

CLAIMS

1. ~~Use of a~~An isolated Rspo1 protein, ~~for use as in the manufacture of a medicament for~~
~~treating, preferably in the treatment of~~ diabetes in a subject in need thereof.
- 5 2. The ~~Rspo1 protein for use of~~ Claim 1, which is either
 - (i) a protein comprising a R-spondin 1 polypeptide,
 - (ii) a protein comprising a functional fragment of R-spondin 1 polypeptide, or
 - 10 (iii) a protein comprising a functional variant of R-spondin 1 polypeptide.
3. The ~~Rspo1 protein for use of~~ any of the preceding claims, which is either
 - (i) a protein comprising a human R-spondin 1 polypeptide of any one of SEQ ID
 NOs:2-4,
 - 15 (ii) a protein comprising a functional fragment of human R-spondin 1 polypeptide
 of any one of SEQ ID NOs:2-4, or
 - (iii) a protein comprising a functional variant of R-spondin 1 polypeptide of any one
 of SEQ ID NOs:2-4.
- 20 4. The ~~Rspo1 protein for use of~~ any of the preceding claims, which is a protein comprising
 a functional fragment of R-spondin 1 polypeptide, said functional fragment preferably
 comprising or consisting of a polypeptide having at least 40-100 consecutive amino
 acid residues in the FU1 and/or FU2 domains of R-spondin 1 protein, typically at least
 40-100 consecutive amino acid residues in the FU1 and/or FU2 domains of any of the
 25 polypeptides of SEQ ID NO:1-4 and SEQ ID NO:8-24.
5. The ~~Rspo1 protein for use of~~ any of the preceding Claims, which is a recombinant
 protein comprising either
 - (i) any one of SEQ ID NO: 1-4 and SEQ ID NO:8-24, or
 - 30 (ii) a combination of fragments of Rspo1 protein of SEQ ID NO:1, typically including
 the functional domain FU1 and the functional domain FU2, ~~and, and~~ optionally
 the functional domain TSP.
6. The ~~Rspo1 protein for use of~~ any of the preceding claims, which binds to LGR4
 35 receptor.

7. The ~~Rspo1 protein for use of any of the preceding claims, wherein said Rspo1 protein is a protein comprising a functional fragment or functional variant of a native R-spondin 1 polypeptide preferably, of human R-spondin 1 of SEQ ID NO :3 or 4, and said Rspo1 protein exhibits at least 50%, 60%, 70%, 80%, 90%, 100% or more of one or more of the following activities relative to said native R-spondin 1:~~
 - i. Binding affinity to LGR4 receptor, for example as determined by SPR ~~assay ;assay;~~
 - ii. Induction of the proliferation of functional beta cells, for example as determined in an in vitro beta cell proliferation assay;
 - iii. Induction of the proliferation of functional beta cells, for example as determined in an in vivo beta cell proliferation assay;
 - iv. Increase of glucose-stimulated insulin secretion (GSIS), for example as determined in an in vitro beta cell proliferation assay; or,
 - v. Increase of glucose-stimulated insulin secretion (GSIS), for example as determined in an in vivo beta cell proliferation assay.
8. The ~~Rspo1 protein or use of any of the preceding Claims, which is a protein comprising a functional variant of R-spondin 1, wherein said functional variant comprises or essentially consists of a polypeptide having at least 70%, 80%, 90% or at least 95% identity to a parent R-spondin 1 polypeptide sequence, preferably at least 70%, 80%, 90% or at least 95% identity to one of polypeptides of SEQ ID NOs :1-4 and SEQ ID NO :8-24.~~
9. The ~~Rspo1 protein for use of Claim 8, wherein said functional variant of R-spondin 1 differs from the corresponding native R-spondin 1 sequence through only amino acid substitutions.~~
10. The ~~Rspo1 protein for use of any one of the preceding claims, which is a fusion protein, for example a fusion protein comprising an Fc region of an antibody.~~
11. The ~~Rspo1 protein for use of any of the preceding Claims, which is a pegylated or PASylated protein.~~
12. Use of t~~The Rspo1 protein for use of~~according to any of the preceding Claims in the manufacture of a medicament for treating type 1 or type 2 diabetes in a subject in need thereof., in the treatment of diabete type 1 or type 2.

13. The ~~Rspo1 protein~~ for use of any of the preceding Claims, wherein a therapeutically efficient amount of Rspo1 protein is to be administered via the subcutaneous or intravenous route to the subject.

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14. The ~~Rspo1 protein~~ for use of any of the preceding Claims, wherein said subject is a human subject.

15. A pharmaceutical composition comprising the Rspo1 protein as defined in any one of
10 Claims 1-11, and one or more pharmaceutically acceptable excipients.