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SUMMARY

It is a surprising finding of the present disclosure that the optimal composition for inhalation comprising RPL554 is a liquid pharmaceutical composition comprising a suspension of particles of RPL554. Suspensions of RPL554 have been found to have highly desirable properties for a clinical setting. A number of benefits have been found to be associated with a liquid pharmaceutical composition which comprises a diluent and a suspension of particles of RPL554 or a pharmaceutically acceptable salt thereof.

The liquid pharmaceutical composition of the present disclosure has greatly improved properties over previous formulations, for instance when compared with a solution formulation of RPL554. Regarding toxicokinetic properties, the suspension formulation has been found to have delayed release characteristics compared to those of a solution. This can reduce the number of treatments that must be administered to a patient. The suspension has also been found to allow a much greater dosage of RPL554 to be administered, as can be seen from plasma C_{max} and AUC values. This can also reduce the frequency of administrations required.

The liquid pharmaceutical composition of the present disclosure also shows excellent stability, with compositions showing no degradation after 12 months at ambient conditions (25°C), nor after 6 months at accelerated conditions (40°C). Degradation is observed in a comparable solution composition under the same conditions. The compositions may show no degradation after 12 months at ambient conditions (25°C/60%RH), nor after 6 months at accelerated conditions (40°C/75%RH).

Accordingly, the present disclosure provides a liquid pharmaceutical composition comprising a diluent and a suspension of particles of 9,10-dimethoxy-2-(2,4,6-trimethylphenylimino)-3-(N-carbamoyl-2-aminoethyl)-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-4-one (RPL554) or a pharmaceutically acceptable salt thereof.

In one aspect of the present disclosure, there is provided a liquid pharmaceutical composition suitable for administration by inhalation comprising a diluent and a suspension of particles of 9,10-dimethoxy-2-(2,4,6-trimethylphenylimino)-3-(N-carbamoyl-2-aminoethyl)-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-4-one (RPL554) or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a nebulizer comprising a composition disclosed herein.

In a further aspect of the present disclosure, there is provided a liquid pharmaceutical composition disclosed herein for use in the treatment of the human or animal body.

In another aspect of the present disclosure, there is provided a liquid pharmaceutical composition disclosed herein for use in the treatment or prevention of a disease or condition selected from asthma, allergic asthma, hay fever, allergic rhinitis, bronchitis, emphysema, bronchiectasis, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), steroid resistant asthma, severe asthma, paediatric asthma, cystic fibrosis, lung fibrosis, pulmonary fibrosis, interstitial lung disease, skin disorders, atopic dermatitis, psoriasis, ocular inflammation, cerebral ischaemia, inflammatory diseases and auto-immune diseases.

The present disclosure also provides a liquid pharmaceutical composition according to the present disclosure for use in the treatment of the human or animal body. A liquid pharmaceutical composition according to the present disclosure may be used in the treatment or prevention of a disease or

condition selected from asthma, allergic asthma, hay fever, allergic rhinitis, bronchitis, emphysema, bronchiectasis, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), steroid resistant asthma, severe asthma, paediatric asthma, cystic fibrosis, lung fibrosis, pulmonary fibrosis, interstitial lung disease, skin disorders, atopic dermatitis, psoriasis, ocular inflammation, cerebral ischaemia, inflammatory diseases and auto-immune diseases.

Typically, said disease or condition is asthma or COPD, more typically COPD.

The present disclosure also provides a method of treating or preventing a disease or condition as defined herein in a subject, which method comprises administering to said subject an effective amount of a liquid pharmaceutical composition according according to the present disclosure.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 - The provocation concentration (PC) of acetylcholine which cumulatively produced a 50% increase in total airway resistance (Acetylcholine RL PC50) in animals treated with saline or RPL554 solution formulation: 2 and 5 h time point: Acetylcholine RL PC50 was log transformed for the purposes of statistical analysis. Post hoc t-test of the untransformed data showed differences between groups vs saline. *Non parametric analysis did show a significant difference between 2 h (1 mg/mL RPL554 solution, P = 0.0190 unadjusted) and 5 h (2.5 mg/mL solution, P = 0.0095 unadjusted) vs saline group. N values = 6, 4, 4; 4, 4 left to right. (Note 5 h control not plotted).

Figure 2 - Acetylcholine RL PC50 in animals treated with vehicle or the RPL554 suspension formulation: 2 and 5 h time point: Acetylcholine RL PC50 was log transformed for the purposes of statistical analysis (upper panel). Non parametric analysis did show a significant difference between 2 h (10 mg/mL RPL554 suspension, P = 0.0268 unadjusted) vs vehicle control group. Re-analysis of the data by combining the vehicle data (2 + 5 h), revealed an overall significant bronchoprotection (P=0.0016) which was reflected by a significant degree of bronchoprotection with 2.5 mg/mL RPL554 suspension (2.52 fold (1-5.72), $P < 0.05$ and 10 mg/mL RPL554 suspension (4.67 fold (2-11), $*P < 0.05$) vs vehicle. At the 5 h time point, RPL554 10 mg/mL suspension caused a significant degree of bronchoprotection (2.77 fold (1.3-6.0), $*P < 0.05$). (N=8,4,4,3, 6, left to right) (lower panel).