We claim:

1. Use of LEPR agonist in the manufacture of a medicament for reducing or preventing pain, anxiety and/or depression, in a patient in need thereof, wherein the patient is to be administered the medicament.

2. The use of claim 1 wherein the patient achieves one or more of:
- a reduction in pain,
- a reduction in the use of analgesics,
- a reduction in the use of anxiolytics,
- a reduction in the use of anti-depressants,
- a reduction in analgesic seeking behavior,
- a reduction in *pro re nata* use of analgesics,
- a reduction in incidence of analgesic overdose, and/or
- a reduction in the incidence of death due to abuse of analgesics.

3. The use of claim 2 wherein the analgesic is oxycodone.

4. The use of any one of claims 1-3 wherein the pain, anxiety and/or depression is associated with a leptin deficiency or leptin resistance condition.

5. Use of LEPR agonist in the manufacture of a medicament for the treatment of pain and/or a leptin deficiency or leptin resistance condition, in a patient in need thereof, wherein the patient is to be administered an effective amount of the medicament, thereby reducing or maintaining a reduction in:
- pain,
- use of analgesics,
- use of anxiolytics,
- use of anti-depressants,
- analgesic seeking behavior,
- *pro re nata* use of analgesics,
- analgesic overdose, and/or
- the incidence of death due to abuse of analgesics.

6. The use of any one of claims 1-5 wherein said reduction is within less than 1, 1, 2, 3, 4, or 5 days of the first administration or second administration of the LEPR agonist.

7. The use of any one of claims 1-6 wherein the pain is generalized pain, abdominal pain, renal pain, liver pain and/or pain due to hepatomegaly, liver stiffness and/or pancreatitis.

8. The use of claim 7 wherein the abdominal pain is accompanied by nausea and/or vomiting.

9. The use of any one of claims 1-8 wherein the pain is neuropathy pain, arthritis pain, chronic back pain, fibromyalgia pain, myopathy pain, central pain, chronic central pain, pain caused by centralization and/or hypersensitization of pain by the central nervous system and/or central pain syndrome pain.

10. The use of any one of claims 1-9 wherein the use of analgesics, anxiolytics and/or anti-depressants is reduced concomitantly with or prior to the first administration of the LEPR agonist.

11. The use of any one of claims 1-10 wherein the patient continues episodic use of analgesics.

12. The use any one of claims 1-11 wherein said pain, use of analgesics, anxiolytics and/or anti-depressants is chronic.

13. The use of any one of claims 1-12 wherein a reduction in pain, anxiety and/or depression is as measured by PHQ-9 and/or SF-36 score.

14. The use of any one of claims 1-13 wherein a reduction in *pro re nata* use of analgesics does not include episodic use of analgesics.

15. The use of claim 14 wherein episodic use of analgesics comprises use of analgesics for up to 5, 6, 7 or 8 days.

16. The use of any one of claims 1-15 wherein the analgesic is an opioid, a non-opioid, a calcitonin gene-related peptide (CGRP) inhibitor, a cyclooxygenase-2 inhibitor, a gepant, an anti-CGRP monoclonal antibody, a nonsteroidal anti-inflammatory drug, a salicylate, acetaminophen, acetylsalicylic acid, alfentanil, aspirin & citric acid & sodium bicarbonate, bromfenac, celecoxib, choline salicylate & magnesium salicylate, codeine, concentrate of poppy straw, dextromoramide, dextropropoxyphene, diclofenac, diclofenac & misoprostol, diflunisal, diflunisal, dihydrocodeine, dihydroetorphine, diphenoxylate, eptinezumab, erenumab, esomeprazole & naproxen, ethylmorphine, etodolac, etorphine, famotidine & ibuprofen, fenoprofen, fentanyl, flurbiprofen, fremanezumab, gabapentin, galcanezumab, heroin, hydrocodone, hydromorphone, ibuprofen, indomethacin, ketamin, ketobemidone, ketoprofen, ketorolac, levorphanol, magnesium salicylate, meclofenamat, mefenamic acid, meloxicam, methadone, methadone, morphine, morphine-n-oxide, nabumetone, naproxen, nicomorphine, norcodeine, opium, oripavine, oxaprozin, oxycodone, oxymorphone, pethidine, pethidine intermediate, phenylbutazone, pholcodine, piritramide, piroxicam, remifentanil, rimegepant sulfate, salsalate, sufentanil, sulindac, thebaine or tilidine, tolmetin, ubrogepant or valdecoxib.

17. The use of claim 16 wherein the analgesic is an opioid.

18. The use of claim 16 wherein the analgesic is not a non-opioid.

19. The use of any one of claims 1-18 wherein the anxiolytic is a benzodiazepine, a tricyclic antidepressant, alprazolam, alprazolam, an agonist of melatonin receptor, an anesthetic, an antihistamine, an SNRI, an SSRI, buspirone, clonazepam, diazepam, estazolam, eszopiclone, flurazepam, lorazepam, quazepam, temazepam, triazolam, zaleplon, zolpidem or zopiclone.

20. The use of any one of claims 1-19 wherein the anti-depressant is a monoamine oxidase inhibitor, a selective serotonin reuptake inhibitors (SSRI), a serotonin and norepinephrine reuptake inhibitors (SNRI), a tricyclic antidepressant, amitriptyline, an atypical antidepressant, bupropion, citalopram, desipramine, desvenlafaxine and levomilnacipran, doxepin, duloxetine, escitalopram, fluoxetine, imipramine, isocarboxazid, mirtazapine,

nortriptyline, paroxetine, phenelzine, selegiline, sertraline, tranylcypromine, trazodone, venlafaxine, vilazodone or vortioxetine.

21. Use of LEPR agonist in the manufacture of a medicament for the treatment of pain and/or a leptin deficiency or leptin resistance condition due to pain, anxiety and/or depression, in a patient in need thereof, wherein the patient is to be administered an effective amount of the medicament, thereby reducing hospitalization or emergency medical intervention of the patient.

22. The use of any one of claims 1-21 wherein the leptin deficiency or leptin resistance condition is monogenic obesity, obesity, metabolic syndrome, diet-induced food craving, functional hypothalamic amenorrhea, type 1 diabetes, type 2 diabetes, insulin resistance, possession of neutralizing anti-leptin autoantibodies, severe insulin resistance including severe insulin resistance due to mutation in insulin receptor, severe insulin resistance not caused by mutation in the insulin receptor, severe insulin resistance caused by a mutation in downstream signaling pathways or induced by other causes, non-alcoholic and alcoholic fatty liver diseases, Alzheimer's disease, leptin deficiency, leptin resistance, a lipodystrophy, Leprechaunism/Donohue syndrome or Rabson-Mendenhall syndrome.

23. The use of any one of claims 1-22 wherein the leptin deficiency or leptin resistance condition is a lipodystrophy which is congenital generalized lipodystrophy, acquired generalized lipodystrophy, familial partial lipodystrophy, acquired partial lipodystrophy, centrifugal abdominal lipodystrophy, lipoatrophia annularis, localized lipodystrophy, and HIV-associated lipodystrophy.

24. The use of any one of claims 1-23 wherein the LEPR agonist is an isolated agonist antibody or antigen-binding fragment that binds specifically to LEPR.

25. The use of any one of claims 1-24 wherein the LEPR agonist is an isolated agonist antibody or antigen-binding fragment that binds specifically to LEPR comprising:
(i) a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and

a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 2;
(ii) a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and
a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 18;
(iii) a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and
a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 26;
(iv) a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and
a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 34;
(v) a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and
a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 42;
(vi) a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and
a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 50;
(vii) a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and
a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 58;

(viii) a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and
a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 66;
(ix) a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and
a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 74;
(x) a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90; and
a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 82;
(xi) a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90; and
a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 98; or
(xii) a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90; and
a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 106; or
an antibody or antigen-binding fragment that binds to the same epitope as any one or more of (i)-(xii) and/or competes for binding to LEPR with any one or more of (i)-(xii).

26. The use of any one of claims 1-25 wherein the LEPR agonist is an isolated agonist antibody or antigen-binding fragment that binds specifically to LEPR comprising:

(i) a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and

a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 2;

(ii) a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and

a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 18;

(iii) a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and

a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 26;

(iv) a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and

a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 34;

(v) a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and

a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 42;

(vi) a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and

a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 50;

(vii) a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and

a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 58;

(viii) a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and

a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 66;

(ix) a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; and
a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 74;
(x) a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90; and
a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 82;
(xi) a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90; and
a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 98;
or
(xii) a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90; and
a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 106;
or
an antibody or antigen-binding fragment that binds to the same epitope as any one or more of (i)-(xii) and/or competes for binding to LEPR with any one or more of (i)-(xii).

27. The use of any one of claims 1-26 wherein the LEPR agonist is mibavademab.

28. The use of any one of claims 1-27 wherein the effective amount of LEPR agonist is one or more intravenous doses of about 5 mg/kg and one or more subcutaneous doses of about 250-450 mg once weekly thereafter.

29. The use of claim 28 wherein 250-450 mg is 300 or 450 mg.

30. The use of claim 28 wherein the effective amount of LEPR agonist is one intravenous dose of about 5 mg/kg and one or more subcutaneous doses of about 300 mg or 450 mg once weekly thereafter.

31. The use of any one of claims 1-30 wherein a further chemotherapeutic agent is to be administered to the patient.

32. The use of claim 31 wherein the further chemotherapeutic agent is human leptin, metreleptin, a PCSK9 inhibitor, an anti-PCSK9 antibody, alirocumab, evolocumab, bococizumab, lodelcizumab, ralpancizumab, an HMG-CoA reductase inhibitor, atorvastatin, rosuvastatin, cerivastatin, pitavastatin, fluvastatin, simvastatin, lovastatin, pravastatin, ezetimibe, insulin, an insulin variant, an insulin secretagogue, metformin, a sulfonylurea, a sodium glucose cotransporter 2 (SGLT2) inhibitor, dapaglifozin, canaglifozin, empagliflozin, a selective agonist of the MC_4 receptor, setmelanotide, a GLP-1 agonist or analogue, extendin-4, exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, a glucagon (GCG) inhibitor, an anti-GCG antibody, a glucagon receptor (GCGR) inhibitor, an anti-GCGR antibody, a small molecule GCGR antagonist, a GCGR-specific antisense oligonucleotide, an anti-GCGR aptamer, an angiopoietin-like protein (ANGPTL) inhibitor, an anti-ANGPTL3 antibody, an anti-ANGPTL4 antibody, an anti-ANGPTL8 antibody, phentermine, orlistat, topiramate, bupropion, topiramate and phentermine, bupropion and naltrexone, bupropion and zonisamide, pramlintide and metrelepin, lorcaserin, cetilistat, tesofensine and/or velneperit.

33. The use of any one of claims 1-32 wherein the patient further achieves one or more of:
- a reduction in body weight,
- a reduction in food intake,
- a reduction in adiposity,
- a reduction in hepatic stiffness
- improved glycemic control,
- improved insulin sensitivity,
- an improvement in dyslipidemia,
- an improvement in hepatic steatosis,
- an improvement in hepatomegaly,
- a reduction in pancreatitis,
- reduced serum triglyceride levels,
- a reduction in the frequency of plasmapheresis,
- reduced total cholesterol levels, and/or

- reduced serum LDL-C levels.

34. The use of any one of claims 1-33 wherein the patient suffers from:
- obesity,
- hyperphagia,
- excess adiposity,
- hepatic stiffness,
- low glycemic control,
- diabetes,
- insulin resistance,
- dyslipidemia,
- hepatic steatosis,
- hepatomegaly,
- pancreatitis,
- elevated serum triglyceride levels,
- elevated total cholesterol levels, and/or
- elevated serum LDL-C levels;

and/or receives regular plasmapheresis.