<110> HANMI PHARM. CO., LTD.

<120> USE OF THERAPEUTIC ENZYME FUSION PROTEIN IN PREVENTION AND TREATMENT OF NEUROPATHY CAUSED BY OR ACCOMPANIED BY FABRY DISEASE

<130> OPA21349

<150> KR 10-2020-0152246
<151> 2020-11-13

<160> 15

<170> KoPatentIn 3.0

<210> 1
<211> 43
<212> DNA
<213> Artificial Sequence

<220>
<223> Fc(S2P)_F

<400> 1
ctggcggtgg cggatcgcca ccatgcccag cacctgagtt cct 43

<210> 2
<211> 43
<212> DNA
<213> Artificial Sequence

<220>
<223> Fc(S2P)_R

<400> 2
aggaactcag gtgctgggca tggtggcgat ccgccaccgc cag 43

<210> 3
<211> 43
<212> DNA
<213> Artificial Sequence

<220>
<223> Fc(N71Q)_F

<400> 3
agccgcggga ggagcagttc caaagcacgt accgtgtggt cag 43

<210> 4
<211> 43
<212> DNA
<213> Artificial Sequence

<220>
<223> Fc(N71Q)_R

<400> 4
ctgaccacac ggtacgtgct ttggaactgc tcctcccgcg gct 43

<210> 5
<211> 1287
<212> DNA
<213> Homo sapiens

<400> 5
atgcagctga ggaacccaga actacatctg ggctgcgcgc ttgcgcttcg cttcctggcc 60

ctcgtttcct gggacatccc tggggctaga gcactggaca atggattggc aaggacgcct 120

accatgggct ggctgcactg ggagcgcttc atgtgcaacc ttgactgcca ggaagagcca 180

gattcctgca tcagtgagaa gctcttcatg gagatggcag agctcatggt ctcagaaggc 240

tggaaggatg caggttatga gtacctctgc attgatgact gttggatggc tccccaaaga 300

gattcagaag gcagacttca ggcagaccct cagcgctttc ctcatgggat tcgccagcta 360

gctaattatg ttcacagcaa aggactgaag ctagggattt atgcagatgt tggaaataaa 420

acctgcgcag gcttccctgg gagttttgga tactacgaca ttgatgccca gacctttgct 480

gactggggag tagatctgct aaaatttgat ggttgttact gtgacagttt ggaaaatttg 540

gcagatggtt ataagcacat gtccttggcc ctgaatagga ctggcagaag cattgtgtac 600

tcctgtgagt ggcctcttta tatgtggccc tttcaaaagc ccaattatac agaaatccga 660

cagtactgca atcactggcg aaattttgct gacattgatg attcctggaa aagtataaag 720

agtatcttgg actggacatc ttttaaccag gagagaattg ttgatgttgc tggaccaggg 780

ggttggaatg acccagatat gttagtgatt ggcaactttg gcctcagctg gaatcagcaa 840

gtaactcaga tggccctctg ggctatcatg gctgctcctt tattcatgtc taatgacctc 900

cgacacatca gccctcaagc caaagctctc cttcaggata aggacgtaat tgccatcaat 960

caggacccct tgggcaagca agggtaccag cttagacagg gagacaactt tgaagtgtgg 1020

gaacgacctc tctcaggctt agcctgggct gtagctatga taaaccggca ggagattggt 1080

ggacctcgct cttataccat cgcagttgct tccctgggta aaggagtggc ctgtaatcct 1140

gcctgcttca tcacacagct cctccctgtg aaaaggaagc tagggttcta tgaatggact 1200

tcaaggttaa gaagtcacat aaatcccaca ggcactgttt tgcttcagct agaaaataca 1260

atgcagatgt cattaaaaga cttactt 1287

<210> 6
<211> 429
<212> PRT
<213> Homo sapiens

<400> 6
Met Gln Leu Arg Asn Pro Glu Leu His Leu Gly Cys Ala Leu Ala Leu
1 5 10 15

Arg Phe Leu Ala Leu Val Ser Trp Asp Ile Pro Gly Ala Arg Ala Leu
20 25 30

Asp Asn Gly Leu Ala Arg Thr Pro Thr Met Gly Trp Leu His Trp Glu
35 40 45

Arg Phe Met Cys Asn Leu Asp Cys Gln Glu Glu Pro Asp Ser Cys Ile
50 55 60

Ser Glu Lys Leu Phe Met Glu Met Ala Glu Leu Met Val Ser Glu Gly
65 70 75 80

Trp Lys Asp Ala Gly Tyr Glu Tyr Leu Cys Ile Asp Asp Cys Trp Met
85 90 95

Ala Pro Gln Arg Asp Ser Glu Gly Arg Leu Gln Ala Asp Pro Gln Arg
100 105 110

Phe Pro His Gly Ile Arg Gln Leu Ala Asn Tyr Val His Ser Lys Gly
115 120 125

Leu Lys Leu Gly Ile Tyr Ala Asp Val Gly Asn Lys Thr Cys Ala Gly
130 135 140

Phe Pro Gly Ser Phe Gly Tyr Tyr Asp Ile Asp Ala Gln Thr Phe Ala
145 150 155 160

Asp Trp Gly Val Asp Leu Leu Lys Phe Asp Gly Cys Tyr Cys Asp Ser
165 170 175

Leu Glu Asn Leu Ala Asp Gly Tyr Lys His Met Ser Leu Ala Leu Asn
180 185 190

Arg Thr Gly Arg Ser Ile Val Tyr Ser Cys Glu Trp Pro Leu Tyr Met
195 200 205

Trp Pro Phe Gln Lys Pro Asn Tyr Thr Glu Ile Arg Gln Tyr Cys Asn
210 215 220

His Trp Arg Asn Phe Ala Asp Ile Asp Asp Ser Trp Lys Ser Ile Lys
225 230 235 240

Ser Ile Leu Asp Trp Thr Ser Phe Asn Gln Glu Arg Ile Val Asp Val
245 250 255

Ala Gly Pro Gly Gly Trp Asn Asp Pro Asp Met Leu Val Ile Gly Asn
260 265 270

Phe Gly Leu Ser Trp Asn Gln Gln Val Thr Gln Met Ala Leu Trp Ala
275 280 285

Ile Met Ala Ala Pro Leu Phe Met Ser Asn Asp Leu Arg His Ile Ser
290 295 300

Pro Gln Ala Lys Ala Leu Leu Gln Asp Lys Asp Val Ile Ala Ile Asn
305 310 315 320

Gln Asp Pro Leu Gly Lys Gln Gly Tyr Gln Leu Arg Gln Gly Asp Asn
325 330 335

Phe Glu Val Trp Glu Arg Pro Leu Ser Gly Leu Ala Trp Ala Val Ala
340 345 350

Met Ile Asn Arg Gln Glu Ile Gly Gly Pro Arg Ser Tyr Thr Ile Ala
355 360 365

Val Ala Ser Leu Gly Lys Gly Val Ala Cys Asn Pro Ala Cys Phe Ile
370 375 380

Thr Gln Leu Leu Pro Val Lys Arg Lys Leu Gly Phe Tyr Glu Trp Thr
385 390 395 400

Ser Arg Leu Arg Ser His Ile Asn Pro Thr Gly Thr Val Leu Leu Gln
405 410 415

Leu Glu Asn Thr Met Gln Met Ser Leu Lys Asp Leu Leu
420 425

<210> 7
<211> 666
<212> DNA
<213> Artificial Sequence

<220>
<223> Fc varinat

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cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 120

agccaggaag accctgaggt ccagttcaac tggtacgtgg acggcgtgga ggtgcataat 180

gccaagacaa agccgcggga ggagcagttc caaagcacgt accgtgtggt cagcgtcctc 240

accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa 300

ggcctcccat cctccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 360

caggtgtaca ccctgccccc atcccaggag gagatgacca agaaccaggt cagcctgacc 420

tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag 480

ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc 540

tacagcaggc taaccgtgga caagagcagg tggcaggagg ggaacgtctt ctcatgctcc 600

gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctctgggt 660

aaatga 666

<210> 8
<211> 221
<212> PRT
<213> Artificial Sequence

<220>
<223> Fc variant

<400> 8
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> 9
<211> 221
<212> PRT
<213> Artificial Sequence

<220>
<223> Fc varinat

<400> 9
Pro Pro 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 Gln 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> 10
<211> 90

<212> DNA
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 10
ggcggcggag gttcaggtgg tggtggctct ggcggtggag ggtcgggggg aggcggctct 60

ggaggagggg gctccggtgg gggaggtagc 90

<210> 11
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 11
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25 30

<210> 12
<211> 2043
<212> DNA
<213> Artificial Sequence

<220>
<223> alpha galactosidase-Fc fusion protein

<400> 12
atgcagctga ggaacccaga actacatctg ggctgcgcgc ttgcgcttcg cttcctggcc 60

ctcgtttcct gggacatccc tggggctaga gcactggaca atggattggc aaggacgcct 120

accatgggct ggctgcactg ggagcgcttc atgtgcaacc ttgactgcca ggaagagcca 180

gattcctgca tcagtgagaa gctcttcatg gagatggcag agctcatggt ctcagaaggc 240

tggaaggatg caggttatga gtacctctgc attgatgact gttggatggc tccccaaaga 300

gattcagaag gcagacttca ggcagaccct cagcgctttc ctcatgggat tcgccagcta 360

gctaattatg ttcacagcaa aggactgaag ctagggattt atgcagatgt tggaaataaa 420

acctgcgcag gcttccctgg gagttttgga tactacgaca ttgatgccca gacctttgct 480

gactggggag tagatctgct aaaatttgat ggttgttact gtgacagttt ggaaaatttg 540

gcagatggtt ataagcacat gtccttggcc ctgaatagga ctggcagaag cattgtgtac 600

tcctgtgagt ggcctcttta tatgtggccc tttcaaaagc ccaattatac agaaatccga 660

cagtactgca atcactggcg aaattttgct gacattgatg attcctggaa aagtataaag 720

agtatcttgg actggacatc ttttaaccag gagagaattg ttgatgttgc tggaccaggg 780

ggttggaatg acccagatat gttagtgatt ggcaactttg gcctcagctg gaatcagcaa 840

gtaactcaga tggccctctg ggctatcatg gctgctcctt tattcatgtc taatgacctc 900

cgacacatca gccctcaagc caaagctctc cttcaggata aggacgtaat tgccatcaat 960

caggacccct tgggcaagca agggtaccag cttagacagg gagacaactt tgaagtgtgg 1020

gaacgacctc tctcaggctt agcctgggct gtagctatga taaaccggca ggagattggt 1080

ggacctcgct cttataccat cgcagttgct tccctgggta aaggagtggc ctgtaatcct 1140

gcctgcttca tcacacagct cctccctgtg aaaaggaagc tagggttcta tgaatggact 1200

tcaaggttaa gaagtcacat aaatcccaca ggcactgttt tgcttcagct agaaaataca 1260

atgcagatgt cattaaaaga cttacttggc ggcggaggtt caggtggtgg tggctctggc 1320

ggtggagggt cgggggggagg cggctctgga ggagggggct ccggtggggg aggtagccca 1380

ccatgcccag cacctgagtt cctgggggga ccatcagtct tcctgttccc cccaaaaccc 1440

aaggacaccc tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc 1500

caggaagacc ctgaggtcca gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 1560

aagacaaagc cgcgggagga gcagttccaa agcacgtacc gtgtggtcag cgtcctcacc 1620

gtcctgcacc aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaaggc 1680

ctcccatcct ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag 1740

gtgtacaccc tgcccccatc ccaggaggag atgaccaaga accaggtcag cctgacctgc 1800

ctggtcaaag gcttctatcc cagcgacatc gccgtggagt gggagagcaa tgggcagccg 1860

gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt cttcctctac 1920

agcaggctaa ccgtggacaa gagcaggtgg caggagggga acgtcttctc atgctccgtg 1980

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tga 2043

<210> 13
<211> 680
<212> PRT
<213> Artificial Sequence

<220>
<223> alpha galactosidase-Fc fusion protein

<400> 13
Met Gln Leu Arg Asn Pro Glu Leu His Leu Gly Cys Ala Leu Ala Leu
1 5 10 15

Arg Phe Leu Ala Leu Val Ser Trp Asp Ile Pro Gly Ala Arg Ala Leu
20 25 30

Asp Asn Gly Leu Ala Arg Thr Pro Thr Met Gly Trp Leu His Trp Glu
35 40 45

Arg Phe Met Cys Asn Leu Asp Cys Gln Glu Glu Pro Asp Ser Cys Ile
50 55 60

Ser Glu Lys Leu Phe Met Glu Met Ala Glu Leu Met Val Ser Glu Gly
65 70 75 80

Trp Lys Asp Ala Gly Tyr Glu Tyr Leu Cys Ile Asp Asp Cys Trp Met
85 90 95

Ala Pro Gln Arg Asp Ser Glu Gly Arg Leu Gln Ala Asp Pro Gln Arg
100 105 110

Phe Pro His Gly Ile Arg Gln Leu Ala Asn Tyr Val His Ser Lys Gly
115 120 125

Leu Lys Leu Gly Ile Tyr Ala Asp Val Gly Asn Lys Thr Cys Ala Gly
130 135 140

Phe Pro Gly Ser Phe Gly Tyr Tyr Asp Ile Asp Ala Gln Thr Phe Ala
145 150 155 160

Asp Trp Gly Val Asp Leu Leu Lys Phe Asp Gly Cys Tyr Cys Asp Ser
165 170 175

Leu Glu Asn Leu Ala Asp Gly Tyr Lys His Met Ser Leu Ala Leu Asn
180 185 190

Arg Thr Gly Arg Ser Ile Val Tyr Ser Cys Glu Trp Pro Leu Tyr Met
195 200 205

Trp Pro Phe Gln Lys Pro Asn Tyr Thr Glu Ile Arg Gln Tyr Cys Asn
210 215 220

His Trp Arg Asn Phe Ala Asp Ile Asp Asp Ser Trp Lys Ser Ile Lys
225 230 235 240

Ser Ile Leu Asp Trp Thr Ser Phe Asn Gln Glu Arg Ile Val Asp Val
245 250 255

Ala Gly Pro Gly Gly Trp Asn Asp Pro Asp Met Leu Val Ile Gly Asn
260 265 270

Phe Gly Leu Ser Trp Asn Gln Gln Val Thr Gln Met Ala Leu Trp Ala
275 280 285

Ile Met Ala Ala Pro Leu Phe Met Ser Asn Asp Leu Arg His Ile Ser

290 295 300

Pro Gln Ala Lys Ala Leu Leu Gln Asp Lys Asp Val Ile Ala Ile Asn
305 310 315 320

Gln Asp Pro Leu Gly Lys Gln Gly Tyr Gln Leu Arg Gln Gly Asp Asn
325 330 335

Phe Glu Val Trp Glu Arg Pro Leu Ser Gly Leu Ala Trp Ala Val Ala
340 345 350

Met Ile Asn Arg Gln Glu Ile Gly Gly Pro Arg Ser Tyr Thr Ile Ala
355 360 365

Val Ala Ser Leu Gly Lys Gly Val Ala Cys Asn Pro Ala Cys Phe Ile
370 375 380

Thr Gln Leu Leu Pro Val Lys Arg Lys Leu Gly Phe Tyr Glu Trp Thr
385 390 395 400

Ser Arg Leu Arg Ser His Ile Asn Pro Thr Gly Thr Val Leu Leu Gln
405 410 415

Leu Glu Asn Thr Met Gln Met Ser Leu Lys Asp Leu Leu Gly Gly Gly
420 425 430

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
435 440 445

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Pro Pro Cys Pro Ala
450 455 460

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
465 470 475 480

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
485 490 495

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
500 505 510

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
515 520 525

Phe Gln Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
530 535 540

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
545 550 555 560

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
565 570 575

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
580 585 590

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
595 600 605

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
610 615 620

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
625 630 635 640

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
645 650 655

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
660 665 670

Ser Leu Ser Leu Ser Leu Gly Lys
675 680

<210> 14
<211> 12
<212> PRT
<213> Homo sapiens

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

<210> 15
<211> 4
<212> PRT

<213> Artificial Sequence

<220>
<223> Hinge region

<400> 15
Pro Pro Cys Pro
1