[0006] Nagai et al. conducted an uncontrolled, open-label study of pirfenidone in patients ("Open label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis." Internal Medicine 41:1118–1123, 2002). During treatment, no liver dysfunctions, hematologic abnormalities, or allergic or shock reactions were reported.

[0007] Moises et al. "A double-blind, multicenter study comparing pirfenidone and prednisone for moderate-to-severe pulmonary fibrosis." Chest 124:116S, 2003 reported administration of pirfenidone.

[0008] Azuma et al. "Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis." Am J Respir Crit Care Med 171:1040–1047, 2005) describes administration of pirfenidone to a maximum of 1800 mg/day of pirfenidone, and reports a protocol for stepwise reduction and rechallenge with drug after an adverse event.

[0009] Abnormal liver function may manifest as abnormalities in levels of biomarkers of liver function, including alanine transaminase, aspartate transaminase, bilirubin, and/or alkaline phosphatase, and may be an indicator of drug-induced liver injury. See *FDA Draft Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation,* October 2007.

SUMMARY

[0009a] In one aspect of the present disclosure, there is provided the use of pirfenidone in the manufacture of a medicament for treating a patient suffering from fibrosis, said patient having exhibited a Grade 2 abnormality in one or both of alanine transaminase (ALT) and aspartate transaminase (AST) that is greater than 2.5-times and less than or equal to 5-times the upper limit of normal, after pirfenidone administration, wherein (a) said patient is administered pirfenidone at doses of at least 1600 mg/day.

[0010] ~~One aspect of the invention~~The present disclosure also provides methods for administering a therapeutically effective dose of pirfenidone to a patient that has exhibited abnormal biomarkers of liver function after pirfenidone administration for the treatment of fibrosis, e.g. idiopathic pulmonary fibrosis (IPF). In some embodiments, a patient is identified who exhibits a significantly abnormal level of one, two, three or more biomarkers of liver function, e.g. the level of a Grade 2 abnormality, after administration of an original full target dose of pirfenidone, e.g. about 2400 mg/day or 2403 mg/day. In such patients, the dose of pirfenidone is reduced or discontinued until levels of the abnormal biomarkers approach or are within normal range, after which patients are administered increasing doses of pirfenidone, up to the original full target dose. Alternatively, the dose of pirfenidone is not reduced at all, but liver biomarkers continue to be monitored. In another embodiment, after an optional temporary dose reduction or discontinuation, patients are administered pirfenidone at a permanently reduced dose of 1602 mg/day. As used herein, "original full

target dose" means the therapeutically effective dose approved by the U.S. Food and Drug Administration or a similar agency in a foreign country, optionally other than Japan. In some embodiments, the original full target dose is about 2400 mg/day or 2403 mg/day pirfenidone,

or about 34 mg/kg/day (e.g. 33-35 mg/kg/day), or from 2200 to 2600 mg/day pirfenidone, or from 31 mg/kg/day to 37 mg/kg/day. The total daily dose is administered one, two or three times per day.

[0011] Thus, the ~~invention~~present disclosure provides methods of administering pirfenidone to a patient at doses of 2400 mg/day or 2403 mg/day after identifying that the patient has exhibited a liver function Grade 2 abnormality after pirfenidone administration. In some embodiments, the methods involve continuing the full target dose, e.g. of 2400 mg/day or 2403 mg/day, without temporarily discontinuing or reducing the dose. The patient's biomarkers of liver function may continue to be monitored. In some embodiments, the method involves (a) administering a dose lower than 2400 mg/day for a time period, e.g., one week, two weeks, three weeks, four weeks, one month, six weeks, or two months, followed by (b) administering a dose of 2400 mg/day or 2403 mg/day. In specific embodiments, the pirfenidone is temporarily discontinued before step (a).

[0012] In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, and (b) administering the original full target dose for at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

[0013] In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering about 800 mg/day or 801 mg/day pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, (b) administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, and (c) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

[0014] In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, (b) administering about 800 mg/day or 801 mg/day pirfenidone for about one week, (c)

administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, and (d) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

[0015] Alternatively, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality at a permanently reduced dose, e.g. 800 or 801 mg/day, or 1600 or 1602 mg/day. In some embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. In some embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering about 800 mg/day or 801 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits, and (b) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years.

[0016] In other embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, (b) administering about 800 mg/day or 801 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits, and (c) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. In still other embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, and (b) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years.

[0017] The ~~invention~~present disclosure also provides methods of administering pirfenidone to a patient at doses of 2400 mg/day or 2403 mg/day after identifying that the patient has exhibited a liver

What is claimed is:

1. Use of pirfenidone in the manufacture of a medicament for treating a patient suffering from fibrosis, said patient having exhibited a Grade 2 abnormality in one or both of alanine transaminase (ALT) and aspartate transaminase (AST) that is greater than 2.5-times and less than or equal to 5-times the upper limit of normal, after pirfenidone administration, wherein (a) said patient is ~~to be~~ administered pirfenidone at doses of at least 1600 mg/day.

2. The use according to claim 1, wherein (a) said patient is administered pirfenidone at doses of 2200 to 2600 mg/day.

3. The use according to claim 1, wherein (a) said patient is ~~to be~~ administered pirfenidone at doses of 2400 mg/day or 2403 mg/day.

4. The use according to claim 1, wherein, prior to step (a), said patient is ~~to be~~ administered pirfenidone at doses lower than 2400 mg/day for a time period.

5. The use according to claim 1, wherein, prior to step (a), said patient is ~~to be~~ administered pirfenidone at doses lower than 1600 mg/day for a time period.

6. The use according to any of claims 1-5, wherein, prior to step (a), ~~administration of~~ pirfenidone administration to the patient is discontinued ~~for a time period~~ until ~~the~~ biomarkers of liver function are within normal limits, and ~~then~~ 800 mg/day or 801 mg/day pirfenidone is administered to the patient ~~for a time period~~ until the biomarkers of liver function are within normal limits, and ~~then~~ 1600 mg/day or 1602 mg/day pirfenidone is administered to the patient ~~for a time period~~ until ~~the~~ biomarkers of liver function are within normal limits.

7. The use according to any of claims 1-6 wherein, prior to step (a), pirfenidone administration to the patient is ~~to be~~ discontinued ~~for a period of time~~ until ~~the~~ biomarkers of liver function are within normal limits.

8. The use according to any of claims 1-7, wherein the pirfenidone is ~~to be~~ administered three times per day with food.