CLAIMS

1. An antibody or antigen-binding fragment thereof that binds human Glial-Cell-Line-Derived Neurotrophic Factor (GDNF) Family Receptor Alpha-like protein (GFRAL) (SEQ ID NO: 1797), which comprises: a heavy chain variable region (VH) complementarity determining region (CDR)1, a VH CDR2, and a VH CDR3 of a VH comprising the amino acid sequence set forth in SEQ ID NO: 3, and a light chain variable region (VL) CDR1, a VL CDR2, and a VL CDR3 of a VL comprising the amino acid sequence set forth in SEQ ID NO: 4.

2. The antibody or antigen-binding fragment thereof of claim 1, wherein
   (a) the VH CDR1, the VH CDR2, the VH CDR3 comprise the amino acid sequence set forth in SEQ ID NO: 46, SEQ ID NO: 137, and SEQ ID NO: 225, respectively, and the VL CDR1, the VL CDR2, and the VL CDR3 comprise the amino acid sequence set forth in SEQ ID NO: 301, SEQ ID NO: 376, and SEQ ID NO: 426, respectively;
   (b) the VH CDR1, the VH CDR2, the VH CDR3 comprise the amino acid sequence set forth in SEQ ID NO: 47, SEQ ID NO: 138, and SEQ ID NO: 226, respectively, and the VL CDR1, the VL CDR2, and the VL CDR3 comprise the amino acid sequence set forth in SEQ ID NO: 302, SEQ ID NO: 377, and SEQ ID NO: 426, respectively;
   (c) the VH CDR1, the VH CDR2, the VH CDR3 comprise the amino acid sequence set forth in SEQ ID NO: 48, SEQ ID NO: 137, and SEQ ID NO: 225, respectively, and the VL CDR1, the VL CDR2, and the VL CDR3 comprise the amino acid sequence set forth in SEQ ID NO: 301, SEQ ID NO: 376, and SEQ ID NO: 426, respectively;
   (d) the VH CDR1, the VH CDR2, the VH CDR3 comprise the amino acid sequence set forth in SEQ ID NO: 49, SEQ ID NO: 139, and SEQ ID NO: 227, respectively, and the VL CDR1, the VL CDR2, and the VL CDR3 comprise the amino acid sequence set forth in SEQ ID NO: 303, SEQ ID NO: 377, and SEQ ID NO: 427, respectively;
   (e) the VH CDR1, the VH CDR2, the VH CDR3 comprise the amino acid sequence set forth in SEQ ID NO: 50, SEQ ID NO: 140, and SEQ ID NO: 228, respectively, and the VL CDR1, the VL CDR2, and the VL CDR3 comprise the amino acid sequence set forth in SEQ ID NO: 304, SEQ ID NO: 378, and SEQ ID NO: 428, respectively; or
   (f) the VH CDR1, the VH CDR2, the VH CDR3 comprise the amino acid sequence set forth in SEQ ID NO: 46, SEQ ID NO: 141, and SEQ ID NO: 225, respectively, and the VL CDR1, the VL CDR2, and the VL CDR3 comprise the amino acid sequence set forth in SEQ ID NO: 301, SEQ ID NO: 376, and SEQ ID NO: 426, respectively.

3. The antibody or antigen-binding fragment thereof of claim 1 or 2, which comprises:
   (a) a VH that is at least 80% sequence identical to the amino acid sequence set forth in SEQ ID NO: 3;
   (b) a VL that is at least 80% sequence identical to the amino acid sequence set forth in SEQ ID NO: 4;
   (c) a VH that is at least 85% sequence identical to the amino acid sequence set forth in SEQ ID NO: 3;
   (d) a VL that is at least 85% sequence identical to the amino acid sequence set forth in SEQ ID NO: 4;
   (e) a VH that is at least 80% sequence identical to the amino acid sequence set forth in SEQ ID NO: 3 and a VL that is at least 80% sequence identical to SEQ ID NO: 4;
   (f) a VH that is at least 85% sequence identical to the amino acid sequence set forth in SEQ ID NO: 3 and a VL that is at least 85% sequence identical to SEQ ID NO: 4;
   (g) a VH that is at least 90 % sequence identical to the amino acid sequence set forth in SEQ ID NO: 3 and a VL that is at least 90% sequence identical to SEQ ID NO: 4;
   (h) a VH that is at least 95% sequence identical to the amino acid sequence set forth in SEQ ID NO: 3 and a VL that is at least 95% sequence identical to SEQ ID NO: 4; or
   (i) a VH comprising the amino acid sequence set forth in SEQ ID NO: 3 and a VL comprising the amino acid sequence set forth in SEQ ID NO: 4.

4. The antibody or antigen-binding fragment thereof of claim 1 or 2, which comprises:
   (a) a VH that is at least 80% sequence identical to the amino acid sequence set forth in SEQ ID NO: 1982;
   (b) a VL that is at least 80% sequence identical to the amino acid sequence set forth in SEQ ID NO: 1997;
   (c) a VH that is at least 85% sequence identical to the amino acid sequence set forth in SEQ ID NO: 1982;
   (d) a VL that is at least 85% sequence identical to the amino acid sequence set forth in SEQ ID NO: 1997;
   (e) a VH that is at least 90% sequence identical to the amino acid sequence set forth in SEQ ID NO: 1982;
   (f) a VL that is at least 90% sequence identical to the amino acid sequence set forth in SEQ ID NO: 1997;

(g) a VH that is at least 80% sequence identical to the amino acid sequence set forth in SEQ ID NO: 1982 and a VL that is at least 80% sequence identical to the amino acid sequence set forth in SEQ ID NO: 1997;

(h) a VH that is at least 85% sequence identical to the amino acid sequence set forth in SEQ ID NO: 1982 and a VL that is at least 85% sequence identical to the amino acid sequence set forth in SEQ ID NO: 1997;

(i) a VH that is at least 90% sequence identical to the amino acid sequence set forth in SEQ ID NO: 1982 and a VL that is at least 90% sequence identical to the amino acid sequence set forth in SEQ ID NO: 1997

(j) a VH that is at least 95% sequence identical to the amino acid sequence set forth in SEQ ID NO: 1982 and a VL that is at least 95% sequence identical to the amino acid sequence set forth in SEQ ID NO: 1997; or

(k) a VH comprising the amino acid sequence set forth in SEQ ID NO: 1982 and a VL comprising the amino acid sequence set forth in SEQ ID NO: 1997.

5. The antibody or antigen-binding fragment thereof of claim 1 or 2, which comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 1982.

6. The antibody or antigen-binding fragment thereof of claim 1 or 2, which comprises a VL comprising the amino acid sequence set forth in SEQ ID NO: 1997.

7. The antibody or antigen-binding fragment thereof of claim 1 or 2, which comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 1982 and a VL comprising the amino acid sequence set forth in SEQ ID NO: 1997.

8. The antibody or antigen-binding fragment thereof of claim 1 or 2, which binds within domain 3 of human GFRAL.

9. The antibody or antigen-binding fragment thereof of claim 1 or 2, which binds within amino acid residues 220-316 of SEQ ID NO: 1797.

10. An antibody or antigen-binding fragment thereof that competes for binding to human GFRAL with an antibody or antigen-binding fragment thereof of any one of claims 1 to 9.

11. The antibody or antigen-binding fragment thereof of claim 10, wherein the antibody or antigen-binding fragment thereof that competes for binding to human GFRAL comprises:

(a) a VH CDR1, a VH CDR2, and a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 56, SEQ ID NO: 147, and SEQ ID NO: 233, respectively; and a VL CDR1, a VL CDR2, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 309, SEQ ID NO: 382, and SEQ ID NO: 432, respectively;

(b) a VH CDR1, a VH CDR2, and a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 86, SEQ ID NO: 177, and SEQ ID NO: 261, respectively; and a VL CDR1, a VL CDR2, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 337, SEQ ID NO: 401, and SEQ ID NO: 453, respectively;

(c) a VH CDR1, a VH CDR2, and a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 91, SEQ ID NO: 182, and SEQ ID NO: 265, respectively; and a VL CDR1, a VL CDR2, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 341, SEQ ID NO: 385, and SEQ ID NO: 456, respectively;

(d) a VH CDR1, a VH CDR2, and a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 95, SEQ ID NO: 187, and SEQ ID NO: 269, respectively; and a VL CDR1, a VL CDR2, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 345, SEQ ID NO: 404, and SEQ ID NO: 459, respectively;

(e) a VH CDR1, a VH CDR2, and a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124, SEQ ID NO: 210, and SEQ ID NO: 289, respectively; and a VL CDR1, a VL CDR2, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 365, SEQ ID NO: 418, and SEQ ID NO: 474, respectively; or

(f) a VH CDR1, a VH CDR2, and a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 127, SEQ ID NO: 215, and SEQ ID NO: 293, respectively; and a VL CDR1, a VL CDR2, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 369, SEQ ID NO: 421, and SEQ ID NO: 477, respectively.

12. An antibody or antigen-binding fragment thereof that binds human GFRAL (SEQ ID NO: 1797), which comprises:

(a) a VH CDR1, a VH CDR2, and a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 56, SEQ ID NO: 147, and SEQ ID NO: 233, respectively; and a light chain variable region CDR (VL CDR) 1, a VL CDR2, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 309, SEQ ID NO: 382, and SEQ ID NO: 432, respectively;

(b) a VH CDR1, a VH CDR2, and a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 86, SEQ ID NO: 177, and SEQ ID NO: 261, respectively; and a VL CDR1, a VL CDR2, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 337, SEQ ID NO: 401, and SEQ ID NO: 453, respectively;

(c) a VH CDR1, a VH CDR2, and a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 91, SEQ ID NO: 182, and SEQ ID NO: 265, respectively; and a VL CDR1, a VL CDR2, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 341, SEQ ID NO: 385, and SEQ ID NO: 456, respectively;

(d) a VH CDR1, a VH CDR2, and a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 95, SEQ ID NO: 187, and SEQ ID NO: 269, respectively; and a VL CDR1, a VL CDR2, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 345, SEQ ID NO: 404, and SEQ ID NO: 459, respectively;

(e) a VH CDR1, a VH CDR2, and a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 124, SEQ ID NO: 210, and SEQ ID NO: 289, respectively; and a VL CDR1, a VL CDR2, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 365, SEQ ID NO: 418, and SEQ ID NO: 474, respectively; or

(f) a VH CDR1, a VH CDR2, and a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 127, SEQ ID NO: 215, and SEQ ID NO: 293, respectively; and a VL CDR1, a VL CDR2, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 369, SEQ ID NO: 421, and SEQ ID NO: 477, respectively.

13. An antibody or antigen-binding fragment thereof that specifically binds human GFRAL, wherein the antibody or antigen-binding fragment binds within amino acid residues 220-316 of SEQ ID NO: 1797.

14. An antibody or antigen-binding fragment thereof that specifically binds human GFRAL, wherein the antibody or antigen-binding fragment binds to one or more residues selected from the group consisting of: Met214, Pro216, Pro217, Gln290, Cys291, Thr292, Cys293, Arg294, Thr295, Ile296, Thr297, Gln298, Ser299, Glu301, Lys305, Gln308, His309, His312, and Ser315 of SEQ ID NO: 1797.

15. The antibody or antigen-binding fragment thereof of claim 14, which binds to Thr297, Gln298, and Ser299 of human GFRAL (SEQ ID NO: 1797).

16. The antibody or antigen-binding fragment thereof of any one of claims 1 to 15, which inhibits binding of GFRAL to RET.

17. The antibody or antigen-binding fragment thereof of any one of claims 1 to 16, which does not inhibit binding of GFRAL to GDF15.

18. The antibody or antigen-binding fragment thereof of any one of claims 1, 2, 10, 12, or 14, which is a humanized antibody, a human antibody, a chimeric antibody, or a bispecific antibody.

19. The antibody or antigen-binding fragment thereof of any one of claims 1 to 18, which is a monoclonal antibody.

20. The antibody or antigen-binding fragment thereof of claim 19, which is an IgG1 antibody, an IgG2 antibody, or an IgG4 antibody.

21. The antibody or antigen-binding fragment thereof of claim 19, which is an IgG1 antibody.

22. The antibody or antigen-binding fragment thereof of claim 19 or 21, which comprises a kappa light chain.

23. The antibody or antigen-binding fragment thereof of any one of claims 1 to 19, wherein the antigen-binding fragment is an Fab, Fab', $F(ab')_2$, Fv, scFv, $(scFv)_2$, single chain antibody molecule, dual variable region antibody, or a multispecific antibody formed from antibody fragments.

24. The antibody or antigen-binding fragment thereof of any one of claims 1 to 23, which is conjugated or recombinantly fused to a diagnostic agent, detectable agent, or therapeutic agent.

25. An isolated polynucleotide or polynucleotides encoding the antibody or antigen-binding fragment thereof of any one of claims 1 to 23.

26. A vector or vectors comprising the polynucleotide or polynucleotides of claim 25.

27. A host cell comprising the polynucleotide or polynucleotides of claim 25.

28. A host cell comprising the vector or vectors of claim 26.

29. A host cell that produces the antibody or antigen-binding fragment thereof of any one of claims 1 to 23.

30. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1 to 24 and a pharmaceutically acceptable carrier.

31. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 24 in the manufacture of a medicament for treating involuntary body weight loss in a human subject.

32. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 24 in the manufacture of a medicament for preventing involuntary body weight loss in a human subject.

33. The use of claim 31 or 32, wherein the human subject has cachexia.

34. The use of any one of claims 31 to 33, wherein the human subject has cancer.

35. The use of any one of claims 31 to 34, wherein the human subject is undergoing treatment for cancer.

36. The use of claim 31 or 32, wherein the human subject has anorexia nervosa.

37. The use of claim 31 or 32, wherein the human subject has a chronic disease.

38. The use of claim 37, wherein the chronic disease is selected from the group consisting of liver cirrhosis, hyperthyroidism, Parkinson's disease, cancer, chronic renal disease, chronic obstructive pulmonary disease, AIDS, tuberculosis, chronic inflammatory disease, sepsis, muscle wasting, and anorexia nervosa.

39. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 24 in the manufacture of a medicament for treating anorexia nervosa in a human subject.

40. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 24 in the manufacture of a medicament for treating a GDF15-mediated disease or disorder in a human subject.

41. The use of claim 40, wherein the GDF15-mediated disease or disorder is sarcopenia, muscle wasting, bone wasting, a cardiovascular disease, a chronic inflammatory disease, or cancer.

42. The use of any one of claims 31 to 41, wherein the subject has an elevated level of GDF15.

43. The use of any one of claims 31 to 42, which comprises combination therapy with one or more additional therapeutic agents.

44. Use of the antibody or antigen-binding fragment thereof of claim 24 in diagnosing a disorder associated with expression of GFRAL, wherein the antibody or antigen-binding fragment thereof is conjugated or recombinantly fused to a diagnostic agent.