once every one or two weeks for 2 hours to 6 hours, the daily life of the patients and their family members may be restricted. Since the half-lives of the recombinant enzymes used for the treatment of lysosomal storage diseases in humans are very short to be in a range of 10 minutes to less than 3 hours, the recombinant enzymes are required to be administered life-time thus causing inconvenience to patients. Accordingly, it is of high necessity to extend the half-lives of the recombinant enzymes.

Additionally, there is an increasing need for the development of a therapeutic agent for lysosomal storage diseases due to the problems in that the *in vivo* storage locations of the enzymes used for the treatment of lysosomal storage diseases differ from each other, the therapeutic enzymes fail to arrive at the bone marrow, *etc*.

[Disclosure]

[Technical Problem]

An object of the present invention is to provide an enzyme conjugate in which a therapeutic enzyme and an immunoglobulin Fc region are linked through a non-peptide polymer linkage moiety.

Another object of the present invention is to provide a pharmaceutical composition for preventing or treating lysosomal storage diseases containing the enzyme conjugate.

Still another object of the present invention is to provide a method for preparing the enzyme conjugate.

[Technical Solution]

In one aspect, the present disclosure refers to an enzyme conjugate, wherein a therapeutic enzyme for treating lysosomal storage disease (LSD) and an immunoglobulin Fc region are linked through a non-peptide polymer linkage moiety, wherein the enzyme is not α-galactosidase A; wherein the enzyme conjugate has increased bioavailability (BA) compared to the enzyme, to which an immunoglobulin Fc region is not linked; and wherein the enzyme conjugate is an enzyme conjugate where a non-peptide polymer linkage moiety is linked to the N-terminus of the immunoglobulin Fc region. An example of the present disclosure provides an enzyme conjugate, wherein a therapeutic enzyme for treating lysosomal storage disease (LSD) and an immunoglobulin Fc region are linked through a non-peptide polymer linkage moiety.

In a specific example, the enzyme is selected from the group consisting of β-glucosidase, β-galactosidase, galactose-6-sulfatase, acid ceramidase, acid sphingomyelinase, galactocerebrosidase, arylsulfatase A, β-hexosaminidase A, β-hexosaminidase B, heparan N-sulfatase, α-D-mannosidase, β-glucuronidase, N-acetylgalactosamine-6 sulfatase, lysosomal acid lipase, α-N-acetyl-D-glucosaminidase (NAGLU), glucocerebrosidase, butyrylcholinesterase,

wherein the immunoglobulin Fc region is an IgG4 Fc fragment.

In still another specific example, the present disclosure provides an enzyme conjugate wherein the immunoglobulin Fc region is a human aglycosylated IgG4 Fc fragmentIn still another specific example, the present disclosure provides an enzyme conjugate wherein the enzyme conjugate is an enzyme conjugate where a non-peptide polymer linkage moiety is linked to the N-terminus of the enzyme.

Still another aspect of the present disclosure provides a pharmaceutical composition for preventing or treating lysosomal storage disease (LSD) containing the enzyme conjugate.

Still another example of the present disclosure provides a pharmaceutical composition for preventing or treating lysosomal storage disease (LSD) containing the α-galactosidase A conjugate.

Still another example of the present disclosure provides a pharmaceutical composition for preventing or treating lysosomal storage disease (LSD) containing the arylsulfatase B (ARSB) conjugate.

Still another example of the present disclosure provides a pharmaceutical composition for preventing or treating lysosomal storage disease (LSD) containing the iduronidase conjugate.

Still another example of the present disclosure provides a pharmaceutical composition for preventing or treating lysosomal storage disease (LSD) containing the α-glucosidase conjugate.

Still another example of the present disclosure provides a pharmaceutical composition for preventing or treating lysosomal storage disease (LSD) containing the imiglucerase conjugate.

In a specific example, the present disclosure provides a pharmaceutical composition wherein the pharmaceutical composition increases transcytosis, bioavailability, tissue distribution, and bone marrow targetability.

Still another aspect of the present disclosure provides a method for preparing an enzyme conjugate, comprising:

(a) a step of linking a therapeutic enzyme for treating lysosomal storage disease (LSD) and a non-peptide polymer; and

(b) a step of linking the linked material from step (a) where the enzyme and the

non-peptide polymer are linked to a biocompatible material capable of increasing the *in vivo* half-life of the enzyme, wherein the enzyme is not α-galactosidase A; wherein the enzyme conjugate has increased bioavailability(BA) compared to the enzyme, to which an immunoglobulin Fc region is not linked; wherein the enzyme conjugate is an enzyme conjugate where a non-peptide polymer linkage moiety is linked to the N-terminus of the immunoglobulin Fc region; and wherein the biocompatible material is selected from the group consisting of a polymer, fatty acid, cholesterol, albumin and a fragment thereof, an albumin-binding material, a polymer of repeating units of particular amino acid sequences, an antibody, an antibody fragment, an FcRn-binding material, an in vivo connective tissue, a nucleotide, fibronectin, transferrin, a saccharide, heparin, and elastin.

In one example, the present disclosure provides a method for preparing an enzyme conjugate, including:

(a) a step of linking a therapeutic enzyme for treating lysosomal storage disease (LSD) and a non-peptide polymer; and

(b) a step of linking the linked material, where the enzyme and the non-peptide polymer are linked to a biocompatible material capable of increasing the *in vivo* half-life of the enzyme.

In a specific example, the present disclosure provides a method for preparing an enzyme conjugate, wherein the enzyme is selected from the group consisting of β-glucosidase, β-galactosidase, galactose-6-sulfatase, acid ceramidase, acid sphingomyelinase, galactocerebrosidase, arylsulfatase A, β-hexosaminidase A, β-hexosaminidase B, heparan N-sulfatase, α-D-mannosidase, β-glucuronidase, N-acetylgalactosamine-6 sulfatase, lysosomal acid lipase, α-N-acetyl-D-glucosaminidase (NAGLU), glucocerebrosidase, butyrylcholinesterase, chitinase, glutamate decarboxylase, lipase, uricase, platelet-activating factor acetylhydrolase, neutral endopeptidase, myeloperoxidase, acetyl-CoA-glucosaminide N-acetyltransferase, N-acetylglucosamine-6-sulfatase, galactosamine 6-sulfatase (GALN), hyaluronidase, α-fucosidase, β-mannosidase, α-neuraminidase (sialidase), N-acetyl-glucosamine-1-phosphotransferase, mucolipin-1, α-N-acetyl-galactosaminidase, N-aspartyl-β-glucosaminidase, LAMP-2, cystinosin, sialin, ceramidase, acid-β-glucosidase, galactosylceramidase, NPC1, cathepsin A, SUMF-1, lysosomal acid lipase (LIPA), and tripeptidyl peptidase 1.

Still another example of the present provides a method for preparing an enzyme conjugate, including:

(a) a step of linking α-galactosidase A for treating lysosomal storage disease (LSD) and a non-peptide polymer; and

(b) a step of linking the linked material, where the α-galactosidase A and the non-peptide polymer are linked to a biocompatible material capable of increasing the *in vivo* half-life of the enzyme.

Still another example of the present disclosure provides a method for preparing an enzyme conjugate, including:

(a) a step of linking arylsulfatase B (ARSB) for treating lysosomal storage disease (LSD)

preparing an enzyme conjugate, wherein the non-peptide polymer is polyethylene glycol.

In still another specific example, the present disclosure provides a method for preparing an enzyme conjugate, wherein the reactive group of the non-peptide polymer of step (a) is selected from the group consisting of an aldehyde group, a maleimide group, and a succinimide derivative.

In still another specific example, the present disclosure provides a method for preparing an enzyme conjugate, wherein the aldehyde group is a propionaldehyde group or butyraldehyde group.

In still another specific example, the present disclosure provides a method for preparing an enzyme conjugate, wherein the succinimide derivative is succinimidyl carboxymethyl, succinimidyl valerate, succinimidyl methylbutanoate, succinimidyl methylpropionate, succinimidyl butanoate, succinimidyl propionate, N-hydroxysuccinimide, or succinimidyl carbonate.

In still another specific example, the present disclosure provides an enzyme conjugate, wherein the non-peptide polymer has an aldehyde group as a reactive group at both ends.

In still another specific example, the present disclosure provides an enzyme conjugate, wherein the non-peptide polymer has an aldehyde group and a maleimide group as a reactive group at both ends, respectively.

In still another specific example, the present disclosure provides an enzyme conjugate, wherein the non-peptide polymer has an aldehyde group and a succinimide group as a reactive group at both ends, respectively.

In still another specific example, the present disclosure provides a method for preparing an enzyme conjugate, wherein the method further includes a step of isolating a linked material, to which a non-peptide polymer linkage moiety is linked to the N-terminus of the enzyme.

Still another aspect of the present disclosure provides a composition for increasing the transcytosis of an enzyme comprising the enzyme conjugate as disclosed herein.Still another aspect of the present disclosure provides a composition for increasing the tissue distribution of an enzyme comprising the enzyme conjugate as disclosed herein.

Still another aspect of the present disclosure provides a use of the enzyme conjugate as disclosed herein in the manufacture of a medicament for treating lysosomal storage disease (LSD)

by increasing the transcytosis of an enzyme.

Still another aspect of the present disclosure provides a use of the enzyme conjugate as disclosed herein in the manufacture of a medicament for treating lysosomal storage disease (LSD) by increasing the tissue distribution of an enzyme.

Still another aspect of the present disclosure provides an enzyme conjugate, wherein α-galactosidase A for treating lysosomal storage disease (LSD) and an immunoglobulin Fc region are linked through a non-peptide polymer linkage moiety, wherein the enzyme conjugate has increased bioavailability(BA) compared to the enzyme, to which an immunoglobulin Fc region is not linked; and wherein the enzyme conjugate is an enzyme conjugate where a non-peptide polymer linkage moiety is linked to the N-terminus of the immunoglobulin Fc region.

Still another aspect of the present disclosure provides a method for preparing an enzyme conjugate, comprising: a) a step of linking α-galactosidase A for treating lysosomal storage disease (LSD) and a non-peptide polymer; and b) a step of linking the linked material from step (a) where the α-galactosidase A and the non-peptide polymer are linked to a biocompatible material capable of increasing the in vivo half-life of the enzyme, wherein the enzyme conjugate has increased bioavailability(BA) compared to the enzyme, to which an immunoglobulin Fc region is not linked; wherein the enzyme conjugate is an enzyme conjugate where a non-peptide polymer linkage moiety is linked to the N-terminus of the immunoglobulin Fc region; and wherein the biocompatible material is selected from the group consisting of a polymer, fatty acid, cholesterol, albumin and a fragment thereof, an albumin-binding material, a polymer of repeating units of particular amino acid sequences, an antibody, an antibody fragment, an FcRn-binding material, an in vivo connective tissue, a nucleotide, fibronectin, transferrin, a saccharide, heparin, and elastin.

[Advantageous Effects of the Invention]

The present invention relates to a therapeutic enzyme conjugate, and specifically to an enzyme conjugate, in which a therapeutic enzyme, a non-peptide polymer linkage moiety, and an immunoglobulin Fc are linked together by covalent bonds, thereby having enhanced transcytosis, *in vivo* bioavailability, tissue distribution, and bone marrow targetability as well as *in vivo* duration of the enzyme. The enzyme conjugate prepared by the present invention can be effectively used for the treatment of lysosomal storage disease (LSD).

[Brief Description of Drawings]

FIG. 1 shows the results of PK experiments for a agalsidase beta conjugate.

FIG. 2 shows the results of *in vitro* enzyme activity for a agalsidase beta conjugate.

a is 0 or natural integer, with the proviso that when a is 2 or higher, each L is independent from each other; and

F is a material capable of increasing the *in vivo* half-life of X.

In still another specific embodiment, the present invention provides a method for preparing an enzyme conjugate represented by the following Formula 1, wherein the method includes:

(a) a step of linking imiglucerase for treating lysosomal storage disease (LSD) and a non-peptide polymer; and

(b) a step of linking the linked material, where the enzyme and a non-peptide polymer are linked, and a biocompatible material capable of increasing the *in vivo* half-life of imiglucerase;

[Formula 1]

X-La-F

wherein:

X is imiglucerase for treating lysosomal storage disease (LSD);

L is a non-peptide polymer;

a is 0 or natural integer, with the proviso that when a is 2 or higher, each L is independent from each other; and

F is a material capable of increasing the *in vivo* half-life of X.

In the present invention, F may be selected from the group consisting of polymer, fatty acid, cholesterol, albumin and a fragment thereof, an albumin-binding material, a polymer of repeating units of particular amino acid sequences, an antibody, an antibody fragment, an FcRn-binding material, an *in vivo* connective tissue, a nucleotide, fibronectin, transferrin, a saccharide, heparin, and elastin, and more specifically, the FcRn-binding material may be an immunoglobulin Fc region, but is not limited thereto.

[CLAIMS]

[Claim 1]

An enzyme conjugate, wherein a therapeutic enzyme for treating lysosomal storage disease (LSD) and an immunoglobulin Fc region are linked through a non-peptide polymer linkage moiety,

wherein the enzyme is not α-galactosidase A;

wherein the enzyme conjugate has increased bioavailability (BA) compared to the enzyme, to which an immunoglobulin Fc region is not linked; and

wherein the enzyme conjugate is an enzyme conjugate where a non-peptide polymer linkage moiety is linked to the N-terminus of the immunoglobulin Fc region.

[Claim 2]

The enzyme conjugate of claim 1, wherein the enzyme is selected from the group consisting of β-glucosidase, β-galactosidase, galactose-6-sulfatase, acid ceramidase, acid sphingomyelinase, galactocerebrosidase, arylsulfatase A, β-hexosaminidase A, β-hexosaminidase B, heparan N-sulfatase, α-D-mannosidase, β-glucuronidase, N-acetylgalactosamine-6 sulfatase, lysosomal acid lipase, α-N-acetyl-D-glucosaminidase (NAGLU), glucocerebrosidase, butyrylcholinesterase, chitinase, glutamate decarboxylase, lipase, uricase, platelet-activating factor acetylhydrolase, neutral endopeptidase, myeloperoxidase, acetyl-CoA-glucosaminide N-acetyltransferase, N-acetylglucosamine-6-sulfatase, galactosamine 6-sulfatase (GALN), hyaluronidase, α-fucosidase, β-mannosidase, α-neuraminidase (sialidase), N-acetyl-glucosamine-1-phosphotransferase, mucolipin-1, α-N-acetyl-galactosaminidase, N-aspartyl-β-glucosaminidase, LAMP-2 (Lysosome-associated membrane protein 2), cystinosin, sialin, ceramidase, acid-β-glucosidase, galactosylceramidase, NPC1 (Niemann-Pick disease, type C1), cathepsin A, SUMF-1 (Sulfatase-modifying factor 1), lysosomal acid lipase (LIPA), tripeptidyl peptidase 1, arylsulfatase B (ARSB), iduronidase, α-glucosidase and imiglucerase.

[Claim 3]

The enzyme conjugate of claim 1, wherein the enzyme is selected from the group consisting of arylsulfatase B (ARSB), iduronidase, α-glucosidase and imiglucerase.

[Claim 4]

The enzyme conjugate according to any one of claim 1 to 3, wherein the lysosomal storage disease is selected from the group consisting of mucopolysaccharidosis (MPS), glycogen storage disease, and sphingolipidosis.

[Claim 5]

The enzyme conjugate of claim 4, wherein the mucopolysaccharidosis (MPS) is selected from the group consisting of mucopolysaccharidosis I (MPS I) and mucopolysaccharidosis VI (MPS VI).

[Claim 6]

The enzyme conjugate of claim 4, wherein the glycogen storage disease is Pompe disease.

[Claim 7]

The enzyme conjugate of claim 4, wherein the sphingolipidosis is Gaucher's disease.

[Claim 8]

The enzyme conjugate according to any one of claims 1 to 7, wherein the enzyme conjugate has increased transcytosis and bioavailability (BA) compared to the enzyme, to which an immunoglobulin Fc region is not linked.

[Claim 9]

The enzyme conjugate of claim 8, wherein the transcytosis is mediated by binding between an immunoglobulin Fc region and a neonatal Fc receptor (FcRn).

[Claim 10]

The enzyme conjugate according to any one of claims 1 to 7, wherein the enzyme conjugate has an increased tissue distribution compared to the enzyme, to which an immunoglobulin Fc region is not linked.

[Claim 11]

The enzyme conjugate of claim 10, wherein the enzyme conjugate has an increased bone marrow targetability compared to the enzyme, to which an immunoglobulin Fc region is not linked.

[Claim 12]

The enzyme conjugate according to any one of claims 1 to 7, wherein the immunoglobulin Fc region is aglycosylated.

[Claim 13]

The enzyme conjugate according to any one of claims 1 to 7, wherein the immunoglobulin Fc region comprises one to four domains selected from the group consisting of CH1, CH2, CH3, and CH4 domains.

[Claim 14]

The enzyme conjugate according to any one of claims 1 to 7, wherein the immunoglobulin Fc region comprises a hinge region.

[Claim 15]

The enzyme conjugate according to any one of claims 1 to 7, wherein the immunoglobulin Fc region is an immunoglobulin Fc fragment derived from IgG, IgA, IgD, IgE, or IgM.

[Claim 16]

The enzyme conjugate according to any one of claims 1 to 7, wherein each domain of the immunoglobulin Fc region is a hybrid of domains having different origins derived from the immunoglobulins selected from the group consisting of IgG, IgA, IgD, IgE, and IgM.

[Claim 17]

The enzyme conjugate according to any one of claims 1 to 7, wherein the immunoglobulin Fc region is a dimer or multimer consisting of single-chain immunoglobulins composed of domains of the same origin.

[Claim 18]

The enzyme conjugate according to any one of claims 1 to 7, wherein the immunoglobulin Fc regionis an IgG4 Fc fragment.

[Claim 19]

The enzyme conjugate of claim 18, wherein the immunoglobulin Fc region is a human aglycosylated IgG4 Fc fragment.

[Claim 20]

The enzyme conjugate according to any one of claims 1 to 7, wherein the enzyme conjugate is an enzyme conjugate where a non-peptide polymer linkage moiety is linked to the N-terminus of the enzyme.

[Claim 21]

A pharmaceutical composition for preventing or treating lysosomal storage disease (LSD) comprising the enzyme conjugate of any one of claims 1 to 3.

[Claim 22]

The pharmaceutical composition of claim 21, wherein the enzyme conjugate is selected from the group consisting of arylsulfatase B (ARSB), iduronidase, α-glucosidase and imiglucerase.

[Claim 23]

The pharmaceutical composition according to claim 21 or 22, wherein the pharmaceutical composition increases transcytosis, bioavailability, tissue distribution, and bone marrow targetability.

[Claim 24]

A method for preparing an enzyme conjugate, comprising:

(a) a step of linking a therapeutic enzyme for treating lysosomal storage disease (LSD) and a non-peptide polymer; and

(b) a step of linking the linked material from step (a) where the enzyme and the non-peptide polymer are linked to a biocompatible material capable of increasing the *in vivo* half-life of the enzyme,

wherein the enzyme is not α-galactosidase A;

wherein the enzyme conjugate has increased bioavailability(BA) compared to the enzyme, to which an immunoglobulin Fc region is not linked;

wherein the enzyme conjugate is an enzyme conjugate where a non-peptide polymer linkage moiety is linked to the N-terminus of the immunoglobulin Fc region; and

wherein the biocompatible material is selected from the group consisting of a polymer, fatty acid, cholesterol, albumin and a fragment thereof, an albumin-binding material, a polymer of repeating units of particular amino acid sequences, an antibody, an antibody fragment, an FcRn-binding material, an in vivo connective tissue, a nucleotide, fibronectin, transferrin, a saccharide, heparin, and elastin.

[Claim 25]

The method of claim 24, wherein the enzyme is selected from the group consisting of β-glucosidase, β-galactosidase, galactose-6-sulfatase, acid ceramidase, acid sphingomyelinase, galactocerebrosidase, arylsulfatase A, β-hexosaminidase A, β-hexosaminidase B, heparan N-sulfatase, α-D-mannosidase, β-glucuronidase, N-acetylgalactosamine-6 sulfatase, lysosomal acid lipase, α-N-acetyl-D-glucosaminidase (NAGLU), glucocerebrosidase, butyrylcholinesterase, chitinase, glutamate decarboxylase, lipase, uricase, platelet-activating factor acetylhydrolase, neutral endopeptidase, myeloperoxidase, acetyl-CoA-glucosaminide N-acetyltransferase, N-acetylglucosamine-6-sulfatase, galactosamine 6-sulfatase (GALN), hyaluronidase, α-fucosidase, β-mannosidase, α-neuraminidase (sialidase), N-acetyl-glucosamine-1-phosphotransferase, mucolipin-1, α-N-acetyl-galactosaminidase, N-aspartyl-β-glucosaminidase, LAMP-2 (Lysosome-associated membrane protein 2), cystinosin, sialin, ceramidase, acid-β-glucosidase, galactosylceramidase, NPC1 (Niemann-Pick disease, type C1), cathepsin A, SUMF-1 (Sulfatase-modifying factor 1), lysosomal acid lipase (LIPA), and tripeptidyl peptidase 1.

[Claim 26]

The method of claim 24, wherein the enzyme conjugate represented by the following

Formula 1,

[Formula 1]

X-La-F

wherein:

X is arylsulfatase B (ARSB), iduronidase, α-glucosidase or imiglucerase for treating lysosomal storage disease (LSD);

L is a non-peptide polymer;

a is 0 or natural integer, with the proviso that when a is 2 or higher, each L is independent from each other; and

F is a material capable of increasing the *in vivo* half-life of X,

wherein F is selected from the group consisting of a polymer, fatty acid, cholesterol, albumin and a fragment thereof, an albumin-binding material, a polymer of repeating units of particular amino acid sequences, an antibody, an antibody fragment, an FcRn-binding material, an in vivo connective tissue, a nucleotide, fibronectin, transferrin, a saccharide, heparin, and elastin.

[Claim 27]

The method of claim 24, wherein the enzyme is selected from the group consisting of arylsulfatase B (ARSB), iduronidase, α-glucosidase and imiglucerase.

[Claim 28]

The method according to claim 26, wherein F is an FcRn-binding material.

[Claim 29]

The method of claim 28, wherein the FcRn-binding material is an immunoglobulin Fc region.

[Claim 30]

The method according to any of claims 24 to 27, wherein the non-peptide polymer is selected from the group consisting of polyethylene glycol, polypropylene glycol, an ethylene glycol/propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, a polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid

polymer, chitin, hyaluronic acid, and a combination thereof.

[Claim 31]

The method of claim 30, wherein the non-peptide polymer is polyethylene glycol.

[Claim 32]

The method according to any of claims 24 to 27, wherein a reactive group of the non-peptide polymer of step (a) is selected from the group consisting of an aldehyde group, a maleimide group, and a succinimide derivative.

[Claim 33]

The method of claim 32, wherein the aldehyde group is a propionaldehyde group or butyraldehyde group.

[Claim 34]

The method of claim 32, wherein the succinimide derivative is succinimidyl carboxymethyl, succinimidyl valerate, succinimidyl methylbutanoate, succinimidyl methylpropionate, succinimidyl butanoate, succinimidyl propionate, N-hydroxysuccinimide, or succinimidyl carbonate.

[Claim 35]

The method of claim 32, wherein the non-peptide polymer has an aldehyde group as the reactive group at both ends.

[Claim 36]

The method of claim 32, wherein the non-peptide polymer has an aldehyde group and the maleimide group as a reactive group at both ends, respectively.

[Claim 37]

The method of claim 32, wherein the non-peptide polymer has an aldehyde group and the succinimide group as a reactive group at both ends, respectively.

[Claim 38]

The method according to any of claims 24 to 27, further comprising a step of isolating the linked material, to which a non-peptide polymer linkage moiety is linked to the N-terminus of the enzyme.

[Claim 39]

A composition for increasing the transcytosis of an enzyme comprising the enzyme conjugate of any one of claims 1 to 3.

[Claim 40]

A composition for increasing the tissue distribution of an enzyme comprising the enzyme conjugate of any one of claims 1 to 3.

[Claim 41]

Use of the enzyme conjugate of any one of claims 1 to 3 in the manufacture of a medicament for treating lysosomal storage disease (LSD) by increasing the transcytosis of an enzyme.

[Claim 42]

Use of the enzyme conjugate of any one of claims 1 to 3 in the manufacture of a medicament for treating lysosomal storage disease (LSD) by increasing the tissue distribution of an enzyme.

[Claim 43]

An enzyme conjugate, wherein α-galactosidase A for treating lysosomal storage disease (LSD) and an immunoglobulin Fc region are linked through a non-peptide polymer linkage moiety,

wherein the enzyme conjugate has increased bioavailability(BA) compared to the enzyme, to which an immunoglobulin Fc region is not linked; and

wherein the enzyme conjugate is an enzyme conjugate where a non-peptide polymer linkage moiety is linked to the N-terminus of the immunoglobulin Fc region.

[Claim 44]

The enzyme conjugate of claim 43, wherein the sphingolipidosis is Fabry disease.

[Claim 45]

A pharmaceutical composition for preventing or treating lysosomal storage disease (LSD) comprising the enzyme conjugate of claim 43.

[Claim 46]

A method for preparing an enzyme conjugate, comprising:

a) a step of linking α-galactosidase A for treating lysosomal storage disease (LSD) and a non-peptide polymer; and

b) a step of linking the linked material from step (a) where the α-galactosidase A and the non-peptide polymer are linked to a biocompatible material capable of increasing the in vivo half-life of the enzyme,

wherein the enzyme conjugate has increased bioavailability(BA) compared to the enzyme, to which an immunoglobulin Fc region is not linked;

wherein the enzyme conjugate is an enzyme conjugate where a non-peptide polymer linkage moiety is linked to the N-terminus of the immunoglobulin Fc region; and

wherein the biocompatible material is selected from the group consisting of a polymer, fatty acid, cholesterol, albumin and a fragment thereof, an albumin-binding material, a polymer of repeating units of particular amino acid sequences, an antibody, an antibody fragment, an FcRn-binding material, an in vivo connective tissue, a nucleotide, fibronectin, transferrin, a saccharide, heparin, and elastin.

[Claim 47]

The method of claim 46, wherein the enzyme conjugate represented by the following Formula 1,

[Formula 1]

X-La-F

wherein:

X is α-galactosidase A for treating lysosomal storage disease (LSD);

L is a non-peptide polymer;

a is 0 or natural integer, with the proviso that when a is 2 or higher, each L is independent from each other; and

F is a material capable of increasing the in vivo half-life of X,

wherein F is selected from the group consisting of a polymer, fatty acid, cholesterol, albumin and a fragment thereof, an albumin-binding material, a polymer of repeating units of particular amino acid sequences, an antibody, an antibody fragment, an FcRn-binding material, an in vivo connective tissue, a nucleotide, fibronectin, transferrin, a saccharide, heparin, and elastin.

CONJUGATE OF THERAPEUTIC ENZYMES

[ABSTRACT]

The present invention relates to a conjugate in which an immunoglobulin Fc region is linked to therapeutic enzymes through a non-peptide polymer linkage moiety, and more specifically, to a conjugate in which a non-peptide polymer linkage moiety is specifically linked to an immunoglobulin Fc, a method of preparing the same, and a composition comprising the same.

[FIG. 1]