

TREATMENT OF MST1 RELATED DISEASES AND DISORDERS

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/211,364, filed June 16, 2021, which application is incorporated herein by reference.

BACKGROUND

[0002] Lung disorders are a common problem, and may affect a wide variety of persons. Improved therapeutics are needed for treating these disorders.

SUMMARY

[0002a] In one aspect, provided herein is a composition comprising an oligonucleotide that targets *MST1* and wherein the composition improves: (a) a lung function measurement; (b) a leukocyte measurement; (c) a chronic obstructive pulmonary disease (COPD) symptom or exacerbation measurement; or (d) an asthma symptom or exacerbation measurement.

[0002b] In another aspect, provided herein is a composition comprising an oligonucleotide that inhibits the expression of *MST1*, wherein the oligonucleotide comprises (a) an siRNA comprising a sense strand and an antisense strand, each strand is independently 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising 12-30 contiguous nucleosides of SEQ ID NO: 6185; or an antisense oligonucleotide (ASO) comprising 12-30 nucleosides in length and a nucleoside sequence complementary to 12-30 contiguous nucleosides of SEQ ID NO: 6185.

[0002c] In another aspect, provided herein is use of a composition comprising an oligonucleotide that modulates the expression of *MST1* in the manufacture of a medicament for treating a subject having a lung disorder, wherein the oligonucleotide comprises (a) an siRNA comprising a sense strand and an antisense strand, each strand is independently 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising 12-30 contiguous nucleosides of SEQ ID NO: 6185; or (b) an antisense oligonucleotide (ASO) comprising 12-30 nucleosides in length and a nucleoside sequence complementary to 12-30 contiguous nucleosides of SEQ ID NO: 6185.

[0002d] In another aspect, provided herein is a composition comprising an oligonucleotide that modulates the expression of *MST1* for use in therapy, wherein the oligonucleotide comprises: (a) an siRNA comprising a sense strand and an antisense strand, each strand is independently 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising 12-30 contiguous nucleosides of SEQ ID NO: 6185; or (b) an antisense oligonucleotide (ASO) comprising 12-30 nucleosides in length and a nucleoside sequence complementary to 12-30 contiguous nucleosides of SEQ ID NO: 6185.

[0003] Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets *MST1*. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets *MST1* and when administered to a subject in an effective amount increases a lung function measurement. In some embodiments, the lung function measurement comprises a forced expiratory volume in 1 second (FEV1) measurement, a forced expiratory volume in 1 second percent predicted

(FEV1pp) measurement, a forced vital capacity (FVC) measurement, a FEV1/FVC ratio measurement, a forced expiratory volume, or a peak expiratory flow measurement. In some embodiments, the lung function measurement is increased by about 10% or more, as compared to prior to administration. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets *MST1* and when administered to a subject in an effective amount decreases a leukocyte measurement. In some embodiments, the leukocyte measurement comprises a lung leukocyte measurement. In some embodiments, the leukocyte measurement comprises a circulating leukocyte measurement. In some embodiments, the leukocyte measurement comprises a neutrophil measurement, eosinophil measurement, basophil measurement, monocyte measurement, or lymphocyte measurement, or a combination thereof. In some embodiments, the leukocyte measurement is decreased by about 10% or more, as compared to prior to administration. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets *MST1* and when administered to a subject in an effective amount decreases a chronic obstructive pulmonary disease (COPD) or asthma exacerbation measurement. In some embodiments, the COPD or asthma exacerbation measurement is decreased by about 10% or more, as compared to prior to administration. In some embodiments, the oligonucleotide comprises a modified internucleoside linkage. In some embodiments, the modified internucleoside linkage comprises alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof. In some embodiments, the modified internucleoside linkage comprises one or more phosphorothioate linkages. In some embodiments, the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modified internucleoside linkages. In some embodiments, the oligonucleotide comprises a modified nucleoside. In some embodiments, the modified nucleoside comprises a locked nucleic acid (LNA), hexitol nucleic acid (HLA), cyclohexene nucleic acid (CeNA), 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, or a combination thereof. In some