WE CLAIM

1. Use of an antibody specifically recognizing human tumor necrosis factor receptor 1 (huTNFR1) in the manufacture of a pharmaceutical preparation for treating nonalcoholic steatohepatitis (NASH) and disease conditions associated thereto.

2. The use according to claim 1, wherein the antibody specifically recognizes an epitope within the membrane-distal CRD1 and/or subdomain A1 of CRD2 of huTNFR1, preferably specifically recognizing an epitope represented by amino acid 1 to 115 in the N-terminal region of huTNFR1.

3. The use according to claim 1 or 2, wherein the antibody is a monoclonal antibody.

4. The use according to any one of claims 1 to 3, wherein the antibody is a monospecific, bivalent full-length antibody.

5. The use according to claim 4, wherein the antibody comprises an IgG1 Fc domain which is deficient in mediating effector function, preferably comprising at least one mutation selected from the group consisting of E233P, L234V, L235A, ΔG236, A327G, A330S and P331S, preferably comprising A327G/A330S/P331S, wherein numbering is according to the Kabat EU index.

6. The use according to any one of claims 1 to 3, wherein the antibody monovalently recognizes the huTNFR1.

7. The use according to any one of claims 1 to 6, wherein the antibody comprises
a) a heavy chain variable domain (VH) comprising the complementarity-determining regions (CDRs): VH-CDR1, VH-CDR2, and VH-CDR3; and
b) a light chain variable domain (VL) comprising the CDRs: VL-CDR1, VL-CDR2, and VL-CDR3,
wherein

i)
VH-CDR1 comprises or consists of SEQ ID NO:1;
VH-CDR2 comprises or consists of SEQ ID NO:2
VH-CDR3 comprises or consists of SEQ ID NO:3
VL-CDR1 comprises or consists of SEQ ID NO:4
VL-CDR2 comprises or consists of SEQ ID NO:5
VL-CDR3 comprises or consists of SEQ ID NO:6;
or
ii)
VH-CDR1 comprises or consists of SEQ ID NO:23;
VH-CDR2 comprises or consists of SEQ ID NO:24
VH-CDR3 comprises or consists of SEQ ID NO:25
VL-CDR1 comprises or consists of SEQ ID NO:26
VL-CDR2 comprises or consists of SEQ ID NO:27
VL-CDR3 comprises or consists of SEQ ID NO:28;
wherein numbering is according to the Kabat EU index;
or a functionally active variant of any of i) or ii) above, which comprises 0, 1, or 2 point mutations in each of the CDR sequences, and which specifically recognizes the huTNFR1.

8. The use according to any one of claims 1 to 7, wherein the antibody comprises a VH sequence comprising or consisting of SEQ ID NO:7 or 9; and a VL sequence comprising or consisting of SEQ ID NO:8 or 10, or a functionally active variant thereof comprising up to 1 point mutation in each of the CDR sequences, and at least 60% sequence identity in the framework (FR) sequences FR1-4 of VH and VL.

9. The use according to any one of claims 1 to 8, wherein the disease conditions are any of hepatic steatosis, inflamed liver, liver fibrosis and hepatocellular carcinoma.

10. The use according to any one of claims 1 to 9, wherein an effective amount of the antibody is administered to a patient suffering from NASH, to antagonize TNFa/huTNFR1 signaling.

11. The use according to any one of claims 1 to 10, wherein an effective amount of the antibody is administered to a patient suffering from NASH, to reduce any one or more of
a) steatosis, triglyceride content, inflammation, and/ or apoptosis in liver tissue;
b) the serum aminotransferase level;
c) insulin-resistance and optionally to improve glucose-tolerance; and/or
d) the NAFLD activity score.

12. The use according to any one of claims 1 to 11, wherein the antibody is administered to a patient suffering from NASH at a dose ranging from 0.05 mg/kg to 20 mg/kg.

13. The use according to any one of claims 1 to 12, wherein the antibody is administered to a patient suffering from NASH in combination with a treatment with anti-inflammatory drugs, or therapies using a farnesoid X receptor (FXR) agonist, a glucagon-like peptide-1 receptor (GLP1R) agonist, or a peroxisome proliferator-activated receptor (PPAR) agonist.

14. The use according to any one of claims 1 to 13, wherein the antibody is administered to a patient also suffering from type II diabetes mellitus, type I diabetes mellitus, pre-diabetes, insulin resistance, or obesity, wherein obesity is defined as the patient having a body mass index of at least 30.

15. The use according to any one of claims 1 to 14, wherein the pharmaceutical preparation comprises an effective amount of the antibody.