

P14-123_ST25
SEQUENCE LISTING

<110> Merck Patent GmbH
 <120> Anti-TNFα antibodies with pH-dependent Antigen Binding
 <130> P14-123
 <160> 44
 <170> PatentIn version 3.5
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 <400> 1

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Tyr
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Arg Tyr Asn Arg Ala Pro Tyr
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190

P14-123_ST25

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

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<220>
<223> Adalimumab light chain sequence, variable region (VL)

<400> 2

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Arg Tyr Asn Arg Ala Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

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<223> Adalimumab CDR1 sequence of VL

<400> 3

Arg Ala Ser Gln Gly Ile Arg Asn Tyr Leu Ala
1 5 10

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<220>

<223> Adalimumab CDR2 sequence of VL

<400> 4

Ala Ala Ser Thr Leu Gln Ser
1 5

<210> 5

<211> 9

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<223> Adalimumab CDR3 sequence of VL

<400> 5

Gln Arg Tyr Asn Arg Ala Pro Tyr Thr
1 5

<210> 6

<211> 451

<212> PRT

<213> Artificial sequence

<220>

<223> Adalimumab full heavy chain sequence

<400> 6

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr Ala Asp Ser Val
50 55 60

Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Val Ser Tyr Leu Ser Thr Ala Ser Ser Leu Asp Tyr Trp Gly
100 105 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

P14-123_ST25

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

P14-123_ST25

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 435 440 445

Pro Gly Lys
 450

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<220>
 <223> Adalimumab heavy chain sequence, variable region (VH)

<400> 7

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
 20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr Ala Asp Ser Val
 50 55 60

Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Val Ser Tyr Leu Ser Thr Ala Ser Ser Leu Asp Tyr Trp Gly
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 8
 <211> 5
 <212> PRT
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<220>
 <223> Adalimumab CDR1 sequence of VH

<400> 8

Asp Tyr Ala Met His
 1 5

P14-123_ST25

<210> 9
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Adalimumab CDR2 sequence of VH

<400> 9

Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr Ala Asp Ser Val Glu
 1 5 10 15

Gly

<210> 10
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 <213> Artificial Sequence

<220>
 <223> Adalimumab CDR3 sequence of VH

<400> 10

Val Ser Tyr Leu Ser Thr Ala Ser Ser Leu Asp Tyr
 1 5 10

<210> 11
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<220>
 <223> Adalimumab human heavy chain IgG1 constant region

<400> 11

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

P14-123_ST25

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 12
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<220>
<223> adalimumab mutated CDR3 heavy chain

<400> 12

P14-123_ST25

| | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Ser | Tyr | His | Ser | Thr | Ala | Ser | Ser | Leu | Asp | Tyr |
| 1 | | | | 5 | | | | | 10 | | |

<210> 13
 <211> 12
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<400> 13

| | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Ser | Tyr | Leu | Ser | Thr | Ala | His | His | Leu | Asp | Tyr |
| 1 | | | | 5 | | | | | 10 | | |

<210> 14
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 14

| | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Ser | Tyr | His | Ser | Thr | Ala | His | His | Leu | Asp | Tyr |
| 1 | | | | 5 | | | | | 10 | | |

<210> 15
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Adalimumab mutated CDR1 light chain

<400> 15

| | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Ala | Ser | Gln | Gly | Ile | Arg | Asn | His | Leu | Ala |
| 1 | | | | 5 | | | | | 10 | |

<210> 16
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Adalimumab mutated CDR1 light chain

<400> 16

| | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Ala | Ser | Gln | Gly | Ile | Arg | Asn | His | His | Ala |
| 1 | | | | 5 | | | | | 10 | |

<210> 17
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Adalimumab mutated CDR3 light chain

<400> 17

His His Tyr His Arg Ala Pro Tyr Thr
1 5

<210> 18

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Adalimumab mutated CDR3 light chain

<400> 18

Gln His Tyr His Arg Ala Pro Tyr His
1 5

<210> 19

<211> 9

<212> PRT

<213> Artificial Sequence

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<223> Adalimumab mutated CDR3 light chain, wherein X1 is Q or H and X2 is T or H

<220>

<221> X1

<222> (1)..(1)

<223> X1 is Q or H

<220>

<221> X2

<222> (9)..(9)

<223> X2 is T or H

<400> 19

Xaa His Tyr His Arg Ala Pro Tyr Xaa
1 5

<210> 20

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> histidine-mutated adalimumab light chain variable region, wherein X1 is L or H

<220>

<221> X1

<222> (33)..(33)

<223> X1 is L or H

<400> 20

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn His
Seite 9

| P14-123_ST25 | | | | | | | | | | | | | | | |
|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 20 | | | | | | | | 25 | | | | 30 | | | |
| Xaa | Ala | Trp | Tyr | Gln | Gln | Lys | Pro | Gly | Lys | Ala | Pro | Lys | Leu | Leu | Ile |
| | | 35 | | | | | 40 | | | | | 45 | | | |
| Tyr | Ala | Ala | Ser | Thr | Leu | Gln | Ser | Gly | Val | Pro | Ser | Arg | Phe | Ser | Gly |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Ser | Gly | Ser | Gly | Thr | Asp | Phe | Thr | Leu | Thr | Ile | Ser | Ser | Leu | Gln | Pro |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| Glu | Asp | Val | Ala | Thr | Tyr | Tyr | Cys | Gln | Arg | Tyr | Asn | Arg | Ala | Pro | Tyr |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Thr | Phe | Gly | Gln | Gly | Thr | Lys | Val | Glu | Ile | Lys | | | | | |
| | | | 100 | | | | | 105 | | | | | | | |

| | |
|-------|---------------------|
| <210> | 21 |
| <211> | 107 |
| <212> | PRT |
| <213> | Artificial Sequence |

<220> histidine-mutated adalimumab light chain variable region, wherein
<223> X1 is Q or H and X2 is T or H

```
<220>
<221> x1
<222> (89)..(89)
<223> x1 is Q or H
```

```
<220>
<221> x2
<222> (97)..(97)
<223> x2 is T or H
```

<400> 21

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Xaa His Tyr His Arg Ala Pro Tyr
85 90 95

P14-123_ST25

Xaa Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 22
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> histidine-mutated adalimumab light chain variable region, wherein
X1 is T or H

<220>
<221> X1
<222> (97)..(97)
<223> X1 is T or H

<400> 22

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys His His Tyr His Arg Ala Pro Tyr
85 90 95

Xaa Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 23
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> histidine-mutated adalimumab light chain variable region, wherein
X1 is Q or H

<220>
<221> X1
<222> (89)..(89)
<223> X1 is Q or H

<400> 23

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

P14-123_ST25

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Xaa His Tyr His Arg Ala Pro Tyr
85 90 95

His Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 24
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<212> PRT
<213> Artificial sequence

<220>
<223> histidine-mutated adalimumab light chain variable region,),
wherein X1 is L or H, and X2 is Q or H and X3 is T or H

<220>
<221> X1
<222> (33)..(33)
<223> X1 is L or H

<220>
<221> X2
<222> (89)..(89)
<223> X2 is Q or H

<220>
<221> X3
<222> (97)..(97)
<223> X3 is T or H

<400> 24

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn His
20 25 30

Xaa Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

P14-123_ST25

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Xaa His Tyr His Arg Ala Pro Tyr
85 90 95

Xaa Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 25
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> histidine-mutated adalimumab heavy chain variable region

<400> 25

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr Ala Asp Ser Val
50 55 60

Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Val Ser Tyr His Ser Thr Ala Ser Ser Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

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<220>
<223> histidine-mutated adalimumab comprising the variable heavy chain sequence

<400> 26

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg

P14-123_ST25

<210> 28
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 <213> Artificial Sequence

<220>
 <223> histidine-mutated adalimumab variable light chain sequence
 <400> 28

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Tyr
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys His His Tyr His Arg Ala Pro Tyr
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 29
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> histidine-mutated adalimumab variable light chain
 <400> 29

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Tyr
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

P14-123_ST25

Glu Asp Val Ala Thr Tyr Tyr Cys Gln His Tyr His Arg Ala Pro Tyr
85 90 95

His Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 30
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> histidine-mutated adalimumab variable light chain

<400> 30

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln His Tyr His Arg Ala Pro Tyr
85 90 95

His Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 31
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> mutated adalimumab CDR3 heavy chain

<400> 31

Val His Tyr His Ser Thr Ala Ser Ser Leu Asp Tyr
1 5 10

<210> 32
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<223> mutated adalimumab CDR2 light chain

<400> 32

Ala Ala His Thr Leu Gln Ser
1 5

<210> 33

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> histidine-mutated adalimumab light chain variable region

<400> 33

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln His Tyr His Arg Ala Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 34

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> histidine-mutated adalimumab light chain variable region

<400> 34

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn His
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

P14-123_ST25

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Arg Tyr Asn His Ala Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 35
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<213> Artificial Sequence

<220>
<223> histidine-mutated adalimumab light chain variable region
<400> 35

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn His
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Arg Tyr Asn Arg Ala Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 36
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<212> PRT
<213> Artificial Sequence

<220>
<223> histidine-mutated adalimumab light chain variable region
<400> 36

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

P14-123_ST25

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Tyr
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Arg His Asn Arg Ala Pro Tyr
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 37
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<220>
 <223> histidine-mutated adalimumab light chain variable region
 <400> 37

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn His
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala His Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Arg Tyr Asn Arg Ala Pro Tyr
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 38
 <211> 9
 <212> PRT
 <213> Artificial Sequence
 <220>

P14-123_ST25
<223> mutated adalimumab CDR3 light chain

<400> 38

Gln Arg His Asn Arg Ala Pro Tyr Thr
1 5

<210> 39

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> mutated adalimumab variable heavy chain

<400> 39

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr Ala Asp Ser Val
50 55 60

Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Val His Tyr His Ser Thr Ala Ser Ser Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 40

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> mutated adalimumab CDR3 heavy chain, wherein X1 is S or H; X2
is L or H, X3 is S or H, and X4 is S or H, and wherein at least
X1 or X2 or X3 or X4 is H

<220>

<221> X1

<222> (2)..(2)

<223> X1 is S or H

<220>

<221> X2

P14-123_ST25

<222> (4)..(4)
<223> X2 is L or H

<220>
<221> X3
<222> (8)..(8)
<223> X3 is S or H

<220>
<221> X4
<222> (9)..(9)
<223> X4 is S or H

<400> 40

Val Xaa Tyr Xaa Ser Thr Ala Xaa Xaa Leu Asp Tyr
1 5 10

<210> 41
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> mutated adalimumab CDR3 light chain, wherein X1 is Q or H, X2 is R or H, X3 is Y or H, X4 is N or H, and X5 is T or H, wherein at least X1 or X2 or X3 or X4 or X5 is H

<220>
<221> X1
<222> (1)..(1)
<223> X1 is Q or H

<220>
<221> X2
<222> (2)..(2)
<223> X2 is R or H

<220>
<221> X3
<222> (3)..(3)
<223> X3 is Y or H

<220>
<221> X4
<222> (4)..(4)
<223> X4 is N or H

<220>
<221> X5
<222> (9)..(9)
<223> X5 is T or H

<400> 41

Xaa Xaa Xaa Xaa Arg Ala Pro Tyr Xaa
1 5

<210> 42
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> mutated adalimumab CDR1 light chain , wherein X1 is Y or H, X2 is
Seite 21

P14-123_ST25

L or H, wherein at least X1 or X2 is H.

<220>
<221> X1
<222> (9)..(9)
<223> X1 is Y or H

<220>
<221> X2
<222> (10)..(10)
<223> X2 is L or H

<400> 42

Arg Ala Ser Gln Gly Ile Arg Asn Xaa Xaa Ala
1 5 10

<210> 43
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> mutated adalimumab light chain variable region, wherein X1 is Y or H, X2 is L or H, X3 is S or H, X4 is Q or H, X5 is R or H, X6 is Y or H, X7 is N or H, X8 is T or H, wherein at least X1 or X2 or X3 or X4 or X5 or X6 or X7 or X8 is H.

<220>
<221> X1
<222> (32)..(32)
<223> X1 is Y or H

<220>
<221> X2
<222> (33)..(33)
<223> X2 is L or H

<220>
<221> X3
<222> (52)..(52)
<223> X3 is S or H

<220>
<221> X4
<222> (89)..(89)
<223> X4 is Q or H

<220>
<221> X5
<222> (90)..(90)
<223> X5 is R or H

<220>
<221> X6
<222> (91)..(91)
<223> X6 is Y or H

<220>
<221> X7
<222> (92)..(92)
<223> X7 is N or H

<220>
<221> X8

P14-123_ST25

<222> (97)..(97)
<223> X8 is T or H

<400> 43

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Xaa
20 25 30

Xaa Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Xaa Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Xaa Xaa Xaa Arg Ala Pro Tyr
85 90 95

Xaa Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 44
<211> 121
<212> PRT
<213> Artificial sequence

<220>
<223> mutated adalimumab heavy chain variable region, wherein X1 is S or H, X2 is L or H, X3 is S or H, X4 is S or H, wherein at least X1 or X2 or X3 or X4 is H.

<220>
<221> X1
<222> (100)..(100)
<223> X1 is S or H

<220>
<221> X2
<222> (102)..(102)
<223> X2 is L or H

<220>
<221> X3
<222> (106)..(106)
<223> X3 is S or H

<220>
<221> X4
<222> (107)..(107)
<223> X4 is S or H

<400> 44

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

P14-123_ST25

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr Ala Asp Ser Val
50 55 60

Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Val Xaa Tyr Xaa Ser Thr Ala Xaa Xaa Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120