

<110> HANMI PHARM. CO., LTD.

<120> COMBINATION THERAPY OF INSULINOTROPIC PEPTIDE AND GLP-2, FOR PREVENTING OR TREATING SHORT BOWEL SYNDROME

<130> OPA21376

<150> KR 10-2020-0183440

<151> 2020-12-24

<160> 35

<170> KoPatentIn 3.0

<210> 1

<211> 33

<212> PRT

<213> Homo sapiens

<400> 1

His Ala Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp Asn
1 5 10 15

Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile Thr
20 25 30

Asp

<210> 2

<211> 34

<212> PRT

<213> Artificial Sequence

<220>

<223> GLP-2 derivative

<220>

<221> MISC_FEATURE

<222> (1)

<223> Xaa is imidazoacetyldeshistidine

<400> 2

Xaa Gly Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp Asn
1 5 10 15

Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile Thr
20 25 30

Asp Cys

<210> 3
 <211> 34
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> GLP-2 derivative

<220>
 <221> MISC_FEATURE
 <222> (1)
 <223> Xaa is imidazoacetyldeshistidine

<400> 3
 Xaa Gly Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp Asn
 1 5 10 15

Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile Thr
 20 25 30

Asp Lys

<210> 4
 <211> 34
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> GLP-2 derivative

<220>
 <221> MISC_FEATURE
 <222> (1)
 <223> Xaa is imidazoacetyldeshistidine

<400> 4
 Xaa Gly Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp Asn
 1 5 10 15

Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Arg Ile Thr
 20 25 30

Asp Lys

<210> 5
 <211> 34
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> GLP-2 derivative

<220>
 <221> MISC_FEATURE
 <222> (1)
 <223> Xaa is imidazoacetyldeshistidine

<220>
 <221> MISC_FEATURE
 <222> (34)
 <223> Xaa is 6-azidolysine

<400> 5
 Xaa Gly Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp Asn
 1 5 10 15
 Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile Thr
 20 25 30

Asp Xaa

<210> 6
 <211> 34
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> GLP-2 derivative

<220>
 <221> MISC_FEATURE
 <222> (1)
 <223> Xaa is imidazoacetyldeshistidine

<400> 6

Xaa Gly Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp Asn
 1 5 10 15

Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Arg Ile Thr
 20 25 30

Asp Cys

<210> 7
 <211> 34
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> GLP-2 derivative

<220>
 <221> MISC_FEATURE
 <222> (1)
 <223> Xaa is imidazoacetyldeshistidine

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

<400> 7
 Xaa Xaa Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp Asn
 1 5 10 15

Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile Thr
 20 25 30

Asp Cys

<210> 8
 <211> 34
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> GLP-2 derivative

<220>

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

<400> 8
 His Xaa Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp Asn
 1 5 10 15
 Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile Thr
 20 25 30

Asp Cys

<210> 9
 <211> 34
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> GLP-2 derivative

<220>
 <221> MISC_FEATURE
 <222> (1)
 <223> Xaa = Histidine, imidazoacetyldeshistidine, desaminohistidine,
 beta-hydroxyimidazopropionyl-deshistidine, N-dimethylhistidine, or
 beta-carboxyimidazopropionyl-deshistidine

<220>
 <221> MISC_FEATURE
 <222> (2)
 <223> Xaa is Alanine, Glycine, or Aib(2-aminoisobutyric acid)

<220>
 <221> MISC_FEATURE
 <222> (30)
 <223> Xaa is Lysine, or Arginine

<220>
 <221> MISC_FEATURE
 <222> (34)
 <223> Xaa is absent, Lysine, Arginine, Glutamine, Histidine,
 6-azidolysine, or Cysteine

<400> 9
Xaa Xaa Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp Asn
1 5 10 15

Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Xaa Ile Thr
20 25 30

Asp Xaa

<210> 10
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> GLP-2 derivative

<220>
<221> MISC_FEATURE
<222> (1)
<223> Xaa = Histidine, imidazoacetyldeshistidine, desaminohistidine,
beta-hydroxyimidazopropionyl-deshistidine, N-dimethylhistidine, or
beta-carboxyimidazopropionyl-deshistidine

<220>
<221> MISC_FEATURE
<222> (2)
<223> Xaa is Alanine, Glycine, or Aib(2-aminoisobutyric acid)

<220>
<221> MISC_FEATURE
<222> (30)
<223> Xaa is Lysine, or Arginine

<220>
<221> MISC_FEATURE
<222> (34)
<223> Xaa = any one or more amino acid or any one or more amino acid
which is modified

<400> 10
Xaa Xaa Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp Asn
1 5 10 15

Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Xaa Ile Thr

20

25

30

Asp Xaa

<210> 11
 <211> 12
 <212> PRT
 <213> HOMO SAPIENS

<400> 11
 Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro
 1 5 10

<210> 12
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Variant of hinge region

<400> 12
 Glu Ser Lys Tyr Gly Pro Pro Pro Ser Cys Pro
 1 5 10

<210> 13
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Variant of hinge region

<400> 13
 Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Pro
 1 5 10

<210> 14
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Variant of hinge region

<400> 14
 Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser
 1 5 10

<210> 15
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Variant of hinge region

<400> 15
 Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
 1 5 10

<210> 16
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Variant of hinge region

<400> 16
 Lys Tyr Gly Pro Pro Cys Pro Ser
 1 5

<210> 17
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Variant of hinge region

<400> 17
 Glu Ser Lys Tyr Gly Pro Pro Cys
 1 5

<210> 18
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 18
Glu Lys Tyr Gly Pro Pro Cys
1 5

<210> 19
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 19
Glu Ser Pro Ser Cys Pro
1 5

<210> 20
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 20
Glu Pro Ser Cys Pro
1 5

<210> 21
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 21
Pro Ser Cys Pro
1

<210> 22
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Variant of hinge region

<400> 22
 Glu Ser Lys Tyr Gly Pro Pro Ser Cys Pro
 1 5 10

<210> 23
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Variant of hinge region

<400> 23
 Lys Tyr Gly Pro Pro Pro Ser Cys Pro
 1 5

<210> 24
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Variant of hinge region

<400> 24
 Glu Ser Lys Tyr Gly Pro Ser Cys Pro
 1 5

<210> 25
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Variant of hinge region

<400> 25

Glu Ser Lys Tyr Gly Pro Pro Cys
 1 5

<210> 26
 <211> 7
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Variant of hinge region

<400> 26
 Lys Tyr Gly Pro Pro Cys Pro
 1 5

<210> 27
 <211> 7
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Variant of hinge region

<400> 27
 Glu Ser Lys Pro Ser Cys Pro
 1 5

<210> 28
 <211> 6
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Variant of hinge region

<400> 28
 Glu Ser Pro Ser Cys Pro
 1 5

<210> 29
 <211> 4
 <212> PRT
 <213> Artificial Sequence

 <220>

<223> Variant of hinge region

<400> 29
Glu Pro Ser Cys
1

<210> 30
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant of hinge region

<400> 30
Ser Cys Pro
1

<210> 31
<211> 221
<212> PRT
<213> homo sapiens

<400> 31
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

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				

<210> 32
 <211> 31
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> GLP-1(7-37)

<400>	32														
His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu	Glu	Gly
1				5					10					15	
Gln	Ala	Ala	Lys	Glu	Phe	Ile	Ala	Trp	Leu	Val	Lys	Gly	Arg	Gly	
			20					25					30		

<210> 33
 <211> 39
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Exendin-3

<400>	33														
His	Ser	Asp	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Met	Glu	Glu
1				5					10					15	

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
 35

<210> 34
 <211> 39
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Exendin-4

<400> 34
 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
 35

<210> 35
 <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> 35
 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	
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			
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								