

What is Claimed is:

1. A pharmaceutical composition comprising a chimeric peptide sequence, comprising:
 - (A) (i) (a) an N-terminal region comprising at least seven amino acid residues, the N-terminal region having a first amino acid position and a last amino acid position, wherein the N-terminal region comprises DSSPL (SEQ ID NO:121) or DASPH (SEQ ID NO:122); and

(b) a C-terminal region comprising a portion of SEQ ID NO:99 (FGF19), the C-terminal region having a first amino acid position and a last amino acid position, wherein the C-terminal region comprises amino acid residues 16-29 of SEQ ID NO:99 (FGF19), WGDPIRLRHLYTSG (SEQ ID NO:169), wherein the W residue corresponds to the first amino acid position of the C-terminal region;
 - (ii) (a) an N-terminal region comprising a portion of SEQ ID NO:100 (FGF21), the N-terminal region having a first amino acid position and a last amino acid position, wherein the N-terminal region comprises amino acid residues GQV, and wherein the V residue corresponds to the last amino acid position of the N-terminal region; and

(b) a C-terminal region comprising a portion of SEQ ID NO:99 (FGF19), the C-terminal region having a first amino acid position and a last amino acid position, wherein the C-terminal region comprises amino acid residues 21-29 of SEQ ID NO:99 (FGF19), RLRHLYTSG (SEQ ID NO:185), and wherein the R residue corresponds to the first position of the C-terminal region; or
 - (iii)(a) an N-terminal region comprising a portion of SEQ ID NO:100 (FGF21), the N-terminal region having a first amino acid position and a last amino acid position, wherein the N-terminal region comprises at least 5 contiguous amino acids of SEQ ID NO:100 (FGF21) including the amino acid residues GQV, and wherein the V residue corresponds to the last amino acid position of the N-terminal region;wherein optionally the N-terminal region comprises
 - (1) at least 6 contiguous amino acids of SEQ ID NO:100 (FGF21) including the amino acid residues GQV; or
 - (2) at least 7 contiguous amino acids of SEQ ID NO:100 (FGF21) including the amino acid residues GQV;

and

(b) a C-terminal region comprising a portion of SEQ ID NO:99 (FGF19), the C-terminal region having a first amino acid position and a last amino acid position, wherein the C-terminal region comprises amino acid residues 21-29 of SEQ ID NO:99 (FGF19), RLRHLYTSG (SEQ ID NO:185), and wherein the R residue corresponds to the first position of the C-terminal region;

and

(B) a pharmaceutically acceptable carrier comprising Tris, trehalose and polysorbate-20 (TWEEN-20).

2. A pharmaceutical composition comprising a peptide sequence, comprising or consisting of:

(A) (i) a FGF19 sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF19;

(ii) a FGF21 sequence variant having one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF21;

(iii) a portion of a FGF19 sequence fused to a portion of a FGF21 sequence; or

(iv) a portion of a FGF19 sequence fused to a portion of a FGF21 sequence, wherein the FGF19 and/or FGF21 sequence portion(s) have one or more amino acid substitutions, insertions or deletions compared to a reference or wild type FGF19 and/or FGF21; and

(B) a pharmaceutically acceptable carrier comprising Tris, trehalose and polysorbate-20 (TWEEN-20).

3. The pharmaceutical composition of claim 2, wherein

(i) the peptide sequence comprises or consists of amino-terminal amino acids 1-16 of SEQ ID NO:100 (FGF21) fused to carboxy-terminal amino acids 21-194 of SEQ ID NO:99 (FGF19);

(ii) the peptide sequence comprises or consists of amino-terminal amino acids 1-147 of SEQ ID NO:99 (FGF19) fused to carboxy-terminal amino acids 147-181 of SEQ ID NO:100 (FGF21) (M41);

- (iii) the peptide sequence comprises or consists of amino-terminal amino acids 1-20 of SEQ ID NO:99 (FGF19) fused to carboxy-terminal amino acids 17-181 of SEQ ID NO:100 (FGF21) (M44);
- (iv) the peptide sequence comprises or consists of amino-terminal amino acids 1-146 of SEQ ID NO:100 (FGF21) fused to carboxy-terminal amino acids 148-194 of SEQ ID NO:99 (FGF19) (M45);
- (v) the peptide sequence comprises or consists of amino-terminal amino acids 1-20 of SEQ ID NO:99 (FGF19) fused to internal amino acids 17-146 of SEQ ID NO:100 (FGF21) fused to carboxy-terminal amino acids 148-194 of SEQ ID NO:99 (FGF19) (M46);
- (vi) the reference or wild type FGF19 sequence is set forth as:

RPLAFSDAGPHVHYGWGDPRLRLHLYTSGPHGLSSCFLRIRADGV
VDCARGQSAHSLLEIKAVALLRTVAIKGVHVSRYLCMGADGKMQG
LLQYSEEDCAFEIEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNR
GFLPLSHFLPMLPMVPEEPEDLRGHLESDFSSPLETDSMDPFGLV
TGLEAVRSPSF EK (SEQ ID NO:99); or

- (vii) the reference or wild type FGF21 sequence is set forth as:

RHPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDDGTGGA
ADQSPESLLQLKALKPGVIQILGVKTSRFLCQRPDGALYGSLHFD
EACSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDPAPRGPAR
FLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS
(SEQ ID NO:100).

4. The pharmaceutical composition of claim 2, wherein the peptide sequence comprises

- (A) at least one amino acid substitution to the EIRPD (amino acids 2-6 SEQ ID NO:190) of SEQ ID NO:99 (FGF19);
- (B) at least one amino acid substitution to the IRP (amino acids 3-5 of SEQ ID NO:190) of SEQ ID NO:99 (FGF19); or
- (C) at least one amino acid substitution to RP (amino acids 4-5 of SEQ ID NO:190) of SEQ ID NO:99 (FGF19);

wherein optionally the at least one amino acid substitution is an Arg(R) to Leu(L) substitution or a Pro(P) to Glu(E) substitution;

wherein optionally the peptide sequence comprises

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCAR
GQSAHSLLEIKAVALLRTVAIKGVHVSRYLCMGADGKMQLLQYSEEDCA
FEEEILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPM
VPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFKEK (M3)
(SEQ ID NO:3); or

RPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFLRIRADGVVDCAR
GQSAHSLLEIKAVALLRTVAIKGVHVSRYLCMGADGKMQLLQYSEEDCA
FEEEIREDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPM
VPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFKEK (M140)
(SEQ ID NO:194).

5. The pharmaceutical composition of claim 4, wherein the peptide sequence further comprises at least one amino acid substitution to amino acid residues 1-124 of SEQ ID NO:99 (FGF19) and/or to amino acid residues 130-194 of SEQ ID NO:99 (FGF19);

wherein optionally the peptide sequence is

RPLAFSDAGPHVHYGWGDPIRQRHLYTSGPHGLSSCFLRIRADGVVDCAR
GQSAHSLLEIKAVALLRTVAIKGVHVSRYLCMGADGKMQLLQYSEEDCA
FEEEILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPM
VPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFKEK (M160)
(SEQ ID NO:196);

wherein optionally the N-terminal region further comprises: RHPIP (SEQ ID NO:106), where R is the first amino acid position of the N-terminal region; or HPIP (SEQ ID NO:107), where H is the first amino acid position of the N-terminal region; or RPLAF (SEQ ID NO:108), where R is the first amino acid position of the N-terminal region; or PLAF (SEQ ID NO:109), where P is the first amino acid position of the N-terminal region; or R, where R is the first amino acid position of the N-terminal region.

6. The pharmaceutical composition of claim 1 or 2, wherein
- (i) the peptide sequence comprises or consists of a sequence set forth herein as SEQ ID NOs:1 to 98, 101 to 135, or 138 to 196;
 - (ii) the peptide sequence comprises or consists of any sequence set forth in Table 1;
 - (iii) the peptide sequence comprises or consists of any sequence set forth in the Sequence Listing herein;

- (iv) the peptide has a WGDPI (SEQ ID NO:170) sequence motif corresponding to the WGDPI (SEQ ID NO:170) sequence of amino acids 16-20 of SEQ ID NO:99 (FGF19);
 - wherein optionally the peptide maintains or increases a FGFR4 mediated activity;
 - wherein optionally the subsequence or fragment thereof has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more amino acid deletions from the amino terminus, the carboxy-terminus or internally;
- (v) the peptide has a substituted, mutated or absent WGDPI (SEQ ID NO:170) sequence motif corresponding to FGF19 WGDPI (SEQ ID NO:170) sequence of amino acids 16-20 of FGF19;
 - wherein optionally the WGDPI (SEQ ID NO:170) sequence has one or more amino acids substituted, mutated or absent;
- (vi) the sequence of the peptide is distinct from a FGF 19 variant sequence having any of GQV, GDI, WGPI (SEQ ID NO:171), WGDPI (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDPI (SEQ ID NO:183) or FGDPPI (SEQ ID NO:184) substituted for the FGF19 WGDPI (SEQ ID NO:170) sequence at amino acids 16-20;
- (vii) the N-terminal or C-terminal region is from about 20 to about 200 amino acid residues in length;
- (viii) the N-terminal region further comprises amino acid residues DSSPLLQFGGQV (SEQ ID NO:105), and wherein the V residue corresponds to the last position of the N-terminal region;
- (ix) wherein the N-terminal region comprises amino acid residues VHYG (SEQ ID NO:101), wherein the N-terminal region comprises amino acid residues DASPHVHYG (SEQ ID NO:102), or wherein the N-terminal region comprises amino acid residues DSSPLVHYG (SEQ ID NO:103);
 - wherein optionally the G corresponds to the last position of the N-terminal region;

- (x) wherein the N-terminal region comprises amino acid residues DSSPLLQ (SEQ ID NO:104), and wherein the Q residue is the last amino acid position of the N-terminal region;
- (xi) the peptide sequence comprises or consists of any of M1 to M98 or M101 to M160 variant peptide sequences, or a subsequence or fragment of any of the M1 to M98 or M101 to M160 variant peptide sequences;
- (xii) the peptide sequence comprises or consists of any of:

RDSSPLVHYGWDPIRLRHL YTSGPHGLSSCFLRIRADGVVDCARGQSAH
 SLLEIKAVALRTVAIKGVH SVRYLCMGADGKMQGLLQYSEEDCAFEEEEIR
 PDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPE
 DLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (M69) (SEQ ID
 NO: 69);

RDSSPLLQWGDPIRLRHL YTSGPHGLSSCFLRIRADGVVDCARGQSAHSL
 LEIKAVALRTVAIKGVH SVRYLCMGADGKMQGLLQYSEEDCAFEEEEIRPD
 GYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDL
 RGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (M52) (SEQ ID
 NO:52);

RHIPDSSPLLQFGGQVRLRHL YTSGPHGLSSCFLRIRADGVVDCARGQSA
 HSLLEIKAVALRTVAIKGVH SVRYLCMGADGKMQGLLQYSEEDCAFEEEEI
 RPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEP
 EDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (M5) (SEQ ID
 NO:5);

HPIP DSSPLLQFGGQVRLRHL YTSGPHGLSSCFLRIRADGVVDCARGQSAH
 SLLEIKAVALRTVAIKGVH SVRYLCMGADGKMQGLLQYSEEDCAFEEEEIR
 PDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPE
 DLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (M5-R) (SEQ ID
 NO:160);

HPIP DSSPLLQFGGQVRQRYLYTDDAQQT EAHLEIREDGTVGGAADQSPE
 SLLQLKALKPGVIQILGVKTSRFLCQRPDGALYGS LHFDPEACSFRELLLE
 DGYNVYQSEAHSLPLHLP GNKSPHRDPAPRGPARFLPLPGLPPALPEPPGI
 LAPQPPDVGSSDPLSMVGPSQGRSPSYAS (M71) (SEQ ID NO:71);

HPIP DSSPLLQFGGQVRQRYLYTDDAQQT EAHLEIREDGTVGGAADQSPE
 SLLQLKALKPGVIQILGVKTSRFLCQRPDGALYGS LHFDPEACSFRELLLE

DGYNVYQSEAHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPAPPEPPGI
LAPQPPDVGSSDPLSMVGPSQGRSPSYAS (M72) (SEQ ID NO:72);

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIREDGTVGGAADQSPE
SLLQLKALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEACSFRELLLE
DGYNVYQSEAHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPEPPGI
LAPQPPDVGSSDPLSMVVQDELQGVGGEGCHMHPENCKTLLTDIDRHTHT
EKPVWDGITGE (M73) (SEQ ID NO:73);

RPLAFSDASPHVHYGWGDPIRLRHLTYSGPHGLSSCFLRIRADGVVDCAR
GQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGGLLYSEEDCA
FEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPM
VPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEEK (M1)
(SEQ ID NO:1 or 139);

RPLAFSDSSPLVHYGWGDPIRLRHLTYSGPHGLSSCFLRIRADGVVDCAR
GQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGGLLYSEEDCA
FEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPM
VPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEEK (M2)
(SEQ ID NO:2 or 140);

RPLAFSDAGPHVHYGWGDPIRLRHLTYSGPHGLSSCFLRIRADGVVDCAR
GQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGGLLYSEEDCA
FEEEILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPM
VPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEEK (M3)
(SEQ ID NO:3);

RDSSPLLQFGGQVRLRHLTYSGPHGLSSCFLRIRADGVVDCARGQSAHSL
LEIKAVALRTVAIKGVHSVRYLCMGADGKMQGGLLYSEEDCAFEEEEIRPD
GYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDL
RGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEEK (M48) (SEQ ID
NO:48 or 6 or 148);

RPLAFSDSSPLLQFGGQVRLRHLTYSGPHGLSSCFLRIRADGVVDCARGQS
AHSLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGGLLYSEEDCAFEE
EIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPE
EPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEEK (M49) (SEQ
ID NO:49 or 7 or 149);

RHPIPDSSPLLQFGDQVRLRHLTYSGPHGLSSCFLRIRADGVVDCARGQSA
HSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGGLLYSEEDCAFEEI
LEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEP

EDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (M50) (SEQ ID NO:50);

RHPIPDSSPLLQFGGNVRLRHL YTSGPHGLSSCFLRIRADGVVDCARGQSA
HSLLEIKAVALRTVAIKGVH SVRYLCMGADGKMQG LLQYSEEDCAFE EEI
RPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEP
EDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (M51) (SEQ ID
NO:51 or 36 or 155);

MDSSPLLQWGDPIRLRHL YTSGPHGLSSCFLRIRADGVVDCARGQSAHSL
LEIKAVALRTVAIKGVH SVRYLCMGADGKMQG LLQYSEEDCAFE EEI
RPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEP
EDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (M53) (SEQ ID
NO:192);

MRDSSPLVHYGWGDPIRLRHL YTSGPHGLSSCFLRIRADGVVDCARGQSA
HSLLEIKAVALRTVAIKGVH SVRYLCMGADGKMQG LLQYSEEDCAFE EEI
RPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEP
EDLRGHLESDMFSSPLETDS16MDPFGLVTGLEAVRSPSF EK (M70) (SEQ
ID NO:70);

RPLAFSDAGPHVHYGWGDPIRLRHL YTSGPHGLSSCFLRIRADGVVDCAR
GQSAHSLLEIKAVALRTVAIKGVH SVRYLCMGADGKMQG LLQYSEEDCA
FEE EILPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPM
VPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (M139)
(SEQ ID NO:193);

RPLAFSDAGPHVHYGWGDPIRLRHL YTSGPHGLSSCFLRIRADGVVDCAR
GQSAHSLLEIKAVALRTVAIKGVH SVRYLCMGADGKMQG LLQYSEEDCA
FEE EIRE DGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPM
VPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (M140)
(SEQ ID NO:194);

RPLAFSDAGPHVHYGWGDPIRLRHL YTSGPHGLSSCFLRIRADGVVDCAR
GQSAHSLLEIKAVALRTVAIKGVH SVRYLCMGADGKMQG LLQYSEEDCA
FEE EILCDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPM
VPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (M141)
(SEQ ID NO:195); or

RPLAFSDAGPHVHYGWGDPIRQRHL YTSGPHGLSSCFLRIRADGVVDCAR
GQSAHSLLEIKAVALRTVAIKGVH SVRYLCMGADGKMQG LLQYSEEDCA
FEE EILEDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPM

VPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (M160)
(SEQ ID NO:196);

or a subsequence or fragment of any of the foregoing peptide sequences, or any of the foregoing peptide sequences wherein the R terminal residue is deleted;

- (xiii) amino acid residues HPIP (SEQ ID NO:107) are the first 4 amino acid residues of the N-terminal region;
- (xiv) the first position of the N-terminal region is an R residue, or wherein the first position of the N-terminal region is an M residue, or wherein the first and second positions of the N-terminal region is an MR sequence, or wherein the first and second positions of the N-terminal region is an RM sequence, or wherein the first and second positions of the N-terminal region is an RD sequence, or wherein the first and second positions of the N-terminal region is an DS sequence, or wherein the first and second positions of the N-terminal region is an MD sequence, or wherein the first and second positions of the N-terminal region is an MS sequence, or wherein the first through third positions of the N-terminal region is an MDS sequence, or wherein the first through third positions of the N-terminal region is an RDS sequence, or wherein the first through third positions of the N-terminal region is an MSD sequence, or wherein the first through third positions of the N-terminal region is an MSS sequence, or wherein the first through third positions of the N-terminal region is an DSS sequence, or wherein the first through fourth positions of the N-terminal region is an RDSS (SEQ ID NO:115) sequence, or the first through fourth positions of the N-terminal region is an MDSS (SEQ ID NO:116) sequence, or the first through fifth positions of the N-terminal region is an MRDSS (SEQ ID NO:117) sequence, or the first through fifth positions of the N-terminal region is an MSSPL (SEQ ID NO:118) sequence, or the first through sixth positions of the N-terminal region is an MDSSPL (SEQ ID NO:119) sequence, or the first through seventh positions of the N-terminal region is an MSDSSPL (SEQ ID NO:120) sequence;
- (xv) the last position of the C-terminal region corresponds to about residue 194 of SEQ ID NO:99 (FGF19);
- (xvi) the peptide has a sequence comprising or consisting of:
HPIPSSPLLQFGGQVRLRHLTYTSGPHGLSSCFLRIRADGVVDCARGQSAH
SLLEIKAVALRTVAIKGVHVSRYLCMGADGKMQLLYSEEDCAFEEIEIR
PDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPPEEPE
DLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (SEQ ID
NO:160);

DSSPLLQFGGQVRLRHL YTSGPHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAV
ALRTVAIKGVH SVRYLCMGADGKM QGLLQYSEEDCAFE EEEIRPD
GYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDL
RGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (SEQ ID NO:138 or
161);

RPLAFSDASPHVHYGWGDPIRLRHL YTSGPHGLSSCFLRIRADGVVDCAR
GQSAHSLLEIKAV ALRTVAIKGVH SVRYLCMGADGKM QGLLQYSEEDCA
FE EEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPM
VPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (SEQ ID
NO:1 or 139);

RPLAFSDSSPLVHYGWGDPIRLRHL YTSGPHGLSSCFLRIRADGVVDCAR
GQSAHSLLEIKAV ALRTVAIKGVH SVRYLCMGADGKM QGLLQYSEEDCA
FE EEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPM
VPEEPEDLRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (SEQ ID
NO:2 or 140); or

DSSPLVHYGWGDPIRLRHL YTSGPHGLSSCFLRIRADGVVDCARGQSAHS
LLEIKAV ALRTVAIKGVH SVRYLCMGADGKM QGLLQYSEEDCAFE EEEIRP
DGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPED
LRGHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK (SEQ ID NO:141);

or a subsequence or fragment of any of the foregoing peptide sequences, or any of the foregoing peptide sequences wherein the R terminal residue is deleted;

wherein optionally the subsequence or fragment thereof has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more amino acid deletions from the amino terminus, the carboxy-terminus or internally;

- (xvii) said N-terminal region, or said C-terminal region, comprises or consists of an amino acid sequence of about 5 to 10, 10 to 20, 20 to 30, 30 to 40, 40 to 50, 60 to 70, 70 to 80, 80 to 90, 90 to 100 or more amino acids;
- (xviii) said FGF19 sequence portion, or said FGF21 sequence portion, comprises or consists of an amino acid sequence of about 5 to 10, 10 to 20, 20 to 30, 30 to 40, 40 to 50, 50 to 60, 60 to 70, 70 to 80, 80 to 90, 90 to 100 or more amino acids of FGF19 or FGF21;
- (xix) said N-terminal region, or said C-terminal region, or said FGF19 sequence portion, or said FGF21 sequence portion, are joined by a linker or spacer;

(xx) the peptide comprises or consists of any of:

HPIPDSSPLLQFGGQVRLRHLYTSG (M5-R) (amino acids 1-25 of SEQ ID NO:160);

DSSPLLQFGGQVRLRHLYTSG (M6-R) (amino acids 2-22 of SEQ ID NO:6);

RPLAFSDSSPLLQFGGQVRLRHLYTSG (M7) (amino acids 1-27 of SEQ ID NO:7);

HPIPDSSPLLQWGDPIRLRHLYTSG (M8-R) (amino acids 2-26 of SEQ ID NO:8);

HPIPDSSPLLQFGWGDPIRLRHLYTSG (M9-R) (amino acids 2-28 of SEQ ID NO:9);

HPIPDSSPHVHYGWGDPIRLRHLYTSG (M10-R) (amino acids 2-28 of SEQ ID NO:10);

RPLAFSDAGPLLQWGDPIRLRHLYTSG (M11) (amino acids 1-27 of SEQ ID NO:11);

RPLAFSDAGPLLQFGWGDPIRLRHLYTSG (M12) (amino acids 1-29 of SEQ ID NO:12);

RPLAFSDAGPLLQFGGQVRLRHLYTSG (M13) (amino acids 1-27 of SEQ ID NO:13);

HPIPDSSPHVHYGGQVRLRHLYTSG (M14-R) (amino acids 2-26 of SEQ ID NO:14);

RPLAFSDAGPHVHYGGQVRLRHLYTSG (M15) (amino acids 1-27 of SEQ ID NO:15);

RPLAFSDAGPHVHWGDPIRLRHLYTSG (M16) (amino acids 1-27 of SEQ ID NO:16);

RPLAFSDAGPHVGWGDPIRLRHLYTSG (M17) (amino acids 1-27 of SEQ ID NO:17);

RPLAFSDAGPHYGWGDPIRLRHLYTSG (M18) (amino acids 1-27 of SEQ ID NO:18);

RPLAFSDAGPVYGWGDPIRLRHLYTSG (M19) (amino acids 1-27 of SEQ ID NO:19);

RPLAFSDAGPVHGWGDPIRLRHLYTSG (M20) (amino acids 1-27 of SEQ ID NO:20);

RPLAFSDAGPVHYWGDPIRLRHLYTSG (M21) (amino acids 1-27 of SEQ ID NO:21);

RPLAFSDAGPHVHGWGDPIRLRHLYTSG (M22) (amino acids 1-27 of SEQ ID NO:22);

RPLAFSDAGPHHGWGDPIRLRHLYTSG (M23) (amino acids 1-27 of SEQ ID NO:23);

RPLAFSDAGPHHYWGDPIRLRHLYTSG (M24) (amino acids 1-27 of SEQ ID NO:24);

RPLAFSDAGPHVYWGDPIRLRHLYTSG (M25) (amino acids 1-27 of SEQ ID NO:25);

RPLAFSDSSPLVHWGDPIRLRHLYTSG (M26) (amino acids 1-27 of SEQ ID NO:26);

RPLAFSDSSPHVHWGDPIRLRHLYTSG (M27) (amino acids 1-27 of SEQ ID NO:27);

RPLAFSDAGPHVWGDPIRLRHLYTSG (M28) (amino acids 1-26 of SEQ ID NO:28);

RPLAFSDAGPHVHYWGDPIRLRHLYTSG (M29) (amino acids 1-28 of SEQ ID NO:29);

RPLAFSDAGPHVHYAWGDPIRLRHLYTSG (M30) (amino acids 1-29 of SEQ ID NO:30);

RHPIPDSSPLLQFGAQVRLRHLYTSG (M31) (amino acids 1-26 of SEQ ID NO:31);

RHPIPDSSPLLQFGDQVRLRHLYTSG (M32) (amino acids 1-26 of SEQ ID NO:32);

RHPIPDSSPLLQFGPQVRLRHLYTSG (M33) (amino acids 1-26 of SEQ ID NO:33);

RHPIPDSSPLLQFGGAVRLRHL YTSG (M34) (amino acids 1-26 of SEQ ID NO:34);

RHPIPDSSPLLQFGGEVRLRHL YTSG (M35) (amino acids 1-26 of SEQ ID NO:35);

RHPIPDSSPLLQFGGNVRLRHL YTSG (M36) (amino acids 1-26 of SEQ ID NO:36);

RHPIPDSSPLLQFGGQARLRHL YTSG (M37) (amino acids 1-26 of SEQ ID NO:37);

RHPIPDSSPLLQFGGQIRLRHL YTSG (M38) (amino acids 1-26 of SEQ ID NO:38);

RHPIPDSSPLLQFGGQTRLRHL YTSG (M39) (amino acids 1-26 of SEQ ID NO:39);

RHPIPDSSPLLQFGWGQPVRLRHL YTSG (M40) (amino acids 1-28 of SEQ ID NO:40);

DAGPHVHYGWGDPIRLRHL YTSG (M74-R) (amino acids 2-24 of SEQ ID NO:74);

VHYGWGDPIRLRHL YTSG (M75-R) (amino acids 2-19 of SEQ ID NO:75);

RLRHL YTSG (M77-R) (amino acids 2-10 of SEQ ID NO:77);

or any of the foregoing peptide sequences wherein the amino terminal R residue is deleted;

wherein optionally the peptide sequence further comprises the addition of amino acid residues 30-194 of SEQ ID NO:99 (FGF19) at the C-terminus, resulting in a chimeric polypeptide; or

wherein optionally the peptide sequence further comprises all or a portion of a FGF19 sequence set forth as:

PHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALTVAIKGVHS
VRYLCMGADGKMQLLQYSEEDCAFEIEIRPDGYNVYRSEKHRL
PVSLSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESD
MFSSPLETDSMDPFGLVTGLEAVRSPSFEK (SEQ ID NO:188)
positioned at the C-terminus of the peptide, or wherein the amino terminal
“R” residue is deleted from the peptide;

(xxi) wherein the N-terminus of the peptide sequence comprises or consists of any of:

RHPIPDSSPLLQFGWGDPIRLRHLTYTSG (M9) (amino acids 1-28 of SEQ ID NO:9);

RHPIPDSSPLLQWGDPIRLRHLTYTSG (M8) (amino acids 1-26 of SEQ ID NO:8);

RPLAFSDAGPLLQFGWGDPIRLRHLTYTSG (M12) (amino acids 1-29 of SEQ ID NO:12);

RHPIPDSSPHVHYGWGDPIRLRHLTYTSG (M10) (amino acids 1-28 of SEQ ID NO:10);

RPLAFSDAGPLLQFGGQVRLRHLTYTSG (M13) (amino acids 1-27 of SEQ ID NO:13);

RHPIPDSSPHVHYGGQVRLRHLTYTSG (M14) (amino acids 1-26 of SEQ ID NO:14);

RPLAFSDAGPHVHYGGDIRLRHLTYTSG (M43) amino acids 1-27 of SEQ ID NO:43); or

RDSSPLLQFGGQVRLRHLTYTSG (M6) (amino acids 1-22 of SEQ ID NO:6);

or any of the foregoing peptide sequences wherein the amino terminal R residue is deleted;

wherein optionally the peptide sequence further comprises the addition of amino acid residues 30-194 of SEQ ID NO:99 (FGF19) at the C-terminus, resulting in a chimeric polypeptide; or

wherein optionally the peptide sequence further comprises all or a portion of a FGF19 sequence set forth as:

PHGLSSCFLRIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHS
VRYLCMGADGKMQGLLQYSEEDCAFEIEIRPDGYNVYRSEKHRL
PVSLSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESD
MFSSPLETDSMDPFGLVTGLEAVRSPSF EK (SEQ ID NO:188)

positioned at the C-terminus of the peptide, or wherein the amino terminal "R" residue is deleted from the peptide;

(xxii) the subsequence has at least one amino acid deletion;

wherein optionally the subsequence has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more amino acid deletions from the amino terminus, the carboxy-terminus or internally;

- (xxiii) the N-terminal region first amino acid position is a “M” residue, an “R” residue, a “S” residue, a “H” residue, a “P” residue, a “L” residue or an “D” residue, or wherein the peptide sequence does not have a “M” residue or an “R” residue at the first amino acid position of the N-terminal region;
- (xxiv) the N-terminal region comprises any one of the following sequences: MDSSPL (SEQ ID NO:119), MSDSSPL (SEQ ID NO:120), SDSSPL (SEQ ID NO:112), MSSPL (SEQ ID NO:113), or SSPL (SEQ ID NO:114);
- (xxv) the peptide has reduced hepatocellular carcinoma (HCC) formation compared to FGF19, or a FGF 19 variant sequence having any of GQV, GDI, WGPI (SEQ ID NO:171), WGDPI (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDPI (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the WGDPI (SEQ ID NO:170) sequence at amino acids 16-20 of FGF19;
- (xxvi) the peptide has greater glucose lowering activity compared to FGF19, or a FGF 19 variant sequence having any of GQV, GDI, WGPI (SEQ ID NO:171), WGDPI (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDPI (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the WGDPI (SEQ ID NO:170) sequence at amino acids 16-20 of FGF19;
- (xxvii) the peptide has less lipid increasing activity compared to FGF19, or a FGF 19 variant sequence having any of GQV, GDI, WGPI (SEQ ID NO:171), WGDPI (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDPI (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the WGDPI (SEQ ID NO:170) sequence at amino acids 16-20 of FGF19;

- (xxviii) the peptide has less triglyceride, cholesterol, non-HDL or HDL increasing activity compared to FGF19, or a FGF 19 variant sequence having any of GQV, GDI, WGPI (SEQ ID NO:171), WGDPI (SEQ ID NO:172), WGDI (SEQ ID NO:173), GDPI (SEQ ID NO:174), GPI, WGQPI (SEQ ID NO:175), WGAPI (SEQ ID NO:176), AGDPI (SEQ ID NO:177), WADPI (SEQ ID NO:178), WGDAI (SEQ ID NO:179), WGDPA (SEQ ID NO:180), WDPI (SEQ ID NO:181), WGDI (SEQ ID NO:182), WGDPI (SEQ ID NO:183) or FGDPI (SEQ ID NO:184) substituted for the WGDPI (SEQ ID NO:170) substituted for the WGDPI sequence at amino acids 16-20 of FGF19;
- (xxix) the peptide has less lean mass reducing activity compared to FGF21;
- (xxx) the peptide sequence binds to fibroblast growth factor receptor 4 (FGFR4) or activates FGFR4, or does not detectably bind to FGFR4 or activate FGFR4;
- (xxxi) the peptide sequence binds to FGFR4 with an affinity less than, comparable to or greater than FGF19 binding affinity for FGFR4;
- (xxxii) the peptide sequence activates FGFR4 to an extent or amount less than, comparable to or greater than FGF19 activates FGFR4;
- (xxxiii) the peptide sequence has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions, deletions or insertions;
 wherein optionally
 (1) the amino acid deletions are at the N- or C-terminus, or internal; or
 (2) the amino acid substitution, or deletion is at any of amino acid positions 8-20 of FGF19 (AGPHVHYGWGDPI) (SEQ ID NO:187); or
- (xxxiv) the peptide sequence comprises one or more L-amino acids, D-amino acids, non-naturally occurring amino acids, or amino acid mimetic, derivative or analogue.
7. The pharmaceutical composition of any one of claims 1 to 6, comprising the peptide at a concentration of from 1 to 10 mg/mL;
- wherein optionally
- (i) the peptide is at a concentration of 1 mg/mL;
 - (ii) the peptide is at a concentration of 5 mg/mL; or
 - (iii) the peptide is at a concentration of 10 mg/mL.

8. The pharmaceutical composition of any one of claims 1 to 7, wherein the peptide is fused with an immunoglobulin Fc region.
9. The pharmaceutical composition of any one of claims 1 to 8, wherein
- (i) the peptide comprises an amino acid sequence of SEQ ID NO:70;
 - (ii) the peptide consists of an amino acid sequence of SEQ ID NO:70;
 - (iii) the peptide comprises an amino acid sequence of SEQ ID NO:69;
 - (iv) the peptide consists of an amino acid sequence of SEQ ID NO:69; or
 - (v) the peptide comprises or consists of an amino acid sequence of SEQ ID NO:204.
10. The pharmaceutical composition of any one of claims 1 to 9,
- (i) wherein the Tris is present in the range of 5 and 50 mM, 15 and 40 mM, 20 and 35 mM, 20 and 30 mM, or 20 and 25 mM;
wherein optionally the Tris is present at 20 mM; or
 - (ii) wherein a formulation volume of 1000 mL comprises 2.0, 2.1, 2.2., 2.3., 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 or 3.0 g of Tris, or any range thereof;
wherein optionally a formulation volume of 1000 mL comprises from 2.4 to 2.5 g of Tris.
11. The pharmaceutical composition of any one of claims 1 to 10, wherein
- (i) the trehalose is present in the range of 1 and 20%, 2 and 15%, 3 and 10%, 4 and 9.5%, 5 and 9.25%, 6 and 9%, 7 and 8.5%, 8 and 8.4%, or 8.1 and 8.3%;
wherein optionally the trehalose is present at 8.2%, 8.3% or 8.4%;
 - (ii) a formulation volume of 1000 mL comprises 92.0, 92.1, 92.2, 92.3, 92.4, 92.5, 92.6, 92.7, 92.8, 92.9 or 93.0 g of trehalose dehydrate;
wherein optionally a formulation volume of 1000 mL comprises from 92.4 to 92.5 g of trehalose dehydrate; or
 - (iii) the molarity of the trehalose dehydrate is from 240 to 300 mM, 240 to 290 mM, 250 to 290 mM, 260 to 290 mM, 270 to 290 mM, or 244 to 245 mM;

wherein optionally the molarity of the trehalose dehydrate is about 280 mM.

12. The pharmaceutical composition of any one of claims 1 to 11, wherein the concentration of TWEEN-20 is in the range of from 0.001 to 0.1% (v/v), 0.0025 to 0.075% (v/v), 0.005 to 0.05% (v/v), or 0.0075 to 0.025% (v/v);

wherein optionally the concentration of TWEEN-20 is 0.01% (v/v).

13. The pharmaceutical composition of any one of claims 1 to 12, wherein the pharmaceutical composition has a pH in a range of 6.5 and 9.5, 6.8 and 9.3, 7.0 and 9.0, 7.3 and 8.7, 7.5 and 8.5, or 7.7 and 8.2;

wherein optionally the pharmaceutical composition has a pH of 7.3, 7.5, 8.0, or 8.5;

wherein optionally the pH is taken at 4°C;

wherein optionally the pH is taken at 25°C; or

wherein optionally the pH is 8.0 at 25°C;

14. The pharmaceutical composition of any one of claims 1 to 9,

- (ii) comprising 20 mM Tris, 8.37% (w/v) trehalose, and 0.01% TWEEN-20;

wherein optionally the pH is 8.0 at 25°C;

- (iii) comprising 20 mM Tris, 8.2% (w/v) trehalose, and 0.01% TWEEN-20;

wherein optionally the pH is 8.0 at 25°C; or

- (iv) comprising 20 mM Tris, 280 mM trehalose, and 0.01% TWEEN-20;

wherein optionally the pH is 8.0 at 25°C.

15. A pharmaceutical composition comprising:

- a. a peptide comprising or consisting of SEQ ID NO:70 or SEQ ID NO:69, and

- b. a pharmaceutically acceptable carrier comprising:

- i. 20 mM Tris,

- ii. from 8.2% to 8.4% (w/v) trehalose, and

- iii. 0.01% TWEEN-20;
 - c. wherein the pH is 8.0 at 25°C.
- 16. The pharmaceutical composition of claim 15,
 - (i) comprising the peptide at a concentration of 1 mg/mL;
 - (ii) comprising the peptide at a concentration of 5 mg/mL;
 - (iii) comprising the peptide at a concentration of 10 mg/mL; or
 - (iv) wherein the peptide is fused with an immunoglobulin Fc region.
- 17. The pharmaceutical composition of any one of claims 1 to 16, wherein the pharmaceutical composition does not comprise a salt;

wherein optionally the salt is NaCl.
- 18. The pharmaceutical composition of any one of claims 1 to 17, wherein the pharmaceutical composition is in a liquid form or is lyophilized.
- 19. The pharmaceutical composition of any one of claims 1 to 18, wherein less than 20%, less than 15%, less than 10%, less than 5% or less than 2% of the peptide aggregates after a period of time;

wherein optionally the period of time is 1 day, 7 days, 14 days, 28 days, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11, months, 12 months, 18 months, 24 months or longer; or

wherein optionally the pharmaceutical composition is stored at -80°C, 4°C, 25°C or 37°C.
- 20. Use of a pharmaceutical composition in the manufacture of a medicament for preventing, treating or managing a disease or disorder in a subject, comprising an effective amount of the pharmaceutical composition of any one of claims 1 to 21;

wherein optionally

 - (i) the disease or disorder comprises bile acid homeostasis or a bile acid-related or associated disorder;
 - (ii) the disease or disorder comprises a disease or disorder selected from the group consisting of a metabolic syndrome; a lipid or glucose disorder; cholesterol or

triglyceride metabolism; type 2 diabetes; cholestasis, intrahepatic cholestasis, primary biliary cirrhosis (PBC), primary familial intrahepatic cholestasis (PFIC), progressive PFIC, primary sclerosing cholangitis (PSC), pregnancy intrahepatic cholestasis (PIC), neonatal cholestasis, and drug induced cholestasis, diseases of extrahepatic cholestasis, bile duct compression from tumor, bile duct blockade by gall stones, bile acid malabsorption and other disorders involving the distal small intestine, ileal resection, inflammatory bowel diseases, Crohn's disease, ulcerative colitis, idiopathic disorders impairing absorption of bile acids, diarrhea, bile acid diarrhea (BAD), GI symptoms, GI cancers, liver cancers, biliary cancers, colon cancer, hepatocellular cancer, bile acid synthesis abnormalities, non-alcoholic steatohepatitis (NASH), cirrhosis, portal and hypertension, and combinations thereof;

- (iii) the disease or disorder comprises a lipid- or glucose-related disorder;
- (iv) the disease or disorder comprise bile acid malabsorption or diarrhea;
- (v) the disease or disorder comprises cholestasis or primary biliary cirrhosis;
- (vi) the disease or disorder comprises primary sclerosing cholangitis;
- (vii) the disease or disorder comprises PFIC or progressive PFIC;
- (viii) the disease or disorder comprises NASH;
- (ix) the disease or disorder comprises a metabolic disorder;

wherein optionally the metabolic disorder comprises a hyperglycemic condition, insulin resistance, hyperinsulinemia, glucose intolerance or a metabolic syndrome;

wherein optionally the hyperglycemic condition comprises diabetes;

wherein optionally the hyperglycemic condition comprises insulin-dependent (type I) diabetes, type II diabetes, or gestational diabetes;

- (x) the disease or disorder comprises obesity or an undesirable body mass;
- (xi) the method results in reduced glucose levels, increased insulin sensitivity, reduced insulin resistance, reduced glucagon, an improvement in glucose tolerance, or glucose metabolism or homeostasis, improved pancreatic function, a reduced triglyceride, cholesterol, IDL, LDL or VLDL levels, a decrease in blood pressure, a decrease in intimal thickening of the blood vessel, or a decrease in body mass or weight gain;
- (xii) the disease or disorder is a cancer or tumor;

wherein optionally the cancer or tumor is a FGF19-dependent cancer or tumor;

wherein optionally

- (a) the FGF19-dependent cancer or tumor is hepatocellular carcinoma;
 - (b) the cancer or tumor is a colon cancer or tumor;
 - (c) the cancer or tumor is a prostate cancer or tumor;
 - (d) the cancer or tumor is a lung cancer or tumor; or
 - (e) the method results in a reduction of tumor number, tumor size, or tumor weight; or
- (viii) wherein the subject is a subject in need thereof.