CLAIMS

1. A method of increasing an effector function of a parent polypeptide comprising an Fc-domain of an immunoglobulin and a binding region, which method comprises introducing a mutation to the parent polypeptide in at least one amino acid residue selected from those corresponding to E345, E430, S440, Q386, P247, I253, S254, Q311, D/E356, T359, E382, Y436, and K447 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W.

2. The method according to claim 1 of increasing an effector function of a parent antibody, comprising introducing a mutation to the parent antibody in at least one amino acid residue selected from those corresponding to E345, E430, S440, Q386, P247, I253, S254, Q311, D/E356, T359, E382, Y436, and K447 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W.

3. A method of decreasing an effector function of a parent polypeptide comprising an Fc-domain of an immunoglobulin and a binding region, which method comprises introducing a mutation to the parent polypeptide in one amino acid residue selected from those corresponding to K439 and S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W, such as wherein the mutation in the position corresponding to K439 in the Fc-region of human IgG1 heavy chain is K439D/E, and/or the mutation in the position corresponding to S440 in the Fc-region of human IgG1 heavy chain is S440K/H/R.

4. The method according to claim 3 of decreasing an effector function of a parent antibody comprising introducing a mutation to the parent antibody in one amino acid residue selected from those corresponding to K439 and S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W, such as wherein the mutation in the position corresponding to K439 in the Fc-region of human IgG1 heavy chain is K439D/E, and/or the mutation in the position corresponding to S440 in the Fc-region of human IgG1 heavy chain is S440K/H/R.

5. The method according to any one of the claims 2 or 4, wherein the parent antibody is a monospecific, bispecific or multispecific antibody.

6. The method according to claim 5, wherein the parent antibody is a bispecific antibody which comprises a first polypeptide comprising a first CH2-CH3 region of an immunoglobulin and a first antigen-binding region, and a second polypeptide comprising a second CH2-CH3 region of an immunoglobulin and a second antigen-binding region, wherein the first and second antigen-binding regions bind different epitopes on the same antigen or on different antigens, and wherein said first CH2-CH3 region comprises a further amino acid substitution at a position selected from those corresponding to K409, T366, L368, K370, D399, F405, and Y407 in the Fc-region of a human IgG1 heavy chain; and wherein said second CH2-CH3 region comprises a further amino acid substitution at a position selected from those corresponding to F405, T366, L368, K370, D399, Y407, and K409 in the Fc-region of a human IgG1 heavy chain, and wherein said further amino acid substitution in the first CH2-CH3 region is different from the said further amino acid substitution in the second CH2-CH3 region.

7. The method according to claim 5 or 6, wherein the parent antibody is a bispecific antibody and comprises a first polypeptide and a second polypeptide, wherein said first polypeptide comprises a first CH2-CH3 region of an immunoglobulin and a first antigen-binding region, and said second polypeptide comprises a second CH2-CH3 region of an immunoglobulin and a second antigen-binding region, wherein the first and second antigen-binding regions bind different epitopes on the same antigen or on different antigens, said method comprising introducing to each of the first and second CH2-CH3 region a mutation in at least one amino acid residue selected from those corresponding to E345, E430, S440, Q386, P247, I253, S254, Q311, D/E356, T359, E382, Y436, and K447 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W.

8. A method according to any one of the claims 1 to 2 and 5 to 7, said method comprises introducing the mutation in one or more positions other than S440 and K447, and further introducing a mutation

(i) in each of the amino acid residues corresponding to K439 and S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W,
(ii) in each of the amino acid residues corresponding to K447 and 448 in the Fc-region of a human IgG1 heavy chain, such as K447K/R/H and 448E/D in the Fc-region of a human IgG1 heavy chain, preferably K447K and 448E in the Fc-region of a human IgG1 heavy chain, or
(iii) in each of the amino acid residues corresponding to K447, 448 and 449 in the Fc-region of a human IgG1 heavy chain, such as K447D/E, 448K/R/H and 449P in the Fc-region of a human IgG1 heavy chain, preferably K447E, 448K and 449P in the Fc-region of a human IgG1 heavy chain.

9. The method according to claim 8, said method comprises introducing the mutation in one or more positions other than S440, and further introducing a mutation in each of the amino acid residues corresponding to K439 and S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W.

10. The method according to claim 9, wherein the mutation in the position corresponding to K439 in the Fc-region of human IgG1 heavy chain is K439D/E, and/or the mutation in the position corresponding to S440 in the Fc-region of human IgG1 heavy chain is S440K/H/R.

11. A method of increasing an effector function of a combination of at least a first and a second parent polypeptide, wherein the at least first and second parent polypeptide each comprises an Fc-domain of an immunoglobulin and a binding region, wherein said method comprises
(i) introducing to the at least first and/or second parent polypeptide a mutation in one or more amino acid residues selected from the group consisting of:
(a) an amino acid residue within the CH2-CH3 region providing allosteric mutations,
(b) an amino acid residue within the hydrophobic knobs of the CH2-CH3 region,
(c) an amino acid residue within the N-terminal CH3 helix,

(d) an amino acid residue within the C-terminal CH3 beta-strand, with the proviso that in case of a mutation corresponding to S440 in the Fc-region of a human IgG1 heavy chain the mutation is S440Y or S440W, and

(e) an amino acid residue corresponding to E345, E382 or Q386 in the Fc-region of a human IgG1 heavy chain.

12. The method according to claim 11 of increasing an effector function of a combination of at least a first and a second parent antibody, wherein the at least first and second parent antibody each comprises a Fc-domain of an immunoglobulin and an antigen-binding region, wherein said method comprises

(i) introducing to the at least first and/or second parent antibody a mutation in one or more amino acid residues selected from the group consisting of:

(a) an amino acid residue within the CH2-CH3 region providing allosteric mutations,

(b) an amino acid residue within the hydrophobic knobs of the CH2-CH3 region,

(c) an amino acid residue within the N-terminal CH3 helix,

(d) an amino acid residue within the C-terminal CH3 beta-strand, with the proviso that in case of a mutation corresponding to S440 in the Fc-region of a human IgG1 heavy chain the mutation is S440Y or S440W, and

(e) an amino acid residue corresponding to E345, E382 or Q386 in the Fc-region of a human IgG1 heavy chain.

13. The method according to claim 12, wherein the mutation in the at least first and/or second parent antibody is in at least one amino acid residue selected from those corresponding to E345, E430, S440, Q386, P247, I253, S254, Q311, D/E356, T359, E382, Y436, and K447 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W.

14. The method according to claim 12 to 13, wherein said method comprises introducing a mutation in both the first and second parent antibodies.

15. The method according to claim 12, wherein said method comprises

(i) introducing a mutation to the first parent antibody in at least one amino acid residue selected from those corresponding to E345, E430, S440, Q386, P247,

I253, S254, Q311, D/E356, T359, E382, Y436, and K447 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W,

(ii) providing the second parent antibody which does not comprise a mutation in an amino acid residue selected from those corresponding to E345, E430, S440, Q386, P247, I253, S254, Q311, D/E356, T359, E382, Y436, and K447 in the Fc-region of a human IgG1 heavy chain.

16. The method according to any one of the claims 12 to 15, wherein said method comprises introducing the mutation in one or more positions other than S440, and wherein said method further comprises the steps of

(i) introducing to the first parent antibody a second mutation in the amino acid residue corresponding to position K439 in the Fc-region of a human IgG1 heavy chain; and

(ii) introducing to the second parent antibody a second mutation in the amino acid residue corresponding to position S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W; wherein steps (ii) and (iii) may alternatively be

(i) introducing to the first parent antibody a second mutation in the amino acid residue corresponding to position S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W; and

(ii) introducing to the second parent antibody a second mutation in the amino acid residue corresponding to position K439 in the Fc-region of a human IgG1 heavy chain.

17. The method according to claim 16, wherein the mutation in the position corresponding to K439 in the Fc-region of human IgG1 heavy chain is K439D/E, and the mutation in the position corresponding to S440 in the Fc-region of human IgG1 heavy chain is S440K/H/R.

18. The method according to any one of the claims 12 to 17, wherein said at least first and second parent antibodies may each be selected from the group of monospecific, bispecific and multispecific antibodies.

19. The method according to claim 18, wherein said at least first and second parent antibodies are bispecific or multispecific antibodies which bind different epitopes on the same antigen or on different antigens.

20. The method according to claim 18 or 19, wherein said at least first and second parent antibodies are each a bispecific antibody which comprises a first polypeptide comprising a first CH2-CH3 region of an immunoglobulin and a first antigen-binding region, and a second polypeptide comprising a second CH2-CH3 region of an immunoglobulin and a second antigen-binding region, wherein the first and second antigen-binding regions bind different epitopes on the same antigen or on different antigens, and wherein said first CH2-CH3 region comprises a further amino acid substitution at a position selected from those corresponding to K409, T366, L368, K370, D399, F405, and Y407 in the Fc-region of a human IgG1 heavy chain; and wherein said second CH2-CH3 region comprises a further amino acid substitution at a position selected from those corresponding to F405, T366, L368, K370, D399, Y407, and K409 in the Fc-region of a human IgG1 heavy chain, and wherein said further amino acid substitution in the first CH2-CH3 region is different from the said further amino acid substitution in the second CH2-CH3 region.

21. The method according to any one of the claims 1 to 2, 5 to 7, 11 to 15, and 18 to 20, wherein the mutation is in at least one amino acid residue selected from those corresponding to E345, E430, S440 to Y or W, and Q386 in the Fc-region of a human IgG1 heavy chain, preferably wherein the mutation is at least one amino acid substitution of the following: E345 to R, Q, N, or K, E430 to T, S, or G, S440 to Y or W, or Q386 to K.

22. The method according to any one of the claims 1 to 2, 5 to 7, 11 to 15, and 18 to 20, comprising introducing to the parent antibody a mutation in at least two amino acid residues selected from those corresponding to E345, E430, S440, Q386, P247, I253, S254, Q311, D/E356, T359, E382, Y436, and K447 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W.

23. The method according to claim 22, comprising introducing to the parent antibody a mutation in at least two amino acid residues selected from those corresponding to

E345, E430, Q386, and S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W, such as wherein the mutation in the at least two amino acids are selected from the following: E345 to R, Q, N, or K, E430 to T, S, or G, S440 to Y or W, or Q386 to K.

24. The method according to any one of the claims 1 to 23, wherein the effector function is an Fc-mediated effector function selected from an Fc-mediated effector function selected from C1q-binding, complement activation, complement dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxity (ADCC), FcRn-binding, Fc-receptor binding including Fc-gamma receptor-binding, Protein A-binding, Protein G-binding, antibody-dependent cellular phagocytosis (ADCP), complement-dependent cellular cytotoxicity (CDCC), complement-enhanced cytotoxicity , opsonisation, Fc-containing polypeptide internalization, target downmodulation, ADC uptake, induction of apoptosis, cell death, cell cycle arrest, and any combination thereof.

25. The method according to any one of the claims 1 to 2 and 5 to 24, wherein the effector function is increased when the antibody is bound to its antigen.

26. The method according to claim 25, wherein the antigen is on an antigen-expressing cell, cell membrane, or virion.

27. A method of inducing an effector response, against a cell, cell membrane, or virion expressing a target to which a parent polypeptide comprising an Fc-domain of an immunoglobulin and a binding region binds, comprising

(i) providing a parent polypeptide or a combination of at least a first parent polypeptide and a second parent polypeptide which has been mutated according to any one of the claims 1 to 24; and

(ii) contacting a preparation of the mutated parent polypeptide of step (i) or the mutated combination of at least a first parent polypeptide and a second parent polypeptide of step (i) with the cell, cell membrane, or virion expressing an antigen in the presence of human complement or an effector cell.

28. The method according to claim 27 of inducing an effector response, against a cell, cell membrane, or virion expressing an antigen to which a parent antibody binds, comprising

(i) providing a parent antibody or a combination of at least a first parent antibody and a second parent antibody which has been mutated according to any one of the claims 1 to 24; and

(ii) contacting a preparation of the mutated parent antibody of step (i) or the mutated combination of at least a first parent antibody and a second parent antibody of step (i) with the cell, cell membrane, or virion expressing an antigen in the presence of human complement or an effector cell.

29. The method according to claim 27 or 28, wherein the effector response is complement dependent cytotoxicity (CDC), an Fc-mediated effector response selected from an Fc-mediated effector response selected from C1q-binding, complement activation, complement dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxity (ADCC), FcRn-binding, Fc-receptor binding including Fc-gamma receptor-binding, Protein A-binding, Protein G-binding, antibody-dependent cellular phagocytosis (ADCP), complement-dependent cellular cytotoxicity (CDCC), complement-enhanced cytotoxicity , opsonisation, Fc-containing polypeptide internalization, target downmodulation, ADC uptake, induction of apoptosis, cell death, cell cycle arrest, and any combination thereof.

30. A method of increasing the specificity of a combination of at least a first and a second parent polypeptide comprising an Fc-domain of an immunoglobulin and a binding region, comprising

A)

(i) introducing to the first parent polypeptide a mutation in an amino acid residue in the position corresponding to K439 in the Fc region of a human IgG1 heavy chain; and

(ii) introducing to the second parent polypeptide a mutation in an amino acid residue in the position corresponding to S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W,

B)

(i) introducing to the first parent polypeptide a mutation in an amino acid residue in the position corresponding to K447D/E in the Fc region of a human IgG1 heavy chain; and

(ii) introducing to the second parent polypeptide a mutation in an amino acid residue in the position corresponding to K447K/R/H and 448P in the Fc-region of a human IgG1 heavy chain; or

C)

(i) introducing to the first parent polypeptide a mutation in an amino acid residue in the position corresponding to K447D/E in the Fc region of a human IgG1 heavy chain; and

(ii) introducing to the second parent polypeptide a mutation in an amino acid residue in the position corresponding to K447K/R/H, 448K/R/H and 449P in the Fc-region of a human IgG1 heavy chain.

31. The method according to claim 30 of increasing the specificity of a combination of at least a first and a second parent antibody, comprising

(i) introducing to the first parent antibody a mutation in an amino acid residue in the position corresponding to K439 in the Fc region of a human IgG1 heavy chain; and

(ii) introducing to the second parent antibody a mutation in an amino acid residue in the position corresponding to S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W.

32. The method according to claim 31, wherein the mutation in the position corresponding to K439 in the Fc-region of human IgG1 heavy chain is K439D/E, and the mutation in the position corresponding to S440 in the Fc-region of human IgG1 heavy chain is S440K/H/R.

33. The method according to any one of the claims 1 to 32, wherein the parent antibody or the combination of a first parent antibody and a second parent antibody is a human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD or IgE, optionally a human full-length antibody, such as a human full-length IgG1 antibody.

34. A variant of a parent polypeptide comprising an Fc-domain of an immunoglobulin and a binding region, wherein the variant comprises a mutation in at least one amino acid residue selected from those corresponding to E345, E430, S440, Q386, P247, I253, S254, Q311, D/E356, T359, E382, Y436, and K447 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W.

35. The variant according to claim 34 of a parent antibody comprising an antigen-binding region and a Fc-domain, wherein the variant comprises a mutation in at least one amino acid residue selected from those corresponding to E345, E430, S440, Q386, P247, I253, S254, Q311, D/E356, T359, E382, Y436, and K447 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W.

36. The variant according to claim 35, wherein the mutation in at least one amino acid residue is selected from those corresponding to E345X, E430X, S440W/Y, Q386K, P247G, I253V, S254L, Q311L/W, D/E356R, E382V, and Y436I in the Fc region of a human IgG1 heavy chain, wherein X is any amino acid, such as a natural occurring amino acid.

37. The variant according to claim 36, wherein the mutation in at least one amino acid residue is selected from those corresponding to E345X, E430X, S440W/Y, Q386K, in the Fc region of a human IgG1 heavy chain, wherein X is any amino acid, such as a natural occurring amino acid.

38. The variant according to claim 37, wherein the mutation in at least one amino acid residue is selected from those corresponding to
E345R/Q/N/K/A/C/D/F/G/H/I/L/M/P/S/T/V/W/Y,
E430T/S/G/A/C/D/F/H/I/L/K/M/N/P/Q/R/V/W/Y,
S440W/Y,
and Q386K
in the Fc region of a human IgG1 heavy chain.

39. The variant according to claim 38, wherein the mutation in at least one amino acid residue is selected from those corresponding to E345R/Q/N/K, E430T/S/G, S440Y/W, and Q386K in the Fc-region of a human IgG1 heavy chain.

40. A variant of a parent polypeptide comprising an Fc-domain of an immunoglobulin and a binding region, wherein the variant comprises a mutation in at least two amino acid residues selected from the group of

(a) an amino acid residue within the CH2-CH3 region providing allosteric mutations,

(b) an amino acid residue within the hydrophobic knobs of the CH2-CH3 region,

(c) an amino acid residue within the N-terminal CH3 helix,

(d) an amino acid residue within the C-terminal CH3 beta-strand, with the proviso that in case of a mutation corresponding to S440 in the Fc-region of a human IgG1 heavy chain the mutation is S440Y or S440W, and

(e) an amino acid residue corresponding to E345, E382 or Q386 in the Fc-region of a human IgG1 heavy chain,

wherein the at least two amino acid mutations are different.

41. The variant according to claim 40 of a parent antibody comprising an antigen-binding region and a Fc-domain, wherein the variant comprises a mutation in at least two amino acid residues selected from the group of

(a) an amino acid residue within the CH2-CH3 region providing allosteric mutations,

(b) an amino acid residue within the hydrophobic knobs of the CH2-CH3 region,

(c) an amino acid residue within the N-terminal CH3 helix,

(d) an amino acid residue within the C-terminal CH3 beta-strand, with the proviso that in case of a mutation corresponding to S440 in the Fc-region of a human IgG1 heavy chain the mutation is S440Y or S440W, and

(e) an amino acid residue corresponding to E345, E382 or Q386 in the Fc-region of a human IgG1 heavy chain,

wherein the at least two amino acid mutations are different.

42. The variant according to claim 41, wherein the variant comprises a mutation in at least two amino acid residues selected from those corresponding to E345, E430, S440, Q386, P247, I253, S254, Q311, D/E356, T359, E382, Y436, and K447 in the

Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W.

43. The variant according to claim 42, wherein the variant comprises a mutation in at least two amino acid residues selected from those corresponding to E345X, E430X, S440W/Y, Q386K, P247G, I253V, S254L, Q311L/W, D/E356R, E382V, and Y436I in the Fc region of a human IgG1 heavy chain, wherein X is any amino acid, such as a natural occurring amino acid.

44. The variant according to claim 43, wherein the variant comprises a mutation in at least two amino acid residues selected from the group of corresponding to those of E345X, E430X, S440W/Y, and Q386K in the Fc-region of a human IgG1 heavy chain, wherein X is any amino acid, such as a natural occurring amino acid.

45. The variant according to claim 44, wherein the variant comprises a mutation in at least two amino acid residues selected from those corresponding to E345R/Q/N/K/A/C/D/F/G/H/I/L/M/P/S/T/V/W/Y, E430T/S/G/A/C/D/F/H/I/L/K/M/N/P/Q/R/V/W/Y, S440W/Y, and Q386K in the Fc region of a human IgG1 heavy chain.

46. The variant according to claim 45, wherein the mutation in at least two amino acid residues are selected from those corresponding to E345R/Q/N/K, E430T/S/G, S440Y/W, and Q386K in the Fc-region of a human IgG1 heavy chain.

47. The variant according to any one of the claims 34 to 46, wherein the mutation is on position(s) other than S440 and K447, and wherein the variant further comprises a mutation
(i) in at least one amino acid residue corresponding to K439 or S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440W or S440Y;

(ii) in at least one amino acid residue corresponding to K447D/E or corresponding to K447K/R/H and 448P in the Fc region of a human IgG1 heavy chain; or
(iii) in at least one amino acid residue corresponding to K447D/E or corresponding to K447K/R/H and 448K/R/H and 449P in the Fc region of a human IgG1 heavy chain.

48. The variant according to claim 47, wherein the mutation is on position(s) other than S440, and wherein the variant further comprises a mutation in at least one amino acid residue corresponding to K439 or S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440W or S440Y.

49. A variant of a parent polypeptide comprising an Fc-domain of an immunoglobulin and a binding region, wherein the variant comprises a mutation in at least one amino acid residues selected from the group of

(a) an amino acid residue within the CH2-CH3 region providing allosteric mutations,

(b) an amino acid residue within the hydrophobic knobs of the CH2-CH3 region,

(c) an amino acid residue within the N-terminal CH3 helix,

(d) an amino acid residue within the C-terminal CH3 beta-strand, with the proviso that it does not comprise a mutation corresponding to S440 in the Fc-region of a human IgG1 heavy chain, and

(e) an amino acid residue corresponding to E345, E382 or Q386 in the Fc-region of a human IgG1 heavy chain, and

wherein the variant comprises a further mutation

(i) in at least one amino acid residue corresponding to K439 or S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440W or S440Y;

(ii) in at least one amino acid residue corresponding to K447D/E or corresponding to K447K/R/H and 448P in the Fc region of a human IgG1 heavy chain; or

(iii) in at least one amino acid residue corresponding to K447D/E or corresponding to K447K/R/H and 448K/R/H and 449P in the Fc region of a human IgG1 heavy chain.

50. The variant according to claim 49 of a parent antibody comprising an antigen-binding region and a Fc-domain of an immunoglobulin, wherein the variant comprises a mutation in at least one amino acid residues selected from the group of

(a) an amino acid residue within the CH2-CH3 region providing allosteric mutations,

(b) an amino acid residue within the hydrophobic knobs of the CH2-CH3 region,

(c) an amino acid residue within the N-terminal CH3 helix,

(d) an amino acid residue within the C-terminal CH3 beta-strand, with the proviso that it does not comprise a mutation corresponding to S440 in the Fc-region of a human IgG1 heavy chain, and

(e) an amino acid residue corresponding to E345, E382 or Q386 in the Fc-region of a human IgG1 heavy chain, and

wherein the variant comprises a further mutation

(i) in at least one amino acid residue corresponding to K439 or S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440W or S440Y,

(ii) in at least one amino acid residue corresponding to K447D/E or corresponding to K447K/R/H and 448P in the Fc region of a human IgG1 heavy chain; or

(iii) in at least one amino acid residue corresponding to K447D/E or corresponding to K447K/R/H and 448K/R/H and 449P in the Fc region of a human IgG1 heavy chain.

51. The variant according to claim 49 or 50, wherein the variant comprises an amino acid mutation in both of the positions corresponding to K439 and S440 in the Fc-region of an IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W.

52. The variant according to any one of the claims 47 to 51, wherein the mutation in the position corresponding to K439 in the Fc-region of human IgG1 heavy chain is K439D/E, and/or the mutation in the position corresponding to S440 in the Fc-region of human IgG1 heavy chain is S440K/H/R.

53. A variant of a parent polypeptide comprising an Fc-domain of an immunoglobulin and a binding region, wherein the variant comprises a mutation

(i) in at least one amino acid residue selected from those corresponding to K439 and S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W, such as wherein the mutation in the position corresponding to K439 in the Fc-region of human IgG1 heavy chain is K439D/E, and/or the mutation in the position corresponding to S440 in the Fc-region of human IgG1 heavy chain is S440K/H/R;

(ii) in at least one amino acid residue corresponding to K447D/E or corresponding to K447K/R/H and 448P in the Fc region of a human IgG1 heavy chain; or
(iii) in at least one amino acid residue corresponding to K447D/E or corresponding to K447K/R/H and 448K/R/H and 449P in the Fc region of a human IgG1 heavy chain.

54. The variant according to claim 53 of a parent antibody comprising an antigen-binding region and an Fc-domain of an immunoglobulin, wherein the variant comprises a mutation in at least one amino acid residue selected from those corresponding to K439 and S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W, such as wherein the mutation in the position corresponding to K439 in the Fc-region of human IgG1 heavy chain is K439D/E, and/or the mutation in the position corresponding to S440 in the Fc-region of human IgG1 heavy chain is S440K/H/R.

55. The variant according to any one of the claims 34 to 54, wherein the variant is selected from a monospecific antibody, bispecific antibody or multispecific antibody.

56. The variant according to claim 55 which is a bispecific antibody comprising a first polypeptide comprising a first CH2-CH3 region of an immunoglobulin and a first antigen-binding region, and a second polypeptide comprising a second CH2-CH3 region of an immunoglobulin and a second antigen-binding region, wherein the first and second antigen-binding regions bind different epitopes on the same antigen or on different antigens, and wherein

the first and second CH2-CH3 region each comprises a first mutation in at least one amino acid residue selected from those corresponding to E345, E430, S440, Q386, P247, I253, S254, Q311, D/E356, T359, E382, Y436, and K447 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W.

57. The variant according to claim 56 which is a bispecific antibody, wherein the first polypeptide comprises a further mutation in an amino acid residue selected from those corresponding to K409, T366, L368, K370, D399, F405, and Y407 in the Fc-region of a human IgG1 heavy chain; and

the second polypeptide comprises a further mutation in an amino acid residue selected from those corresponding to F405, T366, L368, K370, D399, Y407 and K409

in the Fc-region of a human IgG1 heavy chain, and wherein the said further mutation in the first polypeptide is different from the said further mutation in the second polypeptide.

58. The variant according to any one of the claims 34 to 57, wherein said variant is conjugated to a drug, toxin or radiolabel, such as wherein the variant is conjugated to a toxin via a linker.

59. The variant according to any one of the claims 34 to 57, wherein said variant is part of a fusion protein.

60. The variant according to any one of the claims 34 to 59, wherein the variant is a human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD or IgE antibody, optionally a human full-length antibody, such as a human full-length IgG1 antibody.

61. A composition comprising a first variant of a parent polypeptide and a second variant of a parent polypeptide, wherein the first variant comprises a first Fc-domain of an immunoglobulin and a binding region, wherein the second variant comprises a second Fc-domain of an immunoglobulin and a binding region, and wherein
(i) said first variant comprises a mutation in the position corresponding to K439 in the Fc-region of a human IgG1 heavy chain, and said second variant comprises a mutation in the position corresponding to S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W,
(ii) said first variant comprises a mutation in the position corresponding to K447D/E in the Fc region of a human IgG1 heavy chain; and said second variant comprises a mutation in the position corresponding to K447K/R/H and 448P in the Fc-region of a human IgG1 heavy chain, or
(iii) said first variant comprises a mutation in the position corresponding to K447D/E in the Fc region of a human IgG1 heavy chain; and said second variant comprises a mutation in the position corresponding to K447K/R/H, 448K/R/H and 449P in the Fc-region of a human IgG1 heavy chain.

62. The composition according to claim 61 comprising a first variant of a parent antibody and a second variant of a parent antibody, wherein the first variant comprises a first Fc-domain of an immunoglobulin and an antigen-binding region,

wherein the second variant comprises a second Fc-domain of an immunoglobulin and an antigen-binding region, and wherein
(i) said first variant comprises a mutation in the position corresponding to K439 in the Fc-region of a human IgG1 heavy chain, and said second variant comprises a mutation in the position corresponding to S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W,
(ii) said first variant comprises a mutation in the position corresponding to K447D/E in the Fc region of a human IgG1 heavy chain; and said second variant comprises a mutation in the position corresponding to K447K/R/H and 448P in the Fc-region of a human IgG1 heavy chain, or
(iii) said first variant comprises a mutation in the position corresponding to K447D/E in the Fc region of a human IgG1 heavy chain; and said second variant comprises a mutation in the position corresponding to K447K/R/H, 448K/R/H and 449P in the Fc-region of a human IgG1 heavy chain.

63. The composition according to claim 62 comprising a first variant of a parent antibody and a second variant of a parent antibody, wherein the first variant comprises a first Fc-domain of an immunoglobulin and an antigen-binding region, wherein the second variant comprises a second Fc-domain of an immunoglobulin and an antigen-binding region, and wherein said first variant comprises a mutation in the position corresponding to K439 in the Fc-region of a human IgG1 heavy chain, and wherein the second variant comprises a mutation in the position corresponding to S440, with the proviso that the mutation in S440 is not S440Y or S440W.

64. The composition according to claim 63, wherein the first variant comprises a first Fc-domain of an immunoglobulin and an antigen-binding region, wherein said first variant comprises (i) a first mutation in at least one amino acid residue other than a mutation in K439 selected from the group of

(a) an amino acid residue within the CH2-CH3 region providing allosteric mutations,

(b) an amino acid residue within the hydrophobic knobs of the CH2-CH3 region,

(c) an amino acid residue within the N-terminal CH3 helix,

(d) an amino acid residue within the C-terminal CH3 beta-strand, with the proviso that in case of a mutation corresponding to S440 in the Fc-region of a human IgG1 heavy chain the mutation is S440Y or S440W, and

(e) an amino acid residue corresponding to E345, E382 or Q386 in the Fc-region of a human IgG1 heavy chain, and

(ii) a second mutation in the position corresponding to K439 in the Fc-region of a human IgG1 heavy chain; and

wherein the second variant comprises a second Fc-domain of an immunoglobulin and an antigen-binding region, wherein said second variant comprises (i) a first mutation in at least one amino acid residue other than a mutation in S440 selected from the group of

(a) an amino acid residue within the CH2-CH3 region providing allosteric mutations,

(b) an amino acid residue within the hydrophobic knobs of the CH2-CH3 region,

(c) an amino acid residue within the N-terminal CH3 helix,

(d) an amino acid residue within the C-terminal CH3 beta-strand, and

(e) an amino acid residue corresponding to E345, E382 or Q386 in the Fc-region of a human IgG1 heavy chain, and

(ii) a second mutation in the position corresponding to S440 in the Fc region of an IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W.

65. A composition according to claim 63, wherein the first variant comprises (i) a first mutation in at least one amino acid residue other than a mutation in K439 selected from the group of

(a) an amino acid residue within the CH2-CH3 region providing allosteric mutations,

(b) an amino acid residue within the hydrophobic knobs of the CH2-CH3 region,

(c) an amino acid residue within the N-terminal CH3 helix,

(d) an amino acid residue within the C-terminal CH3 beta-strand, with the proviso that in case of a mutation corresponding to S440 in the Fc-region of a human IgG1 heavy chain the mutation is S440Y or S440W, and

(e) an amino acid residue corresponding to E345, E382 or Q386 in the Fc-region of a human IgG1 heavy chain, and

(ii) a second mutation in the position corresponding to K439 in the Fc-region of a human IgG1 heavy chain, and

wherein the second variant comprises a mutation in the position corresponding to S440 in the Fc-region of a human IgG1 heavy chain, which is not is not S440Y or S440W.

66. A composition according to claim 63, wherein the first variant comprises a mutation in the position corresponding to K439 in the Fc-region of a human IgG1 heavy chain; and

wherein the second variant comprises a second Fc-domain of an immunoglobulin and an antigen-binding region, wherein said second variant comprises (i) a first mutation in at least one amino acid residue other than a mutation in S440 selected from the group of

(a) an amino acid residue within the CH2-CH3 region providing allosteric mutations,

(b) an amino acid residue within the hydrophobic knobs of the CH2-CH3 region,

(c) an amino acid residue within the N-terminal CH3 helix,

(d) an amino acid residue within the C-terminal CH3 beta-strand, and

(e) an amino acid residue corresponding to E345, E382 or Q386 in the Fc-region of a human IgG1 heavy chain,

and (ii) a second mutation in the position corresponding to S440 in the Fc region of an IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W.

67. The composition according to any one of the claims 61 to 66, wherein the mutation in the position corresponding to K439 in the Fc-region of human IgG1 heavy chain is K439D/E, and/or the mutation in the position corresponding to S440 in the Fc-region of human IgG1 heavy chain is S440K/H/R.

68. A composition comprising a first variant of an parent polypeptide comprising an Fc-domain of an immunoglobulin and a binding region and a second variant of a

parent polypeptide comprising an Fc-domain of an immunoglobulin and a binding region, wherein
the first variant comprises a first Fc-domain of an immunoglobulin and a first antigen-binding region, wherein the first variant comprises a first mutation in at least an amino acid residue selected from the group of

(a) an amino acid residue within the CH2-CH3 region providing allosteric mutations,

(b) an amino acid residue within the hydrophobic knobs of the CH2-CH3 region,

(c) an amino acid residue within the N-terminal CH3 helix,

(d) an amino acid residue within the C-terminal CH3 beta-strand, with the proviso that in case of a mutation corresponding to S440 in the Fc-region of a human IgG1 heavy chain the mutation is S440Y or S440W, and

(e) an amino acid residue corresponding to E345, E382 or Q386 in the Fc-region of a human IgG1 heavy chain, and wherein
the second variant does not comprise a mutation in an amino acid residue selected from the group of

(a) an amino acid residue within the CH2-CH3 region providing allosteric mutations,

(b) an amino acid residue within the hydrophobic knobs of the CH2-CH3 region,

(c) an amino acid residue within the N-terminal CH3 helix,

(d) an amino acid residue within the C-terminal CH3 beta-strand, with the proviso that in case of a mutation corresponding to S440 in the Fc-region of a human IgG1 heavy chain the mutation is S440Y or S440W, and

(e) an amino acid residue corresponding to E345, E382 or Q386 in the Fc-region of a human IgG1 heavy chain.

69. The composition according to claim 68 comprising a first variant of an antibody and a second variant of a parent antibody, wherein
the first variant comprises a first Fc-domain of an immunoglobulin and a first antigen-binding region, wherein the first variant comprises a first mutation in at least an amino acid residue selected from the group of

(a) an amino acid residue within the CH2-CH3 region providing allosteric mutations,

(b) an amino acid residue within the hydrophobic knobs of the CH2-CH3 region,

(c) an amino acid residue within the N-terminal CH3 helix,

(d) an amino acid residue within the C-terminal CH3 beta-strand, with the proviso that in case of a mutation corresponding to S440 in the Fc-region of a human IgG1 heavy chain the mutation is S440Y or S440W, and

(e) an amino acid residue corresponding to E345, E382 or Q386 in the Fc-region of a human IgG1 heavy chain, and

wherein the second variant comprises a second Fc-domain of an immunoglobulin and a second antigen-binding region, wherein said second variant does not comprise a mutation in an amino acid residue selected from the group of

(a) an amino acid residue within the CH2-CH3 region providing allosteric mutations,

(b) an amino acid residue within the hydrophobic knobs of the CH2-CH3 region,

(c) an amino acid residue within the N-terminal CH3 helix,

(d) an amino acid residue within the C-terminal CH3 beta-strand, with the proviso that in case of a mutation corresponding to S440 in the Fc-region of a human IgG1 heavy chain the mutation is S440Y or S440W, and

(e) an amino acid residue corresponding to E345, E382 or Q386 in the Fc-region of a human IgG1 heavy chain.

70. The composition according to any one of the claims 61 to 67, wherein the first and second variant comprise a mutation in at least one amino acid residue selected from those corresponding to E345, E430, Q386, P247, I253, S254, Q311, D/E356, T359, E382, Y436, and K447 in the Fc-region of a human IgG1 heavy chain.

71. The composition according to claim 70, wherein the mutation in the first and second variants are different.

72. The composition according to claim 68 or 69, wherein the first variant comprises a mutation in at least one amino acid residue selected from those corresponding to E345, E430, S440, Q386, P247, I253, S254, Q311, D/E356, T359, E382, Y436, and

K447 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W.

73. The composition according to any one of the claims 61 to 72, wherein the first variant and second variant is each a human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD or IgE antibody, optionally each a human full-length antibody, such as each a human full-length IgG1 antibody.

74. The composition according to any one of the claims 61 to 73, wherein the first variant and second variant is selected from a monospecific antibody, bispecific antibody or multispecific antibody.

75. The composition according to any one of the claims 61 to 74, wherein the first and the second variant bind different epitopes on the same antigen or on different antigens.

76. The composition according to any one of the claims 61 to 75, wherein one or both of the first variant and second variant is conjugated to a drug, toxin or radiolabel, such as wherein one or both of the first variant and second variant is conjugated to a toxin via a linker.

77. The composition according to any one of the claims 61 to 75, wherein one or both of the first variant and second variant is part of a fusion protein.

78. A composition comprising the variant according to any one of the claims 34 to 60 or the composition according to any one of the claims 61 to 77 and a pharmaceutically acceptable carrier.

79. A kit-of-parts comprising a first variant and a second variant as defined in any one of the claims 34 to 60 for simultaneous, separate or sequential use in therapy.

80. The variant, composition or kit-of-parts according to any one of the claims 34 to 79 for treatment of a disease, such as cancer.

81. The use of the variant, the composition or the kit-of-parts according to any one of the claims 34 to 79 in the manufacture of a medicament for the treatment of a human.

82. The use of the variant, the composition or the kit-of-parts according to any one of the claims 34 to 79 in the manufacture of a medicament for the treatment of cancer in a human.

CLAIMS

1. A method of increasing an effector function of a parent polypeptide comprising an Fc-domain of an immunoglobulin and a binding region, which method comprises introducing a mutation to the parent polypeptide in the amino acid residue corresponding to E345K, in the Fc-region of a human IgG1 heavy chain.

2. The method according to claim 1 of increasing an effector function of a parent antibody, comprising introducing a mutation to the parent antibody in the amino acid residue corresponding to E345K in the Fc-region of a human IgG1 heavy chain,.

3. The method according to claim 2, wherein the parent antibody is a monospecific, bispecific or multispecific antibody.

4. The method according to claim 3, wherein the parent antibody is a bispecific antibody which comprises a first polypeptide comprising a first CH2-CH3 region of an immunoglobulin and a first antigen-binding region, and a second polypeptide comprising a second CH2-CH3 region of an immunoglobulin and a second antigen-binding region, wherein the first and second antigen-binding regions bind different epitopes on the same antigen or on different antigens, and wherein said first CH2-CH3 region comprises a further amino acid substitution at a position selected from those corresponding to K409, T366, L368, K370, D399, F405, and Y407 in the Fc-region of a human IgG1 heavy chain; and wherein said second CH2-CH3 region comprises a further amino acid substitution at a position selected from those corresponding to F405, T366, L368, K370, D399, Y407, and K409 in the Fc-region of a human IgG1 heavy chain, and wherein said further amino acid substitution in the first CH2-CH3 region is different from the said further amino acid substitution in the second CH2-CH3 region.

5. The method according to claim 3 or 4, wherein the parent antibody is a bispecific antibody and comprises a first polypeptide and a second polypeptide, wherein said first polypeptide comprises a first CH2-CH3 region of an immunoglobulin and a first antigen-binding region, and said second polypeptide comprises a second CH2-CH3 region of an immunoglobulin and a second antigen-binding region, wherein the first and second antigen-binding regions bind different epitopes on the same antigen or on different antigens, said method comprising introducing to each of the first and second CH2-CH3 region a mutation in the amino acid residue corresponding to E345K in the Fc-region of a human IgG1 heavy chain.

6. A method according to any one of the claims 1 to 5, said method comprises introducing further introducing a mutation

(i) in each of the amino acid residues corresponding to K439 and S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W, (ii) in each of the amino acid residues corresponding to K447 and 448 in the Fc-region of a human IgG1 heavy chain, such as K447K/R/H and 448E/D in the Fc-region of a human IgG1 heavy chain, preferably K447K and 448E in the Fc-region of a human IgG1 heavy chain, or (iii) in each of the amino acid residues corresponding to K447, 448 and 449 in the Fc-region of a human IgG1 heavy chain, such as K447D/E, 448K/R/H and 449P in the Fc-region of a human IgG1 heavy chain, preferably K447E, 448K and 449P in the Fc-region of a human IgG1 heavy chain.

7. The method according to claim 6, said method further introducing a mutation in each of the amino acid residues corresponding to K439 and S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440Y or S440W.

8. The method according to claim 7, wherein the mutation in the position corresponding to K439 in the Fc-region of human IgG1 heavy chain is K439D/E, and/or the mutation in the position corresponding to S440 in the Fc-region of human IgG1 heavy chain is S440K/H/R.

9. The method according to any one of the claims 1 to 5, comprising introducing to the parent antibody a mutation in at least one further amino acid residues selected from those corresponding to, E430, S440, Q386, P247, I253, S254, Q311, D/E356, T359, E382, Y436, and K447 in the Fc region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W.

10. The method according to claim 9, comprising introducing to the parent antibody a mutation in at least one further amino acid residues selected from those corresponding to E430, Q386, and S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W, such as wherein the mutation in the at least one further amino acids are selected from the following: E430 to T, S, or G, S440 to Y or W, or Q386 to K.

11. The method according to any one of the claims 1 to 10, wherein the effector function is an Fc-mediated effector function selected from an Fc-mediated effector function selected from

C1q-binding, complement activation, complement dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxity (ADCC), FcRn-binding, Fc-receptor binding including Fc-gamma receptor-binding, Protein A-binding, Protein G-binding, antibody-dependent cellular phagocytosis (ADCP), complement-dependent cellular cytotoxicity (CDCC), complement-enhanced cytotoxicity , opsonisation, Fc-containing polypeptide internalization, target downmodulation, ADC uptake, induction of apoptosis, cell death, cell cycle arrest, and any combination thereof.

12. The method according to any one of the claims 1 to 11, wherein the effector function is increased when the antibody is bound to its antigen.

13. The method according to claim 12, wherein the antigen is on an antigen-expressing cell, cell membrane, or virion.

14. A method of inducing an effector response, against a cell, cell membrane, or virion expressing a target to which a parent polypeptide comprising an Fc-domain of an immunoglobulin and a binding region binds, comprising

(i) providing a parent polypeptide which has been mutated according to any one of the claims 1 to 11; and

(ii) contacting a preparation of the mutated parent polypeptide of step (i) with the cell, cell membrane, or virion expressing an antigen in the presence of human complement or an effector cell.

15. The method according to claim 14 of inducing an effector response, against a cell, cell membrane, or virion expressing an antigen to which a parent antibody binds, comprising

(i) providing a parent antibody which has been mutated according to any one of the claims 1 to 11; and

(ii) contacting a preparation of the mutated parent antibody of step (i) with the cell, cell membrane, or virion expressing an antigen in the presence of human complement or an effector cell.

16. The method according to claim 14 or 15, wherein the effector response is complement dependent cytotoxicity (CDC), an Fc-mediated effector response selected from an Fc-mediated effector response selected from C1q-binding, complement activation, complement dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxity (ADCC), FcRn-binding, Fc-receptor binding including Fc-gamma receptor-binding, Protein A-binding, Protein G-binding, antibody-dependent cellular phagocytosis (ADCP), complement-dependent cellular cytotoxicity

(CDCC), complement-enhanced cytotoxicity , opsonisation, Fc-containing polypeptide internalization, target downmodulation, ADC uptake, induction of apoptosis, cell death, cell cycle arrest, and any combination thereof.

17. The method according to any one of the claims 1 to 16, wherein the parent is a human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD or IgE, optionally a human full-length antibody, such as a human full-length IgG1 antibody.

18. A variant of a parent polypeptide comprising an Fc-domain of an immunoglobulin and a binding region, wherein the variant comprises a mutation in the amino acid residue corresponding to E345K, in the Fc-region of a human IgG1 heavy chain.

19. The variant according to claim 18 of a parent antibody comprising an antigen-binding region and a Fc-domain, wherein the variant comprises a mutation in the amino acid residue corresponding to E345K, in the Fc-region of a human IgG1 heavy chain.

20. A variant of a parent polypeptide comprising an Fc-domain of an immunoglobulin and a binding region, wherein the variant comprises a mutation corresponding to E345K in the Fc-region of human IgG1 heavy chain and at least one further amino acid residue selected from those corresponding to E430, S440, Q386, P247, I253, S254, Q311, D/E356, T359, E382, Y436, and K447 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is S440Y or S440W.

21. The variant according to claim 20, wherein the variant comprises a mutation corresponding to E345K in the Fc-region of human IgG1 heavy chain and in at least one further amino acid residue selected from those corresponding to E430X, S440W/Y, Q386K, P247G, I253V, S254L, Q311L/W, D/E356R, E382V, and Y436I in the Fc region of a human IgG1 heavy chain, wherein X is any amino acid, such as a natural occurring amino acid.

22. The variant according to claim 21, wherein the variant comprises a mutation corresponding to E345K in the Fc-region of human IgG1 heavy chain and in at least one further amino acid residue selected from the group of corresponding to those of E430X, S440W/Y, and Q386K in

the Fc-region of a human IgG1 heavy chain, wherein X is any amino acid, such as a natural occurring amino acid.

23. The variant according to claim 22, wherein the variant comprises a mutation corresponding to E345K in the Fc-region of human IgG1 heavy chain and in at least one further amino acid residue selected from those corresponding to E430T/S/G/A/C/D/F/H/I/L/K/M/N/P/Q/R/V/W/Y, S440W/Y, and Q386K in the Fc region of a human IgG1 heavy chain.

24. The variant according to claim 23, wherein the mutation corresponding to E345K in the Fc-region og human IgG1 heavy chain and in at least one further amino acid residue selected from those corresponding to E430T/S/G, S440Y/W, and Q386K in the Fc-region of a human IgG1 heavy chain.

25. The variant according to any one of the claims 18 to 24, wherein the at least one further mutation is in position(s) other than S440 and K447, and wherein the variant further comprises a mutation
(i) in at least one amino acid residue corresponding to K439 or S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440W or S440Y;

(ii) in at least one amino acid residue corresponding to K447D/E or corresponding to K447K/R/H and 448P in the Fc region of a human IgG1 heavy chain; or
(iii) in at least one amino acid residue corresponding to K447D/E or corresponding to K447K/R/H and 448K/R/H and 449P in the Fc region of a human IgG1 heavy chain.

26. The variant according to claim 25, wherein the at least one further mutation is in position(s) other than S440, and wherein the variant further comprises a mutation in at least one amino acid residue corresponding to K439 or S440 in the Fc-region of a human IgG1 heavy chain, with the proviso that the mutation in S440 is not S440W or S440Y.

27. The variant according to any one of the claims 25 to 26, wherein the mutation in the position corresponding to K439 in the Fc-region of human IgG1 heavy chain is K439D/E, and/or the mutation in the position corresponding to S440 in the Fc-region of human IgG1 heavy chain is S440K/H/R.

28. The variant according to any one of the claims 18 to 27, wherein said variant is conjugated to a drug, toxin or radiolabel, such as wherein the variant is conjugated to a toxin via a linker.

29. The variant according to any one of the claims 18 to 27, wherein said variant is part of a fusion protein.

30. The variant according to any one of the claims 18 to 29, wherein the variant is a human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD or IgE antibody, optionally a human full-length antibody, such as a human full-length IgG1 antibody.

31. A composition comprising the variant according to any one of the claims 18 to 30 and a pharmaceutically acceptable carrier.

32. A kit-of-parts comprising a first variant and a second variant as defined in any one of the claims 18 to 30 for simultaneous, separate or sequential use in therapy.

33. The variant, composition or kit-of-parts according to any one of the claims 18 to 32 for use in the treatment of a disease, such as cancer.

34. The use of the variant, the composition or the kit-of-parts according to any one of the claims 18 to 32 in the manufacture of a medicament for the treatment of a human.

35. The use of the variant, the composition or the kit-of-parts according to any one of the claims 18 to 32 in the manufacture of a medicament for the treatment of cancer in a human.