115 Gly<sup>8</sup>Asp<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>37</sup>-(GAB-GHex) GLP-1(7-37); Gly<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>39</sup>-(GAB-GHex) GLP-1(7-38); Gly<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-38); Gly<sup>8</sup>Asp<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-38); Gly<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-38); Gly<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GHex) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GHex) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-37); Gly<sup>8</sup>Asp<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-38); Gly<sup>8</sup>Asp<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-36); Val<sup>8</sup>Glu<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-36); Val<sup>8</sup>Glu<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-36); Val<sup>8</sup>Glu<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-36); Val<sup>8</sup>Glu<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-36); Val<sup>8</sup>Glu<sup>37</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-36); Val<sup>8</sup>Glu<sup>37</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-36); Val<sup>8</sup>Glu<sup>37</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-36); Val<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-Ser<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GHex) GLP-1(7-36); Ser<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GHex) GLP-1(7-36)amide; Ser<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-36)amide; Ser<sup>8</sup>Asp<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>37</sup>-(GAB-GHex) GLP-1(7-37); 45 Ser<sup>8</sup>Asp<sup>37</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>38</sup>-(GAB-GHex) GLP-1(7-38); Ser<sup>8</sup>Asp<sup>38</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>30</sup>-(GAB-GHex) GLP-1(7-39); Thr<sup>8</sup>Glu<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup>Glu<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>37</sup>-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup>Glu<sup>37</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>38</sup>-(GAB-GHex) GLP-1(7-38); Thr<sup>8</sup>Glu<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>39</sup>-(GAB-GHex) GLP-1(7-38); Thr<sup>8</sup>Glu<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>39</sup>-(GAB-GHex) GLP-1(7-38); Thr $^{8}$ Glu<sup>35</sup>Arg<sup>26</sup>,  $^{34}$ Lys<sup>36</sup>-(GAB-GHex) GLP-1(7-36); Thr $^{8}$ Glu<sup>35</sup>Arg<sup>26</sup>,  $^{34}$ Lys<sup>36</sup>-(GAB-GHex) GLP-1(7-36)amide; Thr<sup>8</sup>Glu<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GHex) GLP-1(7-36)amide; Thr<sup>8</sup>Glu<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>37</sup>-(GAB-GHex) GLP-1(7-37); 55 Thr<sup>8</sup>Glu<sup>37</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>38</sup>-(GAB-GHex) GLP-1(7-38); Thr<sup>8</sup>Glu<sup>38</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GHex) GLP-1(7-39); Thr<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup>Asp<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup>Asp<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>37</sup>-(GAB-GHex) GLP-1(7-37); 60 Thr<sup>8</sup>Asp<sup>38</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>39</sup>-(GAB-GHex) GLP-1(7-38); Thr<sup>8</sup>Asp<sup>38</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>39</sup>-(GAB-GHex) GLP-1(7-39); Thr<sup>8</sup>Asp<sup>38</sup>Arg<sup>26, 34</sup>Lys<sup>39</sup>-(GAB-GHex) GLP-1(7-39); Thr Asp Arg Lys -(GAB-GHex) GLP-1(7-39); Thr<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GHex) GLP-1(7-36)amide; Thr<sup>8</sup>Asp<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>37</sup>-(GAB-GHex) GLP-1(7-37); 65 Thr<sup>8</sup>Asp<sup>37</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>38</sup>-(GAB-GHex) GLP-1(7-38); Thr<sup>8</sup>Asp<sup>38</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>39</sup>-(GAB-GHex) GLP-1(7-39);

**116** Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36)amide; Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-37); Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-38); Gly<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>17</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>17</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>17</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-38); Gly<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-38); Gly<sup>8</sup>Asp<sup>17</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-38); GAB-GHex) GLP-1(7-36)amide; Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-36); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-37); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-38); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-38); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-38); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-38); Arg<sup>26, 34</sup>Lys<sup>3</sup>-(GAB-GHex) GLP-1(7-38); Arg<sup>36</sup>, Arg<sup>36</sup>,

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(7-38);  $Gly^8Asp^{19}Arg^{26}$ ,  ${}^{34}Lys^{23}$ -(GAB-GHex) GLP-1(7-36);  $Gly^8Asp^{19}Arg^{26}$ ,  ${}^{34}Lys^{23}$ -(GAB-GHex) GLP-1(7-36);  $Gly^8Asp^{19}Arg^{26}$ ,  ${}^{34}Lys^{23}$ -(GAB-GHex) GLP-1(7-36);  $Gly^8Asp^{17}Arg^{26}$ ,  ${}^{34}Lys^{23}$ -(GAB-GHex) GLP-1(7-36);  $Gly^8Asp^{19}Arg^{26}$ ,  ${}^{34}Lys^{23}$ -(GAB-GHex) GLP-1(7-37);  $Gly^8Asp^{10}Arg^{26}$ ,  ${}^{34}Lys^{23}$ -(GAB-GHex) GLP-1(7-38);  $Gly^8Asp^{17}Arg^{26}$ ,  ${}^{34}Lys^{23}$ -(GAB-GHex) GLP-1(7-38);  $Gly^8Asp^{17}Arg^{26}$ ,  ${}^{34}Lys^{23}$ -(GAB-GHex) GLP-1(7-38);  $Arg^{26}$ ,  ${}^{34}Lys^{27}$ -(GAB-GHex) GLP-1(7-36);  $Arg^{26}$ ,  ${}^{34}Lys^{27}$ -(GAB-GHex) GLP-1(7-36)amide;  $Arg^{26}$ ,  ${}^{34}Lys^{27}$ -(GAB-GHex) GLP-1 (7-38);  $Gly^8Asp^{19}Arg^{26}$ ,  ${}^{34}Lys^{27}$ -(GAB-GHex) GLP-1(7-36);  $Gly^8Asp^{19}Arg^{26}$ ,  ${}^$ 

Val<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Val<sup>18</sup>Asp<sup>17</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Val<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36)amide; Val<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36)amide; Val<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-37); Val<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-38); Val<sup>8</sup>Asp<sup>17</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-38); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-36); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-37); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-38); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-38); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-38); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) Arg<sup>26, 34</sup>Lys<sup>3</sup>-(GAB-GHex) Arg<sup>36</sup>-(GAB-GHex) Arg<sup>36</sup>-(GAB-GHe

 $\begin{array}{l} \mbox{$(7-38)$;} \\ \mbox{Val}^8 A {\rm sp}^{19} A {\rm rg}^{26, 34} L {\rm ys}^{23} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-36)$; \\ \mbox{Val}^8 A {\rm sp}^{19} A {\rm rg}^{26, 34} L {\rm ys}^{23} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-36)$; \\ \mbox{Val}^8 A {\rm sp}^{19} A {\rm rg}^{26, 34} L {\rm ys}^{23} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-36)$ amide; \\ \mbox{Val}^8 A {\rm sp}^{19} A {\rm rg}^{26, 34} L {\rm ys}^{23} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-36)$ amide; \\ \mbox{Val}^8 A {\rm sp}^{19} A {\rm rg}^{26, 34} L {\rm ys}^{23} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-36)$ amide; \\ \mbox{Val}^8 A {\rm sp}^{19} A {\rm rg}^{26, 34} L {\rm ys}^{23} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-38)$; \\ \mbox{Val}^8 A {\rm sp}^{17} A {\rm rg}^{26, 34} L {\rm ys}^{23} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-38)$; \\ \mbox{Val}^{26, 34} L {\rm ys}^{27} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-36)$; \\ \mbox{Arg}^{26, 34} L {\rm ys}^{27} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-36)$; \\ \mbox{Arg}^{26, 34} L {\rm ys}^{27} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-36)$; \\ \mbox{GLP} - 1(7-37)$; \\ \mbox{Arg}^{26, 34} L {\rm ys}^{27} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-38)$; \\ \mbox{GHex}) \ {\rm GLP} - 1(7-37)$; \\ \mbox{Arg}^{26, 34} L {\rm ys}^{27} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-38)$; \\ \mbox{GHex}) \ {\rm GLP} - 1(7-37)$; \\ \mbox{Arg}^{26, 34} L {\rm ys}^{27} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-38)$; \\ \mbox{Arg}^{26, 34} L {\rm ys}^{27} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-37)$; \\ \mbox{Arg}^{26, 34} L {\rm ys}^{27} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-37)$; \\ \mbox{Arg}^{26, 34} L {\rm ys}^{27} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-37)$; \\ \mbox{Arg}^{26, 34} L {\rm ys}^{27} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-38)$; \\ \mbox{Arg}^{26, 34} L {\rm ys}^{27} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-38)$; \\ \mbox{Arg}^{26, 34} L {\rm ys}^{27} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-38)$; \\ \mbox{Arg}^{26, 34} L {\rm ys}^{27} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-38)$; \\ \mbox{Arg}^{26, 34} L {\rm ys}^{27} - ({\rm GAB} - {\rm GHex}) \ {\rm GLP} - 1(7-38)$; \\ \mbox{Arg}^{26, 34} L {\rm y$ (7-38);

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(7-38); Val<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>27</sup>-(GAB-GHex) GLP-1(7-36); Val<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>27</sup>-(GAB-GHex) GLP-1(7-36); Val<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>27</sup>-(GAB-GHex) GLP-1(7-36)amide; Val<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>27</sup>-(GAB-GHex) GLP-1(7-36)amide; Val<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>27</sup>-(GAB-GHex) GLP-1(7-37); Val<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>27</sup>-(GAB-GHex) GLP-1(7-38); Val<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>27</sup>-(GAB-GHex) GLP-30 1(7-38); Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-37); Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-37); Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-37); Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-37); Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-38); (7-38);

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117/ Ser<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Ser<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Ser<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36)amide; Ser<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36)amide; Ser<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-37); 5 Ser<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-38); Ser<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-38); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-36); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-36)amide; Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-37); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1 10 (7-38):

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 $Ser^8Asp^{19}Arg^{26}$ ,  ${}^{34}Lys^{27}$ -(GAB-GHex) GLP-1(7-36); Ser<sup>8</sup>Asp^{17}Arg^{26},  ${}^{34}Lys^{27}$ -(GAB-GHex) GLP-1(7-36); Ser<sup>8</sup>Asp^{19}Arg^{26},  ${}^{34}Lys^{27}$ -(GAB-GHex) GLP-1(7-36)amide; 25 Ser<sup>8</sup>Asp<sup>17</sup>Arg<sup>26, 34</sup>Lys<sup>27</sup>-(GAB-GHex) GLP-1(7-36)amide; Ser<sup>7</sup>Asp<sup>-7</sup>Arg<sup>2-6</sup>, <sup>34</sup>Lys<sup>2-7</sup>-(GAB-GHex) GLP-1(7-36)amide; Ser<sup>8</sup>Asp<sup>19</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>27</sup>-(GAB-GHex) GLP-1(7-37); Ser<sup>8</sup>Asp<sup>19</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>27</sup>-(GAB-GHex) GLP-1(7-38); Ser<sup>8</sup>Asp<sup>17</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>27</sup>-(GAB-GHex) GLP-1(7-38); Arg<sup>26</sup>, <sup>34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Arg<sup>26</sup>, <sup>34</sup>Lys<sup>18</sup>- 30 (GAB-GHex) GLP-1(7-36)amide; Arg<sup>26</sup>, <sup>34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-37); Arg<sup>26</sup>, <sup>34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-38); Arg<sup>26</sup>, <sup>34</sup>Lys<sup>18</sup>-(38); Arg<sup>26</sup>

(7-38);

Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup>Asp<sup>17</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36); 35 Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36)amide; Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-36)amide; Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-37); Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-38); Thr<sup>8</sup>Asp<sup>17</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-38); Thr<sup>8</sup>Asp<sup>17</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-38); Thr<sup>8</sup>Asp<sup>17</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GHex) GLP-1(7-38); (GAB-GHex) GLP-1(7-36)amide; Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-37); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-38).

(7-38):

Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GHex) GLP-1(7-36); 45

Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-36); Arg<sup>26. 34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36);  $\operatorname{Arg}^{26}\operatorname{Lys}^{34}$ -(GAB-GOct) GLP-1(7-36)amide; Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-36)amide; Arg<sup>26</sup>, 65 <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36)amide; Arg<sup>26</sup> Lys<sup>34</sup>-(GAB-GOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-

1(7-37); Arg<sup>26, 34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-38); Arg<sup>26, 34</sup>Lys<sup>38</sup>-(GAB-GOct) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-39); Arg<sup>26, 34</sup>Lys<sup>39</sup>-(GAB-GOct) GLP-1(7-39);

 $Gly^8Arg^{26}Lys^{34}$ -(GAB-GOct) GLP-1(7-36); Gly<sup>8</sup>Arg^{34}Lys^{26}-(GAB-GOct) GLP-1(7-36); Gly<sup>8</sup>Arg^{26},  $^{34}Lys^{36}$ -(GAB-GOct) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GOct) GLP-1(7-36)amide; Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-36)amide; Gly<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36)amide; Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GOct) GLP-1(7-36)amide; Gly<sup>8</sup>Arg<sup>4</sup>Lys<sup>4</sup>-(GAB-GOct) GLP-1(7-36)amide; Gly<sup>8</sup>Arg<sup>4</sup>-(GAB-GOct) GLP-1(7-36)amide; Gly<sup>8</sup>Arg<sup>4</sup>-(GAB-GOct) GLP-1(7-36)amide; Gly<sup>8</sup>Arg<sup>4</sup>-1(7-36)amide; GLP-1(7-36)amide; GLP-1(7-3 

Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GOct) GLP-1(7-36)amide; Val<sup>8</sup>Arg<sup>26</sup>+(SAB-GOct) GLP-1(7-36)amide; Val<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-36)amide; Val<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36)amide; Val<sup>8</sup>Arg<sup>26</sup>+(SAB-GOct) GLP-1(7-36)amide; Val<sup>8</sup>+(SAB-GOct) GLP 1(7-36)amide; Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GOct) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GOct) GLP-1(7-38); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>38</sup>-(GAB-GOct) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup> Lys<sup>34</sup>-(GAB-GOct) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26</sup> Lys<sup>34</sup>-(GAB-GOct) GLP-1(7-39); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26</sup>. Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>39</sup>-(GAB-GOct) GLP-1(7-39); Scr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GOct) GLP-1(7-36); Scr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1 (7-36); Scr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36); Scr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GOct) GLP-1(7-36)amide; Scr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-36)amide; Scr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36)amide; Scr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-37); Scr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-37); Scr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-37); Scr<sup>8</sup>Arg<sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-37); Scr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-37); Scr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-37); Scr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-38); Scr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>38</sup>-(GAB-GOct) GLP-1(7-38); Scr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>38</sup>-(SAB-GOct) GLP-1(7-38); Scr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>38</sup>-(SAB-GOct) GLP-1(7-38); Scr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>38</sup>-(SA Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GOct) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GOct) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>26</sup>,

<sup>1</sup><sup>1</sup><sup>34</sup>Lys<sup>39</sup>-(GAB-GOct) GLP-1(7-39); Gly<sup>8</sup>Glu<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36); Gly<sup>8</sup>Glu<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36)amide; Gly<sup>8</sup>Glu<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>37</sup>-(GAB-GOct) GLP-1(7-37); Clu<sup>8</sup>Glu<sup>37</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>37</sup>-(GAB-GOct) GLP-1(7-38); Gly<sup>8</sup>Glu<sup>37</sup>Arg<sup>26, 34</sup>Lys<sup>38</sup>-(GAB-GOct) GLP-1(7-38); Gly<sup>8</sup>Glu<sup>38</sup>Arg<sup>26, 34</sup>Lys<sup>39</sup>-(GAB-GOct) GLP-1(7-39); Gly<sup>8</sup>Glu<sup>35</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36); Gly<sup>8</sup>Glu<sup>35</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36)amide; Gly<sup>8</sup>Glu<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>37</sup>-(GAB-GOct) GLP-1(7-37);

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Ser<sup>8</sup>Glu<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>37</sup>-(GAB-GOct) GLP-1(7-37); 35 Ser<sup>8</sup>Glu<sup>37</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>38</sup>-(GAB-GOct) GLP-1(7-38); Ser<sup>8</sup>Glu<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>39</sup>-(GAB-GOct) GLP-1(7-39); Ser<sup>8</sup>Glu<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36); Ser<sup>8</sup>Glu<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36); Ser<sup>8</sup>Glu<sup>36</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>37</sup>-(GAB-GOct) GLP-1(7-37); 40 Ser<sup>8</sup>Glu<sup>37</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>39</sup>-(GAB-GOct) GLP-1(7-38); Ser<sup>8</sup>Glu<sup>38</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>39</sup>-(GAB-GOct) GLP-1(7-39); Ser<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36); Ser<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36); Ser<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36); Ser<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>37</sup>-(GAB-GOct) GLP-1(7-36); Ser<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>37</sup>-(GAB-GOct) GLP-1(7-37); 45 Ser<sup>8</sup>Asp<sup>35</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>38</sup>-(GAB-GOct) GLP-1(7-38);

Ser<sup>8</sup>Asp<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>37</sup>-(GAB-GOct) GLP-1(7-37); 45 Ser<sup>8</sup>Asp<sup>37</sup>Arg<sup>26, 34</sup>Lys<sup>38</sup>-(GAB-GOct) GLP-1(7-38); Ser<sup>8</sup>Asp<sup>38</sup>Arg<sup>26, 34</sup>Lys<sup>39</sup>-(GAB-GOct) GLP-1(7-39); Ser<sup>8</sup>Asp<sup>35</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36); Ser<sup>8</sup>Asp<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>37</sup>-(GAB-GOct) GLP-1(7-36); Ser<sup>8</sup>Asp<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>37</sup>-(GAB-GOct) GLP-1(7-37); 50 Ser<sup>8</sup>Asp<sup>37</sup>Arg<sup>26, 34</sup>Lys<sup>38</sup>-(GAB-GOct) GLP-1(7-38); Ser<sup>8</sup>Asp<sup>38</sup>Arg<sup>26, 34</sup>Lys<sup>39</sup>-(GAB-GOct) GLP-1(7-39); Thr<sup>8</sup>Glu<sup>35</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36); Thr<sup>8</sup>Glu<sup>35</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>-(GAB-GOct) GLP-1(7-36);

The Asp  $^{36}$ Arg $^{26}$ ,  $^{34}$ Lys $^{36}$ -(GAB-GOct) GLP-1(7-36)amide; The Asp $^{36}$ Arg $^{26}$ ,  $^{34}$ Lys $^{37}$ -(GAB-GOct) GLP-1(7-36)amide; The Asp $^{36}$ Arg $^{26}$ ,  $^{34}$ Lys $^{37}$ -(GAB-GOct) GLP-1(7-37); 65 The Asp $^{37}$ Arg $^{26}$ ,  $^{34}$ Lys $^{38}$ -(GAB-GOct) GLP-1(7-38); The Asp $^{38}$ Arg $^{26}$ ,  $^{34}$ Lys $^{39}$ -(GAB-GOct) GLP-1(7-39);

 
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 Description

 Gly<sup>6</sup>Glu<sup>3</sup>Arg<sup>2,6,-1</sup>Lys<sup>2,6</sup> (GAB-GOC) GLP-1(7-30); Gly<sup>2</sup>Asp<sup>2</sup>Arg<sup>2,6,-1</sup>Lys<sup>2,6</sup> (GAB-GOC) GLP-1(7-30); Gly<sup>3</sup>Asp<sup>3</sup>Arg<sup>2,6,-1</sup>Lys<sup>2,6</sup>  $\begin{array}{l} \label{eq:value} Val^8 A sp^{19} Arg^{26, \ 34} Lys^{18} - (GAB-GOct) \ GLP-1(7-37); \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{18} - (GAB-GOct) \ GLP-1(7-38); \\ Val^8 A sp^{17} Arg^{26, \ 34} Lys^{18} - (GAB-GOct) \ GLP-1(7-38); \\ Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36); \ Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36); \\ Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36); \\ GAB-GOct) \ GLP-1(7-37); \ Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36); \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36); \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36); \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36); \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36) amide; \\ Val^8 A sp^{19} Arg^{26, \ 34} Lys^{23} - (GAB-GOct) \ GLP-1(7-36)$ Val<sup>8</sup>Asp<sup>17</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>27</sup>-(GAB-GOct) GLP-1(/-36)amide; Val<sup>8</sup>Asp<sup>17</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>27</sup>-(GAB-GOct) GLP-1(7-36)amide; Val<sup>8</sup>Asp<sup>19</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>27</sup>-(GAB-GOct) GLP-1(7-37); Val<sup>8</sup>Asp<sup>19</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>27</sup>-(GAB-GOct) GLP-1(7-38); Val<sup>8</sup>Asp<sup>17</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>27</sup>-(GAB-GOct) GLP-1(7-38); Arg<sup>26</sup>, <sup>34</sup>Lys<sup>18</sup>(GAB-GOct) GLP-1(7-36); Arg<sup>26</sup>, <sup>34</sup>Lys<sup>18</sup>-(GAB-GOct) Arg<sup>26</sup>-(GAB-GOct) Arg<sup>26</sup>-(GAB-GOct) Arg<sup>26</sup>-(GAB-

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Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GOct) GLP-1(7-36)amide; Thr<sup>8</sup>Asp<sup>17</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GOct) GLP-1(7-36)amide; 35 Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GOct) GLP-1(7-37); Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>18</sup>-(GAB-GOct) GLP-1(7-38); Arg<sup>26, 34</sup>Lys<sup>23</sup>(GAB-GOct) GLP-1(7-36); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GOct) GLP-1(7-37); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GOct) GLP-1(7-37); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GOct) GLP-1(7-38); Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GOct) GLP-1(7-36); 

(7-36)amide; Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GLit) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GLit) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>  $^{34}$ Lys<sup>36</sup>-(GAB-GLit) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GLit) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GLit) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>38</sup>-(GAB-GLit) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GLit) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GLit) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GLit) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>26</sup>, 34Lys39-(GAB-GLit) GLP-1(7-39);

Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>-(GAB-GLit) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>-(GAB-GLit) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26</sup>,

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123 124 Gly<sup>8</sup>Asp<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>37</sup>. (GAB-GLii) GLP-1(7-37); Gly<sup>8</sup>Asp<sup>37</sup>Arg<sup>26, 34</sup>Lys<sup>38</sup>. (GAB-GLii) GLP-1(7-38); Gly<sup>8</sup>Asp<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>. (GAB-GLii) GLP-1(7-39); Gly<sup>8</sup>Asp<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>. (GAB-GLii) GLP-1(7-39); Gly<sup>8</sup>Asp<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>. (GAB-GLii) GLP-1(7-30); Gly<sup>8</sup>Asp<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>. (GAB-GLii) GLP-1(7-37); Gly<sup>8</sup>Asp<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>. (GAB-GLii) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>. (GAB-GLii) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>. (GAB-GLii) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>16</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>. (GAB-GLii) GLP-1(7-36); Al<sup>8</sup>Glu<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>. (GAB-GLii) GLP-1(7-36); Al<sup>8</sup>Sa<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>. (GAB-GLii) GLP-1(7-36); Al<sup>8</sup>Asp<sup>36</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>. 
$$\begin{split} & v_1^{ab} a_{sp}^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-37); \\ & z \in Glu^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in Glu^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in Glu^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in Glu^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in Glu^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in Glu^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in Glu^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in Glu^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in Glu^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in Glu^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in Glu^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in Glu^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in Glu^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in Glu^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in A_{sp}^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in A_{sp}^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in A_{sp}^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in A_{sp}^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in A_{sp}^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in A_{sp}^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in A_{sp}^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in A_{sp}^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in A_{sp}^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in A_{sp}^{ab} A_{rg}^{ab} a_{s}^{ab} L_{sp}^{ab} - (GAB-GLi) \ GLP-1(7-30); \\ & z \in A_{sp}^{ab} A_{rg}^{ab$$
Val<sup>8</sup>Asp<sup>37</sup>Arg<sup>26, 34</sup>Lys<sup>38</sup>-(GAB-GLit) GLP-1(7-38); Val<sup>8</sup>Asp<sup>38</sup>Arg<sup>26, 34</sup>Lys<sup>39</sup>-(GAB-GLit) GLP-1(7-39);

Arg<sup>26, 9</sup>Lys<sup>27</sup>-(GAB-GLit) GLP-1(7-36); Arg<sup>26, 9</sup>Lys<sup>27</sup>-(GAB-GLit) GLP-1(7-36) amide;  $Arg^{26, 34}Lys^{27}$ -(GAB-GLit) GLP-1(7-37);  $Arg^{26, 34}Lys^{27}$ -(GAB-GLit) GLP-1(7-38); Gly<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>27</sup>-(GAB-GLit) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>19</sup>Arg^{26, 34}Lys^{27}-(GAB-GLit) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>19</sup>Arg^{26, 34}Lys^{27}-(GAB-GLit) GLP-1(7-36); Gly<sup>8</sup>Asp<sup>19</sup>Arg^{26, 34}Lys^{27}-(GAB-GLit) GLP-1(7-36)amide; Gly<sup>8</sup>Asp<sup>17</sup>Arg^{26, 34}Lys^{27}-(AB-GLit) GLP-1(7-36)Amide; Gly<sup>8</sup>Asp<sup>17</sup>Arg^{26, 34}Lys^{27}-(AB-GLit) GLP-1(7-36)Amide; Gly<sup>8</sup>Asp<sup>17</sup>Arg^{26, 34}Lys^{27}-(AB-GLit) GLP-1(7-36)Amide; Gly<sup>8</sup>Asp<sup>17</sup>Arg^{26, 34}Lys^{27}-(AB-GLit) GLP-1(7-36)Amide; Gly<sup>8</sup>Asp<sup>17</sup>Arg^{26}-36 Amid<sup>8</sup>Asp<sup>17</sup>Arg^{26} Amid

**FRESENIUS EXHIBIT 1020** Page 65 of 129  $\begin{array}{l} Ser^8 A sp^{19} A rg^{26}, \ \ ^{34} Lys^{18} \text{-} (GAB \text{-} GLit) \ \ GLP \text{-} 1(7 \text{-} 37); \\ Ser^8 A sp^{19} A rg^{26}, \ \ ^{34} Lys^{18} \text{-} (GAB \text{-} GLit) \ \ GLP \text{-} 1(7 \text{-} 38); \\ Ser^8 A sp^{17} A rg^{26}, \ \ ^{34} Lys^{18} \text{-} (GAB \text{-} GLit) \ \ GLP \text{-} 1(7 \text{-} 38); \\ A rg^{26}, \ \ ^{36} Lys^{18} \text{-} (GAB \text{-} GLit) \ \ GLP \text{-} 1(7 \text{-} 38); \\ A rg^{26}, \ \ ^{36} Lys^{18} \text{-} (GAB \text{-} GLit) \ \ GLP \text{-} 1(7 \text{-} 38); \\ A rg^{26}, \ \ ^{36} Lys^{18} \text{-} (GAB \text{-} GLit) \ \ GLP \text{-} 1(7 \text{-} 38); \\ A rg^{26}, \ \ ^{36} Lys^{18} \text{-} (GAB \text{-} GLit) \ \ ^{36} Lys^{16} \text{-} (GAB \text{-} GLit) \ \ ^{36} Lys^{18} \text{-} (GAB \text{-} GLit) \ \ ^{36} Lys^{16} \text{-} (GAB \text{-} SLit) \ \ ^{36} Lys^{16} \text$ <sup>34</sup>Lys<sup>23</sup>-(GAB-GLit)-GLP-1 (7-36)

Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GLit) GLP-1(7-36); Arg<sup>26, 34</sup>Lys<sup>23</sup>- 35 (GAB-GLit) GLP-1(7-36)amide; Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GLit) GLP-1(7-37); Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GLit) GLP-1(7-38); Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GLit) GLP-1(7-36); Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GLit) GLP-1(7-36); Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GLit) GLP-1(7-36)amide; 40 Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GLit) GLP-1(7-36)amide; Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GLit) GLP-1(7-37); Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26, 34</sup>Lys<sup>23</sup>-(GAB-GLit) GLP-1(7-37); Thr<sup>8</sup>Asp<sup>19</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>23</sup>-(GAB-GLit) GLP-1(7-38); Thr<sup>8</sup>Asp<sup>17</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>23</sup>-(GAB-GLit) GLP-1(7-38); Arg<sup>26</sup>, <sup>34</sup>Lys<sup>27</sup>-(GAB-GLit) GLP-1(7-36); Arg<sup>26</sup>, <sup>34</sup>Lys<sup>27</sup>- 45

Other preferred derivatives of GLP-1 analogs of the 55 present invention are:

Lys<sup>26, 34</sup>-bis-(Glut-ADod) GLP-1(7-36); Lys<sup>26, 34</sup>-bis-(Glut-ADod) GLP-1(7-37); Lys26, 34-bis-(Glut-ADod) GLP-

Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-ADod) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18, 34</sup>-bis-(Glut-ADod) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-Ser<sup>8</sup> Asp<sup>17</sup> Arg<sup>26</sup>, <sup>34</sup>Lys<sup>24</sup> (GAB-GLi) GLP-1(7-36), Arg<sup>26</sup>, <sup>34</sup>Lys<sup>23</sup>, GAB-GLi) GLP-1(7-36), Arg<sup>26</sup>, <sup>34</sup>Lys<sup>23</sup>, GAB-GLi) GLP-1(7-36), Arg<sup>26</sup>, <sup>34</sup>Lys<sup>23</sup>, GAB-GLi) GLP-1(7-37), Arg<sup>26</sup>, <sup>34</sup>Lys<sup>23</sup>, GAB-GLi) GLP-1(7-36), Arg<sup>26</sup>, <sup>34</sup>Lys<sup>23</sup>, GAB-GLi) GLP-1(7-36), Arg<sup>26</sup>Lys<sup>23</sup>, <sup>34</sup>-bis-(Glut-ADod) GLP-1(7-37), Arg<sup>26</sup>Lys<sup>27</sup>, <sup>34</sup>-bis-(Glut-ADod) GLP-1(7-37), GH<sup>3</sup>Lys<sup>27</sup>, GAB-GLi) GLP-1(7-38), Arg<sup>34</sup>Lys<sup>27</sup>, <sup>26</sup>-bis-(Glut-ADod) GLP-1(7-37), GH<sup>3</sup>Lys<sup>27</sup>, GAB-GLi) GLP-1(7-38), Arg<sup>34</sup>Lys<sup>27</sup>, <sup>26</sup>-bis-(Glut-ADod) GLP-1(7-37), GH<sup>3</sup>Lys<sup>27</sup>, GAB-GLi) GLP-1(7-38), Arg<sup>34</sup>Lys<sup>27</sup>, <sup>34</sup>-bis-(Glut-ADod) GLP-1(7-37), GH<sup>3</sup>Lys<sup>27</sup>, <sup>34</sup>-bis-(Glut-ADod) GLP-1(7-37), GH<sup>3</sup>Lys<sup>37</sup>, <sup>34</sup>-bis-(Glut-ADod) GLP-1(7-37), GH<sup>3</sup>Lys<sup>37</sup>, <sup>34</sup>-bis-( ADod) GLP-1(7-37);  $\operatorname{Arg}^{34}$ Lys<sup>18,26</sup>-bis-(Glut-ADod) GLP-1(7-37);  $\operatorname{Arg}^{26}$ Lys<sup>18, 34</sup>-bis-(Glut-ADod) GLP-1(7-38);

Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glut-ADod) GLP-1(7-36); Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glut-ADod) GLP-1(7-37); Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glut-ADod) GLP-1(7-38); Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glut-ADod) ADD

Abd)  $GLP^{-1}(7-36)$ ,  $Val Lys^{-0}$  -bis-(Glut-Abd)  $GLP^{-1}(7-36)$ ;  $Val^8Arg^{34}Lys^{26}$ ,  $3^6$ -bis-(Glut-Abd)  $GLP^{-1}(7-36)$ ;  $Val^8Arg^{26}Lys^{34,36}$ -bis-(Glut-Abd)  $GLP^{-1}(7-37)$ ;  $Val^8Arg^{34}Lys^{26}$ ,  $3^6$ -bis-(Glut-Abd)  $GLP^{-1}(7-37)$ ;  $Val^8Arg^{34}Lys^{26}$ ,  $3^6$ -bis-(Glut-Abd)  $GLP^{-1}(7-37)$ ; Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-ADod) GLP-1(7-37); Val8Arg34Lys26,37-bis-(Glut-ADod) GLP-1(7-37); Val8Arg26Lys34.38-bis-(Glut-ADod) GLP-1(8-38);

Abd) GLP-1(7-38); Ser Lys --bis-(Ghut-Abd) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>,  ${}^{36}$ -bis-(Ghut-Abd) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Ghut-Abd) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>26</sup>,  ${}^{36}$ -bis-(Ghut-Abd) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Ghut-Abd) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Ghut-Abd) GLP-1(7-37);

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ADod) GLP-1(7-38); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ADod) GLP-Abod) GLP-1(7-56), fill Lys -ols-(Glut-Abod) GLP-1(7-36); 1(7-39) Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-Abod) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Glut-Abod) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Glut-Abod) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Glut-Abod) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-ADod) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glut-ADod) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glut-ADod) GLP-1(7-38); Thr Arg  $^{26}$  Lys  $^{26,38}$ -bis-(Glut-ADod) GLP-1(7-38); Thr Arg  $^{26}$  Lys  $^{34}$  Lys  $^{26,38}$ -bis-(Glut-ADod) GLP-1(7-38); 10 Thr Arg  $^{26}$  Lys  $^{34}$   $^{39}$ -bis-(Glut-ADod) GLP-1(7-39); 10 Thr Arg  $^{26}$  Lys  $^{34}$   $^{39}$ -bis-(Glut-ADod) GLP-1(7-39); 10

Lys<sup>26, 34</sup>-bis-(Glut-ATet) GLP-1(7-39)

Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-ATet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26</sup>, Arg Lys -ois-(Glut-Aret) GLP-1(7-36); Arg  $^{26}$ Lys  $^{36}$ -bis-(Glut-ATet) GLP-1(7-36); Arg  $^{26}$ Lys  $^{34}$ -bis-(Glut-ATet) GLP-1(7-37); Arg  $^{26}$ Lys  $^{34}$ Lys  $^{26}$ ,  $^{36}$ -bis-(Glut-ATet) GLP-1(7-37); 20 Arg  $^{34}$ Lys  $^{26,37}$ -bis-(Glut-ATet) GLP-1(7-37); Arg  $^{26}$ Lys  $^{34}$ . <sup>39</sup>-bis-(Glut-ATet) GLP-1(7-39);  $\operatorname{Arg}^{34}\operatorname{Lys}^{26,39}$ -bis-(Glut-ATet) GLP-1(7-39);  $\operatorname{Arg}^{26,34}\operatorname{Lys}^{36,39}$ -bis-(Glut-ATet) GLP-1(7-39);

1(7-39); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-ATet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18, 25</sup> 26-bis-(Glut-ATet) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-ATet) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glut-ATet) GLP-1 (7-37); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-ATet) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glut-ATet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-ATet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-ATet) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-ATet) GLP-1 (7-36); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glut-ATet) GLP-1(7-36) Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-ATet) GLP-1(7-36) Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-ATet) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glut-ATet) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-ATet) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glut-ATet) GLP-1 35 (7-38); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-ATet) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>23, 26</sup>-bis-(Glut-ATet) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-ATet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-ATet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 34</sup>-bis-(Glut-ATet) GLP-1(7-36); Ar

Arg Lys<sup>27, 26</sup>-bis-(Glut-Afet) GLP-1(7-50); Arg Lys<sup>27, 26</sup>-bis-(Glut-Afet) GLP-13(7-36); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glut-Afet) GLP-1 (7-37); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glut-Afet) GLP-1 (7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-Afet) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-Afet) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-Afet) GLP-1(7-39); Arg<sup>4</sup>Lys<sup>27, 26</sup>-bis-(Glut-Afet) GLP-1(7-30); Arg<sup>4</sup>Lys<sup>27, 36</sup>-bis-(Glut-Afet) GLP-1(7-30); Arg<sup>4</sup>Lys<sup>27, 36</sup>-bis-(Glut-Afet) GLP-1(7-30); Arg<sup>4</sup>Lys<sup>27, 36</sup>-bis-(Glut-Afet) GLP-1(7-30)

Arg<sup>--</sup>Lys <sup>34</sup>-bis-(Glut-ATet) GLP-1(7-39); Arg<sup>-</sup>Lys ATet) GLP-1(7-39); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ATet) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ATet) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ATet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26, 37</sup>-bis-(Glut-AHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26, 39</sup>-bis-(Glut-ATet) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-ATet) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-ATet) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 36</sup>-bis-(Glut-ATet) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 36</sup>-bis-(Glut-ATet) GLP-1(7-37); 50 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 36</sup>-bis-(Glut-ATet) GLP-1(7-37); 50 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 36</sup>-bis-(Glut-ATet) GLP-1(7-37); 50 Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-ATet) GLP-1(7-37); 50 Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glut-ATet) GLP-1(7-37); 50 Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glut-ATet) GLP-1(7-37); 50 Gly<sup>8</sup>Arg<sup>34</sup> 39)

 $Val^8Arg^{26}Lys^{34,36}$ -bis-(Glut-ATet) GLP-1(7-36); Val<sup>8</sup>Arg^{34}Lys^{26, 36}-bis-(Glut-ATet) GLP-1(7-36); 65 Val<sup>8</sup>Arg^{26}Lys^{34,36}-bis-(Glut-ATet) GLP-1(7-37); Val<sup>8</sup>Arg^{34}Lys^{26, 36}-bis-(Glut-ATet) GLP-1(7-37);

Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-ATet) GLP-1(7-37); Val Arg Lys  $^{-015}$ -(Glut-ATet) GLP-1(7-37); Val Arg  $^{26}$ Lys  $^{26,37}$ -bis-(Glut-ATet) GLP-1(7-37); Val Arg  $^{26}$ Lys  $^{34,38}$ -bis-(Glut-ATet) GLP-1(7-38); Val Arg  $^{26}$ Lys  $^{26,38}$ -bis-(Glut-ATet) GLP-1(7-38); Val Arg  $^{26,38}$ -bis-(Glut-ATet) GLP-1(7 <sup>34</sup>Lys<sup>36,38</sup>-bis-(Glut-ATet) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>. <sup>39</sup>-bis-(Glut-ATet) GLP-1(7-39); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glut-ATet) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glut-ATet) GLP-1(7-39); Ser<sup>8</sup>Lys<sup>26,34</sup>=bis-(Glut-ATet) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ATet) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ATet) GLP-1(7-38); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ATet) GLP-1(7-39) Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-ATet) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glut-ATet) GLP-1(7-37); Ser<sup>8</sup> Arg<sup>26</sup> Lys<sup>34,38</sup>-bis-(Glut-ATet) GLP-1(7-38); Ser<sup>8</sup> Arg<sup>34</sup> Lys<sup>26,38</sup>-bis-(Glut-ATet) GLP-1(7-38); Ser<sup>8</sup> Arg<sup>26</sup>, 34 Set Arg Lys -565-(Glut-ATet) GLP-1(7-38); Set Arg<sup>26</sup>Lys<sup>36</sup>, <sup>39</sup>-bis-(Glut-ATet) GLP-1(7-38); Set Arg<sup>26</sup>Lys<sup>36,39</sup>-bis-(Glut-ATet) GLP-1(7-39); Set  $^{8}$ Arg<sup>26, 34</sup>Lys<sup>26,39</sup>-bis-(Glut-Glut-ATet) GLP-1(7-39); Set  $^{8}$ Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glut-(Glut-ATet) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glut-ATet) GLP-1(7-39); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ATet) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ATet) GLP-1(7-37); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ATet) GLP-1(7-38); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ATet) GLP-1(7-30); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-ATet) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-ATet) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-ATet) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-ATet) GLP-1(7-7); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glut-ATet) GLP-1(7-7); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glut-ATet) GLP-1(7-7); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glut-ATet) GLP-1(7-7); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glut-ATet) GLP-1(7-7); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glut-ATet) GLP-1(7-7); Thr<sup>8</sup>Lys<sup>34,38</sup>-bis-(Glut-ATet) GLP-1(7-7); Thr<sup>8</sup>Lys<sup>34,38</sup>-bis-(Glut-ATet) GLP-1(7-7); Thr<sup>8</sup>Lys<sup>34,38</sup>-bis-(Glut-ATet) Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glut-ATet) GLP-1(7-38); Thr Arg Lys --bis-(Glut-Aret) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26,38</sup>-bis-(Glut-ATet) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36,38</sup>-bis-(Glut-ATet) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(Glut-ATet) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glut-ATet) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36,39</sup>-bis-(Glut-ATet) GLP-1(7-39); Lys<sup>26</sup>, <sup>34</sup>-bis-(Glut-AHex) GLP-1(7-36); Lys<sup>26</sup>, <sup>34</sup>-bis-(Glut-AHex) GLP-1(7-37); Lys<sup>26, 34</sup>-bis-(Glut-AHex) GLP-1(7-38); Lys<sup>26, 34</sup>-bis-(Glut-AHex) GLP-13(7-39)

38); Lys<sup>25, 57</sup>-bis-(Glut-Aflex) GLP-13(7-39) Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-Aflex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26</sup>, <sub>36</sub>-bis-(Glut-Aflex) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-Aflex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-Aflex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glut-Aflex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Glut-Aflex) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>36,39</sup>-bis-(Glut-Aflex) GLP-1(7-39); Arg<sup>26, 34</sup>Lys<sup>26,39</sup>-bis-(Glut-Aflex) GLP-1(7-39); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glut-Aflex) GLP-1(7-39); Arg<sup>26, 34</sup>Lys<sup>26,39</sup>-bis-(Glut-Aflex) GLP-1(7-39); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glut-Aflex)

Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-AHex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>23, 26</sup>-bis-(Glut-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-AHex) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-AHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glut-AHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glut-AHex) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glut-AHex) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>27, 26</sup>-bis-(Glut-AHex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-AHex) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glut-AHex) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27</sup>, 26-bis-(Glut-AHex) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27</sup>, 26-bis-(Glut-AH

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1(7-39); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-AHex) GLP-1(7-36); Gly8Lys26. 34-bis-(Glut-AHex) GLP-1(7-37); Gly8Lys26. Gly Lys  $^{-505+(Glut-AHex)}$  GLP- $^{1}(7-37)$ ; Gly Lys  $^{34}$ -bis-(Glut-AHex) GLP- $^{1}(7-38)$ ; Gly  $^{8}Lys^{26}$ ,  $^{34}$ -bis-(Glut-AHex) GLP- $^{1}(7-39)$ ; Gly  $^{8}Arg^{26}Lys^{34,36}$ -bis-(Glut-AHex) GLP- $^{1}(7-36)$ ; Gly  $^{8}Arg^{26}Lys^{34,36}$ -bis-(Glut-AHex) GLP- $^{1}(7-37)$ ; Gly  $^{8}Arg^{34}Lys^{26}$ ,  $^{36}$ -bis-(Glut-AHex) GLP- $^{1}(7-37)$ ; Gly  $^{8}Arg^{34}Lys^{26}$ ,  $^{36}Arg^{34}Lys^{26}$ ,  $^{36}Arg^{34}Lys^{26}$ ,  $^{36}Arg^{34}Lys^{26}$ ,  $^{36}Arg^{34}Lys^{26}$ ,  $^{36}Arg^{34}Lys^{26}$ ,  $^{36}Arg^{34}Lys^{26}$ ,  $^{36}Arg^{34}Lys^{34}Lys^{26}$ ,  $^{36}Arg^{34}Lys^{34}Ly$ Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-AHex) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glut-AHex) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glut-AHex) GLP-1(7-38); 10 Gly<sup>8</sup>Arg<sup>26</sup>, Jys<sup>26, 38</sup>-bis-(Glut-AHex) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>26, 38</sup>-bis-(Glut-AHex) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>, Jys<sup>36, 38</sup>-bis-(Glut-AHex) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>36, 39</sup>-bis-(Glut-AHex) GLP-11(7-39); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 39</sup>-bis-(Glut-AHex) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36, 39</sup>-bis-(Glut-AHex) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>26, 39</sup>-bis-(Glut-AHex) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>26, 39</sup>-bis-(Glut-AHex) GLP-1(7-39); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-AHex) GLP-1(7-36); Val<sup>8</sup>Lys<sup>26,</sup> <sup>34</sup>-bis-(Glut-AHex) GLP-1(7-37); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-AHex) GLP-1(7-38); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-AHex) GLP-1 (7-39) Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AHex) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AHex) GLP-1(7-36); 20 Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AHex) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,36</sup>-bis-(Glut-AHex) GLP-1(7-37);  $Val^8 Arg^{26} Lys^{34,37}$ -bis-(Glut-Affex) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glut-AHex) GLP-1(7-37); Val8Arg26Lys34,38-bis-(Glut-AHex) GLP-1(7-38); 25 Val<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}$ Lys<sup>26</sup>,  ${}^{38}$ -bis-(Glut-AHex) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}$ Lys<sup>26</sup>,  ${}^{38}$ -bis-(Glut-AHex) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup> Lys<sup>36</sup>,  ${}^{39}$ -bis-(Glut-AHex) GLP-1(7-39);  $Val^8 Arg^{34} Lys^{26,39}$ -bis-(Glut-AHex) GLP-1(7-39); Val^8 Arg^{26, 34} Lys^{36,39}-bis-(Glut-AHex) GLP-1(7-39); Ser<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glut-AHex) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glut-AHex) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glut-AHex) GLP-1(7-38); Ser<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glut-AHex) Ser<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Slut-AHex) Ser<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Slut-AHex) Ser<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Slut-AHex) Ser<sup>8</sup>Lys<sup>26</sup> (7-39) Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AHex) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,36</sup>-bis-(Glut-AHex) GLP-1(7-36); 35 Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AHex) GLP-1(7-30); 35 Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AHex) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-AHex) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>26,37</sup>-bis-(Glut-AHex) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glut-AHex) GLP-1(7-38); 40 Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Glut-AHex) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>26,38</sup>-bis-(Glut-AHex) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,39</sup>-bis-(Glut-AHex) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glut-AHex) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glut-AHex) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glut-AHex) GLP-1(7-38); 55 Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Glut-AHex) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,38</sup>-bis-(Glut-AHex) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Glut-AHex) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glut-AHex) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glut-AHex) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glut-AHex) GLP-1(7-39); Clus<sup>26, 34</sup>-bis-(Glut-AOct) GLP-1(7-36); Lys<sup>26, 34</sup>-bis-(Glut-AOct) GLP-1(7-30); Lys<sup>26, 34</sup>-bis-(Glut-AOct) GLP-1(7-30); Lys<sup>26, 34</sup>-bis-(Glut-AOct) GLP-1(7-30); Clus<sup>26, 34</sup>-bis-(Clut-AOct) GLP-1(7-30); Clus<sup>34</sup>-bis-(Clut-AOct) Clus<sup>34</sup>-bis-(Clut-AOct) GLP-1(7-30); Clus<sup>34</sup>-bis-(Clut-AOct) Clus<sup>34</sup>-bis-(Clut-AOct) Clus<sup>34</sup>-bis-(Clut-AOct) Clus<sup>34</sup>-b 38); Lys<sup>26, 34</sup>-bis-(Glut-AOct) GLP-1(7-39) Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Glut-AOct) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-AOct) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-AOct) GLP-1(7-37);

Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glut-AOct) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(Glut-AOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glut-AOct) GLP-1(7-39); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glut-AOct) GLP-1(7-39);

GLP-1(7-39);
Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-AOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18, 34</sup>-bis-(Glut-AOct) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-AOct) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-AOct) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glut-AOct) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-AOct) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-AOct) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-AOct) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-AOct) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-AOct) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-AOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>23</sup>, 26-bis-(Glut-AOct) GLP-1(7-37); Arg<sup>24</sup>Lys<sup>23, 23</sup>-bis-(Glut-AOct) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-AOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glut-AOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-AOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-AOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>25</sup>, 26-bis-(Glut-AOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-AOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-AOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>25</sup>, 26-bis-(Glut-AOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-AOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, </sup> <sup>34</sup>-bis-(Glut-AOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-AOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-AOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-AOct) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glut-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27</sup>, 26-bis-(Glut-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27</sup>, 27-bis-(Glut-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27</sup>, 28-bis-(Glut-AOct) Arg<sup>34</sup>Lys<sup>27</sup>, 28-bis-(Glut-AOct) Arg<sup>34</sup>Lys<sup>27</sup>, 28-bis-(Glut-AOct) Arg<sup>34</sup>Lys<sup>27</sup>, 28-bis-(Glut-AOct) Arg<sup>34</sup>Lys<sup>34</sup>Lys<sup>34</sup>Lys<sup>34</sup>L <sup>26</sup>-bis-(Glut-AOct) GLP-1(7-38);  $\operatorname{Arg}^{26}$ Lys<sup>27, 34</sup>-bis-(Glut-AOct) GLP-1(7-39);  $\operatorname{Arg}^{34}$ Lys<sup>27, 26</sup>-bis-(Glut-AOct) GLP-1(7-39);

 $Gly^8Lys^{26,34}bis-(Glut-AOct) GLP-1(7-36); Gly^8Lys^{26,34}-bis-(Glut-AOct) GLP-1(7-37); Gly^8Lys^{26,34}-bis-(Glut-AOct) GLP-1(7-38); Gly^8Lys^{26,34}-bis-(Glut-AOct) GLP-1$ (7-39)  $Gly^8Arg^{26}Lys^{34,36}$ -bis-(Glut-AOct) GLP-1(7-36);  $Gly^8Arg^{34}Lys^{26}$ ,  $^{36}$ -bis-(Glut-AOct) GLP-1(7-36);  $Gly^8Arg^{26}Lys^{34,36}$ -bis-(Glut-AOct) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-AOct) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-AOct) GLP-1(7-37);  $Gly^8 Arg^{34} Lys^{26,37}$ -bis-(Glut-AOct) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glut-AOct) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Glut-AOct) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}Lys^{36,38}$ -bis-(Glut-AOct) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>,  ${}^{39}$ -bis-(Glut-AOct) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glut-AOct) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}Lys^{36,39}$ -bis-(Glut-AOct) GLP-1(7-39); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-AOct) GLP-1(7-36); Val<sup>8</sup>Lys<sup>26,</sup> <sup>34</sup>-bis-(Glut-AOct) GLP-1(7-37); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-AOct) GLP-1(7-37); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-AOct) GLP-1 (7-39) Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AOct) GLP-1(7-36); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-AOct) GLP-1(7-36); Ser Aug  $2^{6}$ ,  $3^{4}$ Lys<sup>26, 39</sup>-bis-(Glut-AHex) GLP-1(7-39); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-AHex) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-AHex) GLP-1(7-37); Marg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AHex) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AHex) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AHex) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AHex) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AHex) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AHex) GLP-1(7-37); Marg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AHex) GLP-1(7-37); Marg<sup>26</sup>Lys<sup>34,39</sup>-bis-(Glut-AOct) GLP-1(7-39); Marg<sup>26</sup>Lys<sup>34,39</sup>-bis-(Glut-AOct) GLP-1(7-39); Marg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glut-AOct) G Val8Arg26, 34Lys36,39-bis-(Glut-AOct) GLP-1(7-39); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-AOct) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-AOct) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-AOct) GLP-1(7-38); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-AOct) GLP-1 (7-39)Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AOct) GLP-1(7-36);

Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-AOct) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-AOct) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-AOct) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-AOct) GLP-1(7-37);  $Ser^{8}Arg^{34}Lys^{26,37}$ -bis-(Glut-AOct) GLP-1(7-37); Ser^{8}Arg^{26}Lys^{34,38}-bis-(Glut-AOct) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Glut-AOct) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,38</sup>-bis-(Glut-AOct) GLP-1(7-38);

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131 132 Ser<sup>8</sup> Arg<sup>26</sup> Lys<sup>34, 39</sup>-bis-(Glut-AOct) GLP-1(7-39); Ser<sup>8</sup> Arg<sup>26</sup> Lys<sup>34, 36</sup>-bis-(Glut-AOct) GLP-1(7-39); Th<sup>8</sup> Lys<sup>26, 34</sup>-bis-(Glut-AOct) GLP-1(7-36); Thr<sup>8</sup> Arg<sup>26</sup> Lys<sup>34, 36</sup>-bis-(Glut-AOct) GLP-1(7-37); Thr<sup>8</sup> Arg<sup>26</sup> Lys<sup>34, 36</sup>-bis-(Glut-AOct) GLP-1(7-39); Ser<sup>8</sup> Lys<sup>26, 34</sup>-bis-(Glut-ALit) GLP-1(7-39); Ser<sup>8</sup> Lys<sup>26, 34</sup>-bis-(Glut-ALit) GLP-1(7-39); Ser<sup>8</sup> Arg<sup>26</sup> Lys<sup>34, 36</sup>-bis-(Glut-ALit) GLP

ALit) GLP-1(7-37); Lys<sup>26, 34</sup>-bis-(Glut-ALit) GLP-1(7-38); Lys<sup>26, 34</sup>-bis-(Glut-ALit) GLP-1(7-39)

Lys<sup>26, 34</sup>-bis-(Glut-ALit) GLP-1(7-39) Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-ALit) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-ALit) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-ALit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-ALit) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-ALit) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-ALit) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-ALit) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,39</sup>-bis-(Glut-ALit) GLP-1(7-39); Arg<sup>26,39</sup>-bis-(Glut-ALit) GLP-1(7-30); Arg<sup>26,34</sup>Lys<sup>36,39</sup>-bis-(Glut-ALit) GLP-1(7-30). 13(7-39);

13(7-39); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-ALit) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glut-ALit) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-ALit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glut-ALit) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glut-ALit) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-ALit) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glut-ALit) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-ALit) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-ALit) GLP-1(7-36); 35 Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-ALit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glut-ALit) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-ALit) GLP-1(7-36); 35 Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-ALit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glut-ALit) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-ALit) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glut-ALit) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glut-ALit) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>27, 40</sup> 34-bis-(Glut-ALit) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-ALit) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glut-ALit) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>27, 40</sup> 34-bis-(Glut-ALit) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-<sup>34</sup>-bis-(Glut-ALit) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glut-ALit) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glut-ALit) GLP-1 (7-37); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glut-ALit) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glut-ALit) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27</sup>, <sup>34</sup>-bis-(Glut-ALit) GLP-1(7-38); Arg<sup>4</sup>Lys<sup>27</sup>, <sup>34</sup>-bis-(Glut-ALit) GLP-1(7-38); Arg<sup>4</sup>Lys<sup>27</sup>, <sup>34</sup>-<sup>26</sup>-bis-(Glut-ALit) GLP-1(7-38);  $\operatorname{Arg}^{26}\operatorname{Lys}^{27}$ . <sup>34</sup>-bis-(Glut- 45 ALit) GLP-1(7-39);  $\operatorname{Arg}^{34}\operatorname{Lys}^{27}$ . <sup>26</sup>-bis-(Glut-ALit) GLP-1

Gly8Arg26Lys34,36-bis-(Glut-ALit) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>26,36</sup>-bis-(Glut-ALit) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>26,36</sup>-bis-(Glut-ALit) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-ALit) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glut-ALit) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>26,38</sup>-bis-(Glut-ALit) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,38</sup>-bis-(Glut-ALit) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,38</sup>-bis-(Glut-ALit) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>24</sup>Lys<sup>26,39</sup>-bis-(Glut-ALit) GLP-1(7-39); 39)

Val8Arg26Lys34,36-bis-(Glut-ALit) GLP-1(7-36);  $Va1^8Arg^{34}Lys^{26}$ , <sup>36</sup>-bis-(Glut-ALit) GLP-1((7-36); Va1<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-ALit) GLP-1((7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Glut-ALit) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-ALit) GLP-1(7-37); Val8Arg34Lys26,37-bis-(Glut-ALit) GLP-1(7-37); Val8Arg26Lys34,38-bis-(Glut-ALit) GLP-1(7-38); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Glut-ALit) GLP-1(7-38); Val<sup>8</sup>Arg<sup>20</sup> var Arg Lys -565-(Glut-ALt) GLP-1(7-36); var Arg  $^{34}$ Lys $^{36}$ ,  $^{38}$ -bis-(Glut-ALt) GLP-1(7-38); Val<sup>8</sup>Arg $^{26}$ Lys $^{34}$ ,  $^{39}$ -bis-(Glut-ALt) GLP-1(7-39); Val<sup>8</sup>Arg $^{34}$ Lys $^{26}$ ,  $^{39}$ -bis-(Glut-ALt) GLP-1(7-39); Val<sup>8</sup>Arg $^{26}$ ,  $^{34}$ Lys $^{36}$ ,  $^{39}$ -bis-(Glut-ALt) GLP-1(7-39); Val<sup>8</sup>Arg $^{26}$ ,  $^{34}$ -bis-(Glut-ALt) GLP-1(7-36); Ser<sup>8</sup>Lys $^{26}$ ,  $^{34}$ -bis-(Glut-ALt) GLP-1(7-37); Cast 26,  $^{34}$ -bis-(Glut-ALt) GLP-1(7-37); Ser $^{8}$ Lys $^{26}$ ,  $^{34}$ -bis-(Glut-ALt) GLP-1(7-37); Cast 26,  $^{34}$ -bis-(Glut-ALt) Cast 26,  $^{3$ Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ALit) GLP-1(7-38); Ser<sup>8</sup>Lys<sup>26</sup>, Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-ALit) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Glut-ALit) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-ALit) GLP-1(7-37); Set Arg  $^{34}$ Lys $^{26}$ ,  $^{36}$ -bis-(Glut-ALit) GLP-1(7-37); Set  $^{8}$ Arg $^{26}$ Lys $^{34,37}$ -bis-(Glut-ALit) GLP-1(7-37); Set  $^{8}$ Arg $^{26}$ Lys $^{26,37}$ -bis-(Glut-ALit) GLP-1(7-37); Set  $^{8}$ Arg $^{26}$ Lys $^{34,38}$ -bis-(Glut-ALit) GLP-1(7-37); Set  $^{8}$ Arg $^{26}$ Lys $^{34,38}$ -bis-(Glut-ALit) GLP-1(7-38); 20 Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Glut-ALit) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup> <sup>34</sup>Lys<sup>36,38</sup>-bis-(Glut-ALit) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(Glut-ALit) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glut-ALit) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glut-ALit) GLP-1(7-39); Thr8Lys26, 34-bis-(Glut-ALit) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ALit) GLP-1(7-37); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ALit) GLP-1(7-38); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ALit) GLP-1(7-39) Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-ALit) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-ALit) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glut-ALit) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glut-ALit) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glut-ALit) GLP-1(7-37); Thr  $^{A}$  Arg  $^{34}$  Lys  $^{26,37}$ -bis-(Glut-ALit) GLP-1(7-37); Thr  $^{8}$  Arg  $^{26}$  Lys  $^{34,38}$ -bis-(Glut-ALit) GLP-1(7-38); Thr  $^{8}$  Arg  $^{34}$  Lys  $^{26,38}$ -bis-(Glut-ALit) GLP-1(7-38); Thr  $^{8}$  Arg  $^{26}$ .  $^{34}$  Lys  $^{36,38}$ -bis-(Glut-ALit) GLP-1(7-38); Thr  $^{8}$  Arg  $^{26}$ .  $^{34}$  Lys  $^{36,38}$ -bis-(Glut-ALit) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Glut-ALit) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Glut-ALit) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glut-ALit) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glut-ALit) GLP-1(7-39); Lys<sup>26, 34</sup>-bis-(Aspa-ADod) GLP-1(7-36); Lys<sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-36); Lys<sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-36); Lys<sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-36); Lys<sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-36); Lys<sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-36); Lys<sup>36</sup>-bis-(Aspa-ADod) BLP-1(Aspa-ADod) BLP-1(Aspa 38); Lys<sup>26, 34</sup>-bis-(Aspa-ADod) GLP-1(7-39) Arg<sup>26</sup>Lys<sup>34,36</sup>-

bis-(Aspa-ADod) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>34</sup>, <sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>36</sup>, <sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>-bis-(Aspa-ADod) GLP-1(7-37); Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>-bis-(Aspa-ADod) GLP-1(7-37); Aspa-ADod) GLP-1(7-37); Aspa-ADod) Aspa-ADod) Aspa-ADod) Aspa-ADod) Aspa-ADod) Aspa-ADod) Aspa-ADod ALit) GLP-1(7-39); Arg Lys (7-39); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ALit) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ALit) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ALit) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glut-ALit) GLP-1(7-50 (Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26, 39</sup>-bis-(Aspa-ADod) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26, 39</sup>-bis-(Aspa-ADod) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>36, 39</sup>-bis-(

Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-ADod) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18,</sup> Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-ADod) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18, 34</sup>-bis-(Aspa-ADod) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-ADod) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Aspa-ADod) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Aspa-ADod) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Aspa-ADod) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-ADod) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-ADod) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-ADod) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-ADod) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23</sup>, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23</sup>, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23</sup>, 34</sup>-bis-(Aspa-ADod) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>23,26</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23</sup>, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23</sup>, 34</sup>-bis-(Aspa-ADod) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>23,36</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23</sup>, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27</sup>, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27</sup>, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>28</sup>, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>28</sup>, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>28</sup>, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>28</sup>, 34</sup>-bis-(

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**LJJ** ADod) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Aspa-ADod) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Aspa-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Aspa-ADod) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Aspa-ADod) GLP-1(7-39); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ADod) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ADod) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ADod) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ADod) GLP-1(7-39); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26</sup>-bis-(Aspa-ADod) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>3</sup>-bis-(Aspa-ADod) GLP-1(7-38); Gly<sup>8</sup>L Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ADod) GLP-1(7-39) Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ADod) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-ADod) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-ADod)-GLP)1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-ADod)-GLP)1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-ADod) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-ADod) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-ADod) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-ADod) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,39</sup>-bis-(Aspa-ADod) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,39</sup>-bis-(Aspa-ADod) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,39</sup>-bis-(Aspa-ADod) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,39</sup>-bis-(Aspa-ADod) GLP-1(7-39): Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-ADod) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-ADod) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36,39</sup>-bis-(Aspa-ADod) GLP-1(7-39); Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Aspa-ADod) GLP-1(7-36); Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Aspa-ADod) GLP-1(7-37); Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Aspa-ADod) GLP-<sup>26</sup>, <sup>34,36</sup> bis-(Aspa-ADod) GLP-1(7-36);  $\begin{array}{l} \text{ADd} (\text{GLP-1}(7-36); \text{ Val}^{8}\text{Arg}^{26}\text{Lys}^{34,36}\text{-bis-(Aspa-ADod) GLP-1}(7-36); \\ \text{Val}^{8}\text{Arg}^{34}\text{Lys}^{26}\text{-}\text{vis-(Aspa-ADod) GLP-1}(7-36); \\ \text{Val}^{8}\text{Arg}^{26}\text{Lys}^{34,36}\text{-bis-(Aspa-ADod) GLP-1}(7-37); \\ \end{array}$  $Val^8 Arg^{34} Lys^{26}$ , <sup>36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-ADod) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Aspa-ADod) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Aspa-ADod) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-ADod) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>26,38</sup>-bis-(Aspa-ADod) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,38</sup>-bis-(Aspa-ADod) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(Aspa-ADod) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26</sup> Lys<sup>26,39</sup>-bis-(Aspa-ADod) GLP-1(7-39); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-ADod) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,39</sup>-bis-(Aspa-ADod) GLP-1(7-39); Ser<sup>8</sup>Lys<sup>26,34</sup>-bis-(Aspa-ADod) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26,35</sup> <sup>34</sup>-bis-(Aspa-ADod) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26,34</sup>-bis-(Aspa-ADod) GLP-1(7-38); Ser<sup>8</sup>Lys<sup>26,34</sup>-bis-(Aspa-ADod) GLP-1(7-30); Ser<sup>8</sup>Lys<sup>26,34</sup>-bis-(Aspa-ADod) SER<sup>3</sup>-bis-(Aspa-ADod) SER<sup></sup> 1(7-39) Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ADod) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ADod) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ADod) GLP-1(7-37); 40 Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-ADod) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Aspa-ADod) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-ADod) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Aspa-ADod) GLP-1(7-38); 45 Ser<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36,38</sup>-bis-(Aspa-ADod) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(Aspa-ADod) GLP-1(7-39); Ser<sup>8</sup> Arg<sup>34</sup> Lys<sup>26,39</sup>-bis-(Aspa-ADod) GLP-1(7-39); Ser<sup>8</sup> Arg<sup>26, 34</sup> Lys<sup>36,39</sup>-bis-(Aspa-ADod) GLP-1(7-39); Set Alg Lys - 56; (Aspa-ADod) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26</sup>, 50; ADod) GLP-1(7-38); Thr°Lys<sup>20, 34</sup>-bis-(Aspa-ADod) GLP-1(7-39) Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ADod) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ADod) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ADod) GLP-1(7-37); 55 Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-ADod) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-ADod) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-ADod) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-ADod) GLP-1(7-38); Th<sup>2</sup><sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Aspa-ADod) GLP-1(7-38); Th<sup>2</sup><sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Aspa-ADod) GLP-1(7-38); 60 Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-ADod) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,38</sup>-bis-(Aspa-ADod) GLP-1(7-39); Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1(7-36); Lys<sup>26, 34</sup>-bis-(Aspa-65 ATet) GLP-1(7-37); Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1(7-38); Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1(7-39)

Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ATet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Aspa-ATet) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ATet) GLP-1(7-37);  $\operatorname{Arg}^{34}\operatorname{Lys}^{26}$ ,  $\operatorname{36-bis}$ -(Aspa-ATet) GLP-1(7-37);  $\operatorname{Arg}^{26}\operatorname{Lys}^{34}$ ,  $\operatorname{37-bis}$ -(Aspa-ATet) GLP-1(7-37);  $\operatorname{Arg}^{26}\operatorname{Lys}^{34}$ ,  $\operatorname{37-bis}$ -(Aspa-ATet) GLP-1(7-37);  $\operatorname{Arg}^{26}\operatorname{Lys}^{34}$ ,  $\operatorname{37-bis}$ -(Aspa-ATet) GLP-1(7-37);  $\operatorname{Arg}^{26}\operatorname{Lys}^{34}$ ,  $\operatorname{47-37}$ ;  $\operatorname{Arg}^{26}\operatorname{Lys}^{34}$ ,  $\operatorname{47-37}$ ;  $\operatorname{47-26}^{26}\operatorname{Lys}^{34}$ ,  $\operatorname{47-26}^{26}\operatorname{Ly$ <sup>39</sup>-bis-(Aspa-ATet) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-ATet) GLP-1(7-39); Arg<sup>26,34</sup>Lys<sup>36,39</sup>-bis-(Aspa-ATet) GLP-1(7-39);

1(7-39); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-ATet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18, 34</sup>-bis-(Aspa-ATet) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-ATet) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-ATet) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Aspa-ATet) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Aspa-ATet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-ATet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-ATet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-ATet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-ATet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-ATet) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Aspa-ATet) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>23, 26</sup>-bis-(Aspa-ATet) GLP-1(7-37); Arg<sup>34</sup>-bis-(Aspa-ATet) GLP-1(7-37); Arg<sup>34</sup>-bis-(Aspa-ATet) GLP-1(7-37); Arg<sup>34</sup>-bis-(Aspa-ATet) GLP-1(7-37); Arg<sup>34</sup>-<sup>26</sup>-bis-(Aspa-ATet) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Aspa-ATet) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-ATet) GLP-1 (7-38); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Aspa-ATet) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-ATet) GLP-1(7-39);  $^{27}$ 20

Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Aspa-ATet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27,</sup> Arg Lys  $^{-505}$ (Aspa-Attet) GLP-1(7-36); Arg $^{26}$ Lys $^{27}$ ,  $^{34}$ -bis-(Aspa-Attet) GLP-1(7-36); Arg $^{26}$ Lys $^{27}$ ,  $^{26}$ -bis-(Aspa-Attet) GLP-1(7-37); Arg $^{26}$ Lys $^{27}$ ,  $^{34}$ -bis-(Aspa-Attet) GLP-1(7-38); Arg $^{26}$ Lys $^{27}$ ,  $^{26}$ -bis-(Aspa-Attet) H 34-bis-(Aspa-ATet) GLP-1(7-39); Arg34Lys27, 26-bis-(Aspa-ATet) GLP-1(7-39);

Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1 (7-39)

Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ATet) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-ATet) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ATet) GLP-1(7-37); Gly  $^{A}$   $rg^{2-}$   $Lys^{-6-}$   $^{-5}$   $rs^{-}$  (Aspa-Atet) GLP-1(7-37); Gly  $^{8}$   $Arg^{34}$   $Lys^{26}$ ,  $^{36}$  -bis-(Aspa-Atet) GLP-1(7-37); Gly  $^{8}$   $Arg^{26}$   $Lys^{34,37}$  -bis-(Aspa-Atet) GLP-1(7-37); Gly  $^{8}$   $Arg^{26}$   $Lys^{34,37}$  -bis-(Aspa-Atet) GLP-1(7-37); Gly  $^{8}$   $Arg^{26}$   $Lys^{34,37}$  -bis-(Aspa-Atet) GLP-1(7-38); Gly  $^{8}$   $Arg^{26}$ ,  $^{34}$   $Lys^{26,38}$  -bis-(Aspa-Atet) GLP-1(7-38); Gly  $^{8}$   $Arg^{26}$ ,  $^{34}$   $Lys^{36,38}$  -bis-(Aspa-Atet) GLP-1(7-38); Gly  $^{8}$   $Arg^{26}$ ,  $^{42}$   $Lys^{36,38}$  -bis-(Aspa-Atet) GLP-1(7-38); Gly  $^{8}$   $Arg^{26}$   $Lys^{34}$ ,  $^{39}$  bis (Aspa-Atet) GLP-1(7-38);  $Gly^8Arg^{26}Lys^{34}$ , <sup>39</sup>-bis-(Aspa-ATet) GLP-1(7-39);  $Gly^8Arg^{34}Lys^{26,39}$ -bis-(Asps-ATet) GLP-1(7-39);  $Gly^8Arg^{26,34}Lys^{26,34}$ -bis-(Asps-ATet) GLP-1(7-39); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1(7-36); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1(7-37); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1(7-38); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1 Alef) GLP-1(7-36); val Lys -565 (Aspa-Alef) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-Alef) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-Alef) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-Alef) GLP-1(7-37);  $Val^8 Arg^{34} Lys^{26}$ , <sup>36</sup>-bis-(Aspa-ATet) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-ATet) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Aspa-ATet) GLP-1(7-37); Va18Arg26Lys34,38-bis-(Aspa-ATet) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}Lys^{26,38}$ -bis-(Aspa-ATet) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}Lys^{36,38}$ -bis-(Aspa-ATet) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36,39</sup>-bis-(Aspa-Afet) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(Aspa-Afet) GLP-1(7-39); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-Afet) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-Afet) GLP-1(7-39); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-Afet) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-Afet) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-Afet) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-Afet) GLP-1(7-38); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-Afet) Ser<sup>8</sup>Lys<sup>26</sup>, 34}-bis-(Aspa-Afet) Ser<sup>8</sup>Lys<sup>26</sup>, 34}-bis-(Aspa-Afet) Ser<sup>8</sup>Lys<sup>26</sup>, 34}-bis-(Aspa-Afet) Ser<sup>8</sup>Lys<sup>26</sup>, 34}-bis-(Aspa-Afet) Ser<sup>8</sup>Lys<sup>26</sup>, 34}-bis-(Aspa-Afet) Ser<sup>8</sup>Lys<sup>26</sup>, 34}-bis-(Aspa-Afet) Ser<sup></sup> (7-39)Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ATet) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-ATet) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ATet) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-ATet) GLP-1(7-37);

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Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-ATet) GLP-1(7-37); Set<sup>8</sup>Arg<sup>26</sup>Lys<sup>26,37</sup>-bis-(Aspa-Afet) GLP-1(7-37); Set<sup>8</sup>Arg<sup>26</sup>Lys<sup>26,37</sup>-bis-(Aspa-Afet) GLP-1(7-37); Set<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-Afet) GLP-1(7-38); Set<sup>8</sup>Arg<sup>26</sup>,  $^{34}$ Lys<sup>26,38</sup>-bis-(Aspa-Afet) GLP-1(7-38); Set<sup>8</sup>Arg<sup>26</sup>,  $^{34}$ Lys<sup>36,38</sup>-bis-(Aspa-Afet) GLP-1(7-38); 5 Set<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>,  $^{39}$ -bis-(Aspa-Afet) GLP-1(7-39); CLP 1(7-39); CLP 1(7-39); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-ATet) GLP-1(7-39);

Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-ATet) GLP-1(7-39);

Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1(7-37); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa- 10 ATet) GLP-1(7-38); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1 (7-39)

Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ATet) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-ATet) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-ATet) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Aspa-ATet) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-ATet) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Aspa-ATet) GLP-1(7-38); 20 Thr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36,38</sup>-bis-(Aspa-ATet) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Aspa-ATet) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-ATet) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-ATet) GLP-1(7-39); Lys<sup>26, 34</sup>-bis-(Aspa-ATet) GLP-1(7-39); Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-36); Lys<sup>26, 34</sup>-bis- 25 (Aspa-AHex) GLP-1(7-37); Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-38): Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-39)

GLP-1(7-38); Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-39)

<sup>39</sup>-bis-(Aspa-AHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-AHex) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>36,39</sup>-bis-(Aspa-AHex) GLP-1(7-39);

Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-AHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18,</sup> 

<sup>26-bis-</sup>(Aspa-AHex) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Aspa-AHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>23</sup>, 26-bis-(Aspa-AHex) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-<sup>26-bis-(Aspa-AHex)</sup> GLP-1(7-36); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Aspa-AHex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Aspa-AHex) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23,26</sup>-bis-(Aspa-AHex) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Aspa-AHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23, 26</sup>-bis-(Aspa-AHex) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Aspa-AHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Aspa-AHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Aspa-AHex) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Aspa-AHex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Aspa-AHex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Aspa-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Aspa-AHex) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Aspa-AHex) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-<sup>1</sup>II 26-bis-(Aspa-AHex) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Aspa-AHex) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Aspa-AHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Aspa-55 AHex) GLP-1(7-39); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-37); Cls<sup>8</sup>L e<sup>26, 34</sup> bis (Aspa-AHex) GLP-1(7-37); Cls<sup>8</sup>L e<sup>26, 34</sup> bis (Aspa-AHex) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26</sup>, Gly<sup>8</sup>Lys<sup>26, 5\*</sup>-bis-(Aspa-AHex) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-39) Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AHex) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AHex) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AHex) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-AHex) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-AHex) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-AHex) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-AHex) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-AHex) GLP-1(7-38); 65 Gly<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26,38</sup>-bis-(Aspa-AHex) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36,38</sup>-bis-(Aspa-AHex) GLP-1(7-38); 61 y<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36,38</sup>-bis-(Aspa-AHex) GLP-1(7-38); 61 y<sup>8</sup>Arg<sup>36</sup>, <sup>36</sup>Arg<sup>36</sup>, <sup>36</sup>Arg<sup>36</sup>, <sup>36</sup>Arg<sup>36</sup>, <sup>36</sup>Arg<sup>36</sup>, <sup>36</sup>Arg<sup>36</sup>, <sup>36</sup>Ar

Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Aspa-AHex) GLP-1(7-39);  $Gly^{8}Arg^{34}Lys^{26,39}$ -bis-(Aspa-AHex) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-AHex) GLP-1(7-39); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-36); Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Aspa-AHex) GLP-1(7-36); Val<sup>8</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Aspa-AHex) GLP-1(7-36); <sup>36</sup>-bis-(Aspa-AHex) GLP-1(Aspa-AHex) GLP-1(Aspa

<sup>34</sup>-bis-(Aspa-AHex) GLP-1(7-37); Val<sup>8</sup>Lys<sup>26,34</sup>bis-(Aspa-AHex) GLP-1(7-38); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-39)

- Va18Arg26Lys34,36-bis-(Aspa-AHex) GLP-1(7-36); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-AHex) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AHex) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AHex) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-AHex) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>26,37</sup>-bis-(Aspa-AHex) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Aspa-AHex) GLP-1(7-37);  $Val^8 Arg^{26} Lys^{34,38}$ -bis-(Aspa-AHex) GLP-1(7-38); Thi Arg Lys -bis-(Aspa-After) GLP-1(7-36), var Arg Lys -bis-(Aspa-After) GLP-1(7-36), Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>26, 36</sup>-bis-(Aspa-After) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>26, 38</sup>-bis-(Aspa-After) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-After) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Aspa-After) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-After) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Aspa-After) GLP-1(7-39); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-AHex) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-AHex) GLP-1(7-39);
  - Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-38); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AHex) Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-1(7-36); Ser<sup>8</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Ly 1(7-39)
  - Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AHex) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-AHex) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AHex) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-AHex) GLP-1(7-37); Set<sup>-</sup>Arg<sup>2-</sup>Lys<sup>-</sup>-Dis-(Aspa-Aftex) GLP-1(7-37); Set<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-Aftex) GLP-1(7-37); Set<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Aspa-Aftex) GLP-1(7-37); Set<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-Aftex) GLP-1(7-38); Set<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Aspa-Aftex) GLP-1(7-38); Set<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,39</sup>-bis-(Aspa-Aftex) GLP-1(7-38); Set<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,39</sup>-bis-(Aspa-Aftex) GLP-1(7-39); Set<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,39</sup>-bis-(Aspa-Aftex) GLP-1(7-39); Set<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-Aftex) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-AHex) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-AHex) GLP-1(7-39); 35
    - Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AHex) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26,</sup>
  - $Thr^8Arg^{26}Lys^{34,36}$ -bis-(Aspa-AHex) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-AHex) GLP-1(7-37); Thr Arg<sup>26</sup>Lys<sup>34</sup> <sup>37</sup>-bis-(Aspa-AHex) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Aspa-AHex) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-AHex) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>26,38</sup>-bis-(Aspa-AHex) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}$ Lys<sup>26,38</sup>-bis-(Aspa-AHex) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,39</sup>-bis-(Aspa-AHex) GLP-1(7-39); Thr  $^{8}$ Arg  $^{34}$ Lys  $^{26,39}$ -bis-(Aspa-AHex) GLP-1(7-39); Thr  $^{8}$ Arg  $^{26,34}$ Lys  $^{36,39}$ -bis-(Aspa-AHex) GLP-1(7-39);
  - Thr<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-AHex) GLP-1(7-39); Lys<sup>26, 34</sup>-bis-(Aspa-AOct) GLP-1(7-36); Lys<sup>26, 34</sup>-bis-(Aspa-AOct) GLP-1(7-37); Lys<sup>26, 34</sup>-bis-(Aspa-AOct) GLP-1(7-38); Lys<sup>26, 34</sup>-bis-(Aspa-AOct) GLP-1(7-39)
  - Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Aspa-AOct) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-AOct) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-AOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Aspa-AOct) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34</sup>. <sup>39</sup>-bis-(Aspa-AOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-AOct) GLP-1(7-39); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-AOct) GLP-1(7-39).

Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-AOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18,</sup> <sup>26</sup>-bis-(Aspa-AOct) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-AOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>18, 26</sup>-bis-(Aspa-AOct) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18, 26</sup>-bis -(Aspa -AOct) -G LP-1(7-38);

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Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Aspa-AOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>18,</sup> 26-bis -(Aspa -AOct) GLP-1(7-39);

Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Aspa-AOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>23,</sup> 26-bis-(Aspa-AOct) GLP-1(7-36); Arg26Lys23, 34-bis-(Aspa-AOct) GLP-1(7-37);  $\operatorname{Arg}^{34}$ Lys<sup>23,26</sup>-bis-(Aspa-AOct) GLP-1 5 (7-37);  $\operatorname{Arg}^{26}$ Lys<sup>23, 34</sup>-bis-(Aspa-AOct) GLP-1(7-38);  $\operatorname{Arg}^{34}$ Lys<sup>23,26</sup>-bis-(Aspa-AOct) GLP-1(7-38);  $\operatorname{Arg}^{26}$ Lys<sup>26</sup>-bis-(Aspa-AOct) GLP-1(7-38);  $\operatorname{Arg}^{26}$ Lys<sup>26</sup>-bis-(Aspa-AOct) GLP-1(7-38);  $\operatorname{Arg}^{26}$ Lys<sup>26</sup>-bis-(Aspa-AOct) GLP-1(7-38);  $\operatorname{Arg}^{26}$ Lys<sup>26</sup>-bis-(Aspa-AOct) GLP-1(7-38); {Arg}^{26}Lys<sup>26</sup>-bis-(Aspa-AOct) GLP-1(7-38); {Arg}^{26}Lys<sup>26</sup>-bis-(Aspa-AOct) GLP-1(Aspa-AOct) GLP-1(Aspa-AOct) GLP-1(Aspa-AOct) GLP-1(Aspa-AOct) GLP-1(Aspa-AOct) GLP-1(Aspa-<sup>34</sup>-bis-(Aspa-AOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-

AOct) GLP-1(7-39);

Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AOct) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26,</sup> <sup>34</sup>-bis-(Aspa-AOct) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AOct) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AOct) GLP-1 (7-39)

Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AOct) GLP-1(7-36);  $Gly^8Arg^{34}Lys^{26}$ . <sup>36</sup>-bis-(Aspa-AOct) GLP-1(7-36);  $Gly^8Arg^{26}Lys^{34,36}$ -bis-(Aspa-AOct) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-AOct) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-AOct) GLP-1(7-37); 25 Gly8Arg34Lys26,37-bis-(Aspa-AOct) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-AOct) GLP-1(7-38);  $Gly^8Arg^{34}Lys^{26,38}$ -bis-(Aspa-AOct) GLP-1(7-38);  $Gly^8Arg^{26, 34}Lys^{36,38}$ -bis-(Aspa-AOct) GLP-1(7-38); AOct) GLP-1(7-38); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AOct) GLP-1 35 <sup>34</sup>-bis-(Aspa-ALit) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Aspa-AUCI) GLP-1(7-38); Val<sup>2</sup>Lys<sup>2-7-2-</sup>-bis-(Aspa-AUCI) GLP-1 35 (7-39) Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AUCI) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AUCI) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AUCI) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-AUCI) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>26,37</sup>-bis-(Aspa-AUCI) GLP-1(7-37); 40 Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Aspa-AUCI) GLP-1(7-37); 40 Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup> bis (Aspa-AUCI) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-AOct) GLP-1(7-38); Val8Arg34Lys26,38-bis-(Aspa-AOct) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36,38</sup>-bis-(Aspa-AOct) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(Aspa-AOct) GLP-1(7-39); 45 Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-AOct) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-AOct) GLP-1(7-39); (7-39)Ser<sup>8</sup>Árg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AOct) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-AOct) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-AOct) GLP-1(7-39);

Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AOct) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AOct) GLP-1(7-37); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AOct) GLP-1(7-38); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-AOct) GLP-1 (7-39) Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-AOct) GLP-1(7-36);

Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-AOct) GLP-1(7-36); Thr $^{8}$ Arg $^{26}$ Lys $^{34,36}$ -bis-(Aspa-AOct) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-AOct) GLP-1(7-37); Thr  $^{8}$ Arg  $^{26}$ Lys  $^{34,37}$ -bis-(Aspa-AOct) GLP-1(7-37); Thr  $^{8}$ Arg  $^{34}$ Lys  $^{26,37}$ -bis-(Aspa-AOct) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-AOct) GLP-1(7-38); Thr  $^{8}$ Arg  $^{26}$ ,  $^{34}$ Lys  $^{26,38}$ -bis-(Aspa-AOct) GLP-1(7-38); Thr  $^{8}$ Arg  $^{26}$ ,  $^{34}$ Lys  $^{36,38}$ -bis-(Aspa-AOct) GLP-1(7-38); Thr  $^{8}$ Arg  $^{26}$ Lys  $^{34}$ ,  $^{39}$ -bis-(Aspa-AOct) GLP-1(7-39);

Arg Lys -bis-(Aspa-ALit) GLP-1(7-30), Arg Lys  $^{36}$ -bis-(Aspa-ALit) GLP-1(7-36), Arg  $^{26}$ Lys  $^{34,36}$ -bis-(Aspa-ALit) GLP-1(7-37); Arg  $^{34}$ Lys  $^{26,36}$ -bis-(Aspa-ALit) GLP-1(7-37); Arg  $^{26}$ Lys  $^{34,37}$ -bis-(Aspa-ALit) GLP-1(7-37); Arg  $^{26}$ Lys  $^{34,37}$ -bis-(Aspa-ALit) GLP-1(7-37); Arg  $^{26}$ Lys  $^{34,37}$ -bis-(Aspa-ALit) GLP-1(7-37); Arg  $^{26}$ Lys  $^{34}$ . <sup>39</sup>-bis-(Aspa-ALit) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-ALit) GLP-1(7-39); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-ALit) GLP-1(7-39); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-ALit) GLP-

1(7-39);

 $Arg^{26}Lys^{18}$ , <sup>34</sup>-bis-(Aspa-ALit) GLP-1(7-36); Arg^{34}Lys^{18}, 26-bis-(Aspa-ALit) GLP-1(7-36); Arg^{26}Lys^{18}, <sup>34</sup>-bis-(Aspa-ALit) GLP-1(7-37); Arg^{34}Lys^{18,26}-bis-(Aspa-ALit) GLP-1 (7-37); Arg^{26}Lys^{18}, <sup>34</sup>-bis-(Aspa-ALit) GLP-1(7-38); Arg^{34}Lys^{18,26}-bis-(Aspa-ALit) GLP-1(7-38); Arg^{26}Lys^{18},  $Arg^{34}Lys^{18,26}$ -bis-(Aspa-ALit) GLP-1(7-38); Arg^{26}Lys^{18}, 34-bis-(Aspa-ALit) GLP-1(7-39); Arg34Lys18,26-bis-(Aspa-ALit) GLP-1(7-39);

ALit) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Aspa-ALit) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Aspa-ALit) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Aspa-ALit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Aspa-ALit) GLP-1(7-38); (7-37); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Aspa-ALit) GLP-1(7-38);  $2^{46}$ ,  $2^{7-26}$ ,  $2^{7-26}$ ,  $2^{7-34}$ -bis-(Aspa-ALit) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Aspa-ALit) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Aspa-ALit) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Aspa-ALit) GLP-1(7-39);

ALit) GLP-1(7-39), Gly<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Aspa-ALit) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Aspa-ALit) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Aspa-ALit) GLP-1 ALit) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Aspa-ALit) GLP-1 (7-39) Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ALit) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-ALit) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ALit) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-ALit) GLP-1(7-37); Gly8Arg34Lys26,37-bis-(Aspa-ALit) GLP-1(7-38); (7-39)Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ALit) GLP-1(7-36); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-ALit) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ALit) GLP-1(7-37);

 $Val^8Arg^{34}Lys^{26}$ , <sup>36</sup>-bis-(Aspa-ALit) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-ALit) GLP-1(7-37); FRESENIUS EXHIBIT 1020 Page 72 of 129

Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Aspa-ALit) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-ALit) GLP-1(7-38); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Aspa-ALit) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,38</sup>-bis-(Aspa-ALit) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>. <sup>39</sup>-bis-(Aspa-ALit) GLP-1(7-39); 5 Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-ALit) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-ALit) GLP-1(7-39); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ALit) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ALit) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ALit) GLP-1(7-38); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ALit) GLP-1 10 (7-39)Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup> <sup>36</sup>-bis-(Aspa-ALit) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Aspa-ALit) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Aspa-ALit) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Aspa-ALit) GLP-1(7-37); 15

Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Aspa-ALit) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Aspa-ALit) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-ALit) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>26,38</sup>-bis-(Aspa-ALit) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,38</sup>-bis-(Aspa-ALit) GLP-1(7-38); 20 Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Aspa-ALit) GLP-1(7-39);

Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-ALit) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-ALit) GLP-1(7-39);

Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ALit) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ALit) GLP-1(7-37); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa- 25 ALit) GLP-1(7-38); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Aspa-ALit) GLP-1 (7-39)

Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Aspa-ALit) GLP-1(7-38); Infr Arg Lys --bis-(Aspa-ALit) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Aspa-ALit) GLP-1(7-38); 35 Thr<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,38</sup>-bis-(Aspa-ALit) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Aspa-ALit) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Aspa-ALit) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Aspa-ALit) GLP-1(7-39); Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-36); Lys<sup>26, 34</sup>-bis- 40 Clus ADod) GLP 1(7-37); Lys<sup>26, 34</sup>-bis- 40

(Glyc-ADod) GLP-1(7-37);  $Lys^{26, 34}$ -bis-(Glyc-ADod) GLP-1(7-38);  $Lys^{26, 34}$ -bis-(Glyc-ADod) GLP-1(7-39)

Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ADod) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26</sup>, Arg<sup>2-</sup>Lys<sup>2-,63-</sup>bis-(Glyc-ADod) GLP-1(7-36); Arg<sup>3-</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Glyc-ADod) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,36</sup>-bis-(Glyc-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glyc-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glyc-ADod) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-ADod) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-ADod) GLP-1(7-39); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glyc-ADod) GLP-1(7-30); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glyc-ADod)

GLP-1(7-39); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-ADod) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18, 34</sup>-bis-(Glyc-ADod) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-26-bis-(Glyc-ADod) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-ADod) GLP-1(7-37);  $\operatorname{Arg}^{34}$ Lys<sup>18,26</sup>-bis-(Glyc-ADod) GLP-1(7-37);  $\operatorname{Arg}^{26}$ Lys<sup>18, 34</sup>-bis-(Glyc-ADod) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 55</sup> <sup>34</sup>-bis-(Glyc-ADod) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ADod) GLP-1(7-39);

Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glyc-ADod) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>23</sup>, Arg Eys  $-613+(Gryc-ADod) GLP -1(7-36); Arg <math>^{25}, ^{34}-bis-(Gryc-ADod) GLP -1(7-36); Arg <math>^{26}Lys^{23}, ^{34}-bis-(Gryc-ADod) GLP -1(7-37); Arg <math>^{34}Lys^{23,26}-bis-(Gryc-ADod) GLP -1(7-38); Arg <math>^{34}Lys^{23,26}-bis-(Gryc-ADod) GLP -1(7-38); Arg <math>^{34}Lys^{23,26}-bis-(Gryc-ADod) GLP -1(7-38); Arg <math>^{26}Lys^{23,26}-bis-(Gryc-ADod) GLP -1(7-38); Arg {}^{26}Lys^{23,26}-bis-(Gryc-ADod) GLP -1(7-36); Arg {}^{26}Lys$ <sup>34</sup>-bis-(Glyc-ADod) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glyc-ADod) GLP-1(7-39);

Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glyc-ADod) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 65</sup> <sup>26</sup>-bis-(Glyc-ADod) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glyc-ADod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glyc-ADod) GLP-

1(7-37); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glyc-ADod) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glyc-ADod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glyc-ADod) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glyc-ADod) GLP-1(7-39); ADod) GLP-1(7-39); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ADod) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>24</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ADod) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>24</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ADod) GLP-1(7-36); Glx<sup>8</sup>Arg<sup>24</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ADod) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ADod) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ADod) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-ADod) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>26,37</sup>-bis-(Glyc-ADod) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glyc-ADod) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glyc-ADod) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glyc-ADod) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}$ Lys<sup>26,38</sup>-bis-(Glyc-ADod) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}$ Lys<sup>36,38</sup>-bis-(Glyc-ADod) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup> Lys<sup>34</sup>,  ${}^{39}$ -bis-(Glyc-ADod) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26</sup>, Lys<sup>36, 39</sup>-bis-(Glyc-ADod) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-ADod) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glyc-ADod) GLP-1(7-39); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-36); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-37); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-38); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ADod) ADD 1 - (7 - 39)Val8Arg26Lys34,36-bis-(Glyc-ADod) GLP-1(7-36); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ADod) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ADod) GLP-1(7-37); Va18Arg34Lys26, 36-bis-(Glyc-ADod) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-ADod) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-ADod) GLP-1(7-39); Val<sup>8</sup>Arg<sup>25, 34</sup>Lys<sup>36,39</sup>-bis-(Glyc-ADod) GLP-1(7-39); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26,</sup> Scr Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-30); Scr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-37); Scr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-38); Scr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-36); Scr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ADod) GLP-1(7-36); Scr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ADod) GLP-1(7-37); Scr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ADod) GLP-1(7-37); Scr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ADod) GLP-1(7-37); Scr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-ADod) GLP-1(7-37); Scr<sup>8</sup>Arg<sup>34</sup>Lys<sup>4</sup>-bis-(Glyc-ADod) GLP-1(7-37); Scr<sup>8</sup>Arg<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>-bis-(Glyc-ADod) GLP-1(7-37); Scr<sup>8</sup>Arg<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>-bis-(Glyc-ADod) GLP-1(7-37); Scr<sup>8</sup>Arg<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>-bis-(Blyc-ADod) GLP-1(7-37); Scr<sup>8</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Lys<sup>4</sup>Ly Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-ADod) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glyc-ADod) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glyc-ADod) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Glyc-ADod) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36,38</sup>-bis-(Glyc-ADod) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(Glyc-ADod) GLP-1(7-39); Ser<sup>8</sup> Arg<sup>26</sup> Lys<sup>26, 39</sup>-bis-(Glyc-ADod) GLP-1(7-39); Ser<sup>8</sup> Arg<sup>26, 34</sup>Lys<sup>26, 39</sup>-bis-(Glyc-ADod) GLP-1(7-39); Ser<sup>8</sup> Arg<sup>26, 34</sup>-Lys<sup>36, 39</sup>-bis-(Glyc-ADod) GLP-1(7-39); Thr<sup>8</sup> Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-36); Thr<sup>8</sup> Lys<sup>26, 34</sup>-bis-(Glyc-ADod) GLP-1(7-38); Thr<sup>8</sup> Lys<sup>26</sup>, 34 -bis-(Glyc-ADod) Hys<sup>26</sup>, 34 -bis-(Glyc-ADod) Hys<sup>26</sup>, 34 -bis-(G 1(7-39) Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ADod) GLP-1(7-36); 1(7-59) fm Arg Lys --ois-(Glyc-ADod) GLP-1(7-50); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ADod) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ADod) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ADod) GLP-5 1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-ADod) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glyc-ADod) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glyc-ADod) GLP-1(7-38); The Arg  $^{34}$ Lys  $^{26,38}$ -bis-(Glyc-ADod) GLP-1(7-38); Thr  $^{8}$ Arg  $^{26,34}$ Lys  $^{26,38}$ -bis-(Glyc-ADod) GLP-1(7-38); Thr  $^{8}$ Arg  $^{26,34}$ Lys  $^{36,38}$ -bis-(Glyc-ADod) GLP-1(7-38); Thr  $^{8}$ Arg  $^{26}$ Lys  $^{34,39}$ -bis-(Glyc-ADod) GLP-1(7-39); Thr Arg Lys  $^{26,39}$ -bis-(Glyc-ADod) GLP-1(7-39); Thr Arg  $^{26,34}$ Lys  $^{26,39}$ -bis-(Glyc-ADod) GLP-1(7-39); Lys  $^{26,34}$ -bis-(Glyc-ATet) GLP-1(7-36); Lys  $^{26,34}$ -bis-(Glyc-ATet) GLP-1(Tet) GLP-1(Tet) GLP-1(Tet) GLP-1(Tet) GLP-1(Te ATet) GLP-1(7-37); Lys<sup>26, 34</sup>-bis-(Glyc-ATet) GLP-1(7-38);

Lvs<sup>26, 34</sup>-bis-(Glyc-ATet) GLP-1(7-39)

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Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ATet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Glyc-ATet) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-Aret) GLP-1(7-37);  $Arg^{34}Lys^{26}$ ,  $^{36}$ -bis-(Glyc-ATet) GLP-1(7-37);  $Arg^{34}Lys^{26}$ ,  $^{36}$ -bis-(Glyc-ATet) GLP-1(7-37);  $Arg^{34}Lys^{26,37}$ -bis-(Glyc-ATet) GLP-1(7-37);  $Arg^{34}Lys^{26,37}$ -bis-(Glyc-ATet) GLP-1(7-37);  $Arg^{26}Lys^{34}$ ,  $^{39}$ -bis-(Glyc-ATet) GLP-1(7-39);  $Arg^{34}Lys^{26,39}$ -bis-(Glyc-ATet) GLP-1(7-39);  $Arg^{34}Lys^{26,39}$ -bis-(Glyc-ATet) GLP-1(7-39);  $Arg^{34}Lys^{26,39}$ -bis-(Glyc-ATet) GLP-1(7-39);  $Arg^{34}Lys^{26,39}$ -bis-(Glyc-ATet) GLP-1(7-39);  $Arg^{26,34}Lys^{36,39}$ -bis-(Glyc-ATet) GLP-1(7-39);  $Arg^{36,39}$ -bis-(Glyc-ATet) Arg^{36,39}-bis-(Glyc-ATet) Arg^{36,39}-bis-(Glyc-ATet) Arg^{36,39}-bis-(Glyc-ATet) Arg^{36,39}-bis-(Glyc-ATet) Arg 5 1(7-39);

1(7-39); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-ATet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18, 26</sup>-bis-(Glyc-ATet) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc- 10 ATet) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ATet) GLP-1 (7-37); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-ATet) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ATet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-ATet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-ATet) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ATet) GLP-1(7-30); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ATet) GLP-1(7-30); Arg<sup>4</sup>Lys<sup>18,26</sup>-bis-(Glyc-ATet) Arg<sup>4</sup>Lys<sup>18,26</sup>-bis-(Glyc-ATet) Arg<sup>4</sup>Lys<sup>18,26</sup>-bis-(Glyc-ATet) Arg<sup>4</sup> ATet) GLP-1(7-39);

Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glyc-ATet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>23,</sup> 26-bis-(Glyc-ATet) GLP-1(7-36); Arg26Lys23, 34-bis-(Glyc-ATet) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glyc-ATet) GLP-1 (7-37); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glyc-ATet) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glyc-ATet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23,26</sup>  $^{34}$ -bis-(Glyc-ATet) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glyc-ATet) GLP-1(7-39);

Arel GLP-1(7-39), Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glyc-ATet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glyc-ATet) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glyc-ATet) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glyc-ATet) GLP-1 25 (7-37); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glyc-ATet) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glyc-ATet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27</sup>, 26 bis-(Glyc-ATet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27</sup>, 36 bis-(Glyc-ATet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27</sup>, 34bis-(Glyc-ATet) GLP-1(7-39); Arg34Lys27, 26-bis-(Glyc-ATet) GLP-1(7-39);

Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ATet) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26, 30</sup> <sup>34</sup>-bis -(Glyc-ATet) GLP-1(7-37) ; Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ATet) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ATet) GLP-1 (7-39)

Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ATet) GLP-1(7-36); Gly  $^{3}$ Arg  $^{26}$ Lys  $^{34}$ . Js  $^{36}$ -bis-(Glyc-ATet) GLP-1(7-37); Gly  $^{8}$ Arg  $^{34}$ Lys  $^{26}$ ,  $^{36}$ -bis-(Glyc-ATet) GLP-1(7-37); Gly  $^{8}$ Arg  $^{26}$ Lys  $^{34}$ -bis-(Glyc-ATet) GLP-1(7-37); Gly  $^{8}$ Arg  $^{26}$ Lys  $^{34}$ -bis-(Glyc-ATet) GLP-1(7-38); 40 Gly  $^{8}$ Arg  $^{26}$ Lys  $^{34}$ Lys  $^{26}$ -38-bis-(Glyc-ATet) GLP-1(7-38); 40 Gly  $^{8}$ Arg  $^{26}$ .  $^{34}$ Lys  $^{26}$ -38-bis-(Glyc-ATet) GLP-1(7-38); Gly  $^{8}$ Arg  $^{26}$ Lys  $^{34}$ -39-bis-(Glyc-ATet) GLP-1(7-38); Gly  $^{8}$ Arg  $^{26}$ Lys  $^{34}$ .  $^{39}$ -bis-(Glyc-ATet) GLP-1(7-39); Gly  $^{8}$ Arg  $^{34}$ Lys  $^{26}$ .  $^{39}$ -bis-(Glyc-ATet) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-ATet) GLP-1(7-39);

 $Val^8 Arg^{34} Lys^{26}$ , <sup>36</sup>-bis-(Glyc-ATet) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ATet) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ATet) GLP-1(7-37); Val8Arg26Lys34,37-bis-(Glyc-ATet) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glyc-ATet) GLP-1(7-37); 55 Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glyc-ATet) GLP-1(7-38); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Glyc-ATet) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>, 260 Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, 260 Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>Lys<sup>34</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>34</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>34</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys Val Alg Lys - ols (Olyc-Alet) OLP-1(7-38); Val Alg  $^{34}$ Lys  $^{36,38}$ -bis-(Glyc-Alet) GLP-1(7-38); Val Arg  $^{26}$ Lys  $^{24}$ .  $^{39}$ -bis-(Glyc-Alet) GLP-1(7-39); Val Arg  $^{36}$ Arg  $^{34}$ Lys  $^{26,39}$ -bis-(Glyc-Alet) GLP-1(7-39); Val Arg  $^{26}$ .  $^{34}$ Lys  $^{36,39}$ -bis-(Glyc- 60) ATet) GLP-1(7-39);

Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ATet) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ATet) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ATet) GLP-1(7-38); Ser8Lys26, 34-bis-(Glyc-ATet) GLP-1(7-39) 65

Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ATet) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ATet) GLP-1(7-36);

Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ATet) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ATet) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-ATet) GLP-1(7-37);  $Ser^{8}Arg^{34}Lys^{26,37}$ -bis-(Glyc-ATet) GLP-1(7-37);  $Ser^8Arg^{26}Lys^{34,38}$ -bis-(Glyc-ATet) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}Lys^{26,38}$ -bis-(Glyc-ATet) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}Lys^{36,38}$ -bis-(Glyc-ATet) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>,  ${}^{39}$ -bis-(Glyc-ATet) GLP-1(7-39); Ser<sup>8</sup> Arg<sup>34</sup> Lys<sup>26,39</sup>-bis-(Glyc-ATet) GLP-1(7-39); Ser<sup>8</sup> Arg<sup>26, 34</sup> Lys<sup>36,39</sup>-bis-(Glyc-ATet) GLP-1(7-39);  $x = \frac{1}{2}$ Ser<sup>8</sup>Arg<sup>2</sup>

Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ATet) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ATet) GLP-1(7-37); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ATet) GLP-1(7-38); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-ATet) GLP-1 (7-39)

- 15 Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ATet) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ATet) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ATet) GLP-1(7-37); Thr  $^{8}$ Arg  $^{34}$ Lys  $^{26}$ ,  $^{36}$ -bis-(Glyc-ATet) GLP -1(7-37); Thr  $^{8}$ Arg  $^{26}$ Lys  $^{34}$ .37-bis-(Glyc-ATet) GLP -1(7-37); Thr  $^{8}$ Arg  $^{34}$ Lys  $^{26}$ .37-bis-(Glyc-ATet) GLP -1(7-37); Thr  $^{8}$ Arg  $^{26}$ Lys  $^{34}$ .38-bis-(Glyc-ATet) GLP -1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}Lys^{26,38}$ -bis-(Glyc-ATet) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}Lys^{26,38}$ -bis-(Glyc-ATet) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}Lys^{36,38}$ -bis-(Glyc-ATet) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>26</sup>,  ${}^{39}$ -bis-(Glyc-ATet) GLP-1(7-39);

Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Glyc-ATet) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-ATet) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glyc-ATet) GLP-1(7-39); Lys<sup>26, 34</sup>-bis-(Glyc-AHex) GLP-1(7-36); Lys<sup>26, 34</sup>-bis-(Glyc-AHex) GLP-1(7-37); Lys<sup>26, 34</sup>-bis-(Glyc-AHex) GLP-1(7-38); Lys<sup>26, 34</sup>-bis-(Glyc-AHex) GLP-1(7-39) Arg<sup>26</sup>Lys<sup>34,36</sup>bis-(Glyc-AHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-AHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AHex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AHex) Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AHex) Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AHex) Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AHex) Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-

GLP-1(7-39)  $\operatorname{Arg}^{26}\operatorname{Lys}^{18, 34}$ -bis-(Glyc-AHex) GLP-1(7-36);  $\operatorname{Arg}^{34}\operatorname{Lys}^{18, 34}$ 26-bis-(Glyc-AHex) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-AHex) GLP-1(7-37);  $\operatorname{Arg}^{34}\operatorname{Lys}^{18,26}$ -bis-(Glyc-AHex) GLP-1(7-37);  $\operatorname{Arg}^{26}\operatorname{Lys}^{18, -34}$ -bis-(Glyc-AHex) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-AHex) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18</sup> <sup>34</sup>-bis-(Glyc-AHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-AHex) GLP-1(7-39);

Gly<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36,39</sup>-bis-(Glyc-ATet) GLP-1(7-39);  $Al^8Lys^{26, 34}Lys^{36,39}$ -bis-(Glyc-ATet) GLP-1(7-36); Val<sup>8</sup>Lys^{26}, <sup>34</sup>-bis-(Glyc-ATet) GLP-1(7-37); Val<sup>8</sup>Lys^{26, 34}-bis-(Glyc-ATet) GLP-1(7-38); Val<sup>8</sup>Lys^{26, 34}-bis-(Glyc-ATet) GLP-1(7-39) Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ATet) GLP-1(7-36); Arg<sup>34</sup>Lys^{23, 26}-bis-(Glyc-AHex) GLP-1(7-38); Arg<sup>26</sup>Lys^{23, 34}-bis-(Glyc-AHex) GLP-1(7-38); Arg<sup>26</sup>Lys^{23, 26}-bis-(Glyc-AHex) GLP-1(7-38); Arg<sup>34</sup>Lys^{23, 26}-bis-(Glyc-AHex) GLP-1(7-38); Arg<sup>34</sup> AHex) GLP-1(7-39);

Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glyc-AHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27,</sup> <sup>26</sup>-bis-(Glyc-AHex) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glyc-Altex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glyc-Altex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glyc-Altex) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glyc-Altex) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 26</sup>-bis-(Glyc-Altex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis -(Glyc-AHex) GLP-1(7-39);

Gly<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-AHex) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-AHex) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-AHex) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-AHex) GLP-1(7-39)

Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AHex) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-AHex) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AHex) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-AHex) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-AHex) GLP-1(7-37);

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143  $Gly^8Arg^{34}Lys^{26,37}$ -bis-(Glyc-AHex) GLP-1(7-37);  $Gly^8Arg^{26}Lys^{34,38}$ -bis-(Glyc-AHex) GLP-1(7-38);  $Gly^8Arg^{34}Lys^{26,38}$ -bis-(Glyc-AHex) GLP-1(7-38);  $Gly^8Arg^{26}$ ,  $^{34}Lys^{36,38}$ -bis-(Glyc-AHex) GLP-1(7-38);  $Gly^8Arg^{26}Lys^{34}$ ,  $^{39}$ -bis-(Glyc-AHex) GLP-1(7-39);  $Gly^8Arg^{26}$ ,  $^{34}Lys^{36,39}$ -bis-(Glyc-AHex) GLP-1(7-39);  $Gly^8Arg^{26}$ ,  $^{34}Lys^{36,39}$ -bis-(Glyc-AHex) GLP-1(7-39);  $Gly^8Arg^{26}$ ,  $^{34}$ -bis-(Glyc-AHex) GLP-1(7-39);  $Val^8Lys^{26}$ ,  $^{34}$ -bis-(Glyc-AHex) GLP-1(7-36);  $Val^8Lys^{26}$ ,  $^{34}$ -bis-(Glyc-AHex) GLP-1(7-37);  $Val^8Lys^{26}$ ,  $^{34}$ -bis-(Glyc-AHex) GLP-1(7-39); (7-39)

(7-39)

Val<sup>8</sup>Árg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AHex) GLP-1(7-36);  $Val^8 Arg^{34} Lys^{26}$ , <sup>36</sup>-bis-(Glyc-AHex) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AHex) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-AHex) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-AHex) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-AHex) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glyc-AHex) GLP-1(7-38); 15 Val<sup>8</sup>Arg<sup>26</sup> Lys<sup>26,38</sup>-bis-(Glyc-AHex) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26, 34</sup> Lys<sup>26,38</sup>-bis-(Glyc-AHex) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26, 34</sup> Lys<sup>36,38</sup>-bis-(Glyc-AHex) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup> Lys<sup>34, 39</sup>-bis-(Glyc-AHex) GLP-1(7-39); 20 Val<sup>8</sup>Arg<sup>26, 34</sup> Lys<sup>26,39</sup>-bis-(Glyc-AHex) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26, 34</sup> Lys<sup>26,39</sup>-bis-(Glyc-AHex) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26, 34</sup> Lys<sup>26,39</sup>-bis-(Glyc-AHex) GLP-1(7-39);

Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AHex) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AHex) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AHex) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AHex) GLP-1(7-38); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AHex) GLP- 25

1(7-39)

Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Glyc-AHex) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>,  ${}^{34}Lys^{36,38}$ -bis-(Glyc-AHex) GLP-1(7-38); 35 Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>,  ${}^{39}$ -bis-(Glyc-AHex) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AHex) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glyc-AHex) GLP-1(7-39); (26)

Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AHex) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AHex) GLP-1(7-37); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc- 40 AHex) GLP-1(7-38); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AHex) GLP-1(7-39)

Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AHex) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-AHex) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AHex) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glyc-AHex) GLP-1(7-39); Lys<sup>26, 34</sup>-bis-(Glyc-AOct) GLP-1(7-36); Lys<sup>26, 34</sup>-bis-55

(Glyc-AOct) GLP-1(7-37); Lys<sup>26, 34</sup>-bis-(Glyc-AOct) GLP-1(7-38); Lys<sup>26, 34</sup>-bis-(Glyc-AOct) GLP-1(7-39)

Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26</sup>, Arg Lys  $^{-01s}$ (Glyc-AOct) GLP-1(7-30); Arg  $^{26}$ Lys $^{34,36}$ -bis-(Glyc-AOct) GLP-1(7-36); Arg $^{26}$ Lys $^{34,36}$ -bis-(Glyc-AOct) GLP-1(7-37); Arg $^{34}$ Lys $^{26,36}$ -bis-(Glyc-AOct) GLP-1(7-37); Arg $^{26}$ Lys $^{34,37}$ -bis-(Glyc-AOct) GLP-1(7-37); Arg}  $^{26}$ Lys $^{34,37}$ -bis-(Glyc-AOct) GLP-1(7-37); Arg} ^{26}Lys $^{34,37}$ -bis-(Glyc-AOct) Hys  $^{34,37}$ -bis-(Glyc-AOct) <sup>39</sup>-bis-(Glyc-AOct) GLP-1(7-39);  $\operatorname{Arg}^{34}$ Lys<sup>26,39</sup>-bis-(Glyc-AOct) GLP-1(7-39);  $\operatorname{Arg}^{26, -34}$ Lys<sup>36,39</sup>-bis-(Glyc-AOct)

GLP-1(7-39); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-AOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18,</sup> 26-bis-(Glyc-AOct) GLP-1(7-36); Arg26Lys18, 34-bis-(GlycAOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-AOct) GLP-1 (7-37); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18</sup>, <sup>34</sup>-bis-(Glyc-AOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-AOct) GLP-1(7-39);

Aug<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glyc-AOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>23, 24</sup>-bis-(Glyc-AOct) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glyc-AOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23, 24</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23, 26</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23, 26</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>34</sup>-bis-(Glyc-AOct) Arg<sup>34</sup>-bis-(Glyc-AOct) Arg<sup>34</sup>-bis-(Glyc-AOct) Arg<sup>34</sup>-bis-(Glyc-AOct) Arg<sup>34</sup>-bis-(Glyc-AOct) Arg<sup>34</sup>-bis-(Glyc-AOct) Arg<sup>34</sup>-bis-(Glyc-

- <sup>26</sup>Jys<sup>27, 34</sup>-bis-(Glyc-AOct) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glyc-AOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 34</sup>-bis-(Glyc-AOct) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(Glyc-AOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 26</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glyc-AOct) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 26</sup>-bis-(Glyc-AOct) Arg<sup>26</sup>Lys<sup>27, 26</sup>-bis-(Glyc-AOct) Arg<sup>26</sup>Lys<sup>27, 26</sup>-bis-(Glyc-AOct) Arg<sup>26</sup>Lys<sup>27, 26</sup>-bis-(Glyc-AOct) Arg<sup>26</sup>Lys<sup>27, 26</sup>-bis-(Glyc-AOct) A <sup>34</sup>-bis-(Glyc-AOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(Glyc-AOct) GLP-1(7-39);
- Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AOct) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AOct) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AOct) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AOct) GLP-1 (7-39)
- Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AOct) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>. <sup>36</sup>-bis-(Glyc-AOct) GLP-1(7-36); Gly8Arg26Lys34,36-bis-(Glyc-AOct) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AOct) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glyc-AOct) GLP-1(7-39);
  - Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-AOct) GLP-1(7-36); Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-AOct) GLP-1(7-37); Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-AOct) GLP-1(7-38); Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-AOct) GLP-1 (7-39)
  - Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AOct) GLP-1(7-36); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-AOct) GLP-1(7-36);  $Val^8 Arg^{26} Lys^{34,36}$ -bis-(Glyc-AOct) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-AOct) GLP-1(7-37); Val8Arg26Lys34,37-bis-(Glyc-AOct) GLP-1(7-37);

<sup>34</sup>-bis-(Glyc-AOct) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-AOct) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-AOct) GLP-1 (7-39)

Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AOct) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Glyc-AOct) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AOct) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-AOct) GLP-1(7-37);  $Ser^{8}Arg^{26}Lys^{34,37}$ -bis-(Glyc-AOct) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glyc-AOct) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glyc-AOct) GLP-1(7-38); Ser Arg Lys -bis-(Glyc-AOct) GLP-1(7-38); Ser Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(Glyc-AOct) GLP-1(7-38); Ser Arg<sup>26, 34</sup>Lys<sup>36,38</sup>-bis-(Glyc-AOct) GLP-1(7-38); Ser Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Glyc-AOct) GLP-1(7-39); Ser Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-AOct) GLP-1(7-39); Ser Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glyc-AOct) GLP-1(7-39);

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Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AOct) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AOct) GLP-1(7-37); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AOct) GLP-1(7-38); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(Glyc-AOct) GLP-1 (7-39)

Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AOct) GLP-1(7-36); 5 Thr Arg Lys<sup>26</sup>, <sup>36</sup>-bis-(Glyc-AOct) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Glyc-AOct) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-AOct) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Glyc-AOct) GLP-1(7-37); CLP 1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-AOct) GLP-1(7-37); Intr Arg Lys<sup>26,37</sup>-bis-(Glyc-AOct) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>26,37</sup>-bis-(Glyc-AOct) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glyc-AOct) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26,38</sup>-bis-(Glyc-AOct) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(Glyc-AOct) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(Glyc-AOct) GLP-1(7-39); Thr<sup>8</sup> Arg<sup>34</sup> Lys<sup>26,39</sup>-bis-(Glyc-AOct) GLP-1(7-39); Thr<sup>8</sup> Arg<sup>34</sup> Lys<sup>26,39</sup>-bis-(Glyc-AOct) GLP-1(7-39); Thr<sup>8</sup> Arg<sup>26, 34</sup> Lys<sup>36,39</sup>-bis-(Glyc-AOct) GLP-1(7-39); Lys<sup>26, 34</sup>-bis-(Glyc-ALit) GLP-1(7-36); Lys<sup>26, 34</sup>-bis-(Glyc-ALit) GLP-1(7-38);  $\sum_{i=2}^{20} \frac{34}{i} \frac{1}{i} \frac{1$ 

Lys<sup>26, 34</sup>-bis-(Glyc-ALit) GLP-1(7-39)

Lys<sup>26, 5\*</sup>-bis-(Glyc-ALit) GLP-1(7-39) Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ALit) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ALit) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc- 20 ALit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ALit) GLP-1 (7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-ALit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glyc-ALit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glyc-ALit) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Glyc-ALit) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-ALit) GLP-1(7-20); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glyc-ALit) GLP- 25 1(7-39);

1(7-39); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-ALit) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18, 26</sup>-bis-(Glyc-ALit) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-ALit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ALit) GLP-1(7-38); 30 Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ALit) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-ALit) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-ALit) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(Glyc-ALit) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ALit) GLP-1(7-30); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ALit) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ALit) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ALit) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ALit) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ALit) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ALit) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(Glyc-ALit) A

ALit) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(Glyc-ALit) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>23</sup>, 26-bis-(Glyc-ALit) GLP-1(7-36); Arg26 Lys23, 34-bis-(Glyc- 35 26-bis-(Giye-ALit) GLP-1(7-30), Arg  $^{23}$ /26-bis-(Giye-ALit) GLP-1 (7-37); Arg $^{26}$ Lys $^{23}$ ,  $^{34}$ -bis-(Giye-ALit) GLP-1(7-38); Arg $^{23}$ /26-bis-(Giye-ALit) GLP-1(7-38); Arg $^{26}$ Lys $^{23}$ ,  $^{24}$ <sup>34</sup>-bis-(Glyc-ALit) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(Glyc-ALit) GLP-1(7-39);

At l) GLP-1(7-39), Arg<sup>26</sup>Lys<sup>27</sup> <sup>34</sup>-bis-(Glyc-ALit) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27</sup>, <sup>26</sup>-bis-(Glyc-ALit) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>27</sup>, <sup>34</sup>-bis-(Glyc-ALit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27</sup>, <sup>26</sup>-bis-(Glyc-ALit) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27</sup>, <sup>26</sup>-bis-(Glyc-ALit) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27</sup>, <sup>45</sup> <sup>34</sup>Lis (Class ALit) (CLP 1(7-28)); Arg<sup>34</sup>Lys<sup>27</sup>, <sup>45</sup> <sup>34</sup>Lis (Class ALit) (CLP 1(7-28)); Arg<sup>45</sup>Lys<sup>27</sup>, <sup>45</sup> <sup>35</sup>Lis (Class ALit) (CLP 1(7-28)); Arg<sup>45</sup>Lys<sup>27</sup>, <sup>45</sup> <sup>35</sup>Lis (C

- Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ALit) GLP-1(7-36); Gly8Arg26Lys34,36-bis-(Glyc-ALit) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ALit) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ALit) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-ALit) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glyc-ALit) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26,38</sup>-bis-(Glyc-ALit) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,38</sup>-bis-(Glyc-ALit) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Glyc-ALit) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>24</sup>Lys<sup>26,39</sup>-bis-(Glyc-ALit) GLP-1(7-39);  $Gly^8 Arg^{34} Lys^{26,39}$ -bis-(Glyc-ALit) GLP-1(7-39);  $Gly^8 Arg^{26,34} Lys^{36,39}$ -bis-(Glyc-ALit) GLP-1(7-39);
- Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-ALit) GLP-1(7-36); Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-ALit) GLP-1(7-37); Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc- 65 ALit) GLP-1(7-38); Val<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-ALit) GLP-1(7-39)

146 Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ALit) GLP-1(7-36); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Glyc-ALit) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ALit) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Glyc-ALit) GLP-1(7-37);  $\begin{array}{lll} \label{eq:Valsarg} Val^8 Arg^{34} Lys^{26, \ 36} -bis-(Giyc-ALit) \ GLP-1(7-37); \\ Val^8 Arg^{26} Lys^{34,37} -bis-(Giyc-ALit) \ GLP-1(7-37); \\ Val^8 Arg^{24} Lys^{26,37} -bis-(Giyc-ALit) \ GLP-1(7-37); \\ Val^8 Arg^{26} Lys^{34,38} -bis-(Giyc-ALit) \ GLP-1(7-38); \\ Val^8 Arg^{26, \ 34} Lys^{26,38} -bis-(Giyc-ALit) \ GLP-1(7-38); \\ Val^8 Arg^{26, \ 34} Lys^{36,38} -bis-(Giyc-ALit) \ GLP-1(7-38); \\ Val^8 Arg^{26, \ 34} Lys^{26,39} -bis-(Giyc-ALit) \ GLP-1(7-39); \\ Val^8 Arg^{26, \ 34} Lys^{26,39} -bis-(Giyc-ALit) \ GLP-1(7-39); \\ Val^8 Arg^{26, \ 34} Lys^{26,39} -bis-(Giyc-ALit) \ GLP-1(7-39); \\ Ser^8 Lys^{26, \ 34} -bis-(Giyc-ALit) \ GLP-1(7-36); \ Ser^8 Lys^{26, \ 34} -bis-(Giyc-ALit) \ GLP-1(7-37); \\ Ser^8 Lys^{26, \ 34} -bis-(Giyc-ALit) \ GLP-1(7-36); \\ Ser^8 Lys^{26, \ 34} -bis-(Giyc-ALit) \ GLP-1(7-37); \\ Ser^8 Lys^{26, \ 34} -bis-(Giyc-ALit) \ Ser^8 Lys^{26, \ 34} -bis-(Siyc-ALit) \ Ser^8 Lys^{26,$ 15 39) Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ALit) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ALit) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ALit) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ALit) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-ALit) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-ALit) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glyc-ALit) GLP-1(7-38); Ser Arg<sup>2</sup> Lys<sup>26,38</sup>-bis-(Glyc-ALit) GLP-1(7-38); Ser<sup>8</sup> Arg<sup>26</sup>,  ${}^{34}$ Lys<sup>26,38</sup>-bis-(Glyc-ALit) GLP-1(7-38); Ser<sup>8</sup> Arg<sup>26</sup>,  ${}^{34}$ Lys<sup>36,38</sup>-bis-(Glyc-ALit) GLP-1(7-38); Ser<sup>8</sup> Arg<sup>26</sup> Lys<sup>34</sup>,  ${}^{39}$ -bis-(Glyc-ALit) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(Glyc-ALit) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glyc-ALit) GLP-1(7-39); Thr<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-ALit) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-ALit) GLP-1(7-37); Thr<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-ALit) GLP-1(7-38); Thr<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(Glyc-ALit) GLP-1 (7-39) Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ALit) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(Glyc-ALit) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(Glyc-ALit) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(Glyc-ALit) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-ALit) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(Glyc-ALit) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(Glyc-ALit) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(Glyc-ALit) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26,38</sup>-bis-(Glyc-ALit) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Glyc-ALit) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(Glyc-ALit) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>26,39</sup>-bis-(Glyc-ALit) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(Glyc-ALit) GLP-1(7-39); Lys<sup>26, 34</sup>-bis-(GAB-GDod) GLP-1(7-36); Lys<sup>26, 34</sup>-bis-(GAB-GDod) GLP-1(7-37); Lys<sup>26, 34</sup>-bis-(GAB-GDod) GLP-1(7-38): Lys<sup>26, 34</sup>-bis-(GAB-GDod) GLP-1(7-39) GLP-1(7-38); Lys<sup>26, 34</sup>-bis-(GAB-GDod) GLP-1(7-39) ArgLysClysLysSolutionClysLysSolutionSolution $^{34}$ -bis-(Glyc-ALit)GLP-1(7-39);ArgArg $^{26}$ Lys $^{34}$ -bis-(GAB-GDod)GLP-1(7-36);Arg $^{34}$ Lys $^{26}$ ,  $^{26}$ -bis-(GAB-GDod)GLP-1(7-36);Arg $^{36}$ -bis-(GAB-GDod)GLP-1(7-37);Arg $^{36}$ -bis-(GAB-GDod)GLP-1(7-39);Arg $^{36}$ -bis-(36)-39-bis-(36)-39-bis-(36)-39-bis-(36)-39-bis-(36)-39-bis-(36)-39-bis-(36)-39-bis-(36)-39-bis-(36)-39-bis-(36)-39-bis-(36)-39-bis-(36)-39-bis-(36)-39-bis-(36 (GAB-GDod) GLP-1(7-39);

Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GDod) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18,</sup> Ang Lys --ois-(GAB-GDod) GLP-1(7-30); Ang Lys<sup>25</sup>, 26-bis-(GAB-GDod) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GDod) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GDod) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GDod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GDod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GDod) GLP-1(7-39); Arg<sup>24</sup>Lys<sup>18,25</sup>-bis-(GAB-GDod) GLP-1(7-39); Arg<sup>24</sup>Lys<sup>23, 34</sup>-bis-(GAB-GDod) GLP-1(7-39); Arg<sup>24</sup>Lys<sup>23, 34</sup>-bis-(GAB-GDod) GLP-1(7-39); Arg<sup>24</sup>Lys<sup>23, 34</sup>-bis-(GAB-GDod) GLP-1(7-39); Arg<sup>25</sup>Lys<sup>18, 56</sup>-bis-(GAB-GDod) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>18, 56</sup>-bis-(GAB-GDod) GLP-1(7-30); Arg<sup>26</sup>Lys<sup>18, 56</sup>-bis-(GAB-GDod) GLP-1(7-30); Arg<sup>36</sup>Lys<sup>28</sup>-bis-(GAB-GDod) GLP-1(7-30); Arg<sup>36</sup>Lys<sup>36</sup>-bis-(GAB-GDod) GLP-1(7-30); Arg<sup>36</sup>Lys<sup>36</sup>-bis-(BAB-GDod) Arg<sup>36</sup>Lys<sup>36</sup>-bis-(BAB-GDod) Arg<sup>36</sup>Lys<sup>36</sup>-bis-(BAB-G

Arg<sup>-1</sup>Lys<sup>-3,25</sup>-bis-(GAB-GDod) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(GAB-GDod) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>23, 34</sup>-bis-(GAB-GDod) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(GAB-GDod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(GAB-GDod) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(GAB-GDod) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(GAB-GDod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(GAB-GDod) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(GAB-GDod) GLP-1(7-39);

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Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GDod) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 34</sup>-bis-(GAB-GDod) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GDod) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GDod) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GDod) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GDod) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 34</sup>bis-(GAB-GDod) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GDod) GLP-1(7-39); (Lt<sup>81</sup>Ly<sup>26, 34</sup>-bis-(GAB-GDod) GLP-1(7-39);

Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>27, 27</sup>-bls-(GAB-GDod) GLP-1(7-39), Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(GAB-GDod) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GDod) GLP-1(7-39); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GDod) GLP-1(7-36); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GDod) GLP-1(7-37); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-25 GDod) GLP-1(7-38); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GDod) GLP-Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GDod) GLP-1(7-36); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-25); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-26); Val<sup>8</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>26</sup>Lys<sup>2</sup>

 $\begin{array}{l} \text{(17-39) Val^8Arg^{26}Lys^{34,36}\text{-bis-(GAB-GDod) GLP-1(7-36);} \\ \text{Val^8Arg^{34}Lys^{26}, 3^6\text{-bis-(GAB-GDod) GLP-1(7-36);} \\ \text{Val^8Arg^{26}Lys^{34,36}\text{-bis-(GAB-GDod) GLP-1(7-37);} \\ \end{array}$ Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>26, 36</sup>-bis-(GAB-GDod) GLP-1(7-37); 30 Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GDod) GLP-1(7-37);  $Val^{8}Arg^{34}Lys^{26,37}$ -bis-(GAB-GDod) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GDod) GLP-1(7-38); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-GDod) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,38</sup>-bis-(GAB-GDod) GLP-1(7-38); 35 Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(GAB-GDod) GLP-1(7-39); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(GAB-GDod) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GDod) GLP-1(7-39); (26)

Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GDod) GLP-1(7-36);

Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GDod) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26, 55</sup>  $^{34}$ -bis-(GAB-GDod) GLP-1(7-37); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GDod) GLP-1(7-38); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(7-38); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(7-38); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-1(7-38); Thr<sup>8</sup>L 1(7-39)

Thr8Arg26Lys34,36-bis-(GAB-GDod) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GDod) GLP-1(7-36); 60 Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GDod) GLP-1(7-37); Thr8Arg34Lys26, 36-bis-(GAB-GDod) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GDod) GLP-1(7-37); Thr  $^{8}$ Arg  $^{34}$ Lys  $^{26,37}$ -bis-(GAB-GDod) GLP-1(7-37); Thr  $^{8}$ Arg  $^{26}$ Lys  $^{34,38}$ -bis-(GAB-GDod) GLP-1(7-38); 65 Thr  $^{8}$ Arg  $^{34}$ Lys  $^{26,38}$ -bis-(GAB-GDod) GLP-1(7-38); Thr  $^{8}$ Arg  $^{26,34}$ Lys  $^{36,38}$ -bis-(GAB-GDod) GLP-1(7-38);

Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(GAB-GDod) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(GAB-GDod) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GDod) GLP-1(7-39); Lys<sup>26, 34</sup>-bis-(GAB-GTet) GLP-1(7-36); Lys<sup>26, 34</sup>-bis-

(GAB-GTet) GLP-1(7-37); Lys<sup>26, 34</sup>-bis-(GAB-GTet) GLP-

GLP-1(7-38); Arg<sup>24</sup>Lys<sup>27, 24</sup>-bis-(GAB-GDod) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GDod) GLP-1(7-39); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GDod) GLP-1(7-39);  $^{34}$ -bis-(GAB-GDod) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GTet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GTet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GTet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GTet) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GTet) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>36,39</sup>-bis-(GAB-GTet) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>36</sup>

Gret) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(GAB-GTet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>23, 26</sup>-bis-(GAB-GTet) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>23, 26</sup>-bis-(GAB-GTet) GLP-1 (7-37); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(GAB-GTet) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(GAB-GTet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23, 26</sup>-bis-(GAB-GTet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23</sup>-bis-(CAB-GTet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23</sup>-bis-(CAB-GTet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23</sup>-bis-(CAB-GTet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23</sup>-bis-(CAB-GTet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>24</sup>-bis-(CAB-GTet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>24</sup>-bis-(CAB-GTet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>24</sup>-bis-(CAB-GTet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>24</sup>-bis-(CAB-GTet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>24</sup>-bis-(CAB-GTet) GLP-1(7-38); Arg<sup>26</sup>-bis-(CAB-GTet) GLP-1(7-38); Arg<sup>26</sup>-bis-(CAB-GTet) GLP-1(7-38); Arg<sup>26</sup>-bis-(CAB-GTE) Arg<sup>26</sup>-bis-(CAB-GTet) Arg<sup>26</sup>-bis-(CAB-GTet) Arg<sup>26</sup>-bis-(CAB-GTet) Arg<sup>26</sup>-bis-(CAB-GTet) Arg<sup>26</sup>-bis-(CAB-GTet) Arg<sup>26</sup>-bis-(CAB-GTE) Arg<sup>26</sup>-bis-(CAB-GTE) Arg<sup>26</sup>-bis-(CAB-GTE) A <sup>34</sup>-bis-(GAB-GTet) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(GAB-

<sup>27</sup>-bis-(GAB-G1et) GLP-1(7-59); Aig Lys <sup>27</sup>-bis-(GAB-GTet) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GTet) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GTet) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GTet) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GTet) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GTet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GTet) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GTet) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GTet) GLP-1(7-30); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(BAB-GTet) GLP-1(7-30); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(BAB-GTet) Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(BAB-GTet) Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(BAB-GTet) Arg<sup>34</sup>Lys<sup>27</sup>, 26</sub>-bis-(BAB-GTet) Arg<sup>34</sup>Lys<sup>27</sup>, 26</sub>-bis-(BAB-GTet) Arg<sup>34</sup>Lys<sup>27</sup>, 26-bis-(BAB-GTE) Arg<sup>34</sup>Lys<sup>27</sup>, 26-bis-(B GTet) GLP-1(7-39);

Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GTet) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GTet) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GTet) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GTet) GLP-1

Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GTet) GLP-1(7-37); Ser  $^{8}$ Arg  $^{34}$ Lys  $^{26, 36}$ -bis-(GAB-GDod) GLP-1(7-37); 45 Uly  $^{45}$ Gly  $^{8}$ Arg  $^{26}$ Lys  $^{34,38}$ -bis-(GAB-GTet) GLP-1(7-38); Ser  $^{8}$ Arg  $^{26}$ Lys  $^{34,37}$ -bis-(GAB-GDod) GLP-1(7-37); Gly  $^{8}$ Arg  $^{26}$ Lys  $^{34,38}$ -bis-(GAB-GTet) GLP-1(7-38); Ser  $^{8}$ Arg  $^{26}$ Lys  $^{34,37}$ -bis-(GAB-GDod) GLP-1(7-37); Gly  $^{8}$ Arg  $^{26, 34}$ Lys  $^{26,38}$ -bis-(GAB-GTet) GLP-1(7-38); Ser  $^{8}$ Arg  $^{26}$ Lys  $^{34,38}$ -bis-(GAB-GDod) GLP-1(7-38); Gly  $^{8}$ Arg  $^{26}$ Lys  $^{34,38}$ -bis-(GAB-GTet) GLP-1(7-39); Ser  $^{8}$ Arg  $^{26}$ Lys  $^{34,38}$ -bis-(GAB-GDod) GLP-1(7-38); 50 Gly  $^{8}$ Arg  $^{26}$ Lys  $^{34,39}$ -bis-(GAB-GTet) GLP-1(7-39); Ser  $^{8}$ Arg  $^{26}$ Lys  $^{34,39}$ -bis-(GAB-GDod) GLP-1(7-38); 50 Gly  $^{8}$ Arg  $^{26,34}$ Lys  $^{26,39}$ -bis-(GAB-GTet) GLP-1(7-39); Ser  $^{8}$ Arg  $^{26}$ Lys  $^{34,39}$ -bis-(GAB-GDod) GLP-1(7-38); 50 Gly  $^{8}$ Arg  $^{26,34}$ Lys  $^{26,39}$ -bis-(GAB-GTet) GLP-1(7-39); Ser  $^{8}$ Arg  $^{26}$ Lys  $^{34,39}$ -bis-(GAB-GDod) GLP-1(7-39); Gly  $^{8}$ Arg  $^{26,34}$ Lys  $^{26,39}$ -bis-(GAB-GTet) GLP-1(7-39); Ser  $^{8}$ Arg  $^{34}$ Lys  $^{26,39}$ -bis-(GAB-GDod) GLP-1(7-39); Gly  $^{8}$ Lys  $^{26,34}$ -bis-(GAB-GTet) GLP-1(7-36); Val  $^{8}$ Lys  $^{26,34}$ -bis-(GAB-GTet) GLP-1(7-36); Val  $^{8}$ Lys  $^{26,34}$ -bis-(GAB-GTet) GLP-1(7-36); CAB-GTet) GLP-1(7-36); CA Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GTet) GLP-1(7-37);

 $Val^8Arg^{26}Lys^{34,36}$ -bis-(GAB-GTet) GLP-1(7-36); Val<sup>8</sup>Arg^{34}Lys^{26}, <sup>36</sup>-bis-(GAB-GTet) GLP-1(7-36); Val<sup>8</sup>Arg^{26}Lys^{34,36}-bis-(GAB-GTet) GLP-1(7-37);  $Val^8 Arg^{34} Lys^{26}$ , <sup>36</sup>-bis-(GAB-GTet) GLP-1(7-37);  $Val^8 Arg^{26} Lys^{34,37}$ -bis-(GAB-GTet GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(GAB-GTet) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GTet) GLP-1(7-38); val Arg Lys -bis-(GAB-Gret) GLP-1(7-38); val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-Gret) GLP-1(7-38); val<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36,38</sup>-bis-(GAB-Gret) GLP-1(7-38); val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(GAB-Gret) GLP-1(7-39); val<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>26,39</sup>-bis-(GAB-Gret) GLP-1(7-39); val<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-Gret) GLP-1(7-39);

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Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GTet) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GTet) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GTet) GLP-1(7-38); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GTet) GLP-1 (7-39)

 $Ser^8Arg^{26}Lys^{34,36}$ -bis-(GAB-GTet) GLP-1(7-36); 5 Ser<sup>8</sup>Arg^{34}Lys^{26}, <sup>36</sup>-bis-(GAB-GTet) GLP-1(7-36); Ser<sup>8</sup>Arg^{26}Lys^{34,36}-bis-(GAB-GTet) GLP-1(7-37); Ser<sup>8</sup>Arg^{34}Lys^{26}, <sup>36</sup>-bis-(GAB-GTet) GLP-1(7-37); Ser<sup>8</sup>Arg^{34}Lys^{26}, <sup>36</sup>-bis-(GAB-GTet) GLP-1(7-37); Ser<sup>8</sup>Arg^{34}Lys^{26}, <sup>36</sup>-bis-(GAB-GTet) GLP-1(7-37); Ser<sup>8</sup>Arg^{26}Lys^{34,37}-bis-(GAB-GTet) Ser<sup>8</sup>Arg^{34}Lys^{37}-bis-(GAB-GTet) Ser<sup>8</sup>Arg^{37}-bis-(GAB-GTet) Ser<sup>8</sup>Arg^{36}-bis-(GAB-GTet) Ser<sup>8</sup>Arg^{37}-bis-(GAB-GTet) Ser<sup>8</sup>Arg^{37}-bis-(GAB-GTet) Ser<sup>8</sup>Arg^{37}-bis-(GAB-GTet) Ser<sup>8</sup>Arg^{37}-bis-(GAB-GTet) Ser<sup>8</sup>Arg^{37}-bis-(GAB-GTet) Ser<sup>8</sup>Arg^{37}-bis-(GAB-GTet) Ser<sup>8</sup>Arg^{37}-bis-(GAB-GTET) Ser<sup>8</sup>Arg^{37}-bis-(GAB-Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GTet) GLP-1(7-37); Ser Arg<sup>2</sup> Lys<sup>26,37</sup>-bis-(GAB-GTet) GLP-1(7-37); Ser Arg<sup>26</sup>Lys<sup>26,37</sup>-bis-(GAB-GTet) GLP-1(7-37); Ser Arg<sup>26</sup>Lys<sup>26,38</sup>-bis-(GAB-GTet) GLP-1(7-38); Ser Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-GTet) GLP-1(7-38); Ser Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36,38</sup>-bis-(GAB-GTet) GLP-1(7-38); Ser Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(GAB-GTet) GLP-1(7-39); Ser Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(GAB-GTet) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(GAB-GTet) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GTet) GLP-1(7-39);  $Ser^{8}$ Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GTet) GLP-1(7-39);

Set Alg Lys -565 (GAB-GTet) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26</sup>,  $^{34}$ -bis-(GAB-GTet) GLP-1(7-37); Thr<sup>8</sup>Lys<sup>26</sup>,  $^{34}$ -bis-(GAB-GTet) GLP-1(7-37); Thr<sup>8</sup>Lys<sup>26</sup>,  $^{34}$ -bis-(GAB-GTet) GLP-1(7-38); Thr<sup>8</sup>Lys<sup>26</sup>,  $^{34}$ -bis-(GAB-GTet) GLP-1 (7-39)

 $Thr^8 Arg^{26}Lys^{34,36}$ -bis-(GAB-GTet) GLP-1(7-36); 20 Thr^8 Arg^{34}Lys^{26, 36}-bis-(GAB-GTet) GLP-1(7-36); Thr^8 Arg^{26}Lys^{34,36}-bis-(GAB-GTet) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GTet) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GTet) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(GAB-GTet) GLP-1(7-37); 25 Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GTet) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>26,38</sup>-bis-(GAB-GTet) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-GTet) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,39</sup>-bis-(GAB-GTet) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,39</sup>-bis-(GAB-GTet) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>26,39</sup>-bis-(GAB-GTet) GLP-1(7-39); Lys<sup>26,34</sup>-bis-(GAB-GTet) GLP-1(7-39); Lys<sup>26,34</sup>-bis-(GAB-GHex) GLP-1(7-36); Lys<sup>26,34</sup>-bis-(GAB-GHex) GLP-1(7-37); Lys<sup>26,34</sup>-bis-(GAB-GHex) GLP-1(7-39) As<sup>26</sup>Lys<sup>34,36</sup>bis-(GAB-GHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26,35</sup>bis-(GAB-GHex) GLP-1(7-36); Lys<sup>26,34</sup>-bis-(GAB-GHex) GLP-1(7-36); Lys<sup>26,35</sup>-bis-(GAB-GHex) GLP-1(7-36); Lys<sup>26,35</sup>-bis-(BAB-GHex) GLP-1(7-36); Lys<sup>34</sup>-bis-(BAB-GHex) dLP-1(7-36); Lys<sup>34</sup>-bis-(BAB-GHex) dLP-1(7-36); Lys<sup>26,35</sup>-bis-(BAB-GHex) dLP-1(7-36); Lys<sup>26,35</sup>-bis-(BAB-GHex) dLP-1(7-36); Lys<sup>34</sup>-bis-(BAB-GHex) dLP-1(7-36); Lys<sup>34</sup>-bis-(BAB-GHex) dLP-1(7-36); Lys<sup>34</sup>-bis-(BAB-GHex) dLP-1(7-36); Lys<sup>34</sup>-bis-(BAB-GHex) dLP-1(DAB-GHex) dLP-1(DAB-GH

Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26</sup>, 35 Arg<sup>2-</sup>Lys<sup>2-,5-</sup>oils-(GAB-GHex) GLP-1(7-50); Arg<sup>2-</sup>Lys<sup>2-,5</sup> 35 <sup>36</sup>-bis-(GAB-GHex) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GHex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(GAB-GHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26, 40</sup> <sup>39</sup>-bis-(GAB-GHex) GLP-i(7-39); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GHex) GLP-i(7-39); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GHex) GLP 1(7-30); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-

(GAB-GHex) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18, 34</sup>-bis-26-bis-(GAB-GHex) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-<sup>26-bis-(GAB-GHex)</sup> GLP-1(7-30); Arg<sup>-1</sup>Lys<sup>18,26</sup>-bis-(GAB- 45 (GAB-GHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GHex) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GHex) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GHex) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>18,26</sup>-bis-(GAB-GHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GHex) GLP-1(7-30); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GHex) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GHex) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GHex) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GHex) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GHex) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GHex) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GHex) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis

Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>23, 50</sup> Arg<sup>-5</sup>Lys<sup>-5, 5-7</sup>-bis-(GAB-GHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>23, 50</sup> 26-bis-(GAB-GHex) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(GAB-GHex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(GAB-GHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(GAB-GHex) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(GAB-GHex) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>23, 34</sup>-bis-(GAB-GHex) GLP-1(7-39); 55 Arg<sup>34</sup>Lys<sup>23,26</sup>-bis-(GAB-GHex) GLP-1(7-39); 55 Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 34</sup>-bis-(34)-bis-

Arg<sup>26</sup>Lys<sup>27, 27</sup>-bis-(GAB-GHex) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GHex) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GHex) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GHex) 60 GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GHex) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GHex) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-30); Arg<sup>34</sup>Lys<sup>34</sup>Lys<sup>34</sup>-bis-(Arg<sup>34</sup>Lys<sup>34</sup>Lys<sup>34</sup>-bis-(Arg<sup>34</sup>Lys<sup>34</sup>Lys<sup>34</sup>-bis-(Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Arg<sup>34</sup>Lys<sup>34</sup>-bis-(Arg<sup>34</sup>Lys

Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-39)

 $Gly^8Arg^{26}Lys^{34,36}$ -bis-(GAB-GHex) GLP-1(7-36);  $Gly^8Arg^{34}Lys^{26}$ . <sup>36</sup>-bis-(GAB-GHex) GLP-1(7-36);  $Gly^8Arg^{26}Lys^{34,36}$ -bis-(GAB-GHex) GLP-1(7-37);  $Gly^8Arg^{34}Lys^{26}$ . <sup>36</sup>-bis-(GAB-GHex) GLP-1(7-37);  $Gly^8Arg^{34}Lys^{34}Lys^{36}$ . Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GHex) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GHex) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(GAB-GHex) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-GHex) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,38</sup>-bis-(GAB-GHex) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GHex) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>26,39</sup>-bis-(GAB-GHex) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GHex) GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GHex) GLP-1(7-39); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-39); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-39); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-37); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-39)] 15 1(7-39) $Val^8 Arg^{26}Lys^{34,36}$ -bis-(GAB-GHex) GLP-1(7-36); Val<sup>8</sup> Arg^{34}Lys^{26, 36}-bis-(GAB-GHex) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GHex) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GHex) GLP-1(7-37), Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GHex) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GHex) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GHex) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GHex) GLP-1(7-38); Ul<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GHex) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GHex) GLP-1(7-38); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-GHex) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,38</sup>-bis-(GAB-GHex) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(GAB-GHex) GLP-1(7-39); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(GAB-GHex) GLP-1(7-39); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>36,39</sup>-bis-(GAB-GHex) GLP-1(7-39); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-39); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26</sup>, S 1(7-39) Scr<sup>8</sup>Arg<sup>26</sup>Lys<sup>24,36</sup>-bis-(GAB-GHex) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GHex) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(GAB-GHex) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GHex) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(GAB-GHex) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GHex) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(GAB-GHex) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>24,38</sup>-bis-(GAB-GHex) GLP-1(7-38); Cast and Ser<sup>8</sup> Arg<sup>26</sup> Lys<sup>34,38</sup>-bis-(GAB-GHex) GLP-1(7-38); Ser<sup>8</sup> Arg<sup>34</sup> Lys<sup>26,38</sup>-bis-(GAB-GHex) GLP-1(7-38); Ser<sup>8</sup> Arg<sup>26, 34</sup> Lys<sup>36,38</sup>-bis-(GAB-GHex) GLP-1(7-38); Ser<sup>8</sup> Arg<sup>34</sup> Lys<sup>34, 39</sup>-bis-(GAB-GHex) GLP-1(7-39); Ser<sup>8</sup> Arg<sup>34</sup> Lys<sup>26,39</sup>-bis-(GAB-GHex) GLP-1(7-39); Ser<sup>8</sup> Arg<sup>25, 34</sup> Lys<sup>36,39</sup>-bis-(GAB-GHex) GLP-1(7-39); Thr<sup>8</sup> Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-39); Thr<sup>8</sup> Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup> Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup> Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup> Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup> Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-37); Thr<sup>8</sup> Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup> Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup> Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-37); Thr<sup>8</sup> Lys<sup>26, 34</sup>-bis-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup> Lys<sup>26</sup>, 34-bis-(GAB-GHex) Lys<sup>26</sup>, 34-bis-(GAB-GHex GHex) GLP-1(7-38); Inr Lys<sup>-7--</sup>-bis-(GAB-GHex) GLP-1(7-39) Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GHex) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GHex) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GHex) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GHex) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GHex) GLP-1(7-37); Thr  $^{8}$ Arg  $^{34}$ Lys  $^{26,37}$ -bis-(GAB-GHex) GLP-1(7-37);  $Thr^{8}Arg^{26}Lys^{34,38}bis-(GAB-GHex)$  GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-GHex) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-GHex) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup> Lys<sup>36,38</sup>-bis-(GAB-GHex) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(GAB-GHex) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(GAB-GHex) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GHex) GLP-1(7-39); Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1(7-36); Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1(7-37); Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1(7-38); Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1(7-39) GLP-1(7-38); Lys<sup>-5, St</sup>-bis-(GAB-GOct) GLP-1(7-39) Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GOct) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(GAB-GOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(GAB-GOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(GAB-GOct) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>34, 37</sup>-bis-(GAB-GOct) GLP-1(7-37); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GOct) GLP-1(7-37); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GOct) GLP-1(7-39); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GOct) GLP-1(7-39); Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GOct) GLP-1(7-30); Arg<sup>34</sup>Lys<sup>36,39</sup>-bis-(GAB-GOct) GLP-1(7-30); Arg<sup>34</sup>Lys<sup>36,39</sup>-bis-(AB-GOct) GLP-1(7-30); Arg<sup>34</sup>Lys<sup>36,39</sup>-bis-(AB-GOct) GLP-1(7-30); Arg<sup>34</sup>Lys<sup>36,39</sup>-bis-(AB-GOct) GLP-1(7-30); Arg<sup>34</sup>Lys<sup>36,39</sup>-bis-(AB-GOct) GLP-1(7-30); Arg<sup>34</sup>Lys<sup>36,39</sup>-bis-(AB-GOct) Arg<sup>34</sup>-bis-(AB-GOct) Arg<sup>34</sup>-bis-(AB-GOct) Arg<sup>34</sup>-bis-(AB-GOct) Arg<sup>34</sup>-bis-(AB-GOct) Arg<sup>34</sup>-b GLP-1(7-39);

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Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18, 34</sup>bis-(GAB-GOct) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18,34</sup>bis-(GAB-GOct) GLP-1(7-36); Arg<sup>36</sup>Lys<sup>18,34</sup>bis-(GAB-GOCt) GLP-1(7-36); Arg<sup>36</sup>Lys<sup>18,34</sup>b Goct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GOct) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GOct) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GOct) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GOct) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GOct) Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GOct) Arg<sup>34</sup>Lys<sup>18,26</sup>-bi

26-bis-(GAB-GOct) GLP-1(7-39);

26-bis-(GAB-GOCt) GLP-1(7-39); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GOct) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 15</sup> <sup>26</sup>-bis-(GAB-GOct) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GOct) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GOct) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GOct) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GOct) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 20</sup> <sup>26</sup> bis-(GAB-GOct) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 20</sup> 26-bis-(GAB-GOct) GLP-1(7-39);

Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26,</sup> <sup>34</sup>-bis-(GAB-GOct) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1 (7-39)

Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GOct) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GOct) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GOct) GLP-1(7-36); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GOct) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GOct) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GOct) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GOct) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-GOct) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-GOct) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(GAB-GOct) GLP-1(7-39); 35 Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(GAB-GOct) GLP-1(7-39); 35  $Gly^8 Arg^{34} Lys^{26,39}$ -bis-(GAB-GOct) GLP-1(7-39);  $Gly^8 Arg^{26,34} Lys^{36,39}$ -bis-(GAB-GOct) GLP-1(7-39);

 $Gly^8Arg^{26, 34}Lys^{36,39}$ -bis-(GAB-GOct) GLP-1(7-39); Val<sup>8</sup>Lys^{26, 34}-bis-(GAB-GOct) GLP-1(7-36); Val<sup>8</sup>Lys^{26}, 34-bis-(GAB-GOct) GLP-1(7-36); Val<sup>8</sup>Lys^{26}, 34 <sup>34</sup>-bis-(GAB-GOct) GLP-1(7-37); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1(7-38); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1 40 (7-39)

Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GOct) GLP-1(7-36); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GOct) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GOct) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GOct) GLP-1(7-37); 45 Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GOct) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GOct) GLP-1(7-37); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GOct) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-GOct) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>36,38</sup>-bis-(GAB-GOct) GLP-1(7-38); 50 Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(GAB-GOct) GLP-1(7-39); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(GAB-GOct) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GOct) GLP-1(7-39);

Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1(7-36); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1(7-37); Ser<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1 GAB-GOct) GLP-1 (7-39)

Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GOct) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GOct) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GOct) GLP-1(7-37); 60 Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GOct) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GOct) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(GAB-GOct) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>26,38</sup>-bis-(GAB-GOct) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-GOct) GLP-1(7-38); 65 Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,38</sup>-bis-(GAB-GOct) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>, <sup>39</sup>-bis-(GAB-GOct) GLP-1(7-39);

Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(GAB-GOct) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GOct) GLP-1(7-39); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1(7-37); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GOct) GLP-1(7-38); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(7-38); Thr<sup>8</sup>Lys<sup>26, 34</sup>-bis-(7-38); Thr<sup>8</sup>Lys<sup>26</sup>, 34-bis-(7-38); Thr<sup>8</sup>Lys<sup>26</sup>, 34-b (7-39)

Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GOct) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GOct) GLP-1(7-36); Thr $^{8}$ Arg $^{26}$ Lys $^{34,36}$ -bis-(GAB-GOct) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GOct) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GOct) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GOct) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GOct) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GOct) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>26,38</sup>-bis-(GAB-GOct) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,38</sup>-bis-(GAB-GOct) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,39</sup>-bis-(GAB-GOct) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,39</sup>-bis-(GAB-GOct) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,39</sup>-bis-(GAB-GOct) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,39</sup>-bis-(GAB-GOct) GLP-1(7-39); Lys<sup>26,34</sup>-bis-(GAB-GLit) GLP-1(7-36); Lys<sup>26,34</sup>-bis-(GAB-GLit) GLP-1(7-37); Lys<sup>36,34</sup>-bis-(GAB-GLit) GLP-1(7-37); Lys<sup>36,34</sup>-bis-(GAB-GLit) GLP-1(7-37); Lys<sup>36,34</sup>-bis-(GAB-GLit) GLP-1(7-37); Lys<sup>36,34</sup>-bis-(GAB-GLit) GLP-1(7-37); Lys<sup>36,34</sup>-bis-(GAB-GLit) GLP-1(7-37); Lys<sup>36,34</sup>-bis-(BAB-GLit) Lys<sup>36,34</sup>-bis-(BAB-GLit) Lys<sup>36,34</sup>-bis-(BAB-GLit) Lys<sup>36,34</sup>-b

(GAB-GLit) GLP-1(7-37); Lys<sup>26, 34</sup>-bis-(GAB-GLit) GLP-

- (GAB-GLit) GLP-1(7-37); Lys<sup>26, 34</sup>-bis-(GAB-GLit) GLP-1(7-38); Lys<sup>26, 34</sup>-bis-(GAB-GLit) GLP-1(7-39) Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GLit) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GLit) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GLit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GLit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26, 37</sup>-bis-(GAB-GLit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(GAB-GLit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(GAB-GLit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>26,36</sup>-bis-(GAB-GLit) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26,36</sup>-bis-(GAB-GLit) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>26,36</sup>-bis-(GAB-GLit) GLP-1(7-39); Arg<sup>36</sup>-bis-(GAB-GLit) GLP-1(7-30); Arg<sup>36</sup>-bis-(GAB-GLit) Arg<sup>36</sup>-bis-(GAB-GLit) Arg<sup>36</sup>-bis-(GAB-GLit) Arg<sup>36</sup>-bis-(GAB-GLit) Arg<sup>36</sup>-bis-(GAB-GLit) Arg<sup>36</sup>-bis-(GAB-GLit) Arg<sup>36</sup>-bis-(GAB-GLit) Arg<sup>36</sup>-bis-(GAB-GLit) 1(7-39);
- 1(7-39); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GLit) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>18, 26</sup>-bis-(GAB-GLit) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GLit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>18, 26</sup>-bis-(GAB-GLit) GLP-1(7-37); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GLit) GLP-1(7-38); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GLit) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GLit) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>18, 34</sup>-bis-(GAB-GLit) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>18,26</sup>-bis-(GAB-GLit) GLP-1(7-30); Arg<sup>3</sup>
- GLP-1(7-39); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GLit) GLP-1(7-36); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GLit) GLP-1(7-36); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GLit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GLit) GLP-1(7-37); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GLit) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 34</sup>-bis-(GAB-GLit) GLP-1(7-38); Arg<sup>26</sup>Lys<sup>27, 26</sup>-bis-(GAB-GLit) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GLit) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GLit) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-GLit) GLP-1(7-39); Arg<sup>34</sup>Lys<sup>27, 26</sup>-bis-(GAB-G Lit) GLP-1(7-39); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GLit) GLP-1(7-36); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GLit) GLP-1(7-37); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GLit) GLP-1(7-38); Gly<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GLit) GLP-1 (7-39)

 $Gly^8Arg^{26}Lys^{34,36}$ -bis-(GAB-GLit) GLP-1(7-36);  $Gly^8Arg^{34}Lys^{26, 36}$ -bis-(GAB-GLit) GLP-1(7-36);  $Gly^8Arg^{26}Lys^{34,36}$ -bis-(GAB-GLit) GLP-1(7-37);  $Gly^8Arg^{34}Lys^{26, 36}$ -bis-(GAB-GLit) GLP-1(7-37);  $Gly^8Arg^{34}Lys^{26, 36}$ -bis-(GAB-GLit) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>24,37</sup>-bis-(GAB-GLit) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>26,37</sup>-bis-(GAB-GLit) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>24,38</sup>-bis-(GAB-GLit) GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>24,38</sup>-bis-(GAB-GLit) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-GLit) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,38</sup>-bis-(GAB-GLit) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup> Lys<sup>34, 39</sup>-bis-(GAB-GLit) GLP-1(7-38); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(GAB-GLit) GLP-1(71-39);  $Gly^8 Arg^{34}Lys^{26,39}$ -bis-(GAB-GLit) GLP-1(7-39);  $Gly^8 Arg^{26,34}Lys^{36,39}$ -bis-(GAB-GLit) GLP-1(7-39); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GLit) GLP-1(7-36); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GLit) GLP-1(7-37); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GLit) GLP-1(7-38); Val<sup>8</sup>Lys<sup>26, 34</sup>-bis-(GAB-GLit) GLP-1 (7-39)

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Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GLit) GLP-1(7-36); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(GAB-GLit) GLP-1(7-36); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GLit) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26</sup>, <sup>36</sup>-bis-(GAB-GLit) GLP-1(7-37);  $Val^8 Arg^{26} Lys^{34,37}$ -bis-(GAB-GLit) GLP-1(7-37); Val<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,37</sup>-bis-(GAB-GLit) GLP-1(7-37); Val8Arg26Lys34,38-bis-(GAB-GLit) GLP-1(7-38);

(7-39)

Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GLit) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>26, 36</sup>-bis-(GAB-GLit) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GLit) GLP-1(7-36); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GLit) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GLit) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GLit) GLP-1(7-37); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GLit) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GLit) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-GLit) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>.  ${}^{34}Lys^{26,38}$ -bis-(GAB-GLit) GLP-1(7-38); Ser<sup>8</sup>Arg<sup>26</sup>.  ${}^{34}Lys^{36,38}$ -bis-(GAB-GLit) GLP-1(7-38); 25 Ser<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>.  ${}^{39}$ -bis-(GAB-GLit) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(GAB-GLit) GLP-1(7-39); Ser<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>bis-(GAB-GLit) GLP-1(7-39);

Set Alg Lys bis-(GAB-GLit) GLP-1(7-39); Thr<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(GAB-GLit) GLP-1(7-36); Thr<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(GAB-GLit) GLP-1(7-37); Thr<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(GAB-GLit) GLP-1 (GAB-GLit) GLP-1 (7-38); Thr<sup>8</sup>Lys<sup>26</sup>, <sup>34</sup>-bis-(GAB-GLit) GLP-1 (7-39)

Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GLit) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GLit) GLP-1(7-36); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,36</sup>-bis-(GAB-GLit) GLP-1(7-37); 35 Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>24,30</sup>-bis-(GAB-GLit) GLP-1(7-3/); 35 Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26, 36</sup>-bis-(GAB-GLit) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,37</sup>-bis-(GAB-GLit) GLP-1(7-37); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GLit) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GLit) GLP-1(7-38); 40 Thr<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26,38</sup>-bis-(GAB-GLit) GLP-1(7-38); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(GAB-GLit) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26</sup>Lys<sup>34, 39</sup>-bis-(GAB-GLit) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>34</sup>Lys<sup>26,39</sup>-bis-(GAB-GLit) GLP-1(7-39); Thr<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36,39</sup>-bis-(GAB-GLit) GLP-1(7-39).

## Pharmaceutical Compositions

The present invention also relates to pharmaceutical compositions comprising a GLP-1 derivative of the present invention and a pharmaceutically acceptable vehicle or carrier.

Preferably, the pharmaceutical compositions comprise an isotonic agent, a preservative and a buffer. Examples of isotonic agents are sodium chloride, mannitol and glycerol. Examples of preservatives are phenol, m-cresol, methyl p-hydroxybenzoate and benzyl alcohol. Suitable buffers 55 include sodium acetate and sodium phosphate.

The pharmaceutical compositions preferably further comprise a surfactant in order to improve the solubility and/or the stability of the GLP-1 derivative. Individual embodiments of the surfactant, such as a detergent, for use in the 60 pharmaceutical composition of the invention include ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, such as 188 and 407, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives such as alkylated and alkoxy- 65 lated derivatives (tweens, e.g. Tween-20), monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxy-

ethylene derivatives thereof, glycerol, cholic acid or derivatives thereof, lecithins, alcohols and phospholipids, glycerophospholipids (lecithins, kephalins, phosphatidyl serine), glyceroglycolipids (galactopyransoide), sphingophospholipids (sphingomyelin), and sphingoglycolipids (ceramides, gangliosides), DSS (docusate sodium, CAS registry no [577-11-7]), docusate calcium, CAS registry no [128-49-4]), Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,38</sup>-bis-(GAB-GLit) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>Lys<sup>34,39</sup>-bis-(GAB-GLit) GLP-1(7-38); Val<sup>8</sup>Arg<sup>26</sup>, <sup>34</sup>Lys<sup>26,39</sup>-bis-(GAB-GLit) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>26,39</sup>-bis-(GAB-GLit) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>26,39</sup>-bis-(GAB-GLit) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>26,39</sup>-bis-(GAB-GLit) GLP-1(7-39); Val<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,39</sup>-bis-(GAB-GLit) GLP-1(7-39); Ser<sup>8</sup>Lys<sup>26,34</sup>-bis-(GAB-GLit) GLP-1(7-39); Ser<sup>8</sup>Lys<sup>26,34</sup>-bis-(GAB-GLit) GLP-1(7-39); Ser<sup>8</sup>Lys<sup>26,34</sup>-bis-(GAB-GLit) GLP-1(7-37); lysophosphatidyl-L-serine, lysophospholipids (e.g. 1-acylsn-glycero-3-phosphate esters of ethanolamine, choline, serine or threonine), alkyl, alkoxyl (alkyl ester), alkoxy (alkyl ether)-derivatives of lysophosphatidyl and phosphatidylcholines, e.g. lauroyl and myristoyl derivatives 20 lysophosphatidylcholine, of dipalmitoylphosphatidylcholine, and modifications of the polar head group, that is cholines, ethanolamines, phosphatidic acid, serines, threonines, glycerol, inositol, and the postively charged DODAC, DOTMA, DCP, BISHOP, lysophosphatidylserine and lysophosphatidylthreonine, zwitterionic surfactants (e.g. N-alkyl-N,N-dimethylammonio-1propanesulfonates, 3-cholamido-1propyldimethylammonio-1-propanesulfonate, dodecylphosphocholine, myristoyl lysophosphatidylcholine, hen egg lysolecithin), cationic surfactants (quarternary ammonium bases) (e.g. cetyltrimethylammonium bromide, cetylpyridinium chloride), non-ionic surfactants, polyethyleneoxide/polypropyleneoxide block copolymers (Pluronics/Tetronics, Triton X-100, Dodecyl  $\beta$ -D-glucopyranoside) or polymeric surfactants (Tween-40, Tween-80, Brij-35). Other preferred surfactants include fusidic acid derivatives-(e.g. sodium tauro-dihydrofusidate etc.), long-chain fatty acids and salts thereof C6-C12(eg. oleic acid and caprylic acid), acylcarnitines and derivatives,  $N^{\alpha}$ -acylated derivatives of lysine, arginine or histidine, or side-chain acylated derivatives of lysine or arginine, N<sup>a</sup>-acylated derivatives of dipeptides comprising any combination of lysine, arginine or histidine and a neutral or acidic amino acid, N<sup> $\alpha$ </sup>-acylated derivative of a tripeptide 45 comprising any combination of a neutral amino acid and two charged amino acids, or the surfactant may be selected from the group of imidazoline derivatives.

> One group of preferred surfactants consists of zwitterionic 50 surfactants, cationic surfactants, non-ionic surfactants and polymeric surfactants.

Another group of preferred surfactants consists of SDS, sodium caprylate, sodium cholate, sodium deoxycholate, sodium taurocholate and sodium glycocholate.

A further group of preferred surfactants consists of lauroyl lysophosphatidylcholine, palmitoyl lysophosphatidyl-Lserine, myristoyl lysophosphatidylcholine and N-Hexadecyl-N, N-dimethyl-3-ammonio-1propanesulfonate.

The pharmaceutical compositions preferably also comprise zinc.

The pharmaceutial compositions preferably further comprise another antidiabetic agent. The term "antidiabetic agent" includes compounds for the treatment and/or prophylaxis of insulin resistance and diseases wherein insulin resistance is the pathophysiological mechanism.

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In one embodiment of this invention, the antidiabetic agent is an insulin, more preferably human insulin.

In another embodiment the antidiabetic agent is a hypoglycaemic agent, preferably an oral hypoglycaemic agent. Oral hypoglycaemic agents are preferably selected <sup>5</sup> from the group consisting of sulfonylureas, biguanides, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potasium channel openers, insulin sensitizers, hepatic enzyme inhibitors, glucose uptake modulators, compounds modifying the lipid <sup>10</sup> metabolism, compounds lowering food intake, and agents acting on the ATP-dependent potassium channel of the  $\beta$ -cells.

Preferred sulfonylureas are tolbutamide, glipicale and gliclazide. A preferred biguanide is metformin. Preferred thiazolidinediones are troglitazone and ciglitazone. A preferred glucosidase inhibitors is acarbose. Preferred agents acting on the ATP-dependent potassium channel of the  $\beta$ -cells are: glibenclamide, glipizide, gliclazide, and repaglinide.

The pharmaceutical compositions of the present invention may further comprise another antiobesity agent.

In one embodiment of this invention, the antiobesity agent is leptin.

In another embodiment the antiobesity agent is amphetamin.

In another embodiment the antiobesity agent is dexfenfluramine.

In another embodiment the antiobesity agent is sibutra-  $^{\rm 30}$  mine.

In another embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is selected from a group of CART agonists, NPY antagonists, orexin antagonists, H3-antagonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists,  $\beta$ 3 agonists, MSH agonists, CCK agonists, serotonin re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, glucagon, TRH agonists, uncoupling protein 2 or 3 modulators, leptin agonists, DA agonists (Bromocriptin, Doprexin), lipase/ amylase inhibitors, PPAR modulators, PXR modulators or TR P agonists.

The present invention also relates to pharmaceutical compositions comprising water and a GLP-1 derivative which has a helix content as measured by CD at 222 nm in H<sub>2</sub>O at 22±2° C. exceeding 25%, preferably in the range of 25% to 50%, at a peptide concentration of about 10  $\mu$ M. The size of the partially helical, micelle-like aggregates may be estimated by size-exclusion chromatography. Similarly, the apparent (critical micelle concentrations) CMC's of the peptides may be estimated from the concentration dependent fluorescence in the presence of appropriate dyes (e.g. Brito, S. & Vaz, W. (1986) Anal. Biochem. 152, 250–255).

That the derivatives have a partially structured micellarlike aggregate conformation in aqueous solutions makes them more soluble and stable in solution as compared to the native peptide. The increased solubility and stability can be seen by comparing the solubility after 9 days of standing for a derivative and native GLP-1(7-37) in a pharmaceutical formulation, e.g. 5 mM phosphate buffer, pH 6.9 added 0.1 M NaCl.

Circular Dichroism (CD) can be used to show that the 65 GLP-1 derivatives have a certain partially structured conformation independent of their concentration. In contrast, for

native GLP-1(7-37) an increase in the helix content is seen with increasing concentration, from 10–15% to 30–35% (at 500  $\mu$ M concentration) in parallel with peptide selfassociation. For the GLP-1 derivatives forming partially 5 structured micellar-like aggregates in aqueous solution the helix content remains constant above 30% at concentrations of 10  $\mu$ M. The aggregated structured conformation is an inherent property of the derivative present in water or dilute aqueous buffer without the need for any additional structure-10 inducing components.

The pharmaceutical compositions of the present invention may be prepared by conventional techniques, e.g. as described in Remington's *Pharmaceutical Sciences*, 1985 or in Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

For example, injectable compositions of the GLP-1 derivative of the invention can be prepared using the conventional techniques of the pharmaceutical industry which involves dissolving and mixing the ingredients as appropriate to give the desired end product.

A composition for nasal administration of certain peptides may, for example, be prepared as described in European Patent No. 272097(to Novo Nordisk A/S) or in WO 93/18785.

In a preferred embodiment of the present invention, the GLP-1 derivative is provided in the form of a composition suitable for administration by injection. Such a composition can either be an injectable solution ready for use or it can be an amount of a solid composition, e.g. a lyophilised product, which has to be dissolved in a solvent before it can be injected. The injectable solution preferably contains not less than about 2 mg/ml, preferably not less than about 5 mg/ml, more preferred not less than about 10 mg/ml of the GLP-1 derivative.

### Uses

The present invention also relates to the use of a GLP-1 40 derivative of the invention for the preparation of a medicament which has a protracted profile of action relative to GLP-1(7-37).

The present invention relates also to the use of a GLP-1 derivative of the invention for the preparation of a medicament with protracted effect for the treatment of non-insulin dependent diabetes mellitus.

The present invention also relates to the use of a GLP-1 derivative of the invention for the preparation of a medicament with protracted effect for the treatment of insulin dependent diabetes mellitus.

The present invention also relates to the use of a GLP-1 derivative of the invention for the preparation of a medicament with protracted effect for the treatment of obesity.

The present invention also relates to the use of a GLP-1 derivative of the present invention for treating insulin resistance.

The present invention also relates to the use of a GLP-1 derivative of the present invention for the preparation of a medicament with protracted effect for the treatment of obesity.

The present invention relates to a method of treating insulin dependent or non-insulin dependent diabetes mellitus in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of a GLP-1 derivative of the present invention together with a pharmaceutically acceptable carrier.

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The present invention relates to a method of treating obesity in a patient in need of such a treatment, comprising administering to the patient a therapeutically effective amount of a GLP-1 derivative of the present invention together with a pharmaceutically acceptable carrier.

The particular GLP-1 derivative to be used and the optimal dose level for any patient will depend on the disease to be treated and on a variety of factors including the efficacy of the specific peptide derivative employed, the age, body weight, physical activity, and diet of the patient, on a 10 possible combination with other drugs, and on the severity of the case.

The pharmaceutical compositions of the present invention may be administered parenterally to patients in need of such a treatment. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe. Alternatively, parenteral administration can be performed by means of an infusion pump. A further option is a composi-20 tion which may be a powder or a liquid for the administration of the GLP-1 derivative in the form of a nasal or pulmonal spray. As a still further option, the GLP-1 derivatives of the invention can also be administered transdermally, e.g. from a patch, optionally a iontophoretic patch, or transmucosally, e.g. bucally.

## Methods of Production

The parent peptide can be produced by a method which comprises culturing a host cell containing a DNA sequence 30 encoding the polypeptide and capable of expressing the polypeptide in a suitable nutrient medium under conditions permitting the expression of the peptide, after which the resulting peptide is recovered from the culture.

The medium used to culture the cells may be any con- 35 ventional medium suitable for growing the host cells, such as minimal or complex media containing appropriate supplements. Suitable media are available from commercial suppliers or may be prepared of published recipes (e.g. in catalogues of the American Type Culture Collection). The 40 peptide produced by the cells may then be recovered from the culture medium by conventional procedures including separating the host cells from the medium by centrifugation or filtration, precipitating the proteinaceous components of the supernatant or filtrate by means of a salt, e.g. ammonium 45 sulphate, purification by a variety of chromatographic procedures, e.g. ion exchange chromatography, gel filtration chromatography, affinity chromatography, or the like, dependent on the type of peptide in question.

The DNA sequence encoding the parent peptide may 50 suitably be of genomic or cDNA origin, for instance obtained by preparing a genomic or cDNA library and screening for DNA sequences coding for all or part of the peptide by hybridisation using synthetic oligonucleotide probes in accordance with standard techniques (see, for 55 example, Sambrook, J, Fritsch, EF and Maniatis, T, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, New York, 1989). The DNA sequence encoding the peptide may also be prepared synthetically by established standard methods, e.g. the phosphoamidite 60 method described by Beaucage and Caruthers, Tetrahedron Letters 22(1981), 1859-1869, or the method described by Matthes et al., EMBO Journal 3(1984), 801-805. The DNA sequence may also be prepared by polymerase chain reaction using specific primers, for instance as described in U.S. 65 Pat. No. 4,683,202 or Saiki et al., Science 239(1988), 487-491.

The DNA sequence may be inserted into any vector which may conveniently be subjected to recombinant DNA procedures, and the choice of vector will often depend on the host cell into which it is to be introduced. Thus, the vector 5 may be an autonomously replicating vector, i.e. a vector which exists as an extrachromosomal entity, the replication of which is independent of chromosomal replication, e.g. a plasmid. Alternatively, the vector may be one which, when introduced into a host cell, is integrated into the host cell genome and replicated together with the chromosome(s) into which it has been integrated.

The vector is preferably an expression vector in which the DNA sequence encoding the peptide is operably linked to additional segments required for transcription of the DNA, such as a promoter. The promoter may be any DNA sequence which shows transcriptional activity in the host cell of choice and may be derived from genes encoding proteins either homologous or heterologous to the host cell. Examples of suitable promoters for directing the transcription of the DNA encoding the peptide of the invention in a variety of host cells are well known in the art, cf. for instance Sambrook et al., supra.

The DNA sequence encoding the peptide may also, if necessary, be operably connected to a suitable terminator, polyadenylation signals, transcriptional enhancer sequences, and translational enhancer sequences. The recombinant vector of the invention may further comprise a DNA sequence enabling the vector to replicate in the host cell in question.

The vector may also comprise a selectable marker, e.g. a gene the product of which complements a defect in the host cell or one which confers resistance to a drug, e.g. ampicillin, kanamycin, tetracyclin, chloramphenicol, neomycin, hygromycin or methotrexate.

To direct a parent peptide of the present invention into the secretory pathway of the host cells, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) may be provided in the recombinant vector. The secretory signal sequence is joined to the DNA sequence encoding the peptide in the correct reading frame. Secretory signal sequences are commonly positioned 5' to the DNA sequence encoding the peptide. The secretory signal sequence may be that normally associated with the peptide or may be from a gene encoding another secreted protein.

The procedures used to ligate the DNA sequences coding for the present peptide, the promoter and optionally the terminator and/or secretory signal sequence, respectively, and to insert them into suitable vectors containing the information necessary for replication, are well known to persons skilled in the art (cf., for instance, Sambrook et al., supra).

The host cell into which the DNA sequence or the recombinant vector is introduced may be any cell which is capable of producing the present peptide and includes bacteria, yeast, fungi and higher eukaryotic cells. Examples of suitable host cells well known and used in the art are, without limitation, E. coli, Saccharomyces cerevisiae, or mammalian BHK or CHO cell lines.

The GLP-1 derivatives of this invention can be used in the treatment of various diseases.

The particular GLP-1 derivative to be used and the optimal dose level for any patient will depend on the disease to be treated and on a variety of factors including the efficacy of the specific peptide derivative employed, the age, body weight, physical activity, and diet of the patient, on a possible combination with other drugs, and on the severity

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of the case. It is recommended that the dosage of the GLP-1 derivative of this invention be determined for each individual patient by those skilled in the art.

In particular, it is envisaged that the GLP-1 derivative will be useful for the preparation of a medicament with a 5 protracted profile of action for the treatment of non-insulin dependent diabetes mellitus and/or for the treatment of obesity.

The present invention is further illustrated by the following examples which, however, are not to be construed as 10 limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

## **EXAMPLES**

The following acronyms for commercially available chemicals are used:

DMF: N,N-Dimethylformamide

DCC: N,N-Dicyclohexylcarbodiimide

NMP: N-Methyl-2-pyrrolidone

EDPA: N-Ethyl-N,N-diisopropylamine

EGTA: Ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'tetraacetic acid

GTP: Guanosine 5'-triphosphate

TFA: Trifluoroacetic acid

THF: Tetrahydrofuran

H-Glu(OH)-OBu': L-Glutamic acid  $\alpha$ -tert-butyl ester

Cac-ONSu: Decanoic acid 2,5-dioxopyrrolidin-1-yl ester

Cap-ONSu: Octanoic acid 2,5-dioxopyrrolidin-1-yl ester

Lau-ONSu: Dodecanoic acid 2,5-dioxopyrrolidin-1-yl ester 30

- Myr-ONSu: Tetradecanoic acid 2,5-dioxopyrrolidin-1-yl
- ester Pal-ONSu: Hexadecanoic acid 2,5-dioxopyrrolidin-1-yl
- ester Ste-ONSu Octadecanoic acid 2,5-dioxopyrrolidin-1-yl ester 35

Abbreviations:

PDMS: Plasma Desorption Mass Spectrometry

MALDI-MS: Matrix Assisted Laser Desorptiont/Ionisation Mass Spectrometry

HPLC: High Performance Liquid Chromatography

amu: atomic mass units

- Lit-Glu(ONSu)-OBu': N<sup>a</sup>-Lithochoyl-L-glutamic acid a-tbutyl ester y-2,5-dioxopyrrolidin-1-yl ester
- Cap-Glu(ONSu)-OBu': N<sup>α</sup>-Octanoyl-L-glutamic acid α-tbutyl ester y-2,5-dioxopyrrolidin-1-yl ester
- Cac-Glu(ONSu)-OBut: Nα-Decanoyl-L-glutamic acid α-tbutyl ester γ-2,5-dioxopyrrolidin-1-yl ester

Lau-Glu(ONSu)-OBu': Na-Dodecanoyl-L-glutamic acid  $\alpha$ -t-butyl ester  $\gamma$ -2,5-dioxopyrrolidin-1-yl ester

 $\alpha$ -t-butyl ester  $\gamma$ -2,5-dioxopyrrolidin-1-yl ester

Pal-Glu(ONSu)-OBut: Na-Hexadecanoyl-(L)-glutamic acid α-t-butyl-γ-2,5-dioxopyrrolidin-1-yl diester

Ste-Glu(ONSu)-OBut: Na-Octadecanoyl-(L)-glutamic acid α-t-butyl-γ-2,5-dioxopyrrolidin-1-yl diester

Lau-\beta-Ala-ONSu: N<sup>B</sup>-Dodecanoyl-\beta-alanine 2,5dioxopyrrolidin-1-yl ester

Pal-β-Ala-ONSu: N<sup>β</sup>-Hexadecanoyl-β-alanine 2,5dioxopyrrolidin-1-yl ester

Lau-GABA-ONSu: N7-Dodecanoyl-y-aminobutyric acid 60 2,5-dioxopyrrolidin-1-vl ester

Myr-GABA-ONSu: NY-Tetradecanovl-y-aminobutyric acid 2,5-dioxopyrrolidin-1-yl ester

Pal-GABA-ONSu: NY-Hexadecanoyl-y-aminobutyric acid 2,5-dioxopyrrolidin-1-yl ester

Ste-GABA-ONSu: N7-Octadecanoyl-y-aminobutyric acid 2,5-dioxopyrrolidin-1-yl ester

- Pal-Isonip-ONSu: N-Hexadecanoyl-piperidine-4-carboxylic acid 2,5-dioxopyrrolidin-1-yl ester
- Pal-Glu(OBu')-ONSu: N<sup>a</sup>-Hexadecanoyl-L-glutamic acid α-2,5-dioxopyrrolidin-1-yl ester γ-t-butyl ester
- HOOC-(CH<sub>2</sub>)<sub>6</sub>-COONSu: ω-Carboxyheptanoic acid 2,5-dioxopyrrolidin-1-yl ester
- HOOC-(CH<sub>2</sub>)<sub>10</sub>-COONSu: ω-Carboxyundecanoic acid 2,5-dioxopyrrolidin-1-yl ester

HOOC-(CH2)12-COONSu: ω-Carboxytridecanoic acid 2,5-dioxopyrrolidin-1-yl ester

- HOOC-(CH<sub>2</sub>)<sub>14</sub>-COONSu: ω-Carboxypentadecanoic acid 2,5-dioxopyrrolidin-1-yl ester
- HOOC-(CH<sub>2</sub>)<sub>16</sub>-COONSu: ω-Carboxyheptadecanoic acid 2,5-dioxopyrrolidin-1-yl ester
- 15 HOOC-(CH<sub>2</sub>)<sub>18</sub>-COONSu: ω-Carboxynonadecanoic acid 2,5-dioxopyrrolidin-1-yl ester
  - $N^{\alpha}$ -alkanoyl-Glu(ONSu)-OBu<sup>*t*</sup>:  $N^{\alpha}$ -Alkanoyl-(L)-glutamic acid a-t-butyl-y-2,5-dioxopyrrolidin-1-yl diester

### Analytical

Plasma Desorption Mass Spectrometry Sample Preparation:

The sample is dissolved in 0.1% TFA/EtOH (1:1) at a concentration of 1  $\mu g/\mu l$ . The sample solution (5–10  $\mu l$ ) is placed on a nitrocellulose target (Bio-ion AB, Uppsala, Sweden) and allowed to adsorb to the target surface for 2 minutes. The target is subsequently rinsed with  $2 \times 25 \ \mu l$ 0.1% TFA and spin-dried. Finally, the nitrocellulose target is placed in a target carrousel and introduced into the mass spectrometer.

MS Analysis:

PDMS analysis was carried out using a Bio-ion 20 time-of flight instrument (Bio-ion Nordic AB, Uppsala, Sweden). An acceleration voltage of 15 kV was applied and molecular ions formed by bombardment of the nitrocellulose surface with 252-Cf fission fragments were accelerated towards a stop detector. The resulting time-of-flight spectrum was calibrated into a true mass spectrum using the H<sup>+</sup> and NO<sup>+</sup> ions at m/z 1 and 30, respectively. Mass spectra were generally accumulated for 1.0×106 fission events corresponding to 15-20 minutes. Resulting assigned masses all correspond to isotopically averaged molecular masses. The accuracy of mass assignment is generally better than 0.1%.

### MALDI-MS

MALDI-TOF MS analysis was carried out using a Voyager RP instrument (PerSeptive Biosystems Inc., Framingham, Mass.) equipped with delayed extraction and Myr-Glu(ONSu)-OBu': N<sup>\alpha</sup>-Tetradecanoyl-L-glutamic acid 50 operated in linear mode. Alpha-cyano-4-hydroxy-cinnamic acid was used as matrix, and mass assignments were based on external calibration.

#### Example 1

## Synthesis of Lys<sup>26</sup>(N<sup>e</sup>-tetradecanoyl) GLP-1(7-37)

The title compound was synthesised from GLP-1(7-37). A mixture of GLP-1(7-37) (25 mg, 7.45 µm), EDPA (26.7 mg, 208  $\mu$ m), NMP (520  $\mu$ l) and water (260  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of Myr-ONSu (2.5 mg, 7.67  $\mu$ m) in NMP (62.5  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature and then allowed to stand for 20 min. An additional amount of Myr-ONSu (2.5 65 mg, 7.67  $\mu$ m) in NMP (62.5  $\mu$ l) was added and the resulting mixture gently shaken for 5 min. After a total reaction time of 40 min. the reaction was quenched by the addition of a

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solution of glycine (12.5 mg, 166 µmol) in 50% aqueous ethanol (12.5 ml). The title compound was isolated from the reaction mixture by HPLC using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system, yield: 1.3 mg (corresponding to 4.9% of the theo-5 retical vield). The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The isolated product was analysed by PDMS and the m/z value for the protonated molecular ion was found to be 3567.9±3. The resulting molecular weight was thus 3566.9±3 amu 10 µg, 4%) was isolated. (theoretical value: 3565.9 amu). The position of acylation (Lys26) was verified by enzymatic cleavage of the title compound with Staphylococcus aureus V8 protease and subsequent mass determination of the peptide fragments by PDMS.

In addition to the title compound two other GLP-1derivatives were isolated from the reaction mixture by using the same chromatographic column and a more shallow gradient (35-38% acetonitrile in 60 minutes), see Examples 2 and 3.

#### Example 2

### Synthesis of Lys<sup>34</sup>(N<sup>€</sup>-tetradecanovl) GLP-1(7-37)

The title compound was isolated by HPLC from the 25 reaction mixture described in Example 1. PDMS analysis yielded a protonated molecular ion at m/z 3567.7±3. The molecular weight was found to be 3566.7±3 amu (theoretical value: 3565.9 amu). The acylation site was determined on the basis of the fragmentation pattern.

#### Example 3

The title compound was isolated by HPLC from the reaction mixture described in Example 1. PDMS analysis yielded a protonated molecular ion at m/z 3778.4±3. The molecular weight was found to be 3777.4±3 amu (theoretical value: 3776.1 amu).

#### Example 4

# Synthesis of Lys26(N€-tetradecanoyl)Arg34GLP-1(7-37)

The title compound was synthesised from Arg34GLP-1 (7-37). A mixture of Arg<sup>34</sup>GLP-1(7-37) (5 mg, 1.47 µm), EDPA (5.3 mg, 41.1  $\mu$ m), NMP (105  $\mu$ l) and water (50  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of Myr-ONSu (0.71 mg, 2.2  $\mu$ m) in NMP (17.8  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature and then allowed to stand for 20 min. After a total reaction time of 30 min. the reaction was quenched by the addition of a solution of glycine (25 mg, 33.3 µm) in 50% aqueous ethanol (2.5 55 ml). The reaction mixture was purified by HPLC as described in Example 1. PDMS analysis yielded a protonated molecular ion at m/z 3594.9±3. The molecular weight was found to be 3593.9±3 amu (theoretical value: 3593.9 amu).

## Example 5

The title compound was synthesised from Gly8Arg26, <sup>34</sup>Lys<sup>36</sup>GLP-1(7-37) which was purchased from QCB. A

mixture of Gly<sup>8</sup>Arg<sup>26, 34</sup>Lys<sup>36</sup>GLP-1(7-37) (1.3 mg, 0.39 μm), EDPA (1.3 mg, 10 μm), NMP (125 μl) and water (30  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of Myr-ONSu (0.14 mg, 0.44  $\mu$ m) in NMP (3.6 ml), the reaction mixture was gently shaken for 15 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (0.1 mg, 1.33  $\mu$ m) in 50% aqueous ethanol (10  $\mu$ l). The reaction mixture was purified by HPLC, and the title compound (60

#### Example 6

# Synthesis of Arg<sup>26, 34</sup>Lys<sup>36</sup>(N<sup>e</sup>-tetradecanoyl) GLP-1(7-37)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>36</sup>GLP-1(7-37)-OH (5.0 mg, 1.477 µmol), EDPA (5.4 mg, 41.78 µmol), NMP (105 µl) and water (50 µl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of Myr-ONSu (0.721 mg, 2.215 µmol) in NMP (18 µl). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 45 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.5 mg, 33.3 µmol) in 50% aqueous ethanol (250  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (1.49 mg, 28%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3595±3. The resulting molecular weight was thus 3594±3 amu (theoretical value 3594 amu).

### Example 7

# Synthesis of Lys<sup>26,34</sup>bis(N<sup>ε</sup>-(ωcarboxynonadecanoyl)) GLP-1(7-37)-OH

A mixture of GLP-1(7-37)-OH (70 mg, 20.85 µmol), 40 EDPA (75.71 mg, 585.8 µmol), NMP (1.47 ml) and water  $(700 \,\mu\text{L})$  was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution of HOOC-(CH2)18-COONSu (27.44 mg, 62.42 µmol) in NMP (686  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 50 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (34.43 mg, 458.7 µmol) in 50% aqueous ethanol (3.44 ml). The reaction mixture was purified by column chromatography using a 50 cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (8.6 mg, 10%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 4006±3. The resulting molecular weight was thus 4005±3 amu (theoretical value 4005 amu).

### Example 8

# Synthesis of Arg<sup>26, 34</sup>Lys<sup>36</sup>(N<sup>ε</sup>-(ωcarboxynonadecanoyl)) GLP-1(7-36)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>36</sup>GLP-1(7-36)-OH (5.06 mg, 65 1.52 μmol), EDPA (5.5 mg, 42.58 μmol), NMP (106 μl) and water (100 µl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution

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of HOOC-(CH<sub>2</sub>)<sub>18</sub>-COONSu (1.33 mg, 3.04 µmol) in NMP (33.2  $\mu$ ), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2.5 h at room temperature. The reaction was quenched by the addition of a solution of glycine (2.50 mg, 33.34 µmol) in 50% aqueous ethanol (250 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.46 mg, 8%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3652±3. The resulting molecular weight was thus 3651±3 amu (theoretical value 3651 amu).

#### Example 9

Synthesis of Arg26, 34Lys38(Ne-(ωcarboxynonadecanoyl)) GLP-1(7-38)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>38</sup>GLP-1(7-38)-OH (5.556 mg, 20 1.57 µmol), EDPA (5.68 mg, 43.96 µmol), NMP (116.6 µl) and water (50 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH2)18-COONSu (1.38 mg, 3.14 µmol) in NMP  $(34.5 \,\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2.5 h at room temperature. The reaction was quenched by the addition of a solution of glycine (2.5 mg, 33.3  $\mu$ mol) in 50% aqueous ethanol (250  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.7 mg, 12%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3866±3. The resulting molecular weight was thus 3865±3 amu (theoretical value 3865 amu).

#### Example 10

# Synthesis of Arg34Lys26(Ne-(ωcarboxynonadecanoyl)) GLP-1(7-37)-OH

A mixture of Arg34GLP-1(7-37)-OH (5.04 mg, 1.489 µmol), EDPA (5.39 mg, 41.70 µmol), NMP (105 µl) and water (50 µl) was gently shaken for 10 min. at room 45 temperature. To the resulting mixture was added a solution HOOC-(CH2)18-COONSu (1.31 mg, 2.97 µmol) in NMP (32.8  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 30 min. at room temperature. The reaction was 50 quenched by the addition of a solution of glycine (2.46 mg, 32.75 µmol) in 50% aqueous ethanol (246 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. 55 and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (1.2 mg, 22%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3709±3. The resulting molecular weight was thus  $3708\pm3$  amu (theoretical value <sub>60</sub> resulting molecular weight was thus  $3837\pm3$  amu 3708 amu).

## Example 11

Synthesis of Arg34Lys26(Ne-(ωcarboxyheptadecanoyl)) GLP-1(7-37)-OH

A mixture of Arg34GLP-1(7-37)-OH (5.8 mg, 1.714 µmol), EDPA (6.20 mg, 47.99 µmol), NMP (121.8 µl) and

water (58 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH2)16-COONSu (2.11 mg, 5.142 µmol) in NMP (52.8 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (2.83 mg, 37.70  $\mu$ mol) in 50% aqueous ethanol (283  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.81 mg, 13%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3681±3. The resulting <sup>15</sup> molecular weight was thus 3680±3 amu (theoretical value 3680 amu).

#### Example 12

Synthesis of Arg<sup>26, 34</sup>Lys<sup>36</sup>(N<sup>ε</sup>-(ωcarboxyheptadecanoyl)) GLP-1(7-37)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>36</sup>GLP-1(7-37)-OH (3.51 mg, 1.036  $\mu$ mol), EDPA (3.75 mg, 29.03  $\mu$ mol), NMP (73.8  $\mu$ l) and water (35 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>16</sub>-COONSu (1.27 mg, 3.10 µmol) in NMP (31.8  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2 h and 10 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (1.71 30 mg, 22.79 µmol) in 50% aqueous ethanol (171 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.8 mg, 21%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3682±3. The resulting molecular weight was thus 3681±3 amu (theoretical value 3681 amu).

### Example 13

# Synthesis of $Arg^{26,34}Lys^{38}$ (N<sup>68</sup>-( $\omega$ -carboxylheptadecanoyl)) GLP-1(7-38)-OH

A mixture of Arg<sup>25, 34</sup>Lys<sup>38</sup>GLP-1(7-38)-OH (5.168 mg, 1.459 µmol), EDPA (5.28 mg, 40.85 µmol), NMP (108.6 µl) and water (51.8 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>16</sub>--COONSu (1.80 mg, 4.37 μmol) in NMP (45  $\mu$ l), the reaction mixture was gently shaken for 10 min. at room temperature, and then allowed to stand for an additional 2 h and 15 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.41 mg, 32.09  $\mu$ mol) in 50% aqueous ethanol (241  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.8 mg, 14%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3838±3. The (theoretical value 3837 amu).

### Example 14

Synthesis of Arg<sup>26, 34</sup>Lys<sup>36</sup>(N<sup> $\epsilon$ </sup>-( $\omega$ -carboxyheptadecanoyl)) GLP-1(7-36)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>36</sup>GLP-1(7-36)-OH (24.44 mg, 7.34 µmol), EDPA (26.56 mg, 205.52 µmol), NMP (513 µl)

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and water (244.4  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH2)16-COONSu (9.06 mg, 22.02 µmol) in NMP (1.21 ml), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 30 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (12.12 mg, 161.48 µmol) in 50% aqueous ethanol (1.21 ml). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (7.5 mg, 28%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3625±3. The resulting molecular weight was thus 3624±3 amu 15 (theoretical value 3624 amu).

### Example 15

# Synthesis of Arg<sup>26, 34</sup>Lys<sup>36</sup>(N<sup>ε</sup>-(ω-carboxyundecanoyl)) GLP-1(7-37)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>36</sup>GLP-1(7-37)-OH (4.2 mg, 1.24 µmol), EDPA (4.49 mg, 34.72 µmol), NMP (88.2 µl) and water (42 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH2)10-COONSu (1.21 mg, 3.72 µmol) in NMP 25  $(30.25 \,\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 40 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.04 mg,  $27.28 \,\mu\text{mol}$ ) in 50% aqueous ethanol (204  $\mu$ l). The reaction 30 mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.8 mg, 18%) was isolated, and the product 35 was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3598±3. The resulting molecular weight was thus 3597±3 amu (theoretical value 3597 amu).

### Example 16

# Synthesis of Arg<sup>26, 34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(ω-carboxyundecanoyl)) GLP-1(7-38)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>38</sup>GLP-1(7-38)-OH (5.168 mg, 1.46 µmol), EDPA (5.28 mg, 40.88 µmol), NMP (108.6 µl) and water (51.7  $\mu$ l) was gently shaken for 10 min. at room <sup>45</sup> temperature. To the resulting mixture was added a solution HOOC-(CH2)10-COONSu (1.43 mg, 4.38 µmol) in NMP (35.8  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 50 min. at room temperature. The reaction was 50 quenched by the addition of a solution of glycine (2.41 mg, 32.12  $\mu$ mol) in 50% aqueous ethanol (241  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. 55 and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.85 mg, 16%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3753±3. The resulting molecular weight was thus  $3752\pm3$  amu (theoretical value <sub>60</sub> molecular weight was thus  $3596\pm3$  amu (theoretical value 3752 amu).

#### Example 17

## Synthesis of Lys<sup>26,34</sup>bis(N<sup> $\epsilon$ </sup>-( $\omega$ -carboxyundecanoyl)) GLP-1(7-37)-OH

A mixture of GLP-1(7-37)-OH (10.0 mg, 2.98 µmol), EDPA (10.8 mg, 83.43 µmol), NMP (210 µl) and water (100

 $\mu$ l) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>) 10-COONSu (2.92 mg, 8.94 µmol) in NMP (73 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 50 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (4.92 mg, 65.56  $\mu$ mol) in 50% aqueous ethanol (492  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/ TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (1.0 mg, 9%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3781±3. The resulting molecular weight was thus 3780±3 amu (theoretical value 3780 amu).

#### Example 18

# Synthesis of Arg<sup>26, 34</sup>Lys<sup>36</sup>(N<sup>68</sup>-(wcarboxyundecanoyl)) GLP-1(7-36)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>36</sup>GLP-1(7-36)-OH (15.04 mg, 4.52 µmol), EDPA (16.35 mg, 126.56 µmol), NMP (315.8 µl) and water (150.4 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH2)10-COONSu (4.44 mg, 13.56 µmol) in NMP (111  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 40 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (7.5 mg, 99.44  $\mu$ mol) in 50% aqueous ethanol (750  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (3.45 mg, 22%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3540±3. The resulting molecular weight was thus 3539±3 amu (theoretical value 3539 amu).

### Example 19

# Synthesis of Arg $^{34}Lys^{26}(N^{\epsilon}-(\omega-$ carboxyundecanoyl)) GLP-1(7-37)-OH

A mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (5.87 mg, 1.73 µmol), EDPA (6.27 mg, 48.57 µmol), NMP (123.3 µl) and water (58.7 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH2)10-COONSu (1.70 mg, 5.20 µmol) in NMP (42.5  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 40 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.86 mg, 286  $\mu$ mol) in 50% aqueous ethanol (286  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C., and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (1.27 mg, 20%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3597±3. The resulting 3596 amu).

### Example 20

# Synthesis of $\operatorname{Arg}^{34}\operatorname{Lys}^{26}(N^{\varepsilon}-(\omega\operatorname{-carboxyheptanoyl}))$ GLP-1(7-37)-OH

A mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (4.472 mg, 1.32 µmol), EDPA (4.78 mg, 36.96 µmol), NMP (94 µl) and water

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(44.8  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution HOOC (CH<sub>2</sub>)<sub>6</sub>-COONSu (1.07 mg, 3.96 µmol) in NMP (26.8 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 1 h and 50 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.18 mg, 29.04  $\mu$ mol) in 50% aqueous ethanol (218  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.5 mg, 11%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3540±3. The resulting molecular weight was thus 3539±3 amu (theoretical value 3539 amu).

### Example 21

# Synthesis of Arg<sup>26, 34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(ω-carboxyheptanoyl)) GLP-1(7-38)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>38</sup>GLP-1(7-38)-OH (5.168 mg, 1.459 µmol), EDPA (5.28 mg, 40.85 µmol), NMP (108.6 µl) and water (51.6 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH2)6-COONSu (1.18 mg, 4.37 µmol) in NMP 25 (29.5  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 1 h and 50 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.40 mg, 32.09  $\mu$ mol) in 50% aqueous ethanol (240  $\mu$ l). The 30 reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.5 mg, 9%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3697±3. The resulting molecular weight was thus 3695±3 amu (theoretical value 3695 amu).

# Example 22

# Synthesis of Arg<sup>26, 34</sup>Lys<sup>36</sup>(N<sup>ε</sup>-(ω-carboxyheptanoyl)) GLP-1(7-37)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>36</sup>GLP-1(7-37)-OH (5.00 mg, 1.47  $\mu$ mol), EDPA (5.32 mg, 41.16  $\mu$ mol), NMP (105  $\mu$ l) and water (50 µl) was gently shaken for 5 min. at room tem- 45 perature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>6</sub>-COONSu (1.19 mg, 4.41 μmol) in NMP (29.8 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2 h at room temperature. The reaction was 50 quenched by the addition of a solution of glycine (2.42 mg, 32.34  $\mu$ mol) in 50% aqueous ethanol (242  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.78 mg, 15%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3542±3. The resulting molecular weight was thus  $3541\pm3$  amu (theoretical value <sub>60</sub> molecular weight was thus  $3653\pm3$  amu (theoretical value 3541 amu).

### Example 23

# Synthesis of Arg<sup>26, 34</sup>Lys<sup>36</sup>(N<sup>€</sup>-carboxyheptanoyl)) GLP-1(7-36)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>36</sup>GLP-1(7-36)-OH (5.00 mg, 1.50 µmol), EDPA (5.44 mg, 42.08 µmol), NMP (210 µl) and

water (50 µl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH2)613 COONSu (1.22 mg, 4.5 µmol) in NMP (30.5  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (2.47 mg, 33.0  $\mu$ mol) in 50% aqueous ethanol (247  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.71 mg, 14%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3484±3. The resulting 15 molecular weight was thus 3483±3 amu (theoretical value 3483 amu).

#### Example 24

## Synthesis of Lys<sup>26,34</sup>bis(N<sup>€</sup>-(ω-carboxyheptanoyl)) GLP-1(7-37)-OH

A mixture of GLP-1(7-37)-OH (10 mg, 2.5 µmol), EDPA (10.8 mg, 83.56 µmol), NMP (210 µl) and water (100 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2)6</sub> COONSu (2.42 mg, 8.92 µmol) in NMP (60.5 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2 h and 35 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (4.92 mg, 65.54 µmol) in 50% aqueous ethanol (492 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (2.16 mg, 24%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3669±3. The resulting molecular weight was thus 3668±3 amu (theoretical value 3668 amu).

### Example 25

# Synthesis of Arg $^{34}Lys^{26}(N^{\varepsilon}\text{-}(\omega\text{-} carboxypentadecanoyl))$ GLP-1(7-37)-OH

A mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (4.472 mg, 1.321 µmol), EDPA (4.78 mg, 36.99 µmol), NMP (93.9 µl) and water (44.7 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH2)14-COONSu (1.519 mg, 3.963 µmol) in NMP (38  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 1 h at room temperature. The reaction was quenched by the addition of a solution of glycine (2.18 mg, 29.06  $\mu$ mol) in 50% aqueous ethanol (218  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.58 mg, 12%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3654±3. The resulting 3653 amu).

## Example 26

Synthesis of Arg<sup>26, 34</sup>Lys<sup>36</sup>(N<sup> $\epsilon$ </sup>-( $\omega$ -carboxyheptanoyl)) GLP-1(7-36)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>36</sup>GLP-1(7-36)-OH (5.00 mg, 1.50 µmol), EDPA (5.44 mg, 42.08 µmol), NMP (210 µl) and

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water (50 µl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>14</sub>-COONSu (1.72 mg, 4.5 μmol) in NMP (43  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 1 h at room temperature. The reaction was quenched by the addition of a solution of glycine (2.48 mg, 33 µmol) in 50% aqueous ethanol (248  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/ 10 TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.58 mg, 11%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular weight was thus 3595±3 amu (theoretical value 3595 amu).

### Example 27

## Synthesis of Lithocholic Acid 2,5-dioxo-pyrrolidin-1-yl Ester

To a mixture of lithocholic acid (5.44 g, 14.34 mmol), N-hydroxysuccinimide (1.78 g, 15.0 mmol), anhydrous THF 25 (120 ml) and anhydrous acetonitrile (30 ml), kept at to 10° C., was added a solution of N,N'-dicyclohexylcarbodiimide (3.44 g, 16.67 mmol) in anhydrous THF. The reaction mixture was stirred at ambient temperature for 16 h, filtered and concentrated in vacuo. The residue was dissolved in dichloromethane (450 ml), washed with a 10% aqueous Na<sub>2</sub>CO<sub>3</sub> solution (2×150 ml) and water (2×150 ml), and dried (MgSO<sub>4</sub>). Filtered and the filtrate concentrated in vacuo to give a crystalline residue. The residue was recrystallised from a mixture of dichloromethane (30 ml) and n-heptane (30 ml to give the title compound (3.46 g, 51%) as a crystalline solid.

## Example 28

# Synthesis of Arg34Lys26(Ne-lithocholyl) GLP-1(7-37)-OH

A mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (4.472 mg, 1.32 µmol), EDPA (4.78 mg, 36.96 µmol), NMP (94 µl) and water (44.8 µl) was gently shaken for 10 min. at room temperature. 45 To the resulting mixture was added a solution of lithocholic acid 2,5-dioxo-pyrrolidin-1-yl ester (1.87 mg, 3.96 µmol) in NMP (46.8  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 1 h at room temperature. The reaction was 50 4011 amu). quenched by the addition of a solution of glycine (2.18 mg, 29.04  $\mu$ mol) in 50% aqueous ethanol (218  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. 55 and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (1.25 mg, 25%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3744±3. The resulting molecular weight was thus  $3743\pm3$  amu (theoretical value <sub>60</sub> 3743 amu).

### Example 29

## Synthesis of Na-tetradecanoyl-Glu(ONSu)-OBu'

To a suspension of H-Glu(OH)-OBu<sup>t</sup> (2.5 g, 12.3 µmmol), DMF (283 ml) and EDPA (1.58 g, 12.3 mmol) was added

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drop by drop a solution of Myr-ONSu (4.0 g, 12.3 mmol) in DMF (59 ml). The reaction mixture was stirred for 16 h at room temperature and then concentrated in vacuo to a total volume of 20 ml. The residue was partitioned between 5% aqueous citric acid (250 ml) and ethyl acetate (150 ml), and the phases were separated. The organic phase was concentrated in vacuo and the residue dissolved in DMF (40 ml). The resulting solution was added drop by drop to a 10% aqueous solution of citric acid (300 ml) kept at 0° C. The precipitated compound was collected and washed with iced water and dried in a vacuum drying oven. The dried compound was dissolved in DMF (23 ml) and HONSu (1.5 g, 13 mmol) was added. To the resulting mixture was added a solution of N,N'-dicyclohexylcarbodiimide (2.44 g, 11.9 molecular ion was found to be 3596±3. The resulting 15 mmol) in dichloromethane (47 ml). The reaction mixture was stirred for 16 h at room temperature, and the precipitated compound was filtered off. The precipitate was recrystallised from n-heptane/2-propanol to give the title compound (3.03 g, 50%).

#### Example 30

# Synthesis of Glu<sup>22,23,30</sup>Arg<sup>26, 34</sup>Lys<sup>38</sup>(N<sup> $\epsilon$ </sup>-( $\gamma$ -glutamyl(N<sup> $\alpha$ </sup>-tetradecanoyl))) GLP-1(7-38)-OH

A mixture of Glu<sup>22,23,30</sup>Arg<sup>26, 34</sup>Lys<sup>38</sup>-GLP1(7-38)-OH (1.0 mg, 0.272 µmol), EDPA, (0.98 mg, 7.62 µmol), NMP (70 µl) and water (70 µl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of Na-tetradecanoyl-Glu(ONSu)-OBu', prepared as described in Example 29,(0.41 mg, 0.816 µmol) in NMP (10.4  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 45 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (0.448 mg, 35 5.98  $\mu$ mol) in 50% aqueous ethanol (45  $\mu$ l). A 0.5% aqueous solution of ammonium acetate (0.9 ml) was added, and the resulting mixture was immobilised on a Varian 500 mg C8 Mega Bond Elut® cartridge, the immobilised compound washed with 5% aqueous acetonitrile (10 ml), and finally liberated from the cartridge by elution with TFA (10 ml). The eluate was concentrated in vacuo, and the reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.35 mg, 32%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 4012±3. The resulting molecular weight was thus 4011±3 amu (theoretical value

## Example 31

# Synthesis of Glu<sup>23,26</sup>Arg<sup>34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(γ-glutamyl (N<sup>a</sup>-tetradecanoyl))) GLP-1(7-38)-OH

A mixture of Glu<sup>23,26</sup>Arg<sup>34</sup>Lys<sup>38</sup>GLP-1(7-38)-OH (6.07 mg, 1.727 µmol), EDPA (6.25 mg, 48.36 µmol), NMP (425  $\mu$ l) and water (425  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of N<sup>a</sup>-tetradecanoyl-Glu(ONSu)-OBu', prepared as described in example 29,(2.65 mg, 5.18 µmol) in NMP (66.3  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 45 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.85 mg, 38.0 µmol) in 50% aqueous ethanol (285 µl). A 0.5% aqueous solution of ammonium acetate (5.4 ml) was added,

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and the resulting mixture was immobilised on a Varian 500 mg C8 Mega Bond Elut® cartridge, the immobilised compound washed with 5% aqueous acetonitrile (10 ml), and finally liberated from the cartridge by elution with TFA (10 ml). The eluate was concentrated in vacuo, and the reaction 5 mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.78 mg, 12%) was isolated, and the product 10 was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3854±3. The resulting molecular weight was thus 3853±3 amu (theoretical value 3853 amu).

#### Example 32

## Synthesis of Lys26, 34-bis(N<sup>ε</sup>-(ωcarboxytridecanoyl)) GLP-1(7-37)-OH

A mixture of GLP-1(7-37)-OH (30 mg, 8.9 µmol), EDPA 20 (32.3 mg, 250 µmol), NMP (2.1 ml) and water (2.1 ml) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH2)12-COONSu (12.7 mg, 35.8 µmol) in NMP (318 µl), the reaction mixture was gently shaken for 1 h and 40 min. at 25 room temperature. The reaction was quenched by the addition of a solution of glycine (3.4 mg, 44.7 µmol) in 50% aqueous ethanol (335  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA sys- 30 tem. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (10 mg, 29%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3840±3. The resulting molecular weight was 35 thus 3839±3 amu (theoretical value 3839 amu).

### Example 33

# Synthesis of Lys<sup>26, 34</sup>-bis(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>-tetradecanoyl))) GLP-1(7-37)-OH

A mixture of GLP-1(7-37)-OH (300 mg, 79.8 µmol), EDPA (288.9 mg, 2.24 mmol), NMP (21 ml) and water (21 ml) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of N<sup>a</sup>-tetradecanoyl- 45 Glu(ONSu)-OBu', prepared as described in Example 29, (163 mg, 319.3 µmol) in NMP (4.08 ml), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 1 h at room temperature. The reaction was quenched by the addition of 50 a solution of N,N'-dicyclohexylcarbodiimide (3.5 g, 17 a solution of glycine (131.8 mg, 1.76 mmol) in 50% aqueous ethanol (13.2 ml). A 0.5% aqueous solution of ammoniumacetate (250 ml) was added, and the resulting mixture was divided into four equal portions. Each portion was eluted onto a Varian 500 mg C8 Mega Bond Elut® cartridge, the 55 pound (6.6 g, 72%). immobilised compound washed with 0.1% aqueous TFA (3.5 ml), and finally liberated from the cartridge by elution with 70% aqueous acetonitrile (4 ml). The combined eluates were diluted with 0.1% aqueous TFA (300 ml). The precipitated compound was collected by centrifugation, washed 60 with 0.1% aqueous TFA (50 ml), and finally isolated by centrifugation. To the precipitate was added TFA (60 ml), and the resulting reaction mixture was stirred for 1 h and 30 min. at room temperature. Excess TFA was removed in vacuo, and the residue was poured into water (50 ml). The 65 precipitated compound was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and

a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (27.3 mg, 8%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 4036±3. The resulting molecular weight was thus 4035±3 amu (theoretical value 4035 amu).

## Example 34

# Synthesis of Arg<sup>26, 34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(ωcarboxypentadecanoyl)) GLP-1(7-38)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>38</sup>GLP-1(7-38)-OH (30 mg, 8.9 µmol), EDPA (32.3 mg, 250 µmol), NMP (2.1 ml) and water 15 (2.1 ml) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>14</sub>—COONSu (13.7 mg, 35.8 µmol) in NMP (343 µl), the reaction mixture was gently shaken for 1 h at room temperature. The reaction was quenched by the addition of a solution of glycine (3.4 mg, 44.7 µmol) in 50% aqueous ethanol (335  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (4.8 mg, 14%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3894±3. The resulting molecular weight was thus 3893±3 amu (theoretical value 3893 amu).

#### Example 35

### Synthesis of N<sup>a</sup>-hexadecanoyl-Glu(ONSu)-OBu<sup>t</sup>

To a suspension of H-Glu(OH)-OBu' (4.2 g, 20.6 mmol), DMF (500 ml) and EDPA (2.65 g, 20.6 mmol) was added drop by drop a solution of Pal-ONSu (7.3 g, 20.6 mmol) in DMF (100 ml). The reaction mixture was stirred for 64 h at room temperature and then concentrated in vacuo to a total volume of 20 ml. The residue was partitioned between 10% 40 aqueous citric acid (300 ml) and ethyl acetate (250 ml), and the phases were separated. The organic phase was concentrated in vacuo and the residue dissolved in DMF (50 ml). The resulting solution was added drop by drop to a 10% aqueous solution of citric acid (500 ml) kept at 0° C. The precipitated compound was collected and washed with iced water and dried in a vacuum drying oven. The dried compound was dissolved in DMF (45 ml) and HONSu (2.15 g, 18.7 mmol) was added. To the resulting mixture was added mmol) in dichloromethane (67 ml). The reaction mixture was stirred for 16 h at room temperature, and the precipitated compound was filtered off. The precipitate was recrystallised from n-heptane/2-propanol to give the title com-

## Example 36

# Synthesis of Lys<sup>26, 34</sup>-bis(N<sup> $\epsilon$ </sup>-( $\gamma$ -glutamyl(N<sup> $\alpha$ </sup>hexadecanoyl))) GLP-1(7-37)-OH

A mixture of GLP-1(7-37)-OH (10 mg, 2.9 umol), EDPA (10.8 mg, 83.4 µmol), NMP (0.7 ml) and water (0.7 ml) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of N<sup>α</sup>-hexadecanoyl-Glu(ONSu)-OBu<sup>t</sup>, prepared as described in Example 33, (163 mg, 319.3 µmol) in NMP (4.08 ml), the reaction mixture was gently shaken 1 h and 20 min. at room

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temperature. The reaction was quenched by the addition of a solution of glycine (4.9 mg, 65.6 µmol) in 50% aqueous ethanol (492 µl). A 0.5% aqueous solution of ammoniumacetate (9 ml) was added, and the resulting mixture eluted onto a Varian 1 g C8 Mega Bond Elut® cartridge, the 5 immobilised compound washed with 5% aqueous acetonitrile (10 ml), and finally liberated from the cartridge by elution with TFA (10 ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a 10 standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (2.4 mg, 20%) was isolated, and the product was analysed by PDMS. The m/z value for resulting molecular weight was thus 4091±3 amu (theoretical value 4091 amu).

### Example 37

# Synthesis of $Arg^{34}Lys^{26}(N^{\epsilon}-(\gamma-glutamyl(N^{\alpha}$ hexadecanovl))) GLP-1(7-37)-OH

A mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (3.7 mg, 1.1 µmol), EDPA (4.0 mg, 30.8 umol), acetonitrile (260 ul) and water (260  $\mu$ l) was gently shaken for 5 min. at room temperature. 25 To the resulting mixture was added a solution of N<sup>a</sup>-hexadecanoyl-Glu(ONSu)-OBu', prepared as described in Example 35,(1.8 mg, 3.3  $\mu$ mol) in acetonitrile (44.2  $\mu$ l), and the reaction mixture was gently shaken for 1 h and 20 min. at room temperature. The reaction was quenched by the 30 addition of a solution of glycine (1.8 mg, 24.2 µmol) in 50% aqueous ethanol (181 µl). A 0.5% aqueous solution of ammonium-acetate (12 ml) and NMP (300 µl) were added, and the resulting mixture eluted onto a Varian 1 g C8 Mega Bond Elut® cartridge, the immobilised compound washed 35 with 5% aqueous acetonitrile (10 ml), and finally liberated from the cartridge by elution with TFA (6 ml). The eluate was allowed to stand for 2 h at room temperature and then concentrated in vacuo. The residue was purified by column chromatography using a cyanopropyl column (Zorbax 40 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.23 mg, 6 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found 45 to be 3752±3. The resulting molecular weight was thus 3751±3 amu (theoretical value 3751 amu).

#### Example 38

## Synthesis of Arg<sup>26, 34</sup>Lys<sup>38</sup>(N<sup> $\epsilon$ </sup>-( $\gamma$ -glutamyl(N<sup> $\alpha$ </sup>tetradecanoyl))) GLP-1(7-38)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>38</sup>GLP-1(7-38)-OH (14 mg, 4.0 µmol), EDPA (14.3 mg, 110.6 µmol), NMP (980 µl) and water (980 µl) was gently shaken for 5 min. at room 55 temperature. To the resulting mixture was added a solution of N-<sup>a</sup>tetradecanoyl-Glu(ONSu)-OBu<sup>t</sup>, prepared as described in Example 29,(12.1 mg, 23.7 µmol) in NMP (303  $\mu$ l), and the reaction mixture was gently shaken for 2 h at room temperature. The reaction was quenched by the addi- 60 tion of a solution of glycine (6.5 mg, 86.9 mmol) in 50% aqueous ethanol (652 µl). A 0.5% aqueous solution of ammonium-acetate (50 ml) was added, and the resulting mixture eluted onto a Varian 1 g C8 Mega Bond Elut® cartridge, the immobilised compound washed with 5% aque- 65 ous acetonitrile (15 ml), and finally liberated from the cartridge by elution with TFA (6 ml). The eluate was allowed

to stand for 1 h and 45 min. at room temperature and then concentrated in vacuo. The residue was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to  $65^{\circ}$  C. and the acetonitrile gradient was 0–100% in 60 minutes. The title compound (3.9 mg, 26%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3881±3. The resulting molecular weight was thus 3880±3 amu (theoretical value 3880 amu).

#### Example 39

# Synthesis of Arg<sup>26, 34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(ωcarboxypentadecanoyl)) GLP-1(7-38)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>38</sup>GLP-1(7-38)-OH (14 mg, 4.0 the protonated molecular ion was found to be 4092±3. The 15 µmol), EDPA (14.3 mg, 111 µmol), NMP (980 µl) and water (980 µl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of HOOC-(CH<sub>2</sub>)<sub>14</sub>—COONSu (4.5 mg, 11.9 μmol) in NMP (114 μl), the reaction mixture was gently shaken for 1 h and 45 min. at room temperature. An additional solution of HOOC-(CH<sub>2</sub>)<sub>14</sub>--COONSu (4.0 mg, 10.4 µmol) in NMP (100 µl) was added, and the resulting mixture was gently shaken for an additional 1 h and 30 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (1.5 mg, 19.8 µmol) in 50% aqueous ethanol (148 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (3.9 mg, 26%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3809±3. The resulting molecular weight was thus 3808±3 amu (theoretical value 3808 amu).

### Example 40

# Synthesis of Arg<sup>26, 34</sup>Lys<sup>38</sup>(N<sup>68</sup>-(γ-glutamyl(N<sup>α</sup>hexadecanoyl))) GLP-1(7-38)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>38</sup>GLP-1(7-38)-OH (14 mg, 4.0 µmol), EDPA (14.3 mg, 110.6 µmol), NMP (980 µl) and water (980 µl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of N<sup>a</sup>-hexadecanoyl-Glu(ONSu)-OBu', prepared as described in Example 35,(6.4 mg, 11.9 µmol) in NMP (160  $\mu$ l), and the reaction mixture was gently shaken for 1 h and 20 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (6.5 mg, 87 mmol) in 50% aqueous ethanol (653  $\mu$ l). A 0.5% aqueous solution of ammonium-acetate (50 ml) was added, and the resulting mixture eluted onto a Varian 1 g C8 Mega Bond Elut® cartridge, the immobilised compound washed with 5% aqueous acetonitrile (10 ml), and finally liberated from the cartridge by elution with TFA (6 ml). The -eluate was allowed to stand for 1 h and 30 min. at room temperature and then concentrated in vacuo. The residue was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (7.2 mg, 47%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3881±3. The resulting molecular weight was thus 3880±3 amu (theoretical value 3880 amu).

#### Example 41

# Synthesis of Arg<sup>18,23,26,30,34</sup>Lys<sup>38</sup>(N<sup>e</sup>-hexadecanoyl) GLP-1(7-38)-OH

A mixture of Arg<sup>18,23,26,30,34</sup>Lvs<sup>38</sup>GLP-1(7-38)-OH (1.0 mg, 0.27 µmol), EDPA (0.34 mg, 2.7 µmol) and DMSO (600

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ul) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of Pal-ONSu (0.28 mg, 0.8  $\mu$ mol) in NMP (7  $\mu$ l). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 6 h at room temperature. 5 The reaction was quenched by the addition of a solution of glycine (1.6 mg, 21.7 µmol) in 50% aqueous ethanol (163 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was 10 heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.17 mg, 16%) was isolated, and the product was analysed by MALDI-MS. The m/z value for the protonated molecular ion was found to be 3961±3. The resulting molecular weight was thus 3960±3 15 amu (theoretical value 3960 amu).

#### Example 42

# Synthesis of Arg<sup>26, 34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(ω-carboxytridecanoyl)) GLP-1(7-38)-OH

A mixture of Arg<sup>26, 34</sup>Lys<sup>38</sup>GLP-1(7-38)-OH (14 mg, 4.0 µmol), EDPA (14.3 mg, 111 µmol), NMP (980 µl) and water (980  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of HOOC-25 (CH<sub>2</sub>)<sub>12</sub>-COONSu (4.2 mg, 11.9 µmol) in NMP (105 µl), the reaction mixture was gently shaken for 1 h and 50 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (6.5 mg, 87  $\mu$ mol) in 50% aqueous ethanol (652  $\mu$ l). The reaction mixture was purified 30 by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (5.8 mg, 39%) was isolated, and the product was analysed by MALDI-MS. The m/z value for the protonated molecular ion was found to be 3780±3. The resulting molecular weight was thus 3779±3 amu (theoretical value 3781 amu).

### Example 43

# Synthesis of Arg $^{34}Lys^{26}(N^{\varepsilon}\mbox{-}(\gamma\mbox{-}glutamyl(N^{\alpha}\mbox{-}tetradecanoyl))) GLP-1(7-37)\mbox{-}OH$

A mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (15 mg, 4.4 µmol), EDPA (16 mg, 124  $\mu$ mol), NMP (2 ml) and water (4.8 ml) was gently shaken for 5 min. at room temperature. To the 45 resulting mixture was added a solution of Na-tetradecanoyl-Glu(ONSu)-OBu', prepared as described in Example 29, (12.1 mg, 23.7 µmol) in NMP (303 µl), and the reaction mixture was gently shaken for 2 h at room temperature. The reaction was quenched by the addition of a solution of 50 glycine (6.5 mg, 86.9 µmol) in 50% aqueous ethanol (652 ul). A 0.5% aqueous solution of ammonium-acetate (50 ml) was added, and the resulting mixture eluted onto a Varian 1 g C8 Mega Bond Elut® cartridge, the immobilised compound washed with 5% aqueous acetonitrile (15 ml), and 55 finally liberated from the cartridge by elution with TFA (6 ml). The eluate was allowed to stand for 1 h and 45 min. at room temperature and then concentrated in vacuo. The residue was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard 60 acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (3.9 mg, 26%) was isolated, and the product was analysed by MALDI-MS. The m/z value for the protonated molecular ion was found to be 3723±3. The resulting 65 molecular weight was thus 3722±3 amu (theoretical value 3723 amu).

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## Example 44

### Synthesis of N<sup>a</sup>-octadecanoyl-Glu(ONSu)-OBu<sup>t</sup>

To a suspension of H-Glu(OH)-OBu<sup>t</sup> (2.82 g, 13.9 mmol), DMF (370 ml) and EDPA (1.79 g, 13.9 mmol) was added drop by drop a solution of Ste-ONSu (5.3 g, 13.9 mmol) in DMF (60 ml). Dichloromethane (35 ml) was added, and the reaction mixture was stirred for 24 h at room temperature and then concentrated in vacuo. The residue was partitioned between 10% aqueous citric acid (330 ml) and ethyl acetate (200 ml), and the phases were separated. The organic phase was concentrated in vacuo and the residue dissolved in DMF (60 ml). The resulting solution was added drop by drop to a 10% aqueous solution of citric acid (400 ml) kept at 0° C. The precipitated compound was collected and washed with iced water and dried in a vacuum drying oven. The dried compound was dissolved in DMF (40 ml) and HONSu (1.63 g, 14.2 mmol) was added. To the resulting mixture was added a solution of DCC (2.66 g, 12.9 mmol) in dichloromethane (51 ml). The reaction mixture was stirred for 64 h at room temperature, and the precipitated compound was filtered off. The precipitate was recrystallised from n-heptane/2-propanol to give the title compound (4.96 g, 68%).

### Example 45

# Synthesis of Arg<sup>26, 34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>-octadecanoyl))) GLP-1(7-38)-OH

A mixture of Arg<sup>26,34</sup>GLP-1(7-38)-OH (28 mg, 7.9 µmol), EDPA (28.6 mg, 221.5 µmol), NMP (1.96 ml) and water (1.96 ml) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of 35 N<sup>α</sup>-octadecanoyl-Glu(ONSu)-OBu<sup>t</sup> (17.93 g, 31.6 μmol), prepared as described in Example 44, in NMP (448 µl), and the reaction mixture was gently shaken for 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (13.1 mg, 174 µmol) in 50% aqueous ethanol (1.3 ml). A 0.5% aqueous solution of ammoniumacetate (120 ml) was added, and the resulting mixture was divided into two equal portions. Each portion was eluted onto a Varian 5 g C8 Mega Bond Elut® cartridge, the immobilised compound washed with 5% aqueous acetonitrile (25 ml), and finally liberated from the cartridge by elution TFA (25 ml). The combined eluates were allowed to stand for 1 h and 25 min. at room temperature and then concentrated in vacuo. The residue was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65° C. and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (3.6 mg, 11%) was isolated, and the product was analysed by MALDI-MS. The m/z value for the protonated molecular ion was found to be 3940±3. The resulting molecular weight was thus 3939±3 amu (theoretical value 3937 amu).

### BIOLOGICAL FINDINGS

### Protraction of GLP-1 Derivatives After s.c. Administration

The protraction of a number GLP-1 derivatives of the invention was determined by monitoring the concentration thereof in plasma after sc administration to healthy pigs, using the method described below. For comparison also the concentration in plasma of GLP-1(7-37) after sc. administration was followed. The results are given in Table 1. The

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protraction of other GLP-1 derivatives of the invention can be determined in the same way.

Pigs (50% Duroc, 25% Yorkshire, 25% Danish Landrace, app 40 kg) were fasted from the beginning of the experiment. To each pig 0.5 nmol of test compound per kg body 5 weight was administered in a 50 µM isotonic solution (5 mM phosphate, pH 7.4, 0.02% Tween®-20(Merck), 45 mg/ml mannitol (pyrogen free, Novo Nordisk). Blood samples were drawn from a catheter in vena jugularis at the hours indicated in Table 1.5 ml of the blood samples were poured into

activated carbon (Merck) in 40 mM NaH<sub>2</sub>PO<sub>4</sub>/Na<sub>2</sub>HPO<sub>4</sub>, 0.6 mM thiomersal, pH 7.5, was added to each tube. Before use, the suspension was mixed and allowed to stand for 2 h at 4° C. All samples were incubated for 1 h at 4° C. and then centrifuged at 3400\*g for 25 min. Immediately after the centrifugation, the supernatant was decanted and counted in a y-counter. The concentration in the samples was calculated from individual standard curves. The following plasma concentrations were found, calculated as % of the maximum concentration for the individual compounds (n=2):

TABLE 1

Test			Hou	rs after s	c. Admin	nistration			3
compound*)	0.75	1	2	4	6	8	10	12	24
GLP-1(7-37)		100	9	1					
Example 25	73	92	100	98	82	24	16	16	16
Example 17	76	71	91	100	84	68	30		9
Example 43		39	71	93	100	91	59	50	17
Example 37		26	38	97	100	71	81	80	45
Example 11	24	47	59	71	100	94	100		94
Example 12	36	54	65	94	80	100	85		93
Example 32	55	53	90	83	88	70	98	100	100
Example 14	18	25	32	47	98	83	97		100
Example 13	15	22	38	59	97	85	100		76
Example 38	60	53	100	66	48	39	25	29	C
Example 39	38	100	70	47	33	33	18	27	14
Example 40	47	19	50	100	51	56	34	14	C
Example 34	19	32	44	84	59	66	83	84	100

\*)The test compounds are the title compounds of the examples with the numbers given

chilled glasses containing 175  $\mu$ l of the following solution: 0.18 M EDTA, 1500 KIE/ml aprotinin (Novo Nordisk) and 3% bacitracin (Sigma), pH 7.4. Within 30 min, the samples kept at 4° C. The supernatant was pipetted into different glasses and kept at minus 20 ° C. until use.

The plasma concentrations of the peptides were determined by RIA using a monoclonal antibody specific for the 40 N-terminal region of GLP-1(7-37). The cross reactivities were less than 1% with GLP-1(1-37) and GLP-1(8-36) amide and <0.1% with GLP-1(9-37), GLP-1(10-36) amide and GLP-1(11-36)amide. The entire procedure was carried out at 4° C.

The assay was carried out as follows: 100  $\mu$ l plasma was mixed with 271 µl 96% ethanol, mixed using a vortex mixer and centrifuged at 2600\*g for 30 min. The supernatant was decanted into Minisorp tubes and evaporated completely 50 6275) by homogenisation in buffer (10 mmol/l Tris-HCl and (Savant Speedvac AS290). The evaporation residue was reconstituted in the assay buffer consisting of 80 mM NaH<sub>2</sub>PO<sub>4</sub>/Na<sub>2</sub>HPO<sub>4</sub>, 0.1% HSA (Orpha 20/21, Behring), 10 mM EDTA, 0.6 mM thiomersal (Sigma), pH 7.5. Samples were reconstituted in volumes suitable for their expected 55 concentrations, and were allowed to reconstitute for 30 min. To 300  $\mu$ l sample, 100  $\mu$ l antibody solution in dilution buffer containing 40 mM NaH<sub>2</sub>PO<sub>4</sub>/Na<sub>2</sub>HPO<sub>4</sub>, 0.1% HSA, 0.6 mM thiomersal, pH 7.5, was added. A non-specific sample was prepared by mixing 300  $\mu$ l buffer with 100  $\mu$ l dilution buffer. 60 Individual standards were prepared from freeze dried stocks, dissolved in 300 ul assay buffer. All samples were preincubated in Minisorp tubes with antibody as described above for 72 h. 200 µl tracer in dilution buffer containing 6-7000 CPM was added, samples were mixed and incubated 65 for 48 h. 1.5 ml of a suspension of 200 ml per liter of heparin-stabilised bovine plasma and 18 g per liter of

Table 1 shows that the GLP-1 derivatives of the invention have a protracted profile of action relative to GLP-1(7-37) and are much more persistent in plasma than GLP-1(7-37). were centrifuged for 10 min at 5-6000\*g. Temperature was 35 It also appears from Table 1 that the time at which the peak concentration in plasma is achieved varies within wide limits, depending on the particular GLP-1 derivative selected.

> Stimulation of cAMP Formation in a Cell Line Expressing the Cloned Human GLP-1 Receptor

In order to demonstrate efficacy of the GLP-1 derivatives, their ability to stimulate formation of cAMP in a cell line expressing the cloned human GLP-1 receptor was tested. An 45 EC50 was calculated from the dose-response curve.

Baby hamster kidney (BHK) cells expressing the human pancreatic GLP-1 receptor were used (Knudsen and Pridal, 1996, Eur. J. Pharm. 318, 429-435). Plasma membranes were prepared (Adelhorst et al, 1994, J. Biol. Chem. 269, 30 mmol/l NaCl pH 7.4, containing, in addition, 1 mmol/l dithiothreitol, 5 mg/l leupeptin (Sigma, St. Louis, Mo., USA), 5 mg/l pepstatin (Sigma, St. Louis, Mo., USA), 100 mg/l bacitracin (Sigma, St. Louis, Mo., USA), and 16 mg/l aprotinin (Novo Nordisk A/S, Bagsvaerd, Denmark)). The homogenate was centrifuged on top of a layer of 41 w/v % sucrose. The white band between the two layers was diluted in buffer and centrifuged. Plasma membranes were stored at -80° C. until used.

The assay was carried out in 96-well microtiter plates in a total volume of 140  $\mu$ l. The buffer used was 50 mmol/l Tris-HCl, pH 7.4 with the addition of 1 mmol/l EGTA, 1.5 mmol/l MgSO4, 1.7 mmol/l ATP, 20 mM GTP, 2 mmol/l 3-isobutyl-1-methylxanthine, 0.01% Tween-20 and 0.1% human serum albumin (Reinst, Behringwerke AG, Marburg, Germany). Compounds to be tested for agonist activity were dissolved and diluted in buffer, added to the membrane

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preparation and the mixture was incubated for 2 h at 37° C. The reaction was stopped by the addition of 25  $\mu$ l of 0.05 mol/l HCl. Samples were diluted 10 fold before analysis for cAMP by a scintillation proximity assay (RPA 538, Amersham, UK). The following results were obtained:

Test Compound*)	EC <sub>50</sub> , pM	Test Compound*)	EC <sub>50</sub> , pM	
GLP-1(7-37)	61	Example 31	96	
Example 45	120	Example 30	41	
Example 43	24	Example 26	8.8	
Example 40	55	Example 25	99	
Example 39	5.1	Example 19	79	
Example 38	54	Example 16	3.5	
Example 37	60	1999 - 1999 - 1998 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 -		

\*)The test compounds are the title compounds of the examples with the numbers given.

#### Example 46

# Synthesis of Arg<sup>26,34</sup>,Lys<sup>36</sup>(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>hexadecanoyl))) GLP-1(7-36)-OH

To a mixture of Arg<sup>26,34</sup>,Lys<sup>36</sup>GLP-1(7-36)-OH (12.2 mg, 3.67 µmol), EDPA (13.3 mg, 103 µmol), NMP (1.71 ml) and 25 water (855 µl) was added a solution of Pal-Glu(ONSu)-OBut (5.94 mg, 11 µmol), prepared as described in PCT application no. PCT/DK97/00340, in NMP (148 µl). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 90 min. at room 30 temperature. The reaction was quenched by the addition of a solution of glycine (6 mg, 81 µmol) in water (0.6 ml). A 0.5% aqueous solution of ammonium-acetate (38 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 35 5% aqueous acetonitril (20 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The 40 column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (3.1 mg, 23%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3695±3. The resulting molecular weight was thus 3694±3 45 amu (theoretical value 3694 amu).

### Example 47

# Synthesis of Arg<sup>26,34</sup>,Lys<sup>36</sup>(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>octadecanoyl))) GLP-1(7-36)-OH

To a mixture of Arg<sup>26,34</sup>,Lys<sup>36</sup>GLP-1(7-36)-OH (12.2 mg, 3.7 µmol), EDPA (13.3 mg, 103 µmol), NMP (1.71 ml) and water (855 µl) was added a solution of Ste-Glu(ONSu)-OBu4 (6.25 mg, 11 µmol), prepared as described in PCT applica- 55 tion no. PCT/DK97/00340, in NMP (1 ml). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 90 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (6 mg, 81 µmol) in water (0.6 ml). A 60 0.5% aqueous solution of ammonium acetate (54 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (20 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was 65 concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax

300SB-CN) and a standard acetonitril/TFA system. The column was heated to  $65^{\circ}$  C. and the acetonitril gradient was 0–100% in 60 minutes. The title compound (3.7 mg, 27%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3723±3. The resulting molecular weight was thus 3722±3 amu (theoretical value 3722 amu).

## Example 48

### Synthesis of Lithocholic Acid 2,5-dioxopyrrolidin-1-yl Ester

To a solution of lithocholic acid (5.44 g, 14.3 mmol) in a mixture of anhydrous THF (120 ml) and anhydrous aceto-15 nitril (30 ml) was added N-hydroxysuccinimide (1.78 g, 15 mmol). The mixture was cooled to 10° C., a solution of DCC (3.44 g, 16.7 mmol) in anhydrous THF (30 ml) was added drop wise, and the resulting reaction mixture stirred for 16 h at room temperature. The reaction mixture was filtered and 20 partitioned between dichloromethane (450 ml) and 10% aqueous Na<sub>2</sub>CO<sub>3</sub>(150 ml). The phases were separated, and the organic phase washed with 10% aqueous Na<sub>2</sub>CO<sub>3</sub>(150 ml), water (2×150 ml), and dried (MgSO<sub>4</sub>). The solvent was concentrated in vacuo. The residue was crystallised from a mixture of dichloromethane (30 ml) and n-heptane (30 ml). The precipitate was dried in a vacuum drying oven for 36 h to give the title compound (3.46 g, 51%).

### Example 49

### Synthesis of Lit-Glu(ONSu)-OBut

A suspension of H-Glu(OH)-OBut (1.28 g, 6.33 mmol), DMF (88 ml) and EDPA (0.82 g, 6.33 mmol) and lithocholic acid 2,5-dioxopyrrolidin-1-yl ester, prepared as described in example 48, was stirred for 16 h at room temperature. The reaction mixture was concentrated in vacuo and the residue dissolved in ethyl acetate (40 ml). The resulting solution was washed with 5% aqueous citric acid (2×25 ml), brine (10 ml), and filtered). The solvent was concentrated in vacuo and the residue dissolved in DMF (12 ml). The resulting solution was added drop wise to a 10% aqueous solution of citric acid whereby the product precipitates. The precipitate was collected and washed with iced water, and dried in vacuo. The crude product was recrystallised from a mixture of n-heptane (40 ml) and 2-propanol (17 ml). The precipitate was dried in a vacuum drying oven for 4 h to give the free acid intermediate.

To a solution of the free acid intermediate in DMF (18 ml) 50 was added hydroxysuccinimide (0.45 g, 3.91 mmol), followed by a solution of DCC (0.73 g, 3.56 mmol) in dichloromethane (18 ml). The resulting mixture was stirred at ambient temperature for 18 h, and then filtered. The filtrate was concentrated in vacuo to a solid, and the residue 55 was dissolved in dichloromethane (25 ml), and the filtration repeated, the solvent removed in vacuo to give a foam. The residue was dissolved in refluxing n-heptane (35 ml), and the product crystallised b addition of 2-propanol. The precipitate was collected, washed with cold n-heptane, dried at 35° 60 C. in vacuo to give the title compound (1.34 g, 57%).

## Example 50

## Synthesis of Arg<sup>34,</sup>Lys<sup>26</sup>(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>lithochoyl))) GLP-1(7-37)-OH

To a mixture of Arg<sup>34</sup>,Lys<sup>26</sup>GLP-1(7-37)-OH (41.1 mg, 12.2  $\mu$ mol), EDPA (44 mg, 340  $\mu$ mol), NMP (5.76 ml) and

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water (2.88 ml) was added a solution of Lit-Glu(ONSu)-OBu<sup>t</sup> (24 mg, 37  $\mu$ mol), prepared as described in example 49, in NMP (600  $\mu$ l). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 75 min. at room temperature. The 5 reaction was quenched by the addition of a solution of glycine (20 mg, 268 µmol) in water (2 ml). A 0.5% aqueous solution of ammonium acetate (128 ml) was added, and the resulting mixture divided into two equal portions, and each portion eluted onto a Varian 5 g C8 Mega Bond Elut®, the 10 immobilised compound washed with 5% aqueous acetonitril (2×25 ml), and finally liberated from the cartridge by elution with TFA (2×25 ml). The combined eluates were concentrated in vacuo, and the residue purified by column chromato-graphy using a cyanopropyl column (Zorbax 15 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (5 mg, 11%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 20 3872±3. The resulting molecular weight was thus 3871±3 amu (theoretical value 3871 amu).

## Example 51

# Synthesis of Arg<sup>26</sup>,Lys<sup>34</sup>(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>hexadecanoyl))) GLP-1(7-37)-OH

To a mixture of Arg<sup>26</sup>,Lys<sup>34</sup>GLP-1(7-37)-OH (18 mg, 5.3  $\mu$ mol), EDPA (19.3 mg, 149  $\mu$ mol), NMP (2.52 ml) and water (1.26 ml) was added a solution of Pal-Glu(ONSu)- 30 OBu<sup>t</sup> (8.6 mg, 16  $\mu$ mol) in NMP (215  $\mu$ l). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 90 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (8.8 mg,  $117 \,\mu$ mol) in water (0.88 ml). 35 A 0.5% aqueous solution of ammonium acetate (50 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was 40 concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (6 mg, 30%) was 45 isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3752±3. The resulting molecular weight was thus 3751±3 amu (theoretical value 3751 amu).

## Example 52

# Synthesis of Desamino-His<sup>7</sup>, $Arg^{26}$ , $Lys^{34}$ (N<sup> $\epsilon$ </sup>-( $\gamma$ -glutamyl(N<sup> $\alpha$ </sup>-hexadecanoyl))) GLP-1(7-37)-OH

To a mixture of desamino-His<sup>7</sup>,Arg<sup>26</sup>,Lys<sup>34</sup>GLP-1(7-37)-OH (14.3 mg, 4.2  $\mu$ mol), EDPA (15.3 mg, 119  $\mu$ mol), NMP (2 ml) and water (1 ml) was added a solution of Pal-Glu (ONSu)-OBu' (6.84 mg, 12.7  $\mu$ mol) in NMP (171  $\mu$ l). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 50 60 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (7 mg, 99  $\mu$ mol) in water (700  $\mu$ l). A 0.5% aqueous solution of ammonium acetate (42 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised com-55 pound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25

ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to  $65^{\circ}$  C. and the acetonitril gradient was 0–100% in 60 minutes. The title compound (5.6 mg, 35%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be  $3738\pm3$ . The resulting molecular weight was thus  $3737\pm3$  amu (theoretical value 3737 amu).

## Example 53

# Synthesis of Gly<sup>8</sup>, Arg<sup>26,34</sup>, Lys<sup>38</sup>(N<sup>68</sup>-( $\gamma$ -glutamyl (N<sup> $\alpha$ </sup>-hexadecanoyl))) GLP-1(7-38)-OH

To a mixture of Gly<sup>8</sup>,Arg<sup>26,34</sup>,Lys<sup>38</sup>GLP-1(7-38)-OH (11.8 mg, 3.4 µmol), EDPA (12.1 mg, 94 µmol), NMP (1.65 ml) and water (0.83 ml) was added a solution of Pal-Glu (ONSu)-OBu' (5.4 mg, 10 µmol) in NMP (135 µl). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 75 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (5.5 mg, 73.7 µmol) in water (553 µl). A 0.5% aqueous solution of ammonium acetate (36 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (5 mg, 38%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3895±3. The resulting molecular weight was thus 3894±3 amu (theoretical value 3894 amu).

#### Example 54

# Synthesis of Gly<sup>8</sup>,Glu<sup>37</sup>,Arg<sup>26,34</sup>,Lys<sup>38</sup>(N<sup> $\epsilon$ </sup>-( $\gamma$ -glutamyl(N<sup> $\alpha$ </sup>-hexadecanoyl))) GLP-1(7-38)-OH

To a mixture of Gly<sup>8</sup>, Glu<sup>37</sup>, Arg<sup>26,34</sup>, Lys<sup>38</sup>GLP-1(7-38)-OH (9 mg, 2.48 µmol), EDPA (9 mg, 69.4 µmol), NMP (1.25 ml) and water (0.63 ml) was added a solution of Pal-Glu (ONSu)-OBu' (4 mg, 7.4 µmol) in NMP (100 µl). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 105 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (4.1 mg, 54.6 µmol) in water (410 µl). A 0.5% aqueous solution of ammonium acetate (27 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (15 ml), and finally liberated from the cartridge by elution with TFA (15 ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (2.9 mg, 29%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3967±3. The resulting molecular weight was thus 3966±3 amu (theoretical value 3967 amu).

## Example 55

# Synthesis of Gly<sup>8</sup>, Glu<sup>37</sup>, Arg<sup>26,34</sup>, Lys<sup>38</sup>(N<sup> $\epsilon$ </sup>-( $\gamma$ -glutamyl(N<sup> $\alpha$ </sup>-octadecanoyl))) GLP-1(7-38)-OH

To a mixture of Gly<sup>8</sup>,Glu<sup>37</sup>,Arg<sup>26,34</sup>,Lys<sup>38</sup>GLP-1(7-38)-OH (9 mg, 2.5 μmol), EDPA (9 mg, 69.4 μmol), NMP (1.25

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ml) and water (0.63 ml) was added a solution of Ste-Glu (ONSu)-OBu' (4.2 mg, 7.4  $\mu$ mol in NMP (105  $\mu$ l). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 105 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (4.1 mg, 54.6 µmol) in water (409 µl). A 0.5% aqueous solution of ammonium acetate (27 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (15 ml), and 10 finally liberated from the cartridge by elution with TFA (15 ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril 15 (theoretical value 3625 amu). gradient was 0-100% in 60 minutes. The title compound (3.2 mg, 32%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3995±3. The resulting molecular weight was thus 3994±3 amu (theoretical value 3995 amu).

## Example 56

## Synthesis of Cap-Glu(ONSu)-OBu'

To a solution of octanoic acid (5 g, 34.7 mmol) and 25 N-hydroxysuccinimide (4 g, 34.7 mmol) in anhydrous acetonitril (10 ml) was added a solution of DCC (7.15 g, 34.7 mmol) in anhydrous dichloromethane (15 ml), and the resulting reaction mixture stirred for 16 h at room temperature. The precipitated solid was filtered off and recrystallised 30 from a mixture of n-heptane (40 ml) and 2-propanol (2 ml). The precipitate was dried in a vacuum drying oven for 16 h to give the intermediate Cap-ONSu. A suspension of the crude ester intermediate (3.9 g, 16.2 mmol), (L)-H-Glu (OH)-OBu<sup>t</sup> (3.28 g, 16.2 mmol), DMF (268 ml) and EDPA 35 (2.1 g, 16.2 mmol) was stirred for 64 h at room temperature. The reaction mixture was concentrated in vacuo and the residue dissolved in ethyl acetate (50 ml). The resulting solution was washed with 5% aqueous citric acid (2×25 ml). The solvent was concentrated in vacuo and the residue 40 dissolved in DMF (36 ml). The resulting solution was added drop wise to a 10% aqueous solution of citric acid (357 ml) and extracted with ethyl acetate (200 ml), and dried (MgSO<sub>4</sub>). The solvent was concentrated in vacuo to give the crude glutamic acid intermediate. To a mixture of the crude 45 glutamic acid intermediate, N-hydroxysuccinimide (1.85 g, 16.1 mmol) and DMF (25 ml) was added a solution of DCC (3.32 g, 16.1 mmol) in dichloromethane (15 ml). The resulting mixture was stirred at ambient temperature for 20 h. The reaction mixture was filtered and the solvent con- 50 centrated in vacuo. The residue was purified on a silica gel column (40–63 $\mu$ ), eluted with a mixture of dichloromethane and acetonitril (1:1) to give the title compound (0.63 g, 6% over all).

### Example 57

# Synthesis of Desamino-His7,Arg26,Lys34(N€-(γglutamyl(N<sup>a</sup>-octanoyl))) GLP-1(7-37)-OH

To a mixture of desamino-His<sup>7</sup>, Arg<sup>26</sup>, Lys<sup>34</sup>GLP-1(7-37)- 60 OH (14.3 mg, 4.2 umol), EDPA (15.3 mg, 119 umol), NMP (2 ml) and water (1 ml) was added a solution of Cap-Glu (ONSu)-OBu<sup>t</sup> (6.8 mg, 12.7 µmol), prepared as described in example 56, in NMP (135 µl). The reaction mixture was gently shaken for 5 min. at room temperature, and then 65 allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the addition of a solution of

glycine (7 mg, 93 umol) in water (698 ul). A 0.5% aqueous solution of ammonium acetate (42 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (4.1 mg, 27%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3626±3. The resulting molecular weight was thus 3625±3 amu

## Example 58

# Synthesis of Glu37,Arg26,34,Lys38(Ne-(γ-glutamyl (N<sup>a</sup>-hexadecanoyl))) GLP-1(7-38)-OH

To a mixture of Glu<sup>37</sup>,Arg<sup>26,34</sup>,Lys<sup>38</sup>GLP-1(7-38)-OH (17.6 mg, 4.9 µmol), EDPA (17.6 mg, 136 µmol), NMP (1.23 ml) and water (2.46 ml) was added a solution of Pal-Glu (ONSu)OBu' (7.9 mg, 14.6 µmol) in NMP (197 µl). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (8 mg, 107 µmol) in water (804 ul). A 0.5% aqueous solution of ammonium acetate (49 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (5.1 mg, 26%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3981±3. The resulting molecular weight was thus 3980±3 amu (theoretical value 3981 amu).

### Example 59

# Synthesis of $Arg^{34}$ , $Lys^{26}$ (N<sup> $\epsilon$ </sup>-( $\gamma$ -glutamyl(N<sup> $\alpha$ </sup>-octadecanoyl))) GLP-1(7-37)-OH

To a mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (41.1 mg, 12.2 µmol), EDPA (44 mg, 341 µmol), NMP (5.76 ml) and water (2.88 ml) was added a solution of Ste-Glu(ONSu)-OBu' (20.7 mg, 36.5 µmol in NMP (517 µl). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the addition of a solution of 55 glycine (20.1 mg, 268 µmol) in water (2.01 ml). A 0.5% aqueous solution of ammonium-acetate (120 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (15.4 mg, 34%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be

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3781±3. The resulting molecular weight was thus 3780±3 amu (theoretical value 3779 amu).

## Example 60

# Synthesis of Arg<sup>34</sup>,Lys<sup>26</sup>(N<sup>e</sup>-decanoyl) GLP-1(7-37)

To a mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (20 mg, 5.9 µmol), EDPA (21.4 mg, 165 µmol), NMP (2.8 ml) and water (1.4 ml) was added a solution of Cac-ONSu (4.8 mg, 17.7  $\mu$ mol) in NMP (119  $\mu$ l). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (9.8 mg, 130  $\mu$ mol) in water (98  $\mu$ l). The resulting mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (7.4 mg, 35%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3539.6±3. The resulting molecular weight was thus 20 3538.6±3 amu (theoretical value 3538 amu).

### Example 61

# Synthesis of Arg<sup>34</sup>,Lys<sup>26</sup>(N<sup> $\epsilon$ </sup>-(hexadecanoyl)) GLP-1(7-37)-OH

To a mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (41.1 mg, 12.2  $^{25}$  µmol), EDPA (44 mg, 340 µmol), NMP (2.88 ml) and water (2.88 ml) was added a solution of Pal-ONSu (12.9 mg, 36.5  $\mu$ mol) in NMP (3.3 ml). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 110 min. at room temperature. The 30 reaction was quenched by the addition of a solution of glycine (20.1 mg, 268 µmol) in water (201 µl). The solvent was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. 35 The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (15 mg, 34%) was isolated, and the product was analysed by PDMS.

#### Example 62

# Synthesis of Arg<sup>26,34</sup>,Lys<sup>27</sup>(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>-hexadecanoyl))) GLP-1(7-37)-OH

To a mixture of Arg<sup>26,34</sup>, Lys<sup>27</sup>GLP-1(7-37)-OH (11.6 mg, 3.4 µmol), EDPA (12.3 mg, 94.9 µmol), NMP (1.6 ml) and water (0.8 ml) was added a solution of Pal-Glu(ONSu)- 45 OBut (5.5 mg, 10.2 µmol) in NMP (137 µl). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 90 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (5.6 mg, 74.6  $\mu$ mol) in water (560  $\mu$ l). <sub>50</sub> A 0.5% aqueous solution of ammonium acetate (34 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (15 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The solvent was 55 concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (2.1 mg, 16%) <sub>60</sub> was isolated, and the product was analysed by PDMS.

### Example 63

To a mixture of Arg<sup>26,34</sup>, Lys<sup>23</sup>GLP-1(7-37)-OH (11.6 mg, 3.4 µmol), EDPA (12.3 mg, 94.9 µmol), NMP (1.6 ml)

and water (0.8 ml) was added a solution of Pal-Glu(ONSu)-OBut (5.5 mg, 10.2 µmol) in NMP (137 µl). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 90 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (5.6 mg, 74.6 µmol) in water (560 µl). A 0.5% aqueous solution of ammonium acetate (34 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (15 ml), and finally liberated from 10 the cartridge by elution with TFA (25 ml). The solvent was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 15 0-100% in 60 minutes. The title compound (3.1 mg, 24%) was isolated, and the product was analysed by PDMS.

### Example 64

# Synthesis of Arg<sup>26,34</sup>,Lys<sup>18</sup>(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>-hexadecanoyl))) GLP-1(7-37)-OH

To a mixture of Arg<sup>26,34</sup>,Lys<sup>18</sup>GLP-1(7-37)-OH (11.7 mg, 3.4 µmol), EDPA (12.2 mg, 94.6 µmol), NMP (1.6 ml) and water (0.8 ml) was added a solution of Pal-Glu(ONSu)-OBu' (5.5 mg, 10.2 µmol) in NMP (137 µl). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 90 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (5.6 mg, 74.6 µmol) in water (560 µl). A 0.5% aqueous solution of ammonium acetate (34 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The solvent was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (1.9 mg, 15%) was isolated, and the product was analysed by PDMS.

### Example 65

# Synthesis of Arg<sup>34</sup>,Lys<sup>26</sup>(N<sup>c</sup>-(octanoyl)) GLP-1(7-37)-OH

To a mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (41.1 mg, 12.2 µmol), EDPA (44 mg, 341 µmol), NMP (5.76 ml) and water (2.88 ml) was added a solution of Cap-ONSu (8.8 mg, 36.5 umol), prepared as described in example 56, in NMP (106  $\mu$ l). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 115 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (20 mg, 268  $\mu$ mol) in water (200  $\mu$ l). The solvent was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (18.8 mg, 44%) was isolated, and the product was analysed by PDMS.

Example 66

# Synthesis of Arg34,Lys26(N68-(dodecanoyl)) GLP-1 (7-37)-OH

To a mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (41.1 mg, 12.2 µmol), EDPA (44 mg, 341 µmol), NMP (5.76 ml) and water

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(2.88 ml) was added a solution of Lau-ONSu (8.8 mg, 36.5  $\mu$ mol), prepared in a similar manner as described for Cap-ONSu in example 56), in NMP (271  $\mu$ l). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 100 min. at room 5 temperature. The reaction was quenched by the addition of a solution of glycine (20.1 mg, 268  $\mu$ mol) in water (200  $\mu$ l). The solvent was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA 10 system. The column was heated to 65° C. and the acetonitril gradient was 0–100% in 60 minutes. The title compound (18 mg, 42%) was isolated, and the product was analysed by PDMS.

#### Example 67

#### Synthesis of Pal-GABA-ONSu

A mixture of Pal-ONSu (3 g, 8.48 mmol),  $\gamma$ -aminobutyric acid (0.87 g, 8.48 mmol) in DMF (200 ml) was stirred at room temperature for 60 h. The reaction mixture was filtered and the filtrate was added drop wise to 10% aqueous citric acid (500 ml). The precipitated N-acylated intermediate was collected and dried in vacuo. To a suspension of the dried intermediate in DMF (35 ml) was added a solution of DCC (1.45 g, 7.0 mmol) in dichloromethane (20 ml). The resulting mixture was stirred at room temperature for 20 h, and then filtered. The solvent was recrystallised from a mixture of n-heptane (50 ml) and 2-propanol (2.5 ml) to give the title compound (2.5 g, 75%).

#### Example 68

## Synthesis of Arg<sup>34</sup>,Lys<sup>26</sup>(N<sup>ε</sup>-(γ-aminobutyroyl(N<sup>γ</sup>hexadecanoyl))) GLP-1(7-37)-OH

To a mixture of Arg<sup>34</sup>, Lys<sup>26</sup>GLP-1(7-37)-OH (41.1 mg, 12.2  $\mu$ mol), EDPA (44 mg, 341  $\mu$ mol), NMP (5.76 ml) and water (2.88 ml) was added a solution of Pal-GABA-ONSu (16 mg, 36.5  $\mu$ mol), prepared as described in example 67) in NMP (400  $\mu$ l). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 100 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (20 mg, 45 268  $\mu$ mol) in water (200  $\mu$ l). The solvent was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0–100% in 60 50 minutes. The title compound (15.8 mg, 35%) was isolated, and the product was analysed by PDMS.

#### Example 69

#### Synthesis of N<sup>α</sup>-hexadecanoyl-D-glutamic acid α-tbutyl ester-γ-2,5-dioxopyrrolidin-1-yl ester

A mixture of Pal-ONSu (6.64 g, 18.8 mmol), D-glutamic acid  $\alpha$ -tert-butyl ester (4.5 g, 18.8 mmol) and EDPA (4.85 g, 37.5 mmol) in DMF (538 ml) was stirred at room temperature for 60 h. The solvent was removed and the residue dissolved in ethyl acetate (175 ml). The resulting solution was extracted with 10% aqueous citric acid (2×125 ml), and the organic phase concentrated in vacuo. The residue was dissolved in DMF (60 ml), and the resulting mixture slowly 65 added to 10% aqueous citric acid (500 ml). The precipitated compound was collected and dried in vacuo, to give the

crude N-acylated glutamic acid intermediate. The crude intermediate was dissolved in DMF (35 ml), and a solution of DCC (3.5 g, 17 mmol) in dichloromethane (70 ml) was added. The resulting mixture was stirred at room temperature for 20 h, and then filtered. The filtrate was concentrated in vacuo, and the solid residue recrystallised from a mixture of n-heptane (75 ml) and 2-propanol (5 ml), to give the title compound (5.2 g, 50%).

#### Example 70

# Synthesis of Arg<sup>34</sup>,Lys<sup>26</sup>(N<sup> $\epsilon$ </sup>-( $\gamma$ -D-glutamyl(N<sup> $\alpha$ </sup>-hexadecanoyl))) GLP-1(7-37)-OH

To a mixture of Arg<sup>34</sup>, Lys<sup>26</sup>GLP-1(7-37)-OH (41.1 mg, 12.2 µmol), EDPA (44 mg, 341 µmol), NMP (5.76 ml) and <sup>15</sup> water (2.88 ml) was added a solution of  $N^{\alpha}$ -hexadecanoyl-D-glutamic acid a-t-butyl ester-y-2,5-dioxopyrrolidin-1-yl ester (19.7 mg, 36.5 µmol) in NMP (491 µl). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 95 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (20 mg, 268 µmol) in water (2 ml). A 0.5% aqueous solution of ammonium acetate (120 ml) was added, and the resulting mixture divided into to equal portions, and each portion eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The combined eluates were concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C, and the acetonitril gradient was 0-100% in 60 minutes. The title compound (10.5 mg, 23%) was isolated, and the product was analysed by PDMS.

#### Example 71

#### Synthesis of Lys<sup>34</sup>(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>tetradecanoyl))) GLP-1(7-37)

To a mixture of GLP-1(7-37)-OH (33.6 mg, 8.9 µmol), EDPA (32.4 mg, 250 µmol), NMP (2.1 ml) and water (2.1 ml) was added a solution of Myr-Glu(ONSu)-OBut (9.1 mg, 17.9 umol), prepared as described above, in NMP (228 ul). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 80 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (14.8 mg, 197 µmol) in water (1.47 ml). A 0.5% aqueous solution of ammonium acetate (100 ml) was added, and the resulting mixture divided into two equal portions, and each portion eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (2×25 ml), and finally liberated from the cartridge by elution with TFA (2×25 ml). The combined eluates were concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (0.19 mg, 0.6%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3693±3. The resulting molecular weight was thus 3692±3 amu (theoretical value 3695 amu).

#### Example 72

## Synthesis of Arg<sup>26,34</sup>,Lys<sup>8</sup>(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>hexadecanoyl))) GLP-1(7-37)

To a mixture of Arg<sup>26, 34</sup>Lys<sup>8</sup>GLP-1(7-37)-OH (10.3 mg, 3  $\mu$ mol), EDPA (10.8 mg, 83  $\mu$ mol), NMP (1.44 ml) and

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water (0.72 ml) was added a solution of Pal-Glu(ONSu)-OBu' (4.8 mg, 8.9 µmol), prepared as described above, in NMP (120  $\mu$ l). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 70 min. at room temperature. The reaction was quenched by the 5 addition of a solution of glycine (4.9 mg, 65.3 µmol) in water (490 µl). A 0.5% aqueous solution of ammonium acetate (30 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (25 ml), and 10 finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril 15 gradient was 0-100% in 60 minutes. The title compound (3.2 mg, 28%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3836±3. The resulting molecular weight was thus 3835±3 AMU (theoretical value 3836 AMU).

#### Example 73

#### Synthesis of Lau-Glu(ONSu)-OBu<sup>t</sup>

To a solution of H-Glu-OBu<sup>t</sup> (3 g, 15 mmol) in DMF (344 25 ml) was added EDPA (2.58 ml, 15 mmol) and a solution of Lau-ONSu (4.5 g, 15 mmol), prepared in a similar manner as described for Cap-ONSu in example 56, in DMF (74 ml). The resulting mixture was stirred at ambient temperature for 18 h, and the solvent removed in vacuo. The oily residue was 30 partitioned between ethyl acetate (150 ml) and 5% aqueous citric acid (250 ml). The organic phase was concentrated in vacuo. The residue was dissolved in DMF (40 ml) and the solution added drop by drop to a 10% aqueous citric acid solution (350 ml). The precipitated product was collected, 35 washed with water and dried in vacuo for 18 h to give the intermediate free acid. To solution of the free acid intermediate in DMF (25 ml) was added N-hydroxysuccinimide (1.7 g, 14.8 mmol) and a solution of N-(3dimethylaminopropyl)-N'-ethylcarbodiimide (2.58 g, 13.5 40 mmol) in dichloromethane (52 ml). The resulting mixture was stirred at room temperature for 18 h, and the solvents removed in vacuo. The oily residue was partitioned between dichloromethane (80 ml) and water (80 ml). The organic phase was washed with 5% aqueous citric acid, dried 45 (MgSO<sub>4</sub>), and concentrated in vacuo to a solid. The solid residue was crystallised from a mixture of n-heptane (77 ml) and 2-propanol (50 ml), and finally recrystallised from n-heptane (76 ml) to give the title compound (2.96 g, 46%).

#### Example 74

#### Synthesis of Arg<sup>34</sup>,Lys<sup>26</sup>(N<sup> $\epsilon$ </sup>-( $\gamma$ -glutamyl(N<sup> $\alpha$ </sup>dodecanoyl))) GLP-1(7-37)

To a mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (20.6 mg, 6.1 55 µmol), EDPA (22 mg, 171 µmol), NMP (2.88 ml) and water (1.44 ml) was added a solution Lau-Glu(ONSu)-OBut (10.2 mg, 21.2 µmol), prepared as described in example 73, in NMP (255  $\mu$ l). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 75 min. 60 at room temperature. The reaction was quenched by the addition of a solution of glycine (10 mg, 134 µmol) in water (100 µl). A 0.5% aqueous solution of ammonium acetate (61 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised com- 65 pound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25

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ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (8.2 mg, 36%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3693±3. The resulting molecular weight is 3692±3 AMU (theoretical value 3693 AMU).

#### Example 75

#### Synthesis of Lau-β-Ala-ONSu

To a solution of Lau-ONSu (4.25 g, 14.3 mmol), prepared in a similar manner to in DMF (400 ml) was added EDPA (1.84 g, 14.3 mmol) and β-alanine (1.27 g, 14.3 mmol). The resulting mixture was stirred at ambient temperature for 18 h. Water (250 ml) and DMF (50 ml) were added and the solution stirred for 1 h at room temperature. The solvents were removed in vacuo to give a solid. The solid residue was dissolved in DMF (50 ml) and the solution added drop by drop to a 5% aqueous solution of citric acid (200 ml). The precipitate collected, washed with water (50 ml) and dried in vacuo to give the title compound (3.6 g, 93%).

#### Example 76

#### Synthesis of Pal-\beta-Ala-ONSu

To a solution of Pal-ONSu (4.25 g, 14.3 mmol) in DMF (400 ml) was added EDPA (1.84 g, 14.3 mmol) and  $\beta$ -alanine (1.27 g, 14.3 mmol). The resulting mixture was stirred at ambient temperature for 18 h. Water (250 ml) and DMF (50 ml) were added and the solution stirred for 1 h at room temperature. The solvents were removed in vacuo to give a solid. The solid residue was dissolved in DMF (50 ml) and the solution added drop by drop to a 5% aqueous solution of citric acid (200 ml). The precipitate collected, washed with water (50 ml) and dried in vacuo to give the title compound (3.6 g, 93%).

#### Example 77

#### Synthesis of Myr-GABA-ONSu

To a solution of Myr-ONSu (4 g, 12.3 mmol) in DMF (350 ml) was added EDPA (1.58 g, 12.3 mmol) and γ-aminobutyric acid (1.26 g, 12.3 mmol). The resulting mixture was stirred at ambient temperature for 18 h. Water (50 ml) was added and the solution stirred for 1 h at room temperature. The solvents were removed in vacuo to give a solid. The solid residue was dissolved in DMF (75 ml) and the solution added drop by drop to a 5% aqueous solution of citric acid (250 ml). The precipitate collected, washed with water (100 ml) and dried in vacuo to give the free acid intermediate (3.65 g, 95%). To a solution of the free acid intermediate (3 g, 9.6 mmol), N-hydroxysuccinimide (1.65 g, 14.4 mmol) and N-(3-dimethylaminopropyl)-N'ethylcarbodiimide hydrochloride (3.67 g, 19.1 mmol) in DMF (330 ml) was stirred for 18 h at room temperature, and the solvent removed in vacuo to give a solid. The solid residue was dissolved in dichloromethane (100 ml) and washed with brine (100 ml). The organic phase was dried  $(MgSO_4)$  and concentrated in vacuo to give a solid. The solid residue was recrystallised from n-heptane (75 ml) to give the title compound (2.8 g, 71%).

#### Example 78

### Synthesis of Pal-β-Ala-ONSu

To a solution of Pal-ONSu (0.9 g, 2.8 mmol) in DMF (100 ml) were added N-hydroxysuccinimide (0.35 g, 3 mmol) and

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N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (0.79 g, 4.1 mmol). The resulting mixture was stirred at ambient temperature for 40 h, and the solvent removed in vacuo. The solid residue was partitioned between water (50 ml) and dichloromethane (50 ml). The organic phase was separated, dried (MgSO<sub>4</sub>) and the solvent removed in vacuo to give the title compound (1.1 g, 94%)

#### Example 79

#### Synthesis of Arg34, Lys26 (N68-(\beta-alanyl(Nahexadecanoyl))) GLP-1(7-37)

To a mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (19.2 mg, 5.7  $\mu$ mol), EDPA (20.5 mg, 159  $\mu$ mol), NMP (2.7 ml) and water 15 (1.35 ml) was added a solution Pal-β-Ala-ONSu (7.2 mg, 17  $\mu$ mol), prepared as described in example 79, in NMP (181 µl). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 90 min. at room temperature. The reaction was quenched by the addition of 20 a solution of glycine (9.3 mg, 125  $\mu$ mol) in water (93  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (11.6 mg, 55%) was isolated, <sup>25</sup> and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3694±3. The resulting molecular weight was thus 3693±3 AMU (theoretical value 3693 AMU).

#### Example 80

#### Synthesis of Pal-Glu(OBu')-ONSu

To a solution of H-Glu(OH)-OBu<sup>t</sup> (2.7 g, 11.3 mmol) and 35 Pal-ONSu (3.98 g, 11.3 mmol) in DMF (300 ml) was added EDPA (3.2 g, 24.8 mmol). The resulting mixture was stirred at ambient temperature for 18 h, and the solvent concentrated in vacuo to give an oil. The oily residue was dissolved in DMF (60 ml) and the solution added drop by drop to a  $_{40}$ 10% aqueous solution of citric acid (300 ml) whereby a precipitate was formed. The precipitate was collected, washed with cold water (25 ml), and dried in vacuo to give free acid intermediate (4.44 g, 89%). The free acid intermediate (4 g, 9.1 mmol) was dissolved in DMF (50 ml) and 45 N-hydroxysuccinimide (1.15 g, 10 mmol) and N-(3dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (2.6 g, 13.6 mmol) were added. The resulting mixture was stirred at room temperature for 60 h, the solvent concentrated in vacuo to give the crude title compound (8.2 g).

#### Example 81

# Synthesis of Arg<sup>34</sup> ,Lys<sup>26</sup>(N<sup>ε</sup>-(α-glutamyl(N<sup>α</sup>-hexadecanoyl))) GLP-1(7-37)

To a mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (25.6 mg, 7.6 µmol), EDPA (27.4 mg, 212 µmol), NMP (3.5 ml) and water (1.75 ml) was added a solution of Pal-Glu(OBu')-ONSu (12.2 mg, 22.7 µmol), prepared as described in example 80, in NMP (305 µl). The reaction mixture was gently shaken for 60 5 min., and then allowed to stand for an additional 100 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (12.5 mg, 168  $\mu$ mol) in water (125  $\mu$ l). A 0.5% aqueous solution of ammonium acetate (72.5 ml) was added, and the resulting mixture eluted 65 onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (25 ml), and

finally liberated from the cartridge by elution with TFA (30 ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (6.1 mg, 22%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3751±3. The resulting molecular weight was 10 thus 3750±3 AMU (theoretical value 3751 AMU).

### Example 82

#### Synthesis of Ste-GABA-ONSu

To a solution of Ste-ONSu (3 g, 7.9 mmol) in DMF (270 ml) was added EDPA (1 g, 7.9 mmol) and a solution of γ-aminobutyric acid (0.81 g, 7.9 mmol) in water (40 ml). The resulting suspension was stirred at ambient temperature for 18 h, and then concentrated in vacuo to a final volume of 50 ml. The resulting suspension was added to a 5% aqueous solution of citric acid (500 ml) whereby a precipitate is formed. The precipitate was collected and washed with water (50 ml), and dried in vacuo for 4 h to give the free acid intermediate (2.8 g, 97%). To a mixture of the free acid intermediate (2.6 g, 7 mmol), N-hydroxysuccinimide (1.21 g, 10.5 mmol) and N-(3-dimethylaminopropyl)-N'ethylcarbodiimide hydrochloride (2.69 g, 14 mmol) in NMP (300 ml) was stirred for 70 h, and the solvent removed in vacuo to give a solid. The solid residue was dissolved in 30 dichloromethane (100 ml) and washed with brine (2×100 ml). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give a solid. The solid residue was recrystallised from n-heptane (75 ml) to give the title compound (2.2 g, 67%).

#### Example 83

#### Synthesis of Pal-Isonip-ONSu

To a suspension of 1-hexadecanoylbenzotriazole (3 g, 8.4 mmol), prepared as described in the literature (Kreutzberger; van der Goot, Arch. Pharm., 307, 1974), in DMF (350 ml) were added EDPA (1.08 g, 8.4 mmol) and a solution of piperidine-4-carboxylic acid in water (20 ml). The resulting suspension was stirred at room temperature for 12d, and then concentrated in vacuo to an oil. The oily residue was added drop by drop to a 5% aqueous solution of citric acid (300 ml) whereby a precipitate was formed. The precipitate was collected and washed with water (50 ml), dried in vacuo for  $_{50}$  2 h to give the free acid intermediate (3 g, 97%). To a solution of the free acid intermediate (2.8 g, 7.6 mmol), N-hydroxysuccinimide (1.31 g, 11.4 mmol) in DMF (250 ml) was added N-(3-dimethylaminopropyl)-N'ethylcarbodiimide hydrochloride (2.92 g, 15.2 mmol). The resulting mixture was stirred at ambient temperature for 18 h, and the solvent removed in vacuo to give an oil. The oily residue was dissolved in dichloromethane (100 ml), washed with brine (50 ml), dried (MgSO<sub>4</sub>) and concentrated in vacuo to give the crude title compound (4.1 g, quant.).

#### Example 84

# Synthesis of Arg<sup>34</sup>,Lys<sup>26</sup>(N<sup>€</sup>-(piperidinyl-4-carbonyl (N-hexadecanoyl))) GLP-1(7-37)

To a mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (25 mg, 7.4 µmol), EDPA (26.7 mg, 207 µmol), NMP (3.5 ml) and water (1.75 ml) was added a solution Pal-Isonip-ONSu (13.7 mg,

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30 µmol), prepared as described in example 83 in NMP (343 ul). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 90 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (12.2 mg, 163  $\mu$ mol) in water (122  $\mu$ l). 5 The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (12 mg, 44%) was isolated, and 10 sis techniques as explained above. the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3734±3. The resulting molecular weight was thus 3733±3 amu (theoretical value 3733 amu).

#### Example 85

# Synthesis of Arg<sup>34</sup>,Lys<sup>26</sup>(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>-decanoyl))) GLP-1(7-37)

20 To a mixture of Arg<sup>34</sup>GLP-1(7-37)-OH (25 mg, 7.4 µmol), EDPA (26.7 mg, 207 µmol), NMP (3.5 ml) and water (1.75 ml) was added a solution of Cac-Glu(ONSu)-OBu<sup>t</sup> (10 mg, 22.1  $\mu$ mol) in NMP (252  $\mu$ l). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 140 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (12.2 mg, 162 umol) in water (122 ul). A 0.5% aqueous solution of ammonium acetate (73 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the 30 immobilised compound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard 35 acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (12.2 mg, 45%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3669.7±3. The resulting 40 molecular weight was thus 3668.7±3 amu (theoretical value 3667 amu).

#### Example 86

#### General Method A

#### Synthesis of Alkanoic Acid 2,5-dioxopyrrolidin-1-yl Ester

To a solution of the alkanoic acid (34.7 mmol) and N-hydroxysuccinimide (4 g, 34.7 mmol) in anhydrous acetonitril (10 ml) was added a solution of DCC (7.15 g, 34.7 mmol) in anhydrous dichloromethane (15 ml), and the resulting reaction mixture was stirred for 16 h at room temperature. The precipitated solid was filtered off and recrystallised from a mixture of n-heptane and 2-propanol. The precipitate was dried in vacuo for 16 h to give the title compound.

#### Synthesis of Lys(Ne-alkanoyl)-peptide

To a mixture of the peptide (5.9 umol), EDPA (21 mg, 164 umol), NMP (5.8 ml) and water (2.9 ml) was added a solution of the alkanoic acid 2,5-dioxopyrrolidin-1-yl ester (37  $\mu$ mol), prepared as described above, in NMP (0.5 ml). The reaction mixture was gently shaken for 5 min at room 65 temperature, and then allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the

addition of a solution of glycine (9.7 mg, 129 µmol) in water (97  $\mu$ l). The solvent was removed in vacuo, and the residue was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/ TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% for 60 minutes.

Coupling of a desired group A comprising the 5- or 6-membered ring system Y to the N-terminal end of the peptide may be performed using solid phase protein synthe-

#### Example 87

#### General Method B

#### Synthesis of N<sup>a</sup>-alkanoyl-(L)-glutamic acid a-tertbutyl-y-(2,5-dioxopyrrolidin-1-yl) Diester

A suspension of the alkanoic acid 2,5-dioxopyrrolidin-1yl ester (16.2 mmol), prepared as described under General method A, (L)-glutamic acid  $\alpha$ -tert-butyl ester (3.28 g, 16.2 mmol), DMF (268 ml) and EDPA (2.1 g, 16.2 mmol) was stirred for 64 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 ml). The resulting solution was washed with 5% aqueous citric acid (2×25 ml). The solvent was concentrated removed in vacuo and the residue dissolved in DMF (36 ml). The resulting solution was carefully added to a 10% aqueous solution of citric acid (357 ml) and extracted with ethyl acetate (200 ml) and dried (MgSO<sub>4</sub>). The solvent was concentrated removed in vacuo to give the crude glutamic diester intermediate. To a mixture of the crude diester, N-hydroxysuccinimide (1.85 g, 16.1 mmol) and anhydrous DMF (25 ml) was added a solution of DCC (3.32 g, 16.1 mmol) in anhydrous dichloromethane (15 ml). The resulting mixture was stirred at ambient temperature for 20 h. The reaction mixture was filtered and the solvent was concentrated removed in vacuo. The residue was purified on a silica gel column (40-63  $\mu$ M) and eluted with a mixture of dichloromethane and acetonitril (1:1) to give the title compound.

#### Synthesis of Lys( $N^{\epsilon}$ -( $\gamma$ -glutamyl( $N^{\alpha}$ -alkanoyl))) peptide

To a mixture of the peptide (4.2 µmol), EDPA (15.3 mg, 119 µmol), NMP (2 ml) and water (1 ml) was added a solution of N<sup>α</sup>-alkanoyl-(L)-glutamic acid α-tert-butyl-γ-(2, 5-dioxopyrrolidin-1-yl) diester (12.7 umol), prepared as described above, in NMP (135 ml). The reaction mixture was gently shaken for 5 min at room temperature and then 50 allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (7 mg, 93 µmol) in water (698 µl). A 0.5% aqueous solution of ammonium acetate (42 ml) was added, and the resulting mixture was eluted onto a Varian 5 g C8 Mega 55 Bond Elut® cartridge, the immobilised compound was washed with 5% aqueous acetonitril (25 ml) and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated in vacuo, and the residue was purified by column chromatography using a cyanopropyl 60 column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% for 60 minutes.

Coupling of a desired group A comprising the 5- or 6-membered ring system Y to the N-terminal end of the peptide may be performed using solid phase protein synthesis techniques as explained above.

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#### Example 88

#### Synthesis of N-terminal Modified Peptides

Peptides were synthesised according to the Fmoc strategy on an Applied Biosystems 431A peptide synthesiser in 0.25 mmol scale using the manufacturer supplied FastMoc UV protocols starting with a Fmoc-Gly-Wang resin (NovaBiochem). The protected amino acid derivatives used were commercially obtained Fmoc amino acids, and Adoc-Imidazolylpropionic acid. The derivatives used where side chain protection was needed were: Fmoc-Arg(Pmc), Fmoc-Trp(Boc), Fmoc-Glu(OBut), Fmoc-Lys(Boc), Fmoc-Gln (Trt), Fmoc-Tyr(But), Fmoc-Ser(But), Fmoc-Thr(But), Fmoc-His(Trt) and Fmoc-Asp(OBut), and Adoc-Imidazolylpropionic acid.

The peptides were cleaved from the resin and side chain deprotected in TFA/phenol/thioanisole/water/ethanedithiol (83.25:6.25:4.25:4.25:2.00) for 180 min. The cleavage mixture was filtered and the filtrate was concentrated by a stream 20 of nitrogen. The crude peptide was precipitated from this oil with diethyl ether and washed twice with diethyl ether. After drying the crude peptide was dissolved in 50% aqueous acetic acid and diluted to 10% acetic acid with water and purified by semipreparative HPLC on a 25 mm×250 mm column packed with 7 m  $\mu$ C-18 silica. The column was eluted with a gradient of acetonitril against 0.05 M (NH<sub>4</sub>) 2SO4, pH 2.5 at 10 ml/min. at 40° C. The peptide-containing fractions were collected, diluted with 3 volumes of water and applied to a Sep-Pak® C18 cartridge (Waters part. 30 51910) which was equilibrated with 0.1% TFA. The peptide was cluted from the Sep-Pak® cartridge with 70% acetonitrile/0.1% TFA, water and isolated from the eluate by lyophilization after dilution with water. The final product obtained was characterised by amino acid analysis, analyti-35 cal RP-HPLC and by PDMS. Amino acid analysis and mass spectrometry agreed with the expected structure within the experimental error of the method (mass spectrometry +/-2 amu, amino acid analysis +/- 10%, RP-HPLC showed a peptide purity >95%).

The RP-HPLC analysis was performed using UV detection at 214 nm and a Vydac 218TP54 4.6 mm×250 mm, 5  $\mu$ m C-18 silica column which was eluted at 1 ml/min. at 42° C. Two different elution conditions were used: a gradient of 5–60% acetonitrile/0.1 M ammonium sulfate, water pH 2.5; 45 and a gradient of 5–60% acetonitrile, 0.1% TFA/0.1% TFA, water.

#### Example 89

#### Synthesis of Cap-Glu(ONSu)-OBut

To a solution of octanoic acid (5 g, 34.7 mmol) and N-hydroxysuccinimide (4 g, 34.7 mmol) in anhydrous acetonitril (10 ml) was added a solution of DCC (7.15 g, 34.7 mmol) in anhydrous dichloromethane (15 ml), and the 55 resulting reaction mixture stirred for 16 h at room temperature. The precipitated solid was filtered off and recrystallised from a mixture of n-heptane (40 ml) and 2-propanol (2 ml). The precipitate was dried in a vacuum drying oven for 16 h to give the intermediate Cap-ONSu. A suspension of the 60 crude ester intermediate (3.9 g, 16.2 mmol), (L)-H-Glu (OH)-OBu<sup>t</sup> (3.28 g, 16.2 mmol), DMF (268 ml) and EDPA (2.1 g, 16.2 mmol) was stirred for 64 h at room temperature. The reaction mixture was concentrated in vacuo and the residue dissolved in ethyl acetate (50 ml). The resulting 65 solution was washed with 5% aqueous citric acid (2×25 ml). The solvent was concentrated in vacuo and the residue

dissolved in DMF (36 ml). The resulting solution was added drop wise to a 10% aqueous solution of citric acid (357 ml) and extracted with ethyl acetate (200 ml), and dried (MgSO<sub>4</sub>). The solvent was concentrated in vacuo to give the crude glutamic acid intermediate. To a mixture of the crude glutamic acid intermediate, N-hydroxysuccinimide (1.85 g, 16.1 mmol) and DMF (25 ml) was added a solution of DCC (3.32 g, 16.1 mmol) in dichloromethane (15 ml). The resulting mixture was stirred at ambient temperature for 20 h. The reaction mixture was filtered and the solvent concentrated in vacuo. The residue was purified on a silica gel column (40–63  $\mu$ m), eluted with a mixture of dichloromethane and acetonitril (1:1) to give the title compound (0.63 g, 6% over all).

#### Example 90

#### Synthesis of Desamino-His<sup>7</sup>,Arg<sup>34</sup>,Lys<sup>26</sup>(N<sup>ε</sup>-(γglutamyl(N<sup>α</sup>-hexadecanoyl))) GLP-1(7-37)

To a mixture of desamino-His7,Arg34GLP-1(7-37)-OH (20 mg, 5.9 µmol), EDPA (21.5 mg, 166 µmol), NMP (2.8 ml) and water (1.4 ml) was added a solution Pal-Glu (ONSu)-OBu' (9.6 mg, 17.8 µmol in NMP (240 µl). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 75 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (9.8 mg, 130  $\mu$ mol) in water (979  $\mu$ l). A 0.5% aqueous solution of ammonium acetate (58 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (9.1 mg, 41%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3739±3. The resulting molecular weight was thus 3738±3 amu (theoretical value 3736 amu).

#### Example 91

#### Synthesis of Myr-GABA-ONSu

To a solution of Myr-ONSu (4 g, 12.3 mmol) in DMF (350 ml) was added EDPA (1.58 g, 12.3 mmol) and γ-aminobutyric acid (1.26 g, 12.3 mmol). The resulting mixture was stirred at ambient temperature for 18 h. Water (50 ml) was added and the solution stirred for 1 h at room temperature. The solvents were removed in vacuo to give a solid. The solid residue was dissolved in DMF (75 ml) and the solution added drop by drop to a 5% aqueous solution of citric acid (250 ml). The precipitate collected, washed with water (100 ml) and dried in vacuo to give the free acid intermediate (3.65 g, 95%). To a solution of the free acid intermediate (3 g, 9.6 mmol), N-hydroxysuccinimide (1.65 g, 14.4 mmol) and N-(3-dimethylaminopropyl)-N'ethylcarbodiimide hydrochloride (3.67 g, 19.1 mmol) in DMF (330 ml) was stirred for 18 h at room temperature, and the solvent removed in vacuo to give a solid. The solid residue was dissolved in dichloromethane (100 ml) and washed with brine (100 ml). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give a solid. The solid residue was recrystallised from n-heptane (75 ml) to give the title compound (2.8 g, 71%).

Example 92

Synthesis of Desamino-His<sup>7</sup>, Arg<sup>34</sup>, Lys<sup>26</sup>(N<sup> $\epsilon$ </sup>-( $\gamma$ -aminobutyroyl(N<sup> $\gamma$ </sup>-hexadecanoyl))) GLP-1(7-37)

To a mixture of desamino-His<sup>7</sup>,Arg<sup>34</sup>GLP-1(7-37)-OH (20 mg, 8.9 µmol), EDPA (21.5 mg, 166 µmol), NMP (2.8

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ml) and water (1.4 ml) was added a solution Pal-GABA-ONSu (7.8 mg, 17.8 µmol) in NMP (181 µl). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 90 min. at room temperature. The reaction was quenched by the addition of a solution of 5 glycine (9.3 mg, 125  $\mu$ mol) in water (93  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The 10 title compound (11.6 mg, 55%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3692±3. The resulting molecular weight was thus 3691±3 amu (theoretical value 3693 amu).

#### Example 93

#### Synthesis of Desamino-His<sup>7</sup>, Arg<sup>34</sup>, Lys<sup>26</sup>(N<sup>e</sup>-(βalanyl(N<sup>γ</sup>-hexadecanoyl))) GLP-1(7-37)

To a mixture of desamino-His7,Arg34GLP-1(7-37)-OH 20 (25 mg, 7.4 µmol), EDPA (26.8 mg, 208 µmol), NMP (3.5 ml) and water (1.75 ml) was added a solution Pal-β-Ala-ONSu (9.4 mg, 22.2 µmol) in NMP (236 µl). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 130 min. at room temperature. The 25 reaction was quenched by the addition of a solution of glycine (12.2 mg, 163 µmol) in water (122 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (13.4 mg, 49%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3681±3. The resulting 35 molecular weight was thus 3680±3 amu (theoretical value 3678 amu).

#### Example 94

#### Synthesis of Ste-GABA-ONSu

To a solution of Ste-ONSu (3 g, 7.9 mmol) in DMF (270 ml) was added EDPA (1 g, 7.9 mmol) and a solution of γ-aminobutyric acid (0.81 g, 7.9 mmol) in water (40 ml). The resulting suspension was stirred at ambient temperature for 18 h, and then concentrated in vacuo to a final volume of 50 45 ml. The resulting suspension was added to a 5% aqueous solution of citric acid (500 ml) whereby a precipitate is formed. The precipitate was collected and washed with water (50 ml), and dried in vacuo for 4 h to give the free acid intermediate (2.8 g, 97%). To a mixture of the free acid  $_{50}$ intermediate (2.6 g, 7 mmol), N-hydroxysuccinimide (1.21 g, 10.5 mmol) and N-(3-dimethylaminopropyl)-N'ethylcarbodiimide hydrochloride (2.69 g, 14 mmol) in NMP (300 ml) was stirred for 70 h, and the solvent removed in vacuo to give a solid. The solid residue was dissolved in dichloromethane (100 ml) and washed with brine (2×100 ml). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give a solid. The solid residue was recrystallised from n-heptane (75 ml) to give the title compound (2.2 g, 67%).

#### Example 95

Synthesis of Arg<sup>34</sup>,Ala<sup>8</sup>(N<sup>α</sup>-(imidazol-4-ylprop-2enoyl),Lys<sup>26</sup>(N<sup>ε</sup>-(γ-aminobutyroyl(N<sup>γ</sup>hexadecanoyl))) GLP-1(8-37)

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To a mixture of Arg<sup>34</sup>,Ala<sup>8</sup>(N<sup> $\alpha$ </sup>-(imidazol-4-ylprop-2enoyl) GLP-1(8-37)-OH (5.6 mg, 1.7  $\mu$ mol), EDPA (6 mg,

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46.2  $\mu$ mol), NMP (0.78 ml) and water (0.39 ml) was added a solution Pal-GABA-ONSu (2.2 mg, 5  $\mu$ mol) in NMP (54  $\mu$ l). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 80 min. at room 5 temperature. The reaction was quenched by the addition of a solution of glycine (2.7 mg, 36  $\mu$ mol) in water (27  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 10 65° C. and the acetonitril gradient was 0–100% in 60 minutes. The title compound (1.9 mg, 31%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3690±3. The resulting molecular weight was thus 3689±3 amu 15 (theoretical value 3690 amu).

#### Example 96

#### Synthesis of Arg<sup>34</sup>,Ala<sup>8</sup>(N<sup> $\alpha$ </sup>-(imidazol-4-ylacetyl), Lys<sup>26</sup>(N<sup> $\epsilon$ </sup>-( $\gamma$ -aminobutyroyl(N<sup> $\gamma$ </sup>-hexadecanoyl))) GLP-1(8-37)

To a mixture of Arg<sup>34</sup>,Ala<sup>8</sup>(N<sup> $\alpha$ </sup>-(imidazol-4-ylacetyl) GLP-1(8-37)-OH (5.3 mg, 1.6  $\mu$ mol), EDPA (5.7 mg, 43.9 umol), NMP (0.74 ml) and water (0.37 ml) was added a solution Pal-GABA-ONSu (2 mg, 4.7 µmol) in NMP (52 µl). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 80 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.6 mg, 34  $\mu$ mol) in water (26  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (2.2 mg, 38%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3676±3. The resulting molecular weight was thus be 3675±3 amu (theoretical value 3678 amu).

#### Example 97

# Synthesis of Desamino-His<sup>7</sup>,Arg<sup>34</sup>,Lys<sup>26</sup>(N<sup> $\epsilon$ </sup>-( $\gamma$ -aminobutyroyl(N<sup> $\gamma$ </sup>-tetradecanoyl))) GLP-1(7-37)

To a mixture of desamino-His<sup>7</sup>, Arg<sup>34</sup>GLP-1(7-37)-OH (25 mg, 7.4 µmol), EDPA (26.9 mg, 208 µmol), NMP (3.5 ml) and water (1.75 ml) was added a solution Myr-GABA-ONSu (9.1 mg, 22.2 µmol), prepared as described in example 91, in NMP (228 µl). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 90 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (12.2 mg, 163  $\mu$ mol) in water (122  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA 55 system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (10.5 mg, 39%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3667±3. The resulting molecular weight 60 was thus 3664±3 amu (theoretical value 3662 amu).

#### Example 98

Synthesis of Desamino-His<sup>7</sup>,Arg<sup>34</sup>,Lys<sup>26</sup>(N<sup> $\epsilon$ </sup>-( $\gamma$ -aminobutyroyl(N<sup> $\gamma$ </sup>-octadecanoyl))) GLP-1(7-37)

To a mixture of desamino-His<sup>7</sup>,Arg<sup>34</sup>GLP-1(7-37)-OH (25 mg, 7.4  $\mu$ mol), EDPA (26.8 mg, 207  $\mu$ mol), NMP (3.5

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ml) and water (1.75 ml) was added a solution Ste-GABA-ONSu (10.4 mg, 22.2  $\mu$ mol), prepared as described in example 94, in NMP (259  $\mu$ l). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 170 min. at room temperature. The reaction was 5 quenched by the addition of a solution of glycine (12.2 mg, 163  $\mu$ mol) in water (122  $\mu$ l) and the reaction mixture purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient 10 was 0–100% in 60 minutes. The title compound (7 mg, 25%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3719±3. The resulting molecular weight was thus 3718±3 amu (theoretical value 3720 amu).

## Example 99

#### General Method A

#### Synthesis of Alkanoic Acid 2,5-dioxopyrrolidin-1-yl Ester

To a solution of the alkanoic acid (34.7 mmol) and N-hydroxysuccinimide (4 g, 34.7 mmol) in anhydrous acetonitril (10 ml) was added a solution of DCC (7.15 g, 34.7 <sup>25</sup> mmol) in anhydrous dichloromethane (15 ml), and the resulting reaction mixture was stirred for 16 h at room temperature. The precipitated solid was filtered off and recrystallised from a mixture of n-heptane and 2-propanol. The precipitate was dried in vacuo for 16 h to give the title <sup>30</sup> compound.

#### Synthesis of Lys(N<sup>€</sup>-alkanoyl)-peptide

To a mixture of the desired parent peptide (5.9  $\mu$ mol), 35 EDPA (21 mg, 164  $\mu$ mol), NMP (5.8 ml) and water (2.9 ml) was added a solution of the alkanoic acid 2,5dioxopyrrolidin-1-yl ester (37  $\mu$ mol), prepared as described above, in NMP (0.5 ml). The reaction mixture was gently shaken for 5 min at room temperature, and then allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (9.7 mg, 129  $\mu$ mol) in water (97  $\mu$ l). The solvent was removed in vacuo, and the residue was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient is 0–100% for 60 minutes.

#### General Method B

#### Synthesis of N<sup>α</sup>-alkanoyl-(L)-glutamic Acid α-tertbutyl-γ-(2,5-dioxopyrrolidin-1-yl) Diester

A suspension of the alkanoic acid 2,5-dioxopyrrolidin-1yl ester (16.2 mmol), prepared as described under General 55 method A, (L)-glutamic acid  $\alpha$ -tert-butyl ester (3.28 g, 16.2 mmol), DMF (268 ml) and EDPA (2.1 g, 16.2 mmol) was stirred for 64 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 ml). The resulting solution was washed 60 with 5% aqueous citric acid (2×25 ml). The solvent was removed in vacuo and the residue dissolved in DMF (36 ml). The resulting solution was carefully added to a 10% aqueous solution of citric acid (357 ml) and extracted with ethyl acetate (200 ml) and dried (MgSO<sub>4</sub>). The solvent was 65 removed in vacuo to give the crude glutamic diester intermediate. To a mixture of the crude diester,

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N-hydroxysuccinimide (1.85 g, 16.1 mmol) and anhydrous DMF (25 ml) was added a solution of DCC (3.32 g, 16.1 mmol) in anhydrous dichloromethane (15 ml). The resulting mixture was stirred at ambient temperature for 20 h. The reaction mixture was filtered and the solvent was removed in vacuo. The residue was purified on a silica gel column (40–63  $\mu$ m) and eluted with a mixture of dichloromethane and acetonitril (1:1) to give the title compound.

#### Synthesis of Lys( $N^{\epsilon}$ -( $\gamma$ -glutamyl( $N^{\alpha}$ -alkanoyl))) peptide

To a mixture of the desired parent peptide (4.2  $\mu$ mol), EDPA (15.3 mg, 119 µmol), NMP (2 ml) and water (1 ml) was added a solution of N<sup>\alpha</sup>-alkanoyl-(L)-glutamic acid <sup>15</sup>  $\alpha$ -tert-butyl- $\gamma$ -(2,5-dioxopyrrolidin-1-yl) diester (12.7 µmol), prepared as described above, in NMP (135 ml). The reaction mixture was gently shaken for 5 min at room temperature and then allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the 20 addition of a solution of glycine (7 mg, 93 µmol) in water (698 ul). A 0.5% aqueous solution of ammonium acetate (42 ml) was added, and the resulting mixture was eluted onto a Varian 5 g C8 Mega Bond Elut® cartridge, the immobilised compound was washed with 5% aqueous acetonitril (25 ml) and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated in vacuo, and the residue was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient is 0-100% for 60 minutes.

#### Example 100

#### Synthesis of Arg<sup>34</sup>,Lys<sup>26</sup>(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>tetradecanoyl))) GLP-1(9-37)

To a mixture of Arg<sup>34</sup>GLP-1(9-37)-OH (22.4 mg, 7.1 µmol), EDPA (25.5 mg, 197 µmol), NMP (3.14 ml) and water (1.57 ml) was added a solution of Myr-Glu(ONSu)-OBut (10.8 mg, 21.2 µmol) in NMP (270 µl). The reaction mixture was gently shaken for 5 min., and then allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (11.6 mg, 155 µmol) in water (116 µl). A 0.5% aqueous solution of ammonium acetate (67 ml) was added, and the resulting mixture eluted onto a Varian 5 g C8 Mega Bond Elut®, the immobilised compound washed with 5% aqueous acetonitril (25 ml), and finally liberated from the cartridge by elution with TFA (25 ml). The eluate was concentrated in vacuo, and the residue purified by column chromatography using a 50 cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitril/TFA system. The column was heated to 65° C. and the acetonitril gradient was 0-100% in 60 minutes. The title compound (2.3 mg, 9.2%) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3516.0±3. The resulting molecular weight was thus 3515.0±3 amu (theoretical value 3515 amu).

#### Example 101

In this example and examples 102 and 103,

- the phrase "8 mM phosphate buffer of pH 7.4" means 4 mM NaH<sub>2</sub>PO<sub>4</sub>, 2H<sub>2</sub>O and 4 mM Na<sub>2</sub>HPO<sub>4</sub>, 2H<sub>2</sub>O pH adjusted to 7.4 (using Sodium Hydroxide and/or Hydrochloric acid).
- the term "Compound 1" means  $Arg^{34}$ ,  $Lys^{26}(N^{\epsilon}-(\gamma-Glu (N^{\alpha}-tetradecanoyl)))$  GLP-1(7-37).

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the term "Compound 2" means  $\operatorname{Arg}^{34}$ ,Lys<sup>26</sup>(N<sup> $\epsilon$ </sup>-( $^{\gamma}$ -Glu (N<sup> $\alpha$ </sup>-hexadecanoyl))) GLP-1(7-37). the term "Compound 3" means  $\operatorname{Arg}^{26,34}$ ,Lys<sup>36</sup>(N<sup> $\epsilon$ </sup>-( $^{\gamma}$ -Glu (N<sup> $\alpha$ </sup>-hexadecanoyl))) GLP-1(7-36).

the term "Compound 4" means  $\operatorname{Arg}^{26}$ , Lys<sup>34</sup>(N<sup> $\epsilon$ </sup>(<sup> $\gamma$ </sup>-Glu(N<sup> $\alpha$ </sup>- <sup>5</sup> hexadecanoyl))) GLP-1(7-37).

the term "Compound 5" means Gly<sup>8</sup>, Glu<sup>37</sup>, Arg<sup>26,34</sup>, Lys<sup>38</sup> (N<sup> $\epsilon$ </sup>-(<sup>7</sup>-Glu(N<sup> $\alpha$ </sup>-hexadecanoyl))) GLP-1(7-38).

General	Example 101	
Compound	2-7.5 mg/ml	
Mannitol	34-50 mg/ml	
Phenol	5-7.5 mg/ml	
8 mM phosphate but		

Mannitol and phenol were dissolved in the phosphate buffer preadjusted to pH 7.4. The compound was then dissolved under slow stirring. The pH was adjusted to 7.4 using sodium hydroxide and/or hydrochloric acid. Finally, the formulation was sterilised by filtration through an appropriate filter.

The following specific formulations were produced using 25 this procedure:

Example 101-A		
Compound 1 Mannitol		mg/ml mg/ml
Phenol		mg/ml
8 mM phosphate	ad 100	ml
buffer of pH 7.4		
Example 101-B		
Compound 1	5	mg/ml
Mannitol		mg/ml
Phenol		mg/ml
8 mM phosphate	ad 100	ml
buffer of pH 7.4		
Example 101-C		
Compound 1		mg/ml
Mannitol		mg/ml
Phenol		mg/ml
8 mM phosphate	ad 100	ml
buffer of pH 7.4		
Example 101-D		
Compound 2		mg/ml
Mannitol	38	mg/ml
Phenol		mg/ml
8 mM phosphate	ad 100	ml
buffer of pH 7.4		
Example 101-E		
Compound 2	5	mg/ml
Mannitol		mg/ml
Phenol		mg/ml
8 mM phosphate	ad 100	ml
buffer of pH 7.4		
Example 101-F		
Compound 2	7.5	mg/ml
Mannitol		mg/ml
Phenol		mg/ml
8 mm phosphate	ad 100	ml
buffer of pH 7.4		
Example 101-G		
		tere contractor
Compound 3	2.0	mg/ml
Compound 3 Mannitol Phenol	38	mg/ml mg/ml mg/ml

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8 mM phosphate buffer of pH 7.4 Example 101-H	ad 100 ml
Compound 3	5 mg/m
Mannitol	36.9 mg/m
Phenol	5 mg/m
8 mM phosphate buffer of pH 7.4 Example 101-I	ad 100 ml
Compound 3	7.5 mg/m
Mannitol	34 mg/m
Phenol	7.5 mg/m
8 mm phosphate buffer of pH 7.4 Example 101-J	ad 100 ml
Compound 4	2.0 mg/m
Mannitol	38 mg/m
Phenol	5 mg/m
8 mM phosphate buffer of pH 7.4 Example 101-K	ad 100 ml
Compound 4	5 mg/m
Mannitol	36.9 mg/m
Phenol	5 mg/m
8 mM phosphate buffer of pH 7.4 Example 101-L	ad 100 ml
Compound 4	7.5 mg/m
Mannitol	34 mg/m
Phenol	7.5 mg/m
8 mM phosphate	ad 100 ml
buffer of pH 7.4 Example 102	
Compound	2-7.5 mg/m
Mannitol	19-25 mg/m
Benzyl Alcohol	14-18 mg/m

Mannitol and benzyl alcohol were dissolved in the phosphate buffer preadjusted to pH 7.4. The compound was then dissolved under slow stirring. The pH was adjusted to 7.4 using sodium hydroxide and/or hydrochloric acid. Finally, the formulation was sterilised by filtration through an appropriate filter.

The following specific formulations were produced using this procedure:

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	Example 102-A		
	Compound 1	2.0	mg/ml
55	Mannitol	25	mg/ml
	Benzyl alcohol	14	mg/ml
	8 mM phosphate	ad 100	ml
	buffer of pH 7.4		
	Example 102-B		
2	Compound 1	7.5	mg/ml
60	Mannitol	19	mg/ml
	Benzyl alcohol	18	mg/ml
	8 mM phosphate	ad 100	ml
	buffer of pH 7.4		
	Example 102-C		
55	Compound 2	2.0	mg/ml
	Mannitol	25	mg/ml

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-cont	inued		-continued				
Benzyl alcohol mM phosphate puffer of pH 7.4 Example 102-D	14 mg/ml ad 100 ml	5	8 mM phosphate buffer of pH 7.4 Example 103-D	ad 100 ml			
Compound 2 Mannitol 3enzyl alcohol 8 mM phosphate puffer of pH 7.4 Example 102-E	7.5 mg/ml 19 mg/ml 18 mg/ml ad 100 ml	10	Compound 2 Mannitol Metacresol 8 mM phosphate buffer of pH 7.4 Example 103-E	7.5 mg/ml 42 mg/ml 4 mg/ml ad 100 ml			
Compound 3 Mannitol Benzyl alcohol 8 mM phosphate buffer of pH 7.4 Example 102-F	2.0 mg/ml 25 mg/ml 14 mg/ml ad 100 ml	15	Compound 3 Mannitol Metacresol 8 mM phosphate buffer of pH 7.4 Example 103-F	2.0 mg/ml 44 mg/ml 2.5 mg/ml ad 100 ml			
Compound 3 Mannitol Benzyl alcohol 8 mM phosphate buffer of pH 7.4 Example 102-G	7.5 mg/ml 19 mg/ml 18 mg/ml ad 100 ml	20	Compound 3 Mannitol Metacresol 8 mM phosphate buffer of pH 7.4 Example 103-G	7.5 mg/ml 42 mg/ml 4 mg/ml ad 100 ml			
Compound 5 Mannitol Benzyl alcohol 8 mM phosphate buffer of pH 7.4 Example 102-H	2.0 mg/ml 25 mg/ml 14 mg/ml ad 100 ml	25	Compound 5 Mannitol Metacresol 8 mM phosphate buffer of pH 7.4 Example 103-H	2.0 mg/ml 44 mg/ml 2.5 mg/ml ad 100 ml			
Compound 5 Mannitol Benzyl alcohol 8 mM phosphate buffer of pH 7.4 Example 103	7.5 mg/ml 19 mg/ml 18 mg/ml ad 100 ml	30	Compound 5 Mannitol Metacresol 8 mM phosphate buffer of pH 7.4	7.5 mg/ml 42 mg/ml 4 mg/ml ad 100 ml			
Compound Mannitol Metacresol 8 mM phosphate buffer o	2–7.5 mg/ml 42–44 mg/ml 2.5–4.0 mg/ml of pH 7.4	pep buff	Examplification Examplification Examplification Examplification for peptier, pH 8, and 23° C. was and the following eight G.	tides dissolved in 10 measured for native			

40 Mannitol and metacresol were dissolved in the phosphate buffer preadjusted to pH 7.4. The compound was then dissolved under slow stirring. The pH was adjusted to 7.4 using sodium hydroxide and/or hydrochloric acid. Finally, the formulation was sterilised by filtration through an appro-45 priate filter.

The following specific formulations were produced using this:

Compound 1	2.0	mg/ml
Mannitol	44	mg/ml
Metacresol	2.5	mg/ml
8 mM phosphate	ad 100	ml
buffer of pH 7.4		
Example 103-B		
Compound 1	7.5	mg/ml
Mannitol	42	mg/ml
Metacresol	4	mg/ml
8 mM phosphate	ad 100	ml
buffer of pH 7.4		
Example 103-C		
Compound 2	2.0	mg/ml
Mannitol	44	mg/ml
Metacresol	2.5	mg/ml

of S 37) and the following eight GLP-1 derivatives of the present invention:

	1.3			
- 1	9	Exam	nle	17
	a	LAam	pic	21

- (b) Example 50
- (c) Example 63
- (d) Example 51
- (e) Example 55
- (f) Example 61
- (g) Example 68

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(h) Example 64

The results are shown in FIG. 1. Note that the CD signal 50 is proportional to the average content of a-helix in the peptides, i.e., a CD value of -1 corresponds to 10% a-helix content under these conditions. The figure shows that, as the concentration of native GLP-1(7-37) is raised between 25 and 1000  $\mu$ M, the content of  $\alpha$ -helix increases from about 55 15% to about 30-35% in parallel with the formation of higher oligomers. In contrast with this concentration dependent behaviour, the figure shows that the helix content remains high and essentially independent of the concentration in the 1–200  $\mu$ M range for the GLP-1 derivatives of the present invention forming partially structured micelle-like aggregates under the same conditions.

#### Example 105

#### Equilibrium Solubility

For pH-solubility profiles, solutions containing the peptide and additives (surfactant and, where indicated, other

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excipients) at the appropriate concentrations were prepared at pH 9–10. The solutions were filtered, samples were withdrawn, and the pH was adjusted to the desired value in the range of 3–8. The samples were left for 24 hours at 23° C. to attain solubility equilibrium. After centrifugation (20, 000 g for 20 minutes, 23° C.) of each sample, the pH was measured, and the solubility was determined from measurement of the absorbance at 276 nm of the supernatant. Long Term Physical Stability

acylated GLP-1(7-37) analogue were dissolved at twice 10 the desired final concentration and incubated briefly (<10 minutes) at pH 11.5, 23° C. before filtration and mixing with an equal volume of a filtered solution containing all the excipients in twice the desired final concentration. The pH was then measured and adjusted as needed. The solution was 15 transferred to pen-fill cartridges containing a small glass ball (to allow visual determination of changes in solution

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viscosity). The containers were sealed and incubated at the desired temperature between 4° C. and 37° C. At appropriate time intervals, the samples were gently turned and visually examined using a light box. When physical changes were apparent (precipitation, crystallization or gelation), the sample was centrifuged and the absorbance was measured in the supernatant to determine whether the component coming out of solution was the peptide or not.

Equilibrium solubility was determined as a function of pH for 1 mg/ml solutions of the acylated GLP-1(7-37) analogue N<sup> $\epsilon$ </sup>-hexadecanoyl- $\gamma$ -glutamyl-Lys26,Art34GLP-1(7-37) in the absence of additives and in the presence of increasing amounts of the surfactant LPCL (lauroyl lysophosphatidyl choline). The results show that 1 mM and 2 mM LPCL enhance solubility relative to the reference composition, while full solubility is obtained in the presence of 5 mM LPCL.

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Arg Gly Arg Arg Lys

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-continued 1 5 10 15 Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly 20 25 30 Arg Arg Glu Lys 35 <210> SEQ ID NO 78 <211> LENGTH: 37 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: mutagen <400> SEQUENCE: 78 Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu 5 10 Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly 20 25 30 Arg Arg Glu Phe Lys 35 <210> SEQ ID NO 79 <211> LENGTH: 38 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: mutagen <400> SEQUENCE: 79 Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu 1 5 10 15 Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly 20 25 30 Arg Arg Glu Phe Pro Lys 35 <210> SEQ ID NO 80 <211> LENGTH: 39 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: mutagen <400> SEQUENCE: 80 Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu 15 1 5 10 Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly 20 25 30 Arg Arg Glu Phe Pro Glu Lys 35 <210> SEQ ID NO 81 <211> LENGTH: 40 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: mutagen <400> SEQUENCE: 81 Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu 5 10 15 1 Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly

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									-	con	tin	ued	
	20					25					30		
Arg Arg Glu 35	Phe	Pro	Glu	Glu	Lys 40								
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Ser Ser Tyr	Leu 20	Glu	Gly	Gln	Ala	Ala 25	Arg	Glu	Phe	Ile	Ala 30	Trp	Leu
Val Lys Gly 35	Arg	Gly	Lys										
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Ser Ser Tyr	Leu 20	Glu	Gly	Gln	Ala	Ala 25	Lys	Glu	Phe	Ile	Ala 30	Trp	Leu
Val Arg Gly 35	Arg	Gly	Lys										
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Ser Ser Tyr	Leu 20	Glu	Gly	Gln	Ala	Ala 25	Arg	Glu	Phe	Ile	Ala 30	Trp	Leu
Val Arg Gly 35	Lys	Gly	Lys										
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Gln Ala Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Lys	Gly	Arg	Gly	Lys

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	2477					2400	1411101				ane.	2253 S.S.	12-00		
	GTY	Glu	GLY		Pne	Thr	Ser	Asp		Ser	Ser	Tyr	Leu		GIY
1				5					10					15	
Gln	Ala	Ala	Arg	Glu	Dhe	Tle	Ala	Trn	Len	Val	Lve	Glv	Ara	Clv	Lve
0.111	6 A.A. 64	4 4 4 4	20	010	1 110	110	111.04	25	Dea	THE	n'i o	orl	30	ory	-10
112121	201 00			02020											
		EQ II													
100000000	800 BBC	ENGTH	22.072	2											
- 27.73	700 - 201	PE:	- T. C. C. T. I												
		RGANI		Art	ificia	al Se	equer	ice							
	399) - <b>R</b> .C	EATUR		100107072	102240										
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<400	)> SI	EQUEN	NCE :	96											
						200	2000	120000		12000	42-53		427-021	12415	
	Gly	Glu	GLY		Phe	Thr	Ser	Asp		Ser	Ser	Tyr	Leu		GIY
1				5					10					15	
Glr	Ale	Ala	Arc	Glu	Phe	T1c	Alc	Tre	Len	Val	Arc	G1	Lve	G1	Tave
0111	ALG	Ala	20	oru	THE	TTC	nia	25	Leu	Tar	ALY	ory	30	OLA	-175
			20					25					20		

What is claimed is: 1. A glucagon-like peptide-1 (GLP-1) derivative of formula I (SEQ ID NO:2):

8 9 10 11 12 13 14 15 16 17 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-18 19 20 21 22 23 24 25 26 27 28 Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-29 30 31 32 33 34 35 36 37

Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Glu

wherein

- (a) the  $\epsilon$ -amino group of Lys at position 26 is substituted with a lipophilic substituent optionally via a spacer, and 45
- (b) the lipophilic substituent is (i) CH<sub>3</sub>(CH<sub>2</sub>), COwherein n is 6, 8, 10, 12, 14, 16, 18, 20 or 22 (ii) HOOC(CH2)mCO- wherein m is 10, 12, 14, 16, 18, 20 or 22, or (iii) lithocholyl, and
- (c) the spacer is an amino acid residue except Cys, or the  $_{50}$  the antidiabetic agent is human insulin. spacer is y-aminobutanoyl.

2. The GLP-1 derivative of claim 1, wherein the lipophilic substituent is linked to the  $\epsilon$ -amino group of Lys via a spacer.

- 3. The GLP-1 derivative of claim 2, wherein the spacer is is y-glutamyl.
- 4. The GLP-1 derivative of claim 2, wherein the spacer is 55 β-asparagyl.
- 5. The GLP-1 derivative of claim 2, wherein the spacer is glycyl.
- 6. The GLP-1 derivative of claim 2, wherein the spacer is y-aminobutanoyl.

7. The GLP-1 derivative of claim 2, wherein the spacer is β-alanyl.

8. A pharmaceutical composition comprising a GLP-1 derivative of claim 1 and a pharmaceutically acceptable vehicle or carrier.

9. The pharmaceutical composition of claim 8, further 35 comprising an isotonic agent, a preservative and a buffer.

- 10. The pharmaceutical composition of claim 9, wherein the isotonic agent is sodium chloride, mannitol and glycerol.
- 11. The pharmaceutical composition of claim 9, wherein the preservative is phenol, m-cresol, methyl 40 p-hydroxybenzoate or benzyl alcohol.

12. The pharmaceutical composition of claim 9, wherein the buffer is sodium acetate or sodium phosphate.

- 13. The pharmaceutical composition of claim 8, further comprising a surfactant.
- 14. The pharmaceutical composition of claim 8, further comprising zinc.
- 15. The pharmaceutical composition of claim 8, further comprising an antidiabetic agent.

The pharmaceutical composition of claim 15, wherein

17. The pharmaceutical composition of claim 15, wherein the antidiabetic agent is a hypoglycemic agent.

- 18. The pharmaceutical composition of claim 8, further comprising an antiobesity agent.
- 19. A method of treating diabetes, comprising adminstering to a patient a therapeutically effective amount of a GLP-1 derivative of claim 1.
- 20. A method of treating obesity, comprising administering to a patient a therapeutically effective amount of a 60 GLP-1 derivative of claim 1.

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# UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

 PATENT NO.
 : 6,458,924 B2

 APPLICATION NO.
 : 09/398111

 DATED
 : October 1, 2002

 INVENTOR(S)
 : Knudsen et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 1, Column 249, Line 41: "Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Glu" should read --Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly-.

Signed and Sealed this

First Day of July, 2008

JON W. DUDAS Director of the United States Patent and Trademark Office

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