

compared with placebo, with also a trend towards a reduced death rate although the studies were not powered to detect differences in mortality (Richeldi et al., 2014).

[0009] Both treatments appear to slow disease progression, but they do not stop said progression and are frequently associated with side effects potentially limiting the use in clinical practice (Raghu et al., 2015). Consequently, in order to avoid overdosing which may result in undesirable side effects, or underdosing which may compromise the treatment efficacy, it is essential to be able to measure the patient response and thus identify the optimal dose.

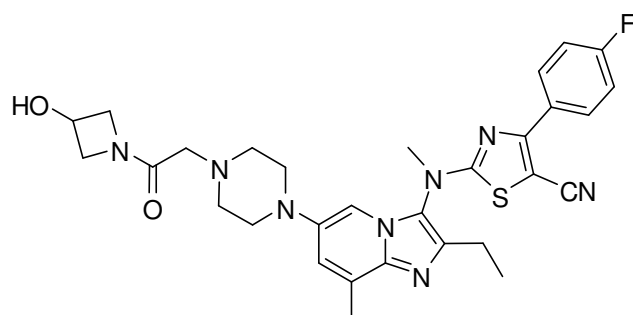
[0010] WO 2014/125059 discloses a general method for determining a respiratory condition based on functional respiratory imaging, however without any fibrotic disease specific treatment agent, more particularly IPF.

[0011] There thus remains a significant unmet medical need for the investigation and development of novel IPF treatments, more particularly treatments addressing the specific patient profile and requirements.

SUMMARY

[0012] The present disclosure relates to the use of the compound according to Formula I in the treatment of fibrotic diseases, more particularly idiopathic pulmonary fibrosis.

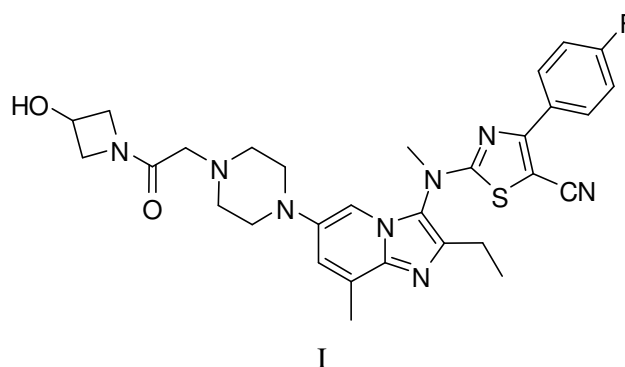
[0012a] In one aspect, the present disclosure refers to a use of a compound according to Formula I (Cpd 1), or a pharmaceutically acceptable salt thereof:



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in the manufacture of a medicament for treating fibrotic diseases, said use comprising the steps of:

- a) obtaining three-dimensional image data of a subject's respiratory system, which image data has been acquired during an assessment period, wherein the assessment period comprises a breathing cycle and the image data comprise high-resolution computer tomography (CT) high-resolution images at functional residual capacity (FRC) and high-resolution computer tomography (CT) images at total lung capacity (TLC);
- b) calculating a specific three-dimensional structural model of the subject's respiratory system using the three-dimensional image data of step a) to determine one or more outcome parameters as described in WO2014125059;
- c) the compound according to Formula I (Cpd 1), or a pharmaceutically acceptable salt thereof:



is to be administered with a daily dose of between 100 mg to 1000 mg to the subject;

d) repeating steps a and b above after that the compound is to be administered;

e) comparing the three-dimensional structural models and/or outcome parameters of step b) and d) with each other;

f) calculating the response of said subject from step e);

g) determining whether the dose of the compound according to Formula I should be increased, decreased or maintained at the same level based on the results obtained in step f).

[0012b] In another aspect, the present disclosure refers to a use of a subject a daily dose of compound according to formula I in the manufacture of a medicament for treating idiopathic pulmonary fibrosis comprising that a daily dose of compound according to formula I of 100 mg or more is to be administered to a subject, such as 100 to 1000 mg, 100 to 600 mg, 200 to 1000 mg, or, 200 to 600 mg.

[0012c] In another aspect, the present disclosure refers to a use of compound according to formula I in the manufacture of a medicament for treating idiopathic pulmonary fibrosis comprising that a daily dose of 200 mg of compound according to formula I is to be administered to a subject.

[0013] In a first example of the disclosure is provided a method of treatment of fibrotic diseases, which method comprises the steps of:

a) obtaining three-dimensional image data of a subject's respiratory system, which image data has been acquired during an assessment period, wherein the assessment period comprises a breathing cycle and the image data comprise high-resolution computer tomography (CT) images at functional residual capacity (FRC) and high-resolution computer tomography (CT) images at total lung capacity (TLC);

b) calculating a specific three-dimensional structural model of the subject's respiratory system using the three-dimensional image data of step a) to determine one or more outcome parameters as described in WO 2014/125059, the content of which are herein incorporated by reference ;

c) administering a daily dose of between 100 mg to 1000 mg to the subject of one or more compounds disclosed in WO 2014/139882 and WO 2014/202458;

d) repeating steps a and b above after administration of the compounds;

e) comparing the three-dimensional structural models and/or outcome parameters of step b) and d) with each other;

f) calculating the response to the treatment of said subject from step e);

g) determining whether the dose of the compound according to Formula I should be increased, decreased or maintained at the same level based on the results obtained in step f).

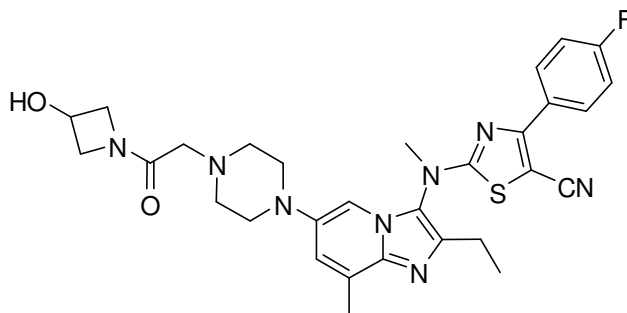
[0014] In a second example of the disclosure is provided a method of treatment of fibrotic diseases, which method comprises the steps of:

a) obtaining three-dimensional image data of a subject's respiratory system, which image data has been acquired during an assessment period, wherein the assessment period comprises a breathing cycle and the

image data comprise high-resolution computer tomography (CT) images at functional residual capacity (FRC) and high-resolution computer tomography (CT) images at total lung capacity (TLC);

b) calculating a specific three-dimensional structural model of the subject's respiratory system using the three-dimensional image data of step a) to determine one or more outcome parameters as described in WO 2014/125059, the content of which are herein incorporated by reference ;

c) administering a daily dose of between 100 mg to 1000 mg to the subject of a compound according to Formula I (Cpd 1), or a pharmaceutically acceptable salt thereof:



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d) repeating steps a and b above after administration of the compound;

e) comparing the three-dimensional structural models and/or outcome parameters of step b) and d) with each other;

f) calculating the response to the treatment of said subject from step e);

g) determining whether the dose of the compound according to Formula I should be increased, decreased or maintained at the same level based on the results obtained in step f).

[0015] In a more particular example the fibrotic disease is IPF.

[0016] In a further example, the present disclosure provides pharmaceutical compositions comprising the compound of the disclosure, and a pharmaceutical carrier, excipient or diluent for use in the treatment of fibrotic diseases. In a particular example, the pharmaceutical composition may additionally comprise further therapeutically active ingredients suitable for use in combination with the compounds of the disclosure. In a more particular example, the further therapeutically active ingredient is an agent for the treatment of fibrotic disease. In a most particular example, the fibrotic disease is IPF.

[0017] Moreover, the compounds of the disclosure, useful in the pharmaceutical compositions and treatment methods disclosed herein, are pharmaceutically acceptable as prepared and used.

[0018] In a further example of the disclosure, this disclosure provides a method of treating a mammal, in particular humans, afflicted with a condition selected from among those listed herein, particularly fibrotic diseases, and more particularly IPF, which method comprises administering an effective amount of the pharmaceutical composition or compounds of the disclosure as described herein.

[0019] The present disclosure also provides pharmaceutical compositions comprising a compound of the disclosure, and a suitable pharmaceutical carrier, excipient or diluent for use in the treatment of fibrotic diseases, more particularly IPF.

[0020] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

[0021] It will be appreciated that compounds of the disclosure may be metabolized to yield biologically active metabolites.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1: shows the variation in serum LPA 18:2 levels for the compound according to Formula I (Cpd 1) dosed at 600mg qd (filled squares) vs the placebo (filled diamonds) over the 12 weeks study and follow up visit.

FIGURE 2: shows the variation in Forced vital capacity (FVC) for the compound according to Formula I (Cpd 1) dosed at 600mg qd (filled circles) vs the placebo (filled triangle) over the 12 weeks study and follow up visit.

FIGURE 3: shows the comparison in specific airway volume between the placebo and the compound according to Formula I (Cpd 1) dosed at 600 mg qd at baseline and at 12 weeks.

FIGURE 4: shows the comparison in specific airway resistance between the placebo and the compound according to Formula I (Cpd 1) dosed at 600 mg qd at baseline and at 12 weeks.

FIGURE 5: shows percentiles (solid line: 50th %ile; regular dashed line: 25th %ile; irregular dashed line: 10th %ile; dotted line: 2.5th %ile) of individual simulated steady state area under the curve (5A), maximum plasma concentration (5B), area under the effect curve (5C), and maximal plasma lysophosphatidic acid 18:2 reduction (5D) at doses of compound according to Formula I between 50 and 1000 mg daily as calculated for example 2.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

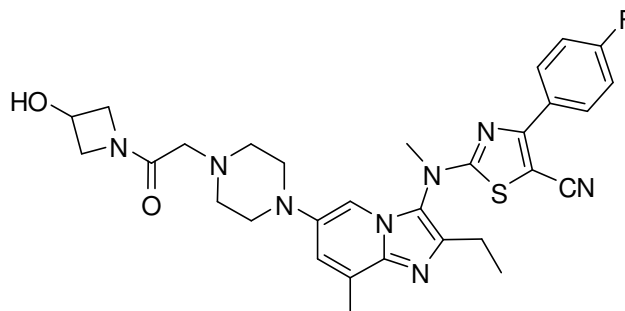
[0022] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

[0023] When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term “substituted” is to be defined as set out below. It should be further understood that the terms “groups” and “radicals” can be considered interchangeable when used herein.

[0024] The articles ‘a’ and ‘an’ may be used herein to refer to one or to more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example ‘an analogue’ means one analogue or more than one analogue.

CLAIMS

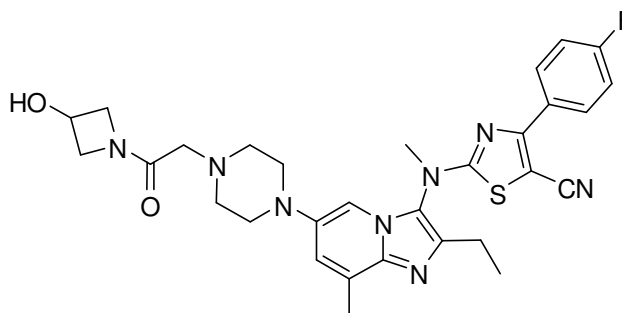
1. Use of a compound according to Formula I (Cpd 1), or a pharmaceutically acceptable salt thereof:



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in the manufacture of a medicament for treating fibrotic diseases, said use comprising the steps of:

- a) obtaining three-dimensional image data of a subject's respiratory system, which image data has been acquired during an assessment period, wherein the assessment period comprises a breathing cycle and the image data comprise high-resolution computer tomography (CT) high-resolution images at functional residual capacity (FRC) and high-resolution computer tomography (CT) images at total lung capacity (TLC);
- b) calculating a specific three-dimensional structural model of the subject's respiratory system using the three-dimensional image data of step a) to determine one or more outcome parameters as described in WO2014125059;
- c) the compound according to Formula I (Cpd 1), or a pharmaceutically acceptable salt thereof:



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is to be administered with a daily dose of between 100 mg to 1000 mg to the subject;

- d) repeating steps a and b above after that the compound is to be administered;
- e) comparing the three-dimensional structural models and/or outcome parameters of step b) and d) with each other;
- f) calculating the response of said subject from step e);
- g) determining whether the dose of the compound according to Formula I should be increased, decreased or maintained at the same level based on the results obtained in step f).

2. The use according to claim 1, wherein the specific three-dimensional structural model of the subject's respiratory system comprises a three-dimensional structural model of the subject's lung lobar structure and a three-dimensional structural model of the subject's airway structure,

3. The use according to claim 1, wherein the one or more outcome parameters comprise the lobar volume, preferably at FRC and TLC; or wherein the one or more outcome parameters comprise the airway volume, preferably at FRC and TLC; or wherein the one or more outcome parameters comprise lobar emphysema; or wherein the one or more outcome parameters comprise lobar blood vessel volume; or wherein the one or more outcome parameters comprise the airway wall thickness; or wherein the one or more outcome parameters comprise the airway resistance, preferably at FRC and TLC; or wherein the one or more outcome parameters comprise the airway volume and/or resistance.
4. The use according to claim 3, wherein the one or more outcome parameters comprise the airway volume and/or resistance.
5. The use according to claim 1, wherein the compound of step c) is to be administered over a period of at least 1 week, at least 2 weeks, at least 4 weeks, at least 8 weeks or at least 12 weeks.
6. The use according to claim 1, wherein the compound of step c) is to be administered over a period of at least 12 weeks.
7. The use according to claim 1, wherein step d is performed after 4 weeks, after 8 weeks, or after 12 weeks that the compound is to be administered according to formula I.
8. The use according to claim 1 or 5, wherein the compound, or a pharmaceutically acceptable salt thereof of step c) is to be administered at a dose of 600 mg qd.
9. The use according to any one of claims 1-7, comprising measuring the forced vital capacity FVC in the subject, wherein the FVC does not decrease compared to after treatment.
10. The use according to any one of claims 1-7, comprising measuring the forced vital capacity FVC in the subject, wherein said FVC increases by at least 1 mL, at least 2 mL, at least 3 mL, at least 4 mL, at least 5 mL, at least 6 mL, at least 7 mL or at least 8 mL over a period of 12 weeks.
11. The use according to any one of claims 1-7, comprising measuring the airway volume wherein said airway volume decrease is no more than 5 mL/L, no more than 4 mL/L, or no more than 3 mL/L after 12 weeks.
12. The use according to any one of claims 1-7, comprising measuring the airway resistance wherein said airway resistance increase is at least 0.05 kPa/s, at least 0.06 kPa/s, at least 0.07 kPa/s, at least 0.08 kPa/s, at least 0.09 kPa/s, or at least 1.0 kPa/s after 12 weeks.
13. The use according to claim 1, wherein the compound or a pharmaceutically acceptable salt thereof of step c) is to be administered as a pharmaceutical composition.
14. The use according to claim 12, wherein the pharmaceutical composition comprises a pharmaceutically acceptable carrier, and an effective amount of the compound according to Formula I.
15. The use according to claim 1, wherein the fibrotic disease is IPF.
16. Use of a subject a daily dose of compound according to formula I in the manufacture of a medicament for treating idiopathic pulmonary fibrosis comprising that a daily dose of compound

according to formula I of 100 mg or more is to be administered to a subject, such as 100 to 1000 mg, 100 to 600 mg, 200 to 1000 mg, or, 200 to 600 mg.

17. The use according to claim 16 wherein the daily dose is a single dose of 600 mg of compound according to formula I.
18. Use of compound according to formula I in the manufacture of a medicament for treating idiopathic pulmonary fibrosis comprising that a daily dose of 200 mg of compound according to formula I is to be administered to a subject.
19. The use according to any of claims 16 to 18, further comprising measuring forced vital capacity (FVC) in the subject, wherein said FVC does not decrease following treatment.
20. The use according to any of claims 16 to 18, further comprising measuring forced vital capacity (FVC) in the subject, wherein said FVC does not decrease following 12 weeks of treatment.
21. The use according to claim 19 or 20, wherein said FVC increases by at least 1 mL, at least 2 mL, at least 3 mL, at least 4 mL, at least 5 mL, at least 6 mL, at least 7 mL or at least 8 mL over a period of 12 weeks.
22. The use according to any of claims 16 to 21, further comprising measuring the airway volume wherein said airway volume decrease is no more than 5 mL/L, no more than 4 mL/L, or no more than 3 mL/L after 12 weeks.
23. The use according to any of claims 16 to 22, further comprising measuring the airway resistance wherein said airway resistance increase is at least 0.05 kPa/s, at least 0.06 kPa/s, at least 0.07 kPa/s, at least 0.08 kPa/s, at least 0.09 kPa/s, or at least 1.0 kPa/s after 12 weeks.