CLAIMS

1. A method for the diagnosis of non-alcoholic steatohepatitis (NASH) or for determining the activity, the stage, or the severity of NASH in a subject, comprising the step of measuring the blood, serum, or plasma level of:

(i) alpha 2 macroglobulin;

(ii) glycated haemoglobin (HbA1c);

(iii) N-terminal pro-peptide of collagen type III;

(iv) hsa-miR-34a-5p; and

(v) hsa-miR-200a-3p.

2. The method according to claim 1, comprising the implementation of the following measures from a blood, serum or plasma sample of said subject:

(i) determining the level of alpha 2 macroglobulin;

(ii) determining the level of HbA1c, ;

(iii) determining the level of N-terminal pro-peptide of collagen type III;

(iv) determining the level of hsa-miR-34a-5p; and

(v) determining the level of hsa-miR-200a-3p;

wherein an increase in said levels relative to that of a control sample is indicative of NASH and/or of the activity, the stage, or the severity of NASH.

3. The method according to claim 1 or 2, wherein a NASH score is calculated from the levels determined in measures (i) to (v) and wherein NASH is diagnosed and/or NASH stage or activity or severity is determined on the basis of said NASH score.

4. The method according to claim 3, wherein a NASH score is calculated according to the following logistic function:

$$S = \frac{e^{Y}}{1 + e^{Y}}$$

wherein:

$$Y=k+a*A+b*B+c*C+d*D+f*F$$

wherein:

S is the NASH score;

A is the level of alpha 2 macroglobulin in g/L;

B is the level of HbA1c in percent;

C is the level of N-terminal pro-peptide of collagen type III in ng/mL;
D is the level of hsa-miR-34a-5p in Cq;
F is the level of hsa-miR-200a-3p in Cq;
k is a number comprised between 5.26 and 36.76;
a is a number comprised between 0.11 and 1.07;
b is a number comprised between 0 and 1.02;
c is a number comprised between 0 and 0.23;
d is a number comprised between -0.77 and 0; and
f is a number comprised between -0.78 and 0.

5. The method according to claim 4, wherein a NASH score higher than a threshold value comprised between 0.102 and 0.6465 is indicative of a severe NASH, or of a moderate or high NASH activity.

6. A method for classifying a subject as a receiver or non receiver of a treatment for NASH, comprising the step of measuring the blood, serum, or plasma level of:

(i) alpha 2 macroglobulin;
(ii) glycated haemoglobin (HbA1c);
(iii) N-terminal pro-peptide of collagen type III;
(iv) hsa-miR-34a-5p; and
(v) hsa-miR-200a-3p.

7. The method according to claim 6, comprising the implementation of the following measures from a blood, serum or plasma sample of said subject:

(i) determining the level of alpha 2 macroglobulin;
(ii) determining the level of HbA1c;
(iii) determining the level of N-terminal pro-peptide of collagen type III;
(iv) determining the level of hsa-miR-34a-5p; and
(v) determining the level of hsa-miR-200a-3p;

wherein a NASH score is calculated from the levels determined in measures (i) to (v) and wherein the subject is classified as a receiver or non receiver of the treatment for NASH based on said score.

8. The method according to claim 6 or 7, comprising determining the level of alpha 2 macroglobulin, HbA1c, N-terminal pro-peptide of collagen type III, hsa-miR-34a-5p and hsa-miR-200a-3p wherein the NASH score is calculated according to the following logistic function:

$$S = \frac{e^{Y}}{1 + e^{Y}}$$

wherein:

$$Y=k+a*A+b*B+c*C+d*D+f*F$$

wherein:

S is the NASH score;

A is the level of alpha 2 macroglobulin in g/L;

B is the level of HbA1c in percent;

C is the level of N-terminal pro-peptide of collagen type III in ng/mL;

D is the level of hsa-miR-34a-5p in Cq;

F is the level of hsa-miR-200a-3p in Cq;

k is a number comprised between 5.26 and 36.76;

a is a number comprised between 0.11 and 1.07;

b is a number comprised between 0 and 1.02;

c is a number comprised between 0 and 0.23;

d is a number comprised between -0.77 and 0;

f is a number comprised between -0.78 and 0.

9. The method according to claim 8, wherein the subject is classified as a receiver of the treatment if S is higher than a threshold value comprised between 0.102 and 0.6465.

10. A method for calculating a NASH score which is indicative of non-alcoholic steatohepatitis (NASH), or of the activity, the stage, or the severity of NASH in a subject, wherein said score is based on the measure of the blood, serum, or plasma level of:

(i) alpha 2 macroglobulin;

(ii) glycated haemoglobin (HbA1c);

(iii) N-terminal pro-peptide of collagen type III;

(iv) hsa-miR-34a-5p; and

(v) hsa-miR-200a-3p.

11. The method of claim 10, comprising determining the level of alpha 2 macroglobulin, HbA1c, N-terminal pro-peptide of collagen type III, hsa-miR-34a-5p and hsa-miR-200a-3p, wherein the NASH score is calculated according to the following

logistic function:

$$S = \frac{e^{Y}}{1 + e^{Y}}$$

wherein:

$$Y=k+a*A+b*B+c*C+d*D+f*F$$

wherein:

S is the NASH score;

A is the level of alpha 2 macroglobulin in g/L;

B is the level of HbA1c in percent;

C is the level of N-terminal pro-peptide of collagen type III in ng/mL;

D is the level of hsa-miR-34a-5p in Cq;

F is the level of hsa-miR-200a-3p in Cq;

k is a number comprised between 5.26 and 36.76;

a is a number comprised between 0.11 and 1.07;

b is a number comprised between 0 and 1.02;

c is a number comprised between 0 and 0.23;

d is a number comprised between -0.77 and 0;

f is a number comprised between -0.78 and 0.

12. A kit comprising means for determining the level of:

(i) alpha 2 macroglobulin;

(ii) HbA1c;

(iii) N-terminal pro-peptide of collagen type III;

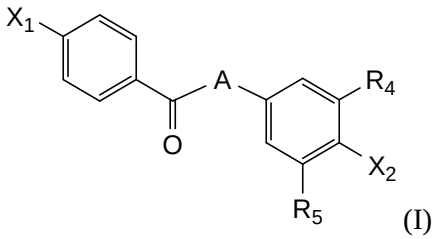
(iv) hsa-miR-34a-5p; and

(v) hsa-miR-200a-3p;

wherein the kit comprises as means antibodies specific for a protein to be quantified and/or primers useful for quantifying micro-RNA levels.

13. Use of a compound suitable for the treatment of non-alchoholic steatohepatitis (NASH) in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH) in a subject, wherein the subject has been diagnosed according to the method of any one of claims 1 to 5, or classified according to the method of any one of claims 6 to 11.

14. The use according to claim 13, wherein the compound is a compound of formula (I):



(I)

wherein:

X1 represents a halogen, a R1, or G1-R1 group;

A represents a CH=CH or a CH2-CH2 group;

X2 represents a G2-R2 group;

G1 and G2, identical or different, represent an atom of oxygen or sulfur;

R1 represents a hydrogen atom, an unsubstituted alkyl group, an aryl group or an alkyl group that is substituted by one or more halogen atoms, an alkoxy or an alkylthio group, cycloalkyl groups, cycloalkylthio groups or heterocyclic groups;

R2 represents an alkyl group substituted by at least a –COOR3 group, wherein R3 represents a hydrogen atom, or an alkyl group that is substituted or not by one or more halogen atoms, cycloalkyl groups, or heterocyclic groups.

R4 and R5, identical or different, representing an alkyl group that is substituted or not by one or more halogen atoms, cycloalkyl groups, heterocyclic groups;

or a pharmaceutically acceptable salt thereof.

15. The use according to claim 14, wherein the compound is selected in the group consisting of 1-[4-methylthiophenyl]-3-[3,5-dimethyl-4-carboxydimethylmethyloxy phenyl]prop-2-en-1-one, 1-[4-methylthiophenyl]-3-[3,5-dimethyl-4-isopropyloxy carbonyldimethylmethyloxyphenyl]prop-2-en-1-one, 1-[4-methylthiophenyl]-3-[3,5-dimethyl-4-tertbutyloxycarbonyldimethylmethyloxyphenyl] prop-2-en-1-one, 1-[4-trifluoromethylphenyl]-3-[3,5-dimethyl-4-tertbutyloxycarbonyl dimethylmethyloxyphenyl]prop-2-en-1-one, 1-[4-trifluoromethylphenyl]-3-[3,5-dimethyl-4-carboxydimethylmethyloxyphenyl]prop-2-en-1-one, 1-[4-trifluoromethyl oxyphenyl]-3-[3,5-dimethyl-4-tertbutyloxycarbonyldimethylmethyloxy phenyl] prop-2-en-1-one, 1-[4-trifluoromethyloxyphenyl]-3-[3,5-dimethyl-4-carboxydimethylmethyl oxyphenyl]prop-2-en-1-one, 2-[2,6-dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-propyl] phenoxy]-2-methylpropanoic acid, and 2-[2,6-dimethyl-4-[3-[4-(methylthio) phenyl]-3-oxo-propyl]phenoxy]-2-methyl-propanoic acid isopropyl ester; or a pharmaceutically acceptable salt thereof.

16. The use for according to any one of claims 13 to 15, wherein said compound is 1-[4-methylthiophenyl]-3-[3,5-dimethyl-4-carboxydimethylmethyloxyphenyl]prop-2-en-1-one or a pharmaceutically acceptable salt thereof.