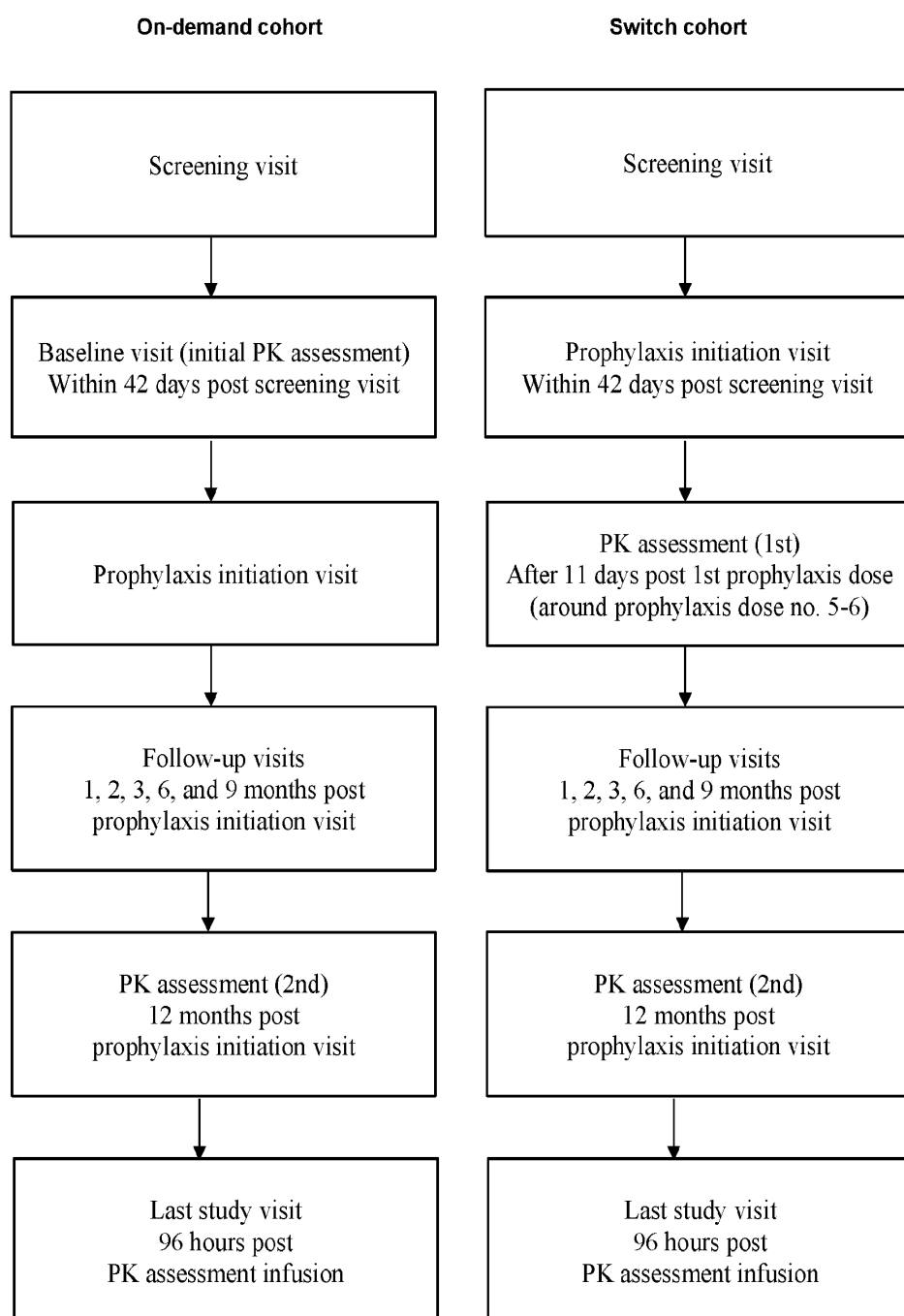


FIG. 1



PK, pharmacokinetic.

FIG. 2

Key study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Documented diagnosis of severe VWD: Type 1 VWD (VWF:RCo <20 IU/dL) or Type 2A (as verified by multimer pattern), type 2B (as diagnosed by genotype), type 2M, or Type 3 (VWF:Ag ≤3 IU/dL) VWD diagnosis confirmed by genetic testing and multimer analysis, documented in patient history or at screening Patients in the pdVWF switch cohort who have received prophylactic treatment with pdVWF products for ≥12 months prior to screening Patients in the on-demand cohort who are currently receiving on-demand treatment for whom prophylactic treatment is recommended by the investigator Patients in the on-demand cohort who have ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the previous 12 months	Diagnosed with type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD Currently receiving prophylactic treatment with >5 infusions per week Currently receiving prophylactic treatment with a weekly dose >240 IU/kg History or presence of a VWF inhibitor at screening Known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins
pdVWF, plasma-derived von Willebrand factor; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:RCo, von Willebrand factor ristocetin cofactor activity; VWF:Ag, von Willebrand factor antigen.	

FIG. 3

Example dosing schedules for rVWF prophylaxis

Schedule	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Mon	Tue	Wed	Thu	Fri	Sat	Sun
A	✓				✓			✓				✓		
B	✓		✓			✓		✓		✓			✓	

FIG. 4

Main study outcome measures

Type	Measure
Primary	ABRs for spontaneous BEs (i.e., BEs not related to trauma) during prophylactic treatment with rVWF
Secondary	Efficacy - Proportion of patients in the on-demand cohort achieving a reduction of $\geq 25\%$ in ABR for spontaneous BEs during rVWF prophylaxis relative to their prestudy ABR - Proportion of patients in the switch cohort achieving an ABR for spontaneous BEs during rVWF prophylaxis that is no greater than their prestudy ABR obtained during prophylactic treatment with pdVWF - ABR for spontaneous BEs by bleed location during prophylactic treatment with rVWF - Categorized ABR for spontaneous BEs defined as 0, 1–2, 3–5, or >5 BEs during 12 months of prophylactic treatment with rVWF - Total and average number of rVWF infusions per week during prophylactic treatment - Total weight-adjusted consumption of rVWF during prophylactic treatment Safety - Adverse events – incidence, severity, and causality - Thromboembolic events - Hypersensitivity reactions - Development of neutralizing antibodies to VWF and FVIII - Development of total binding antibodies to VWF and FVIII - Development of binding antibodies to Chinese hamster ovary proteins, mouse immunoglobulin G, and rFurin - Clinically significant changes in vital signs and clinical laboratory parameters relative to baseline PK and PD parameters - PK and PD parameters (on-demand cohort) and steady-state parameters (on-demand and switch cohorts) - PK parameters: based on VWF:RCo, VWF:Ag, and VWF collagen-binding capacity activity versus time profiles - PD parameters: based on FVIII:C, measured by the 1-stage clotting assay versus time profiles
Exploratory	Assessments of health-related quality of life parameters will be carried out

ABR, annualized bleeding rate; BE, bleeding episode; FVIII, factor VIII; FVIII:C, FVIII activity; PD, pharmacodynamic; pdVWF, plasma-derived von Willebrand factor; PK, pharmacokinetic; rVWF, recombinant von Willebrand factor; VWF:RCo, von Willebrand factor ristocetin cofactor activity; VWF:Ag, von Willebrand factor antigen.

FIG. 5A

SEQ ID NO: 1

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FIG. 5B

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FIG. 5C

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tcttgcaaaa	ggc					8833

FIG. 6A

SEQ ID NO:2

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Met Ile Pro Ala Arg Phe Ala Gly Val Leu Leu Leu Ile Leu Pro Gly
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Thr Leu Cys Ala Glu Gly Thr Arg Gly Arg Ser Ser Thr Ala Arg Cys
20           25           30

Ser Leu Phe Gly Ser Asp Phe Val Asn Thr Phe Asp Gly Ser Met Tyr
35           40           45

Ser Phe Ala Gly Tyr Cys Ser Tyr Leu Leu Ala Gly Gly Cys Gln Lys
50           55           60

Arg Ser Phe Ser Ile Ile Gly Asp Phe Gln Asn Gly Lys Arg Val Ser
65           70           75           80

Leu Ser Val Tyr Leu Gly Glu Phe Phe Asp Ile His Leu Phe Val Asn
85           90           95

Gly Thr Val Thr Gln Gly Asp Gln Arg Val Ser Met Pro Tyr Ala Ser
100          105          110

Lys Leu Glu Thr Glu Ala Gly Tyr Tyr Lys Leu Ser Gly Glu Ala Tyr
115          120          125

Gly Phe Val Ala Arg Ile Asp Gly Ser Gly Asn Phe Gln Val Leu Leu
130          135          140

Ser Asp Arg Tyr Phe Asn Lys Thr Cys Gly Leu Cys Gly Asn Phe Asn
145          150          155          160

Ile Phe Ala Glu Asp Asp Phe Met Thr Gln Glu Gly Thr Leu Thr Ser
165          170          175

Asp Pro Tyr Asp Phe Ala Asn Ser Trp Ala Leu Ser Ser Gly Glu Gln
180          185          190

Trp Cys Glu Arg Pro Ser Ser Ser Cys Asn Ile Ser Ser Gly Glu Met
195          200          205

Gln Lys Gly Leu Trp Glu Gln Cys Gln Leu Leu Lys Ser Thr Ser Val
210          215          220

Phe Ala Arg Cys His Pro Leu Val Asp Pro Glu Pro Phe Cys Glu Lys
225          230          235          240

Thr Leu Cys Glu Cys Ala Gly Gly Leu Glu Cys Ala Cys Pro Ala Leu
245          250          255

Leu Glu Tyr Ala Arg Thr Cys Ala Gln Glu Gly Met Val Leu Tyr Gly
260          265          270

Trp Thr Asp His Ser Ala Cys Ser Pro Val Cys Pro Ala Gly Met Glu
275          280          285

Tyr Arg Gln Cys Val Ser Pro Cys Ala Arg Thr Cys Gln Ser Leu His
290          295          300

```

FIG. 6B

Ile Asn Glu Met Cys Gln Glu Arg Cys Val Asp Gly Cys Ser Cys Pro
 305 310 315 320
 Glu Gly Gln Leu Leu Asp Glu Gly Leu Cys Val Glu Ser Thr Glu Cys
 325 330 335
 Pro Cys Val His Ser Gly Lys Arg Tyr Pro Pro Gly Thr Ser Leu Ser
 340 345 350
 Arg Asp Cys Asn Thr Cys Ile Cys Arg Asn Ser Gln Trp Ile Cys Ser
 355 360 365
 Asn Glu Glu Cys Pro Gly Glu Cys Leu Val Thr Gly Gln Ser His Phe
 370 375 380
 Lys Ser Phe Asp Asn Arg Tyr Phe Thr Phe Ser Gly Ile Cys Gln Tyr
 385 390 395 400
 Leu Leu Ala Arg Asp Cys Gln Asp His Ser Phe Ser Ile Val Ile Glu
 405 410 415
 Thr Val Gln Cys Ala Asp Asp Arg Asp Ala Val Cys Thr Arg Ser Val
 420 425 430
 Thr Val Arg Leu Pro Gly Leu His Asn Ser Leu Val Lys Leu Lys His
 435 440 445
 Gly Ala Gly Val Ala Met Asp Gly Gln Asp Val Gln Leu Pro Leu Leu
 450 455 460
 Lys Gly Asp Leu Arg Ile Gln His Thr Val Thr Ala Ser Val Arg Leu
 465 470 475 480
 Ser Tyr Gly Glu Asp Leu Gln Met Asp Trp Asp Gly Arg Gly Arg Leu
 485 490 495
 Leu Val Lys Leu Ser Pro Val Tyr Ala Gly Lys Thr Cys Gly Leu Cys
 500 505 510
 Gly Asn Tyr Asn Gly Asn Gln Gly Asp Asp Phe Leu Thr Pro Ser Gly
 515 520 525
 Leu Ala Glu Pro Arg Val Glu Asp Phe Gly Asn Ala Trp Lys Leu His
 530 535 540
 Gly Asp Cys Gln Asp Leu Gln Lys Gln His Ser Asp Pro Cys Ala Leu
 545 550 555 560
 Asn Pro Arg Met Thr Arg Phe Ser Glu Glu Ala Cys Ala Val Leu Thr
 565 570 575
 Ser Pro Thr Phe Glu Ala Cys His Arg Ala Val Ser Pro Leu Pro Tyr
 580 585 590
 Leu Arg Asn Cys Arg Tyr Asp Val Cys Ser Cys Ser Asp Gly Arg Glu
 595 600 605

FIG. 6D

Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys Arg Pro Met Lys Asp
 915 920 925
 Glu Thr His Phe Glu Val Val Glu Ser Gly Arg Tyr Ile Ile Leu Leu
 930 935 940
 Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg His Leu Ser Ile Ser
 945 950 955 960
 Val Val Leu Lys Gln Thr Tyr Gln Glu Lys Val Cys Gly Leu Cys Gly
 965 970 975
 Asn Phe Asp Gly Ile Gln Asn Asn Asp Leu Thr Ser Ser Asn Leu Gln
 980 985 990
 Val Glu Glu Asp Pro Val Asp Phe Gly Asn Ser Trp Lys Val Ser Ser
 995 1000 1005
 Gln Cys Ala Asp Thr Arg Lys Val Pro Leu Asp Ser Ser Pro Ala
 1010 1015 1020
 Thr Cys His Asn Asn Ile Met Lys Gln Thr Met Val Asp Ser Ser
 1025 1030 1035
 Cys Arg Ile Leu Thr Ser Asp Val Phe Gln Asp Cys Asn Lys Leu
 1040 1045 1050
 Val Asp Pro Glu Pro Tyr Leu Asp Val Cys Ile Tyr Asp Thr Cys
 1055 1060 1065
 Ser Cys Glu Ser Ile Gly Asp Cys Ala Cys Phe Cys Asp Thr Ile
 1070 1075 1080
 Ala Ala Tyr Ala His Val Cys Ala Gln His Gly Lys Val Val Thr
 1085 1090 1095
 Trp Arg Thr Ala Thr Leu Cys Pro Gln Ser Cys Glu Glu Arg Asn
 1100 1105 1110
 Leu Arg Glu Asn Gly Tyr Glu Cys Glu Trp Arg Tyr Asn Ser Cys
 1115 1120 1125
 Ala Pro Ala Cys Gln Val Thr Cys Gln His Pro Glu Pro Leu Ala
 1130 1135 1140
 Cys Pro Val Gln Cys Val Glu Gly Cys His Ala His Cys Pro Pro
 1145 1150 1155
 Gly Lys Ile Leu Asp Glu Leu Leu Gln Thr Cys Val Asp Pro Glu
 1160 1165 1170
 Asp Cys Pro Val Cys Glu Val Ala Gly Arg Arg Phe Ala Ser Gly
 1175 1180 1185
 Lys Lys Val Thr Leu Asn Pro Ser Asp Pro Glu His Cys Gln Ile
 1190 1195 1200
 Cys His Cys Asp Val Val Asn Leu Thr Cys Glu Ala Cys Gln Glu
 1205 1210 1215

FIG. 6E

Pro Gly	Gly Leu Val Val	Pro	Pro Thr Asp Ala	Pro	Val Ser Pro
1220		1225		1230	
Thr Thr	Leu Tyr Val Glu	Asp	Ile Ser Glu Pro	Pro	Leu His Asp
1235		1240		1245	
Phe Tyr	Cys Ser Arg Leu	Leu	Asp Leu Val Phe	Leu	Leu Asp Gly
1250		1255		1260	
Ser Ser	Arg Leu Ser Glu	Ala	Glu Phe Glu Val	Leu	Lys Ala Phe
1265		1270		1275	
Val Val	Asp Met Met Glu	Arg	Leu Arg Ile Ser	Gln	Lys Trp Val
1280		1285		1290	
Arg Val	Ala Val Val Glu	Tyr	His Asp Gly Ser	His	Ala Tyr Ile
1295		1300		1305	
Gly Leu	Lys Asp Arg Lys	Arg	Pro Ser Glu Leu	Arg	Arg Ile Ala
1310		1315		1320	
Ser Gln	Val Lys Tyr Ala	Gly	Ser Gln Val Ala	Ser	Thr Ser Glu
1325		1330		1335	
Val Leu	Lys Tyr Thr Leu	Phe	Gln Ile Phe Ser	Lys	Ile Asp Arg
1340		1345		1350	
Pro Glu	Ala Ser Arg Ile	Thr	Leu Leu Leu Met	Ala	Ser Gln Glu
1355		1360		1365	
Pro Gln	Arg Met Ser Arg	Asn	Phe Val Arg Tyr	Val	Gln Gly Leu
1370		1375		1380	
Lys Lys	Lys Lys Val Ile	Val	Ile Pro Val Gly	Ile	Gly Pro His
1385		1390		1395	
Ala Asn	Leu Lys Gln Ile	Arg	Leu Ile Glu Lys	Gln	Ala Pro Glu
1400		1405		1410	
Asn Lys	Ala Phe Val Leu	Ser	Ser Val Asp Glu	Leu	Glu Gln Gln
1415		1420		1425	
Arg Asp	Glu Ile Val Ser	Tyr	Leu Cys Asp Leu	Ala	Pro Glu Ala
1430		1435		1440	
Pro Pro	Pro Thr Leu Pro	Pro	Asp Met Ala Gln	Val	Thr Val Gly
1445		1450		1455	
Pro Gly	Leu Leu Gly Val	Ser	Thr Leu Gly Pro	Lys	Arg Asn Ser
1460		1465		1470	
Met Val	Leu Asp Val Ala	Phe	Val Leu Glu Gly	Ser	Asp Lys Ile
1475		1480		1485	
Gly Glu	Ala Asp Phe Asn	Arg	Ser Lys Glu Phe	Met	Glu Glu Val
1490		1495		1500	

FIG. 6F

Ile Gln Arg Met Asp Val Gly Gln Asp Ser Ile His Val Thr Val 1505 1510 1515
Leu Gln Tyr Ser Tyr Met Val Thr Val Glu Tyr Pro Phe Ser Glu 1520 1525 1530
Ala Gln Ser Lys Gly Asp Ile Leu Gln Arg Val Arg Glu Ile Arg 1535 1540 1545
Tyr Gln Gly Gly Asn Arg Thr Asn Thr Gly Leu Ala Leu Arg Tyr 1550 1555 1560
Leu Ser Asp His Ser Phe Leu Val Ser Gln Gly Asp Arg Glu Gln 1565 1570 1575
Ala Pro Asn Leu Val Tyr Met Val Thr Gly Asn Pro Ala Ser Asp 1580 1585 1590
Glu Ile Lys Arg Leu Pro Gly Asp Ile Gln Val Val Pro Ile Gly 1595 1600 1605
Val Gly Pro Asn Ala Asn Val Gln Glu Leu Glu Arg Ile Gly Trp 1610 1615 1620
Pro Asn Ala Pro Ile Leu Ile Gln Asp Phe Glu Thr Leu Pro Arg 1625 1630 1635
Glu Ala Pro Asp Leu Val Leu Gln Arg Cys Cys Ser Gly Glu Gly 1640 1645 1650
Leu Gln Ile Pro Thr Leu Ser Pro Ala Pro Asp Cys Ser Gln Pro 1655 1660 1665
Leu Asp Val Ile Leu Leu Leu Asp Gly Ser Ser Ser Phe Pro Ala 1670 1675 1680
Ser Tyr Phe Asp Glu Met Lys Ser Phe Ala Lys Ala Phe Ile Ser 1685 1690 1695
Lys Ala Asn Ile Gly Pro Arg Leu Thr Gln Val Ser Val Leu Gln 1700 1705 1710
Tyr Gly Ser Ile Thr Thr Ile Asp Val Pro Trp Asn Val Val Pro 1715 1720 1725
Glu Lys Ala His Leu Leu Ser Leu Val Asp Val Met Gln Arg Glu 1730 1735 1740
Gly Gly Pro Ser Gln Ile Gly Asp Ala Leu Gly Phe Ala Val Arg 1745 1750 1755
Tyr Leu Thr Ser Glu Met His Gly Ala Arg Pro Gly Ala Ser Lys 1760 1765 1770
Ala Val Val Ile Leu Val Thr Asp Val Ser Val Asp Ser Val Asp 1775 1780 1785
Ala Ala Ala Asp Ala Ala Arg Ser Asn Arg Val Thr Val Phe Pro 1790 1795 1800

FIG. 6G

Ile Gly 1805	Ile Gly Asp Arg Tyr 1810	Asp Ala Ala Gln Leu 1815	Arg Ile Leu
Ala Gly 1820	Pro Ala Gly Asp Ser 1825	Asn Val Val Lys Leu 1830	Gln Arg Ile
Glu Asp 1835	Leu Pro Thr Met Val 1840	Thr Leu Gly Asn Ser 1845	Phe Leu His
Lys Leu 1850	Cys Ser Gly Phe Val 1855	Arg Ile Cys Met Asp 1860	Glu Asp Gly
Asn Glu 1865	Lys Arg Pro Gly Asp 1870	Val Trp Thr Leu Pro 1875	Asp Gln Cys
His Thr 1880	Val Thr Cys Gln Pro 1885	Asp Gly Gln Thr Leu 1890	Leu Lys Ser
His Arg 1895	Val Asn Cys Asp Arg 1900	Gly Leu Arg Pro Ser 1905	Cys Pro Asn
Ser Gln 1910	Ser Pro Val Lys Val 1915	Glu Glu Thr Cys Gly 1920	Cys Arg Trp
Thr Cys 1925	Pro Cys Val Cys Thr 1930	Gly Ser Ser Thr Arg 1935	His Ile Val
Thr Phe 1940	Asp Gly Gln Asn Phe 1945	Lys Leu Thr Gly Ser 1950	Cys Ser Tyr
Val Leu 1955	Phe Gln Asn Lys Glu 1960	Gln Asp Leu Glu Val 1965	Ile Leu His
Asn Gly 1970	Ala Cys Ser Pro Gly 1975	Ala Arg Gln Gly Cys 1980	Met Lys Ser
Ile Glu 1985	Val Lys His Ser Ala 1990	Leu Ser Val Glu Leu 1995	His Ser Asp
Met Glu 2000	Val Thr Val Asn Gly 2005	Arg Leu Val Ser Val 2010	Pro Tyr Val
Gly Gly 2015	Asn Met Glu Val Asn 2020	Val Tyr Gly Ala Ile 2025	Met His Glu
Val Arg 2030	Phe Asn His Leu Gly 2035	His Ile Phe Thr Phe 2040	Thr Pro Gln
Asn Asn 2045	Glu Phe Gln Leu Gln 2050	Leu Ser Pro Lys Thr 2055	Phe Ala Ser
Lys Thr 2060	Tyr Gly Leu Cys Gly 2065	Ile Cys Asp Glu Asn 2070	Gly Ala Asn
Asp Phe 2075	Met Leu Arg Asp Gly 2080	Thr Val Thr Thr Asp 2085	Trp Lys Thr

FIG. 6H

Leu Val 2090	Gln Glu Trp Thr	Val 2095	Gln Arg Pro Gly	Gln Thr Cys Gln 2100
Pro Glu 2105	Gln Cys Leu Val	Pro Asp Ser Ser His 2110	Cys Gln Val Leu 2115	
Leu Leu 2120	Pro Leu Phe Ala	Glu Cys His Lys Val 2125	Leu Ala Pro Ala 2130	
Thr Phe 2135	Tyr Ala Ile Cys	Gln Gln Asp Ser Cys 2140	His Gln Glu Gln 2145	
Val Cys 2150	Glu Val Ile Ala	Ser Tyr Ala His Leu 2155	Cys Arg Thr Asn 2160	
Gly Val 2165	Cys Val Asp Trp	Arg Thr Pro Asp Phe 2170	Cys Ala Met Ser 2175	
Cys Pro 2180	Pro Ser Leu Val	Tyr Asn His Cys Glu 2185	His Gly Cys Pro 2190	
Arg His 2195	Cys Asp Gly Asn	Val Ser Ser Cys Gly 2200	Asp His Pro Ser 2205	
Glu Gly 2210	Cys Phe Cys Pro	Pro Asp Lys Val Met 2215	Leu Glu Gly Ser 2220	
Cys Val 2225	Pro Glu Glu Ala	Cys Thr Gln Cys Ile 2230	Gly Glu Asp Gly 2235	
Val Gln 2240	His Gln Phe Leu	Glu Ala Trp Val Pro 2245	Asp His Gln Pro 2250	
Cys Gln 2255	Ile Cys Thr Cys	Leu Ser Gly Arg Lys 2260	Val Asn Cys Thr 2265	
Thr Gln 2270	Pro Cys Pro Thr	Ala Lys Ala Pro Thr 2275	Cys Gly Leu Cys 2280	
Glu Val 2285	Ala Arg Leu Arg	Gln Asn Ala Asp Gln 2290	Cys Cys Pro Glu 2295	
Tyr Glu 2300	Cys Val Cys Asp	Pro Val Ser Cys Asp 2305	Leu Pro Pro Val 2310	
Pro His 2315	Cys Glu Arg Gly	Leu Gln Pro Thr Leu 2320	Thr Asn Pro Gly 2325	
Glu Cys 2330	Arg Pro Asn Phe	Thr Cys Ala Cys Arg 2335	Lys Glu Glu Cys 2340	
Lys Arg 2345	Val Ser Pro Pro	Ser Cys Pro Pro His 2350	Arg Leu Pro Thr 2355	
Leu Arg 2360	Lys Thr Gln Cys	Cys Asp Glu Tyr Glu 2365	Cys Ala Cys Asn 2370	
Cys Val 2375	Asn Ser Thr Val	Ser Cys Pro Leu Gly 2380	Tyr Leu Ala Ser 2385	

FIG. 6I

Thr 2390	Ala	Thr	Asn	Asp	Cys	Gly 2395	Cys	Thr	Thr	Thr	Thr	Cys	Leu	Pro	2400
Asp 2405	Lys	Val	Cys	Val	His	Arg 2410	Ser	Thr	Ile	Tyr	Pro	Val	Gly	Gln	2415
Phe 2420	Trp	Glu	Glu	Gly	Cys	Asp 2425	Val	Cys	Thr	Cys	Thr	Asp	Met	Glu	2430
Asp 2435	Ala	Val	Met	Gly	Leu	Arg 2440	Val	Ala	Gln	Cys	Ser	Gln	Lys	Pro	2445
Cys 2450	Glu	Asp	Ser	Cys	Arg	Ser 2455	Gly	Phe	Thr	Tyr	Val	Leu	His	Glu	2460
Gly 2465	Glu	Cys	Cys	Gly	Arg	Cys 2470	Leu	Pro	Ser	Ala	Cys	Glu	Val	Val	2475
Thr 2480	Gly	Ser	Pro	Arg	Gly	Asp 2485	Ser	Gln	Ser	Ser	Trp	Lys	Ser	Val	2490
Gly 2495	Ser	Gln	Trp	Glu	Asn	Pro 2500	Cys	Leu	Ile	Asn	Glu	Cys	Val	Arg	2505
Val 2510	Lys	Glu	Glu	Val	Phe	Ile 2515	Gln	Gln	Arg	Asn	Val	Ser	Cys	Pro	2520
Gln 2525	Leu	Glu	Val	Pro	Val	Cys 2530	Pro	Ser	Gly	Phe	Gln	Leu	Ser	Cys	2535
Lys 2540	Thr	Ser	Ala	Cys	Cys	Pro 2545	Ser	Cys	Arg	Cys	Glu	Arg	Met	Glu	2550
Ala 2555	Cys	Met	Leu	Asn	Gly	Thr 2560	Val	Ile	Gly	Pro	Gly	Lys	Thr	Val	2565
Met 2570	Ile	Asp	Val	Cys	Thr	Thr 2575	Cys	Arg	Cys	Met	Val	Gln	Val	Gly	2580
Val 2585	Ile	Ser	Gly	Phe	Lys	Leu 2590	Glu	Cys	Arg	Lys	Thr	Thr	Cys	Asn	2595
Pro 2600	Cys	Pro	Leu	Gly	Tyr	Lys 2605	Glu	Glu	Asn	Asn	Thr	Gly	Glu	Cys	2610
Cys 2615	Gly	Arg	Cys	Leu	Pro	Thr 2620	Ala	Cys	Thr	Ile	Gln	Leu	Arg	Gly	2625
Gly 2630	Gln	Ile	Met	Thr	Leu	Lys 2635	Arg	Asp	Glu	Thr	Leu	Gln	Asp	Gly	2640
Cys 2645	Asp	Thr	His	Phe	Cys	Lys 2650	Val	Asn	Glu	Arg	Gly	Glu	Tyr	Phe	2655
Trp 2660	Glu	Lys	Arg	Val	Thr	Gly 2665	Cys	Pro	Pro	Phe	Asp	Glu	His	Lys	2670

FIG. 6J

Cys	Leu	Ala	Glu	Gly	Gly	Lys	Ile	Met	Lys	Ile	Pro	Gly	Thr	Cys
2675						2680					2685			
Cys	Asp	Thr	Cys	Glu	Glu	Pro	Glu	Cys	Asn	Asp	Ile	Thr	Ala	Arg
2690						2695					2700			
Leu	Gln	Tyr	Val	Lys	Val	Gly	Ser	Cys	Lys	Ser	Glu	Val	Glu	Val
2705						2710					2715			
Asp	Ile	His	Tyr	Cys	Gln	Gly	Lys	Cys	Ala	Ser	Lys	Ala	Met	Tyr
2720						2725					2730			
Ser	Ile	Asp	Ile	Asn	Asp	Val	Gln	Asp	Gln	Cys	Ser	Cys	Cys	Ser
2735						2740					2745			
Pro	Thr	Arg	Thr	Glu	Pro	Met	Gln	His	Cys	Thr	Asn	Gly	Ser	Val
2750						2755					2760			
Val	Tyr	His	Glu	Val	Leu	Asn	Ala	Met	Glu	Cys	Lys	Cys	Ser	Pro
2765						2770					2775			
Arg	Lys	Cys	Ser	Lys										
2780														

FIG. 7A

SEQ ID NO: 3

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Ser Leu Ser Cys Arg Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp
1           5           10           15

Asn Leu Arg Ala Glu Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr
20           25           30

Asp Leu Glu Cys Met Ser Met Gly Cys Val Ser Gly Cys Leu Cys Pro
35           40           45

Pro Gly Met Val Arg His Glu Asn Arg Cys Val Ala Leu Glu Arg Cys
50           55           60

Pro Cys Phe His Gln Gly Lys Glu Tyr Ala Pro Gly Glu Thr Val Lys
65           70           75           80

Ile Gly Cys Asn Thr Cys Val Cys Arg Asp Arg Lys Trp Asn Cys Thr
85           90           95

Asp His Val Cys Asp Ala Thr Cys Ser Thr Ile Gly Met Ala His Tyr
100          105          110

Leu Thr Phe Asp Gly Leu Lys Tyr Leu Phe Pro Gly Glu Cys Gln Tyr
115          120          125

Val Leu Val Gln Asp Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile
130          135          140

Leu Val Gly Asn Lys Gly Cys Ser His Pro Ser Val Lys Cys Lys Lys
145          150          155          160

Arg Val Thr Ile Leu Val Glu Gly Gly Glu Ile Glu Leu Phe Asp Gly
165          170          175

Glu Val Asn Val Lys Arg Pro Met Lys Asp Glu Thr His Phe Glu Val
180          185          190

Val Glu Ser Gly Arg Tyr Ile Ile Leu Leu Leu Gly Lys Ala Leu Ser
195          200          205

Val Val Trp Asp Arg His Leu Ser Ile Ser Val Val Leu Lys Gln Thr
210          215          220

Tyr Gln Glu Lys Val Cys Gly Leu Cys Gly Asn Phe Asp Gly Ile Gln
225          230          235          240

Asn Asn Asp Leu Thr Ser Ser Asn Leu Gln Val Glu Glu Asp Pro Val
245          250          255

Asp Phe Gly Asn Ser Trp Lys Val Ser Ser Gln Cys Ala Asp Thr Arg
260          265          270

Lys Val Pro Leu Asp Ser Ser Pro Ala Thr Cys His Asn Asn Ile Met
275          280          285

Lys Gln Thr Met Val Asp Ser Ser Cys Arg Ile Leu Thr Ser Asp Val
290          295          300

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FIG. 7B

Phe Gln Asp Cys Asn Lys Leu Val Asp Pro Glu Pro Tyr Leu Asp Val
 305 310 315 320
 Cys Ile Tyr Asp Thr Cys Ser Cys Glu Ser Ile Gly Asp Cys Ala Cys
 325 330 335
 Phe Cys Asp Thr Ile Ala Ala Tyr Ala His Val Cys Ala Gln His Gly
 340 345 350
 Lys Val Val Thr Trp Arg Thr Ala Thr Leu Cys Pro Gln Ser Cys Glu
 355 360 365
 Glu Arg Asn Leu Arg Glu Asn Gly Tyr Glu Cys Glu Trp Arg Tyr Asn
 370 375 380
 Ser Cys Ala Pro Ala Cys Gln Val Thr Cys Gln His Pro Glu Pro Leu
 385 390 395 400
 Ala Cys Pro Val Gln Cys Val Glu Gly Cys His Ala His Cys Pro Pro
 405 410 415
 Gly Lys Ile Leu Asp Glu Leu Leu Gln Thr Cys Val Asp Pro Glu Asp
 420 425 430
 Cys Pro Val Cys Glu Val Ala Gly Arg Arg Phe Ala Ser Gly Lys Lys
 435 440 445
 Val Thr Leu Asn Pro Ser Asp Pro Glu His Cys Gln Ile Cys His Cys
 450 455 460
 Asp Val Val Asn Leu Thr Cys Glu Ala Cys Gln Glu Pro Gly Gly Leu
 465 470 475 480
 Val Val Pro Pro Thr Asp Ala Pro Val Ser Pro Thr Thr Leu Tyr Val
 485 490 495
 Glu Asp Ile Ser Glu Pro Pro Leu His Asp Phe Tyr Cys Ser Arg Leu
 500 505 510
 Leu Asp Leu Val Phe Leu Leu Asp Gly Ser Ser Arg Leu Ser Glu Ala
 515 520 525
 Glu Phe Glu Val Leu Lys Ala Phe Val Val Asp Met Met Glu Arg Leu
 530 535 540
 Arg Ile Ser Gln Lys Trp Val Arg Val Ala Val Val Glu Tyr His Asp
 545 550 555 560
 Gly Ser His Ala Tyr Ile Gly Leu Lys Asp Arg Lys Arg Pro Ser Glu
 565 570 575
 Leu Arg Arg Ile Ala Ser Gln Val Lys Tyr Ala Gly Ser Gln Val Ala
 580 585 590
 Ser Thr Ser Glu Val Leu Lys Tyr Thr Leu Phe Gln Ile Phe Ser Lys
 595 600 605
 Ile Asp Arg Pro Glu Ala Ser Arg Ile Thr Leu Leu Leu Met Ala Ser
 610 615 620

FIG. 7C

Gln	Glu	Pro	Gln	Arg	Met	Ser	Arg	Asn	Phe	Val	Arg	Tyr	Val	Gln	Gly	625	630	635	640
Leu	Lys	Lys	Lys	Lys	Val	Ile	Val	Ile	Pro	Val	Gly	Ile	Gly	Pro	His	645	650	655	
Ala	Asn	Leu	Lys	Gln	Ile	Arg	Leu	Ile	Glu	Lys	Gln	Ala	Pro	Glu	Asn	660	665	670	
Lys	Ala	Phe	Val	Leu	Ser	Ser	Val	Asp	Glu	Leu	Glu	Gln	Gln	Arg	Asp	675	680	685	
Glu	Ile	Val	Ser	Tyr	Leu	Cys	Asp	Leu	Ala	Pro	Glu	Ala	Pro	Pro	Pro	690	695	700	
Thr	Leu	Pro	Pro	Asp	Met	Ala	Gln	Val	Thr	Val	Gly	Pro	Gly	Leu	Leu	705	710	715	720
Gly	Val	Ser	Thr	Leu	Gly	Pro	Lys	Arg	Asn	Ser	Met	Val	Leu	Asp	Val	725	730	735	
Ala	Phe	Val	Leu	Glu	Gly	Ser	Asp	Lys	Ile	Gly	Glu	Ala	Asp	Phe	Asn	740	745	750	
Arg	Ser	Lys	Glu	Phe	Met	Glu	Glu	Val	Ile	Gln	Arg	Met	Asp	Val	Gly	755	760	765	
Gln	Asp	Ser	Ile	His	Val	Thr	Val	Leu	Gln	Tyr	Ser	Tyr	Met	Val	Thr	770	775	780	
Val	Glu	Tyr	Pro	Phe	Ser	Glu	Ala	Gln	Ser	Lys	Gly	Asp	Ile	Leu	Gln	785	790	795	800
Arg	Val	Arg	Glu	Ile	Arg	Tyr	Gln	Gly	Gly	Asn	Arg	Thr	Asn	Thr	Gly	805	810	815	
Leu	Ala	Leu	Arg	Tyr	Leu	Ser	Asp	His	Ser	Phe	Leu	Val	Ser	Gln	Gly	820	825	830	
Asp	Arg	Glu	Gln	Ala	Pro	Asn	Leu	Val	Tyr	Met	Val	Thr	Gly	Asn	Pro	835	840	845	
Ala	Ser	Asp	Glu	Ile	Lys	Arg	Leu	Pro	Gly	Asp	Ile	Gln	Val	Val	Pro	850	855	860	
Ile	Gly	Val	Gly	Pro	Asn	Ala	Asn	Val	Gln	Glu	Leu	Glu	Arg	Ile	Gly	865	870	875	880
Trp	Pro	Asn	Ala	Pro	Ile	Leu	Ile	Gln	Asp	Phe	Glu	Thr	Leu	Pro	Arg	885	890	895	
Glu	Ala	Pro	Asp	Leu	Val	Leu	Gln	Arg	Cys	Cys	Ser	Gly	Glu	Gly	Leu	900	905	910	
Gln	Ile	Pro	Thr	Leu	Ser	Pro	Ala	Pro	Asp	Cys	Ser	Gln	Pro	Leu	Asp	915	920	925	

Val 930	Ile	Leu	Leu	Leu	Asp	Gly 935	Ser	Ser	Ser	Phe	Pro	Ala	Ser	Tyr	Phe
Asp 945	Glu	Met	Lys	Ser	Phe 950	Ala	Lys	Ala	Phe	Ile 955	Ser	Lys	Ala	Asn	Ile 960
Gly	Pro	Arg	Leu	Thr 965	Gln	Val	Ser	Val	Leu	Gln	Tyr	Gly	Ser	Ile	Thr 975
Thr	Ile	Asp	Val 980	Pro	Trp	Asn	Val	Val 985	Pro	Glu	Lys	Ala	His 990	Leu	Leu
Ser	Leu	Val 995	Asp	Val	Met	Gln	Arg 1000	Glu	Gly	Gly	Pro	Ser 1005	Gln	Ile	Gly
Asp 1010	Ala	Leu	Gly	Phe	Ala	Val 1015	Arg	Tyr	Leu	Thr	Ser 1020	Glu	Met	His	
Gly 1025	Ala	Arg	Pro	Gly	Ala	Ser 1030	Lys	Ala	Val	Val	Ile 1035	Leu	Val	Thr	
Asp 1040	Val	Ser	Val	Asp	Ser	Val 1045	Asp	Ala	Ala	Ala	Asp 1050	Ala	Ala	Arg	
Ser 1055	Asn	Arg	Val	Thr	Val	Phe 1060	Pro	Ile	Gly	Ile	Gly 1065	Asp	Arg	Tyr	
Asp 1070	Ala	Ala	Gln	Leu	Arg	Ile 1075	Leu	Ala	Gly	Pro	Ala 1080	Gly	Asp	Ser	
Asn 1085	Val	Val	Lys	Leu	Gln	Arg 1090	Ile	Glu	Asp	Leu	Pro 1095	Thr	Met	Val	
Thr 1100	Leu	Gly	Asn	Ser	Phe	Leu 1105	His	Lys	Leu	Cys	Ser 1110	Gly	Phe	Val	
Arg 1115	Ile	Cys	Met	Asp	Glu	Asp 1120	Gly	Asn	Glu	Lys	Arg 1125	Pro	Gly	Asp	
Val 1130	Trp	Thr	Leu	Pro	Asp	Gln 1135	Cys	His	Thr	Val	Thr 1140	Cys	Gln	Pro	
Asp 1145	Gly	Gln	Thr	Leu	Leu	Lys 1150	Ser	His	Arg	Val	Asn 1155	Cys	Asp	Arg	
Gly 1160	Leu	Arg	Pro	Ser	Cys	Pro 1165	Asn	Ser	Gln	Ser	Pro 1170	Val	Lys	Val	
Glu 1175	Glu	Thr	Cys	Gly	Cys	Arg 1180	Trp	Thr	Cys	Pro	Cys 1185	Val	Cys	Thr	
Gly 1190	Ser	Ser	Thr	Arg	His	Ile 1195	Val	Thr	Phe	Asp	Gly 1200	Gln	Asn	Phe	
Lys 1205	Leu	Thr	Gly	Ser	Cys	Ser 1210	Tyr	Val	Leu	Phe	Gln 1215	Asn	Lys	Glu	

FIG. 7E

Gln Asp 1220	Leu Glu Val Ile 1225	Leu His Asn Gly Ala Cys 1230	Ser Pro Gly
Ala Arg 1235	Gln Gly Cys Met 1240	Lys Ser Ile Glu Val Lys 1245	His Ser Ala
Leu Ser 1250	Val Glu Leu His 1255	Ser Asp Met Glu Val Thr 1260	Val Asn Gly
Arg Leu 1265	Val Ser Val Pro Tyr 1270	Val Gly Gly Asn Met 1275	Glu Val Asn
Val Tyr 1280	Gly Ala Ile Met 1285	His Glu Val Arg Phe Asn 1290	His Leu Gly
His Ile 1295	Phe Thr Phe Thr 1300	Pro Gln Asn Asn Glu Phe 1305	Gln Leu Gln
Leu Ser 1310	Pro Lys Thr Phe 1315	Ala Ser Lys Thr Tyr Gly 1320	Leu Cys Gly
Ile Cys 1325	Asp Glu Asn Gly 1330	Ala Asn Asp Phe Met Leu 1335	Arg Asp Gly
Thr Val 1340	Thr Thr Asp Trp 1345	Lys Thr Leu Val Gln Glu 1350	Trp Thr Val
Gln Arg 1355	Pro Gly Gln Thr 1360	Cys Gln Pro Ile Leu Glu 1365	Glu Gln Cys
Leu Val 1370	Pro Asp Ser Ser 1375	His Cys Gln Val Leu Leu 1380	Leu Pro Leu
Phe Ala 1385	Glu Cys His Lys 1390	Val Leu Ala Pro Ala Thr 1395	Phe Tyr Ala
Ile Cys 1400	Gln Gln Asp Ser 1405	Cys His Gln Glu Gln Val 1410	Cys Glu Val
Ile Ala 1415	Ser Tyr Ala His 1420	Leu Cys Arg Thr Asn Gly 1425	Val Cys Val
Asp Trp 1430	Arg Thr Pro Asp 1435	Phe Cys Ala Met Ser Cys 1440	Pro Pro Ser
Leu Val 1445	Tyr Asn His Cys 1450	Glu His Gly Cys Pro Arg 1455	His Cys Asp
Gly Asn 1460	Val Ser Ser Cys 1465	Gly Asp His Pro Ser Glu 1470	Gly Cys Phe
Cys Pro 1475	Pro Asp Lys Val 1480	Met Leu Glu Gly Ser Cys 1485	Val Pro Glu
Glu Ala 1490	Cys Thr Gln Cys 1495	Ile Gly Glu Asp Gly Val 1500	Gln His Gln
Phe Leu 1505	Glu Ala Trp Val 1510	Pro Asp His Gln Pro Cys 1515	Gln Ile Cys

FIG. 7F

Thr Cys 1520	Leu Ser Gly Arg Lys 1525	Val Asn Cys Thr Thr 1530	Gln Pro Cys
Pro Thr 1535	Ala Lys Ala Pro Thr 1540	Cys Gly Leu Cys Glu 1545	Val Ala Arg
Leu Arg 1550	Gln Asn Ala Asp Gln 1555	Cys Cys Pro Glu Tyr 1560	Glu Cys Val
Cys Asp 1565	Pro Val Ser Cys Asp 1570	Leu Pro Pro Val Pro 1575	His Cys Glu
Arg Gly 1580	Leu Gln Pro Thr Leu 1585	Thr Asn Pro Gly Glu 1590	Cys Arg Pro
Asn Phe 1595	Thr Cys Ala Cys Arg 1600	Lys Glu Glu Cys Lys 1605	Arg Val Ser
Pro Pro 1610	Ser Cys Pro Pro His 1615	Arg Leu Pro Thr Leu 1620	Arg Lys Thr
Gln Cys 1625	Cys Asp Glu Tyr Glu 1630	Cys Ala Cys Asn Cys 1635	Val Asn Ser
Thr Val 1640	Ser Cys Pro Leu Gly 1645	Tyr Leu Ala Ser Thr 1650	Ala Thr Asn
Asp Cys 1655	Gly Cys Thr Thr Thr 1660	Thr Cys Leu Pro Asp 1665	Lys Val Cys
Val His 1670	Arg Ser Thr Ile Tyr 1675	Pro Val Gly Gln Phe 1680	Trp Glu Glu
Gly Cys 1685	Asp Val Cys Thr Cys 1690	Thr Asp Met Glu Asp 1695	Ala Val Met
Gly Leu 1700	Arg Val Ala Gln Cys 1705	Ser Gln Lys Pro Cys 1710	Glu Asp Ser
Cys Arg 1715	Ser Gly Phe Thr Tyr 1720	Val Leu His Glu Gly 1725	Glu Cys Cys
Gly Arg 1730	Cys Leu Pro Ser Ala 1735	Cys Glu Val Val Thr 1740	Gly Ser Pro
Arg Gly 1745	Asp Ser Gln Ser Ser 1750	Trp Lys Ser Val Gly 1755	Ser Gln Trp
Ala Ser 1760	Pro Glu Asn Pro Cys 1765	Leu Ile Asn Glu Cys 1770	Val Arg Val
Lys Glu 1775	Glu Val Phe Ile Gln 1780	Gln Arg Asn Val Ser 1785	Cys Pro Gln
Leu Glu 1790	Val Pro Val Cys Pro 1795	Ser Gly Phe Gln Leu 1800	Ser Cys Lys

FIG. 7G

Thr	Ser	Ala	Cys	Cys	Pro	Ser	Cys	Arg	Cys	Glu	Arg	Met	Glu	Ala
1805						1810					1815			
Cys	Met	Leu	Asn	Gly	Thr	Val	Ile	Gly	Pro	Gly	Lys	Thr	Val	Met
1820						1825					1830			
Ile	Asp	Val	Cys	Thr	Thr	Cys	Arg	Cys	Met	Val	Gln	Val	Gly	Val
1835						1840					1845			
Ile	Ser	Gly	Phe	Lys	Leu	Glu	Cys	Arg	Lys	Thr	Thr	Cys	Asn	Pro
1850						1855					1860			
Cys	Pro	Leu	Gly	Tyr	Lys	Glu	Glu	Asn	Asn	Thr	Gly	Glu	Cys	Cys
1865						1870					1875			
Gly	Arg	Cys	Leu	Pro	Thr	Ala	Cys	Thr	Ile	Gln	Leu	Arg	Gly	Gly
1880						1885					1890			
Gln	Ile	Met	Thr	Leu	Lys	Arg	Asp	Glu	Thr	Leu	Gln	Asp	Gly	Cys
1895						1900					1905			
Asp	Thr	His	Phe	Cys	Lys	Val	Asn	Glu	Arg	Gly	Glu	Tyr	Phe	Trp
1910						1915					1920			
Glu	Lys	Arg	Val	Thr	Gly	Cys	Pro	Pro	Phe	Asp	Glu	His	Lys	Cys
1925						1930					1935			
Leu	Ala	Glu	Gly	Gly	Lys	Ile	Met	Lys	Ile	Pro	Gly	Thr	Cys	Cys
1940						1945					1950			
Asp	Thr	Cys	Glu	Glu	Pro	Glu	Cys	Asn	Asp	Ile	Thr	Ala	Arg	Leu
1955						1960					1965			
Gln	Tyr	Val	Lys	Val	Gly	Ser	Cys	Lys	Ser	Glu	Val	Glu	Val	Asp
1970						1975					1980			
Ile	His	Tyr	Cys	Gln	Gly	Lys	Cys	Ala	Ser	Lys	Ala	Met	Tyr	Ser
1985						1990					1995			
Ile	Asp	Ile	Asn	Asp	Val	Gln	Asp	Gln	Cys	Ser	Cys	Cys	Ser	Pro
2000						2005					2010			
Thr	Arg	Thr	Glu	Pro	Met	Gln	Val	Ala	Leu	His	Cys	Thr	Asn	Gly
2015						2020					2025			
Ser	Val	Val	Tyr	His	Glu	Val	Leu	Asn	Ala	Met	Glu	Cys	Lys	Cys
2030						2035					2040			
Ser	Pro	Arg	Lys	Cys	Ser	Lys								
2045						2050								