Summary

In a first aspect, the present disclosure refers to a formulation of recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF), comprising

a. rhGM-CSF;
b. albumin; and
c. polyethylene glycol (PEG).

In another aspect, the present disclosure refers to an inhaler comprising the formulation as disclosed herein.

In yet another aspect, the present disclosure refers to a use of the formulation as disclosed herein, in the manufacture of a medicament for pulmonary administration.

In a further aspect, the present disclosure refers to a use of the formulation as disclosed herein, in the manufacture of a medicament for treatment of a lung infection.

In another aspect, the present disclosure refers to a method of manufacturing a formulation of rhGM-CSF, the method comprising:

a) preparing a buffer comprising one or more stabilizers, citric acid monohydrate, disodium hydrogen phosphate, recombinant human serum albumin (rHSA), and PEG-4000;
b) combining the buffer of step a) with rhGM-CSF; and
c) filtering the combination of step b) to generate the formulation of rhGM-CSF.

In yet another aspect, the present disclosure refers to the formulation as disclosed herein, for use in therapy.

The present ~~invention~~ disclosure discloses a stable liquid formulation of rhGM-CSF, which is ready for use for inhalation and does not experience relevant instability upon nebulization.

In one ~~embodiment~~ example of the present ~~invention~~ disclosure the combination of a sugar alcohol or a sugar, albumin and polyethylene glycol (PEG) and water provides a highly stable liquid formulation of rhGM-CSF.

In one ~~embodiment~~ example the liquid formulation described above is for use as a medicament for nebulization.

In one ~~embodiment~~ example the liquid formulation of rhGM-CSF is for use in the treatment of aPAP or NTM infection.

In one ~~embodiment~~ example a method for pulmonary delivery of recombinant rhGM-CSF comprising nebulizing rhGM-CSF, a sugar alcohol, albumin and PEG is disclosed.

In a further ~~embodiment~~ example a nebulizer comprising the liquid formulation of rhGM-CSF is disclosed for use in the treatment of aPAP or NTM infection.

Description of Drawings

Figure 1: Impact of Mannitol on % rhGM-CSF remaining after 3 months at 40°C. The impact of mannitol concentration on stability of liquid formulation of rhGM-CSF was evaluated at accelerated conditions over 3 months. The concentration of mannitol was found to influence drug stability. Higher concentrations (50 mg/mL) of mannitol improved stability of rhGM-CSF. The y-axis is % rhGM-CSF content remaining compared to T0.

Figure 2: Impact of rhGM-CSF level within groupings of mannitol conc. on % GM-CSF remaining after 3 months at 40°C
The impact of rhGM-CSF concentration on stability of the liquid formulation was also evaluated at accelerated conditions over 3 months. The concentration of rhGM-CSF was found to influence drug stability. Higher concentrations of rhGM-CSF (400 µg/mL)

Claims

1. A ~~liquid~~ formulation of recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF), ~~for use in administration by inhalation, wherein the liquid formulation~~ comprisinges
   a. rhGM-CSF; ~~, a sugar alcohol or a sugar,~~
   b. albumin; and
   c. polyethylene glycol~~water~~ (PEG).

2. The ~~liquid~~ formulation ~~for the use according to~~ of claim 1, wherein ~~said~~ the rhGM-CSF is molgramostim (SEQ ID NO: 1), sargramostim (SEQ ID NO: 2), or regramostim.

3. The formulation of claim 2, further comprising a sugar alcohol or a sugar.

~~3.~~4. The ~~liquid~~ formulation ~~for the use according to any one of the preceding claims~~ of claim 3, wherein ~~said~~ the sugar is maltose, trehalose, sucrose, mannose, lactose or galactose, or wherein ~~said~~ the sugar alcohol is mannitol or sorbitol.

~~4.~~5. The ~~liquid~~ formulation ~~for the use according to any one of the preceding claims~~ of claim 4, wherein ~~said~~ the albumin is recombinant human albumin.

~~5.~~6. The ~~liquid~~ formulation ~~for the use according to any one of the preceding claims~~ of claim 5, ~~wherein the formulation further comprises polyethylene glycol (PEG),~~ wherein ~~said~~ the PEG is selected from the group consisting of PEG-1000, PEG-1550, PEG-2000, PEG-3000, PEG-3350, PEG-4000, or PEG-8000~~, preferably PEG-4000~~.

7. The formulation of claim 6, wherein the PEG is PEG-4000.

~~6. The liquid formulation for the use according to any one of the preceding claims wherein the concentration of rhGM-CSF is at least 150 µg/mL.~~

~~7.~~8. The ~~liquid~~ formulation ~~for the use according to~~ of claim 76, wherein: ~~the~~ a concentration of the rhGM-CSF is ~~in the range of~~from 150 µg/mL to ~~-~~ 500

µg/mL~~, preferably 200-300 µg/mL~~;
a concentration of the albumin is from 0.5 mg/mL to 1.50 mg/mL;
a concentration of the PEG is from 0.05 mg/mL to 0.15 mg/mL; and
a concentration of the sugar alcohol is from 45 mg/mL to 100 mg/mL.

~~8. The liquid formulation for the use according to any one of the preceding claims wherein the concentration of the sugar alcohol is at least 25 mg/mL.~~

~~9. The liquid formulation for the use according to claim 8, wherein the concentration of the sugar alcohol is in the range 45-100 mg/mL, preferably 45-55 mg/mL.~~

~~10. The liquid formulation for the use according to any one of the preceding claims wherein the concentration of albumin is at least 0.2 mg/mL~~

~~11. The liquid formulation for the use according to any one of the preceding claims wherein the concentration of albumin is in the range 0.5-1.5 mg/mL.~~

~~12. The liquid formulation for the use according to any one of the preceding claims, wherein the concentration of the PEG is max 50, such as max 40, such as max 30, such as max 20 such as max 10 such as max 1 mg/mL.~~

~~13. The liquid formulation for the use according to any one of the preceding claims wherein the concentration of the PEG is in the range 0.05-0.15 mg/mL.~~

9. The formulation of claim 8, wherein the formulation is a liquid formulation.

10. The formulation of claim 8, wherein the formulation is nebulized.

~~14.~~11. The ~~liquid~~ formulation ~~for the use according to any one of the preceding claims~~ of claim 8, wherein ~~said~~ the rhGM-CSF is molgramostim (SEQ ID NO: 1), ~~said~~ the sugar alcohol is mannitol, ~~said~~ the albumin is recombinant human albumin, and ~~said~~ the PEG is PEG-4000.

~~15.~~12. The ~~liquid~~ formulation ~~for the use according to~~of claim 1~~1~~, wherein
a concentration of the rhGM-CSF is from 150 µg/mL to 500 µg/mL;
a concentration of the recombinant human albumin is from 0.5 mg/mL to 1.50 mg/mL;
a concentration of the PEG-4000 is from 0.05 mg/mL to 0.15 mg/mL; and
a concentration of the mannitol is from 45 mg/mL to 100 mg/mL.~~the concentration of rhGM-CSF is at least 150 µg/mL,~~
~~the concentration of mannitol is at least 25mg/mL,~~
~~the concentration of recombinant human albumin is at least0.2 mg/mL, and the concentration of PEG-4000 is max 1 mg/mL.~~

~~16.~~13. The ~~liquid~~ formulation ~~for the use according to~~of claim 12~~15~~, wherein
~~the~~ a concentration of the rhGM-CSF is from 200 µg/mL to~~-~~ 300 µg/mL;~~,~~
~~the concentration of mannitol is 45-100 mg/mL,~~
~~the~~ a concentration of the recombinant human albumin is from 0.5 mg/mL to~~-~~ 1.50 mg/mL;~~, and~~
~~the~~ a concentration of the PEG-4000 is from 0.05 mg/mL to~~-~~ 0.15 mg/mL; and
a concentration of the mannitol is 45 mg/mL to 100 mg/mL.

~~17.~~14. The ~~liquid~~ formulation ~~for the use according to any one of the preceding claims~~of claim 12, further comprising a buffer, wherein the buffer is ~~such as~~ citric acid monohydrate or Na_2HPO_4.

~~18.~~15. The ~~liquid~~ formulation ~~for the use according to any one of the preceding claims~~of claim 1, wherein ~~the~~ an osmolality of the formulation is from 250 to 375 mOsm/L~~, preferably from 325 to 335 mOsm/L~~.

~~19.~~16. The ~~liquid~~ formulation ~~for the use according to any one of the preceding claims~~of claim 9 or claim 10, wherein ~~the %~~a percentage of the rhGM-CSF remaining after 3 months storage ~~at 40°C~~ is more than 60%~~, and/or wherein the level of impurity formation after 6 months at 25°C is less than 5%~~.

~~20. The liquid formulation for the use according to any one of the preceding claims, wherein at least 90% such as at least 95% such as at least 98% such as at least 99% biologic potency of rhGM-CSF is retained after nebulization.~~

~~21. The liquid formulation for the use according to any one of the preceding claims, wherein the formulation is storage stable for at least 18 months at 25°C.~~

~~22. The liquid formulation for the use according to any of the preceding claims, wherein the liquid formulation for inhalation is nebulized.~~

~~23. The liquid formulation for the use according to any one of the preceding claims, wherein the liquid formulation is for use in pulmonary administration.~~

~~24. The liquid formulation for the use according to any one of the preceding claims, wherein the use is for the treatment of lung infection.~~

~~25. The liquid formulation for the use according to any one of the preceding claims, wherein the use is for the treatment of bacterial, viral or fungal infection in the lungs.~~

~~26. The liquid formulation for the use according to any one of the preceding claims, wherein the use is for the treatment of autoimmune pulmonary alveolar proteinosis (aPAP) or non-tuberculous mycobacterial (NTM) infection.~~

~~27.~~17. An inhaler comprising the ~~liquid~~ formulation ~~according to any one~~ of ~~the preceding~~ claim~~s~~ 12.

~~28. The inhaler according to claim 27, wherein the inhaler is a nebulizer.~~

~~29. A pulmonary formulation of recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF) comprising rhGM-CSF, a sugar alcohol or a sugar, albumin and water.~~

~~30. A method for delivering rhGM-CSF to the lungs comprising nebulization of a liquid formulation of rhGM-CSF, wherein the liquid formulation comprises~~

~~rhGM-CSF, a sugar alcohol or a sugar, albumin and water; whereby said rhGM-CSF is delivered to the lungs.~~

18. Use of the formulation of claim 12, in the manufacture of a medicament for pulmonary administration.

19. Use of the formulation of claim 12, in the manufacture of a medicament for treatment of a lung infection.

20. A method of manufacturing a formulation of rhGM-CSF, the method comprising:
a) preparing a buffer comprising one or more stabilizers, citric acid monohydrate, disodium hydrogen phosphate, recombinant human serum albumin (rHSA), and PEG-4000;
b) combining the buffer of step a) with rhGM-CSF; and
c) filtering the combination of step b) to generate the formulation of rhGM-CSF.

21. The method of claim 20, wherein the formulation of rhGM-CSF comprises:
a concentration of the rhGM-CSF is from 200 µg/mL to 300 µg/mL;
a concentration of the rHSA is from 0.5 mg/mL to 1.50 mg/mL;
a concentration of the PEG-4000 is from 0.05 mg/mL to 0.15 mg/mL; and
a concentration of the mannitol is from 45 mg/mL to 100 mg/mL.

22. The formulation of claim 12, for use in therapy.