(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 November 2021 (25.11.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/237149 A3

(51) International Patent Classification:
A61K 31/232 (2006.01) *A61K 47/24* (2006.01)
A61K 47/10 (2017.01)

(21) International Application Number:
PCT/US2021/033749

(22) International Filing Date:
21 May 2021 (21.05.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

63/029,366	22 May 2020 (22.05.2020)	US
63/030,219	26 May 2020 (26.05.2020)	US
63/113,115	12 November 2020 (12.11.2020)	US
63/146,557	05 February 2021 (05.02.2021)	US

(71) Applicant: **DURECT CORPORATION** [US/US]; 10260 Bubb Road, Cupertino, California 95014-4166 (US).

(72) Inventors: **LIN, WeiQi**; 590 California Way, Emerald Hills, California 94062 (US). **BROWN, James E.**; 126 Blueberry Hill Dr., Los Gatos, California 95032 (US). **BLASCHKE, Terrence**; 855 Allardice Way, Stanford, California 94305 (US).

(74) Agent: **CHIN, Khin K.**; Bozicevic, Field & Francis LLP, 201 Redwood Shores Parkway, Suite 200, Redwood City, California 94065 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: TREATMENT OF NON-ALCOHOLIC STEATOHEPATITIS (NASH)

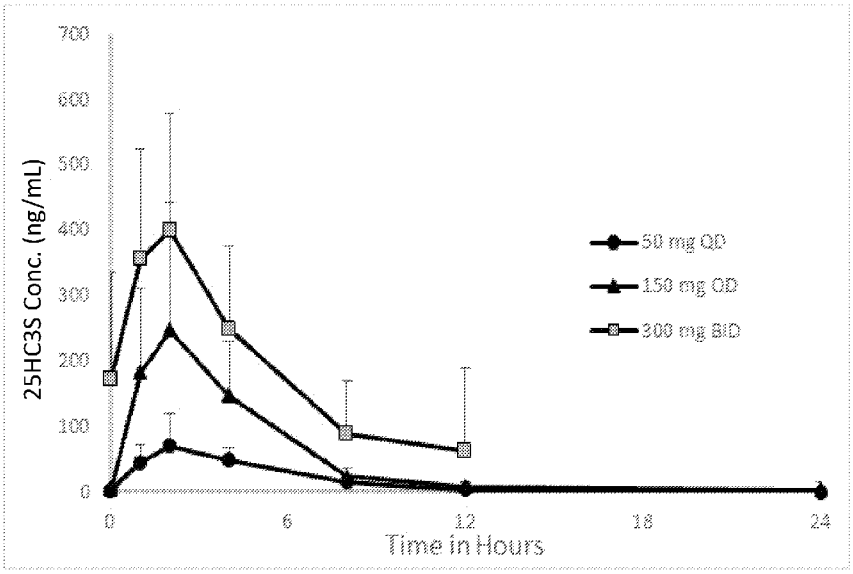

Figure 1

(57) Abstract: Methods of treating non-alcoholic steatohepatitis (NASH) are provided. For instance, the methods comprise administering 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or a salt thereof.

WO 2021/237149 A3

[Continued on next page]

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
30 December 2021 (30.12.2021)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/33749

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/232; A61K 47/10; A61K 47/24 (2021.01)

CPC - A61K 31/202; A61K 31/232; A61K 47/10; A61K 47/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 9,034,859 B2 (REN) 19 May 2015 (19.05.2015), especially: col 1, ln 48-67; col 2, ln 19-31; col 2, ln 32-40; col 14, ln 1-29; col 14, ln 43-47.	1,6-7 --- 35-36,38-39,41-42,44-45
Y	ATHYROS et al. "The use of statins alone, or in combination with pioglitazone and other drugs, for the treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and related cardiovascular risk. An Expert Panel Statement", METABOLISM CLINICAL AND EXPERIMENTAL. 2017. 71, pp 17-32, especially: pg 24, col 1, para 5; pg 24, col 2, para 2; pg 24, col 2, para 4.	35-36,38-39,41-42,44-45
A	KIYICI et al. "Ursodeoxycholic acid and atorvastatin in the treatment of nonalcoholic steatohepatitis", Can J Gastroenterol. 2003. Vol 17 No 12, pp 713-718, entire document.	1,6-7,35-36,38-39,41-42,44-45

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 2021	NOV 22 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/33749

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8-34, 37, 40, 43 and 46
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(see extra sheet)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1,6-7,35-36,38-39,41-42,44-45

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/33749

--BOX III - LACK OF UNITY--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1, 6-7 (in part), 35-36, 38-39, 41-42 and 44-45, directed to a method of treating non-alcoholic steatohepatitis (NASH) in a human subject in need thereof, the method comprising orally administering to the subject 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof in an amount ranging from 300 mg/day to 900 mg/day.

Group II: Claims 2 and 6-7 (in part), directed to a method of lowering serum alanine aminotransferase (ALT) levels in a human subject having non-alcoholic steatohepatitis (NASH), comprising: orally administering to the subject 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof in an amount ranging from 300 mg/day to 900 mg/day.

Group III: Claims 3 and 6-7 (in part), directed to a method of lowering serum aspartate aminotransferase (AST) levels in a human subject having non-alcoholic steatohepatitis (NASH), comprising: orally administering to the subject 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof in an amount ranging from 300 mg/day to 900 mg/day.

Group IV: Claims 4 and 6-7 (in part), directed to a method of lowering gamma-glutamyl transferase (GGT) levels in a human subject having non-alcoholic steatohepatitis, comprising: orally administering to the subject 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof in an amount ranging from 300 mg/day to 900 mg/day.

Group V: Claims 5 and 6-7 (in part), directed to a method of lowering serum triglycerides in a human subject having non-alcoholic steatohepatitis (NASH) and having triglycerides . 200 mg/dL prior to treatment, comprising: orally administering to the subject 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof in an amount ranging from 300 mg/day to 900 mg/day.

Special Technical Features

The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group I requires a method of treating non-alcoholic steatohepatitis (NASH), which is not required by Groups II-V.

Group II requires a method of lowering serum alanine aminotransferase (ALT) levels, which is not required by Group I or Groups III-V.

Group III requires a method of lowering serum aspartate aminotransferase (AST) levels, which is not required by Groups I-II or Groups IV-V.

Group IV requires a method of lowering gamma-glutamyl transferase (GGT) levels, which is not required by Groups I-III or Group V.

Group V requires a method of lowering serum triglycerides, which is not required by Groups I-IV.

Shared Common Features

The only feature shared by Groups I-V that would otherwise unify the groups is a method of treating a disease in a human subject having non-alcoholic steatohepatitis (NASH), comprising: orally administering to the subject 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof in an amount ranging from 300 mg/day to 900 mg/day. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is obvious over US 9,034,859 B2 to Ren (hereinafter 'REN').

Ren teaches a method of treating non-alcoholic steatohepatitis (NASH) in a human subject (col 2, ln 19-31, The present invention provides methods and compositions for use in the prevention and/or treatment of liver disease and damage in subjects in need thereof; see also col 2, ln 32-40, As such, the compounds may be used to both prevent and treat disease and damage of the liver per se (e.g. NAFLD); see also col 1, ln 48-67, The spectrum of NAFLD ranges from simple nonprogressive steatosis to progressive steatohepatitis (NASH); see also col 14, ln 43-47, Subjects to whom the compositions of the invention are administered are generally mammals. In some embodiments, the mammal is a human) comprising: orally administering to the subject 5-cholesten-3,25-diol, 3-sulfate (25HC3S) (col 14, ln 7-29, The 25HC3S and/or 25HC compositions (preparations) of the present invention may be administered by any of the many suitable means which are well known to those of skill in the art, including... orally) in an amount of about 100 mg/kg body weight (col 14, ln 1-29, The amount of 25HC3S to be administered may vary depending on characteristics of the Subject to whom it is administered (for example, the species, gender, age, genetic makeup, general health, etc.), as well as the disease or condition that is being treated. However, the amount will generally be in the range of from about 0.1 mg/kg to about 100 mg/kg, based on body mass of the Subject), but Ren does not specifically teach administering the compound in an amount ranging from 300 mg/day to 900 mg/day. However, it would have been obvious to a person having ordinary skill in the art to administer the composition in an amount of 300 mg/day by routine experimentation in order to develop and commercialize the invention.

As the technical features were known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups. Groups I-V therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Note reg. item 4: Claims 8-34, 37, 40, 43 and 46 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).