids. Virtually any type of lipids can be used, including, but not limited to, lysophospholipids, galactocerebroside, gangliosides, cerebrosides, glycerides, triglycerides, and sterols and sterol derivatives (*e.g.*, a plant sterol, an animal sterol, such as cholesterol, or a sterol derivative, such as a cholesterol derivative). For example, a complex of the disclosure can contain cholesterol or a cholesterol derivative, *e.g.*, a cholesterol ester. The cholesterol derivative can also be a substituted cholesterol or a substituted cholesterol ester. The complexes of the disclosure can also contain an oxidized sterol such as, but not

limited to, oxidized cholesterol or an oxidized sterol derivative (such as, but not limited to, an oxidized cholesterol ester). In some embodiments, the complexes do not include cholesterol and/or its derivatives (such as a cholesterol ester or an oxidized cholesterol ester).

6.1.3.2. Detergents

[0434] The complexes can contain one or more detergents. The detergent can be zwitterionic, nonionic, cationic, anionic, or a combination thereof. Exemplary zwitterionic detergents include 3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS), 3-[(3-Cholamidopropyl)dimethylammonio]-2-hydroxy-1-propanesulfonate (CHAPSO), and N,N-dimethyldodecylamine N-oxide (LDAO). Exemplary nonionic detergents include D-(+)-trehalose 6-monooleate, N-octanoyl-N-methylglucamine, N-nonanoyl-N-methylglucamine, N-decanoyl-N-methylglucamine, 1-(7Z-hexadecenoyl)-*rac*-glycerol, 1-(8Z-hexadecenoyl)-*rac*-glycerol, 1-(8Z-heptadecenoyl)-*rac*-glycerol, 1-(9Z-hexadecenoyl)-*rac*-glycerol, 1-decanoyl-*rac*-glycerol. Exemplary cationic detergents include (S)-O-methyl-serine dodecylamide hydrochloride, dodecylammonium chloride, decyltrimethylammonium bromide, and cetyltrimethylammonium sulfate. Exemplary anionic detergents include cholesteryl hemisuccinate, cholate, alkyl sulfates, and alkyl sulfonates.

6.1.3.3. Fatty Acids

[0435] The complexes can contain one or more fatty acids. The one or more fatty acids can include short-chain fatty acids having aliphatic tails of five or fewer carbons (*e.g.* butyric acid, isobutyric acid, valeric acid, or isovaleric acid), medium-chain fatty acids having aliphatic tails of 6 to 12 carbons (*e.g.*, caproic acid, caprylic acid, capric acid, or lauric acid), long-chain fatty acids having aliphatic tails of 13 to 21 carbons (*e.g.*, myristic acid, palmitic acid, stearic acid, or arachidic acid) , very long chain fatty acids having aliphatic tails of 22 or more carbons (*e.g.*, behenic acid, lignoceric acid, or cerotic acid), or a combination thereof. The one or more fatty acids can be saturated (*e.g.*, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid, or cerotic acid), unsaturated (*e.g.*, myristoleic acid, palmitoleic acid, sapienic acid, oleic acid, elaidic acid, vaccenic acid, linoleic acid, linoelaidic acid, α-linolenic acid, arachidonic acid, eicosapentaenoic acid, erucic acid, or docosahexaenoic acid) or a combination thereof. Unsaturated fatty acids can be cis or trans fatty acids. In some embodiments, unsaturated fatty acids used in the complexes of the disclosure are cis fatty acids.

6.1.3.4. Apolar molecules and sterols attached to a sugar

[0436] The complexes can contain one or more amphipathic molecules that comprise an apolar molecule or moiety (*e.g.*, a hydrocarbon chain, an acyl or diacyl chain) or a sterol (*e.g.*, cholesterol) attached to a sugar (*e.g.*, a monosaccharide such as glucose or galactose, or a disaccharide such as maltose or trehalose). The sugar can be a modified sugar or a substituted sugar. Exemplary amphipathic molecules comprising an apolar molecule attached to a sugar include dodecan-2-yloxy-ß-D-maltoside, tridecan-3-yloxy-ß-D-maltoside, tridecan-2-yloxy-ß-D-maltoside, n-dodecyl-ß-D-maltoside (DDM), n-octyl-ß-D-glucoside, n-nonyl-ß-D-glucoside, n-decyl-ß-D-maltoside, n-dodecyl-β-D-maltopyranoside, 4-n-Dodecyl-α,α-trehalose, 6-n-dodecyl-α,α-trehalose, and 3-n-dodecyl-α,α-trehalose.

[0437] In some embodiments, the apolar moiety is an acyl or a diacyl chain.

[0438] In some embodiments, the sugar is a modified sugar or a substituted sugar.

6.1.4. Formulations

[0439] Lipid binding protein molecules and lipid binding protein-based complexes comprising a lipid binding protein molecule can be formulated for the intended route of administration, for example according to techniques known in the art (*e.g.*, as described in Allen *et al.*, eds., 2012, *Remington: The Science and Practice of Pharmacy*, 22nd Edition, Pharmaceutical Press, London, UK).

[0440] CER-001 intended for administration by infusion can be formulated in a phosphate buffer with sucrose and mannitol excipients, for example as described in WO 2012/109162.

6.2. Subject populations

[0441] Subjects who can be treated according to the methods described herein are preferably mammals, most preferably human.

[0442] In some aspects, the subject has or is at risk of a condition that is associated with an abnormal level of TREM-1. Such conditions include, but are not limited to, acute myocardial infarction (AMI), Alzheimer's Disease, chronic irritable bowel disease (IBD), cardiovascular diseases (CVDs), stroke, transient ischemic attack, organ transplant rejection (such as heart transplant rejection), ischemia reperfusion-induced tissue injury, post-operative inflammation, psoriasis, sepsis (*e.g.*, septic shock), and sepsis-induced acute kidney injury (AKI).

[0443] In some aspects, the subject has or is at risk of a condition that is associated with an abnormal level of albumin. Such conditions include, but are not limited to, hypoalbuminemia (which can be caused by, for example, liver disease, heart failure, malnutrition or a vitamin deficiency, inflammatory bowel disease, kidney disease, infections, stress, thyroid disease, diabetes, nephrotic syndrome, lupus, or cirrhosis).

[0444] In some aspects, the subject has or is at risk of a condition that is associated with an abnormal level of a kynurenine pathway biomarker. Such conditions include, but are not limited to, Alzheimer's Disease, attention deficit/hyperactivity disorder (ADHD), CNS diseases, COVID-19 cognitive impairment, depression and major depressive disorder, epilepsy, HIV-associated neurocognitive disorder, Huntington's Disease, long-term cognitive impairment after sepsis, mortality and neurological outcome following cardiac arrest, multiple sclerosis (MS), Parkinson's Disease, schizophrenia, sepsis, and sepsis-induced AKI.

[0445] In some aspects, the subject has or is at risk of a condition that is associated with an abnormal level of IL-10. Such conditions include, but are not limited to, autoimmune diseases, IBD, rheumatoid arthritis (RA), systemic lupus erythematosus, Type I diabetes, MS, pemphigus vulgaris, ulcerative colitis (UC), Sjogren's syndrome, Grave's disease, myasthenia gravis, psoriasis, autoimmune lymphoproliferative syndrome (ALPS), cytokine release syndrome (CRS, cytokine storm), sepsis, and sepsis-induced AKI.

[0446] In some aspects, the subject has or is at risk of a condition that is associated with an abnormal level of TNFα. Such conditions include, but are not limited to, CRS, sepsis, and sepsis-induced AKI.

[0447] In some aspects, the subject has or is at risk of a condition that is associated with an abnormal level of MCP-1. Such conditions include, but are not limited to, CRS, sepsis, and sepsis-induced AKI.

[0448] In some aspects, the subject has or is at risk of a condition that is associated with an abnormal level of IL-6. Such conditions include, but are not limited to, CRS, sepsis, and sepsis-induced AKI.

[0449] In some aspects, the subject has or is at risk of a condition that is associated with an abnormal level of IL-8. Such conditions include, but are not limited to, CRS, sepsis, and sepsis-induced AKI.

[0450] In some aspects, the subject has or is at risk of a condition that is associated with an abnormal level of VCAM-1 and/or ICAM-1. Such conditions include, but are not limited to, vascular endothelial disorder.

[0451] In some aspects, the subject has or is at risk of a bacterial infection. Examples of bacteria that commonly cause infection and sepsis include *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* (GBD 2019 Antimicrobial Resistance Collaborators, 2023, Lancet 400(10369):2221-2248).

[0452] Other examples of bacteria that can cause infection and sepsis include *Acinetobacter baumanni*, *Bacteroides fragilis*, and *Proteus mirabilis*.

[0453] In some aspects, the subject has or is at risk of a gram-positive bacterial infection.

[0454] In some aspects, the subject has or is at risk of a gram-negative bacterial infection.

[0455] In some aspects, the subject has or is at risk of a viral infection, such as a SARS-CoV-2 (COVID-19) infection or an influenza virus infection.

[0456] In some aspects, the subject has or is at risk of acute myocardial infarction (AMI).

[0457] In some aspects, the subject has or is at risk of Alzheimer's disease.

[0458] In some aspects, the subject has or is at risk of chronic inflammatory bowel disease (IBD).

[0459] In some aspects, the subject has or is at risk of a cardiovascular disease (CVD).

[0460] In some aspects, the subject is having or is at risk of a stroke or transient ischemic attack (TIA). Subjects having or who have had a TIA, commonly referred to as a "mini-stroke," are at risk of a stroke, particularly within the days following the TIA. Accordingly, in some embodiments, a subject experiencing or who has experienced a TIA (*e.g.*, within the previous two days) is administered a lipid binding protein according to an administration regimen described herein.

[0461] In some aspects, the subject has or is at risk of cytokine release syndrome (CRS, cytokine storm). In some embodiments, CRS is secondary to an infection, such as a bacterial infection or a viral infection.

[0462] In some aspects, the subject has or is at risk of organ transplant, such as heart transplant rejection.

[0463] In some aspects, the subject has or is at risk of ischemia reperfusion-induced tissue injury.

[0464] In some aspects, the subject has or is at risk of post-operative inflammation.

[0465] In some aspects, the subject has or is at risk of psoriasis.

[0466] In some aspects, the subject has or is at risk of sepsis, including but not limited to sepsis wherein the subject has an abnormal level of at least two of TNFα, IL-6, IL-8, TREM-1, and a kynurenine pathway biomarker, such as an abnormal level of TREM-1 and at least one of quinolinic acid, kynurenic acid, kynurenine, tryptophan, and kynurenine/tryptophan ratio. In some embodiments, sepsis is secondary to an infection, such as a bacterial infection or a viral infection.

[0467] In some embodiments, a subject with sepsis has a documented or suspected infection and an acute change in total SOFA score (see, Vincent *et al.* 1996, Intensive Care Med, 22:707–710) of greater than or equal to 2 points.

[0468] In some embodiments, the subject has septic shock. In some embodiments, a subject having septic shock has hypotension (*e.g.*, systolic arterial pressure < 90 mm Hg or mean arterial pressure

(MAP) < 65 mm Hg) requiring the use of vasopressors for more than one hour despite intravenous fluid resuscitation. In some embodiments, a subject having septic shock has hypotension requiring vasopressor treatment to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) despite adequate fluid resuscitation.

[0469] In some aspects, the subject has or is at risk of sepsis-induced acute kidney injury (AKI).

[0470] In some aspects, the subject has or is at risk of hypoalbuminemia.

[0471] In some aspects, the subject has or is at risk of hypoalbuminemia associated with a vitamin deficiency.

[0472] In some aspects, the subject has or is at risk of hypoalbuminemia associated with inflammatory bowel disease (IBD).

[0473] In some aspects, the subject has or is at risk of hypoalbuminemia associated with kidney disease.

[0474] In some aspects, the subject has or is at risk of hypoalbuminemia associated with infections.

[0475] In some aspects, the subject has or is at risk of hypoalbuminemia associated with stress.

[0476] In some aspects, the subject has or is at risk of hypoalbuminemia associated with thyroid disease.

[0477] In some aspects, the subject has or is at risk of hypoalbuminemia associated with diabetes.

[0478] In some aspects, the subject has or is at risk of hypoalbuminemia associated with nephrotic syndrome.

[0479] In some aspects, the subject has or is at risk of hypoalbuminemia associated with lupus.

[0480] In some aspects, the subject has or is at risk of hypoalbuminemia associated with cirrhosis.

[0481] In some aspects, the subject has or is at risk of hypoalbuminemia associated with liver disease.

[0482] In some aspects, the subject has or is at risk of hypoalbuminemia associated with heart failure.

[0483] In some aspects, the subject has or is at risk of hypoalbuminemia associated with malnutrition.

[0484] In some aspects, the subject has or is at risk of attention-deficit/hyperactivity disorder (ADHD).

[0485] In some aspects, the subject has or is at risk of a central nervous system (CNS) disease.

[0486] In some aspects, the subject has or is at risk of COVID-19 cognitive decline.

[0487] In some aspects, the subject has or is at risk of depression or major depressive disorder.

[0488] In some aspects, the subject has or is at risk of epilepsy.

[0489] In some aspects, the subject has or is at risk of HIV-associated neurocognitive disorder.

[0490] In some aspects, the subject has or is at risk of Huntington's disease.

[0491] In some aspects, the subject has or is at risk of inflammatory bowel disease (IBD).

[0492] In some aspects, the subject has or is at risk of long-term cognitive decline ("brain fog"), such as can occur after sepsis.

[0493] In some aspects, the subject has or is at risk of mortality or neurological deficit following cardiac arrest.

[0494] In some aspects, the subject has or is at risk of multiple sclerosis (MS).

[0495] In some aspects, the subject has or is at risk of Parkinson's disease.

[0496] In some aspects, the subject has or is at risk of schizophrenia.

[0497] In some aspects, the subject has or is at risk of vascular endothelial disorder.

[0498] In some aspects, the subject has or is at risk of acute respiratory distress syndrome (ARDS).

[0499] In some embodiments, the subject has a SOFA score of 1 to 24 before treatment with a lipid binding protein molecule, *e.g.*, a score of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 (see, Vincent *et al*. 1996, Intensive Care Med, 22:707–710).

[0500] In some embodiments, the subject has acute kidney injury (AKI) or is at risk of AKI, for example due to a viral infection or a bacterial infection (*e.g.*, septic subjects).

[0501] In some aspects, the subject can have CRS or be at risk of CRS, and/or be in need of reduction in serum levels of one or more inflammatory markers such as IL-6. In some embodiments, the subject has CRS. In some embodiments, the subject has CRS secondary to an infection, for example a viral infection or a bacterial infection. In yet other embodiments, the subject is at risk of CRS, for example due to a viral infection or a bacterial infection.

[0502] In another aspect, the subject is a subject in need of a reduction in serum levels of one or more inflammatory markers, for example a subject with elevated levels of the one or more inflammatory markers compared to normal levels. Exemplary inflammatory cytokines include interleukin 6 (IL-6), C-reactive protein, D-dimer, ferritin, interleukin 8 (IL-8), granulocyte-macrophage colony stimulating factor (GM-CSF), monocyte chemoattractant protein (MCP) 1, triggering receptor expressed on myeloid cells-1 (TREM-1), and tumor necrosis factor α (TNFα). In some embodiments, the one or more cytokines comprise IL-6. In some embodiments, the one or more cytokines comprise a combination of the foregoing, for example, 2, 3, 4, 5, 6, 7, 8, or all 9 of interleukin 6 (IL-6), C-reactive protein, D-dimer, ferritin, interleukin 8 (IL-8), granulocyte-macrophage colony stimulating factor (GM-CSF), monocyte chemoattractant protein (MCP) 1, TREM-1, and tumor necrosis factor α (TNFα).

6.3. Dosing Regimens

[0503] The methods of the disclosure typically entail multiple administrations of a lipid binding protein molecule (*e.g.*, ApoA-I), *e.g.*, two to 20 individual doses, although in some embodiments, a single dose can be used. In some embodiments, an administration regimen can include two or more, three or more, or four or more individual doses of a lipid binding protein molecule (*e.g.*, ApoA-I), *e.g.*, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, or more than twenty individual doses. In some embodiments, an administration regimen comprises or consists of a single dose. In some embodiments, an administration regimen comprises or consists of two individual doses. In some embodiments, an administration regimen comprises or consists of three individual doses. In some embodiments, an administration regimen comprises or consists of four individual doses. In some embodiments, an administration regimen comprises or consists of five individual doses. In some embodiments, an administration regimen comprises or consists of six individual doses. In some embodiments, an administration regimen comprises or consists of seven individual doses. In some embodiments, an administration regimen comprises or consists of eight individual doses. In some embodiments, an administration regimen comprises or consists of nine individual doses. In some embodiments, an administration regimen comprises or consists of ten individual doses. In some embodiments, an administration regimen comprises or consists of eleven individual doses. In some embodiments, an administration regimen comprises or consists of twelve individual doses. In some embodiments, an administration regimen comprises or consists of thirteen individual doses. In some embodiments, an administration regimen comprises or consists of fourteen individual doses. In some embodiments, an administration regimen comprises or consists of fifteen individual doses. In some

embodiments, an administration regimen comprises or consists of sixteen individual doses. In some embodiments, an administration regimen comprises or consists of seventeen individual doses. In some embodiments, an administration regimen comprises or consists of eighteen individual doses. In some embodiments, an administration regimen comprises or consists of nineteen individual doses. In some embodiments, an administration regimen comprises or consists of twenty individual doses.

[0504] In some embodiments, the amount of lipid binding protein molecule delivered by each dose can be from 5 mg/kg to 40 mg/kg on a protein weight basis. In some embodiments, the amount of lipid binding protein molecule delivered by each dose can be from 5 mg/kg to 10 mg/kg on a protein weight basis. In some embodiments, the amount of lipid binding protein molecule delivered by each dose can be from 5 mg/kg to 20 mg/kg on a protein weight basis. In some embodiments, the amount of lipid binding protein molecule delivered by each dose can be from 10 mg/kg to 30 mg/kg on a protein weight basis. In some embodiments, the amount of lipid binding protein molecule delivered by each dose can be from 10 mg/kg to 20 mg/kg on a protein weight basis. In some embodiments, a dose is 5 mg/kg on a protein weight basis. In some embodiments, a dose is 6 mg/kg on a protein weight basis. In some embodiments, a dose is 7 mg/kg on a protein weight basis. In some embodiments, a dose is 8 mg/kg on a protein weight basis. In some embodiments, a dose is 9 mg/kg on a protein weight basis. In some embodiments, a dose is 10 mg/kg on a protein weight basis. In some embodiments, a dose is 11 mg/kg on a protein weight basis. In some embodiments, a dose is 12 mg/kg on a protein weight basis. In some embodiments, a dose is 13 mg/kg on a protein weight basis. In some embodiments, a dose is 14 mg/kg on a protein weight basis. In some embodiments, a dose is 15 mg/kg on a protein weight basis. In some embodiments, a dose is 16 mg/kg on a protein weight basis. In some embodiments, a dose is 17 mg/kg on a protein weight basis. In some embodiments, a dose is 18 mg/kg on a protein weight basis. In some embodiments, a dose is 19 mg/kg on a protein weight basis. In some embodiments, a dose is 20 mg/kg on a protein weight basis. In some embodiments, a dose is 21 mg/kg on a protein weight basis. In some embodiments, a dose is 22 mg/kg on a protein weight basis. In some embodiments, a dose is 23 mg/kg on a protein weight basis. In some embodiments, a dose is 24 mg/kg on a protein weight basis. In some embodiments, a dose is 25 mg/kg on a protein weight basis. In some embodiments, a dose is 26 mg/kg on a protein weight basis. In some embodiments, a dose is 27 mg/kg on a protein weight basis. In some embodiments, a dose is 28 mg/kg on a protein weight basis. In some embodiments, a dose is 29 mg/kg on a protein weight basis. In some embodiments, a dose is 30 mg/kg on a protein weight basis. In some embodiments, a dose is 31 mg/kg on a protein weight basis. In some embodiments, a dose is 32 mg/kg on a protein weight basis. In some embodiments, a dose is 33 mg/kg on a protein weight basis. In some embodiments, a dose is 34 mg/kg on a protein weight basis. In some embodiments, a dose is 35 mg/kg on a protein weight basis. In some embodiments, a dose is 36 mg/kg on a protein weight basis. In some embodiments, a dose is 37 mg/kg on a protein weight basis. In some embodiments, a dose is 38 mg/kg on a protein weight basis. In some embodiments, a dose is 39 mg/kg on a protein weight basis. In some embodiments, a dose is 40 mg/kg on a protein weight basis.

[0505] An exemplary dosing regimen for subjects having sepsis (*e.g.*, septic shock) comprises twice daily administration of a lipid binding protein molecule (*e.g.*, ApoA-I) for five days. In some embodiments, ApoA-I (*e.g.*, as CER-001) is administered at a dose of 10 mg/kg on a protein weight basis. In other embodiments, the ApoA-I (*e.g.*, as CER-001) is administered at a dose of 20 mg/kg on a protein weight basis. The two daily doses can be administered, for example, approximately 12 hours apart. In some

embodiments, two daily doses are administered 11-13 hours apart. In some embodiments, two daily doses are administered as a morning dose and an evening dose (which may be more or less than 12 hours apart).

[0506] In some embodiments of the dosing regimens described in this paragraph, the subject has septic shock.

[0507] In some embodiments, the lipid binding protein molecule is administered according to an induction and, optionally, a consolidation regimen as described in Sections 6.3.1 and 6.3.2, respectively. In some embodiments, the lipid binding protein molecule can be administered in a single phase, *e.g.*, according to an administration regimen described in this Section. In some embodiments, the subject is not treated with the lipid binding protein molecule according to a maintenance regimen, *e.g.*, a regimen comprising long-term (*e.g.*, one month or longer) administration of the lipid binding protein molecule. In other embodiments, the subject is treated with the lipid binding protein molecule according to a maintenance regimen, *e.g.*, a regimen comprising long-term (*e.g.*, one month or longer) administration of the lipid binding protein molecule, for example when the subject has a chronic condition such as Alzheimer's disease.

[0508] The lipid binding protein molecule (*e.g.*, ApoA-I) administration regimens of the disclosure can last up to one week, one week, or more than one week (*e.g.*, two weeks or three weeks).

[0509] For example, a lipid binding protein molecule (*e.g.*, ApoA-I) administration regimen can comprise administering:

- five individual doses of ApoA-I over one week;
- six individual doses of ApoA-I over one week;
- seven individual doses of ApoA-I over one week;
- eight individual doses of ApoA-I over one week;
- nine individual doses of ApoA-I over one week;
- ten individual doses of ApoA-I over one week;
- twelve individual doses of ApoA-I over one week;
- fourteen individual doses of ApoA-I over one week;
- ten individual doses of ApoA-I over two weeks;
- twelve individual doses of ApoA-I over two weeks;
- fourteen individual doses of ApoA-I over two weeks.

[0510] In an embodiment, the methods of the disclosure comprise administering seven individual doses of ApoA-I over one week, *e.g.*, on days 1, 2, 3, 4, 5, 6, and 7.

[0511] In some embodiments, the methods of the disclosure comprise administering multiple individual doses over a period of four to six days, for example one to two individual doses per day for four to six days. In some embodiments, the methods of the disclosure comprise administering multiple individual doses over four days, for example one to two individual doses per day for four days. In some embodiments, the methods of the disclosure comprise administering multiple individual doses over five days, for example one to two individual doses per day for five days. In some embodiments, the methods of the disclosure comprise administering multiple individual doses over six days, for example one to two individual doses per day for six days. In some embodiments of the methods described in this paragraph, one individual dose is administered per day. In other embodiments of the methods described in this paragraph, two individual doses are administered per day.

[0512] In some embodiments, of the methods of the disclosure, a plurality of doses of a lipid binding protein molecule (*e.g.*, ApoA-I) are administered no more than one day apart. For example, in some embodiments two or more individual doses are administered approximately 12 hours apart. In some embodiments, two individual doses are administered approximately 12 hours apart. In other embodiments, three individual doses are administered approximately 12 hours apart. In other embodiments, two individual doses are administered approximately 12 hours apart and a third individual dose is administered approximately one day later. In other embodiments, three individual doses are administered approximately 12 hours apart and a fourth individual dose is administered approximately one day later.

[0513] In some embodiments of the methods of the disclosure, a lipid binding protein molecule (*e.g.*, ApoA-I) is administered to a subject (*e.g.*, over a period of 0.5 to 1 hour) at hours 0 and 12, for example at a dose of 10 mg/kg or 15 mg/kg. In some embodiments of the methods of the disclosure, a lipid binding protein molecule (*e.g.*, ApoA-I) is administered to a subject (*e.g.*, over a period of 0.5 to 1 hour) at hours 0 and 12, 24, and 48, for example at a dose of 10 mg/kg or 15 mg/kg.

[0514] In some embodiments of the methods of the disclosure, a lipid binding protein molecule (*e.g.*, ApoA-I) is administered daily, *e.g.*, daily for at least 5 days, at least 6 days, at least 7 days, or more than 7 days (*e.g.*, daily for up to one week or daily for up to two weeks). In other embodiments, a lipid binding protein molecule (*e.g.*, ApoA-I) is administered less frequently, *e.g.*, every other day, two times per week, three times per week, or once a week.

[0515] In practice, an administration window can be provided, for example, to accommodate slight variations to a multi-dosing per week dosing schedule. For example, a window of ± 2 days or ± 1 day around the dosage date can be used.

[0516] A lipid binding protein molecule (*e.g.*, ApoA-I) can be administered in the methods of the disclosure for a pre-determined period of time, *e.g.*, for one week. Alternatively, administration of a lipid binding protein molecule (*e.g.*, ApoA-I) can be continued until one or more symptoms of a condition (are reduced or continued until the serum levels of one or more inflammatory markers are reduced, for example reduced to a normal level or reduced relative to a baseline value for the subject, *e.g.*, a baseline value measured prior to the start of lipid binding protein molecule (*e.g.*, ApoA-I) therapy. Reference or "normal" levels of various markers, for example, inflammatory markers are known in the art. For example, the Mayo Clinic Laboratories test catalog (www.mayocliniclabs.com/test-catalog) provides the following reference values: IL-6: ≤ 1.8 pg/ml; C-reactive protein: ≤ 8.0 mg/ml; D-dimer: ≤ 500 ng/mL Fibrinogen Equivalent Units (FEU); ferritin: 24-336 mcg/L (males), 11-307 mcg/L (females); IL-8 < 57.8 pg/mL; TNF-α < 5.6 pg/mL; albumin: 3.5-5.0 g/dL; tryptophan: 17-80 nmol/mL; serotonin: ≤ 330 ng/mL. Radhakrishnan *et al.*, 2014, Indian J Endocrinol Metab 18(4):505-510 provides the following reference value: MCP-1: 350-450 pg/ml. Ho *et al.*, 2004, World J Gastroenterol 10(14):2014-2018 provides the following reference value: VCAM-1: < 700 ng/mL. Rothlein *et al.*, 1991, J Immunol. 147(11):3788-93 provides the following reference value: ICAM-1: 100-200 ng/mL. The normal range of TREM-1 is estimated to be < 500 pg/mL, and for some subject populations may be < 300 pg/mL. Values falling outside of normal ranges are "abnormal."

[0517] The methods of the disclosure typically comprise administering a high dose of a lipid binding protein molecule (*e.g.*, ApoA-I). The high dose can be the aggregate of multiple individual doses (*e.g.*, two, three, four, five, six, seven, eight, nine or 10 individual doses), for example administered over one or

multiple days (*e.g.*, a period of one day, a period of two days, a period of three days, four days, five days, six days, seven days, eight days, nine days, 10 days, eleven days, 12 days, 13 days, 14 days, or 15 days). The individual doses of a high dose are in some embodiments administered daily, twice daily, or two to three days apart.

[0518] In some embodiments, the high dose is an amount effective to increase the subject's HDL and/or ApoA-I blood levels and/or improve the subject's vascular endothelial function, *e.g.*, measured by circulating vascular cell adhesion molecule 1 (VCAM-1) and/or intercellular adhesion molecule 1 (ICAM-1) levels. In some embodiments, the high dose or an individual dose is an amount which increases the subject's HDL and/or ApoA-I levels by at least 25%, at least 30%, or at least 35% 2 to 4 hours after administration.

[0519] In some embodiments, the high dose is an amount effective to reduce serum levels of one or more inflammatory markers, for example, one or more of IL-6, C-reactive protein, D-dimer, ferritin, IL-8, GM-CSF, MCP1, TREM-1, or TNF-α. In some embodiments, the serum levels of the one or more inflammatory markers are reduced from an elevated range to a normal range, and/or reduced by at least 20%, at least 40%, or at least 60%.

[0520] The dose of a lipid binding protein molecule (*e.g.*, ApoA-I) administered to a subject (*e.g.*, an individual dose which when aggregated with one or more other individual doses forms a high dose) can in some embodiments range from 4 to 40 mg/kg (*e.g.*, 10 to 40 mg/kg) on a protein weight basis (*e.g.,* 5, 10, 15, 20, 25, 30, 35, or 40 mg/kg or any range bounded by any two of the foregoing values, *e.g.*, 10 to 20 mg/kg, 15 to 25 mg/kg, 20 to 40 mg/kg, 25 to 35 mg/kg, or 30 to 40 mg/kg). As used herein, the expression "protein weight basis" means that a dose of a lipid binding protein molecule (*e.g.*, ApoA-I) to be administered to a subject is calculated based upon the amount of the lipid binding protein molecule (*e.g.*, ApoA-I) to be administered and the weight of the subject. For example, a subject who weighs 70 kg and is to receive a 20 mg/kg dose of CER-001 would receive an amount of CER-001 that provides 1400 mg of ApoA-I (70 kg x 20 mg/kg).

[0521] The same amount of lipid binding protein can be administered for each individual dose. Alternatively, the amount of lipid binding protein can vary between individual doses. For example, one or more individual doses can be administered at a first dose amount and, subsequently, one or more individual doses can be administered at a different, second dose amount. For example, a first dose amount can be 5 mg/kg (on a protein weight basis) and the second dose amount can be a higher amount, for example 10 mg/kg (on a protein weight basis). As another example, a first dose amount can be 10 mg/kg (on a protein weight basis) and the second dose amount can be a higher amount, for example 15 mg/kg (on a protein weight basis). As another example, a first dose amount can be 10 mg/kg (on a protein weight basis) and the second dose amount can be a higher amount, for example 20 mg/kg (on a protein weight basis). As another example, a first dose amount can be 15 mg/kg (on a protein weight basis) and the second dose amount can be a higher amount, for example 20 mg/kg (on a protein weight basis). As another example, a first dose amount can be 20 mg/kg (on a protein weight basis) and the second dose amount can be a lower amount, for example 10 mg/kg (on a protein weight basis). As another example, a first dose amount can be 20 mg/kg (on a protein weight basis) and the second dose amount can be a lower amount, for example 5 mg/kg (on a protein weight basis). As another example, a first dose amount can be 10 mg/kg (on a protein weight basis) and the second dose amount can be a lower amount, for example 5 mg/kg (on a protein weight basis).

[0522] In some embodiments, a lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 5 mg/kg to 20 mg/kg (on a protein weight basis) one to two times a day for four to six days. In some embodiments, each individual dose amount is the same; alternatively, different individual dose amounts can be used, for example as described in the preceding paragraph. In some embodiments, a lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 5 mg/kg to 20 mg/kg (on a protein weight basis) one to two times a day for four days. In some embodiments, a lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 5 mg/kg to 20 mg/kg (on a protein weight basis) one to two times a day for five days. In some embodiments, a lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 5 mg/kg to 20 mg/kg (on a protein weight basis) one to two times a day for six days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 5 mg/kg (on a protein weight basis) one to two times a day for four to six days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 5 mg/kg (on a protein weight basis) one to two times a day for four days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 5 mg/kg (on a protein weight basis) one to two times a day for five days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 5 mg/kg (on a protein weight basis) one to two times a day for six days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 10 mg/kg (on a protein weight basis) one to two times a day for four to six days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 10 mg/kg (on a protein weight basis) one to two times a day for four days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 10 mg/kg (on a protein weight basis) one to two times a day for five days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 10 mg/kg (on a protein weight basis) one to two times a day for six days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 15 mg/kg (on a protein weight basis) one to two times a day for four to six days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 15 mg/kg (on a protein weight basis) one to two times a day for four days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 15 mg/kg (on a protein weight basis) one to two times a day for five days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 15 mg/kg (on a protein weight basis) one to two times a day for six days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 20 mg/kg (on a protein weight basis) one to two times a day for four to six days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 20 mg/kg (on a protein weight basis) one to two times a day for four days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 20 mg/kg (on a protein weight basis) one to two times a day for five days. In some embodiments, the lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered at dose of 20 mg/kg (on a protein weight basis) one to two times a day for six days. In some embodiments of the methods

described in this paragraph, the lipid binding protein is administered once a day. In other embodiments of the methods described in this paragraph, the lipid binding protein is administered twice a day.

[0523] In some embodiments, a lipid binding protein (*e.g.*, ApoA-I, optionally in the form of CER-001) is administered to a subject according to one of the following regimens:

- two individual doses per day at a first dose amount (*e.g.*, 5 mg/kg, 10 mg/kg 15 mg/kg, or 20 mg/kg) for at least 3 days, then one individual dose per day at a second dose amount (*e.g.*, 5 mg/kg, 10 mg/kg 15 mg/kg, or 20 mg/kg) that is the same or higher than first dose amount for up to 15 days (*e.g.*, up to 5 days, up to one week, up to 10 days, for one day, two days, three days, four days, five days, six days, seven days, eight days, nine days, 10 days, 11 days, 12 days, 13 days, 14 days, or 15 days);
- two individual doses per day at a first dose amount (*e.g.*, 5 mg/kg, 10 mg/kg 15 mg/kg, or 20 mg/kg) for 3 days, then one individual dose per day at a second dose amount (*e.g.*, 5 mg/kg, 10 mg/kg 15 mg/kg, or 20 mg/kg) that is the same or higher than first dose amount for up to 15 days (*e.g.*, up to 5 days, up to one week, up to 10 days, for one day, two days, three days, four days, five days, six days, seven days, eight days, nine days, 10 days, 11 days, 12 days, 13 days, 14 days, or 15 days);
- two individual doses per day at a first dose amount (*e.g.*, 5 mg/kg, 10 mg/kg 15 mg/kg, or 20 mg/kg) for 4 days, then one individual dose per day at a second dose amount (*e.g.*, 5 mg/kg, 10 mg/kg 15 mg/kg, or 20 mg/kg) that is the same or higher than first dose amount for up to 15 days (*e.g.*, up to 5 days, up to one week, up to 10 days, for one day, two days, three days, four days, five days, six days, seven days, eight days, nine days, 10 days, 11 days, 12 days, 13 days, 14 days, or 15 days);
- two individual doses per day at a first dose amount (*e.g.*, 5 mg/kg, 10 mg/kg 15 mg/kg, or 20 mg/kg) for 5 days, then one individual dose per day at a second dose amount (*e.g.*, 5 mg/kg, 10 mg/kg 15 mg/kg, or 20 mg/kg) that is the same or higher than first dose amount for up to 15 days (*e.g.*, up to 5 days, up to one week, up to 10 days, for one day, two days, three days, four days, five days, six days, seven days, eight days, nine days, 10 days, 11 days, 12 days, 13 days, 14 days, or 15 days);
- two individual doses per day at a first dose amount (*e.g.*, 5 mg/kg, 10 mg/kg 15 mg/kg, or 20 mg/kg) for 6 days, then one individual dose per day at a second dose amount (*e.g.*, 5 mg/kg, 10 mg/kg 15 mg/kg, or 20 mg/kg) that is the same or higher than first dose amount for up to 15 days (*e.g.*, up to 5 days, up to one week, up to 10 days, for one day, two days, three days, four days, five days, six days, seven days, eight days, nine days, 10 days, 11 days, 12 days, 13 days, 14 days, or 15 days);

In some embodiments, the first dose amount is the same as the second dose amount, *e.g.*, in some embodiments the first and second dose amount is 5 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg. In other embodiments, the second dose amount is higher than the first dose amount. For example, in some embodiments, the first dose amount is 5 mg/kg and the second dose amount is 10 mg/kg, 15 mg/kg, or 20 mg/kg; the first dose amount is 10 mg/kg and the second dose amount is 15 mg/kg or 20 mg/kg; or the first dose amount is 15 mg/kg and the second dose amount is 20 mg/kg.

[0524] In yet other aspects, a lipid binding protein molecule (*e.g.*, ApoA-I) can be administered on a unit dosage basis. The unit dosage used in the methods of the disclosure can in some embodiments vary from 300 mg to 4000 mg (*e.g.*, 600 mg to 4000 mg) per administration (on a protein weight basis).

[0525] In particular embodiments, the dosage of a lipid binding protein molecule (*e.g.*, ApoA-I) is 300 mg to 400 mg, 300 mg to 500 mg, 300 mg to 600 mg, 300 mg to 800 mg, 300 mg to 1000 mg, 300 mg to 1200 mg, 300 mg to 1500 mg, 300 mg to 2000 mg, 300 mg to 2400 mg, 300 mg to 3000 mg, 400 mg to 500 mg, 400 mg to 600 mg, 400 mg to 800 mg, 400 mg to 1000 mg, 400 mg to 1200 mg, 400 mg to 1500 mg, 400 mg to 2000 mg, 400 mg to 2400 mg, 400 mg to 3000 mg, 400 mg to 4000 mg, 500 mg to 600 mg, 500 mg to 800 mg, 500 mg to 1000 mg, 500 mg to 1200 mg, 500 mg to 1500 mg, 500 mg to 2000 mg, 500 mg to 2400 mg, 500 mg to 3000 mg, 500 mg to 4000 mg, 600 mg to 800 mg, 600 mg to 1000 mg, 600 mg to 1200 mg, 600 mg to 1500 mg, 600 mg to 2000 mg, 600 mg to 2400 mg, 600 mg to 3000 mg, 600 mg to 4000 mg, 800 mg to 1000 mg, 800 mg to 1200 mg, 800 mg to 1500 mg, 800 mg to 2000 mg, 800 mg to 2400 mg, 800 mg to 3000 mg, 800 mg to 4000 mg, 1000 mg to 1200 mg, 1000 mg to 1500 mg, 1000 mg to 2000 mg, 1000 mg to 2400 mg, 1000 mg to 3000 mg, 1000 mg to 4000 mg, 1200 mg to 1500 mg, 1200 mg to 2000 mg, 1200 mg to 2400 mg, 1200 mg to 3000 mg, 1200 mg to 4000 mg, 1500 mg to 2000 mg, 1500 mg to 2400 mg, 1500 mg to 3000 mg, 1500 mg to 4000 mg, 2000 mg to 2400 mg, 2000 mg to 3000 mg, 2000 mg to 4000 mg, 2400 mg to 3000 mg, 2400 mg to 4000 mg, or 3000 mg to 4000 mg per administration (on a protein weight basis).

[0526] In some aspects, a high dose of a lipid binding protein molecule (*e.g.*, ApoA-I), *e.g.*, the aggregate of multiple individual doses, is 600 mg to 40 g (on a protein weight basis). In particular embodiments, a high dose is 3 g to 35 g or 5 g to 30 g (on a protein weight basis).

[0527] A lipid binding protein molecule (*e.g.*, ApoA-I) is preferably administered as an IV infusion. For example, a stock solution of CER-001 can be diluted in normal saline such as physiological saline (0.9% NaCl) to a total volume between 125 and 250 ml. In some embodiments, subjects weighing less than 80 kg will have a total volume of 125 ml whereas subjects weighing at least 80 kg will have a total volume of 250 ml. In some embodiments, doses of CER-001 are administered in a total volume of 250 ml. A lipid binding protein molecule (*e.g.*, ApoA-I) can be administered over a period ranging from one-hour to 24-hours. Depending on the needs of the subject, administration can be by slow infusion with a duration of more than one hour (*e.g.*, up to 2 hours or up to 24 hours), by rapid infusion of one hour or less, or by a single bolus injection. In an embodiment, a lipid binding protein molecule (*e.g.*, ApoA-I) is administered over a one-hour period, *e.g.*, using an infusion pump at a fixed rate of 125 ml/hr or 250 ml/hr. In an embodiment, a dose of a lipid binding protein molecule (*e.g.*, ApoA-I) is administered as an infusion over a 24-hour period.

6.3.1. Induction Regimen

[0528] In one embodiment, induction regimens suitable for use in the methods of the disclosure entail administering multiple doses of a lipid binding protein molecule (*e.g.*, ApoA-I) over multiple consecutive days, *e.g.*, three consecutive days, four consecutive days, five consecutive days, or six consecutive days. In some embodiments, lipid binding protein molecule (*e.g.*, ApoA-I) is administered for four consecutive days. In some embodiments, lipid binding protein molecule (*e.g.*, ApoA-I) is administered for five consecutive days. In some embodiments, lipid binding protein molecule (*e.g.*, ApoA-I) is administered for six consecutive days.

[0529] In some embodiments, induction regimens suitable for use in the methods of the disclosure entail twice daily administration of a lipid binding protein molecule (*e.g.*, ApoA-I) such as twice daily administration on multiple consecutive days. Twice daily administration can comprise, for example, two doses approximately 12 hours apart or a morning dose and an evening dose (which may be more or less than 12 hours apart).

[0530] In an embodiment, the induction regimen comprises two doses of a lipid binding protein molecule (*e.g.*, ApoA-I) per day for three consecutive days. In an embodiment, the induction regimen comprises two doses of a lipid binding protein molecule (*e.g.*, ApoA-I) per day for four consecutive days. In an embodiment, the induction regimen comprises two doses of a lipid binding protein molecule (*e.g.*, ApoA-I) per day for five consecutive days. In an embodiment, the induction regimen comprises two doses of a lipid binding protein molecule (*e.g.*, ApoA-I) per day for six consecutive days.

[0531] A therapeutic dose of a lipid binding protein molecule (*e.g.*, ApoA-I) administered by infusion in the induction regimen can range from 4 to 40 mg/kg (*e.g.*, 4 to 30 mg/kg) on a protein weight basis (*e.g.*, 4, 5, 6, 7, 8, 9, 10, 12 15, 20, 25, 30 or 40 mg/kg, or any range bounded by any two of the foregoing values, *e.g.*, 5 to 15 mg/kg, 10 to 20 mg/kg, or 15 to 25 mg/kg). In some embodiments, the dose of a lipid binding protein molecule (*e.g.*, ApoA-I) used in the induction regimen is 5 mg/kg. In some embodiments, the dose of a lipid binding protein molecule (*e.g.*, ApoA-I) used in the induction regimen is 10 mg/kg. In some embodiments, the dose of a lipid binding protein molecule (*e.g.*, ApoA-I) used in the induction regimen is 15 mg/kg. In some embodiments, the dose of a lipid binding protein molecule (*e.g.*, ApoA-I) used in the induction regimen is 20 mg/kg. In some embodiments, the induction regimen comprises six doses of a lipid binding protein molecule (*e.g.*, ApoA-I) administered over three days at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg. In some embodiments, the induction regimen comprises eight doses of a lipid binding protein molecule (*e.g.*, ApoA-I) administered over four days at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg. In some embodiments, the induction regimen comprises ten doses of a lipid binding protein molecule (*e.g.*, ApoA-I) administered over five days at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg. In some embodiments, the induction regimen comprises twelve doses of a lipid binding protein molecule (*e.g.*, ApoA-I) administered over six days at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg.

[0532] In yet other aspects, a lipid binding protein molecule (*e.g.*, ApoA-I) can be administered on a unit dosage basis. The unit dosage used in the induction phase can vary from 300 mg to 4000 mg (*e.g.*, 300 mg to 3000 mg) (on a protein weight basis) per administration by infusion.

[0533] In particular embodiments, the dosage of a lipid binding protein molecule (*e.g.*, ApoA-I) used during the induction phase is 300 mg to 1500 mg, 400 mg to 1500 mg, 500 mg to 1200 mg, or 500 mg to 1000 mg (on a protein weight basis) per administration by infusion.

6.3.2. Consolidation Regimen

[0534] Consolidation regimens suitable for use in the methods of the disclosure entail administering one dose or multiple doses of a lipid binding protein molecule (*e.g.*, ApoA-I) following an induction regimen.

[0535] In one embodiment, the consolidation regimen comprises administering two doses of a lipid binding protein molecule (*e.g.*, ApoA-I). For example, the two doses can be administered approximately 12 hours apart, or administered as a morning dose and an evening dose (which may be more or less than 12 hours apart).

[0536] The dose(s) of a lipid binding protein molecule (*e.g.*, ApoA-I) in a consolidation regimen can in some embodiments be administered on day 6 of a dosing regimen that begins with an induction regimen on day 1. The dose(s) of a lipid binding protein molecule (*e.g.*, ApoA-I) in a consolidation regimen can in some embodiments be administered on day 4 of a dosing regimen that begins with an induction regimen on day 1. The dose(s) of a lipid binding protein molecule (*e.g.*, ApoA-I) in a consolidation regimen can in some embodiments be administered on day 5 of a dosing regimen that begins with an induction regimen on day 1. The dose(s) of a lipid binding protein molecule (*e.g.*, ApoA-I) in a consolidation regimen can in some embodiments be administered on day 7 of a dosing regimen that begins with an induction regimen on day 1.

[0537] In some embodiments, a consolidation regimen comprises once daily administration of a lipid binding protein molecule (*e.g.*, ApoA-I) following an induction regimen that comprises twice daily administration of the lipid binding protein molecule (*e.g.*, ApoA-I). Each individual dose of the consolidation regimen can be the same or higher than each individual dose of the induction regimen. For example, following an induction regimen comprising twice daily administration of a lipid binding protein molecule (*e.g.*, ApoA-I) for at least three days (*e.g.*, up to a week, three days, four days, five days, six days, or seven days), the lipid binding protein molecule (*e.g.*, ApoA-I) can be administered once daily for up to 15 days (e.g., up to seven days, up to 10 days, one day, two days, three days, four days, five days, six days, seven days, eight days, nine days, 10 days, 11 days, 12 days, 13 days, 14 days, or 15 days).

[0538] A therapeutic dose of a lipid binding protein molecule (*e.g.*, ApoA-I) administered by infusion in the consolidation regimen can range from 4 mg/kg to 40 mg/kg (*e.g.*, 4 to 30 mg/kg) on a protein weight basis (*e.g.*, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20, 25, 30, or 40 mg/kg, or any range bounded by any two of the foregoing values, *e.g.*, 5 to 15 mg/kg, 10 to 20 mg/kg, or 15 to 25 mg/kg). In some embodiments, the dose of a lipid binding protein molecule (*e.g.*, ApoA-I) used in the consolidation regimen is 5 mg/kg. In some embodiments, the dose of a lipid binding protein molecule (*e.g.*, ApoA-I) used in the consolidation regimen is 10 mg/kg. In some embodiments, the dose of a lipid binding protein molecule (*e.g.*, ApoA-I) in the consolidation regimen is 15 mg/kg. In some embodiments, the dose of a lipid binding protein molecule (*e.g.*, ApoA-I) used in the consolidation regimen is 20 mg/kg. In some embodiments, the consolidation regimen comprises two doses of a lipid binding protein molecule (*e.g.*, ApoA-I) administered on one day at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg.

[0539] In yet other aspects, a lipid binding protein molecule (*e.g.*, ApoA-I) can be administered on a unit dosage basis. The unit dosage used in the consolidation phase can vary from 300 mg to 4000 mg (*e.g.*, 300 mg to 3000 mg) (on a protein weight basis) per administration by infusion.

[0540] In particular embodiments, the dosage of a lipid binding protein molecule (*e.g.*, ApoA-I) used during the consolidation phase is 300 mg to 1500 mg, 400 mg to 1500 mg, 500 mg to 1200 mg, or 500 mg to 1000 mg (on a protein weight basis) per administration by infusion.

[0541] The lipid binding protein molecule (*e.g.*, ApoA-I) can be administered during the consolidation phase in the same manner as described in Section 6.3, *e.g.*, as an IV infusion over a one-hour period.

6.4. Combination therapies

[0542] A lipid binding protein molecule (*e.g.*, ApoA-I) can be administered to a subject as described herein as a monotherapy or a part of a combination therapy regimen. For example, a combination therapy can comprise a lipid binding protein molecule (*e.g.*, ApoA-I) in combination with a standard of

care treatment for the condition from which the subject suffers or is at risk of suffering, *e.g.*, sepsis and/or AKI. *See, e.g.*, Rhodes *et al.*, 2017, Intensive Care Med 43:304–377; Dugar *et al.*, 2020, Cleveland Clinic Journal of Medicine 87(1):53-64; Singer *et al.*, 2016, JAMA 315(8):801-810.

[0543] In some embodiments, for example for subjects having sepsis, the subject is treated with a lipid binding protein molecule (*e.g.*, ApoA-I) in combination with fluid replacement therapy. In some embodiments, for example for subjects having sepsis, the subject is treated with a lipid binding protein molecule (*e.g.*, ApoA-I) in combination with an antimicrobial. In some embodiments, for example for subjects having sepsis, the subject is treated with a lipid binding protein molecule (*e.g.*, ApoA-I) in combination with an antibiotic (*e.g.*, ceftriaxone, meropenem, ceftazidime, cefotaxime, cefepime, piperacillin and tazobactam, ampicillin and sulbactam, imipenem and cilastatin, levofloxacin, or clindamycin). In some embodiments, for example for subjects having a viral infection, the subject is treated with a lipid binding protein molecule (*e.g.*, ApoA-I) in combination with an antiviral. In some embodiments, the subject is treated with a lipid binding protein molecule (*e.g.*, ApoA-I) in combination with a medication that raises blood pressure (*e.g.*, norepinephrine or epinephrine). In some embodiments, the subject is treated with a lipid binding protein molecule (*e.g.*, ApoA-I) in combination with an immunosuppressant such as tacrolimus or everolimus.

[0544] A combination therapy regimen can in some embodiments comprise one or more anti-IL-6 agents and/or one or more other agents for treating CRS such as corticosteroids (*e.g.*, methylprednisolone and/or dexamethasone). Exemplary anti-IL6 agents include tocilizumab, siltuximab, olokizumab, elsilimomab, BMS-945429, sirukumab, levilimab, and CPSI-2364. In some embodiments, a lipid binding protein molecule (*e.g.*, ApoA-I) is administered in combination with tocilizumab.

[0545] In certain embodiments, an antihistamine (*e.g.*, diphenhydramine, cetirizine, fexofenadine, or loratadine) can be administered before administration of a lipid binding protein molecule (*e.g.*, ApoA-I). The antihistamine can reduce the likelihood of allergic reactions.

7. EXAMPLES

7.1. Example 1: Lipid binding protein molecule therapy in a swine model of LPS-induced acute kidney injury

[0546] The ability of the ApoA-I containing complex CER-001 to mitigate sepsis-related cognitive decline was evaluated in a lipopolysaccharide (LPS)-induced swine model of cognitive decline (“brain fog”).

7.1.1. Materials and Methods

[0547] Pigs were randomized into three groups: LPS (endotoxemic pigs, n=3 except as noted), single dose CER- 001 treated pigs (endotoxemic pigs treated with a single dose of CER-001 at 20 mg/kg; n=4 except as noted), and multiple dose CER-001 treated pigs (endotoxemic pigs treated with two doses of CER-001 at 20 mg/kg for a total dose of 40 mg/kg; n=6 except as noted).

7.1.1.1. Kynurenine pathway biomarker assays

[0548] Sepsis was induced in pigs by intravenous infusion of a saline solution containing 300 µg/kg of LPS at T0. Single dose CER-001 treated pigs and CER-001 multiple dose treated pigs received a 20 mg/kg dose of CER-001 at T0. CER-001 multiple dose treated pigs received a second 20 mg/kg dose of CER-001 three hours later (T3). Quinolinic acid, kynurenic acid, tryptophan (Trp), and kynurenine (Kyn)

levels and Kyn:Trp ratios were monitored over time. LPS pigs, n=3 except as noted; single dose endotoxemic pigs treated with a single dose of CER-001 at 20 mg/kg; n=4 except as noted; endotoxemic pigs treated with two doses of CER-001 at 20 mg/kg; n=6 except as noted.

7.1.1.2. Q-PCR of kynurenine pathway and interleukin-6 mRNA in brain tissue

[0549] For all groups, n = 3. Animals were humanely sacrificed. Brain tissue was extracted and qPCR performed on mRNA encoding aromatic-L-amino-acid/L-tryptophan decarboxylase (DDC); indoleamine 2,3-dioxygenase 1 (IDO1); interleukin-6 (IL-6); kynurenine 3-monooxygenase (KMO); kynurenine formamidase isoform X1 (AFMID); and kynurenine--oxoglutarate transaminase 3 (KYAT3).

7.1.2. Results

[0550] LPS injection led to a time-dependent increase of quinolinic acid in endotoxemic animals (**FIG. 1A**, **FIG. 1B**) compared to the basal condition (T0). CER-001 treatment was able to reverse LPS effects, as shown by essentially unchanged quinolinic acid levels, both at one dose of 20 mg/kg (**FIG. 1A**, "20 mg") and two doses of 20 mg/kg each, 40 mg/kg total (**FIG. 1B**, "40 mg"). One of the three pigs in the 20 mg/kg group had a time dependent increase in quinolinic acid at T3 and T6. All ten pigs in the experimental groups had quinolinic acid levels at the end of the experiment that were essentially at baseline. **FIG. 1C** graphically summarizes the results observed for the three groups. *, $p < 0.05$ vs LPS.

[0551] LPS injection also led to a time-dependent increase of kynurenic acid in two of three endotoxemic animals (**FIG. 2A**, **FIG. 2B**) compared to the basal condition (T0). CER-001 treatment was able to reverse LPS effects, as shown by essentially unchanged kynurenic acid levels, both at one dose of 20 mg/kg (**FIG. 2A**, "20 mg") and two doses of 20 mg/kg each, 40 mg/kg total (**FIG. 2B**, "40 mg"). All ten pigs in the experimental groups had kynurenic acid levels at the end of the experiment that were essentially at baseline. **FIG. 2C** graphically summarizes the results observed for the three groups. *, $p < 0.05$ vs LPS for the 40 mg group.

[0552] LPS injection also led to a time-dependent decrease of Trp in endotoxemic animals (**FIG. 3A**, **FIG. 3B**) compared to the basal condition (T0). CER-001 treatment was able to reverse LPS effects, as shown by either no decrease or an increase in Trp levels, both for the 20 mg/kg group (**FIG. 3A**, "20 mg") and the 2x20 mg/kg group (**FIG. 3B**, "40 mg"). All ten pigs in the experimental groups had Trp levels at the end of the experiment that were essentially at or above baseline. **FIG. 3C** graphically summarizes the results observed for the three groups. *, $p < 0.05$ vs LPS for the 20 mg group; **, $p < 0.-05$ vs LPS for the 40 mg group.

[0553] LPS injection also led to a time-dependent increase of Kyn in endotoxemic animals (**FIG. 4A**, **FIG. 4B**) compared to the basal condition (T0). CER-001 treatment was able to reverse LPS effects, as shown by essentially unchanged Kyn levels for some pigs, both for the 20 mg/kg group (**FIG. 4A**, "20 mg," 1 of 2 animals) and the 2x20 mg/kg group (**FIG. 4B**, "40 mg", 5 of 6 animals). In total, six of eight pigs in the experimental groups for which Kyn levels were determined had Kyn levels at the end of the experiment that were essentially at baseline. **FIG. 4C** graphically summarizes the results observed for the three groups. *, $p < 0.05$ vs the 40 mg group for the 20 mg group; **, $p < 0.005$ vs LPS.

[0554] **FIG. 5A** summarizes Kyn:Trp ratios observed for the three groups. *, $p < 0.05$ vs the 40 mg group for the 20 mg group; **, $p < 0.005$ vs LPS. **FIG. 5B** summarizes Kyn:Trp ratios observed for the three groups in a second set of pigs (LPS, n = 5; 20 mg, n = 6; 40 mg, n = 3).

[0555] **FIG. 6A** shows fold gene expression ($2^{-\Delta\Delta Ct}$) of indoleamine 2,3-dioxygenase 1 (IDO1) in brain tissue relative to the housekeeping gene, as determined by qPCR for cohorts from all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg. IDO1 catalyzes the conversion of tryptophan to formylkynurenine. In brain tissue from the LPS cohort, roughly 2-fold greater expression of IDO1 was seen relative to the housekeeping gene, compared to essentially unchanged expression of IDO1 in the 20 mg and 40 mg CER-001 cohorts. *, $p < 0.05$ vs. LPS for 20 mg and 40 mg groups.

[0556] **FIG. 6B** shows relative fold gene expression of aromatic-L-amino-acid/L-tryptophan decarboxylase (DDC) in brain tissue as determined by qPCR for cohorts from all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg. DDC catalyzes the conversion of tryptophan to serotonin. CER-001 led to increased expression of DDC in both test groups. *, $p < 0.05$ vs. LPS for 40 mg group.

[0557] **FIG. 6C** shows relative fold gene expression of kynurenine formamidase isoform X1 (AFMID) in brain tissue as determined by qPCR for cohorts from all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg. AFMID catalyzes the conversion of formylkynurenine to kynurenine. CER-001 partially reversed an increase in AFMID expression induced by LPS.

[0558] **FIG. 6D** shows relative fold gene expression of kynurenine 3-monooxygenase (KMO) in brain tissue as determined by qPCR for cohorts from all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg. KMO catalyzes the conversion of kynurenine to 3-hydroxykynurenine. CER-001 partially reversed an increase in KMO expression induced by LPS. . *, $p < 0.05$ vs. LPS for 40 mg group.

[0559] **FIG. 6E** shows relative fold gene expression of kynurenine--oxoglutarate transaminase 3 (KYAT3) in brain tissue as determined by qPCR for cohorts from all three groups of endotoxemic pigs: LPS, 20 mg, and 40 mg. KYAT3 catalyzes the conversion of 3-hydroxykynurenine to xanthurenic acid. CER-001 partially reversed an increase in KYAT3 expression induced by LPS.

[0560] **FIG. 6F** shows relative fold gene expression of interleukin-6 (IL-6) in brain tissue as determined by qPCR for cohorts from all three groups of endotoxemic pigs: LPS, 20g, and 40 mg. CER-001 partially reversed an increase in IL-6 expression induced by LPS.

[0561] This preclinical data indicates that CER-001 treatment reduces kynurenine pathway dysfunction, by increasing tryptophan levels, decreasing levels of kynurenine pathway products quinolinic acid, kynurenic acid, and kynurenine, and decreasing the kynurenine/tryptophan ratio, and reversing an increase in IDO1 expression and increasing DDC expression (expected to lead to increased serotonin levels and decreased levels of formylkynurenine and subsequent kynurenine pathway biomarkers). Kynurenine pathway activity is associated with various diseases and conditions, including sepsis-induced cognitive deficiency ("brain fog").

7.2. Example 2: Randomized pilot study comparing short-term CER-001 infusions at different doses to prevent sepsis-induced acute kidney injury

[0562] Currently, there are no approved treatments for sepsis-related AKI. Considering that the inflammatory response to endotoxemia is a major cause for hemodynamic destabilization and progression to AKI in septic patients, the main objective of the study was to investigate whether the use of CER-001 at different doses in combination with standard of care (SOC) treatment was safe and

effective, providing a new strategy to treat septic patients, reducing the inflammatory response and preventing the progression to AKI. Without being bound by theory, the anticipated mechanism of action is two-fold, comprising both the binding of endotoxin by CER-001 and a direct anti-inflammatory effect of CER-001.

[0563] The study reported in this example included 20 patients with gram-negative sepsis who were at high risk for acute kidney injury due to high levels of endotoxin activity and decline in function of one or more organ systems. Patients received either standard of care treatment alone, or in combination with one of three dosage regimens of CER-001 (five patients per group), to investigate whether the use of CER-001 at different doses, in combination with standard of care (SOC) treatment, was safe and effective, providing a potential new strategy to treat septic patients, reducing the inflammatory response to endotoxin and preventing the progression to AKI according to KDIGO (Kidney Disease: Improving Global Outcomes) criteria, as well as safety and tolerability of the dosage regimens in order to select the optimal dose of CER-001.

[0564] One of the metabolic characteristics of bacterial (like sepsis) or virus infections (like SARS-CoV-2) is the strong decrease of circulating lipoprotein and particularly the High-Density Lipoprotein (HDL) with its main containing protein apolipoprotein A-I (ApoA-I). As an example, ApoA-I level was recently described as the biomarker predictive of long-term mortality after surgical sepsis.

[0565] One aim of the study was to restore, using CER-001, the ApoA-I levels to reestablish all the functionality of this individualized biomarker, leading to benefit in sepsis pathology.

7.2.1. Study Protocol

[0566] *Study population:* This was a single-center, randomized, dose-ranging (phase II) study including patients with sepsis due to intra-abdominal cavity infection or urosepsis, admitted at the Intensive Care Unit (ICU) of the participating center. The investigators ensured that all patients meeting the following inclusion and exclusion criteria were offered enrollment in the study.

[0567] *Inclusion criteria:*

- Male or non-pregnant female adult ≥18 years of age at time of enrollment;
- Meets Sepsis 3 criteria, defined as an acute increase of at least 2 points in SOFA Score relative to the SOFA score upon admission;
- Endotoxin level (measured by Endotoxin Activity Assay (EEA™); Spectral Medical) >0.6 (see, Marshall *et al.*, 2004, J Infect Dis. 190(3):527-34);
- Signed and dated informed consent by the patient itself or by a legal representative.

[0568] *Exclusion Criteria:*

- Patients weighing more than 100 kg;
- Alanine transaminase/aspartate transaminase (ALT/AST) > 5 times the upper limit of normal;
- Stage 4 severe chronic kidney disease or requiring dialysis (i.e. estimated glomerular filtration rate (eGFR) < 30 ml /min/1.73 m^2);
- Leukocytes<2.0×10^9;
- Pregnancy or breast feeding;
- Undergone organ transplantation during the past one year;
- Anticipated transfer to another hospital, which was not a study site, within 72 hours;

- Terminally ill, including metastases or hematological malignancy, with a life expectancy less than 30 days (as assessed by the attending physician) or had been classified as "Do Not Resuscitate";
- Previous history of end stage chronic organ failure(s);
- Diagnosed with HIV;
- Uncontrolled hemorrhage within the last 24 h;
- Patients who have used an investigational drug or device within 30 days of the first dose of CER-001.

[0569] *Number of subjects:* Twenty subjects were enrolled and randomized (1:1:1:1) into four experimental groups, Groups A-D, defined below. Baseline characteristics of the subjects are summarized in the following table:

Sub.	Sex/ Age	Underlying Condition	SOFA Score	Organ Systems Affected	Mech. Ventilation	Vaso-pressors	Lactate	P/F Ratio	Creatinine
1	M/53	Perforated duodenal ulcer	6	Respiratory, Coagulation, Cardiovascular	Yes	Yes	3.8	99	0.82
2	M/82	Urinary tract infection	5	Cardiovascular, Renal	No	No	0.6	510	5.69
3	F/34	Urinary tract infection	2	Renal	No	No	0.8	443	2.34
4	M/67	Urinary tract infection	3	Respiratory, Coagulation, Renal	No	No	1	300	1.72
5	F/22	Urinary tract infection	2	Respiratory	No	No	1.1	243	0.7
6	F/41	Urinary tract infection	2	Renal	No	No	0.9	414	1.79
7	M/25	Septic shock following abdominal trauma with gastric bleeding	7	Respiratory, Cardiovascular	Yes	Yes	0.9	222	0.61
8	M/79	Post-surgical infection	10	Respiratory, Cardiovascular, CNS, Renal	Yes	Yes	3.5	190	1.43
9	M/74	Urinary tract infection	3	Respiratory, Renal	No	No	0.8	338	3.45
10	M/66	Urinary tract infection	2	Respiratory, Cardiovascular	No	No	0.6	371	0.6

Sub.	Sex/ Age	Underlying Condition	SOFA Score	Organ Systems Affected	Mech. Ventilation	Vaso-pressors	Lactate	P/F Ratio	Creatinine
11	M/53	Pseudomonas + blood cultures (Post-apheresis)	2	Respiratory, Coagulation	No	No	1.4	331	0.9
12	M/63	Urinary tract infection	13	Respiratory, Hepatic, Cardiovascular, CNS, Renal	Yes	Yes	11.3	133	3
13	M/60	Septic shock following colon surgery	10	Respiratory, Cardiovascular, CNS, Renal	Yes	Yes	3.2	240	2.23
14	F/59	Urinary tract infection	6	Respiratory, Coagulation, Renal	No	No	0.4	333	3.6
15	F/61	Nosocomial lung, urinary and blood infections following brain hemorrhage	15	Respiratory, Coagulation, Hepatic, CNS, Renal	Yes	Yes	0.8	304	1.27
16	F/63	Urinary tract infection	3	Renal	No	No	0.6	367	4.8
17	M/59	Sepsis with history of renal graft	6	Respiratory, Coagulation, Renal	Yes	No	2.6	277	3.83
18	F/61	Prolonged nosocomial urinary tract and blood infections	6	Respiratory, Coagulation	No	No	0.7	223	0.8
19	M/71	Septic shock with positive blood cultures	14	Respiratory, Coagulation, Hepatic, Neurologic, Renal	Yes	No	4.1	130	3.6

Sub.	Sex/ Age	Underlying Condition	SOFA Score	Organ Systems Affected	Mech. Ventilation	Vaso-pressors	Lactate	P/F Ratio	Creatinine
20	M/45	Necrotizing pancreatitis	16	Coagulation, Hepatic, Cardiovascular, Neurologic, Renal	Yes	Yes	2.3	447	2.15

[0570] The subject populations had the following baseline clinical and demographic characteristics.

Intervention	**SOC group n=5**	**CER-001 group n=15**	**p-value**
Age (years), mean (SD)	59 (10.29)	56.6 (18.63)	0.789
Male gender, n (%)	2 (40%)	4 (26.4%)	0.573
Site of infection/sepsis, n(%)			
Urine	4 (80%)	7 (46.7%)	
Intra-abdominal	0	6 (40%)	0.238
Other	1 (20%)	2 (13.3%)	
Hospital Unit, n(%)			
Intensive Care Unit	2 (40%)	7 (46.7%)	0.795
Nephrology	3 (60%)	8 (53.3%)	
SOFA score, mean (SD)	6.6 (6.07)	6.07 (4.62)	0.830
Arterial pressure, mean (SD)	85.8 (9.73)	81 (14.22)	0.495
Vasopressors use, n(%)	1 (20%)	5 (33.3%)	0.573
Mechanical Ventilation, n(%)	2 (40%)	6 (40%)	1
Acute Kidney Injury (AKI), n(%)	3 (60%)	8 (53.3%)	0.795
Renal Replacement Therapy (RRT), n(%)	1 (20%)	2 (13.3%)	0.717

[0571] *Duration of study*: This study was completed in 24 weeks (6 months). The enrolment period was approximately 20 weeks (5 months) from the first subject enrolled. The end of the study was the last visit of the last subject.

[0572] *Primary endpoint*: The co-primary endpoints of the study were (1) to define the safety and the optimal dose of CER-001 in combination with standard of care in patients with sepsis sustained by Gram negative bacteria, (2) to determine the onset of AKI according to KDIGO criteria, and (3) to determine the severity of AKI according to KDIGO criteria.

[0573] *Secondary endpoint:* Secondary endpoints were:

- Change in endotoxin and IL-6 levels from baseline to Day 3, Day 6 and Day 9.
- Baseline is defined as the last measurements taken prior to dosing on Day 1.
- Change in the SOFA score (Vincent *et al.* 1996, Intensive Care Med, 22:707–710) from baseline to Day 3, Day 6 and Day 9.
- Changes to the key inflammatory markers (CRP, D-dimer, Ferritin, IL-8, GM-CSF, MCP 1 and TNF-α) from baseline to Day 3, Day 6 and Day 9.
- Changes in AKI biomarkers and onset of AKI according to KDIGO criteria (Kidney Disease Improving Global Outcomes. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplements 2012; 2: 1–138)
- Mortality at Day 30

[0574] *Intervention/exposure*: Twenty patients meeting the eligibility criteria, who signed and dated an ethical committee (EC)-approved informed consent form, were randomized and assigned (1:1:1:1) ratio to conventional therapy (Group A), low dose CER-001 (Group B) or medium dose CER-001 (Group C) or high dose CER-001 (Group D). Conventional therapy was modulated according to the clinical conditions. All non-experimental treatments were allowed to be administered concomitantly during the patient's participation in this study: any medication the patient took, other than study drugs specified per protocol, was considered a concomitant medication and was recorded in the study records.

[0575] Each patient was identified at the screening by a patient number. Once assigned to a patient, the patient number was not reused. The investigators that enrolled patients did not participate in randomization and allocation assignment. The randomization list divided into blocks was adequately concealed to prevent attempts at subversion of randomization.

[0576] *Treatment group:* All patients received conventional therapy. Treated groups received an additional therapy with the study drugs. In particular:

- **Group A:** Conventional therapy (i.e., antibiotic treatments and hemodynamic support according to patient's conditions).
- **Group B:** Conventional therapy + CER-001 5 mg/kg BID for 3 consecutive days, followed by 5 mg/kg BID on Day 6.
- **Group C:** Conventional therapy + CER-001 10 mg/kg BID for 3 consecutive days, followed by 10 mg/kg BID on Day 6.
- **Group D:** Conventional therapy + CER-001 20 mg/kg BID for 3 consecutive days, followed by 20 mg/kg BID on Day 6.

[0577] **FIG. 7** summarizes the study regimen.

[0578] Patients were pretreated with antihistamine prior to each CER-001 dose (*e.g.* dexchlorpheniramine 5 mg or hydroxyzine 100 mg) to avoid any potential infusion reactions.

[0579] *Statistical analysis:* Comparison between groups was performed using the appropriate statistical tests: dichotomous variables (baseline characteristics, mortality, development of AKI) were compared by the use of Chi-square or Fisher's exact test, continuous baseline characteristics by ANOVA or Kruskall-Wallis test, t Student or Mann-Whitney U test, as appropriate. Changes in inflammatory markers were compared between groups by ANOVA and were graphically represented. Proportion of patients of AKI and mortality rate were calculated for each group. All analyses were performed using SPSS 12.0 for Windows; $p<0.05$ was considered statistically significant.

[0580] *Procedures:* The following procedures were performed during the screening visit. Following randomization, subjects initiated treatment within 2 business days.

- Informed consent
- Medical history - included: recording past and present illnesses and collection of the subject's demographic data (birth date, sex, and race).
- Physical examination with a review of systems, height and weight, BMI and wait circumference
- Vital signs (pulse, blood pressure, and oral, auricular, axillary, or core temperature).
- Review of inclusion/exclusion criteria.
- Adverse events were recorded starting from the time informed consent is obtained.
- Prior medications were collected from 4 weeks before the first dose of test article. All current medications were recorded.
- Complete blood count (CBC) – included white blood cell count (WBC) with differential, platelet count, red blood cell count (RBC), hemoglobin (Hb), hematocrit (Hct).
- Fasting chemistry panel/electrolytes: included sodium, potassium, chloride, blood urea nitrogen (BUN; or urea), serum creatinine, calculated clearance creatinine (CKD-EPI), glucose, calcium, phosphorus, total protein, uric acid, AST, ALT, γ GT, ALP, total and direct bilirubin, albumin, total cholesterol, HDL, LDL, triglycerides, LDH, CPK,
- ABG (for assessing respiratory and/or metabolic disorders)
- ApoA-I (for pharmacokinetic and pharmacodynamic assessment)
- Coagulation tests – included prothrombin time (PT) (expressed as international normalized ratio [INR]), and partial thromboplastin time (PTT).
- Urinalysis – included specific gravity, pH, assessment of protein/albumin, glucose, ketones, and hemoglobin/blood.
- Microalbuminuria and Proteinuria g/24 h
- Serum or urine pregnancy test (for women of childbearing potential) within 7 days before randomization.
- Pharmacokinetic and pharmacodynamic assessment included ApoA-I and total cholesterol levels.

- Endotoxin levels were measured using the EAA™ kit. AKI Biomarkers (TIMP-2 and IGFBP-7) are measured using the Nephrocheck® kit. Inflammatory markers include: CRP, D-dimer, Ferritin, IL-6, IL-8, GM-CSF, MCP 1 and TNF-α.

[0581] In addition to biological samples collected for the daily routine laboratory assessments performed at the Central laboratory, biological samples for research purposes were collected, including:

- 2 tubes 5 ml of serum
- 1 tube 3ml of plasma
- urine 30ml

[0582] These samples were used to assess additional inflammatory cytokines and urinary biomolecules in order to obtain a more comprehensive characterization of patients enrolled, to better evaluate response to treatment, to provide more information in the follow-up and more importantly, to discover new potential biomarkers that could be useful for early diagnosis of sepsis-induced AKI. The analysis was performed by ELISA test and protein arrays.

[0583] *On therapy visits (Treatment period)*: Treatment period was defined as from the start of treatment. The visit was planned at Day 3, Day 6 and Day 9. A final visit was planned on Day 30. The following procedures were performed during the therapy visits:

- Recording of adverse events and concomitant medications
- Review of appropriate laboratory information
- Physical examination
- Vital signs (pulse, blood pressure and oral, auricular, axillary, or core temperature) were assessed
- Record adverse events and concomitant medications continually
- Complete blood count (CBC) – included white blood cell count (WBC) with differential, platelet count, red blood cell count (RBC), hemoglobin (Hb), hematocrit (Hct).
- Fasting chemistry panel/electrolytes: includes sodium, potassium, chloride, blood urea nitrogen (BUN; or urea), serum creatinine, calculated clearance creatinine (CKD-EPI),
- glucose, calcium, phosphorus, total protein, uric acid, AST, ALT, □GT, ALP, total and direct bilirubin, albumin, total cholesterol, HDL, LDL, triglycerides, LDH, CPK
- ABG (for assessing respiratory and/or metabolic disorders)
- ApoA-I (for pharmacokinetic and pharmacodynamic assessment)
- Coagulation tests – included prothrombin time (PT) (expressed as international normalized ratio [INR]), and partial thromboplastin time (PTT).
- Urinalysis – included specific gravity, pH, assessment of protein/albumin, glucose, ketones, and hemoglobin/blood.
- Microalbuminuria and Proteinuria g/24 h
- Serum or urine pregnancy test (for women of childbearing potential) within 7 days before randomization.
- Pharmacokinetic and pharmacodynamic assessment included ApoA-I and total cholesterol levels.

- Endotoxin levels were measured using the EAA™ kit. AKI Biomarkers (TIMP-2 and IGFBP-7) were measured using the Nephrocheck® kit. Inflammatory markers included: CRP, D-dimer, Ferritin, IL-6, IL-8, GM-CSF, MCP 1 and TNF-α.

[0584] In addition to biological samples collected for the daily routine laboratory assessments performed at the Central laboratory, biological samples for research purposes were collected, including

- 2 tubes 5 ml of serum
- 1 tube 3ml of plasma
- urine 30ml

[0585] Clinical scores included the SOFA score (Table 2) and the KDIGO criteria for AKI assessment and staging (Table 3). Individual components of each score were documented.

Table 2. The Sequential Organ Failure Assessment (SOFA) score

SOFA Score:	0	1	2	3	4
Respiration					
PaO_2/FIO_2 (mmHg) (P/F ratio)	≥400	<400	<300	<220 and mechanically ventilated	<100 and mechanically ventilated
Coagulation					
Platelets x $10^3/mm^3$	≥150	<150	<100	<50	<20
Liver					
Bilirubin (mg/dL)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	≥12.0
Cardiovascular[a]					
Hypotension	MAP≥70	MAP<70	Dopamine≤5 or dobutamine (any)	Dopamine>5 or norepinephrine≤0.1	Dopamine>15 or norepinephrine>0.1
CNS					
Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal					
Creatinine (mg/dL) or urine output (mL/day)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

MAP = Mean arterial pressure; CNS = central nervous system; SaO_2 = peripheral arterial oxygen saturation

[a]Vasoactive medications administered for at least 1 hr (dopamine and norepinephrine µg/kg/min)

Table 3. KDIGO classification for AKI		
Stage	**Serum creatinine**	**Urine output**
1	1.5 – 1.9 times baseline OR ≥0.3 mg/dl (≥26.5μmol/l) increase	<0.5ml/kg/h for 6-12 hours
2	2.0 – 2.9 times baseline	<0.5ml/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6μmol/l) OR Initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35ml/min per 1.73m^3	<0.3ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

[0586] Table 4 provides a summary of the study protocol of this Example.

Table 4. Overview of study protocol										
		Treatment visits								
		Day 1		**Day 2**		**Day 3**				
Procedure	**Baseline**	**am**	**pm**	**am**	**pm**	**am**	**pm**	**Day 6**	**Day 9**	**Final visit Day 30**
CER-001 Dosing		X	X	X	X	X	X	X		
Endotoxin	X	X		X		X		X	X	X
IL-6	X	X		X		X		X	X	X
Additional Inflammatory Markers[a]	X									X
SOFA Score	X	X		X		X		X	X	X
RIFLE Score	X	X		X		X		X	X	X
ApoA-I and Total Cholesterol		X[b]								
Safety Labs[c]	X									X
Optional samples	X	X		X		X		X	X	X
Concomitant Medication Monitoring	X	X		X		X		X	X	X

Table 4. Overview of study protocol

Procedure	Baseline	Treatment visits								Final visit Day 30
		Day 1		Day 2		Day 3		Day 6	Day 9	
		am	pm	am	pm	am	pm			
Adverse Event Monitoring	X	X		X		X		X	X	X

a) Includes CRP, D-dimer, Ferritin, IL-8,VCAM-1, ICAM-1, GM-CSF, MCP 1 and TNF-α.

b) On dosing days, drawn prior to and 2 hours after the start of each infusion.

c) Tested at local hospital laboratory.

[0587] ***Safety Evaluations:*** Safety evaluations were attained utilizing information collected from the following assessments: physical examination (including weight), vital signs (blood pressure, pulse, temperature), CBC with differential, platelet count, blood chemistries, and fasting lipid profiles [including HDL-cholesterol, LDL-cholesterol and Lipoprotein (a)], urea, glucose, 24 hour urine protein determination, serum creatinine and calculated creatinine clearance (CKD-EPI) and adverse events monitoring. All women of childbearing potential had a qualitative serum pregnancy test during pre-study screening/baseline evaluation and subsequently, if clinically indicated. Patients were monitored throughout the study for the occurrence of adverse events, that were recorded. Adverse events volunteered by the subject or discovered as a result of general questioning by the investigator or by physical examination were recorded. The duration (start and end dates), severity, cause and relationship to study medication, patient outcome, action taken, and an assessment of whether the event was serious were recorded for each reported adverse event.

7.2.2. Results

7.2.2.1. Lipopolysaccharides (LPS)

[0588] **FIG. 8A-FIG. 8F** show lipopolysaccharide (LPS) changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 8A**: LPS changes from baseline for Group A and aggregated Groups B-D. **FIG. 8B**: LPS changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 8C**: LPS changes, reported as a percentage relative to peak LPS levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p<0.0005$. **FIG. 8D**: LPS changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 8E**: LPS changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 8F**: LPS changes from baseline for each subject in each of Groups A-D. LPS levels were measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p>0.05$).

[0589] Generally, treatment regimens providing 5 mg/kg, 10 mg/kg, or 20 mg/kg CER-001 in addition to the SOC reduced LPS more than the SOC alone. Significant or near-significant results are summarized in the following table:

Treatment Effect	Overall	Day 3	Day 6	Day 9
CER-001 vs SOC	p=0.0011	p=0.0494	p=0.0473	p=0.0039
Treatment Groups	p=0.0124			
SOC vs 5		p=0.0567	NS	p=0.0405
SOC vs 10		p=0.0401	p=0.0757	p=0.0329
SOC vs 20		p=0.0790	p=0.0126	p=0.0070
5 vs 10		NS	NS	NS
5 vs 20		NS	p=0.0363	NS
10 vs 20		NS	NS	NS

[0590] Consistent with animal data and the observed ApoA-I increase, treatment with CER-001 significantly decreased LPS bloodstream concentrations compared to SOC subjects (**FIG. 8E**). This observation reinforces the hypothesis of a positive impact of decreasing LPS on clinical outcomes. However, other studies highlighted the need to extend such a hypothesis beyond simply LPS removal (Monard *et al.*, 2023, *Critical Care* 27(1):36; Cavaillon *et al.*, 2020, *EMBO Molecular Medicine* 12(4)). Indeed, a pleiotropic effect including LPS decrease/inactivation and inhibition of cytokine storm cascade and/or endothelial dysfunction could have strong biochemical and clinical impacts. Without being bound by theory, it is believed that CER-001 not only decreases LPS level in animals and humans, but also has a direct interaction with the immune system through ApoA-I and also provides endothelial protection.

7.2.2.2. Endotoxin Activity Assay (EAA)

[0591] **FIG. 9A-FIG. 9D** show endotoxin activity assay (EAA) changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 9A**: EAA changes from baseline for Group A and aggregated Groups B-D. **FIG. 9B**: EAA changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 9C**: EAA changes, reported as a percentage relative to peak EAA levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p<0.1769$. **FIG. 9D**: EAA changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 9E**: EAA changes from baseline for Group A and aggregated Groups B-D. EAA was performed at each timepoint using commercial kits (Spectral Medical, Toronto, Canada). Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p>0.05$).

[0592] Generally, treatment regimens providing 10 mg/kg CER-001 in addition to the SOC reduced EAA more than the SOC alone. Significant or near-significant results are summarized in the following table:

Treatment Effect	Overall	Day 3	Day 6	Day 9
CER-001 vs SOC	NS	NS	p=0.0590	NS

Treatment Groups	NS			
SOC vs 5		NS	NS	NS
SOC vs 10		NS	p=0.0468	NS
SOC vs 20		NS	NS	NT
5 vs 10		NS	NS	NS
5 vs 20		NS	NS	NT
10 vs 20		NS	NS	NT

7.2.2.3. TNF-α

[0593] **FIG. 10A-FIG. 10F** show TNF-α changes for the standard of care group (Group A) and the experimental groups (Groups B-D) measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p>0.05$). **FIG. 10A**: TNF-α changes from baseline for Group A and aggregated Groups B-D. **FIG. 10B**: TNF-α changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 10C**: TNF-α changes, reported as a percentage relative to peak TNF-α levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p<0.0004$. **FIG. 10D**: TNF-α changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 10E**: TNF-α changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 10F**: TNF-α changes from baseline for each subject in each of Groups A-D.

[0594] Generally, treatment regimens providing 10 mg/kg CER-001 in addition to the SOC reduced TNF-α more than the SOC alone.

7.2.2.4. MCP-1

[0595] **FIG. 11A-FIG. 11F** show MCP-1 changes for the standard of care group (Group A) and the experimental groups (Groups B-D) measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p>0.05$). **FIG. 11A**: MCP-1 changes from baseline for Group A and aggregated Groups B-D. **FIG. 11B**: MCP-1 changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 11C**: MCP-1 changes, reported as a percentage relative to peak MCP-1 levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p<0.0090$. **FIG. 11D**: MCP-1 changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 11E**: MCP-1 changes from baseline for Group A and aggregated Groups B-D. **FIG. 11F**: MCP-1 changes from baseline for each subject in each of Groups A-D.

7.2.2.5. Interleukin-6 (IL-6)

[0596] **FIG. 12A-FIG. 12F** show IL-6 changes for the standard of care group (Group A) and the experimental groups (Groups B-D) measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p>0.05$).. **FIG. 12A**: IL-6 changes from baseline for Group A and aggregated Groups B-D. **FIG. 12B**: IL-6 changes from baseline for Group A, Group B, Group C,

and Group D. **FIG. 12C**: IL-6 changes, reported as a percentage relative to peak IL-6 levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was p<0.0037. **FIG. 12D**: IL-6 changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 12E**: IL-6 changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 12F**: IL-6 changes from baseline for each subject in each of Groups A-D.

[0597] Generally, treatment regimens providing CER-001 in addition to the SOC, and particular CER-001 at 10 mg/kg, reduced IL-6 more than the SOC alone. Significant or near-significant results are summarized in the following table:

Treatment Effect	**Overall**	**Day 3**	**Day 6**	**Day9**
CER-001 vs SOC	p=0.0309	p=0.0329	NS	p=0.0290
Treatment Groups	NS			
SOC vs 5		NS	NS	NS
SOC vs 10		p=0.0304	NS	NS
SOC vs 20		NS	NS	NS
5 vs 10		NS	NS	NS
5 vs 20		NS	NS	NS
10 vs 20		NS	NS	NS

7.2.2.6. Interleukin-8 (IL-8)

[0598] **FIG. 13A-FIG. 13F** show IL-8 changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 13A**: IL-8 changes from baseline for Group A and aggregated Groups B-D measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: p>0.05). **FIG. 13B**: IL-8 changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 13C**: IL-8 changes, reported as a percentage relative to peak IL-8 levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was p<0.0001. **FIG. 13D**: IL-8 changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 13E**: IL-8 changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 13F**: IL-8 changes from baseline for each subject in each of Groups A-D.

[0599] Generally, treatment regimens providing CER-001 in addition to the SOC reduced IL-8 more than the SOC alone. Significant or near-significant results are summarized in the following table:

Treatment Effect	**Overall**	**Day 3**	**Day 6**	**Day9**
CER-001 vs SOC	p=0.0453	p=0.0523	p=0.0040	p=0.0305
Treatment Groups	p=0.0681			

SOC vs 5		p=0.0525	p=0.0671	
SOC vs 10		p=0.0594	p=0.0197	p=0.0851
SOC vs 20			p=0.0476	p=0.0488
5 vs 10		NS	NS	NS
5 vs 20		NS	NS	NS
10 vs 20		NS	NS	NS

7.2.2.7. Interleukin-10 (IL-10)

[0600] **FIG. 14A-FIG. 14D** show IL-10 changes for the standard of care group (Group A) and the experimental groups (Groups B-D) measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p>0.05$). **FIG. 14A**: IL-10 changes from baseline for Group A and aggregated Groups B-D. **FIG. 14B**: IL-10 changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 14C**: IL-10 changes, reported as a percentage relative to peak IL-10 levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p<0.3780$. **FIG. 14D**: IL-10 changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center.

7.2.2.8. TREM-1

[0601] **FIG. 15A-FIG. 15F** show TREM-1 changes for the standard of care group (Group A) and the experimental groups (Groups B-D) measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p>0.05$). **FIG. 15A**: TREM-1 changes from baseline for Group A and aggregated Groups B-D. **FIG. 15B**: TREM-1 changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 15C**: TREM-1 changes, reported as a percentage relative to peak TREM-1 levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p<0.0003$. **FIG. 15D**: TREM-1 changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 15E**: TREM-1 changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 15F**: TREM-1 changes from baseline for each subject in each of Groups A-D.

[0602] Generally, treatment regimens providing CER-001 in addition to the SOC reduced TREM-1 more than the SOC alone. Significant or near-significant results are summarized in the following table:

Treatment Effect	**Overall**	**Day 3**	**Day 6**	**Day9**	**Day 30**
CER-001 vs SOC	p=0.0103	p=0.0218	p=0.0382	p=0.0001	p=0.0005
Treatment Groups	p=0.0903				
SOC vs 5		p=0.0229	p=0.0600	p=0.0199	p=0.0199
SOC vs 10		p=0.0653	NS	p=0.0831	p=0.0831
SOC vs 20		NS	NS	p=0.0357	p=0.0357

5 vs 10		NS	NS	NS	NS
5 vs 20		NS	NS	NS	NS
10 vs 20		NS	NS	NS	NS

7.2.2.9. VCAM and ICAM

[0603] **FIG. 16A-FIG. 16F** show VCAM changes for the standard of care group (Group A) and the experimental groups (Groups B-D) measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p>0.05$). **FIG. 16A**: VCAM changes from baseline for Group A and aggregated Groups B-D. **FIG. 16B**: VCAM changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 16C**: VCAM changes, reported as a percentage relative to peak VCAM levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p<0.0001$. **FIG. 16D**: VCAM changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 16E**: VCAM changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 16F**: VCAM changes from baseline for each subject in each of Groups A-D.

[0604] Generally, treatment regimens providing CER-001 in addition to the SOC reduced VCAM more than the SOC alone. Significant or near-significant results are summarized in the following table:

Treatment Effect	**Overall**	**Day 3**	**Day 6**	**Day9**
CER-001 vs SOC	p=0.0090	NS	p=0.0520	p=0.0510
Treatment Groups	p=0.0870			
SOC vs 5		NS	p=0.0687	p=0.0805
SOC vs 10		NS	p=0.0556	p=0.0558
SOC vs 20		NS	p=0.0646	NS
5 vs 10		NS	NS	NS
5 vs 20		NS	NS	NS
10 vs 20		NS	NS	NS

[0605] **FIG. 17A-FIG. 17F** show ICAM changes for the standard of care group (Group A) and the experimental groups (Groups B-D) measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p>0.05$). **FIG. 17A**: ICAM changes from baseline for Group A and aggregated Groups B-D. **FIG. 17B**: ICAM changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 17C**: ICAM changes, reported as a percentage relative to peak ICAM levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p<0.0001$. **FIG. 17D**: ICAM changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 17E**:

ICAM changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 17F**: ICAM changes from baseline for each subject in each of Groups A-D.

[0606] Generally, treatment regimens providing CER-001 in addition to the SOC reduced ICAM more than the SOC alone. Significant or near-significant results are summarized in the following table:

Treatment Effect	**Overall**	**Day 3**	**Day 6**	**Day9**
CER-001 vs SOC	p=0.0015	NS	p=0.0020	p=0.0003
Treatment Groups	p=0.0127			
SOC vs 5		p=0.0552	p=0.0056	p=0.0454
SOC vs 10		NS	p=0.0213	p=0.0329
SOC vs 20		p=0.0831	p=0.0087	p=0.0023
5 vs 10		NS	NS	NS
5 vs 20		NS	NS	NS
10 vs 20		NS	NS	NS

7.2.2.10. Ferritin

[0607] **FIG. 18A-FIG. 18D** show ferritin changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 18A**: ferritin changes from baseline for Group A and aggregated Groups B-D. **FIG. 18B**: ferritin changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 18C**: ferritin changes, reported as a percentage relative to peak ferritin levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p<0.0962$. **FIG. 18D**: ferritin changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center.

7.2.2.11. White Blood Cells

[0608] **FIG. 19A-FIG. 19D** show white blood cell count changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 19A**: white blood cell count changes from baseline for Group A and aggregated Groups B-D. **FIG. 19B**: white blood cell count changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 19C**: white blood cell count changes, reported as a percentage relative to peak white blood cell counts (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p=0.5492$. **FIG. 19D**: white blood cell count changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center.

7.2.2.12. C-Reactive Protein

[0609] **FIG. 20A-FIG. 20F** show CRP changes for the standard of care group (Group A) and the experimental groups (Groups B-D). Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p>0.05$). **FIG. 20A**: CRP changes from baseline for Group A and aggregated Groups B-D. **FIG. 20B**: CRP changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 20C**:

CRP changes, reported as a percentage relative to peak CRP levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was p<0.6446. **FIG. 20D**: CRP changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 20E**: CRP changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 20F**: CRP changes from baseline for each subject in each of Groups A-D.

7.2.2.13. KIM-1

[0610] **FIG. 21A-FIG. 21D** show KIM-1 changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 21A**: KIM-1 changes from baseline for Group A and aggregated Groups B-D. **FIG. 21B**: KIM-1 changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 21C**: KIM-1 changes, reported as a percentage relative to peak KIM-1 levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was p<0.0001. **FIG. 21D**: KIM-1 changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center.

7.2.2.14. Serum Albumin

[0611] **FIG. 22A-FIG. 22D** show serum albumin changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 22A**: serum albumin changes from baseline for Group A and aggregated Groups B-D. **FIG. 22B**: serum albumin changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 22C**: serum albumin changes, reported as a percentage relative to peak serum albumin levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was p=0.1595. **FIG. 22D**: serum albumin changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 22E**: serum albumin changes from baseline for each subject in Group A and aggregated Groups B-D.

[0612] Generally, treatment regimens providing CER-001 in addition to the SOC raised serum albumin more than the SOC alone.

[0613] Significant or near-significant results are summarized in the following table:

Treatment Effect	**Overall**	**Day 3**	**Day 6**	**Day9**
CER-001 vs SOC	NS	NS	p=0.0603	NS
Treatment Groups	NS			
SOC vs 5		NS	NS	NS
SOC vs 10		NS	NS	NS
SOC vs 20		NS	NS	NS
5 vs 10		NS	NS	NS
5 vs 20		NS	NS	NS

10 vs 20		NS	NS	NS

7.2.2.15. Serum Creatinine

[0614] **FIG. 23A-FIG. 23F** show serum creatinine changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 23A**: serum creatinine changes from baseline for Group A and aggregated Groups B-D. **FIG. 23B**: serum creatinine changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 23C**: serum creatinine changes, reported as a percentage relative to peak serum creatinine levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was p=0.1630. **FIG. 23D**: serum creatinine changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 23E**: area under the curve (AUC) (mean ± SEM) for serum creatinine for Group A and aggregated Groups B-D for all subjects, and subject populations from ICU and nephrology intake routes. **FIG. 23F**: AUC (95% confidence interval) for serum creatinine for Group A and aggregated Groups B-D, and subject populations from ICU and nephrology intake routes..

7.2.2.16. Estimated Glomerular Filtration Rate (eGFR)

[0615] **FIG. 24A-FIG. 24B** show eGFR changes for all subjects in the standard of care group (Group A) and the experimental groups (Groups B-D). Estimated GFR was determined by CKD-EPI. **FIG. 24A**: eGFR changes from baseline for Group A and aggregated Groups B-D. **FIG. 24B**: eGFR changes from baseline for Group A, Group B, Group C, and Group D. **FIG. FIG. 24E** shows eGFR changes, reported as a percentage relative to peak levels (peak = 100%), for Group A and aggregated Groups B-D, for all subjects. The treatment x study day effect relative to peak was p=0.5666.

[0616] **FIG. 24C-FIG. 24D** show eGFR changes for subjects entering the study with AKI. **FIG. 24C** eGFR changes from baseline for Group A and aggregated Groups B-D. **FIG. 24D**: eGFR changes for Group A, Group B, Group C, and Group D. **FIG. FIG. 24F** shows eGFR changes, reported as a percentage relative to peak levels (peak = 100%), for Group A and aggregated Groups B-D, for subjects entering the study with AKI. The treatment x study day effect relative to peak was p=0.2406.

[0617] Significant or near-significant results from **FIG. 24C-FIG. 24D** are summarized in the following table:

Treatment Effect	**Overall**	**Day 3**	**Day 6**	**Day9**
CER-001 vs SOC	NS	NS	NS	NS
Treatment Groups	NS			
SOC vs 5		NS	NS	0.0525
SOC vs 10		NS	NS	NS
SOC vs 20		NT	NT	NT
5 vs 10		NS	NS	NS
5 vs 20		NT	NT	NT

10 vs 20		NT	NT	NT

7.2.2.17. P/F Ratio

[0618] **FIG. 25** shows changes in the P/F ratio for all subjects in the standard of care group (Group A) and aggregated Groups B-D.

7.2.2.18. Days in ICU

[0619] **FIG. 26** shows survival proportions for all subjects after days in ICU for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001").

7.2.2.19. Thirty Day Survival

[0620] **FIG. 27A** shows 30-day survival proportions for all subjects for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001").

[0621] **FIG. 27B** shows 30-day survival proportions for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001").

7.2.2.20. AKI Staging

[0622] **FIG. 28A** shows the evolution of AKI, as assessed by KDIGO staging criteria, for all subjects in the standard of care group (Group A, "SOC"). AKI stages: 0, serum creatinine < 1.5x baseline or increased by less than 0.3 mg/dl within 48 hours, and urine volume > 0.5 ml/kg/h for 6-12 hours; 1, serum creatinine from 1.5 to 1.9x baseline or increased by more than 0.3 mg/dl, or urine volume < 0.5 ml/kg/h for 6-12 hours; 2, serum creatinine from 2.0 to 2.9x baseline or urine volume < 0.5 ml/kg/h for more than 12 hours; 3, serum creatinine 3.0x baseline or more or 4.0 mg/dl or more, or urine output < 0.3 ml/kg/h for more than 24 hours or ≈ 0 for more than 12 hours. About 40% of SOC subjects were at AKI 0 (least severe) and the remainder were at AKI 2-3 (more to most severe) at Day 6.

[0623] **FIG. 28B** shows the evolution of AKI, as assessed by KDIGO staging criteria, for all subjects in aggregated Groups B-D ("CER-001"). About 60% of CER-001 subjects were at AKI 0 and 20% were at AKI 3 at Day 6.

7.2.2.21. Days on Mechanical Ventilation and Vasopressor

[0624] **FIG. 29** shows the number of days on mechanical ventilation for all subjects who entered into the study while in the center's ICU, for the standard of care group (Group A, SOC) and aggregated Groups B-D (CER-001) CER-001 reduced the number of days on mechanical ventilation relative to SOC for 5/7 subject.

[0625] **FIG. 30** shows the number of days on vasopressor for all subjects who entered into the study while in the center's ICU, for the standard of care group (Group A, SOC) and aggregated Groups B-D (CER-001).

7.2.2.22. Days on Dialysis

[0626] **FIG. 31A** shows the number of days on dialysis for all subjects who entered into the study while in the center's ICU, for the standard of care group (Group A) and aggregated Groups B-D. **FIG. 31B** shows this result for all subjects. Both intermittent and continuous modalities were considered. A reduction in the number of days of dialysis is indicative of improved kidney function.

7.2.2.23. Days Alive Without Organ Support, Days Until ICU Discharge, and Changes in Hemodynamics

[0627] **FIG. 32** shows the number of days alive without organ support for all subjects who entered into the study while in the center's ICU, for the standard of care group (SOC) and aggregated Groups B-D (CER-001). Any use of vasopressors, mechanical ventilation, and/or renal support was considered organ support.

[0628] **FIG. 65** shows days until ICU discharge for all subjects who entered the study from the center's ICU, for the standard of care group (SOC) and aggregated Groups B-D (CER-001).

[0629] **FIG. 33A** and **FIG. 33B** show changes in daily average mean arterial pressure (MAP) for all subjects who entered into the study while in the center's ICU, for the standard of care group (SOC) and aggregated Groups B-D (CER-001). Decreases in MAP are generally desirable for ICU subjects.

[0630] **FIG. 34** shows the change in daily average heart rate (HR) for all subjects who entered into the study while in the center's ICU, for the standard of care group (SOC) and aggregated Groups B-D (CER-001). Decreases in MAP are generally desirable for ICU subjects.

[0631] **FIG. 35** shows the change in daily average P/F ratio for all subjects who entered into the study while in the center's ICU, for the standard of care group (SOC) and aggregated Groups B-D (CER-001). Increases in P/F ratio are generally desirable for ICU subjects.

7.2.2.24. Serum ApoA-I

[0632] **FIG. 56A** shows mean ApoA-I levels for the control group and the aggregated study groups in the clinical study of Example 2.

[0633] **FIG. 56** shows mean ApoA-I levels for the control group and the aggregated study group, **FIG. 56B** shows mean ApoA-I levels for the control group and each study group, **FIG. 56** shows ApoA-I changes for each subject in the standard of care group (SOC) and the experimental groups (CER-001), and **FIG. 56** shows changes from baseline of ApoA-I levels for each subject broken out by study group, as measured by ELISA. Serum ApoA-I levels rapidly increased in the first 3 days of treatment in patients receiving CER-001, while the increase in the SOC group was delayed. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p>0.05$).

7.2.2.25. Kynurenine Pathway Markers

[0634] **FIG. 65** shows changes in serum quinolinic acid (QA) levels from baseline (day 1) for subjects in the standard of care (SOC) group (Group A) and aggregated Groups B-D in the clinical study of Example 2.

[0635] **FIG. 67** shows changes in serum kynurenine/tryptophan ratios (Kyn/Trp) levels from baseline (day 1) for subjects in the standard of care (SOC) group (Group A) and aggregated Groups B-D in the clinical study of Example 2.

[0636] **FIG. 68** shows changes in serum serotonin levels from baseline (day 1) for subjects in the standard of care (SOC) group (Group A) and aggregated Groups B-D in the clinical study of Example 2.

7.2.2.26. Additional Results

[0637] Across all subjects, liver enzymes changed by anywhere from about 0.2-fold to about 4-fold of baseline levels after 9 days (**FIG. 57A**, **FIG. 57B**). Subjects receiving CER-001 had comparable changes to liver enzyme levels as the group receiving standard of care only.

[0638] ***Adverse events***: Of the 20 subjects, 9 experienced adverse events, of which 7 were definitely not related to the test article (*i.e.*, the adverse event could be fully explained by the subject's clinical state or other agents/therapies), and 2 were probably not related to the test article (*i.e.*, the adverse event could most likely to be explained by the subject's clinical state or other agents/therapies, rather than the test article).

7.2.3. Conclusions

[0639] Generally, coadministration of CER-001 with the standard of care led to improved scavenging of endotoxins (as shown by the LPS and EAA data), modulation of CRS (most pronounced for IL-6, IL-8, and TREM-1), vascular endothelial protection (as shown by the VCAM and ICAM data), without increasing inflammation or negatively impacting AKI biomarkers or hemodynamics.

[0640] Notably, the trend of endothelial dysfunction markers VCAM and ICAM showed a different trend than ApoA-I among study participants, as their values increased in patients in the SOC group, while they significantly decreased with CER-001 treatment (**FIG. 16E, FIG. 17E**), suggesting an increased vascular protection as these mediators contribute to enhance tubular apoptosis and irreversible mechanisms of renal damage. These effects can be reconciled with the *in vitro* observation of the inhibited eNOS production by endothelial cells by CER-001 discussed in Example 4, thus confirming the positive effect of the ApoA-I complexes on vascular permeability, a hallmark of acute and chronic inflammation.

[0641] Recently the anti-inflammatory capacity of CER-001 was highlighted in a severe COVID-19 patient in ICU where assessment of serum amyloid A-1, inflammatory markers, and cytokines showed predominantly significant decreases during CER-001 infusion (Begue, *et al.*, 2021, *Sci Rep* **11**, 2291). Similarly, the data of this Example showed that CER-001 treatment induced a significant reduction of serum levels of MCP-1, TNF-α, IL-6 and IL-8 in treated-patients compared to SOC group (**FIG. 11E, FIG. 10E, FIG. 12E**, and **FIG. 13E**), suggesting the immunomodulatory and anti-inflammatory effects of CER-001 treatment and its ability to modulate the cytokine storm. Consistent with modulating the cytokine storm, a more pronounced reduction in C-reactive protein (CRP) in the first 9 days in the treated group compared to the SOC group was shown (**FIG. 20E**).

[0642] Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) has been suggested as a strong predictor for poor prognosis and poor survival in septic patients. Persistently high sTREM-1 levels during the first days following ICU admission are associated with mortality in human septic shock (Jolly, *et al.*, 2021, *Cell Mol Immunol* **18**, 2054-2056). The results of this Example suggest that sTREM-1 rapidly decreases with CER-001 treatment within the first 3 days and remains low and stable through at least 30 days (**FIG. 15E**). More importantly, this decrease is accompanied by an amelioration of clinical signs and symptoms. All together, these observations confirm the potential anti-inflammatory effect of the ApoA-I complexes independent of LPS removal. Knowing that HDL and ApoA-I can directly interact with monocytes/macrophages through either receptor interactions such as SR-BI or transporters like ABCA-1 and/or ABCG-1, or by blocking contact-mediated activation of monocytes/macrophages by T

lymphocytes as evidenced by TNF-α decrease (**FIG. 10E**) one can hypothesize a direct cellular effect of HDL and thus CER-001 on such cells leading to a global decrease of cytokine production by a yet unknown mechanism.

[0643] The potential impact of the cytokine cascade and endothelial dysfunction on clinical outcomes was evaluated given the strong effect of CER-001 observed.

[0644] The effects on organ dysfunction were analyzed with the hypothesis that the immunomodulatory effects of CER-001 treatment may limit renal dysfunction. For this purpose, renal function among study participants was analyzed and AKI onset and severity was classified according to KDIGO criteria based on both creatinine and urine output criteria. Overall, a low risk for the onset and/or progression to moderate to severe AKI (AKI stage 2-3) up to day 6 among CER-001 treated patients (26.6%) as compared to SOC group was observed, in which about 60% of patients presented such conditions (**FIG. 28A-FIG. 28B**). These results are consistent with the laboratory and histological data reported in the animal model and confirmed the protective effects of the treatment.

[0645] In addition, the effects of the study drug on liver function were analyzed. As shown in **FIG. 57A-FIG. 57B**, significant alteration of liver enzymes (AST, ALT) among CER-001 subjects were not observed; only 2 patients in the treated group presented a slight and no clinically significant increase in AST and ALT. Conversely, an increase of albumin levels in the CER-001 treated group compared to SOC group was observed (**FIG. 22E**). Overall, these results supported the safety of CER-001 and the possibility that the early and sustained effects of the treatment on the inflammatory status may improve liver function and increase albumin production.

[0646] The effects of the study drug on serum levels of kynurenine pathway markers were also investigated. As shown in **FIG. 66**, subjects receiving the standard of care had a slight increase in serum quinolinic acid (QA) levels over the 30-day study period. In contrast, CER-001 lowered QA levels from baseline within three days. The effect was substantially sustained until the end of the study period.

[0647] As shown in **FIG. 67**, similar effects were observed in serum kynurenine/tryptophan ratios (Kyn/Trp). The SOC group had essentially unchanged Kyn/Trp from baseline (day 1) until the end of the study period. The CER-001 groups had a roughly 40% reduction in Kyn/Trp by day 30.

[0648] **FIG. 68** shows serum serotonin levels remained near baseline for subjects in the CER-001 groups during the entire study period. The SOC group experienced a sizable drop of about 40 ng/mL in serum serotonin at day 6 and did not return to baseline levels even by the end of the study period.

[0649] A subset of critically ill patients enrolled in the ICU were focused on to analyze the main clinical outcomes. Although the small sample size (7 treated patients; 2 SOC subjects) limits statistical evaluation, a reduced length of ICU stay among patients in the treatment group was observed (mean days of ICU stay 23.2 vs 29) (**FIG. 65**). In addition, the daily average mean arterial pressure (MAP) during the study period improved after the second day of treatment as compared to SOC subjects with an overall lower days on vasopressors (mean days 6.5 vs 8 in the SOC group) (**FIG. 33B**, **FIG. 30**). Similarly, days on mechanical ventilation (mean days 16.7 vs 26.5) were lower among CER-001 treated patients (**FIG. 29**). Both SOC subjects required dialysis during the study period, while only 3 of 7 CER-001 treated patients did (**FIG. 31**).

[0650] Finally, the need for any form of organ support (a composite endpoint including mechanical ventilation, dialysis and/or use of vasopressors) was lower in the treated subjects (mean days alive and

without organ support 5.8 vs 2) (**FIG. 32**). Overall, these results suggested a more rapid improvement of clinical conditions among patients who received CER-001 treatment.

[0651] In particular, the results demonstrate:

- Direct and significant effect of CER-001 on endotoxin removal and consequent reduction in the inflammatory cascade or "cytokine storm"
- Significant protective effect of CER-001 on endothelial functionality
- Trends towards fewer ICU days for patients treated, lower requirement for organ support, and improved 30-day survival
- Reinforcement of the well-established safety profile of CER-001

[0652] The results also demonstrate that CER-001 had an effect on three kynurenine pathway biomarkers consistent with a beneficial effect on cognitive impairment or "brain fog."

7.3. Example 3: Lipid binding protein molecule therapy in a swine model of LPS-induced acute kidney injury

[0653] This example describes additional materials and methods, results, and analysis of the study of Example 1.

7.3.1. Materials and Methods

7.3.1.1. Animal model

[0654] The animal study was performed in domestic swine (*Sus scrofa domesticus*), after approval by the ethical committee of the relevant governmental authority. The number of animals was chosen for an appropriate analysis by calculating the number of subjects necessary, using the calculator program Anastat (www.anastats.fr/). The evaluation of six pigs for each group was made in relation to the data obtained in previous studies published on pig models of acute kidney injury (Castellano, et al., 2014, *Crit Care* 18, 520; Stasi, et al., 2021, *Front Immunol* 12, 605212; Castellano, et al., 2019, *Int J Mol Sci* 20; Sallustio, et al., 2019, *FASEB J* 33, 10753-10766; Curci, et al., 2014, *Nephrol Dial Transplant* 29, 799-808; Castellano, et al., 2016, *Am J Transplantation* 16, 325-333). Statistical analysis was performed with a significance level of p=0.05. Briefly, endotoxemia was induced by intravenous infusion of a saline solution containing 300µg/kg of LPS (lipopolysaccharide membrane of *Escherichia coli)*. Left untreated, the swine progress to LPS-induced AKI, as previously described (Sallustio, *et al.*, 2019, *FASEB J* **33**, 10753-10766). The goal of the study was to determine if treatment with CER-001 could prevent AKI from developing. The animals were randomized into three groups: LPS (endotoxemic pigs, n=6), CER20 (endotoxemic pigs treated with a single dose of CER-001 20mg/kg, Abionyx Pharma, Toulouse, France; n=6), and CER20x2 (endotoxemic pigs treated with two doses of CER-001 20mg/kg at time 0 and 3 hours later; n=6).

[0655] A few minutes after the start of LPS infusion, the CER20 group was treated with CER-001 infusion through isolated venous access. The CER20x2 group was treated by administering two doses of CER-001 (20mg/kg) through the previously isolated venous access. The first dose was administered a few minutes after the start of the LPS infusion (T0); the second dose was administered 3h after the start of the LPS infusion (T3/T0 bis). For all CER-001 dosing, the drug product was thawed and then diluted with normal saline to a volume of 250 mL containing 20 mg/kg of CER-001, individualized for each animal

based on weight, and was administered over a period of one hour using an infusion pump at a fixed rate of 250 mL/hr. The LPS group received 250 ml of normal saline solution at the same infusion rate.

[0656] The dose of CER-001 is defined as the human ApoA-I concentration present in the dosing solution. Surviving animals were sacrificed after approximately 24 hours from LPS/saline infusion with an overdose of IV propofol, immediately followed by a 10-ml IV bolus of an oversaturated solution of potassium chloride (2 mEq/ml, Galenica Senese, srl, Italy).

[0657] Domestic swine (*Sus scrofa domesticus*) were infused with 300 µg/kg of LPS without (control group) or with infusion of CER-001 at 20 mg/kg (CER20 group) followed for half of this group by a second infusion at 3 h of 20 mg/kg of CER-001 (CER20x2 group).

7.3.1.2. Collection of Samples

[0658] At sacrifice or earlier death, kidneys and livers were collected from all animals and processed using standard procedures as previously described (Sallustio, *et al.*, 2019, *FASEB J* **33**, 10753-10766). Urine samples were collected via catheter from all animals and urinary output was recorded every hour. Swine sera were collected at baseline (T0; before LPS infusion), and at intermediate time points up to 24h from an indwelling arterial blood catheter. Bile samples were collected from all animals at sacrifice. LPS was extracted from bile samples using the phenol-water extraction method (Harada, *et al.*, 2003, *Lab Invest* **83**, 1657-1667), with an LPS extraction kit (Intron Biotechnology, Kyungki-Do, Korea) according to manufacturer's instructions.

[0659] Total protein extraction was performed from all bile samples (Ciordia, *et al.*, 2021, *J Proteomics* **230**, 103984; Ciordia, *et al.*, 2022, *Methods Mol Biol* **2420**, 1-10. 1000 µl of bile of each sample was centrifuged at 9000 ×g for 3 min at 4 °C, and the supernatant containing the soluble proteins was used for assessment of ApoA-I levels.

7.3.1.3. Assessment of LPS and ApoA-I levels

[0660] The Apo-A1 content of sera and bile samples was determined by ELISA assay (R&D Systems, Minneapolis MN, USA) as well as LPS (R&D Systems, Minneapolis MN, USA).

7.3.1.4. Assessment of pro-inflammatory cytokines and markers of endothelial dysfunction

[0661] Serum IL-6 and TNF-α levels were measured by ELISA (R&D Systems, Minneapolis MN, USA) as well as s-VCAM, s-ICAM and MCP-1 (MyBioSource, San Diego CA, USA).

7.3.1.5. Assessment of the activity of Classical, Lectin and Alternative Complement pathways

[0662] Complement function in swine sera was assessed using ELISA (WIESLAB® Complement System Screen COMPL 300, Euro-Diagnostica) as previously described (Castellano, *et al.*, 2010, *Am J Pathol* **176**, 1648-1659).

7.3.1.6. Kidney and Liver function measurements

[0663] Serum/urine creatinine, serum/urine Kidney Injury Molecule-1 (KIM-1) and serum/urine Cystatin C measurements were performed with commercially available ELISA kits (MyBioSource, San Diego,

USA) according to manufacturer's instructions. Liver function was assessed by serum measurements of ALT enzyme with commercially available ELISA (MyBioSource, San Diego, USA).

7.3.1.7. Histological analysis of renal and hepatic tissue

[0664] Renal and hepatic tissues were processed for histologic staining [hematoxylin and eosin (HE) (Millipore Sigma)]. Digital slides were acquired and analyzed using the AperioScanScope CS2 device (Aperio, Vista, CA, USA) as previously described (Stasi, *et al.*, 2021, *Front Immunol* **12**, 605212; Sallustio, *et al.*, 2019, *FASEB J* **33**, 10753-10766). HE staining was performed to evaluate histological injury in both kidneys and livers. Tubular and glomerular damage was scored semi-quantitatively by two blinded observers. The score index in each animal was expressed as a mean value of all scores obtained. Both tubular and glomerular pathological score for each group was expressed as mean±SEM. Hepatic injury was defined as the amount of destruction of hepatic lobules, infiltration of inflammatory cells, hemorrhage, and hepatocyte necrosis (Baranova, *et al.*, 2016, *J Immunol* **196**, 3135-3147). The score, from 1 through 4, was assessed using criteria from a previously published study (*Ibid.*). Pathological score for each group was expressed as mean±SEM.

7.3.1.8. Western blotting analysis

[0665] Liver tissues were homogenized and treated with RIPA lysis buffer (1 mM PMSF, 5 mM EDTA, 1 mM sodium orthovanadate, 150 mM sodium chloride, 8 µg/mL leupeptin, 1.5% Nonidet P-40, and 20 mM Tris-HCl, pH 7.4)) with phosphatase and protease inhibitors. The samples (30 µg of proteins) were separated in 4–15% polyacrylamide gel and then transferred to PVDF membrane (0.2 mM) by Trans-Blot Turbo (BioRad, Hercules, CA, USA). Nonspecific binding sites on the blots were blocked by incubation in 5% BSA for 1 h, and the membranes were then incubated overnight with primary antibodies and incubated with secondary antibodies for 1 h. Immune complexes were detected by the ECL chemiluminescence system (Amersham Pharmacia, Little Chalfont, UK), according to the manufacturer's instructions. The primary antibodies used were anti-LPS (Abcam) and anti-βactin antibody (1:20,000; Sigma). The secondary antibodies used were HRP-conjugated anti-rabbit (Abcam) and anti-mouse antibodies (Abcam). The chemiluminescent blots were acquired by Chemidoc and analyzed using Image J software. The protein expression levels were standardized relative to the level of β-actin.

7.3.1.9. Statistical analysis

[0666] Survival data were analyzed using a log rank test for trend; values were censored for surviving animals using the time of sacrifice. LPS, cytokines (TNF-α, MCP-1, IL-6), endothelial markers (VCAM, ICAM), complement (classical, alternate, lectin pathways), kidney biomarkers in serum (sCR, sKIM-1, sCystatin-C) and urine (uKIM-1, uCystatin-C) and ALT were analyzed using two-way ANOVA with repeated measures, corrected for multiple comparison of pairwise treatment group differences using Tukey's method. For these analyses, data was transformed to change from baseline, and the last observation was carried forward when necessary to handle any missing values. Urine output, tubular injury score, glomerular injury score and hepatic injury score were analyzed using one-way ANOVA, corrected for multiple comparison of pairwise treatment group differences using Tukey's method. For the ANOVA analyses, pairwise treatments were also tested without correction for multiple comparisons. In general, both corrected and uncorrected tests were consistent in terms of statistically significant findings.

The following table shows the significant findings from both methods and highlights any differences between Tukey's correction and Uncorrected Fisher's LSD.

Parameter	Statistical Test Used	Data Trans-formation	Time Points	Significant Findings (with Tukey Correction)	Significant Findings (No Correction)
Survival	Logrank test for trend	N/A	N/A	Treatment Effect p=0.0265	
LPS	2-Way ANOVA with Repeated Measures	Change from Baseline with LOCF	T0, T1, T3, T6 and T24	Overall Treatment Effect p=0.0029 T1 LPS vs CER20 p=0.0462 T1 LPS vs CER20x2 p=0.0133 T6 LPS vs CER20x2 p=0.0015 *T6 CER20 vs CER20x2 None* T24 LPS vs CER20x2 p=0.0016	Overall Treatment Effect p=0.0029 T1 LPS vs CER20 p=0.0193 T1 LPS vs CER20x2 p=0.0058 T6 LPS vs CER20x2 p=0.0006 *T6 CER20 vs CER20x2 p=0.0303* T24 LPS vs CER20x2 p=0.0007
IL-6				Overall Treatment Effect p=0.0021 T1 LPS vs CER20 p=0.0168 T1 LPS vs CER20x2 p=0.0179 *T3 LPS vs CER20 None* T6 LPS vs CER20x2 p=0.0087 T24 LPS vs CER20x2 p=0.0086	Overall Treatment Effect p=0.0021 T1 LPS vs CER20 p=0.0073 T1 LPS vs CER20x2 p=0.0078 *T3 LPS vs CER20 p=0.0282* T6 LPS vs CER20x2 p=0.0038 T24 LPS vs CER20x2 p=0.0037
TNF-α				Overall Treatment Effect p<0.0001 T3 LPS vs CER20 p=0.0020 T3 LPS vs CER20x2 p=0.0026 T6 LPS vs CER20 p=0.0048 T6 LPS vs CER20x2 p=0.0010 T6 CER20 vs CER20x2 p=0.0255 T24 LPS vs CER20 p=0.0004 T24 LPS vs CER20x2 p<0.0001	Overall Treatment Effect p<0.0001 T3 LPS vs CER20 p=0.0008 T3 LPS vs CER20x2 p=0.0010 T6 LPS vs CER20 p=0.0019 T6 LPS vs CER20x2 p=0.0004 T6 CER20 vs CER20x2 p=0.0104 T24 LPS vs CER20 p=0.0001 T24 LPS vs CER20x2 p<0.0001
MCP-1				Overall Treatment Effect p=0.0113 T1 LPS vs CER20 p=0.0219 T1 LPS vs CER20x2 p=0.0005 T6 LPS vs CER20x2 p=0.0207 T24 LPS vs CER20x2 p=0.0009	Overall Treatment Effect p=0.0113 T1 LPS vs CER20 p=0.0092 T1 LPS vs CER20x2 p=0.0002 T6 LPS vs CER20x2 p=0.0089 T24 LPS vs CER20x2 p=0.0004

Parameter	Statistical Test Used	Data Trans-formation	Time Points	Significant Findings (with Tukey Correction)	Significant Findings (No Correction)
VCAM				Overall Treatment Effect p=0.0101 *T6 LPS vs CER20x2 None* T6 CER20 vs CER20x2 p=.0010 *T24 LPS vs CER20 None* *T24 LPS vs CER20x2 None* T24 CER20 vs CER20x2 p=0.0248	Overall Treatment Effect p=0.0101 *T6 LPS vs CER20x2 p=0.0358* T6 CER20 vs CER20x2 p=.0004 *T24 LPS vs CER20 p=0.0416* *T24 LPS vs CER20x2 p=0.0238* T24 CER20 vs CER20x2 p=0.0107
ICAM				*T3 CER20 vs CER20x2 None* T24 LPS vs CER20x2 p=0.0251	*T3 CER20 vs CER20x2 p=0.0387* T24 LPS vs CER20x2 p=0.0108
ALT				Overall Treatment Effect p=0.0306 *T3 LPS vs CER20x2 None* *T6 LPS vs CER20x2 None* T24 LPS vs CER20 p=0.0409 T24 LPS vs CER20x2 p=0.0098	Overall Treatment Effect p=0.0306 *T3 LPS vs CER20x2 p=0.0463* *T6 LPS vs CER20x2 p=0.0471* T24 LPS vs CER20 p=0.0173 T24 LPS vs CER20x2 p=0.0043
Comp Classic				Overall Treatment Effect p<0.0001 T1 LPS vs CER20 p=0.0030 T1 LPS vs CER20x2 p=0.0061 T3 LPS vs CER20 p=0.0026 T3 LPS vs CER20x2 p=0,0044 T24 LPS vs CER20 p=0.0017 T24 LPS vs CER20x2 p=0.0022	Overall Treatment Effect p<0.0001 T1 LPS vs CER20 p=0.0012 T1 LPS vs CER20x2 p=0.0026 T3 LPS vs CER20 p=0.0011 T3 LPS vs CER20x2 p=0,0017 T24 LPS vs CER20 p=0.0007 T24 LPS vs CER20x2 p=0.0009
Comp Alternate			T0, T1, T3 and T24	Overall Treatment Effect p<0.0001 T1 LPS vs CER20 p=0.0004 T1 LPS vs CER20x2 p=0.0002 T1 CER20 vs CER20x2 p=0.0046 T3 LPS vs CER20 p=0.0009 T3 LPS vs CER20x2 p=0.0011 T24 LPS vs CER20 p=0.0004 T24 LPS vs CER20x2 p=0.0003	Overall Treatment Effect p<0.0001 T1 LPS vs CER20 p=0.0002 T1 LPS vs CER20x2 p<0.0001 T1 CER20 vs CER20x2 p=0.0018 T3 LPS vs CER20 p=0.0004 T3 LPS vs CER20x2 p=0.0004 T24 LPS vs CER20 p=0.0001 T24 LPS vs CER20x2 p=0.0001
Comp Lectin				None	None

Parameter	Statistical Test Used	Data Trans-formation	Time Points	Significant Findings (with Tukey Correction)	Significant Findings (No Correction)
sCR				Overall Treatment Effect p<0.0001 *T3 LPS vs CER20 None* T3 LPS vs CER20x2 p=0.0179 T24 LPS vs CER20 p=0.0003 T24 LPS vs CER20x2 p=0.0005	Overall Treatment Effect p<0.0001 *T3 LPS vs CER20 p=0.0274* T3 LPS vs CER20x2 p=0.0073 T24 LPS vs CER20 p=0.0001 T24 LPS vs CER20x2 p=0.0002
sKIM-1			T0, T3 and T24	None	*T3 LPS vs CER20x2 p=0.0456*
sCystatin-C				Overall Treatment Effect p=0.0033 *T3 LPS vs CER20 None* T3 LPS vs CER20x2 p=0.0115 *T24 LPS vs CER20 None* T24 LPS vs CER20x2 p=0.0446	Overall Treatment Effect p=0.0033 *T3 LPS vs CER20 p=0.0385* T3 LPS vs CER20x2 p=0.0045 *T24 LPS vs CER20 p=0.0310* T24 LPS vs CER20x2 p=0.0196
UKIM-1/ U-Creatinine			T0 and T24	Overall Treatment Effect p<0.0001 T24 LPS vs CER20 p<0.0001 T24 LPS vs CER20x2 p<0.0001	Overall Treatment Effect p<0.0001 T24 LPS vs CER20 p<0.0001 T24 LPS vs CER20x2 p<0.0001
uCystatin-C/ U-Creatinine				Overall Treatment Effect 0.0015 T24 LPS vs CER20 p<0.0010 T24 LPS vs CER20x2 p<0.0010	Overall Treatment Effect 0.0052 T24 LPS vs CER20 p<0.0001 T24 LPS vs CER20x2 p<0.0001
s APO A-I	2-Way ANOVA with Repeated Measures	Change from Baseline with LOCF	T0, T1, T3, T4, T6 and T24	Overall Treatment Effect p<0.0001 T1 LPS vs CER20 p= 0.0004 T1 LPS vs CER20x2 p <0.0001 T3 LPS vs CER20 p= 0.0004 T3 LPS vs CER20x2 p <0.0001 T4 LPS vs CER20 p <0.0001 T4 LPS vs CER20x2 p <0.0001 T4 CER20 vs CER20x2 p<0.0001 T6 LPS vs CER20 p <0.0001 T6 LPS vs CER20x2 p <0.0001 T6 CER20 vs CER20x2 p=0.0001	Overall Treatment Effect p<0.0001 T1 LPS vs CER20 p= 0.0002 T1 LPS vs CER20x2 p <0.0001 T3 LPS vs CER20 p= 0.0002 T3 LPS vs CER20x2 p <0.0001 T4 LPS vs CER20 p <0.0001 T4 LPS vs CER20x2 p <0.0001 T4 CER20 vs CER20x2 p<0.0001 T6 LPS vs CER20 p <0.0001 T6 LPS vs CER20x2 p <0.0001 T6 CER20 vs CER20x2 p<0.0001

Parameter	Statistical Test Used	Data Trans-formation	Time Points	Significant Findings (with Tukey Correction)	Significant Findings (No Correction)
APO A-I bile	1-Way ANOVA	None	N/A	Overall Treatment Effect p<0.0001 LPS vs CER20 p= 0.04 LPS vs CER20x2 p=0.0018 CER20 vs CER20x2 p=0.0006	Overall Treatment Effect p <0.0001 LPS vs CER20 p= 0.0176 LPS vs CER20x2 p <0.0001 CER20 vs CER20x2 p= 0.0002
LPS bile	1-Way ANOVA	None	N/A	Overall Treatment Effect p=0.0016 LPS vs CER20x2 p<0.0001 CER20 vs CER20x2 p=0.0052	Overall Treatment Effect p=0.0016 LPS vs CER20x2 p=0.00007 CER20 vs CER20x2 p=0.0022
LPS liver (WB)	1-Way ANOVA	None	N/A	Overall Treatment Effect p<0.0001 LPS vs CER20 p<0.0001 LPS vs CER20x2 p<0.0001	Overall Treatment Effect p<0.0001 LPS vs CER20 p<0.0001 LPS vs CER20x2 p<0.0001
Urine Output	1-Way ANOVA	None	N/A	Overall Treatment Effect p=0.0385 LPS vs CER20x2 p=0.0380	Overall Treatment Effect p=0.0385 LPS vs CER20x2 p=0.0380
Tubular Injury Score				Overall Treatment Effect p<0.0001 LPS vs CER20 p=0.004 LPS vs CER20x2 p<0.0001 CER20 vs CER20x2 p<0.0001	Overall Treatment Effect p<0.0001 LPS vs CER20 p=0.004 LPS vs CER20x2 p<0.0001 CER20 vs CER20x2 p<0.0001
Glomerular Injury Score				Overall Treatment Effect p<0.0001 LPS vs CER20 p=0073 LPS vs CER20x2 p<0.0001 CER20 vs CER20x2 p=0.0205	Overall Treatment Effect p<0.0001 LPS vs CER20 p=0073 LPS vs CER20x2 p<0.0001 CER20 vs CER20x2 p=0.0205
Hepatic Injury Score				Overall Treatment Effect p<0.0001 LPS vs CER20 p=0017 LPS vs CER20x2 p<0.0001 CER20 vs CER20x2 p=0.0152	Overall Treatment Effect p<0.0001 LPS vs CER20 p=0017 LPS vs CER20x2 p<0.0001 CER20 vs CER20x2 p=0.0152

[0667] For in vitro analysis, data were shown as mean ± standard deviation (SD) and compared with the Student t test.

[0668] All analyses were performed by using GraphPad Prism 9.2.0 (GraphPad software, Inc., San Diego, CA, USA).

7.3.2. Results

[0669] Groups of 6.8 ± 0.7 month-old pigs were infused with the indicated dose of LPS and CER-001, and the mortality was recorded for 24 hours (n=6 per group). Untreated pigs were highly susceptible to LPS challenge and usually succumbed before completing the study protocol with a survival rate of approximately 16.7 %. CER-001 treatment increased median survival of endotoxemic pigs by 50% and

66.7%, in CER20 and CER20x2 groups, respectively (**FIG. 36**). A significant statistical treatment trend was observed by log-rank, in the three groups (p=0.02 log-rank trend test).

[0670] Serum levels of VCAM (**FIG. 37**), ICAM (**FIG. 38**), TNF-α (**FIG. 39**), MCP-1 (**FIG. 40**), and IL-6 (**FIG. 41**) were measured by ELISA assay (n=6 independent samples per time point and group). The gray bands show two infusions (from T0-T1 and T3-T4) of saline or CER-001 with flow rates 250 ml/hour. Results are presented as mean ± SEM. Significant differences were assessed using a two-way ANOVA for repeated measures with Tukey correction for multiple comparisons (n.s.: p> 0.05, *p < 0.05 **p < 0.005, **p < 0.0005 vs the LPS group; §p < 0.05; §§p < 0.005, §§§p < 0.0005 vs the CER20 group).

[0671] Systemic complement activation was measured by Wieslab assay (n=6 independent samples per time point and group) for the classical pathway (**FIG. 42**), the alternative pathway (**FIG. 43**), and the lectin pathway (**FIG. 44**). In each graph, the gray bands show two infusions (0-1h and 3-4 h) of saline or CER-001 with flow rates 250 ml/hour. Results are presented as mean ± SEM. Significant differences were assessed using a two-way ANOVA for repeated measures with Tukey correction for multiple comparisons (n.s.: p> 0.05, *p < 0.05 **p < 0.005, **p < 0.0005 vs the LPS group; §p < 0.05; §§p < 0.005, §§§p < 0.0005 vs the CER20 group).

[0672] As a strong stimulator of the innate immune system, circulating LPS is largely described as rapidly inducing the secretion of chemokines and cytokines (Tucureanu, *et al.,* 2018, *Int J Nanomedicine* **13**, 63-76). The present results agree with this description for a representative set of these pro-inflammatory molecules. TNF-α, typically released by monocytes/macrophages early in the inflammatory cascade, rapidly rises, followed in time by increasing MCP-1 and IL-6 in endotoxemic animals (LPS group, **FIG. 39-FIG. 41**). This increase was significantly impaired by CER-001 (T24, CER20 vs LPS group: TNF-α, p=0.0004) with a more potent effect after 2 doses of CER-001 (T24, CER20x2 vs LPS group, TNF-α, p<0.0001; MCP-1, p=0.0009; IL-6, p=0.0086). As expected, such strong stimulation of the immune system also induced a significant increase in the systemic complement activation cascade which was significantly inhibited by CER-001 treatments no matter the original activating pathway. i.e. classical, alternative and lectin pathways, even if the latter was less stimulated by LPS infusion.

[0673] Endothelial dysfunction is a key pathological feature of septic patients that is also prominent in the swine model of LPS-induced sepsis (Castellano, *et al.,* 2014, *Crit Care* **18**, 520; Stasi, A. *et al.,* 2021, *Front Immunol* **12**, 605212). Several aspects of sepsis contribute to endothelial dysfunction such as the hemodynamic instability, the direct interaction with bacterial components, the release of pro-inflammatory cytokines by pathogens-activated immune cells and pro-coagulant mediators (Boisramé-Helms, *et al.*, 2013, *Curr Vasc Pharmacol* **11**, 150-160). The subsequent activation of endothelial cells induces the up-regulation and expression of different adhesion molecules, such as ICAM and VCAM, that enhance leukocyte migration and homing, amplifying innate and adaptive immune response (de Pablo, R. *et al.,* 2013, *Eur J Intern Med* **24**, 132-138). CER-001 infusion ameliorated systemic endothelial dysfunction by reducing VCAM (**FIG. 37**) and ICAM (**FIG. 38**) serum levels in both treated groups, with an increased effect of the two doses of ApoA-I complexes doses group as emphasized at T6.

[0674] In the continuum of systemic degradation, liver dysfunction is a grave manifestation in the course of sepsis, principally caused by alterations and/or direct and indirect insult to hepatocytes (Yan, *et al.*, 2014, *Int Rev Immunol* **33**, 498-510). In endotoxemic pigs, early manifestations of hepatic dysfunction were observed which included increased ALT levels and histological changes (as shown by H&E staining of hepatic tissue of LPS and treated groups (n =6 independent pigs per group)) such as

microvacuolization and infiltrating inflammatory cells (apparent in the LPS group, **FIG. 45A**). Scale bar: 80 µm. Hepatic injury was defined as the amount of destruction of hepatic lobules (black arrow) and infiltration of inflammatory cells (black dashed arrow) The hepatocytes appeared swollen, and the hepatic cords were disorganized.

[0675] The hepatic damage was resolved by CER-001 infusion (as measured by the modest increase in ALT (**FIG. 45E**) and a statistically significant decrease of liver histology score (**FIG. 45D**). The histology score was calculated from five randomly selected fields per sample shown in **FIG. 45A-FIG. 45C** (n = 6 independent pigs per group) and scored from 1 through 4 according to % area of involvement per high power field, underscoring the protection that CER-001 provides to hepatic tissue. In **FIG. 45E**, the gray bands show two infusions (0-1h and 3-4 h) of saline or CER-001 with flow rates 250 ml/hour.

[0676] The over-production of pro-inflammatory cytokines has been associated with sepsis progression, severity, and acute kidney injury occurrence (Wang, *et al.*, 2008, *Am J Emergency Med* **26**, 711-715). Kidney injury in the swine model was assessed by a time-dependent increase of serum creatinine (**FIG. 47**) with significant reduction in urinary output (mL/kg/h) (**FIG. 48**) compared to basal level (T0). Moreover, the expression of tubular damage biomarkers Cystatin C and KIM-1, both in serum (**FIG. 49A** and **FIG. 50A**, respectively) and urine samples (**FIG. 49B** and **FIG. 50B**, respectively), were increased compared with the basal level (T0). (Serum and urinary creatinine, Cystatin C, and KIM-1 levels were measured by ELISA assay (n=6 independent samples per time point and group); urinary output (ml/kg/h) was recorded for each animal. In **FIG. 45D**, **FIG. 46D**, **FIG. 46E**, and **FIG. 48**, results are presented as mean ± SEM. Significant differences were assessed by one-way ANOVA with Tukey correction (n.s.: $p > 0.05$, *$p < 0.05$ **$p < 0.005$, **$p < 0.0005$ vs the LPS group; §$p < 0.05$; §§$p < 0.005$, §§§$p < 0.0005$ vs the CER20 group). In **FIG. 45E**, **FIG. 47**, and **FIG. 49A-FIG. 50B**, the gray bands show two infusions (0-1h and 3-4 h) of saline or CER-001 with flow rates 250ml/hour. Results are presented as mean ± SEM. Significant differences were assessed using a two-way ANOVA for repeated measures with Tukey correction (n.s.: $p > 0.05$, *$p < 0.05$ **$p < 0.005$, **$p < 0.0005$ vs the LPS group; §$p < 0.05$; §§$p < 0.005$, §§§$p < 0.0005$ vs the CER20 group).

[0677] Taken together, these results confirmed renal damage in endotoxemic pigs, in contrast to pigs receiving CER-001 treatments, which maintained creatinine level, urine output, and the expression of serum/urine Cystatin C and KIM-1 to the median baseline level (T0) as compared to control animals.

[0678] This renal damage was highlighted by significant morphological changes in renal parenchyma, including desquamation, tubular vacuolization, epithelial flattening, necrosis, infiltration of inflammatory cells, marked fibrin deposition, reduced number of capillaries in numerous glomeruli, Bowman's capsule expansion (black arrows) and interstitial inflammatory infiltrate (blue arrows). Compare **FIG. 46A** (LPS group) with **FIG. 46B** and **FIG. 46C** (CER-001 groups). Those observations were reflected by the histopathological score which show significantly less kidney damage in treated groups especially after two doses of ApoA-I complexes (tubular pathology, **FIG. 46D**; glomerular pathology, **FIG. 46E**; tubular and glomerular pathological score was obtained as described in the Methods section (n=6 for each group).

[0679] As a synthetic HDL containing ApoA-I, the potential positive mechanism of action of CER-001 in sepsis could be due to its capacity on the one hand to decrease the inflammatory cytokines (see above) and on the other hand to counteract the action of LPS by direct interactions as previously described for HDL. Indeed, consistent with CER-001's positive effects, it was observed that serum LPS levels

measured by ELISA assay were reduced in treated animals (n=6 independent samples per time point and group) (**FIG. 51**). The effects were especially evident after the second infusion of CER-001 (T6, CER20x2 vs LPS, p=0.0015) with a sustained effect up to 24 h post-infection in both treated groups.

[0680] One hypothesis of such LPS decrease could be the consequence of an accelerated catabolism/elimination induced by a scavenger effect of CER-001 on LPS as described for HDL. Since the natural catabolism of HDL is to be eliminated by the liver as their end-target to allow cholesterol elimination through the bile, one can hypothesize that the LPS-CER-001 complexes formed could rapidly eliminate LPS to the bile through the liver. Indeed, the amount of LPS measured in the liver was higher for LPS group than for both CER-001 treated groups, as shown by representative western blot (**FIG. 52A**) and densitometric analysis (**FIG. 52B**) of LPS and β-actin protein expression. **FIG. 53** shows a dose-dependent increase of endotoxin in the bile of CER-001 treated septic pigs, as determined by ELISA assay. Interestingly, the time course of human ApoA-I serum levels (**FIG. 54**) and a dose-dependent increase of human ApoA-I in bile samples (**FIG. 55**) confirmed the role of CER-001 in this increase of LPS elimination. Human ApoA-I levels were determined by ELISA. Gray bands show two infusions (0-1h and 3-4 h) of saline or CER-001 with flow rates 250ml/hour. The data are presented as the mean ± SEM. Statistically significant differences were assessed by one-way ANOVA with Tukey correction (n.s.: $p>0.05$).

7.4. Example 4: Lipid binding protein molecule therapy in a model of LPS-induced vascular endothelial injury

[0681] The ability of the ApoA-I containing complex CER-001 to mitigate sepsis-induced injury to vascular endothelium was evaluated in a lipopolysaccharide (LPS)-induced *in vitro* model.

7.4.1. Materials and Methods

7.4.1.1. Cell culture

[0682] Human umbilical vein endothelial cells (HUVEC, EC) were purchased from American Type Culture Collection (ATCC-LGC Standards S.r.l., Sesto San Giovanni, Milan, Italy). EC were maintained in their recommended medium, EndGro (Merck Millipore, Darmstadt, Germany).

[0683] Peripheral blood mononuclear cells (PBMCs) were isolated by gradient centrifugation with the Ficoll-Hypaque method from buffy coats of healthy donors (selected from a research repository) as previously described (Sallustio, *et al.*, 2021, *Nephrol Dial Transplant* **36**, 452-464). PBMCs were maintained in their recommended media (*Ibid.*).

[0684] When cells became confluent, they were stimulated with LPS 0.3 µg/ml, 4 µg/ml (E. Coli O111:B4, Sigma-Aldrich, Milan, Italy) and CER-001 50, 100, and 500 µg/ml for the indicated time period.

[0685] PBMCs culture supernatants were collected and analyzed by ELISA for TNF-α (R&D Systems, Minneapolis MN, USA)

7.4.1.2. Cell proliferation assay

[0686] EC and PBMCs were incubated with LPS at 0.3 µg/ml and/or CER-001 at 50 and 500 µg/ml for 60 min and 24 hours. Proliferation rate was measured by MTT Cell Proliferation Assay Kit, according to the manufacturer instructions (Sigma Aldrich). Briefly, 3×10^4 cells/well were seeded in a 96-well plate, and then cells were treated with LPS and CER-001 as indicated. Absorbance at 570 nm was then measured by a spectrophotometer.

7.4.1.3. Immunophenotypic analysis

[0687] After stimulations, EC were permeabilized with IntraPrep kit (Instrumentation Laboratory) and incubated with unconjugated primary antibody p-ENOS (Abcam) for 25 minutes at 4°C. Cells were then washed and labeled with secondary Antibody AlexaFluor 488 (Molecular Probes) for 25 minutes at 4°C. Finally, cells were washed twice and resuspended in FACS buffer for acquisition.

[0688] PBMCs were stained with the following monoclonal antibody, CD14 Monoclonal Antibody (61D3)-PE, (eBioscience™, Thermo Fisher Scientific, Italy), for 20 minutes in the dark at room temperature, washed twice, and resuspended in FACS buffer. Stained PBMCs were then acquired.

[0689] Data were obtained by using a FC500 (Beckman Coulter) flow cytometer and analyzed with Kaluza software. Three independent studies were performed for both EC and PBMCs. The area of positivity was determined by using an isotype-matched mAb, and in total, 104 events for each sample were acquired.

7.4.1.4. Statistical analysis

[0690] Data shown are representative of three independent studies. Data are shown as mean ±standard deviation (SD) and compared with the Student-t test.

7.4.2. Results

[0691] Effects of LPS and CER-001 on endothelial cells and the endothelial nitric oxide synthase (eNOS) activation were analyzed. The MTT cell viability assay results in **FIG. 58** showed a slight reduction in proliferation after LPS stimulation. CER-001 at 50 and 500 µg/ml did not affect endothelial viability. Endothelial cells treated with LPS and CER-001, both at 50 and 500 µg/ml, increased the proliferation rate, in particular at the highest concentration, compared to LPS-stimulated cells.

[0692] Production of eNOS has been described as a marker of the vascular endothelial integrity (Zhao, *et al.*, 2015, *J Pharmacol Sci* **129**, 83-94). In the *in vitro* model of this Example, eNOS phosphorylation and activation (**FIG. 59-FIG. 60**) was altered by LPS and upregulated by CER-001. Specifically, a strong decrease of eNOS (phospho S1177) (p-ENOS) was observed after 60 min of LPS stimulation compared to basal and VEGF (positive control). CER-001 supplementation at 500 µg/ml completely reversed LPS effects. (In **FIG. 60**, representative data from one out of a total of three studies are shown. Histograms indicate p-ENOS expression levels).

[0693] In addition, CER-001 modulated the response of peripheral blood mononuclear cells (PBMC) stimulated with LPS at 0.3 µg/ml and/or CER-001 at 50 and 500 µg/ml for 24 hours, decreasing mCD14 expression and TNF-α secretion. As shown in **FIG. 61**, MTT assay showed no significant difference in cell viability with respect to the basal for the above conditions. PBMC culture supernatants were analyzed by ELISA with results shown in **FIG. 62**. After 24 h from LPS stimulation, PBMCs increased TNF-α synthesis. Stimulation of PBMCs with CER-001 at 50 and 500 µg/m alone did not influence TNF-α production. The addition of CER-001, both at 50 and 500 µg/m, in culture media of LPS-activated PBMCs reverted LPS effects. Also, FACS showed a strong upregulation of CD14 surface expression by PCMBs 24 h following LPS stimulation (**FIG. 63**). PBMCs treated with LPS and CER-001 in combination maintained CD14 expression at basal level (**FIG. 64**).

7.5. Example 5: CER-001 in Subjects with Septic Shock

7.5.1. Objectives

[0694] A clinical Phase 2B/3 trial is conducted to evaluate CER-001 plus the standard of care (SOC) versus placebo plus SOC on 90-day survival in subjects with septic shock. Secondary objectives include observation of the effect of CER-001 on organ dysfunction and use of organ support, morbidity and mortality, and health-related quality of life; and the pharmacokinetics of CER-001; and further evaluation of a range of biomarkers in relation to the mode of action of CER-001.

7.5.2. Endpoints

[0695] The primary endpoint is all-cause mortality (defined as the fraction of subjects that have died, regardless of cause) at Day 90. Secondary endpoints include days alive and not in ICU up to Day 90; days alive and not requiring mechanical ventilation up to Day 90; days alive and not on renal replacement therapy (RRT) up to Day 90; vasopressor-free days up to Day 30; days alive without organ support up to Day 90; and Sepsis Support Index through Day 90.

[0696] Sepsis Support Index (SSI) is a composite end point reflecting organ dysfunction or death within the first 14 days of follow-up. More precisely, within the first 14 days of follow-up, every day on which a vasopressor or mechanical ventilation is used, or renal dysfunction (defined as renal sequential organ failure assessment (SOFA)=4) is apparent, or the patient is deceased, is counted. The sum of counted days over the 14-day follow-up period is defined as the SSI score, which can have a maximum of 14. Further description on how to calculate the SSI is described by Geven, *et al.*, 2019, *BMJ Open* 0:e024475.

[0697] Secondary efficacy endpoints include:

- Organ dysfunction (daily sequential organ failure assessment (SOFA) score through Day 30)
- Health-related quality of life (change in utility, based on the EuroQol group's 5-dimension 5-level (EQ-5D-5L) questionnaire, up to Day 30 and up to Day 90)
- Mental status (determinations at Day 30, Day 60, and Day 90)

[0698] Exploratory endpoints include:

- Subject residence at Day 30, Day 60 and Day 90 (ICU, hospital, step-down unit, or home)
- mean arterial pressure (MAP), until ICU discharge (for a maximum of 7 days)
- pharmacokinetic response (in a subset of approximately 100 subjects during Part 1 of the study)
- ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2 ratio)
- cytokines associated with sepsis
- endothelial biomarkers

7.5.3. Trial Design

[0699] This is a double-blind, randomized, placebo-controlled, two-part adaptive clinical trial.

[0700] The overall trial design includes two parts (Part 1 – Phase 2b and Part 2 – Phase 3) as represented in **FIG. 69**.

[0701] Part 1 has fixed randomization (1:1:1) to placebo, CER-001 10 mg/kg or CER-001 20 mg/kg. When 30-day survival data is available from approximately 150 randomized subjects, the results of Part 1 is used to determine whether the study transitions to Part 2 (with continuing enrollment into Part 1 during

analysis) and whether one dosage arm will be eliminated with the participants from that arm being allocated to the remaining CER-001 arm.

[0702] The investigational medicinal products (IMPs) used are (1) CER-001 sterile solution for intravenous infusion and (2) Placebo: sterile 0.9% sodium chloride solution (250 mL). CER-001 is provided frozen in 20 mL vials containing approximately 18 mL of product at a concentration of 8 mg/mL (ApoA-I content). CER-001 is dosed by weight. All doses are thawed and then diluted with normal saline to a volume of 250 mL and are administered using an infusion pump over a 1-hour period (250 mL/hour).

[0703] The infusion of IMP starts as early as possible and no later 48 hours after ICU admission. To ensure start of IMP treatment without delay, informed consent is obtained, in compliance with local regulations, as early as possible.

[0704] IMP is administered twice a day, twelve hours apart, for five consecutive days.

[0705] Study participation for an individual subject is represented in **FIG. 70**. After Day 15, subjects who are discharged out of hospital to home or step-down care are followed remotely. Survival at Day 180 is determined by phone call.

7.5.4. Inclusion and Exclusion Criteria

[0706] Subjects are at least 11 but less than 80 years of age; have proven or suspected infection; and have septic shock characterized by hypotension (systolic arterial pressure <90mmHg or mean arterial pressure (MAP) <65 mm Hg) requiring the use of vasopressors for more than 1 hour despite intravenous fluid resuscitation.

[0707] Exclusion criteria include inability to initiate IMP treatment within 24 hours from start of vasopressors for septic shock; previous severe sepsis with ICU admission within the last 12 months; hypotension secondary to causes other than sepsis (*e.g.* major trauma including traumatic brain injury, hemorrhage, burns, or congestive heart failure/cardiogenic shock); chronic mechanical ventilation for any reason in the last 6 months OR severe COPD requiring continuous daily oxygen use during the preceding 30 days; chronic kidney disease Stage 4 or 5 OR requiring dialysis for any reason during the preceding 30 days; receipt of bone marrow transplant during the preceding 6 months or chemotherapy during the preceding 12 months; known malignancy within the preceding 12 months, with the exception of basal or squamous cell skin cancer; known to be pregnant; presence of a DNR or other decision to limit full care taken before obtaining informed consent; prior enrollment in this trial; prior use of an investigational medicinal product within the last month OR planned or concurrent participation in a clinical trial for any investigational drug or investigational device.

[0708] In addition, post-randomization, before the start of IMP infusion, no more than 24 hours may have elapsed from the start of vasopressors for septic shock.

7.5.5. Statistical Methods

[0709] The primary analysis compares all subjects treated with a CER-001 dosage regimen, from both parts of the trial (pooled together and treated as a single arm) to all subjects on the placebo arm from both parts of the trial. The primary analysis evaluates CER-001 superiority using a one-sided 5% significance level test. The analysis is based on both the modified intent-to-treat set (mITT) and the per protocol (PP) analysis set, with the mITT being considered the primary analysis to judge statistical

significance and the PP analysis considered as supportive. The mITT comprises all randomized subjects receiving at least one dose of blinded therapy.

[0710] A target of approximately 850 subjects, randomized 1:2 placebo:CER-001, provides 80% power to detect a 10% absolute risk reduction or a 20% relative risk reduction, assuming a 90-day mortality rate of 40% in subjects with septic shock treated according to standard of care.

[0711] The secondary endpoints are aimed at supporting primary efficacy by further demonstrating treatment effect accompanied by an acceptable safety profile. All secondary endpoints are analyzed using both the mITT and the PP analysis set.

[0712] All-cause mortality (at Days 30 and 180) is analyzed in the same manner as the primary endpoint. Mortality is presented graphically by a Kaplan-Meier plot. Parameters measured in days, as well as the Sepsis Support Index, are analyzed with a test of superiority using a two-sided 5% significance level test. Endpoints addressing changes in SOFA score, health-related quality of life, cytokine levels and endothelial dysfunction markers are analyzed by analysis of variance (ANOVA) or covariance (ANCOVA) methods as appropriate and presented graphically.

[0713] The safety profile, including adverse events, vital signs, and safety laboratory variables, are summarized descriptively. The safety analyses are performed using the safety analysis set. The safety analysis set comprises all IMP-treated subjects and are analyzed according to the actual treatment received.

[0714] ApoA-I concentrations by time are presented for Day 1 and Day 5 (first and last day of treatment), with calculation of pharmacokinetic parameters. Peak and trough levels of apoA-I from Days 1 to 6, by CER-001 dosage regimen, are examined graphically.

[0715] Table 5 provides the schedule of study procedures.

Table 5

Study Procedure	Screening	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 15	Days 30, 60, 90 and180
Informed Consent	X								
Inclusion/Exclusion Criteria	X	X							
Study Drug Dosing (BID)		X	X	X	X	X			
ApoA-I Level[#] (pre-dose if applicable)		X	X	X	X	X	X	X	
SOFA Score[$]	X----	------	------	------	-------	------	------	------	---->
Blood sampling for biomarkers[@] (pre-dose if applicable		X	X	X	X	X	X	X	
Documentation for use of organ support	X----	------	------	------	-------	------	------	------	---->
Health-related Quality of Life	X								X
Neurocognitive assessment									X

Mortality assessment									X
Safety Labs[&] (pre-dose if applicable)		X					X	X	
Adverse Events	X----	------	------	------	-------	------	------	------	---->
[#]Additional measurements are made in a subset of patients during Part 1. [$]Daily SOFA scores through Day 30 or hospital discharge if earlier. [@]Sent to central lab for testing. [&]Local hospital lab testing.									

7.5.1. Results

[0716] CER-001 therapy provides a therapeutic benefit to subjects with septic shock.

7.6. Discussion of Examples

[0717] Current treatment guidelines for septic patients are based on hemodynamic resuscitation, supportive therapy and adequate antibiotic therapy. However, in most critically ill patients, these measures are not enough to prevent sepsis-related organ dysfunction and the onset of AKI. The findings described in the Examples demonstrate the targeted anti-inflammatory effects of CER-001 at the renal and hepatic level as well as at systemic circulatory system in a swine model of endotoxemia. The results show that CER-001 enhances the transport of LPS to the liver and promotes its elimination into the bile, indirectly attenuating inflammation. The data showed a dose-dependent decrease of endotoxin amount in sera and hepatic tissue of treated-endotoxemic animals. LPS and ApoA-I levels increased in bile samples of CER-001 treated animals. The pharmacokinetics of human ApoA-I measured in swine sera of both treated groups was consistent with the decreased amount of LPS, and endothelial and inflammatory biomarkers mediated by CER-001 treatment. In a pilot clinical study testing the safety and efficacy of CER-001 in the treatment of a heterogeneous cohort of septic patients, the ability of CER-001 treatment to enhance LPS removal, to modulate the inflammatory response secondary to sepsis and to prevent endothelial and organ dysfunction was confirmed.

8. SPECIFIC EMBODIMENTS

[0718] The present disclosure is exemplified by the numbered embodiments set forth below.

1. A method of treating a subject having or at risk of a condition, which is optionally an acute condition, comprising administering a dose, *e.g.*, a high dose, of a lipid binding protein molecule to the subject.

2. The method of embodiment 1, wherein the condition is associated with an abnormal level of TREM-1, albumin, interleukin 10 (IL-10), a kynurenine pathway biomarker, TNF-α, MCP-1, IL-6, IL-8, VCAM-1, or ICAM-1.

3. The method of embodiment 1 or embodiment 2, wherein the condition is associated with an abnormal level of ApoA-I, eNOS, or CD14.

4. The method of any one of embodiments 1 to 3, wherein the condition is associated with an abnormal level of TREM-1.

5. The method of any one of embodiments 1 to 4, wherein the subject has an above normal level of TREM-1 prior to administration of the lipid protein binding protein molecule.

6. The method of any one of embodiments 1 to 5, further comprising measuring a level of TREM-1 of the subject prior to administering the dose.

7. The method of any one of embodiments 1 to 6, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of TREM-1 in the subject.

8. The method of any one of embodiments 1 to 7, wherein the condition is associated with an abnormal level of albumin.

9. The method of any one of embodiments 1 to 8, wherein the subject has a below normal level of albumin prior to administration of the lipid protein binding protein molecule.

10. The method of any one of embodiments 1 to 9, further comprising measuring a level of albumin of the subject prior to administering the dose.

11. The method of any one of embodiments 1 to 10, wherein the dose comprises an amount of the lipid binding protein molecule which increases a level of albumin in the subject.

12. The method of any one of embodiments 1 to 11, wherein the condition is associated with an abnormal level of a kynurenine pathway biomarker.

13. The method of embodiment 12, wherein the kynurenine pathway biomarker is kynurenine.

14. The method of embodiment 12, wherein the kynurenine pathway biomarker is kynurenic acid.

15. The method of embodiment 12, wherein the kynurenine pathway biomarker is 3-hydroxykynurenine.

16. The method of embodiment 12, wherein the kynurenine pathway biomarker is anthranilic acid.

17. The method of embodiment 12, wherein the kynurenine pathway biomarker is 3-hydroxyanthranilic acid.

18. The method of embodiment 12, wherein the kynurenine pathway biomarker is 2-amino-3-carboxymuconate-semialdehyde.

19. The method of embodiment 12, wherein the kynurenine pathway biomarker is picolinic acid.

20. The method of embodiment 12, wherein the kynurenine pathway biomarker is quinolinic acid.

21. The method of embodiment 12, wherein the kynurenine pathway biomarker is quinaldic acid.

22. The method of embodiment 12, wherein the kynurenine pathway biomarker is tryptophan.

23. The method of embodiment 12, wherein the kynurenine pathway biomarker is serotonin.

24. The method of embodiment 12, wherein the kynurenine pathway biomarker is xanthurenic acid.

25. The method of embodiment 12, wherein the kynurenine pathway biomarker is formylkynurenine.

26. The method of embodiment 12, wherein the kynurenine pathway biomarker is kynurenine/tryptophan ratio.

27. The method of any one of embodiments 1 to 26, wherein the subject has an above normal level of kynurenine prior to administration of the lipid protein binding protein molecule.

28. The method of any one of embodiments 1 to 27, further comprising measuring a level of kynurenine of the subject prior to administering the dose.

29. The method of any one of embodiments 1 to 28, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of kynurenine in the subject.

30. The method of any one of embodiments 1 to 29, wherein the subject has an above normal level of kynurenic acid prior to administration of the lipid protein binding protein molecule.

31. The method of any one of embodiments 1 to 30, further comprising measuring a level of kynurenic acid of the subject prior to administering the dose.

32. The method of any one of embodiments 1 to 31, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of kynurenic acid in the subject.

33. The method of any one of embodiments 1 to 32, wherein the subject has an above normal level of 3-hydroxykynurenine prior to administration of the lipid protein binding protein molecule.

34. The method of any one of embodiments 1 to 33, further comprising measuring a level of 3-hydroxykynurenine of the subject prior to administering the dose.

35. The method of any one of embodiments 1 to 34, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of 3-hydroxykynurenine in the subject.

36. The method of any one of embodiments 1 to 35, wherein the subject has an above normal level of anthranilic acid prior to administration of the lipid protein binding protein molecule.

37. The method of any one of embodiments 1 to 36, further comprising measuring a level of anthranilic acid of the subject prior to administering the dose.

38. The method of any one of embodiments 1 to 37, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of anthranilic acid in the subject.

39. The method of any one of embodiments 1 to 39, wherein the subject has an above normal level of 3-hydroxyanthranilic acid prior to administration of the lipid protein binding protein molecule.

40. The method of any one of embodiments 1 to 39, further comprising measuring a level of 3-hydroxyanthranilic acid of the subject prior to administering the dose.

41. The method of any one of embodiments 1 to 40, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of 3-hydroxyanthranilic acid in the subject.

42. The method of any one of embodiments 1 to 41, wherein the subject has an above normal level of 2-amino-3-carboxymuconate-semialdehyde prior to administration of the lipid protein binding protein molecule.

43. The method of any one of embodiments 1 to 42, further comprising measuring a level of 2-amino-3-carboxymuconate-semialdehyde of the subject prior to administering the dose.

44. The method of any one of embodiments 1 to 43, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of 2-amino-3-carboxymuconate-semialdehyde in the subject.

45. The method of any one of embodiments 1 to 44, wherein the subject has an above normal level of picolinic acid prior to administration of the lipid protein binding protein molecule.

46. The method of any one of embodiments 1 to 45, further comprising measuring a level of picolinic acid of the subject prior to administering the dose.

47. The method of any one of embodiments 1 to 46, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of picolinic acid in the subject.

48. The method of any one of embodiments 1 to 47, wherein the subject has an above normal level of quinolinic acid prior to administration of the lipid protein binding protein molecule.

49. The method of any one of embodiments 1 to 48, further comprising measuring a level of quinolinic acid of the subject prior to administering the dose.

50. The method of any one of embodiments 1 to 49, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of quinolinic acid in the subject.

51. The method of any one of embodiments 1 to 51, wherein the subject has an above normal level of quinaldic acid prior to administration of the lipid protein binding protein molecule.

52. The method of any one of embodiments 1 to 51, further comprising measuring a level of quinaldic acid of the subject prior to administering the dose.

53. The method of any one of embodiments 1 to 52, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of quinaldic acid in the subject.

54. The method of any one of embodiments 1 to 53, wherein the subject has a below normal level of tryptophan prior to administration of the lipid protein binding protein molecule.

55. The method of any one of embodiments 1 to 54, further comprising measuring a level of tryptophan of the subject prior to administering the dose.

56. The method of any one of embodiments 1 to 55, wherein the dose comprises an amount of the lipid binding protein molecule which increases a level of tryptophan in the subject.

57. The method of any one of embodiments 1 to 56, wherein the subject has a below normal level of serotonin prior to administration of the lipid protein binding protein molecule.

58. The method of any one of embodiments 1 to 57, further comprising measuring a level of serotonin of the subject prior to administering the dose.

59. The method of any one of embodiments 1 to 58, wherein the dose comprises an amount of the lipid binding protein molecule which increases a level of serotonin in the subject.

60. The method of any one of embodiments 1 to 59, wherein the subject has an above normal level of xanthurenic acid prior to administration of the lipid protein binding protein molecule.

61. The method of any one of embodiments 1 to 60, further comprising measuring a level of xanthurenic acid of the subject prior to administering the dose.

62. The method of any one of embodiments 1 to 61, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of xanthurenic acid in the subject.

63. The method of any one of embodiments 1 to 62, wherein the subject has an above normal level of formylkynurenine prior to administration of the lipid protein binding protein molecule.

64. The method of any one of embodiments 1 to 63, further comprising measuring a level of formylkynurenine of the subject prior to administering the dose.

65. The method of any one of embodiments 1 to 64, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of formylkynurenine in the subject.

66. The method of any one of embodiments 1 to 65, wherein the subject has an above normal kynurenine/tryptophan ratio prior to administration of the lipid protein binding protein molecule.

67. The method of any one of embodiments 1 to 66, further comprising measuring a kynurenine/tryptophan ratio of the subject prior to administering the dose.

68. The method of any one of embodiments 1 to 67, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a kynurenine/tryptophan ratio in the subject.

69. The method of any one of embodiments 1 to 68, wherein the condition is associated with an abnormal level of TNFα.

70. The method of any one of embodiments 1 to 69, wherein the subject has an above normal level of TNFα prior to administration of the lipid protein binding protein molecule.

71. The method of any one of embodiments 1 to 70, further comprising measuring a level of TNFα of the subject prior to administering the dose.

72. The method of any one of embodiments 1 to 71, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of TNFα in the subject.

73. The method of any one of embodiments 1 to 72, wherein the condition is associated with an abnormal level of MCP-1.

74. The method of any one of embodiments 1 to 73, wherein the subject has an above normal level of MCP-1 prior to administration of the lipid protein binding protein molecule.

75. The method of any one of embodiments 1 to 74, further comprising measuring a level of MCP-1 of the subject prior to administering the dose.

76. The method of any one of embodiments 1 to 75, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of MCP-1 in the subject.

77. The method of any one of embodiments 1 to 76, wherein the condition is associated with an abnormal level of IL-6.

78. The method of any one of embodiments 1 to 77, wherein the subject has an above normal level of IL-6 prior to administration of the lipid protein binding protein molecule.

79. The method of any one of embodiments 1 to 78, further comprising measuring a level of IL-6 of the subject prior to administering the dose.

80. The method of any one of embodiments 1 to 79, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of IL-6 in the subject.

81. The method of any one of embodiments 1 to 80, wherein the condition is associated with an abnormal level of IL-8.

82. The method of any one of embodiments 1 to 81, wherein the subject has an above normal level of IL-8 prior to administration of the lipid protein binding protein molecule.

83. The method of any one of embodiments 1 to 82, further comprising measuring a level of IL-8 of the subject prior to administering the dose.

84. The method of any one of embodiments 1 to 83, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of IL-8 in the subject.

85. The method of any one of embodiments 1 to 84, wherein the condition is associated with an abnormal level of ApoA-I.

86. The method of any one of embodiments 1 to 85, wherein the subject has a below normal level of ApoA-I prior to administration of the lipid protein binding protein molecule.

87. The method of any one of embodiments 1 to 86, further comprising measuring a level of ApoA-I of the subject prior to administering the dose.

88. The method of any one of embodiments 1 to 87, wherein the dose comprises an amount of the lipid binding protein molecule which increases a level of ApoA-I in the subject.

89. The method of any one of embodiments 1 to 88, wherein the condition is associated with an abnormal level of eNOS.

90. The method of any one of embodiments 1 to 89, wherein the subject has a below normal level of eNOS prior to administration of the lipid protein binding protein molecule.

91. The method of any one of embodiments 1 to 90, further comprising measuring a level of eNOS of the subject prior to administering the dose.

92. The method of any one of embodiments 1 to 91, wherein the dose comprises an amount of the lipid binding protein molecule which increases a level of eNOS in the subject.

93. The method of any one of embodiments 1 to 92, wherein the condition is associated with an abnormal level of CD14.

94. The method of any one of embodiments 1 to 93, wherein the subject has an above normal level of CD14 prior to administration of the lipid protein binding protein molecule.

95. The method of any one of embodiments 1 to 94, further comprising measuring a level of CD14 of the subject prior to administering the dose.

96. The method of any one of embodiments 1 to 95, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of CD14 in the subject.

97. The method of any one of embodiments 1 to 96, wherein the condition is associated with an abnormal level of VCAM-1 or ICAM-1.

98. The method of any one of embodiments 1 to 97, wherein the subject has an above normal level of VCAM-1 prior to administration of the lipid protein binding protein molecule.

99. The method of any one of embodiments 1 to 98, further comprising measuring a level of VCAM-1 of the subject prior to administering the dose.

100. The method of any one of embodiments 1 to 99, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of VCAM-1 in the subject.

101. The method of any one of embodiments 1 to 100, wherein the subject has an above normal level of ICAM-1 prior to administration of the lipid protein binding protein molecule.

102. The method of any one of embodiments 1 to 101, further comprising measuring a level of ICAM-1 of the subject prior to administering the dose.

103. The method of any one of embodiments 1 to 102, wherein the dose comprises an amount of the lipid binding protein molecule which decreases a level of ICAM-1 in the subject.

104. The method of any one of embodiments 1 to 103, wherein the condition is a bacterial infection.

105. The method of embodiment 104, wherein the bacterial infection is a *Staphylococcus aureus* infection.

106. The method of embodiment 104, wherein the bacterial infection is a *Escherichia coli* infection.

107. The method of embodiment 104, wherein the bacterial infection is a Str*eptococcus pneumoniae* infection.

108. The method of embodiment 104, wherein the bacterial infection is a *Klebsiella pneumoniae* infection.

109. The method of embodiment 104, wherein the bacterial infection is a *Pseudomonas aeruginosa* infection.

110. The method of embodiment 104, wherein the bacterial infection is a *Acinetobacter baumanni* infection.

111. The method of embodiment 104, wherein the bacterial infection is a *Bacteroides fragilis* infection.

112. The method of embodiment 104, wherein the bacterial infection is a *Klebsiella pneumoniae* infection.

113. The method of embodiment 104, wherein the bacterial infection is a *Proteus mirabilis* infection.

114. The method of embodiment 104, wherein the bacterial infection is a *Pseudomonas aeruginosa* infection.

115. The method of any one of embodiments 1 to 103, wherein the condition is a gram-positive bacterial infection.

116. The method of any one of embodiments 1 to 103, wherein the condition is a gram-negative bacterial infection.

117. The method of any one of embodiments 1 to 116, wherein the subject has a urinary tract infection.

118. The method of any one of embodiments 1 to 116, wherein the subject has a blood infection.

119. The method of any one of embodiments 1 to 116, wherein the subject has a post-surgical infection.

120. The method of any one of embodiments 1 to 116, wherein the subject has gastrointestinal perforation.

121. The method of any one of embodiments 1 to 116, wherein the subject has a perforated duodenal ulcer.

122. The method of any one of embodiments 1 to 116, wherein the subject has a perforated bowel.

123. The method of any one of embodiments 1 to 116, wherein the subject has septic shock following trauma, for example abdominal trauma.

124. The method of any one of embodiments 1 to 116, wherein the subject has pneumonia, *e.g.*, hospital acquired pneumonia.

125. The method of any one of embodiments 1 to 116, wherein the subject has a pancreatitis, *e.g.*, necrotizing pancreatitis.

126. The method of any one of embodiments 1 to 103, wherein the condition is a viral infection.

127. The method of embodiment 126, wherein the viral infection is a SARS-CoV-2 (COVID-19) infection.

128. The method of embodiment 126, wherein the viral infection is an influenza virus infection.

129. The method of any one of embodiments 1 to 128, wherein the subject has sepsis.

130. The method of any one of embodiments 1 to 129, wherein the subject has septic shock.

131. The method of embodiment 129 or embodiment 130, wherein the subject has hypotension requiring the use of vasopressors despite intravenous fluid resuscitation.

132. The method of any one of embodiments 129 to 131, wherein the subject has a systolic arterial pressure < 90 mm Hg.

133. The method of any one of embodiments 129 to 132, wherein the subject has a mean arterial pressure (MAP) < 65 mm Hg.

134. The method of any one of embodiments 129 to 133, wherein the subject has hypotension (*e.g.*, systolic arterial pressure < 90 mm Hg or mean arterial pressure (MAP) < 65 mm Hg) requiring the use of vasopressors despite intravenous fluid resuscitation.

135. The method of any one of embodiments 129 to 134, wherein the subject has hypotension (*e.g.*, systolic arterial pressure < 90 mm Hg or mean arterial pressure (MAP) < 65 mm Hg) requiring the use of vasopressors for more than one hour despite intravenous fluid resuscitation.

136. The method of any one of embodiments 129 to 132, wherein the subject has hypotension requiring vasopressor treatment to maintain a mean arterial pressure of 65 mm Hg or greater.

137. The method of any one of embodiments 130 to 136, wherein the subject has a serum lactate level greater than 2 mmol/L despite intravenous fluid resuscitation.

138. The method of any one of embodiments 129 to 137, wherein administration of the lipid binding protein molecule is commenced within one day of commencement of vasopressor therapy.

139. The method of any one of embodiments 129 to 137, wherein administration of the lipid binding protein molecule is commenced within 24 hours of commencement of vasopressor therapy.

140. The method of any one of embodiments 129 to 137, wherein administration of the lipid binding protein molecule is commenced within 12 hours of commencement of vasopressor therapy.

141. The method of any one of embodiments 129 to 137, wherein administration of the lipid binding protein molecule is commenced within 6 hours of commencement of vasopressor therapy.

142. The method of any one of embodiments 129 to 141, further comprising administering a standard of care therapy for sepsis.

143. The method of embodiment 142, wherein the dose of the lipid binding protein molecule, together with the standard of care therapy, is effective to improve the likelihood of being alive 90 days following commencement of treatment compared to the standard of care therapy alone.

144. The method of embodiment 142 or 143, wherein the dose of the lipid binding protein molecule, together with the standard of care therapy, is effective to reduce the likelihood of organ dysfunction and/or need for organ support compared to the standard of care therapy alone.

145. The method of any one of embodiments 142 to 144, wherein the dose of the lipid binding protein molecule, together with the standard of care therapy, is effective to reduce the likelihood of requiring mechanical ventilation compared to the standard of care therapy alone.

146. The method of any one of embodiments 142 to 145, wherein the dose of the lipid binding protein molecule, together with the standard of care therapy, is effective to reduce the likelihood of requiring renal replacement therapy compared to the standard of care therapy alone.

147. The method of any one of embodiments 142 to 146, wherein the dose of the lipid binding protein molecule, together with the standard of care therapy, is effective to reduce the likelihood of requiring vasopressor therapy compared to the standard of care therapy alone.

148. The method of any one of embodiments 142 to 147, wherein the dose of the lipid binding protein molecule, together with the standard of care therapy, is effective to improve the subject's SOFA score.

149. The method of any one of embodiments 142 to 148, wherein the dose of the lipid binding protein molecule, together with the standard of care therapy, is effective to prevent an increase of the subject's Sepsis Support Index score.

150. The method of any one of embodiments 1 to 128, wherein the subject is at risk of sepsis.

151. The method of any one of embodiments 1 to 130, wherein the subject has acute respiratory distress syndrome (ARDS).

152. The method of any one of embodiments 1 to 130, wherein the subject is at risk of acute respiratory distress syndrome (ARDS).

153. The method of any one of embodiments 1 to 103, wherein the condition is acute myocardial infarction (AMI).

154. The method of any one of embodiments 1 to 103, wherein the condition is Alzheimer's disease.

155. The method of any one of embodiments 1 to 103, wherein the condition is chronic inflammatory bowel disease (IBD).

156. The method of any one of embodiments 1 to 103, wherein the condition is a cardiovascular disease (CVD).

157. The method of any one of embodiments 1 to 103, wherein the condition is a stroke.

158. The method of any one of embodiments 1 to 103, wherein the condition is a transient ischemic attack.

159. The method of any one of embodiments 1 to 103, wherein the condition is cytokine release syndrome (CRS).

160. The method of any one of embodiments 1 to 103, wherein the condition is organ transplant rejection.

161. The method of embodiment 160, wherein the organ transplant rejection is heart transplant rejection.

162. The method of any one of embodiments 1 to 103, wherein the condition is ischemia reperfusion-induced tissue injury.

163. The method of any one of embodiments 1 to 103, wherein the condition is post-operative inflammation.

164. The method of any one of embodiments 1 to 103, wherein the condition is psoriasis.

165. The method of any one of embodiments 1 to 103, wherein the condition is sepsis.

166. The method of embodiment 165, wherein the subject has sepsis and is at risk (*e.g.*, high risk) of developing acute kidney injury.

167. The method of embodiment 165, wherein the subject has an abnormal level of at least two of TNFα, IL-6, IL-8, TREM-1, and a kynurenine pathway biomarker.

168. The method of embodiment 167, wherein the subject has an abnormal level of TREM-1 and at least one of quinolinic acid, kynurenic acid, kynurenine, tryptophan, and kynurenine/tryptophan ratio.

169. The method of any one of embodiments 1 to 103, wherein the condition is sepsis-induced acute kidney injury (AKI).

170. The method of any one of embodiments 1 to 103, wherein the condition is hypoalbuminemia.

171. The method of embodiment 104, wherein the condition is hypoalbuminemia associated with a vitamin deficiency.

172. The method of embodiment 104, wherein the condition is hypoalbuminemia associated with inflammatory bowel disease (IBD).

173. The method of embodiment 104, wherein the condition is hypoalbuminemia associated with kidney disease.

174. The method of embodiment 104, wherein the condition is hypoalbuminemia associated with an infection, optionally wherein the infection is a gram-positive bacterial infection, a gram-negative bacterial infection, or a viral infection such as a SARS-CoV-2 (COVID-19) infection or influenza infection.

175. The method of embodiment 104, wherein the condition is hypoalbuminemia associated with stress.

176. The method of embodiment 104, wherein the condition is hypoalbuminemia associated with thyroid disease.

177. The method of embodiment 104, wherein the condition is hypoalbuminemia associated with diabetes.

178. The method of embodiment 104, wherein the condition is hypoalbuminemia associated with nephrotic syndrome.

179. The method of embodiment 104, wherein the condition is hypoalbuminemia associated with lupus.

180. The method of embodiment 104, wherein the condition is hypoalbuminemia associated with cirrhosis.

181. The method of embodiment 104, wherein the condition is hypoalbuminemia associated with liver disease.

182. The method of embodiment 104, wherein the condition is hypoalbuminemia associated with heart failure.

183. The method of embodiment 104, wherein the condition is hypoalbuminemia associated with malnutrition.

184. The method of any one of embodiments 1 to 103, wherein the condition is attention-deficit/hyperactivity disorder (ADHD).

185. The method of any one of embodiments 1 to 103, wherein the condition is a central nervous system (CNS) disease.

186. The method of any one of embodiments 1 to 103, wherein the condition is COVID-19 cognitive decline.

187. The method of any one of embodiments 1 to 103, wherein the condition is depression or major depressive disorder.

188. The method of any one of embodiments 1 to 103, wherein the condition is epilepsy.

189. The method of any one of embodiments 1 to 103, wherein the condition is HIV-associated neurocognitive disorder.

190. The method of any one of embodiments 1 to 103, wherein the condition is Huntington's disease.

191. The method of any one of embodiments 1 to 103, wherein the condition is inflammatory bowel disease (IBD).

192. The method of any one of embodiments 1 to 103, wherein the condition is long-term cognitive decline ("brain fog").

193. The method of embodiment 192, wherein the long-term cognitive decline is after sepsis.

194. The method of any one of embodiments 1 to 103, wherein the condition is mortality or neurological deficit following cardiac arrest.

195. The method of any one of embodiments 1 to 103, wherein the condition is multiple sclerosis (MS).

196. The method of any one of embodiments 1 to 103, wherein the condition is Parkinson's disease.

197. The method of any one of embodiments 1 to 103, wherein the condition is schizophrenia.

198. The method of any one of embodiments 1 to 103, wherein the condition is a liver disorder.

199. The method of any one of embodiments 1 to 103, wherein the condition is a kidney disorder.

200. The method of any one of embodiments 1 to 103, wherein the condition is vascular endothelial disorder.

201. The method of any one of embodiments 1 to 103, wherein the condition is acute respiratory distress syndrome (ARDS).

202. The method of any one of embodiments 1 to 198, wherein the dose is a high dose.

203. The method of any one of embodiments 1 to 201, which comprises a single individual dose.

204. The method of any one of embodiments 1 to 201, wherein the dose is the aggregate of two or more individual doses, optionally wherein an individual dose is from 4-40 mg/kg (on a protein weight basis).

205. The method of embodiment 204, wherein the dose is the aggregate of two to 20 individual doses.

206. The method of embodiment 204, wherein the dose is the aggregate of two to 16 individual doses.

207. The method of embodiment 204, wherein the dose is the aggregate of two to 12 individual doses.

208. The method of embodiment 204, wherein the dose is the aggregate of two to 10 individual doses.

209. The method of embodiment 204, wherein the dose is the aggregate of four to 20 individual doses.

210. The method of embodiment 204, wherein the dose is the aggregate of four to 16 individual doses.

211. The method of embodiment 204, wherein the dose is the aggregate of four to 12 individual doses.

212. The method of embodiment 204, wherein the dose is the aggregate of four to 10 individual doses.

213. The method of embodiment 204, wherein the dose is the aggregate of six to 20 individual doses.

214. The method of embodiment 204, wherein the dose is the aggregate of six to 16 individual doses.

215. The method of embodiment 204, wherein the dose is the aggregate of six to 12 individual doses.

216. The method of embodiment 204, wherein the dose is the aggregate of six to 10 individual doses.

217. The method of embodiment 204, wherein the dose is the aggregate of eight to 20 individual doses.

218. The method of embodiment 204, wherein the dose is the aggregate of eight to 16 individual doses.

219. The method of embodiment 204, wherein the dose is the aggregate of eight to 12 individual doses.

220. The method of embodiment 204, wherein the dose is the aggregate of eight to 10 individual doses.

221. The method of embodiment 204, wherein the dose is the aggregate of 10 to 20 individual doses.

222. The method of embodiment 204, wherein the dose is the aggregate of 10 to 16 individual doses.

223. The method of embodiment 204, wherein the dose is the aggregate of 10 to 12 individual doses.

224. The method of embodiment 204, wherein the dose is the aggregate of 12 to 20 individual doses.

225. The method of embodiment 204, wherein the dose is the aggregate of two individual doses.

226. The method of embodiment 204, wherein the dose is an aggregate of three or more individual doses.

227. The method of embodiment 204, wherein the dose is an aggregate of three individual doses.

228. The method of embodiment 204, wherein the dose is an aggregate of four or more individual doses.

229. The method of embodiment 204, wherein the dose is an aggregate of four individual doses.

230. The method of embodiment 204, wherein the dose is an aggregate of five or more individual doses.

231. The method of embodiment 204, wherein the dose is an aggregate of five individual doses.

232. The method of embodiment 204, wherein the dose is an aggregate of six or more individual doses.

233. The method of embodiment 204, wherein the dose is an aggregate of six individual doses.

234. The method of embodiment 204, wherein the dose is an aggregate of seven or more individual doses.

235. The method of embodiment 204, wherein the dose is an aggregate of seven individual doses.

236. The method of embodiment 204, wherein the dose is an aggregate of eight or more individual doses.

237. The method of embodiment 204, wherein the dose is an aggregate of eight individual doses.

238. The method of embodiment 204, wherein the dose is an aggregate of nine or more individual doses.

239. The method of embodiment 204, wherein the dose is an aggregate of nine individual doses.

240. The method of embodiment 204, wherein the dose is an aggregate of ten or more individual doses.

241. The method of embodiment 204, wherein the dose is an aggregate of ten individual doses.

242. The method of embodiment 204, wherein the dose is an aggregate of eleven or more individual doses.

243. The method of embodiment 204, wherein the dose is an aggregate of eleven individual doses.

244. The method of embodiment 204, wherein the dose is an aggregate of twelve or more individual doses.

245. The method of embodiment 204, wherein the dose is an aggregate of twelve individual doses.

246. The method of embodiment 204, wherein the dose is an aggregate of thirteen or more individual doses.

247. The method of embodiment 204, wherein the dose is an aggregate of thirteen individual doses.

248. The method of embodiment 204, wherein the dose is an aggregate of fourteen or more individual doses.

249. The method of embodiment 204, wherein the dose is an aggregate of fourteen individual doses.

250. The method of embodiment 204, wherein the dose is an aggregate of fifteen or more individual doses.

251. The method of embodiment 204, wherein the dose is an aggregate of fifteen individual doses.

252. The method of embodiment 204, wherein the dose is an aggregate of sixteen or more individual doses.

253. The method of embodiment 204, wherein the dose is an aggregate of sixteen individual doses.

254. The method of embodiment 204, wherein the dose is an aggregate of seventeen or more individual doses.

255. The method of embodiment 204, wherein the dose is an aggregate of seventeen individual doses.

256. The method of embodiment 204, wherein the dose is an aggregate of eighteen or more individual doses.

257. The method of embodiment 204, wherein the dose is an aggregate of eighteen individual doses.

258. The method of embodiment 204, wherein the dose is an aggregate of nineteen or more individual doses.

259. The method of embodiment 204, wherein the dose is an aggregate of nineteen individual doses.

260. The method of embodiment 204, wherein the dose is an aggregate of twenty or more individual doses.

261. The method of embodiment 204, wherein the dose is an aggregate of twenty individual doses.

262. The method of any one of embodiments 1 to 261, wherein the dose is administered over a period of one day to approximately two weeks.

263. The method of any one of embodiments 1 to 261, wherein the dose is administered over a period of one day to approximately three weeks.

264. The method of embodiment 262, wherein the dose is administered over a period of one day.

265. The method of embodiment 262, wherein the dose is administered over a period of two days.

266. The method of embodiment 262, wherein the dose is administered over a period of three days.

267. The method of embodiment 262, wherein the dose is administered over a period of four days.

268. The method of embodiment 262, wherein the dose is administered over a period of five days.

269. The method of embodiment 262, wherein the dose is administered over a period of six days.

270. The method of embodiment 262, wherein the dose is administered over a period of approximately one week.

271. The method of embodiment 262, wherein the dose is administered over a period of seven days.

272. The method of embodiment 262, wherein the dose is administered over a period of eight days.

273. The method of embodiment 262, wherein the dose is administered over a period of nine days.

274. The method of embodiment 262, wherein the dose is administered over a period of ten days.

275. The method of embodiment 262, wherein the dose is administered over a period of eleven days.

276. The method of embodiment 262, wherein the dose is administered over a period of 12 days.

277. The method of embodiment 262, wherein the dose is administered over a period of 13 days.

278. The method of embodiment 262, wherein the dose is administered over a period of 14 days.

279. The method of embodiment 262, wherein the dose is administered over a period of approximately two weeks.

280. The method of embodiment 262, wherein the dose is administered over a period of 15 days.

281. The method of any one of embodiments 1 to 280, wherein a plurality of individual doses are administered daily or twice daily.

282. The method of embodiment 281, wherein a plurality of individual doses are administered daily.

283. The method of embodiment 281, wherein a plurality of individual doses are administered twice daily.

284. The method of any one of embodiments 1 to 280, wherein a plurality of individual doses are administered two to three days apart.

285. The method of any one of embodiments 1 to 281, wherein a plurality of individual doses are administered no more than one day apart.

286. The method of embodiment 285, which comprises administering two or more doses approximately 12 hours apart.

287. The method of embodiment 286, which comprises administering two doses approximately 12 hours apart.

288. The method of embodiment 286, which comprises administering three doses approximately 12 hours apart.

289. The method of embodiment 287 or embodiment 288, which further comprises administering a dose approximately one day later.

290. The method of any one of embodiments 1 to 281, which comprises administering three doses approximately 12 hours apart and a fourth dose approximately one day later.

291. The method of embodiment 204, wherein a dose is the aggregate of two individual doses administered in one day.

292. The method of embodiment 291, wherein the dose is the aggregate of two individual doses administered approximately 12 hours apart.

293. The method of any one of embodiments 1 to 292, wherein the dose is effective to increase the subject's HDL levels.

294. The method of embodiment 293, wherein the dose is effective to increase the subject's serum HDL levels to normal (*e.g.*, > 0.45 g/L).

295. The method of embodiment 293, wherein each individual dose is effective to increase the subject's HDL levels by at least 25%, at least 30% or at least 35% 2-4 hours after administration.

296. The method of embodiment 295, wherein each individual dose is effective to increase the subject's HDL levels by at least 25%, at least 30% or at least 35% 2 hours after administration.

297. The method of embodiment 295, wherein each individual dose is effective to increase the subject's HDL levels by at least 25%, at least 30% or at least 35% 3 hours after administration.

298. The method of embodiment 295, wherein each individual dose is effective to increase the subject's HDL levels by at least 25%, at least 30% or at least 35% 4 hours after administration.

299. The method of any one of embodiments 1 to 298, wherein each individual dose is effective to increase the subject's ApoA-I levels.

300. The method of embodiment 299, wherein the dose is effective to increase the subject's serum ApoA-I levels to normal (*e.g.*, > 1.1 g/L).

301. The method of embodiment 299, wherein each individual dose is effective to increase the subject's ApoA-I levels by at least 25%, at least 30% or at least 35% 2-4 hours after administration.

302. The method of embodiment 300, wherein each individual dose is effective to increase the subject's ApoA-I levels by at least 25%, at least 30% or at least 35% 2 hours after administration.

303. The method of embodiment 300, wherein each individual dose is effective to increase the subject's ApoA-I levels by at least 25%, at least 30% or at least 35% 3 hours after administration.

304. The method of embodiment 300, wherein each individual dose is effective to increase the subject's ApoA-I levels by at least 25%, at least 30% or at least 35% 4 hours after administration.

305. The method of any one of embodiments 1 to 304, wherein the dose is effective to improve the subject's vascular endothelial function, optionally wherein vascular endothelial function is measured by circulating VCAM-1 and/or ICAM-1.

306. The method of embodiment 305, wherein vascular endothelial function is measured by TNF-α, eNOS, and/or CD14.

307. The method of any one of embodiments 1 to 305, wherein the dose is effective to reduce serum levels of one or more inflammatory markers in the subject.

308. The method of any one of embodiments 1 to 305, wherein the dose is effective to reduce serum levels of two or more inflammatory markers in the subject.

309. The method of any one of embodiments 1 to 305, wherein the dose is effective to reduce serum levels of three or more inflammatory markers in the subject.

310. The method of any one of embodiments 1 to 305, wherein the dose is effective to reduce serum levels of four or more inflammatory markers in the subject.

311. The method of any one of embodiments 1 to 305, wherein the dose is effective to reduce serum levels of five or more inflammatory markers in the subject.

312. The method of any one of embodiments 307 to 311, wherein the dose is effective to reduce serum levels of interleukin-6 ("IL-6"), such as by at least 20%, by at least 40%, or at least 60%.

313. The method of any one of embodiments 307 to 312, wherein the dose is effective to reduce serum levels of C-reactive protein, such as by at least 20%, by at least 40%, or at least 60%.

314. The method of any one of embodiments 307 to 313, wherein the dose is effective to reduce serum levels of D-dimer.

315. The method of any one of embodiments 307 to 314, wherein the dose is effective to reduce serum levels of ferritin, such as by at least 15%, by at least 30%, or at least 45%.

316. The method of any one of embodiments 307 to 315, wherein the dose is effective to reduce serum levels of interleukin 8 (IL-8), such as by at least 20%, by at least 40%, or at least 60%.

317. The method of any one of embodiments 307 to 316, wherein the dose is effective to normalize serum levels of interleukin 8 (IL-8).

318. The method of any one of embodiments 307 to 317, wherein the dose is effective to reduce serum levels of granulocyte-macrophage colony stimulating factor (GM-CSF).

319. The method of any one of embodiments 307 to 318, wherein the dose is effective to reduce serum levels of monocyte chemoattractant protein (MCP) 1, such as by at least 15%, by at least 30%, or at least 45%.

320. The method of any one of embodiments 307 to 319, wherein the dose is effective to reduce serum levels of tumor necrosis factor α (TNF-α) , such as by at least 20%, by at least 40%, or at least 60%.

321. The method of any one of embodiments 307 to 320, wherein the dose is effective to reduce serum levels of the one or more inflammatory markers from an elevated range to a normal range.

322. The method of any one of embodiments 307 to 321, wherein the dose is effective to reduce serum levels of the one or more inflammatory markers by at least 20%, by at least 40% or by at least 60%.

323. The method of any one of embodiments 307 to 322, wherein the dose is effective to reduce serum levels of lipopolysaccharides, such as by at least 15%, at least 30%, or at least 45%.

324. The method of any one of embodiments 307 to 323, wherein the dose is effective to reduce endotoxin activity, such as by at least 10%, at least 20%, or at least 30%.

325. The method of any one of embodiments 307 to 324, wherein the dose is effective to reduce serum levels of IL-10, such as by at least 20%, at least 40%, or at least 60%.

326. The method of any one of embodiments 307 to 325, wherein the dose is effective to reduce serum levels of TREM-1, such as by at least 20%, at least 40%, or at least 60%.

327. The method of any one of embodiments 307 to 326, wherein the dose is effective to reduce serum levels of VCAM-1, such as by at least 10%, at least 20%, or at least 30%.

328. The method of any one of embodiments 307 to 327, wherein the dose is effective to reduce serum levels of ICAM-1, such as by at least 15%, at least 30%, or at least 45%.

329. The method of any one of embodiments 307 to 328, wherein the dose is effective to reduce serum levels of white blood cells, such as by at least 10%, at least 20%, or at least 30%.

330. The method of any one of embodiments 307 to 329, wherein the dose is effective to reduce serum levels of KIM-1, such as by at least 15%, at least 30%, or at least 45%.

331. The method of any one of embodiments 1 to 330, wherein the subject has CRS or is at risk of CRS.

332. The method of embodiment 331, wherein the subject has CRS.

333. The method of embodiment 331, wherein the subject is at risk of CRS.

334. The method of any one of embodiments 1 to 333, wherein the dose is effective to reduce the likelihood that the subject will develop acute kidney injury (AKI).

335. The method of any one of embodiments 1 to 334, wherein the dose is effective to delay the onset of AKI.

336. The method of any one of embodiments 1 to 334, wherein the dose is effective to prevent AKI.

337. The method of any one of embodiments 1 to 333, wherein the subject has or is at risk of developing acute kidney injury (AKI).

338. The method of embodiment 337, wherein the subject has AKI.

339. The method of embodiment 338 , wherein the dose is effective to reduce the severity of the AKI.

340. The method of embodiment 337, wherein the subject is at risk for AKI.

341. The method of embodiment 340, wherein the dose is effective to reduce the likelihood that the subject will develop AKI.

342. The method of embodiment 340, wherein the dose is effective to delay the onset of AKI.

343. The method of embodiment 340, wherein the dose is effective to prevent AKI.

344. The method of embodiment 340, wherein if the subject develops AKI and the dose is a high dose, the high dose is effective to reduce the severity of the AKI.

345. The method of any one of embodiments 1 to 344, wherein the subject has a SOFA score of 1 to 24 prior to administration of the lipid binding protein molecule.

346. The method of any one of embodiments 1 to 344, wherein the subject has a SOFA score of 5 to 24 prior to administration of the lipid binding protein molecule.

347. The method of any one of embodiments 1 to 344, wherein the subject has a SOFA score of 10 to 24 prior to administration of the lipid binding protein molecule.

348. The method of any one of embodiments 1 to 344, wherein the subject has a SOFA score of 15 to 24 prior to administration of the lipid binding protein molecule.

349. The method of any one of embodiments 1 to 344, wherein the subject has a SOFA score of 1 to 20 prior to administration of the lipid binding protein molecule.

350. The method of any one of embodiments 1 to 344, wherein the subject has a SOFA score of 5 to 20 prior to administration of the lipid binding protein molecule.

351. The method of any one of embodiments 1 to 344, wherein the subject has a SOFA score of 10 to 20 prior to administration of the lipid binding protein molecule.

352. The method of any one of embodiments 1 to 344, wherein the subject has a SOFA score of 10 to 15 prior to administration of the lipid binding protein molecule.

353. The method of any one of embodiments 1 to 344, wherein the subject has a SOFA score of 1 to 10 prior to administration of the lipid binding protein molecule.

354. The method of any one of embodiments 1 to 344, wherein the subject has a SOFA score of 2 to 10 prior to administration of the lipid binding protein molecule.

355. The method of any one of embodiments 1 to 344, wherein the subject has a SOFA score of 2 to 5 prior to administration of the lipid binding protein molecule.

356. The method of any one of embodiments 1 to 344, wherein the subject has a SOFA score of 5 to 10 prior to administration of the lipid binding protein molecule.

357. The method of embodiment 345, wherein the subject has a SOFA score of 2 to 24 prior to administration of the lipid binding protein molecule.

358. The method of embodiment 345, wherein the subject has a SOFA score of 1 prior to administration of the lipid binding protein molecule.

359. The method of embodiment 345, wherein the subject has a SOFA score of 2 prior to administration of the lipid binding protein molecule.

360. The method of embodiment 345, wherein the subject has a SOFA score of 3 prior to administration of the lipid binding protein molecule.

361. The method of embodiment 345, wherein the subject has a SOFA score of 4 prior to administration of the lipid binding protein molecule.

362. The method of embodiment 345, wherein the subject has a SOFA score of 5 prior to administration of the lipid binding protein molecule.

363. The method of embodiment 345, wherein the subject has a SOFA score of 6 prior to administration of the lipid binding protein molecule.

364. The method of embodiment 345, wherein the subject has a SOFA score of 7 prior to administration of the lipid binding protein molecule.

365. The method of embodiment 345, wherein the subject has a SOFA score of 8 prior to administration of the lipid binding protein molecule.

366. The method of embodiment 345, wherein the subject has a SOFA score of 9 prior to administration of the lipid binding protein molecule.

367. The method of embodiment 345, wherein the subject has a SOFA score of 10 prior to administration of the lipid binding protein molecule.

368. The method of embodiment 345, wherein the subject has a SOFA score of 11 prior to administration of the lipid binding protein molecule.

369. The method of embodiment 345, wherein the subject has a SOFA score of 12 prior to administration of the lipid binding protein molecule.

370. The method of embodiment 345, wherein the subject has a SOFA score of 13 prior to administration of the lipid binding protein molecule.

371. The method of embodiment 345, wherein the subject has a SOFA score of 14 prior to administration of the lipid binding protein molecule.

372. The method of embodiment 345, wherein the subject has a SOFA score of 15 prior to administration of the lipid binding protein molecule.

373. The method of embodiment 345, wherein the subject has a SOFA score of 16 prior to administration of the lipid binding protein molecule.

374. The method of embodiment 345, wherein the subject has a SOFA score of 17 prior to administration of the lipid binding protein molecule.

375. The method of embodiment 345, wherein the subject has a SOFA score of 18 prior to administration of the lipid binding protein molecule.

376. The method of embodiment 345, wherein the subject has a SOFA score of 19 prior to administration of the lipid binding protein molecule.

377. The method of embodiment 345, wherein the subject has a SOFA score of 20 prior to administration of the lipid binding protein molecule.

378. The method of embodiment 345, wherein the subject has a SOFA score of 21 prior to administration of the lipid binding protein molecule.

379. The method of embodiment 345, wherein the subject has a SOFA score of 22 prior to administration of the lipid binding protein molecule.

380. The method of embodiment 345, wherein the subject has a SOFA score of 23 prior to administration of the lipid binding protein molecule.

381. The method of embodiment 345, wherein the subject has a SOFA score of 24 prior to administration of the lipid binding protein molecule.

382. The method of any one of embodiments 1 to 381, wherein the lipid binding protein molecule is an apolipoprotein.

383. The method of embodiment 382, wherein the apolipoprotein is ApoA-I.

384. The method of embodiment 383, wherein the ApoA-I has the amino acid sequence of amino acids 25-267 of SEQ ID NO:1 of WO 2012/109162.

385. The method of embodiment 383 or embodiment 384, wherein the ApoA-I is a recombinant ApoA-I.

386. The method of embodiment 385, wherein the ApoA-I is produced by a mammalian host cell.

387. The method of embodiment 386, wherein the mammalian host cell is a CHO cell.

388. The method of any one of embodiments 385 to 387, wherein the ApoA-I has undergone post-translational processing (*e.g.*, glycosylation) such that the ApoA-I has one or more structural features (*e.g.*, glycosylation pattern) that are different from human ApoA-I purified from human plasma.

389. The method of any one of embodiments 1 to 388, wherein the lipid binding protein molecule is an apolipoprotein mimetic.

390. The method of any one of embodiments 1 to 389, wherein the lipid binding protein molecule is a component of (*e.g.*, formulated as) a lipid binding protein-based complex, optionally wherein the lipid binding protein-based complex is a reconstituted HDL or HDL mimetic.

391. The method of any one of embodiments 1 to 390, wherein the lipid binding protein molecule is a component of (*e.g.*, formulated as) a lipid binding protein-based complex, and the lipid binding protein-based complex is an Apomer or a Cargomer.

392. The method of any one of embodiments 1 to 391, wherein the lipid binding protein molecule is a component of (*e.g.*, formulated as) a lipid binding protein-based complex, and the lipid binding protein-based complex comprises a sphingomyelin.

393. The method of embodiment 392, wherein the lipid binding protein-based complex comprises ApoA-I and phospholipids in a ApoA-I weight:total phospholipid weight ratio of 1:2.7 +/- 20% and the phospholipids sphingomyelin and DPPG in a sphingomyelin:DPPG weight:weight ratio of 97:3 +/- 20%.

394. The method of embodiment 393, wherein the lipid binding protein-based complex comprises ApoA-I and phospholipids in a ApoA-I weight:total phospholipid weight ratio of 1:2.7 +/- 10% and the phospholipids sphingomyelin and DPPG in a sphingomyelin:DPPG weight:weight ratio of 97:3 +/- 10%.

395. The method of embodiment 394, wherein lipid binding protein-based complex comprises ApoA-I and phospholipids in a ApoA-I weight:total phospholipid weight ratio of 1:2.7 and the phospholipids sphingomyelin and DPPG in a sphingomyelin:DPPG weight:weight ratio of 97:3.

396. The method of any one of embodiments 392 to 395, wherein the lipid binding protein-based complex comprises natural sphingomyelin.

397. The method of embodiment 396, wherein the natural sphingomyelin is chicken egg sphingomyelin.

398. The method of any one of embodiments 392 to 395, wherein the lipid binding protein-based complex comprises synthetic sphingomyelin.

399. The method of embodiment 398, wherein the sphingomyelin comprises palmitoylsphingomyelin.

400. The method of any one of embodiments 1 to 399, wherein the lipid binding protein molecule is a component of (*e.g.*, formulated as) a lipid binding protein-based complex, and the lipid binding protein-based complex comprises a negatively charged lipid.

401. The method of embodiment 400, wherein the negatively charged lipid is 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol) (DPPG) or a salt thereof.

402. The method of embodiment 390, wherein the lipid binding protein-based complex is CER-001, CSL-111, CSL-112, CER-522 ETC-216, or ETC-642.

403. The method of embodiment 402, wherein the lipid binding protein-based complex is CER-001.

404. The method of embodiment 403, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 95% homogeneous.

405. The method of embodiment 404, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 97% homogeneous.

406. The method of embodiment 405, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 98% homogeneous.

407. The method of embodiment 406, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 99% homogeneous.

408. The method of any one of embodiments 1 to 407, wherein the lipid binding protein molecule is administered systemically, optionally by infusion.

409. The method of any one of embodiments 1 to 408, wherein the lipid binding protein molecule is administered until serum levels of one or more inflammatory markers are reduced.

410. The method of embodiment 409, wherein the lipid binding protein molecule is administered until serum levels of one or more inflammatory markers are reduced to a normal range(s).

411. The method of embodiment 409, wherein the lipid binding protein molecule is administered until serum levels of one or more inflammatory markers are reduced below a baseline

level(s) for the one or more inflammatory markers measured prior to lipid binding protein molecule administration.

412. The method of any one of embodiments 1 to 411, wherein each individual dose of the lipid binding protein molecule administered is 4-40 mg/kg (on a protein weight basis).

413. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 4-30 mg/kg (on a protein weight basis).

414. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 15-25 mg/kg (on a protein weight basis).

415. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 10-30 mg/kg (on a protein weight basis).

416. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 10-20 mg/kg (on a protein weight basis).

417. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 5 mg/kg (on a protein weight basis).

418. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 10 mg/kg (on a protein weight basis).

419. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 15 mg/kg (on a protein weight basis).

420. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 20 mg/kg (on a protein weight basis).

421. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 5 to 15 mg/kg (on a protein weight basis).

422. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 4 to 5 mg/kg on a protein weight basis.

423. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 4 to 10 mg/kg on a protein weight basis.

424. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 4 to 15 mg/kg on a protein weight basis.

425. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 4 to 20 mg/kg on a protein weight basis.

426. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 4 to 25 mg/kg on a protein weight basis.

427. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 4 to 35 mg/kg on a protein weight basis.

428. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 5 to 10 mg/kg on a protein weight basis.

429. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 5 to 20 mg/kg on a protein weight basis.

430. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 5 to 25 mg/kg on a protein weight basis.

431. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 5 to 30 mg/kg on a protein weight basis.

432. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 5 to 35 mg/kg on a protein weight basis.

433. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 5 to 40 mg/kg on a protein weight basis.

434. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 10 to 15 mg/kg on a protein weight basis.

435. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 10 to 25 mg/kg on a protein weight basis.

436. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 10 to 35 mg/kg on a protein weight basis.

437. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 10 to 40 mg/kg on a protein weight basis.

438. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 15 to 20 mg/kg on a protein weight basis.

439. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 15 to 30 mg/kg on a protein weight basis.

440. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 15 to 35 mg/kg on a protein weight basis.

441. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 15 to 40 mg/kg on a protein weight basis.

442. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 20 to 25 mg/kg on a protein weight basis.

443. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 20 to 30 mg/kg on a protein weight basis.

444. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 20 to 35 mg/kg on a protein weight basis.

445. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 20 to 40 mg/kg on a protein weight basis.

446. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 25 to 30 mg/kg on a protein weight basis.

447. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 25 to 35 mg/kg on a protein weight basis.

448. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 25 to 40 mg/kg on a protein weight basis.

449. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 30 to 35 mg/kg on a protein weight basis.

450. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 30 to 40 mg/kg on a protein weight basis.

451. The method of embodiment 412, wherein each individual dose of the lipid binding protein molecule is 35 to 40 mg/kg on a protein weight basis.

452. The method of any one of embodiments 1 to 451, wherein the dose is administered according to an induction regimen, optionally followed by a consolidation regimen.

453. The method of embodiment 452, wherein the induction regimen comprises administering the lipid binding protein molecule once daily or twice daily.

454. The method of embodiment 452 or embodiment 453, wherein the consolidation regimen comprises administering the lipid binding protein molecule once daily or once every two days.

455. The method of any one of embodiments 452 to 454, wherein the induction regimen comprises twice daily administration of the lipid binding protein molecule for at least three days (*e.g.*, three days to one week, four days to one week, five days to one week, six days to one week) and the consolidation regimen comprises once daily administration of the lipid binding protein molecule for up to

15 days (*e.g.*, three to five days, five to seven days, one week to two weeks, up to one week, or up to two weeks).

456. The method of embodiment 455, wherein the induction regimen is three days.

457. The method of embodiment 455, wherein the induction regimen is four days.

458. The method of embodiment 455, wherein the induction regimen is five days.

459. The method of embodiment 455, wherein the induction regimen is six days.

460. The method of embodiment 455, wherein the induction regimen is seven days.

461. The method of embodiment 455, wherein the induction regimen is eight days.

462. The method of embodiment 455, wherein the induction regimen is nine days.

463. The method of embodiment 455, wherein the induction regimen is ten days.

464. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is one day.

465. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is two days.

466. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is three days.

467. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is four days.

468. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is five days.

469. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is six days.

470. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is seven days.

471. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is eight days.

472. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is nine days.

473. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is ten days.

474. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is eleven days.

475. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is twelve days.

476. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is thirteen days.

477. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is fourteen days.

478. The method of any one of embodiments 455 to 463, wherein the consolidation regimen is fifteen days.

479. The method of any one of embodiments 455 to 478, wherein the each individual dose of the lipid binding protein molecule in the consolidation regimen is the same as each individual dose of the lipid binding protein molecule in the induction regimen (*e.g.*, 5 mg/kg, 10 mg/kg, 15 mg/kg, or 20 mg/kg on a protein weight basis).

480. The method of any one of embodiments 455 to 478, wherein each individual dose of the lipid binding protein molecule in the consolidation regimen is higher than each individual dose of the lipid binding protein molecule in the induction regimen (*e.g.*, individual doses of 5 mg/kg, 10 mg/kg or 15 mg/kg in the induction regimen and individual doses of 10 mg/kg, 15 mg/kg or 20 mg/kg in the consolidation regimen, provided the individual doses of the consolidation regimen are higher than those of the induction regimen).

481. The method of any one of embodiments 452 to 480, wherein the subject is not treated with a maintenance regimen.

482. The method of any one of embodiments 452 to 480, wherein the subject is treated with a maintenance regimen.

483. The method of any one of embodiments 452 to 482, wherein the consolidation regimen comprises administering one or more doses of the lipid binding protein molecule to the subject one or more days after administration of the final dose of the induction regimen.

484. The method of embodiment 483, wherein the first dose of the lipid binding protein molecule administered during the consolidation regimen is administered two or more days after administration of the final dose of the induction regimen.

485. The method of embodiment 483, wherein the first dose of the lipid binding protein molecule administered during the consolidation regimen is administered three or more days after administration of the final dose of the induction regimen.

486. The method of embodiment 485, wherein the first dose of the lipid binding protein molecule administered during the consolidation regimen is administered three days after administration of the final dose of the induction regimen.

487. The method of any one of embodiments 452 to 486, which comprises an induction regimen comprising twice daily administration of the lipid binding protein molecule on days 1, 2, and 3 and a consolidation regimen comprising two doses of the lipid binding protein molecule on day 6.

488. The method of any one of embodiments 452 to 487, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 4-40 mg/kg (on a protein weight basis).

489. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 4-30 mg/kg (on a protein weight basis).

490. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 15-25 mg/kg (on a protein weight basis).

491. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 10-30 mg/kg (on a protein weight basis).

492. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 10-20 mg/kg (on a protein weight basis).

493. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 5 mg/kg (on a protein weight basis).

494. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 10 mg/kg (on a protein weight basis).

495. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 15 mg/kg (on a protein weight basis).

496. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 20 mg/kg (on a protein weight basis).

497. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 4 to 5 mg/kg on a protein weight basis.

498. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 4 to 10 mg/kg on a protein weight basis.

499. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 4 to 15 mg/kg on a protein weight basis.

500. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 4 to 20 mg/kg on a protein weight basis.

501. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 4 to 25 mg/kg on a protein weight basis.

502. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 4 to 35 mg/kg on a protein weight basis.

503. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 5 to 10 mg/kg on a protein weight basis.

504. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 5 to 20 mg/kg on a protein weight basis.

505. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 5 to 25 mg/kg on a protein weight basis.

506. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 5 to 30 mg/kg on a protein weight basis.

507. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 5 to 35 mg/kg on a protein weight basis.

508. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 5 to 40 mg/kg on a protein weight basis.

509. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 10 to 15 mg/kg on a protein weight basis.

510. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 10 to 25 mg/kg on a protein weight basis.

511. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 10 to 35 mg/kg on a protein weight basis.

512. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 10 to 40 mg/kg on a protein weight basis.

513. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 15 to 20 mg/kg on a protein weight basis.

514. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 15 to 30 mg/kg on a protein weight basis.

515. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 15 to 35 mg/kg on a protein weight basis.

516. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 15 to 40 mg/kg on a protein weight basis.

517. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 20 to 25 mg/kg on a protein weight basis.

518. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 20 to 30 mg/kg on a protein weight basis.

519. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 20 to 35 mg/kg on a protein weight basis.

520. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 20 to 40 mg/kg on a protein weight basis.

521. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 25 to 30 mg/kg on a protein weight basis.

522. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 25 to 35 mg/kg on a protein weight basis.

523. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 25 to 40 mg/kg on a protein weight basis.

524. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 30 to 35 mg/kg on a protein weight basis.

525. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 30 to 40 mg/kg on a protein weight basis.

526. The method of any one of embodiments 452 to 488, wherein each individual dose of the lipid binding protein molecule administered in the induction regimen is 35 to 40 mg/kg on a protein weight basis.

527. The method of any one of embodiments 452 to 526, wherein the dose of the lipid binding protein molecule administered in the consolidation regimen is 5 to 15 mg/kg (on a protein weight basis).

528. The method of any one of embodiments 452 to 526, wherein the dose of the lipid binding protein molecule administered in the consolidation regimen is 10 to 20 mg/kg (on a protein weight basis).

529. The method of any one of embodiments 452 to 526, wherein the dose of the lipid binding protein molecule administered in the consolidation regimen is 15 to 25 mg/kg (on a protein weight basis).

530. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 4 to 5 mg/kg on a protein weight basis.

531. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 4 to 10 mg/kg on a protein weight basis.

532. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 4 to 15 mg/kg on a protein weight basis.

533. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 4 to 20 mg/kg on a protein weight basis.

534. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 4 to 25 mg/kg on a protein weight basis.

535. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 4 to 35 mg/kg on a protein weight basis.

536. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 5 to 10 mg/kg on a protein weight basis.

537. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 5 to 20 mg/kg on a protein weight basis.

538. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 5 to 25 mg/kg on a protein weight basis.

539. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 5 to 30 mg/kg on a protein weight basis.

540. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 5 to 35 mg/kg on a protein weight basis.

541. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 5 to 40 mg/kg on a protein weight basis.

542. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 10 to 15 mg/kg on a protein weight basis.

543. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 10 to 25 mg/kg on a protein weight basis.

544. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 10 to 35 mg/kg on a protein weight basis.

545. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 10 to 40 mg/kg on a protein weight basis.

546. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 15 to 20 mg/kg on a protein weight basis.

547. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 15 to 30 mg/kg on a protein weight basis.

548. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 15 to 35 mg/kg on a protein weight basis.

549. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 15 to 40 mg/kg on a protein weight basis.

550. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 20 to 25 mg/kg on a protein weight basis.

551. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 20 to 30 mg/kg on a protein weight basis.

552. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 20 to 35 mg/kg on a protein weight basis.

553. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 20 to 40 mg/kg on a protein weight basis.

554. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 25 to 30 mg/kg on a protein weight basis.

555. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 25 to 35 mg/kg on a protein weight basis.

556. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 25 to 40 mg/kg on a protein weight basis.

557. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 30 to 35 mg/kg on a protein weight basis.

558. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 30 to 40 mg/kg on a protein weight basis.

559. The method of any one of embodiments 452 to 526, wherein each individual dose of the lipid binding protein molecule administered in the consolidation regimen is 35 to 40 mg/kg on a protein weight basis.

560. The method of any one of embodiments 452 to 526, wherein the dose of the lipid binding protein molecule administered in the consolidation regimen is 5 mg/kg (on a protein weight basis).

561. The method of any one of embodiments 452 to 526, wherein the dose of the lipid binding protein molecule administered in the consolidation regimen is 10 mg/kg (on a protein weight basis).

562. The method of any one of embodiments 452 to 526, wherein the dose of the lipid binding protein molecule administered in the consolidation regimen is 15 mg/kg (on a protein weight basis).

563. The method of any one of embodiments 1 to 562, wherein each dose of the lipid binding protein molecule administered is 300 mg to 4000 mg (on a protein weight basis).

564. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 300 mg to 400 mg on a protein weight basis.

565. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 300 mg to 500 mg on a protein weight basis.

566. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 300 mg to 600 mg on a protein weight basis.

567. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 300 mg to 800 mg on a protein weight basis.

568. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 300 mg to 1000 mg on a protein weight basis.

569. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 300 mg to 1200 mg on a protein weight basis.

570. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 300 mg to 1500 mg on a protein weight basis.

571. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 300 mg to 2000 mg on a protein weight basis.

572. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 300 mg to 2400 mg on a protein weight basis.

573. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 300 mg to 3000 mg on a protein weight basis.

574. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 400 mg to 500 mg on a protein weight basis.

575. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 400 mg to 600 mg on a protein weight basis.

576. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 400 mg to 800 mg on a protein weight basis.

577. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 400 mg to 1000 mg on a protein weight basis.

578. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 400 mg to 1200 mg on a protein weight basis.

579. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 400 mg to 1500 mg on a protein weight basis.

580. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 400 mg to 2000 mg on a protein weight basis.

581. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 400 mg to 2400 mg on a protein weight basis.

582. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 400 mg to 3000 mg on a protein weight basis.

583. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 400 mg to 4000 mg on a protein weight basis.

584. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 500 mg to 600 mg on a protein weight basis.

585. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 500 mg to 800 mg on a protein weight basis.

586. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 500 mg to 1000 mg on a protein weight basis.

587. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 500 mg to 1200 mg on a protein weight basis.

588. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 500 mg to 1500 mg on a protein weight basis.

589. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 500 mg to 2000 mg on a protein weight basis.

590. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 500 mg to 2400 mg on a protein weight basis.

591. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 500 mg to 3000 mg on a protein weight basis.

592. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 500 mg to 4000 mg on a protein weight basis.

593. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 600 mg to 800 mg on a protein weight basis.

594. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 600 mg to 1000 mg on a protein weight basis.

595. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 600 mg to 1200 mg on a protein weight basis.

596. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 600 mg to 1500 mg on a protein weight basis.

597. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 600 mg to 2000 mg on a protein weight basis.

598. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 600 mg to 2400 mg on a protein weight basis.

599. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 600 mg to 3000 mg on a protein weight basis.

600. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 600 mg to 4000 mg on a protein weight basis.

601. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 800 mg to 1000 mg on a protein weight basis.

602. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 800 mg to 1200 mg on a protein weight basis.

603. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 800 mg to 1500 mg on a protein weight basis.

604. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 800 mg to 2000 mg on a protein weight basis.

605. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 800 mg to 2400 mg on a protein weight basis.

606. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 800 mg to 3000 mg on a protein weight basis.

607. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 800 mg to 4000 mg on a protein weight basis.

608. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1000 mg to 1200 mg on a protein weight basis.

609. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1000 mg to 1500 mg on a protein weight basis.

610. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1000 mg to 2000 mg on a protein weight basis.

611. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1000 mg to 2400 mg on a protein weight basis.

612. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1000 mg to 3000 mg on a protein weight basis.

613. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1000 mg to 4000 mg on a protein weight basis.

614. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1200 mg to 1500 mg on a protein weight basis.

615. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1200 mg to 2000 mg on a protein weight basis.

616. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1200 mg to 2400 mg on a protein weight basis.

617. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1200 mg to 3000 mg on a protein weight basis.

618. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1200 mg to 4000 mg on a protein weight basis.

619. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1500 mg to 2000 mg on a protein weight basis.

620. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1500 mg to 2400 mg on a protein weight basis.

621. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1500 mg to 3000 mg on a protein weight basis.

622. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 1500 mg to 4000 mg on a protein weight basis.

623. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 2000 mg to 2400 mg on a protein weight basis.

624. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 2000 mg to 3000 mg on a protein weight basis.

625. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 2000 mg to 4000 mg on a protein weight basis.

626. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 2400 mg to 3000 mg on a protein weight basis.

627. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 2400 mg to 4000 mg on a protein weight basis.

628. The method of embodiment 563, wherein each dose of the lipid binding protein molecule administered is 3000 mg to 4000 mg on a protein weight basis.

629. The method of any one of embodiments 1 to 628, wherein a high dose of the lipid binding protein molecule is 600 mg to 40 g (on a protein weight basis).

630. The method of embodiment 629, wherein a high dose of the lipid binding protein molecule is 3 g to 35 g (on a protein weight basis).

631. The method of embodiment 630, wherein the high dose of the lipid binding protein molecule is 5 g to 30 g (on a protein weight basis).

632. The method of any one of embodiments 1 to 631, wherein the lipid binding protein molecule is administered by infusion.

633. The method of embodiment 632, wherein each dose is administered over a one to 24-hour period.

634. The method of embodiment 633, wherein each dose is administered over a 24-hour period.

635. The method of embodiment 632, wherein each dose is administered over a period of one hour or less.

636. The method of embodiment 632, wherein each dose is administered over a period of one-half hour to one hour.

637. The method of any one of embodiments 1 to 636, which further comprises administering an antihistamine to the subject prior to each dose.

638. The method of embodiment 637, wherein the antihistamine comprises dexchlorpheniramine, hydroxyzine, diphenhydramine, cetirizine, fexofenadine, or loratadine.

639. The method of embodiment 638, wherein the antihistamine comprises dexchlorpheniramine.

640. The method of embodiment 638, wherein the antihistamine comprises hydroxyzine.

641. The method of embodiment 638, wherein the antihistamine comprises diphenhydramine.

642. The method of embodiment 638, wherein the antihistamine comprises cetirizine.

643. The method of embodiment 638, wherein the antihistamine comprises fexofenadine.

644. The method of embodiment 638, wherein the antihistamine comprises loratadine.

645. The method of any one of embodiments 1 to 644, wherein the subject is receiving or has received one or more additional therapies and/or which further comprises administering to the subject one or more additional therapies.

646. The method of embodiment 645, wherein the one or more additional therapies comprises one or more anti-IL-6 agents.

647. The method of embodiment 646, wherein the one or more anti-IL-6 agents comprise tocilizumab, siltuximab, olokizumab, elsilimomab, BMS-945429, sirukumab, levilimab, CPSI-2364, or a combination thereof.

648. The method of embodiment 647, wherein the one or more anti-IL-6 agents comprise tocilizumab.

649. The method of any one of embodiments 645 to 648, wherein the one or more additional therapies comprise one or more corticosteroids.

650. The method of embodiment 649, wherein the one or more corticosteroids comprise methylprednisolone, dexamethasone, or a combination thereof.

651. The method of any one of embodiments 1 to 650, wherein the subject is a human.

652. The method of any one of embodiments 1 to 651, wherein the subject is not mechanically ventilated when the lipid binding protein molecule is administered for the first time.

653. The method of any one of embodiments 1 to 651, wherein the subject is mechanically ventilated when the lipid binding protein molecule is administered for the first time.

654. The method of any one of embodiments 1 to 653, wherein the subject is receiving vasopressor therapy when the lipid binding protein molecule is administered for the first time.

655. The method of any one of embodiments 1 to 653, wherein the subject is not receiving vasopressor therapy when the lipid binding protein molecule is administered for the first time.

656. The method of any one of embodiments 1 to 655, wherein the subject has a blood lactate level of 0.4 mmol/L to 12 mmol/L when the lipid binding protein molecule is administered for the first time.

657. The method of any one of embodiments 1 to 655, wherein the subject has a blood lactate level of 0.4 mmol/L to 5 mmol/L when the lipid binding protein molecule is administered for the first time.

658. The method of any one of embodiments 1 to 655, wherein the subject has a blood lactate level of 1 mmol/L to 5 mmol/L when the lipid binding protein molecule is administered for the first time.

659. The method of any one of embodiments 1 to 655, wherein the subject has a blood lactate level of 1 mmol/L to 4 mmol/L when the lipid binding protein molecule is administered for the first time.

660. The method of any one of embodiments 1 to 659, wherein the subject has a P/F ratio (PaO2 (arterial oxygen partial pressure obtained from an arterial blood gas) to the FiO2 (fraction of inspired oxygen) ratio) of 90 to 550 when the lipid binding protein molecule is administered for the first time.

661. The method of any one of embodiments 1 to 659, wherein the subject has a P/F ratio of 90 to 250 when the lipid binding protein molecule is administered for the first time.

662. The method of any one of embodiments 1 to 659, wherein the subject has a P/F ratio of 150 to 400 when the lipid binding protein molecule is administered for the first time.

663. The method of any one of embodiments 1 to 659, wherein the subject has a P/F ratio of 300 to 510 when the lipid binding protein molecule is administered for the first time.

664. The method of any one of embodiments 1 to 659, wherein the subject has a P/F ratio of 300 to 510 when the lipid binding protein molecule is administered for the first time.

665. The method of any one of embodiments 1 to 664, wherein the subject has a serum creatinine level of 0.5 mg/dL to 6 mg/dL when the lipid binding protein molecule is administered for the first time.

666. The method of any one of embodiments 1 to 664, wherein the subject has a serum creatinine level of 0.5 mg/dL to 6 mg/dL when the lipid binding protein molecule is administered for the first time.

667. The method of any one of embodiments 1 to 664, wherein the subject has a serum creatinine level of 0.5 mg/dL to 3 mg/dL when the lipid binding protein molecule is administered for the first time.

668. The method of any one of embodiments 1 to 664, wherein the subject has a serum creatinine level of 3 mg/dL to 6 mg/dL when the lipid binding protein molecule is administered for the first time.

669. The method of any one of embodiments 1 to 668, wherein the subject is in an intensive care unit (ICU) when the lipid binding protein molecule is administered for the first time.

670. The method of embodiment 669, wherein the dose is a dose which reduces the number of days the subject is in the ICU compared to the standard of care.

671. The method of any one of embodiments 1 to 668, wherein the subject is not in an intensive care unit (ICU) when the when the lipid binding protein molecule is administered for the first time.

672. The method of any one of embodiments 1 to 671, wherein the subject has sepsis and the dose is a dose which increases 30-day survival compared to the standard of care.

673. A method of treating a subject having sepsis (*e.g.*, septic shock), comprising administering a dose of apolipoprotein A-I to the subject twice per day for five days.

674. The method of embodiment 673, wherein each dose of ApoA-I is 10 mg/kg on a protein weight basis.

675. The method of embodiment 673, wherein each dose of ApoA-I is 20 mg/kg on a protein weight basis.

676. The method of any one of embodiments 673 to 675, wherein the doses are administered approximately 12 hours apart.

677. The method of any one of embodiments 673 to 675, wherein the doses are administered 11-13 hours apart.

678. The method of any one of embodiments 673 to 676, wherein the ApoA-I has the amino acid sequence of SEQ ID NO:3.

679. The method of embodiment 678, wherein the ApoA-I is a recombinant ApoA-I.

680. The method of embodiment 679, wherein the ApoA-I is produced by a mammalian host cell.

681. The method of embodiment 680, wherein the mammalian host cell is a CHO cell.

682. The method of any one of embodiments 679 to 681, wherein the ApoA-I has undergone post-translational processing (*e.g.*, glycosylation) such that the ApoA-I has one or more structural features (*e.g.*, glycosylation pattern) that are different from human ApoA-I purified from human plasma.

683. The method of any one of embodiments 673 to 682, wherein the ApoA-I is a component of a ApoA-I-based complex.

684. The method of embodiment 683, wherein the ApoA-I-based complex comprises a sphingomyelin.

685. The method of embodiment 684, wherein the ApoA-I-based complex comprises natural sphingomyelin.

686. The method of embodiment 685, wherein the natural sphingomyelin is chicken egg sphingomyelin.

687. The method of embodiment 684, wherein the ApoA-I-based complex comprises synthetic sphingomyelin.

688. The method of any one of embodiments 684 to 687, wherein the sphingomyelin comprises palmitoylsphingomyelin.

689. The method of any one of embodiments 673 to 688, wherein the ApoA-I is a component of a ApoA-I-based complex, and the ApoA-I-based complex comprises a negatively charged lipid.

690. The method of embodiment 689, wherein the negatively charged lipid is 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol) (DPPG) or a salt thereof.

691. The method of embodiment 683, wherein the ApoA-I-based complex comprises phospholipids in a ApoA-I weight:total phospholipid weight ratio of 1:2.7 +/- 20% and the phospholipids sphingomyelin and DPPG in a sphingomyelin:DPPG weight:weight ratio of 97:3 +/- 20%.

692. The method of embodiment 691, wherein the ApoA-I-based complex comprises phospholipids in a ApoA-I weight:total phospholipid weight ratio of 1:2.7 +/- 10% and the phospholipids sphingomyelin and DPPG in a sphingomyelin:DPPG weight:weight ratio of 97:3 +/- 10%.

693. The method of embodiment 692, wherein ApoA-I-based complex comprises phospholipids in a ApoA-I weight:total phospholipid weight ratio of 1:2.7 and the phospholipids sphingomyelin and DPPG in a sphingomyelin:DPPG weight:weight ratio of 97:3.

694. The method of embodiment 683, wherein the ApoA-I-based complex is CER-001.

695. The method of embodiment 694, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 95% homogeneous.

696. The method of embodiment 695, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 97% homogeneous.

697. The method of embodiment 696, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 98% homogeneous.

698. The method of embodiment 697, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 99% homogeneous.

699. The method of any one of embodiments 673 to 698, wherein the ApoA-I is administered systemically, optionally by infusion.

700. The method of any one of embodiments 673 to 699, wherein the subject has septic shock.

701. The method of any one of embodiments 673 to 700, wherein the subject has hypotension requiring the use of vasopressors despite intravenous fluid resuscitation.

702. The method of any one of embodiments 673 to 701, wherein the subject has a systolic arterial pressure < 90 mm Hg.

703. The method of any one of embodiments 673 to 702, wherein the subject has a mean arterial pressure (MAP) < 65 mm Hg.

704. The method of any one of embodiments 673 to 703, wherein the subject has hypotension (*e.g.*, systolic arterial pressure < 90 mm Hg or mean arterial pressure (MAP) < 65 mm Hg) requiring the use of vasopressors despite intravenous fluid resuscitation.

705. The method of any one of embodiments 673 to 704, wherein the subject has hypotension (*e.g.*, systolic arterial pressure < 90 mm Hg or mean arterial pressure (MAP) < 65 mm Hg) requiring the use of vasopressors for more than one hour despite intravenous fluid resuscitation.

706. The method of any one of embodiments 673 to 701, wherein the subject has hypotension requiring vasopressor treatment to maintain a mean arterial pressure of 65 mm Hg or greater.

707. The method of any one of embodiments 673 to 706, wherein the subject has a serum lactate level greater than 2 mmol/L despite intravenous fluid resuscitation.

708. The method of any one of embodiments 673 to 707, wherein administration of the lipid binding protein molecule is commenced within one day of commencement of vasopressor therapy.

709. The method of any one of embodiments 673 to 707, wherein administration of the lipid binding protein molecule is commenced within 24 hours of commencement of vasopressor therapy.

710. The method of any one of embodiments 673 to 709, further comprising administering a standard of care therapy for sepsis.

711. The method of embodiment 710, wherein the dose of the lipid binding protein molecule, together with the standard of care therapy, is effective to improve the likelihood of being alive 90 days following commencement of treatment compared to the standard of care therapy alone.

712. The method of embodiment 710 or embodiment 711, wherein the dose of the lipid binding protein molecule, together with the standard of care therapy, is effective to reduce the likelihood of organ dysfunction and/or need for organ support compared to the standard of care therapy alone.

713. The method of any one of embodiments 710 to 712 wherein the dose of the lipid binding protein molecule, together with the standard of care therapy, is effective to reduce the likelihood of requiring mechanical ventilation compared to the standard of care therapy alone.

714. The method of any one of embodiments 710 to 713, wherein the dose of the lipid binding protein molecule, together with the standard of care therapy, is effective to reduce the likelihood of requiring renal replacement therapy compared to the standard of care therapy alone.

715. The method of any one of embodiments 710 to 714, wherein the dose of the lipid binding protein molecule, together with the standard of care therapy, is effective to reduce the likelihood of requiring vasopressor therapy compared to the standard of care therapy alone.

716. The method of any one of embodiments 710 to 715, wherein the dose of the lipid binding protein molecule, together with the standard of care therapy, is effective to improve the subject's SOFA score.

717. The method of any one of embodiments 710 to 716, wherein the dose of the lipid binding protein molecule, together with the standard of care therapy, is effective to prevent an increase of the subject's Sepsis Support Index score.

[0719] While various specific embodiments have been illustrated and described, it will be appreciated that various changes can be made without departing from the spirit and scope of the disclosure(s)

9. INCORPORATION BY REFERENCE

[0720] All publications, patents, patent applications and other documents cited in this application are hereby incorporated by reference in their entireties for all purposes to the same extent as if each individual publication, patent, patent application or other document were individually indicated to be incorporated by reference for all purposes.

[0721] Any discussion of documents, acts, materials, devices, articles or the like that has been included in this specification is solely for the purpose of providing a context for the present disclosure. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed anywhere before the priority date of this application.

WHAT IS CLAIMED IS:

1. A method of treating a subject having or at risk of a condition, which is optionally an acute condition, comprising administering a dose of a lipid binding protein molecule to the subject.

2. The method of claim 1, wherein the condition is associated with an abnormal level of TREM-1, albumin, interleukin 10 (IL-10), a kynurenine pathway biomarker, TNF-α, MCP-1, IL-6, IL-8, VCAM-1, ICAM-1, ApoA-I, eNOS, or CD14.

3. The method of claim 2, wherein the kynurenine pathway biomarker is kynurenine, kynurenic acid, 3-hydroxykynurenine, anthranilic acid, 3-hydroxyanthranilic acid, 2-amino-3-carboxymuconate-semialdehyde, picolinic acid, quinolinic acid, quinaldic acid, tryptophan, serotonin, xanthurenic acid, formylkynurenine, or kynurenine/tryptophan ratio.

4. The method of any one of claims 1 to 3, further comprising measuring a level of TREM-1, albumin, kynurenic acid, 3-hydroxykynurenine, anthranilic acid, 3-hydroxyanthranilic acid, 2-amino-3-carboxymuconate-semialdehyde, picolinic acid, quinolinic acid, quinaldic acid, tryptophan, serotonin, xanthurenic acid, formylkynurenine, kynurenine/tryptophan ratio, TNFα, MCP-1, IL-6, IL-8, ApoA-I, eNOS, CD14, VCAM-1, or ICAM-1 of the subject prior to administering the dose.

5. The method of any one of claims 1 to 4, wherein the condition is sepsis, sepsis-induced acute kidney injury (AKI), a bacterial infection, a gram-positive bacterial infection, a gram-negative bacterial infection, a viral infection, acute myocardial infarction (AMI), Alzheimer's disease, chronic inflammatory bowel disease (IBD), a cardiovascular disease (CVD), a stroke, a transient ischemic attack, cytokine release syndrome (CRS), organ transplant rejection, ischemia reperfusion-induced tissue injury, post-operative inflammation, psoriasis, hypoalbuminemia, attention-deficit/hyperactivity disorder (ADHD), a central nervous system (CNS) disease, COVID-19 cognitive decline, depression or major depressive disorder, epilepsy, HIV-associated neurocognitive disorder, Huntington's disease, inflammatory bowel disease (IBD), long-term cognitive decline (“brain fog”), mortality or neurological deficit following cardiac arrest, multiple sclerosis (MS), Parkinson's disease, schizophrenia, a liver disorder, a kidney disorder, a vascular endothelial disorder, or acute respiratory distress syndrome (ARDS).

6. The method of any one of claims 1 to 5, wherein the subject has sepsis.

7. The method of any one of claims 1 to 6, wherein the subject has septic shock.

8. The method of claim 6 or claim 7, wherein the subject has hypotension requiring the use of vasopressors despite intravenous fluid resuscitation.

9. The method of any one of claims 6 to 8, wherein the subject has a systolic arterial pressure < 90 mm Hg.

10. The method of any one of claims 6 to 9, wherein the subject has a mean arterial pressure (MAP) < 65 mm Hg.

11. The method of any one of claims 6 to 10, wherein the subject has hypotension (*e.g.*, systolic arterial pressure < 90 mm Hg or mean arterial pressure (MAP) < 65 mm Hg) requiring the use of vasopressors despite intravenous fluid resuscitation.

12. The method of any one of claims 6 to 11, wherein the subject has hypotension (*e.g.*, systolic arterial pressure < 90 mm Hg or mean arterial pressure (MAP) < 65 mm Hg) requiring the use of vasopressors for more than one hour despite intravenous fluid resuscitation.

13. The method of any one of claims 6 to 8, wherein the subject has hypotension requiring vasopressor treatment to maintain a mean arterial pressure of 65 mm Hg or greater.

14. The method of any one of claims 6 to 13, wherein the subject has a serum lactate level greater than 2 mmol/L despite intravenous fluid resuscitation.

15. The method of any one of claims 6 to 14, wherein administration of the lipid binding protein molecule is commenced within one day of commencement of vasopressor therapy.

16. The method of any one of claims 6 to 14, wherein administration of the lipid binding protein molecule is commenced within 24 hours of commencement of vasopressor therapy.

17. The method of any one of claims 6 to 16, further comprising administering to the subject a standard of care therapy for sepsis.

18. The method of any one of claims 1 to 17, wherein the dose is administered over a period of one day to approximately three weeks.

19. The method of claim 18, wherein the dose is administered over a period of five days.

20. The method of any one of claims 1 to 19, wherein a plurality of individual doses are administered daily or twice daily.

21. The method of claim 20, wherein a plurality of individual doses are administered twice daily.

22. The method of claim 21, which comprises administering two or more doses approximately 12 hours apart.

23. The method of any one of claims 1 to 22, wherein the lipid binding protein molecule is an apolipoprotein.

24. The method of claim 23, wherein the apolipoprotein is ApoA-I.

25. The method of claim 24, wherein the ApoA-I has the amino acid sequence of SEQ ID NO:3.

26. The method of claim 24 or claim 25, wherein the ApoA-I is a recombinant ApoA-I.

27. The method of claim 26, wherein the ApoA-I is produced by a mammalian host cell.

28. The method of claim 27, wherein the mammalian host cell is a CHO cell.

29. The method of any one of claims 1 to 28, wherein the lipid binding protein molecule is a component of a lipid binding protein-based complex.

30. The method of claim 29, wherein the lipid binding protein-based complex is a reconstituted HDL or HDL mimetic.

31. The method of claim 29 or claim 30, wherein the lipid binding protein-based complex comprises a sphingomyelin.

32. The method of claim 31, wherein the lipid binding protein-based complex comprises synthetic sphingomyelin.

33. The method of claim 32, wherein the sphingomyelin comprises palmitoylsphingomyelin.

34. The method of any one of claims 29 to 33, wherein the lipid binding protein-based complex comprises a negatively charged lipid.

35. The method of claim 34, wherein the negatively charged lipid is 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol) (DPPG) or a salt thereof.

36. The method of claim 30, wherein lipid binding protein-based complex comprises ApoA-I and phospholipids in a ApoA-I weight:total phospholipid weight ratio of 1:2.7 and the phospholipids sphingomyelin and 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol) (DPPG) in a sphingomyelin:DPPG weight:weight ratio of 97:3.

37. The method of claim 30, wherein the lipid binding protein-based complex is CER-001, CSL-111, CSL-112, CER-522 ETC-216, or ETC-642.

38. The method of claim 37, wherein the lipid binding protein-based complex is CER-001.

39. The method of any one of claims 1 to 38, wherein the lipid binding protein molecule is administered systemically, optionally by infusion.

40. The method of any one of claims 1 to 39, wherein each individual dose of the lipid binding protein molecule administered is 4-40 mg/kg (on a protein weight basis).

41. The method of claim 40, wherein each individual dose of the lipid binding protein molecule is 10-20 mg/kg (on a protein weight basis).

42. The method of claim 40, wherein each individual dose of the lipid binding protein molecule is 10 mg/kg (on a protein weight basis).

43. The method of claim 40, wherein each individual dose of the lipid binding protein molecule is 20 mg/kg (on a protein weight basis).

44. The method of any one of claims 1 to 43, wherein two individual doses per day are administered to the subject for five days.