

CLAIMS

1. An isolated Rspo1 protein, for use as a medicament, 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 polypeptides of SEQ ID NO:1-4 and SEQ ID NO:8-24.
- 25 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, 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 ;
 - 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. The Rspo1 protein for use of any of the preceding Claims, in the treatment of diabetes 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 administered via the subcutaneous or intravenous route to the subject.
- 5 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 Claims 1-11, and one or more pharmaceutically acceptable excipients.