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Use of sulfated glycosaminoglycans for improving the bioavailability of Factor VIII

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(71) Applicant(s)
CSL Behring GmbH

(72) Inventor(s)
Metzner, Hubert;Zollner, sabine

(74) Agent / Attorney
FB Rice, Level 23 44 Market Street, Sydney, NSW, 2000

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Abstract

The present invention relates to pharmaceutical preparations comprising one or more Factor VIII and a sulfated glycosaminoglycan for increasing the bioavailability of Factor VIII upon non-intravenous administration. The invention further relates to the combined use of Factor VIII and a sulfated glycosaminoglycan for the treatment and prevention of bleeding disorders, whereby the bioavailability of Factor VIII is increased, and to a method for increasing the bioavailability after non-intravenous administration of Factor VIII by coadminstration of a sulfated glycosaminoglycan.

CSL BEHRING GMBH

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Use of sulfated glycosaminoglycans for improving the bioavailability of Factor VIII

The present invention relates to pharmaceutical preparations comprising at least one Factor VIII and a sulfated glycosaminoglycan for increasing the bioavailability of Factor VIII upon non-intravenous administration. The invention further relates to the combined use of a Factor VIII and a sulfated glycosaminoglycan for the treatment and prevention of bleeding disorders, whereby the bioavailability of the Factor VIII is increased, and to a method for increasing the bioavailability after non-intravenous administration of a Factor VIII by co-administration of a sulfated glycosaminoglycan.

Background of the invention

Factor VIII (FVIII)

FVIII is a blood plasma glycoprotein of about 280 kDa molecular mass, produced in the liver of mammals. It is a critical component of the cascade of coagulation reactions that lead to blood clotting. Within this cascade is a step in which Factor IXa (FIXa), in conjunction with activated Factor VIII (FVIIIa), converts Factor X (FX) to an activated form, FXa. FVIIIa acts as a cofactor at this step, being required together with calcium ions and phospholipids for maximizing the activity of FIXa. The most common hemophilic disorder is caused by a deficiency of functional FVIII called hemophilia A.

An important advance in the treatment of Hemophilia A has been the isolation of cDNA clones encoding the complete 2,351 amino acid sequence of human FVIII

(United States Patent No. 4,757,006) and the provision of the human FVIII gene DNA sequence and recombinant methods for its production).

Analysis of the deduced primary amino acid sequence of human FVIII determined from the cloned cDNA indicates that it is a heterodimer processed from a larger precursor polypeptide. The heterodimer consists of a C-terminal light chain of about 80 kDa in a metal ion-dependent association with an about 200 kDa N-terminal heavy chain. (See review by Kaufman, Transfusion Med. Revs. 6:235 (1992)). Physiological activation of the heterodimer occurs through proteolytic cleavage of the protein chains by thrombin. Thrombin cleaves the heavy chain to a 90 kDa protein, and then to 54 kDa and 44 kDa fragments. Thrombin also cleaves the 80 kDa light chain into a 72 kDa protein. It is the latter protein, and the two heavy chain fragments (54 kDa and 44 kDa above), held together by calcium ions, that constitute active FVIII. Inactivation occurs when the 44 kDa A2 heavy chain fragment dissociates from the molecule or when the 72 kDa and 54 kDa domains are further cleaved by thrombin, activated protein C or FXa. In plasma, FVIII is stabilized by association with a 50-fold molar excess of Von Willebrand Factor protein ("VWF"), which appears to inhibit proteolytic destruction of FVIII as described above.

The amino acid sequence of FVIII is organized into three structural domains: a triplicated A domain of 330 amino acids, a single B domain of 980 amino acids, and a duplicated C domain of 150 amino acids. The B domain has no homology to other proteins and provides 18 of the 25 potential asparagine(N)-linked glycosylation sites of this protein. The B domain has apparently no function in coagulation and can be deleted with the B-domain deleted FVIII molecule still having procoagulant activity.

Von Willebrand Factor (VWF)

VWF is a multimeric adhesive glycoprotein present in the plasma of mammals, which has multiple physiological functions. During primary hemostasis VWF acts as a mediator between specific receptors on the platelet surface and components of

the extracellular matrix such as collagen. Moreover, VWF serves as a carrier and stabilizing protein for procoagulant FVIII. VWF is synthesized in endothelial cells and megakaryocytes as a 2813 amino acid precursor molecule. The precursor polypeptide, pre-pro-VWF, consists of a 22-residue signal peptide, a 741- residue pro-peptide and the 2050-residue polypeptide found in mature plasma VWF (Fischer et al., FEBS Lett. 351: 345-348, 1994). Upon secretion into plasma VWF circulates in the form of various species with different molecular sizes. These VWF molecules consist of oligo- and multimers of the mature subunit of 2050 amino acid residues. VWF can be usually found in plasma as one dimer up to multimers consisting of 50 - 100 dimers (Ruggeri et al. Thromb. Haemost. 82: 576-584, 1999). The in vivo half-life of human VWF in the human circulation is approximately 12 hours.

The most frequent inherited bleeding disorder in humans is von Willebrand's disease (VWD). Depending on the severity of the bleeding symptoms, VWD can be treated by replacement therapy with concentrates containing VWF, in general derived from human plasma but recombinant VWF also is under development. VWF can be prepared from human plasma as for example described in EP 0503991. In patent EP 0784632 a method for isolating recombinant VWF is described.

VWF is known to stabilize FVIII in vivo and, thus, plays a crucial role to regulate plasma levels of FVIII and as a consequence is a central factor to control primary and secondary hemostasis. It is also known that after intravenous administration of pharmaceutical preparations containing VWF in VWD patients an increase in endogenous FVIII:C to 1 to 3 units per ml in 24 hours can be observed demonstrating the in vivo stabilizing effect of VWF on FVIII.

The patients in general benefit from the specific mode of action of the active ingredients but currently all commercially available Factor VIII preparations are administered via intravenous administration which involves a risk for infections at

the injection site and is in general a procedure patients would like to avoid especially in the treatment of children with defects in their coagulation system.

Until today the standard treatment of Hemophilia A and VWD involves frequent intravenous infusions of preparations of FVIII and VWF concentrates. The treatment of Hemophilia B requires the biweekly administration of Factor IX and in the treatment of inhibitor patients with FVIIa, multiple administrations of FVIIa per week are used to avoid bleedings.

These replacement therapies are generally effective, however, for example in severe hemophilia A patients undergoing prophylactic treatment Factor VIII has to be administered intravenously (i.v.) about 3 times per week due to the short plasma half life of Factor VIII of about 12 hours. Already by achieving FVIII levels above 1% of normal human plasma corresponding to a raise of FVIII levels by 0.01 U/ml, severe hemophilia A is turned into moderate hemophilia A. In prophylactic therapy the dosing regime is designed such that the trough levels of FVIII activity do not fall below levels of 2-3% of the FVIII activity of non-hemophiliacs.

The administration of a Factor VIII via intravenous administration is cumbersome, associated with pain and entails the risk of an infection especially as this is mostly done in home treatment by the patients themselves or by the parents of children being diagnosed for hemophilia A. In addition, frequent intravenous injections inevitably result in scar formation, interfering with future infusions As prophylactic treatment in severe hemophilia is started early in life, with children often being less than 2 years old, it is even more difficult to inject FVIII 3 times per week into the veins of such small patients. For a limited period of time, implantation of port systems may offer an alternative. However, in these cases repeated infections may occur and ports can cause inconvenience during physical exercise.

Thus there is a great medical need to obviate the need to infuse Factor VIII intravenously.

Subcutaneous administration has been proposed for Factor VIII, e.g. in WO 95/01804 A1 and WO 95/026750. However, very high doses of Factor VIII had to be administered to achieve an acceptable bioavailability.

Another approach to improve the bioavailability upon non-intravenous administration has been to use albumin-fused Factor VIII (WO 2011/020866 A2).

It is highly desirable to improve the bioavailability of Factor VIII upon non-intravenous administration. The inventors of this application surprisingly found that the bioavailability of Factor VIII is substantially increased if it is administered together with sulfated glycosaminoglycans.

Summary of the invention

In a first aspect the present invention therefore relates to a Factor VIII for use in the treatment or prevention of a bleeding disorder, said treatment or prevention comprising the non-intravenous injection of said Factor VIII and of a sulfated glycosaminoglycan,

In a further aspect, the present invention therefore relates to a Factor VIII for use in the treatment or prevention of a bleeding disorder, said treatment or prevention comprising the non-intravenous injection of said Factor VIII and of a sulfated glycosaminoglycan, wherein, during a period from 2 hours after injection to 48 hours after injection, the plasma level of the Factor VIII in the treated subject is continuously higher than 2% of the normal plasma level of the Factor VIII in healthy subjects when the Factor VIII is administered subcutaneously at a dose of 50 to 1000 IU/kg body weight.

A preferred embodiment of this aspect is a Factor VIII for use in the treatment or prophylaxis of hemophilia A in a human individual, said treatment or prophylaxis comprising the administration of said Factor VIII and of a sulfated glycosaminoglycan by subcutaneous, intradermal or intramuscular injection, wherein, during a period from 2 hours after injection to 48 hours after injection, the plasma level of the Factor VIII in the human individual is continuously higher than 2% of the normal plasma level of the Factor VIII in healthy human individuals when the Factor VIII is administered subcutaneously at a dose of 50 to 1000 IU/kg body weight.

Another aspect of the invention is a Factor VIII for use in the treatment or prophylaxis of a bleeding disorder in a human individual, said treatment or prophylaxis comprising the administration of said Factor VIII and of a sulfated glycosaminoglycan by subcutaneous, transdermal or intramuscular injection, wherein the relative bioavailability of the Factor VIII in the human individual is at least 20% higher than that of the Factor VIII administered in the same manner without sulfated glycosaminoglycan.

A preferred embodiment of this aspect is a Factor VIII for use in the treatment or prophylaxis of hemophilia A in a human individual, said treatment or prophylaxis comprising the administration of said Factor VIII and of a sulfated glycosaminoglycan by subcutaneous, intradermal or intramuscular injection, wherein the relative bioavailability of the Factor VIII in the human individual is at least 20% higher than that of the Factor VIII administered in the same manner without sulfated glycosaminoglycan.

In a third aspect, the invention relates to a sulfated glycosaminoglycan for improving the bioavailability of a Factor VIII.

In a further aspect, the invention relates to a sulfated glycosaminoglycan for improving the bioavailability of a Factor VIII, wherein said sulfated

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glycosaminoglycan and said Factor VIII are administered by subcutaneous, transdermal or intramuscular injection.

A further aspect of the invention is a pharmaceutical kit for the therapy or prophylaxis of a bleeding disorder, comprising a Factor VIII and a sulfated glycosaminoglycan.

A further aspect of the invention is a method of treating or preventing a bleeding disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a Factor VIII and a sulfated glycosaminoglycan so as to increase the bioavailability of the Factor VIII, wherein said administration comprises subcutaneous, transdermal or intramuscular injection.

A further aspect of the invention is a method for increasing the bioavailability of a Factor VIII, wherein a sulfated glycosaminoglycan is co-administered with said Factor VIII by subcutaneous, intradermal or intramuscular injection.

In all aspects of the invention, the Factor VIII is preferably human Factor VIII. A preferred sulfated glycosaminoglycan is heparin, most preferably the heparin is unfractionated heparin.

According to the invention there is also provided a method for treating or preventing a bleeding disorder, the method comprising administering non-intravenously Factor VIII and of a sulfated glycosaminoglycan.

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According to the invention there is also provided a method for treating or preventing a bleeding disorder, the method comprising administering non-intravenously Factor VIII together with a sulfated glycosaminoglycan, wherein the Factor VIII is administered subcutaneously at a dose of 50 IU/kg body weight to about 1,000 IU/kg body weight and wherein the amount of the sulfated glycosaminoglycan is between 0.001 and 100mg per mL product applied.

According to the invention there is also provided a method for improving the bioavailability of Factor VIII in the treatment of prevention of a bleeding disorder, the method comprising administering a sulfated glycosaminoglycan, wherein said glycosaminoglycan and said Factor VIII are administered by subcutaneous, transdermal or intramuscular injection.

According to the invention there is also provided a pharmaceutical kit when used for the treatment or prevention of a bleeding disorder, comprising Factor VIII and a sulfated glycosaminoglycan, wherein said sulfated glycosaminoglycan and said Factor VIII are administered non-intraveneously.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each claim of this application.

Description of the Figure

Figure 1 depicts the results of Example 1. The bioavailability of FVIII is increased if a sulfated glycosaminoglycan is co-administered. As can be seen, dextran sulfate has no positive effect.

Detailed Description

The present invention concerns the treatment and prophylaxis of bleeding disorders.

As used herein, the term "bleeding disorders" includes familial and acquired hemophilia A.

According to the first aspect of the invention a therapeutic, non-intravenous use of a Factor VIII is provided which comprises co-administration of a sulfated glycosaminoglycan.

Factor VIII may be wild-type Factor VIII polypeptides or Factor VIII polypeptides which may contain mutations. The degree and location of glycosylation or other post-translation modifications may vary depending on the chosen host cells and the nature of the host cellular environment. When referring to specific amino acid sequences, posttranslational modifications of such sequences are encompassed in this application.

The terms "Factor VIII", and FVIII" are used interchangeably herein. "Factor VIII" includes wild type Factor VIII as well as derivatives of wild type Factor VIII having the procoagulant activity of wild type Factor VIII. Derivatives may have deletions, insertions and/or additions compared with the amino acid sequence of wild type Factor VIII. The term Factor VIII includes proteolytically processed forms of Factor VIII, e.g. the form before activation, comprising heavy chain and light chain.

The term "Factor VIII" includes any Factor VIII variants or mutants having at least 10%, preferably at least 25%, more preferably at least 50%, most preferably at least 75% of the biological activity of wild type Factor VIII. A suitable test to determine the biological activity of Factor VIII is the one stage or the two stage coagulation assay (Rizza et al. 1982. Coagulation assay of FVIII:C and FIXa in Bloom ed. The

Hemophilias. NY Churchchill Livingston 1992) or the chromogenic substrate FVIII activity assay (S. Rosen, 1984. Scand J Haematol 33: 139-145, suppl.). The content of these references is incorporated herein by reference.

As non-limiting examples, Factor VIII molecules include Factor VIII mutants preventing or reducing APC cleavage (Amano 1998. Thromb. Haemost. 79:557-563), albumin-fused FVIII molecules (WO 2011/020866 A2), FVIII-Fc fusion molecules (WO 04/101740 A), Factor VIII mutants further stabilizing the A2 domain (WO 97/40145), FVIII mutants resulting in increased expression (Swaroop et al. 1997. JBC 272:24121-24124), Factor VIII mutants with reduced immunogenicity (Lollar 1999. Thromb. Haemost. 82:505-508), FVIII reconstituted from differently expressed heavy and light chains (Oh et al. 1999. Exp. Mol. Med. 31:95-100), FVIII mutants reducing binding to receptors leading to catabolism of FVIII like HSPG (heparan sulfate proteoglycans) and/or LRP (low density lipoprotein receptor related protein) (Ananyeva et al. 2001. TCM, 11:251-257), disulfide bond-stabilized FVIII variants (Gale et al., 2006. J. Thromb. Hemost. 4:1315-1322), FVIII mutants with improved secretion properties (Miao et al., 2004. Blood 103:3412-3419), FVIII mutants with increased cofactor specific activity (Wakabayashi et al., 2005. Biochemistry 44:10298-304), FVIII mutants with improved biosynthesis and secretion, reduced ER chaperone interaction, improved ER-Golgi transport, increased activation or resistance to inactivation and improved half-life (summarized by Pipe 2004. Sem. Thromb. Hemost. 30:227-237), and FVIII mutants having a deletion of all or part of the B-domain (see, e.g., WO 2004/067566 A1, WO 02/102850 A2, WO 00/24759 A1 and US patent No. 4,868,112). Particularly preferred are FVIII molecules which are "single chain" FVIII molecules. Single chain FVIII have a deletion of all or part of the B-domain and a deletion of all or a part of the acidic a3 region, so that the cleavage site at Arg1648 (which is usually cleaved during secretion) is deleted. Single chain FVIII molecules are disclosed in, e.g., WO 2004/067566 A1; US 2002/132306 A1; Krishnan et al. (1991) European Journal of Biochemistry vol. 195, no. 3, pages 637-644; Herlitschka et al. (1998)

Journal of Biotechnology, vol. 61, no. 3, pages 165-173; Donath et al. (1995) Biochem. J., vol. 312, pages 49-55.

All of these Factor VIII mutants and variants are incorporated herein by reference in their entirety.

The amino acid sequence of the mature wild type form of human Factor VIII is shown in SEQ ID NO:2. The reference to an amino acid position of a specific sequence means the position of said amino acid in the FVIII wild-type protein and does not exclude the presence of mutations, e.g. deletions, insertions and/or substitutions at other positions in the sequence referred to. For example, a mutation in "Glu2004" referring to SEQ ID NO:2 does not exclude that in the modified homologue one or more amino acids at positions 1 through 2332 of SEQ ID NO:2 are missing. A DNA sequence encoding SEQ ID NO:2 is shown in SEQ ID NO:1.

The term "glycosaminoglycan", as used herein, refers to an oligo- or polysaccharide comprising particularly aminohexose units. Sulfated glycosaminoglycans include, but are not limited to chondroitin sulfate, dermatan sulfate, keratan sulfate, heparin and heparan sulfate. Preferably, the sulfated glycosaminoglycan is heparin, most preferably, the sulfated glycosaminoglycan is unfractionated heparin.

The term "heparin" includes unfractionated heparin and heparins having a lower molecular weight. In one embodiment, the heparin used in accordance with this invention is "unfractionated heparin" which may have an average molecular weight of about 8 kDa to about 30 kDa, preferably of about 10 kDa to about 20 kDa, most preferably of about 12 kDa to about 16 kDa, e.g. about 15 kDa. In another embodiment, the heparin used in accordance with this invention is a low molecular weight heparin (LMWH). LMWHs are heparins or heparin salts having an average molecular weight of less than 8000 Da and for which at least 60% of all chains have a molecular weight less than 8000 Da. Preferably, the molecular weight of the LMWH used in accordance with this invention is about 2 kDa to about 8 kDa, more

preferably about 3 kDa to about 6 kDa, most preferably of about 4 kDa to about 5 kDa, e.g. about 4.5 kDa. The LMWHs can be obtained by various methods of fractionation or depolymerisation of polymeric heparin. Examples of LMWHs include, but are not limited to, ardeparin (Normiflo), certoparin (Sandoparin), enoxaparin (Lovenox and Clexane) , parnaparin (Fluxum), tinzaparin (Innohep and Logiparin), dalteparin (Fragmin), reviparin (Clivarin) and nadroparin (Fraxiparin).

The term "heparin" includes also small molecular weight fragments of heparin molecules, either derived from naturally occurring heparin by cleavage and isolation or by synthetic routes. A commercially available sulfated pentasaccharide exists for example that is manufactured synthetically and which structure is derived from heparin. It is available as Fondaparinux sodium.

Chondroitin sulfate includes, e.g., chondroitin sulfate A (chondroitin-4-sulfate), chondroitin sulfate C (chondroitin-6-sulfate), chondroitin sulfate D (chondroitin-2,6-sulfate), and chondroitin sulfate E (chondroitin-4,6-sulfate).

Dermatan sulfate (previously also called chondroitin sulfate B) is another sulfated glycosaminoglycan which is commercially available.

Keratan sulfate is another sulfated glycosaminoglycan. The structure of keratan sulfate is described in, e.g., Funderburgh (2000) Glycobiology vol. 10 no. 10 pp. 951-958.

Heparan sulfate is an N-sulfated polysaccharide which is different from Heparin (see, e.g., Gallagher, J.T., Lyon, M. (2000). "Molecular structure of Heparan Sulfate and interactions with growth factors and morphogens". In Iozzo, M, V.. Proteoglycans: structure, biology and molecular interactions. Marcel Dekker Inc. New York, New York. pp. 27–59; and Gallagher, J. T. Walker, A. (1985). "Molecular distinctions between Heparan Sulphate and Heparin: Analysis of sulphation

patterns indicates Heparan Sulphate and Heparin are separate families of N-sulphated polysaccharides". Biochem. J. 230 (3): 665–74)

In one embodiment of the invention, the plasma level of the Factor VIII in the treated subject is, during a period from 5 hours after injection to 8 hours after injection, continuously higher than 2%, preferably higher than 5%, more preferably higher than 8%, most preferably higher than 10%, of the normal plasma level of the Factor VIII in healthy subjects. The plasma level is to be determined as shown hereinafter in Example 1.

In one embodiment of the invention, the plasma level of the Factor VIII in the treated subject is, during a period from 4 hours after injection to 16 hours after injection, continuously higher than 2%, preferably higher than 5%, more preferably higher than 8%, most preferably higher than 10%, of the normal plasma level of the Factor VIII in healthy subjects.

In another embodiment of the invention, the plasma level of the Factor VIII in the treated subject is, during a period from 3 hours after injection to 24 hours after injection, continuously higher than 2%, preferably higher than 4%, more preferably higher than 6%, most preferably higher than 8%, of the normal plasma level of the Factor VIII in healthy subjects.

In another embodiment of the invention, the plasma level of the Factor VIII in the treated subject is, during a period from 2 hours after injection to 32 hours after injection, continuously higher than 2%, preferably higher than 3%, more preferably higher than 4%, most preferably higher than 5%, of the normal plasma level of the Factor VIII in healthy subjects.

In yet another embodiment of the invention, the plasma level of the Factor VIII in the treated subject is, during a period from 1 hour after injection to 48 hours after injection, continuously higher than 2%, preferably higher than 3%, more preferably

higher than 4%, most preferably higher than 5%, of the normal plasma level of the Factor VIII in healthy subjects.

The above-mentioned plasma levels are preferably obtained when the Factor VIII (e.g. FVIII) is administered by subcutaneous injection at a dose of less than 1,000 IU/kg body weight, or less than 800 IU/kg body weight, or less than 600 IU/kg body weight, or less than 400 IU/kg body weight, e.g. at a dose of from about 10 IU/kg body weight to about 1,000 IU/kg body weight, or from about 20 IU/kg body weight to about 800 IU/kg body weight, or from about 30 IU/kg body weight to about 700 IU/kg body weight, or from about 40 IU/kg body weight to about 600 IU/kg body weight, or from about 50 IU/kg body weight to about 500 IU/kg body weight, or from about 75 IU/kg body weight to about 400 IU/kg body weight, or from about 100 IU/kg body weight to about 300 IU/kg body weight, or from about 50 IU/kg body weight to about 1,000 IU/kg body weight, or from about 50 IU/kg body weight to about 800 IU/kg body weight, or from about 50 IU/kg body weight to about 700 IU/kg body weight, or from about 50 IU/kg body weight to about 600 IU/kg body weight, or from about 50 IU/kg body weight to about 500 IU/kg body weight, or from about 50 IU/kg body weight to about 400 IU/kg body weight, or from about 50 IU/kg body weight to about 300 IU/kg body weight, or about 50 IU/kg body weight to about 200 IU/kg body weight.

In one embodiment, the Factor VIII and the sulfated glycosaminoglycan are contained in the same composition. This composition comprising the two components may be administered to the patient by a single injection or the like.

In another embodiment, the Factor VIII and the sulfated glycosaminoglycan are not present in the same composition. For example, each of the two components may be provided in a separate dosage form in said pharmaceutical preparation.

If the two components are not present in the same composition the separate compositions may either be administered separately, or they may be mixed shortly

before administration so that the Factor VIII and the sulfated glycosaminoglycan will be administered simultaneously. If there is separate administration, the administration may be done sequentially, e.g. in a time-staggered manner. In general, it is preferred that the two components are administered simultaneously by a single administration, e.g. injection. Various routes of administration are discussed below. They apply to the above *mutatis mutandis*.

The components of the pharmaceutical preparation may be dissolved in conventional physiologically compatible aqueous buffer solutions to which there may be added, optionally, pharmaceutical excipients to provide the pharmaceutical preparation. The components of the pharmaceutical preparation may already contain all necessary pharmaceutical, physiologically compatible excipients and may be dissolved in water for injection to provide the pharmaceutical preparation.

Such pharmaceutical carriers and excipients as well as the preparation of suitable pharmaceutical formulations are well known in the art (see for example "Pharmaceutical Formulation Development of Peptides and Proteins", Frokjaer et al., Taylor & Francis (2000) or "Handbook of Pharmaceutical Excipients", 3rd edition, Kibbe et al., Pharmaceutical Press (2000)). In certain embodiments, a pharmaceutical composition can comprise at least one additive such as a filler, bulking agent, buffer, stabilizer, or excipient. Standard pharmaceutical formulation techniques are well known to persons skilled in the art (see, e.g., 2005 Physicians' Desk Reference®, Thomson Healthcare: Montvale, NJ, 2004; Remington: The Science and Practice of Pharmacy, 20th ed., Gennaro et al., Eds. Lippincott Williams & Wilkins: Philadelphia, PA, 2000). Suitable pharmaceutical additives include, e.g., sugars like mannitol, sorbitol, lactose, sucrose, trehalose, or others, amino acids like histidine, arginine, lysine, glycine, alanine, leucine, serine, threonine, glutamic acid, aspartic acid, glutamine, asparagine, phenylalanine, or others, additives to achieve isotonic conditions like sodium chloride or other salts, stabilizers like Polysorbate 80, Polysorbate 20, Polyethylene glycol, propylene glycol, calcium chloride, or others, physiological pH buffering agents like

Tris(hydroxymethyl)aminomethan, and the like. In certain embodiments, the pharmaceutical compositions may contain pH buffering reagents and wetting or emulsifying agents. In further embodiments, the compositions may contain preservatives or stabilizers. In particular, the pharmaceutical preparation comprising the Factor VIII may be formulated in lyophilized or stable soluble form. The Factor VIII may be lyophilized by a variety of procedures known in the art. Also if the sulfated glycosaminoglycan and the Factor VIII are contained in the same composition, such composition may also be provided in lyophilized or in stable soluble form. Lyophilized formulations are reconstituted prior to use by the addition of one or more pharmaceutically acceptable diluents such as sterile water for injection or sterile physiological saline solution or a suitable buffer solution.

The composition(s) contained in the pharmaceutical preparation of the invention may be delivered to the individual by any pharmaceutically suitable means. Various delivery systems are known and can be used to administer the composition by any convenient route. Preferably, the composition(s) contained in the pharmaceutical preparation of the invention are delivered to the individual by non-intravenous injection. More preferably, the composition(s) of the invention are formulated for subcutaneous, intramuscular, intraperitoneal, intracerebral, intrapulmonar, intranasal, intradermal or transdermal adminstration, most preferably for subcutaneous, intramuscular or transdermal administration according to conventional methods. The formulations can be administered continuously by infusion or by bolus injection. Some formulations may encompass slow release systems.

The composition(s) of the pharmaceutical preparation of the present invention is/are administered to patients in a therapeutically effective dose, meaning a dose that is sufficient to produce the desired effects, preventing or lessening the severity or spread of the condition or indication being treated without reaching a dose which produces intolerable adverse side effects. The exact dose depends on many factors

as e.g. the indication, formulation, mode of administration and has to be determined in preclinical and clinical trials for each respective indication.

In the case of Factor VIII, the dose of one administration may be selected such that, during a period from 2 hours after injection to 48 hours after injection, the plasma level of the Factor VIII in the treated subject is continuously higher than 2%, preferably higher than 3%, more preferably higher than 4%, most preferably higher than 5%, of the normal plasma level of Factor VIII in healthy subjects.

Preferably, the dose of Factor VIII for one administration is less than 1,000 IU/kg body weight, or less than 800 IU/kg body weight, or less than 600 IU/kg body weight, or less than 400 IU/kg body weight, e.g. at a dose of from about 10 IU/kg body weight to about 1,000 IU/kg body weight, or from about 20 IU/kg body weight to about 800 IU/kg body weight, or from about 30 IU/kg body weight to about 700 IU/kg body weight, or from about 40 IU/kg body weight to about 600 IU/kg body weight, or from about 50 IU/kg body weight to about 500 IU/kg body weight, or from about 75 IU/kg body weight to about 400 IU/kg body weight, or from about 100 IU/kg body weight to about 300 IU/kg body weight, or from about 50 IU/kg body weight to about 1,000 IU/kg body weight, or from about 50 IU/kg body weight to about 800 IU/kg body weight, or from about 50 IU/kg body weight to about 700 IU/kg body weight, or from about 50 IU/kg body weight to about 600 IU/kg body weight, or from about 50 IU/kg body weight to about 500 IU/kg body weight, or from about 50 IU/kg body weight to about 400 IU/kg body weight, or from about 50 IU/kg body weight to about 300 IU/kg body weight, or about 50 IU/kg body weight to about 200 IU/kg body weight.

The Factor VIII can be administered on its own together with the sulfated glycosaminoglycan. Alternatively, the Factor VIII can be administered in association with vWF, i.e. as a FVIII/vWF complex, together with the sulfated glycosaminoglycan.

The amount of sulfated glycosaminoglycan administered typically ranges from about 0.001 to about 100 mg/mL product applied, from about 0.01 to about 10 mg/mL product applied, from about 0.05 to about 1 mg/mL product applied.

The term „bioavailability", as used herein, refers to the proportion of an administered dose of a Factor VIII (e.g. Factor VIII or a FVIII-related preparation) that can be detected in plasma at predetermined times until a final time point after subcutaneous, intravenous or intradermal administration. Typically, bioavailability is measured in test animals by administering a dose of between 10 IU/kg and 1000 IU/kg of the preparation (e.g. 400 IU/kg body weight); obtaining plasma samples at pre-determined time points after administration; and determining the content of the Factor VIII, e.g. Factor VIII or Factor VIII-related polypeptides in the samples using one or more of a chromogenic or clotting assay (or any bioassay), an immunoassay, or an equivalent thereof. The bioavailability is expressed as the area under the curve (AUC) of the concentration or activity of the Factor VIII in plasma on the y-axis and the time after administration on the x-axis until a predefined final time point after administration. Preferably, this predefined time point is 48 hours after administration. Most preferably, the bioavailability is determined as shown in Example 1 below. Relative bioavailability of a test preparation refers to the ratio between the AUC of the test preparation (e.g. Factor VIII + sulfated glycosaminoglycan) and that of the reference preparation (e.g. Factor VIII alone) which is administered in the same dose and way (e.g. intravenous, subcutaneous or intradermal) as the test preparation.

According to the present invention, the bioavailability of the Factor VIII (when co-administered with the sulfated glycosaminoglycan) is higher than that of the Factor VIII when administered alone. Preferably, the bioavailability is increased by at least 20%, more preferably by at least 50%, more preferably by at least 75%, most preferably by at least 100%. The increase in bioavailability is preferably obtained when the Factor VIII is administered by subcutaneous injection at a dose of less than 1,000 IU/kg body weight, or less than 800 IU/kg body weight, or less than 600

IU/kg body weight, or less than 400 IU/kg body weight, e.g. at a dose of from about 10 IU/kg body weight to about 1,000 IU/kg body weight, or from about 20 IU/kg body weight to about 800 IU/kg body weight, or from about 30 IU/kg body weight to about 700 IU/kg body weight, or from about 40 IU/kg body weight to about 600 IU/kg body weight, or from about 50 IU/kg body weight to about 500 IU/kg body weight, or from about 75 IU/kg body weight to about 400 IU/kg body weight, or from about 100 IU/kg body weight to about 300 IU/kg body weight, or from about 50 IU/kg body weight to about 1,000 IU/kg body weight, or from about 50 IU/kg body weight to about 800 IU/kg body weight, or from about 50 IU/kg body weight to about 700 IU/kg body weight, or from about 50 IU/kg body weight to about 600 IU/kg body weight, or from about 50 IU/kg body weight to about 500 IU/kg body weight, or from about 50 IU/kg body weight to about 400 IU/kg body weight, or from about 50 IU/kg body weight to about 300 IU/kg body weight, or about 50 IU/kg body weight to about 200 IU/kg body weight.

The pharmaceutical composition(s) of the invention may be administered alone or in conjunction with other therapeutic agents. These agents may be incorporated as part of the same pharmaceutical.

Examples

Example 1: Assessment of bioavailability of s.c. applied FVIII and various additives in a Hemophilia A model

Materials and animal model

The Factor VIII used in the experiments was a B-domain truncated, single-chain recombinant factor VIII (hereinafter referred to as "rFVIII"). The Factor VIII was obtained by directly fusing Asn764 with Thr1653. It has been expressed in cell culture cells and purified from the cell culture medium.

The further agents used are summarized in Table 1.

Table 1

Compound class	**Type of compound and/or source**
Unfractionated heparin	Heparin-Natrium-25000-ratiopharm
Low molecular weight heparin	Dalteparin (Fragmin® from Pfizer)
Dextran sulfate	Ca. 500 kDa
Pentosan sulfate	Fondaparinux sodium (Arixtra® from SKB)
N-Acetyl de-O-sulfated Heparin	N-Acetyl-de-O-sulfated heparin sodium salt from Sigma-Aldrich (Sigma product No. A6039) CAS Number 133686-69-8
Chondroitin sulfate	Chondroitin sulfate A sodium salt from bovine trachea, obtained from Sigma-Aldrich (Sigma product No. C9819) CAS Number 39455-18-0

Factor VIII knockout mice were used as animal model for hemophilia A. These mice lack exons 16 and 17 and thus do not express FVIII (Bi L. et al, Nature genetics, 1995, Vol 10(1), 119-121; Bi L. et al, Blood, 1996, Vol 88(9), 3446-3450). This allows the analysis of FVIII levels following treatment by quantification of FVIII activity in the plasma of the ko mice.

Methods

To assess whether extravascular injections might be an option for an improved therapy with rFVIII (human), a typical representative for an extravascular therapy, subcutaneous injection, was chosen. The design of the non-clinical pharmacokinetic study performed is detailed in tables 2 and 3 below. Plasma levels of Factor VIII activity were determined following a single intravenous or

subcutaneous injection of rFVIII together with various additives (detailed treatment groups in table 2) in a hemophilia A model.

Corresponding groups were treated with the same dose of FVIII (chromogenic substrate (CS) activity assay) in the presence of various different additives. For a single application the various different components for each treatment group were mixed together in a volume of 200 µL (identical volumes for all groups) prior to subcutaneous application to FVIII knockout (ko) mice weighing about 25 g. The treatment groups are summarized in table 2.

Under short term anesthesia, blood samples were drawn, anticoagulated using sodium citrate to 10 % citrate blood, processed to plasma and stored at –70°C for the determination of FVIII activity. The sampling time points are detailed in table 3. Quantification of FVIII activity in plasma was performed by a standard, aPTT based approach (Behring Coagulation Timer). The animals were kept at standard housing conditions.

Table 2: Treatment groups

No.	Treatment	FVIII (CS activity assay) / Additive Dose	volume [mL/kg]	schedule	route	N
1	rFVIII	400 IU/kg	8	single injection (t=0)	s.c.	25
2	rFVIII / unfractionated Heparin	400 IU/kg / 5 U/mL product applied	8	single injection	s.c.	25
3	rFVIII / Dextransulfate (ca. 500kDa)	400 IU/kg / 400 µg/mL product applied	8	single injection	s.c.	25
4	rFVIII / Fragmin	400 IU/kg/ 5 U/mL product applied	8	single injection	s.c.	20
5	rFVIII / Fondaparinux	400 IU/kg / 10 µg/mL product applied	8	single injection	s.c.	20
6	rFVIII / N-Acetyl de-O-sulfated Heparin	400 IU/kg / 10 µg/mL product applied	8	single injection	s.c.	20
7	rFVIII / Chondroitin sulfate	400 IU/ kg/ 10 µg/mL product applied	8	single injection	s.c.	20

Results

The results are summarized in Table 3 and Figure 1. Subcutaneous injection of 400 IU/kg rFVIII in presence of various sulfated glycosaminoglycans into FVIII ko mice resulted in a significant increase of FVIII activity in plasma level as compared to

administration of FVIII alone or FVIII+dextran sulfate. The increase for co-administration of heparin was particularly strong.

Table 3. FVIII activity in % of the FVIII activity in normal human plasma

Time-point (h)	rFVIII 400 IU/kg s.c.	rFVIII 400 IU/kg / unfractionated Heparin 5 U/mL (40 U/kg) s.c.	rFVIII 400 IU/kg / Dextransulfate 400 µg/ml s.c.	rFVIII 400 IU/kg / Fragmin 5 U/mL (40 U/kg) s.c.
0.5	1.02 ± 0.85	2.90 ± 2.70	0 ± 0	3.41 ± 0.61
2	13.04 ± 3.90	15.16 ± 4.12	0.98 ± 1.49	10.65 ± 6.38
5	1.15 ± 1.28	26.66 ± 5.74	2.57 ± 2.67	15.19 ± 7.12
8	2.32 ± 2.27	15.56 ± 4.22	0.64 ± 0.64	21.13 ± 8.92
16	4.82 ± 2.35	12.08 ± 2.35	0.84 ± 1.26	13.19 ± 3.58
24	9.72 ± 8.09	14.10 ± 3.76	0.85 ± 0.89	10.21 ± 3.26
32	2.48 ± 2.20	10.84 ± 5.31	0.92 ± 1.30	5.23 ± 2.83
48	1.15 ± 1.72	7.02 ± 1.24	1.47 ± 1.14	4.71 ± 1.74
AUC 0-48h (h x % of the norm SHP)	**202.0**	**598.4**	**50.0**	**475.9**

The peak values are shaded in grey.

Time-point (h)	rFVIII 400 IU/kg/ Fondaparinux (10 µg/mL) s.c.	rFVIII 400 IU/kg/ N-acetyl de-O-sulfated Heparin (10 µg/mL) s.c.	rFVIII 400 IU/kg/ Chondroitin sulfate (10 µg/mL) s.c.
0.5	7.21 ± 6.77	8.24 ± 11.87	1.98 ±4.12
2	20.81 ± 11.42	23.37 ± 8.39	16.83 ± 7.22
5	13.01 ± 8.96	16.75 ± 5.08	11.59 ± 5.28
8	18.03 ± 4.70	28.73 ± 9.39	22.59 ± 7.10
16	8.79 ± 5.67	7.69 ± 5.31	3.86 ± 2.76
24	9.61 ± 5.66	10.49 ± 2.12	8.95 ± 2.25
32	3.81 ± 2.13	4.11 ± 1.99	2.83 ± 1.67
48	6.55 ± 2.93	4.73 ± 1.37	7.11 ± 2.86
AUC (h x % of the norm SHP))	**435.7**	**499.6**	**391.7**

The peak values are shaded in grey.

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Claims

1. A method for treating or preventing a bleeding disorder, the method comprising administering non-intravenously Factor VIII and a sulfated glycosaminoglycan.

2. A method for treating or preventing a bleeding disorder, the method comprising administering non-intravenously Factor VIII together with a sulfated glycosaminoglycan, wherein the Factor VIII is administered subcutaneously at a dose of 50 IU/kg body weight to about 1,000 IU/kg body weight and wherein the amount of the sulfated glycosaminoglycan is between 0.001 and 100mg per mL product applied.

3. The method according to claim 1 or 2, wherein the Factor VIII and the sulfated glycosaminoglycan are administered simultaneously.

4. The method according to claim 1 or 2, wherein the Factor VIII and the sulfated glycosaminoglycan are administered separately.

5. The method according to any preceding claim, wherein the sulfated glycosaminoglycan is heparin.

6. The method according to any one of claims 1 to 5, wherein the Factor VIII is in association with von Willebrand Factor, and the sulfated glycosaminoglycan is heparin.

7. The method according to any preceding claim, wherein the treated subject is a human individual, and the dose of one administration is less than 500 IU/kg body weight.

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8. The method according to any preceding claim, wherein said non-intravenous injection is subcutaneous, transdermal or intramuscular injection.

9. A method for improving the bioavailability of Factor VIII in the treatment or prevention of a bleeding disorder, the method comprising administering a sulfated glycosaminoglycan, wherein said sulfated glycosaminoglycan and said Factor VIII are administered by subcutaneous, transdermal or intramuscular injection.

10. The method according to claim 9, wherein the sulfated glycosaminoglycan is heparin.

11. The method according to claim 9 or 10, wherein the bleeding disorder is hemophilia A.

12. The method according to any one of claims 9 to 11, wherein the Factor VIII and the sulfated glycosaminoglycan are administered simultaneously.

13. The method according to any one of claims 9 to 11, wherein the Factor VIII and the sulfated glycosaminoglycan are administered separately.

14. A pharmaceutical kit when used for the treatment of prevention of a bleeding disorder, comprising Factor VIII and a sulfated glycosaminoglycan, wherein said sulfated glycosaminoglycan and said Factor VIII are administered non-intraveneously.

15. The pharmaceutical kit of claim 14, wherein the sulfated glycosaminoglycan is unfractionated heparin.

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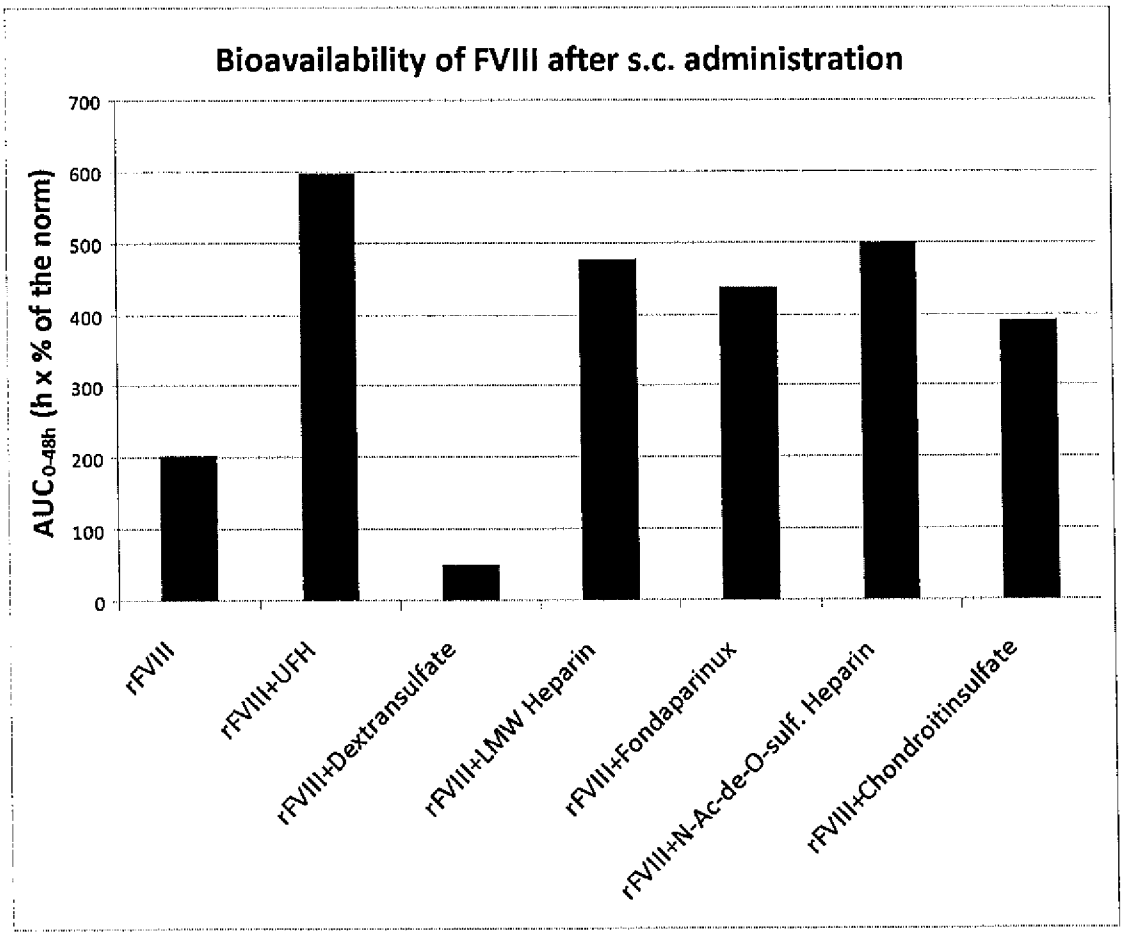
16. Use of a Factor VIII and a sulfated glycosaminoglycan in the manufacture of a medicament for the treatment and prevention of a bleeding disorder.

17. A method for treating or preventing a bleeding disorder according to any one of claims 1 to 8, or a method for improving the bioavailability of Factor VIII in the treatment or prevention of a bleeding disorder according to any one of claims 9 to 13, or a pharmaceutical kit according to any one of claims 14-15, or a use according to claim 16, substantially as described herein.

Figure 1


Bioavailability of FVIII after s.c. administration
AUC0-48h (h x % of the norm)
700
600
500
400
300
200
100
0
rFVIII
rFVIII+UFH
rFVIII+Dextransulfate
rFVIII+LMW Heparin
rFVIII+Fondaparinux
rFVIII+N-Ac-de-O-sulf. Heparin
rFVIII+Chondroitinsulfate

SEQUENCE LISTING

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<120> Use of sulfated glycosaminoglycans for improving the bioavailability of blood coagulation factors

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<151> 2011-10-18

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65                  70                  75                  80

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Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val
        115                 120                 125

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Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu Asn
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Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser Tyr Leu Ser
145                 150                 155                 160

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225                 230                 235                 240

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1296
Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr Thr
420 425 430

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1344
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435 440 445

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610 615 620

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645 650 655

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2016
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660 665 670

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2160
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2256
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Tyr Asp Ser Gln Leu Asp Thr Thr Leu Phe Gly Lys Lys Ser Ser Pro
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2832
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2880
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945                 950                 955                 960

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2928
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3024
Val Ser Ile Ser Leu Leu Lys Thr  Asn Lys Thr Ser Asn  Asn Ser Ala
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aaa aat  gct aca gct ttg agg  cta aat cat atg tca  aat aaa act
3204
Lys Asn  Ala Thr Ala Leu Arg  Leu Asn His Met Ser  Asn Lys Thr
    1055                 1060                 1065

act tca  tca aaa aac atg gaa  atg gtc caa cag aaa  aaa gag ggc
3249
Thr Ser  Ser Lys Asn Met Glu  Met Val Gln Gln Lys  Lys Glu Gly
    1070                 1075                 1080

ccc att  cca cca gat gca caa  aat cca gat atg tcg  ttc ttt aag
3294
Pro Ile  Pro Pro Asp Ala Gln  Asn Pro Asp Met Ser  Phe Phe Lys
    1085                 1090                 1095

atg cta  ttc ttg cca gaa tca  gca agg tgg ata caa  agg act cat
3339
Met Leu  Phe Leu Pro Glu Ser  Ala Arg Trp Ile Gln  Arg Thr His
    1100                 1105                 1110

gga aag  aac tct ctg aac tct  ggg caa ggc ccc agt  cca aag caa
3384
Gly Lys  Asn Ser Leu Asn Ser  Gly Gln Gly Pro Ser  Pro Lys Gln
    1115                 1120                 1125

tta gta  tcc tta gga cca gaa  aaa tct gtg gaa ggt  cag aat ttc
3429
Leu Val  Ser Leu Gly Pro Glu  Lys Ser Val Glu Gly  Gln Asn Phe
    1130                 1135                 1140

ttg tct  gag aaa aac aaa gtg  gta gta gga aag ggt  gaa ttt aca
3474
Leu Ser  Glu Lys Asn Lys Val  Val Val Gly Lys Gly  Glu Phe Thr
    1145                 1150                 1155

aag gac  gta gga ctc aaa gag  atg gtt ttt cca agc  agc aga aac
3519
Lys Asp  Val Gly Leu Lys Glu  Met Val Phe Pro Ser  Ser Arg Asn
    1160                 1165                 1170

cta ttt  ctt act aac ttg gat  aat tta cat gaa aat  aat aca cac
3564
Leu Phe  Leu Thr Asn Leu Asp  Asn Leu His Glu Asn  Asn Thr His
    1175                 1180                 1185

aat caa  gaa aaa aaa att cag  gaa gaa ata gaa aag  aag gaa aca
3609
Asn Gln  Glu Lys Lys Ile Gln  Glu Glu Ile Glu Lys  Lys Glu Thr
    1190                 1195                 1200

tta atc  caa gag aat gta gtt  ttg cct cag ata cat  aca gtg act
3654
Leu Ile  Gln Glu Asn Val Val  Leu Pro Gln Ile His  Thr Val Thr
    1205                 1210                 1215

ggc act  aag aat ttc atg aag  aac ctt ttc tta ctg  agc act agg
3699
Gly Thr  Lys Asn Phe Met Lys  Asn Leu Phe Leu Leu  Ser Thr Arg
    1220                 1225                 1230
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caa aat gta gaa ggt tca tat gac ggg gca tat gct cca gta ctt
3744
Gln Asn Val Glu Gly Ser Tyr Asp Gly Ala Tyr Ala Pro Val Leu
1235 1240 1245

caa gat ttt agg tca tta aat gat tca aca aat aga aca aag aaa
3789
Gln Asp Phe Arg Ser Leu Asn Asp Ser Thr Asn Arg Thr Lys Lys
1250 1255 1260

cac aca gct cat ttc tca aaa aaa ggg gag gaa gaa aac ttg gaa
3834
His Thr Ala His Phe Ser Lys Lys Gly Glu Glu Glu Asn Leu Glu
1265 1270 1275

ggc ttg gga aat caa acc aag caa att gta gag aaa tat gca tgc
3879
Gly Leu Gly Asn Gln Thr Lys Gln Ile Val Glu Lys Tyr Ala Cys
1280 1285 1290

acc aca agg ata tct cct aat aca agc cag cag aat ttt gtc acg
3924
Thr Thr Arg Ile Ser Pro Asn Thr Ser Gln Gln Asn Phe Val Thr
1295 1300 1305

caa cgt agt aag aga gct ttg aaa caa ttc aga ctc cca cta gaa
3969
Gln Arg Ser Lys Arg Ala Leu Lys Gln Phe Arg Leu Pro Leu Glu
1310 1315 1320

gaa aca gaa ctt gaa aaa agg ata att gtg gat gac acc tca acc
4014
Glu Thr Glu Leu Glu Lys Arg Ile Ile Val Asp Asp Thr Ser Thr
1325 1330 1335

cag tgg tcc aaa aac atg aaa cat ttg acc ccg agc acc ctc aca
4059
Gln Trp Ser Lys Asn Met Lys His Leu Thr Pro Ser Thr Leu Thr
1340 1345 1350

cag ata gac tac aat gag aag gag aaa ggg gcc att act cag tct
4104
Gln Ile Asp Tyr Asn Glu Lys Glu Lys Gly Ala Ile Thr Gln Ser
1355 1360 1365

ccc tta tca gat tgc ctt acg agg agt cat agc atc cct caa gca
4149
Pro Leu Ser Asp Cys Leu Thr Arg Ser His Ser Ile Pro Gln Ala
1370 1375 1380

aat aga tct cca tta ccc att gca aag gta tca tca ttt cca tct
4194
Asn Arg Ser Pro Leu Pro Ile Ala Lys Val Ser Ser Phe Pro Ser
1385 1390 1395

att aga cct ata tat ctg acc agg gtc cta ttc caa gac aac tct
4239
Ile Arg Pro Ile Tyr Leu Thr Arg Val Leu Phe Gln Asp Asn Ser
1400 1405 1410

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tct cat  ctt cca gca gca tct  tat aga aag aaa gat  tct ggg gtc
4284
Ser His  Leu Pro Ala Ala Ser  Tyr Arg Lys Lys Asp  Ser Gly Val
    1415                 1420                 1425

caa gaa  agc agt cat ttc tta  caa gga gcc aaa aaa  aat aac ctt
4329
Gln Glu  Ser Ser His Phe Leu  Gln Gly Ala Lys Lys  Asn Asn Leu
    1430                 1435                 1440

tct tta  gcc att cta acc ttg  gag atg act ggt gat  caa aga gag
4374
Ser Leu  Ala Ile Leu Thr Leu  Glu Met Thr Gly Asp  Gln Arg Glu
    1445                 1450                 1455

gtt ggc  tcc ctg ggg aca agt  gcc aca aat tca gtc  aca tac aag
4419
Val Gly  Ser Leu Gly Thr Ser  Ala Thr Asn Ser Val  Thr Tyr Lys
    1460                 1465                 1470

aaa gtt  gag aac act gtt ctc  ccg aaa cca gac ttg  ccc aaa aca
4464
Lys Val  Glu Asn Thr Val Leu  Pro Lys Pro Asp Leu  Pro Lys Thr
    1475                 1480                 1485

tct ggc  aaa gtt gaa ttg ctt  cca aaa gtt cac att  tat cag aag
4509
Ser Gly  Lys Val Glu Leu Leu  Pro Lys Val His Ile  Tyr Gln Lys
    1490                 1495                 1500

gac cta  ttc cct acg gaa act  agc aat ggg tct cct  ggc cat ctg
4554
Asp Leu  Phe Pro Thr Glu Thr  Ser Asn Gly Ser Pro  Gly His Leu
    1505                 1510                 1515

gat ctc  gtg gaa ggg agc ctt  ctt cag gga aca gag  gga gcg att
4599
Asp Leu  Val Glu Gly Ser Leu  Leu Gln Gly Thr Glu  Gly Ala Ile
    1520                 1525                 1530

aag tgg  aat gaa gca aac aga  cct gga aaa gtt ccc  ttt ctg aga
4644
Lys Trp  Asn Glu Ala Asn Arg  Pro Gly Lys Val Pro  Phe Leu Arg
    1535                 1540                 1545

gta gca  aca gaa agc tct gca  aag act ccc tcc aag  cta ttg gat
4689
Val Ala  Thr Glu Ser Ser Ala  Lys Thr Pro Ser Lys  Leu Leu Asp
    1550                 1555                 1560

cct ctt  gct tgg gat aac cac  tat ggt act cag ata  cca aaa gaa
4734
Pro Leu  Ala Trp Asp Asn His  Tyr Gly Thr Gln Ile  Pro Lys Glu
    1565                 1570                 1575

gag tgg  aaa tcc caa gag aag  tca cca gaa aaa aca  gct ttt aag
4779
Glu Trp  Lys Ser Gln Glu Lys  Ser Pro Glu Lys Thr  Ala Phe Lys
    1580                 1585                 1590
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aaa aag  gat acc att ttg tcc  ctg aac gct tgt gaa  agc aat cat
4824
Lys Lys  Asp Thr Ile Leu Ser  Leu Asn Ala Cys Glu  Ser Asn His
    1595                 1600                 1605

gca ata  gca gca ata aat gag  gga caa aat aag ccc  gaa ata gaa
4869
Ala Ile  Ala Ala Ile Asn Glu  Gly Gln Asn Lys Pro  Glu Ile Glu
    1610                 1615                 1620

gtc acc  tgg gca aag caa ggt  agg act gaa agg ctg  tgc tct caa
4914
Val Thr  Trp Ala Lys Gln Gly  Arg Thr Glu Arg Leu  Cys Ser Gln
    1625                 1630                 1635

aac cca  cca gtc ttg aaa cgc  cat caa cgg gaa ata  act cgt act
4959
Asn Pro  Pro Val Leu Lys Arg  His Gln Arg Glu Ile  Thr Arg Thr
    1640                 1645                 1650

act ctt  cag tca gat caa gag  gaa att gac tat gat  gat acc ata
5004
Thr Leu  Gln Ser Asp Gln Glu  Glu Ile Asp Tyr Asp  Asp Thr Ile
    1655                 1660                 1665

tca gtt  gaa atg aag aag gaa  gat ttt gac att tat  gat gag gat
5049
Ser Val  Glu Met Lys Lys Glu  Asp Phe Asp Ile Tyr  Asp Glu Asp
    1670                 1675                 1680

gaa aat  cag agc ccc cgc agc  ttt caa aag aaa aca  cga cac tat
5094
Glu Asn  Gln Ser Pro Arg Ser  Phe Gln Lys Lys Thr  Arg His Tyr
    1685                 1690                 1695

ttt att  gct gca gtg gag agg  ctc tgg gat tat ggg  atg agt agc
5139
Phe Ile  Ala Ala Val Glu Arg  Leu Trp Asp Tyr Gly  Met Ser Ser
    1700                 1705                 1710

tcc cca  cat gtt cta aga aac  agg gct cag agt ggc  agt gtc cct
5184
Ser Pro  His Val Leu Arg Asn  Arg Ala Gln Ser Gly  Ser Val Pro
    1715                 1720                 1725

cag ttc  aag aaa gtt gtt ttc  cag gaa ttt act gat  ggc tcc ttt
5229
Gln Phe  Lys Lys Val Val Phe  Gln Glu Phe Thr Asp  Gly Ser Phe
    1730                 1735                 1740

act cag  ccc tta tac cgt gga  gaa cta aat gaa cat  ttg gga ctc
5274
Thr Gln  Pro Leu Tyr Arg Gly  Glu Leu Asn Glu His  Leu Gly Leu
    1745                 1750                 1755

ctg ggg  cca tat ata aga gca  gaa gtt gaa gat aat  atc atg gta
5319
Leu Gly  Pro Tyr Ile Arg Ala  Glu Val Glu Asp Asn  Ile Met Val
    1760                 1765                 1770
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act ttc  aga aat cag gcc tct  cgt ccc tat tcc ttc  tat tct agc
5364
Thr Phe  Arg Asn Gln Ala Ser  Arg Pro Tyr Ser Phe  Tyr Ser Ser
    1775                 1780                 1785

ctt att  tct tat gag gaa gat  cag agg caa gga gca  gaa cct aga
5409
Leu Ile  Ser Tyr Glu Glu Asp  Gln Arg Gln Gly Ala  Glu Pro Arg
    1790                 1795                 1800

aaa aac  ttt gtc aag cct aat  gaa acc aaa act tac  ttt tgg aaa
5454
Lys Asn  Phe Val Lys Pro Asn  Glu Thr Lys Thr Tyr  Phe Trp Lys
    1805                 1810                 1815

gtg caa  cat cat atg gca ccc  act aaa gat gag ttt  gac tgc aaa
5499
Val Gln  His His Met Ala Pro  Thr Lys Asp Glu Phe  Asp Cys Lys
    1820                 1825                 1830

gcc tgg  gct tat ttc tct gat  gtt gac ctg gaa aaa  gat gtg cac
5544
Ala Trp  Ala Tyr Phe Ser Asp  Val Asp Leu Glu Lys  Asp Val His
    1835                 1840                 1845

tca ggc  ctg att gga ccc ctt  ctg gtc tgc cac act  aac aca ctg
5589
Ser Gly  Leu Ile Gly Pro Leu  Leu Val Cys His Thr  Asn Thr Leu
    1850                 1855                 1860

aac cct  gct cat ggg aga caa  gtg aca gta cag gaa  ttt gct ctg
5634
Asn Pro  Ala His Gly Arg Gln  Val Thr Val Gln Glu  Phe Ala Leu
    1865                 1870                 1875

ttt ttc  acc atc ttt gat gag  acc aaa agc tgg tac  ttc act gaa
5679
Phe Phe  Thr Ile Phe Asp Glu  Thr Lys Ser Trp Tyr  Phe Thr Glu
    1880                 1885                 1890

aat atg  gaa aga aac tgc agg  gct ccc tgc aat atc  cag atg gaa
5724
Asn Met  Glu Arg Asn Cys Arg  Ala Pro Cys Asn Ile  Gln Met Glu
    1895                 1900                 1905

gat ccc  act ttt aaa gag aat  tat cgc ttc cat gca  atc aat ggc
5769
Asp Pro  Thr Phe Lys Glu Asn  Tyr Arg Phe His Ala  Ile Asn Gly
    1910                 1915                 1920

tac ata  atg gat aca cta cct  ggc tta gta atg gct  cag gat caa
5814
Tyr Ile  Met Asp Thr Leu Pro  Gly Leu Val Met Ala  Gln Asp Gln
    1925                 1930                 1935

agg att  cga tgg tat ctg ctc  agc atg ggc agc aat  gaa aac atc
5859
Arg Ile  Arg Trp Tyr Leu Leu  Ser Met Gly Ser Asn  Glu Asn Ile
    1940                 1945                 1950
```

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cat tct  att cat ttc agt gga  cat gtg ttc act gta  cga aaa aaa
5904
His Ser  Ile His Phe Ser Gly  His Val Phe Thr Val  Arg Lys Lys
    1955                 1960                 1965

gag gag  tat aaa atg gca ctg  tac aat ctc tat cca  ggt gtt ttt
5949
Glu Glu  Tyr Lys Met Ala Leu  Tyr Asn Leu Tyr Pro  Gly Val Phe
    1970                 1975                 1980

gag aca  gtg gaa atg tta cca  tcc aaa gct gga att  tgg cgg gtg
5994
Glu Thr  Val Glu Met Leu Pro  Ser Lys Ala Gly Ile  Trp Arg Val
    1985                 1990                 1995

gaa tgc  ctt att ggc gag cat  cta cat gct ggg atg  agc aca ctt
6039
Glu Cys  Leu Ile Gly Glu His  Leu His Ala Gly Met  Ser Thr Leu
    2000                 2005                 2010

ttt ctg  gtg tac agc aat aag  tgt cag act ccc ctg  gga atg gct
6084
Phe Leu  Val Tyr Ser Asn Lys  Cys Gln Thr Pro Leu  Gly Met Ala
    2015                 2020                 2025

tct gga  cac att aga gat ttt  cag att aca gct tca  gga caa tat
6129
Ser Gly  His Ile Arg Asp Phe  Gln Ile Thr Ala Ser  Gly Gln Tyr
    2030                 2035                 2040

gga cag  tgg gcc cca aag ctg  gcc aga ctt cat tat  tcc gga tca
6174
Gly Gln  Trp Ala Pro Lys Leu  Ala Arg Leu His Tyr  Ser Gly Ser
    2045                 2050                 2055

atc aat  gcc tgg agc acc aag  gag ccc ttt tct tgg  atc aag gtg
6219
Ile Asn  Ala Trp Ser Thr Lys  Glu Pro Phe Ser Trp  Ile Lys Val
    2060                 2065                 2070

gat ctg  ttg gca cca atg att  att cac ggc atc aag  acc cag ggt
6264
Asp Leu  Leu Ala Pro Met Ile  Ile His Gly Ile Lys  Thr Gln Gly
    2075                 2080                 2085

gcc cgt  cag aag ttc tcc agc  ctc tac atc tct cag  ttt atc atc
6309
Ala Arg  Gln Lys Phe Ser Ser  Leu Tyr Ile Ser Gln  Phe Ile Ile
    2090                 2095                 2100

atg tat  agt ctt gat ggg aag  aag tgg cag act tat  cga gga aat
6354
Met Tyr  Ser Leu Asp Gly Lys  Lys Trp Gln Thr Tyr  Arg Gly Asn
    2105                 2110                 2115

tcc act  gga acc tta atg gtc  ttc ttt ggc aat gtg  gat tca tct
6399
Ser Thr  Gly Thr Leu Met Val  Phe Phe Gly Asn Val  Asp Ser Ser
    2120                 2125                 2130
```

ggg ata aaa cac aat att ttt aac cct cca att att gct cga tac
6444
Gly Ile Lys His Asn Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr
2135 2140 2145

atc cgt ttg cac cca act cat tat agc att cgc agc act ctt cgc
6489
Ile Arg Leu His Pro Thr His Tyr Ser Ile Arg Ser Thr Leu Arg
2150 2155 2160

atg gag ttg atg ggc tgt gat tta aat agt tgc agc atg cca ttg
6534
Met Glu Leu Met Gly Cys Asp Leu Asn Ser Cys Ser Met Pro Leu
2165 2170 2175

gga atg gag agt aaa gca ata tca gat gca cag att act gct tca
6579
Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser
2180 2185 2190

tcc tac ttt acc aat atg ttt gcc acc tgg tct cct tca aaa gct
6624
Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser Pro Ser Lys Ala
2195 2200 2205

cga ctt cac ctc caa ggg agg agt aat gcc tgg aga cct cag gtg
6669
Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg Pro Gln Val
2210 2215 2220

aat aat cca aaa gag tgg ctg caa gtg gac ttc cag aag aca atg
6714
Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe Gln Lys Thr Met
2225 2230 2235

aaa gtc aca gga gta act act cag gga gta aaa tct ctg ctt acc
6759
Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys Ser Leu Leu Thr
2240 2245 2250

agc atg tat gtg aag gag ttc ctc atc tcc agc agt caa gat ggc
6804
Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly
2255 2260 2265

cat cag tgg act ctc ttt ttt cag aat ggc aaa gta aag gtt ttt
6849
His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe
2270 2275 2280

cag gga aat caa gac tcc ttc aca cct gtg gtg aac tct cta gac
6894
Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val Asn Ser Leu Asp
2285 2290 2295

cca ccg tta ctg act cgc tac ctt cga att cac ccc cag agt tgg
6939
Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His Pro Gln Ser Trp
2300 2305 2310

```
gtg cac  cag att gcc ctg agg  atg gag gtt ctg ggc  tgc gag gca
6984
Val His  Gln Ile Ala Leu Arg  Met Glu Val Leu Gly  Cys Glu Ala
    2315                 2320                 2325

cag gac  ctc tac
6996
Gln Asp  Leu Tyr
    2330
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<210> 2
<211> 2332
<212> PRT
<213> homo sapiens

<400> 2

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1               5                  10                  15

Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg Phe Pro Pro
            20                  25                  30

Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val Tyr Lys Lys
        35                  40                  45

Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile Ala Lys Pro
    50                  55                  60

Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu Val
65                  70                  75                  80

Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val
                85                  90                  95

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

Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val
        115                 120                 125

Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu Asn
    130                 135                 140

Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser Tyr Leu Ser
145                 150                 155                 160

His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala Leu
                165                 170                 175
```

Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr Leu
180 185 190

His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser Trp
195 200 205

His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala Ser
210 215 220

Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn Arg
225 230 235 240

Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val Tyr Trp His
245 250 255

Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile Phe Leu Glu
260 265 270

Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser Leu Glu Ile
275 280 285

Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met Asp Leu Gly
290 295 300

Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly Met
305 310 315 320

Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg
325 330 335

Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp Leu Thr Asp
340 345 350

Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser Pro Ser Phe
355 360 365

Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr Trp Val His
370 375 380

Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Leu Val Leu
385 390 395 400

Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn Asn Gly Pro
405 410 415

```
Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr Thr
            420                 425                 430

Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu Ser Gly Ile
        435                 440                 445

Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile Ile
    450                 455                 460

Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile
465                 470                 475                 480

Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys Gly Val Lys
                485                 490                 495

His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys
            500                 505                 510

Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys
        515                 520                 525

Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu Ala
    530                 535                 540

Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp
545                 550                 555                 560

Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe
                565                 570                 575

Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu Asn Ile Gln
            580                 585                 590

Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp Pro Glu Phe
        595                 600                 605

Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp Ser
    610                 615                 620

Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu
625                 630                 635                 640

Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr
                645                 650                 655

Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro
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660 665 670

Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp
675 680 685

Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly Met Thr Ala
690 695 700

Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp Tyr Tyr Glu
705 710 715 720

Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala
725 730 735

Ile Glu Pro Arg Ser Phe Ser Gln Asn Ser Arg His Arg Ser Thr Arg
740 745 750

Gln Lys Gln Phe Asn Ala Thr Thr Ile Pro Glu Asn Asp Ile Glu Lys
755 760 765

Thr Asp Pro Trp Phe Ala His Arg Thr Pro Met Pro Lys Ile Gln Asn
770 775 780

Val Ser Ser Ser Asp Leu Leu Met Leu Leu Arg Gln Ser Pro Thr Pro
785 790 795 800

His Gly Leu Ser Leu Ser Asp Leu Gln Glu Ala Lys Tyr Glu Thr Phe
805 810 815

Ser Asp Asp Pro Ser Pro Gly Ala Ile Asp Ser Asn Asn Ser Leu Ser
820 825 830

Glu Met Thr His Phe Arg Pro Gln Leu His His Ser Gly Asp Met Val
835 840 845

Phe Thr Pro Glu Ser Gly Leu Gln Leu Arg Leu Asn Glu Lys Leu Gly
850 855 860

Thr Thr Ala Ala Thr Glu Leu Lys Lys Leu Asp Phe Lys Val Ser Ser
865 870 875 880

Thr Ser Asn Asn Leu Ile Ser Thr Ile Pro Ser Asp Asn Leu Ala Ala
885 890 895

Gly Thr Asp Asn Thr Ser Ser Leu Gly Pro Pro Ser Met Pro Val His
900 905 910

Tyr Asp Ser Gln Leu Asp Thr Thr Leu Phe Gly Lys Lys Ser Ser Pro
915 920 925

Leu Thr Glu Ser Gly Gly Pro Leu Ser Leu Ser Glu Glu Asn Asn Asp
930 935 940

Ser Lys Leu Leu Glu Ser Gly Leu Met Asn Ser Gln Glu Ser Ser Trp
945 950 955 960

Gly Lys Asn Val Ser Ser Thr Glu Ser Gly Arg Leu Phe Lys Gly Lys
965 970 975

Arg Ala His Gly Pro Ala Leu Leu Thr Lys Asp Asn Ala Leu Phe Lys
980 985 990

Val Ser Ile Ser Leu Leu Lys Thr Asn Lys Thr Ser Asn Asn Ser Ala
995 1000 1005

Thr Asn Arg Lys Thr His Ile Asp Gly Pro Ser Leu Leu Ile Glu
1010 1015 1020

Asn Ser Pro Ser Val Trp Gln Asn Ile Leu Glu Ser Asp Thr Glu
1025 1030 1035

Phe Lys Lys Val Thr Pro Leu Ile His Asp Arg Met Leu Met Asp
1040 1045 1050

Lys Asn Ala Thr Ala Leu Arg Leu Asn His Met Ser Asn Lys Thr
1055 1060 1065

Thr Ser Ser Lys Asn Met Glu Met Val Gln Gln Lys Lys Glu Gly
1070 1075 1080

Pro Ile Pro Pro Asp Ala Gln Asn Pro Asp Met Ser Phe Phe Lys
1085 1090 1095

Met Leu Phe Leu Pro Glu Ser Ala Arg Trp Ile Gln Arg Thr His
1100 1105 1110

Gly Lys Asn Ser Leu Asn Ser Gly Gln Gly Pro Ser Pro Lys Gln
1115 1120 1125

Leu Val Ser Leu Gly Pro Glu Lys Ser Val Glu Gly Gln Asn Phe
1130 1135 1140

Leu Ser Glu Lys Asn Lys Val Val Val Gly Lys Gly Glu Phe Thr
1145 1150 1155

Lys Asp Val Gly Leu Lys Glu Met Val Phe Pro Ser Ser Arg Asn
1160 1165 1170

Leu Phe Leu Thr Asn Leu Asp Asn Leu His Glu Asn Asn Thr His
1175 1180 1185

Asn Gln Glu Lys Lys Ile Gln Glu Glu Ile Glu Lys Lys Glu Thr
1190 1195 1200

Leu Ile Gln Glu Asn Val Val Leu Pro Gln Ile His Thr Val Thr
1205 1210 1215

Gly Thr Lys Asn Phe Met Lys Asn Leu Phe Leu Leu Ser Thr Arg
1220 1225 1230

Gln Asn Val Glu Gly Ser Tyr Asp Gly Ala Tyr Ala Pro Val Leu
1235 1240 1245

Gln Asp Phe Arg Ser Leu Asn Asp Ser Thr Asn Arg Thr Lys Lys
1250 1255 1260

His Thr Ala His Phe Ser Lys Lys Gly Glu Glu Glu Asn Leu Glu
1265 1270 1275

Gly Leu Gly Asn Gln Thr Lys Gln Ile Val Glu Lys Tyr Ala Cys
1280 1285 1290

Thr Thr Arg Ile Ser Pro Asn Thr Ser Gln Gln Asn Phe Val Thr
1295 1300 1305

Gln Arg Ser Lys Arg Ala Leu Lys Gln Phe Arg Leu Pro Leu Glu
1310 1315 1320

Glu Thr Glu Leu Glu Lys Arg Ile Ile Val Asp Asp Thr Ser Thr
1325 1330 1335

Gln Trp Ser Lys Asn Met Lys His Leu Thr Pro Ser Thr Leu Thr
1340 1345 1350

Gln Ile Asp Tyr Asn Glu Lys Glu Lys Gly Ala Ile Thr Gln Ser
1355 1360 1365

Pro Leu Ser Asp Cys Leu Thr Arg Ser His Ser Ile Pro Gln Ala
1370 1375 1380

Asn Arg Ser Pro Leu Pro Ile Ala Lys Val Ser Ser Phe Pro Ser
1385 1390 1395

Ile Arg Pro Ile Tyr Leu Thr Arg Val Leu Phe Gln Asp Asn Ser
1400 1405 1410

Ser His Leu Pro Ala Ala Ser Tyr Arg Lys Lys Asp Ser Gly Val
1415 1420 1425

Gln Glu Ser Ser His Phe Leu Gln Gly Ala Lys Lys Asn Asn Leu
1430 1435 1440

Ser Leu Ala Ile Leu Thr Leu Glu Met Thr Gly Asp Gln Arg Glu
1445 1450 1455

Val Gly Ser Leu Gly Thr Ser Ala Thr Asn Ser Val Thr Tyr Lys
1460 1465 1470

Lys Val Glu Asn Thr Val Leu Pro Lys Pro Asp Leu Pro Lys Thr
1475 1480 1485

Ser Gly Lys Val Glu Leu Leu Pro Lys Val His Ile Tyr Gln Lys
1490 1495 1500

Asp Leu Phe Pro Thr Glu Thr Ser Asn Gly Ser Pro Gly His Leu
1505 1510 1515

Asp Leu Val Glu Gly Ser Leu Leu Gln Gly Thr Glu Gly Ala Ile
1520 1525 1530

Lys Trp Asn Glu Ala Asn Arg Pro Gly Lys Val Pro Phe Leu Arg
1535 1540 1545

Val Ala Thr Glu Ser Ser Ala Lys Thr Pro Ser Lys Leu Leu Asp
1550 1555 1560

Pro Leu Ala Trp Asp Asn His Tyr Gly Thr Gln Ile Pro Lys Glu
1565 1570 1575

Glu Trp Lys Ser Gln Glu Lys Ser Pro Glu Lys Thr Ala Phe Lys
1580 1585 1590

Lys Lys Asp Thr Ile Leu Ser Leu Asn Ala Cys Glu Ser Asn His

1595 1600 1605

Ala Ile Ala Ala Ile Asn Glu Gly Gln Asn Lys Pro Glu Ile Glu
1610 1615 1620

Val Thr Trp Ala Lys Gln Gly Arg Thr Glu Arg Leu Cys Ser Gln
1625 1630 1635

Asn Pro Pro Val Leu Lys Arg His Gln Arg Glu Ile Thr Arg Thr
1640 1645 1650

Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile
1655 1660 1665

Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp
1670 1675 1680

Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg His Tyr
1685 1690 1695

Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser
1700 1705 1710

Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser Val Pro
1715 1720 1725

Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser Phe
1730 1735 1740

Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
1745 1750 1755

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val
1760 1765 1770

Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser
1775 1780 1785

Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg
1790 1795 1800

Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys
1805 1810 1815

Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys
1820 1825 1830

Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His
1835 1840 1845

Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu
1850 1855 1860

Asn Pro Ala His Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu
1865 1870 1875

Phe Phe Thr Ile Phe Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu
1880 1885 1890

Asn Met Glu Arg Asn Cys Arg Ala Pro Cys Asn Ile Gln Met Glu
1895 1900 1905

Asp Pro Thr Phe Lys Glu Asn Tyr Arg Phe His Ala Ile Asn Gly
1910 1915 1920

Tyr Ile Met Asp Thr Leu Pro Gly Leu Val Met Ala Gln Asp Gln
1925 1930 1935

Arg Ile Arg Trp Tyr Leu Leu Ser Met Gly Ser Asn Glu Asn Ile
1940 1945 1950

His Ser Ile His Phe Ser Gly His Val Phe Thr Val Arg Lys Lys
1955 1960 1965

Glu Glu Tyr Lys Met Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe
1970 1975 1980

Glu Thr Val Glu Met Leu Pro Ser Lys Ala Gly Ile Trp Arg Val
1985 1990 1995

Glu Cys Leu Ile Gly Glu His Leu His Ala Gly Met Ser Thr Leu
2000 2005 2010

Phe Leu Val Tyr Ser Asn Lys Cys Gln Thr Pro Leu Gly Met Ala
2015 2020 2025

Ser Gly His Ile Arg Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr
2030 2035 2040

Gly Gln Trp Ala Pro Lys Leu Ala Arg Leu His Tyr Ser Gly Ser
2045 2050 2055

Ile Asn Ala Trp Ser Thr Lys Glu Pro Phe Ser Trp Ile Lys Val
2060 2065 2070

Asp Leu Leu Ala Pro Met Ile Ile His Gly Ile Lys Thr Gln Gly
2075 2080 2085

Ala Arg Gln Lys Phe Ser Ser Leu Tyr Ile Ser Gln Phe Ile Ile
2090 2095 2100

Met Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn
2105 2110 2115

Ser Thr Gly Thr Leu Met Val Phe Phe Gly Asn Val Asp Ser Ser
2120 2125 2130

Gly Ile Lys His Asn Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr
2135 2140 2145

Ile Arg Leu His Pro Thr His Tyr Ser Ile Arg Ser Thr Leu Arg
2150 2155 2160

Met Glu Leu Met Gly Cys Asp Leu Asn Ser Cys Ser Met Pro Leu
2165 2170 2175

Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser
2180 2185 2190

Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser Pro Ser Lys Ala
2195 2200 2205

Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg Pro Gln Val
2210 2215 2220

Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe Gln Lys Thr Met
2225 2230 2235

Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys Ser Leu Leu Thr
2240 2245 2250

Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly
2255 2260 2265

His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe
2270 2275 2280

Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val Asn Ser Leu Asp
2285 2290 2295

Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His Pro Gln Ser Trp
2300 2305 2310

Val His Gln Ile Ala Leu Arg Met Glu Val Leu Gly Cys Glu Ala
2315 2320 2325

Gln Asp Leu Tyr
2330