<110> HANMI PHARM. CO., LTD.

<120> LIQUID FORMULATION OF LONG-ACTING CONJUGATE OF GLUCAGON, GLP-1, AND GIP TRIGONAL AGONIST

<130> OPA21221-PCT

<150> KR 10-2020-0061875
<151> 2020-05-22

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<170> KoPatentIn 3.0

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Ser Gly Gln Pro Pro Pro Ser Cys
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1 5 10 15

Lys Arg Gln Lys Glu Phe Val Asn Trp Leu Leu Ala Gln Lys Cys
20 25 30

<210> 40
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Trigonal agonist

<220>
<221> MISC_FEATURE
<222> (2)
<223> Xaa is aminoisobutyric acid (Aib)

<220>
<221> MISC_FEATURE
<222> (16)..(20)
<223> amino acids at positions 16 and 20 form a ring

<400> 40
Tyr Xaa Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Glu
1 5 10 15

Lys Arg Ala Lys Glu Phe Val Gln Trp Leu Leu Asp His Cys Pro Ser
20 25 30

Ser Gly Gln Pro Pro Pro Ser
35

<210> 41
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Trigonal agonist

<220>
<221> MISC_FEATURE
<222> (2)
<223> Xaa is aminoisobutyric acid (Aib)

<220>
<221> MISC_FEATURE
<222> (16)..(20)
<223> amino acids at positions 16 and 20 form a ring

<400> 41
Tyr Xaa Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Glu
  1   5   10   15

Lys Arg Ala Lys Glu Phe Val Gln Trp Leu Leu Asp Cys His Pro Ser
             20   25   30

Ser Gly Gln Pro Pro Pro Ser
         35

<210> 42
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Trigonal agonist

<220>
<221> MISC_FEATURE
<222> (2)
<223> Xaa is aminoisobutyric acid (Aib)

<220>
<221> MISC_FEATURE
<222> (16)..(20)
<223> amino acids at positions 16 and 20 form a ring

<400> 42
Tyr Xaa Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Ala Leu Asp Glu
  1   5   10   15

Lys Ala Ala Lys Glu Phe Val Asn Trp Leu Leu Asp His His Pro Ser
            20   25   30

Ser Gly Gln Pro Pro Pro Ser Cys
         35   40

<210>   43
<211>   40
<212>   PRT
<213>   Artificial Sequence

<220>
<223>   Trigonal agonist

<220>
<221>   MISC_FEATURE
<222>   (2)
<223>   Xaa is aminoisobutyric acid (Aib)

<220>
<221>   MISC_FEATURE
<222>   (16)..(20)
<223>   amino acids at positions 16 and 20 form a ring

<400>   43
Tyr Xaa Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Ala Leu Asp Glu
  1   5   10   15

Lys Ala Ala Lys Asp Phe Val Asn Trp Leu Leu Asp His His Pro Ser
            20   25   30

Ser Gly Gln Pro Pro Pro Ser Cys
         35   40

<210>   44
<211>   40
<212>   PRT
<213>   Artificial Sequence

<220>
<223>   Trigonal agonist

<220>
<221>   MISC_FEATURE

<222> (2)
<223> Xaa is aminoisobutyric acid (Aib)

<220>
<221> MISC_FEATURE
<222> (16)..(20)
<223> amino acids at positions 16 and 20 form a ring

<400> 44
Tyr Xaa Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Ala Leu Asp Glu
  1   5   10   15

Lys Ala Ala Lys Glu Phe Val Gln Trp Leu Leu Asp Gln His Pro Ser
             20   25   30

Ser Gly Gln Pro Pro Pro Ser Cys
         35   40

<210> 45
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Trigonal agonist

<220>
<221> MISC_FEATURE
<222> (2)
<223> Xaa is aminoisobutyric acid (Aib)

<220>
<221> MISC_FEATURE
<222> (16)..(20)
<223> amino acids at positions 16 and 20 form a ring

<400> 45
Tyr Xaa Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Ala Leu Asp Glu
  1   5   10   15

Lys Ala Ala Lys Glu Phe Val Asn Trp Leu Leu Asp Gln His Pro Ser
             20   25   30

Ser Gly Gln Pro Pro Pro Ser Cys

35 40

<210> 46
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Trigonal agonist

<220>
<221> MISC_FEATURE
<222> (2)
<223> Xaa is aminoisobutyric acid (Aib)

<220>
<221> MISC_FEATURE
<222> (16)..(20)
<223> amino acids at positions 16 and 20 form a ring

<400> 46
Tyr Xaa Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Ala Leu Asp Glu
1 5 10 15

Lys Ala Ala Lys Asp Phe Val Asn Trp Leu Leu Asp Gln His Pro Ser
20 25 30

Ser Gly Gln Pro Pro Pro Ser Cys
35 40

<210> 47
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> General Formula 1

<220>
<221> MISC_FEATURE
<222> (1)
<223> Xaa is His (H), 4-imidazoacetyl (CA), or Tyr (Y)

<220>
<221> MISC_FEATURE
<222> (2)
<223> Xaa is aminoisobutyric acid (Aib)

<220>
<221> MISC_FEATURE
<222> (3)
<223> Xaa is Glu (E) or Gln (Q)

<220>
<221> MISC_FEATURE
<222> (10)
<223> Xaa is Tyr (Y), or Cys (C)

<220>
<221> MISC_FEATURE
<222> (12)
<223> Xaa is Lys (K), or Ile (I)

<220>
<221> MISC_FEATURE
<222> (13)
<223> Xaa is Tyr (Y), Ala (A), or Cys (C)

<220>
<221> MISC_FEATURE
<222> (14)
<223> Xaa is Leu (L), or Met (M)

<220>
<221> MISC_FEATURE
<222> (15)
<223> Xaa is Cys (C), or Asp (D)

<220>
<221> MISC_FEATURE
<222> (17)
<223> Xaa is Arg (R), Ile (I), Cys (C), or Lys (K)

<220>
<221> MISC_FEATURE

<222> (18)
<223> Xaa is Ala (A), Arg (R), or His (H)

<220>
<221> MISC_FEATURE
<222> (19)
<223> Xaa is Ala (A), Gln (Q), or Cys (C)

<220>
<221> MISC_FEATURE
<222> (21)
<223> Xaa is Glu (E), or Asp (D)

<220>
<221> MISC_FEATURE
<222> (24)
<223> Xaa is Gln (Q), Asn (N), or Asp (D)

<220>
<221> MISC_FEATURE
<222> (28)
<223> Xaa is Ala (A), Asn (N), or Asp (D)

<220>
<221> MISC_FEATURE
<222> (29)
<223> Xaa is Cys (C), Gly (G), Gln (Q), Thr (T), Glu (E), or His (H)

<220>
<221> MISC_FEATURE
<222> (30)
<223> Xaa is Cys (C), Gly (G), Lys (K), or His (H), or is absent; and
Xaa can be further linked to R1, wherein R1 is Cys (C),
m-SSGAPPPS-n, or m-SSGQPPPS-n, or is absent, and wherein m is
-Cys-, or -Pro-, and n is -Cys-, -Gly-, or absent

<220>
<221> MISC_FEATURE
<222> (16)..(20)
<223> amino acids at positions 16 and 20 form a ring

<400> 47

Xaa Xaa Xaa Gly Thr Phe Thr Ser Asp Xaa Ser Xaa Xaa Xaa Xaa Glu
1 5 10 15

Xaa Xaa Xaa Lys Xaa Phe Val Xaa Trp Leu Leu Xaa Xaa Xaa
20 25 30

<210> 48
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> R1

<400> 48
Ser Ser Gly Ala Pro Pro Pro Ser
1 5

<210> 49
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> R1

<400> 49
Ser Ser Gly Gln Pro Pro Pro Ser
1 5

<210> 50
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> R1

<400> 50
Cys Ser Ser Gly Gln Pro Pro Pro Ser
1 5

<210> 51

<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> R1

<400> 51
Pro Ser Ser Gly Ala Pro Pro Pro Ser
  1   5

<210> 52
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> R1

<400> 52
Pro Ser Ser Gly Ala Pro Pro Pro Ser Gly
  1   5   10

<210> 53
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> R1

<400> 53
Pro Ser Ser Gly Gln Pro Pro Pro Ser
  1   5

<210> 54
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> R1

<400> 54
Pro Ser Ser Gly Gln Pro Pro Pro Ser Cys
1 5 10

<210> 55
<211> 12
<212> PRT
<213> HOMO SAPIENS

<400> 55
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro
1 5 10

<210> 56
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 56
Glu Ser Lys Tyr Gly Pro Pro Pro Ser Cys Pro
1 5 10

<210> 57
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 57
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Pro
1 5 10

<210> 58
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 58
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser
1 5 10

<210> 59
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 59
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
1 5 10

<210> 60
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 60
Lys Tyr Gly Pro Pro Cys Pro Ser
1 5

<210> 61
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 61
Glu Ser Lys Tyr Gly Pro Pro Cys
1 5

<210> 62

<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 62
Glu Lys Tyr Gly Pro Pro Cys
  1   5

<210> 63
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 63
Glu Ser Pro Ser Cys Pro
  1   5

<210> 64
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 64
Glu Pro Ser Cys Pro
  1   5

<210> 65
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 65
Pro Ser Cys Pro
1

<210> 66
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 66
Glu Ser Lys Tyr Gly Pro Pro Ser Cys Pro
1 5 10

<210> 67
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 67
Lys Tyr Gly Pro Pro Pro Ser Cys Pro
1 5

<210> 68
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 68
Glu Ser Lys Tyr Gly Pro Ser Cys Pro
1 5

<210> 69
<211> 8
<212> PRT

<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 69
Glu Ser Lys Tyr Gly Pro Pro Cys
  1   5

<210> 70
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 70
Lys Tyr Gly Pro Pro Cys Pro
  1   5

<210> 71
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 71
Glu Ser Lys Pro Ser Cys Pro
  1   5

<210> 72
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 72
Glu Ser Pro Ser Cys Pro

1 5

<210> 73
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 73
Glu Pro Ser Cys
1

<210> 74
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 74
Ser Cys Pro
1

<210> 75
<211> 442
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(442)
<223> Amino acids at position 1 to 442 form Human Immunoglobulin G4 Fc Fragment (homodimer)

<220>
<221> MISC_FEATURE
<222> (1)..(221)
<223> Amino acids at position 1 to 221 form one monomer

<220>

<221> MISC_FEATURE
<222> (222)..(442)
<223> Amino acids at position 222 to 442 form one monomer

<220>
<221> DISULFID
<222> (3)..(224)
<223> Amino acids at position 3 and position 224 form an
       inter-disulfide bond

<220>
<221> DISULFID
<222> (35)..(95)
<223> Amino acids at position 35 and position 95 form an intra-chain
       disulfide bond

<220>
<221> DISULFID
<222> (141)..(199)
<223> Amino acids at position 141 and position 199 form an intra-chain
       disulfide bond

<220>
<221> DISULFID
<222> (256)..(316)
<223> Amino acids at position 256 and position 316 form an intra-chain
       disulfide bond

<220>
<221> DISULFID
<222> (362)..(420)
<223> Amino acids at position 362 and position 420 form an intra-chain
       disulfide bond

<400> 75
Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu
  1   5   10   15

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
             20   25   30

Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln
         35   40   45

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Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
     50                  55                  60

Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu
 65                  70                  75                  80

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
                 85                  90                  95

Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys
            100                 105                 110

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
        115                 120                 125

Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    130                 135                 140

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
145                 150                 155                 160

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
                165                 170                 175

Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
            180                 185                 190

Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        195                 200                 205

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Pro Ser Cys
    210                 215                 220

Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320
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Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
            340                 345                 350

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
                405                 410                 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440


<210>    76
<211>    221
<212>    PRT
<213>    Homo sapiens

<400>    76
Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu
  1               5                  10                  15

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
             20                  25                  30

Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln
         35                  40                  45

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
     50                  55                  60

Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu
 65                  70                  75                  80

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
                 85                  90                  95
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Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys
            100                 105                 110

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
        115                 120                 125

Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    130                 135                 140

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
145                 150                 155                 160

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
                165                 170                 175

Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
            180                 185                 190

Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        195                 200                 205

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
    210                 215                 220
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