

ANNEX A

Defendant's Claim Amendments - EP (UK) 2 797 622 B1

Conditional Amendment A1 / A2 – list of positions

Conditional Amendment B – identity of comparator

Conditional Amendment C – identity of preservative

Claims

Conditional Amendment A1	Conditional Amendment A2
<p>1. A modified PH20 polypeptide, comprising an amino acid replacement in an unmodified PH20 polypeptide, wherein:</p> <p>the unmodified PH20 polypeptide consists of the sequence of amino acids set forth in any of SEQ ID NOS: 3, 7 or 32-66;</p> <p>the amino acid replacement is at an amino acid position corresponding to a position 10, 12, 20, 22, 26, 34, 36, 46, 50, 52, 58, 68, 70, 74, 82, 83, 84, 86, 97, 127, 138, 142, 143, 144, 166, 169, 174, 193, 195, 196, 204, 205, 206, 213, 234, 237, 238, 240, 249, 261, 267, 277, 279, 291, 309, 310, 314, 315, 317, 318, 347, 367, 375, 376, 399, 401, 407, 416, 419, 421, 431, 433, 439, 440, 443 or 445 with reference to amino acid positions set forth in SEQ ID NO:3, with the proviso that if the modified PH20 polypeptide includes only a single amino acid replacement, the replacement does not correspond to amino acid replacements V12A or E249Q with reference to amino acid positions set forth in SEQ ID NO:3;</p> <p>corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide set forth in SEQ ID NO:3;</p> <p>the modified PH20 polypeptide exhibits increased stability in the presence of m-cresol a-phenolic preservative(s) compared to the unmodified PH20 polypeptide not containing the amino acid replacement;</p> <p>increased stability is manifested as increased hyaluronidase activity in the presence of m-cresol the-phenolic-preservative(s) compared to the hyaluronidase activity of the unmodified PH20 polypeptide not containing the amino acid replacement in the presence of m-cresol the-same phenolic-preservative(s), and the activity is compared under the same conditions.</p>	<p>1. A modified PH20 polypeptide, comprising an amino acid replacement in an unmodified PH20 polypeptide, wherein:</p> <p>the unmodified PH20 polypeptide consists of the sequence of amino acids set forth in any of SEQ ID NOS: 3, 7 or 32-66;</p> <p>the amino acid replacement is at an amino acid position corresponding to a position 10, 12, 20, 22, 26, 34, 36, 46, 50, 52, 58, 68, 70, 74, 82, 83, 84, 86, 97, 127, 138, 142, 143, 144, 166, 169, 174, 193, 195, 196, 204, 205, 206, 213, 234, 237, 238, 240, 249, 261, 267, 277, 279, 291, 309, 310, 314, 315, 317, 318, 347, 367, 375, 376, 399, 401, 407, 416, 419, 421, 431, 433, 439, 440, 443 or 445 with reference to amino acid positions set forth in SEQ ID NO:3, with the proviso that if the modified PH20 polypeptide includes only a single amino acid replacement, the replacement does not correspond to amino acid replacements V12A or E249Q with reference to amino acid positions set forth in SEQ ID NO:3;</p> <p>corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide set forth in SEQ ID NO:3;</p> <p>the modified PH20 polypeptide exhibits increased stability in the presence of m-cresol a-phenolic preservative(s) compared to the unmodified PH20 polypeptide not containing the amino acid replacement;</p> <p>increased stability is manifested as increased hyaluronidase activity in the presence of m-cresol the-phenolic-preservative(s) compared to the hyaluronidase activity of the unmodified PH20 polypeptide not containing the amino acid replacement in the presence of m-cresol the-same phenolic-preservative(s), and the activity is compared under the same conditions.</p>
<p>2. The modified PH20 polypeptide of claim 1, wherein the preservative is a phenolic preservative that is m-cresol, phenol, or m-cresol and phenol.</p>	<p>2. The modified PH20 polypeptide of claim 1, wherein the preservative is a phenolic preservative that is m-cresol, phenol, or m-cresol and phenol.</p>
<p>3. The modified PH20 polypeptide of claim 1 or claim 2, comprising at least one amino acid replacement selected from among replacement with:</p> <p>T at a position corresponding to position 52, K at a</p>	<p>3. The modified PH20 polypeptide of claim 1 or claim 2, comprising at least one amino acid replacement selected from among replacement with:</p> <p>T at a position corresponding to position 52, K at a</p>

<p>position corresponding to position 58, R at a position corresponding to position 58, V at a position corresponding to position 83, P at a position corresponding to position 204, M at a position corresponding to position 234, A at a position corresponding to position 261, and Q at a position corresponding to position 310, and H at a position corresponding to position 421, with reference to amino acid residue positions set forth in SEQ ID NO:3.</p>	<p>position corresponding to position 58, R at a position corresponding to position 58, V at a position corresponding to position 83, P at a position corresponding to position 204, M at a position corresponding to position 234, A at a position corresponding to position 261, and Q at a position corresponding to position 310, and H at a position corresponding to position 421, with reference to amino acid residue positions set forth in SEQ ID NO:3.</p>
<p>4. The modified PH20 polypeptide of any of claims 1-3, comprising replacement with P at a position corresponding to position 204 in a PH20 polypeptide with reference to amino acid residue positions set forth in SEQ ID NO:3.</p>	
<p>5. The modified PH20 polypeptide of any of claims 1-4, comprising up to 5 amino acid replacements.</p>	
<p>6. A modified polypeptide of any of claims 2-4, comprising replacement with P at a position corresponding to position 204 in a PH20 polypeptide and up to 5 additional amino acid replacements, wherein the amino acid replacement(s) is/are in an unmodified PH20 polypeptide that consists of the sequence of amino acids set forth in SEQ ID NO: 3.</p>	
<p>7. The modified PH20 polypeptide of any of claims 1-6 that is glycosylated.</p>	
<p>8. The modified PH20 polypeptide of any of claims 1-7 that is modified by conjugation to a polymer, for example dextran or PEG, and/or is conjugated to a moiety selected from among a multimerization domain, toxin, detectable label or drug.</p>	
<p>9. A nucleic acid molecule, encoding a modified PH20 polypeptide of any of claims 1-8.</p>	
<p>10. A vector, comprising the nucleic acid molecule of claim 9.</p>	
<p>11. A cell, comprising the vector of claim 10.</p>	
<p>12. A method of producing a modified PH20 polypeptide, comprising:</p> <p style="padding-left: 40px;">introducing the nucleic acid of claim 9 or the vector of claim 10 into a cell capable of incorporating N-linked sugar moieties into the polypeptide; and</p> <p style="padding-left: 40px;">culturing the cell under conditions whereby an encoded modified PH20 polypeptide is produced and secreted by the cell.</p>	
<p>13. The method of claim 12 further comprising recovering the expressed polypeptide.</p>	
<p>14. A pharmaceutical composition, comprising a modified PH20 polypeptide of any of claims 1-8 in a pharmaceutically acceptable excipient.</p>	
<p>15. The pharmaceutical composition of claim 14, comprising a therapeutically active agent.</p>	
<p>16. The pharmaceutical composition of claim 15, wherein the therapeutic agent is an insulin.</p>	
<p>17. The pharmaceutical composition of claim 15, wherein the therapeutic agent is an insulin that is a fast-acting insulin.</p>	
<p>18. The pharmaceutical composition of claim 15, wherein the therapeutic agent is a fast-acting insulin that is a regular insulin or is an insulin analog.</p>	
<p>19. A pharmaceutical composition of any of claims 14-18 for use in treating a hyaluronan-associated disease or disorder, or for use in treating diabetes, or for use in delivering a therapeutic agent to a subject.</p>	