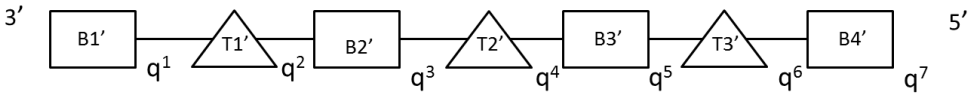
In one aspect, there is provided a double-stranded RNA (dsRNA) agent capable of inhibiting the expression of a target gene, comprising anthe antisense strand sequence complementary to at least one portion of a mRNA corresponding to the target gene, having 19, 20, 21, 22, 23, 24, or 25 nucleotides in length and beingof the dsRNA agent is represented by formula (Ia):



(Ia),

wherein:

B1', B2', B3', and B4' each independently represent a nucleotide containing a modification selected from the group consisting of 2'-Oalkyl, 2'-substituted alkoxy, 2'-substituted alkyl, 2'-halo, ENA, and BNA/LNA; T1', T2', and T3' each independently represent a nucleotide comprising a chemical modification selected from the group consisting of DNA, RNA, LNA, 2'-F, and 2'-F-5'-methyl; q^1 is independently 4 to 15 nucleotides in length; q^3 or q^7 is independently 1-6 nucleotide(s) in length;q^2 or q^6 is independently 1-3 nucleotide(s) in length; q^4 is independently 0-3 nucleotide(s) in length; and q5 is independently 0-10 nucleotide(s) in length; and wherein: four 2'-F modifications at positions 2, 6, 14, and 16 of the antisense strand has 2′-F modifications, and wherein the 2′-F modifications on from 5'-end of the antisense strand consist of four, and only four, 2′-F modifications or six, and only six, 2′-F modifications; or six 2'-F modifications at positions 2, 6, 8-9, 14, and 16 of the antisense strand from 5'-end of the antisense strand.

In another aspect, there is provided a pharmaceutical composition comprising the dsRNA agent as described herein according to the present invention alone or in combination with a pharmaceutically acceptable carrier or excipient.

In another aspect, there is provided the dsRNA agent according to the present invention for use in therapy, wherein the dsRNA agent is to be administered in an amount sufficient to inhibits the expression of athe target gene.

In another aspect, there is provided the dsRNA according to the present invention for use in therapy, wherein the dsRNA agent is to be administered for deliverings a polynucleotide to a specific target in a subject.

In another aspect, there is provided a dsRNA agent according to the present invention for use in therapy, wherein the dsRNA agent is to be administered subcutaneously into a subject, such that a polynucleotide is delivered to a specific target of the subject.