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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 November 2015 (05.11.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/166434 A1

(51) International Patent Classification:
A01N 43/42 (2006.01)

(21) International Application Number:
PCT/IB2015/053123

(22) International Filing Date:
29 April 2015 (29.04.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1184/DEL/2014 1 May 2014 (01.05.2014) IN

(71) Applicant: **SUN PHARMACEUTICAL INDUSTRIES LIMITED** [IN/IN]; Sun House, Plot No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai, Maharashtra 400 063 (IN).

(72) Inventors: **PANDEY, Gyanendra**; C-4/605, SRS Residency, Sector - 88, Faridabad, Haryana 121001 (IN). **..., Javeena**; House No. 83A, First Floor, Madangir Village, New Delhi Taluk, South Delhi, Delhi 110062 (IN). **SINGH, Kaptan**; Flat No. B-02, Saket Enclave, Rajendra Nagar, Sahibabad, Ghaziabad, Uttar Pradesh 201005 (IN). **PRASAD, Mohan**; H. No. P-3/3, Phase-II, DLF Qutab Enclave, Gurgaon, Haryana 122001 (IN).

(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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

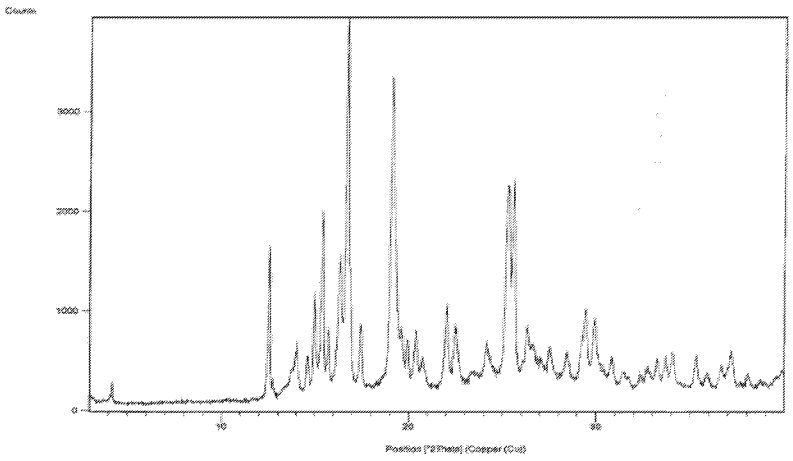
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, 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).

Published:

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

(54) Title: CRYSTALLINE FORM OF BARICITINIB

FIGURE 1: X-RAY POWDER DIFFRACTION (XRPD) PATTERN OF THE CRYSTALLINE FORM OF BARICITINIB.



(57) Abstract: The present invention provides a crystalline form of baricitinib, a process for its preparation, a pharmaceutical composition comprising it, and its use for the treatment of JAK-associated diseases.

WO 2015/166434 A1

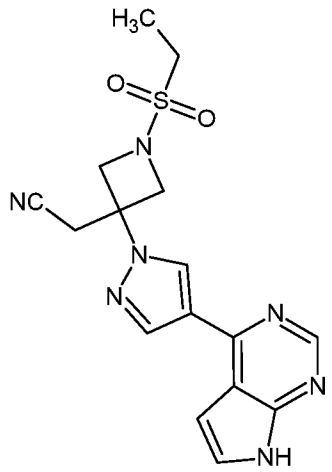
CRYSTALLINE FORM OF BARICITINIB

Field of the Invention

The present invention provides a crystalline form of baricitinib, a process for its preparation, a pharmaceutical composition comprising it, and its use for the treatment of JAK-associated diseases.

Background of the Invention

Baricitinib is a Janus Kinase (JAK) inhibitor. It is chemically designated as {1-(ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile, having the structure as depicted in Formula I.



Formula I

Processes for the preparation of baricitinib are disclosed in U.S. Patent No. 8,158,616.

Polymorphism, the occurrence of different crystal forms, is a property of some molecules. When polymorphism occurs, the molecules arrange themselves in two or more different ways in the crystal, giving rise to differences in crystal structures and physical properties like melting point, thermal behaviors, X-ray Powder Diffraction (XRPD) pattern, Infrared (IR) absorption fingerprint, solid state NMR spectrum, and solubility. Thus, the discovery of new polymorphic forms of a molecule is important in the development of pharmaceuticals, as they may provide materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, ease of purification, improved dissolution profile, and/or improved shelf-life.

There are no reported polymorphs of baricitinib.

Summary of the Invention

The present invention provides a crystalline form of baricitinib, a process for its preparation, a pharmaceutical composition comprising it, and its use for the treatment of JAK-associated diseases. The crystalline form of baricitinib is a highly pure, easy to filter, free-flowing solid with good thermodynamic stability, good solubility, residual solvent content in compliance with the ICH guidelines, prolonged shelf life, and good bioavailability.

A first aspect of the present invention provides a crystalline form of baricitinib characterized by an X-ray Powder Diffraction (XRPD) pattern having peaks at d-spacings of 5.31, 4.65, 3.52, and 3.48 Å.

A second aspect of the present invention provides a process for the preparation of a crystalline form of baricitinib characterized by an XRPD pattern having peaks at d-spacings of 5.31, 4.65, 3.52, and 3.48 Å, comprising the steps of:

i) reacting (4-(1-(3-(cyanomethyl)-1-(ethylsulfonyl)azetidin-3-yl)-1H-pyrazol-4-yl)-7H-pyrrolo [2,3-d]pyrimidin-7-yl)methyl pivalate with a base in the presence of one or more solvents;
ii) partially recovering the solvent(s) from the reaction mixture;
iii) stirring the reaction mixture;
iv) filtering the solid obtained from the reaction mixture;
v) washing the solid with a mixture of acetonitrile and water; and
vi) drying the solid.

A third aspect of the present invention provides a pharmaceutical composition comprising a crystalline form of baricitinib characterized by an XRPD pattern having peaks at d-spacings of 5.31, 4.65, 3.52, and 3.48 Å, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

A fourth aspect of the present invention provides a method of treating JAK-associated diseases comprising administration to a patient a therapeutically effective amount of a composition comprising a crystalline form of baricitinib characterized by an XRPD pattern having peaks at d-spacings of 5.31, 4.65, 3.52, and 3.48 Å.

Brief Description of the Drawings

Figure 1: X-ray Powder Diffraction (XRPD) pattern of the crystalline form of baricitinib.

Figure 2: Differential Scanning Calorimetry (DSC) thermogram of the crystalline form of baricitinib.

Figure 3: Thermogravimetric Analysis (TGA) of the crystalline form of baricitinib.

Figure 4: Infra-red (IR) spectrum of the crystalline form of baricitinib.

Detailed Description of the Invention

Various embodiments and variants of the present invention are described hereinafter.

The term "JAK-associated diseases," as used herein, includes inflammatory diseases, autoimmune disorders, diabetic nephropathy, and cancer.

The term "about," as used herein, refers to any value which lies within the range defined by a number up to ±10% of the value.

The crystalline form of baricitinib is characterized by an XRPD pattern having peaks at d-spacings of 5.31, 4.65, 3.52, and 3.48 Å. The crystalline form of baricitinib is further characterized by an XRPD pattern having peaks at d-spacings of 7.06, 5.91, 5.75, 5.43, and 2.98 Å. Table 1 summarizes the d-spacing values in Å, and the corresponding 2θ values of the crystalline form of baricitinib.

Table 1: XRPD Peaks of the Crystalline Form of Baricitinib

Pos. [°2Th]	d-Spacing [Å]	Rel. Int. [%]
4.20	21.00	5.71
10.16	8.71	0.43
12.53	7.06	40.03
12.73	6.95	4.63
14.05	6.30	12.50
14.59	6.07	11.88
14.99	5.91	28.58
15.41	5.75	49.96
15.73	5.63	19.39
16.32	5.43	36.63
16.70	5.31	100.00
16.88	5.25	33.91
17.48	5.07	18.91
19.09	4.65	84.46
19.60	4.53	19.52
19.34	4.45	15.81
20.40	4.35	17.84
20.74	4.28	11.23
22.05	4.03	24.73
22.50	3.95	18.55
23.36	3.81	7.70
24.14	3.69	15.94
25.25	3.52	56.15
25.31	3.52	56.59
25.57	3.48	57.58
26.29	3.39	18.37
26.69	3.34	13.75
27.48	3.24	13.48
28.42	3.14	12.10
29.42	3.03	24.12
29.92	2.98	22.23
30.82	2.90	10.86
31.39	2.85	7.72
31.73	2.82	6.65
32.32	2.77	7.18
32.70	2.74	8.44
33.26	2.69	11.31
33.66	2.66	11.58
34.01	2.63	12.99
35.31	2.54	12.15
35.88	2.50	7.72
36.62	2.45	9.01
37.18	2.42	12.87
38.05	2.36	7.53
38.71	2.32	5.36

The crystalline form of baricitinib is further characterized by a DSC having endotherms at about 180.63°C and about 207.98°C.

The crystalline form of baricitinib has a water content of about 3%, as determined by TGA.

The crystalline form of baricitinib is also characterized by an XRPD pattern as depicted in Figure 1, a DSC thermogram as depicted in Figure 2, a TGA as depicted in Figure 3, and an IR spectrum as depicted in Figure 4.

The preparation of the crystalline form of baricitinib is carried out by reacting (4-(1-(3-(cyanomethyl)-1-(ethylsulfonyl)azetidin-3-yl)-1H-pyrazol-4-yl)-7H-pyrrolo [2,3-d]pyrimidin-7-yl)methyl pivalate with a base in the presence of one or more solvents at a temperature of about 15°C to 50°C, stirring the reaction mixture for about 30 minutes to about 10 hours, partially recovering the solvent(s) from the reaction mixture at a temperature of about 35°C to about 60°C under reduced pressure, stirring the contents at about 15°C to 35°C for about 5 hours to about 24 hours, filtering the solid, washing the solid with a mixture of acetonitrile and water, and drying.

The (4-(1-(3-(cyanomethyl)-1-(ethylsulfonyl)azetidin-3-yl)-1H-pyrazol-4-yl)-7H-pyrrolo [2,3-d]pyrimidin-7-yl)methyl pivalate may be obtained by following the process disclosed in U.S. Patent No. 8,158,616.

The base may be selected from the group consisting of inorganic and organic bases. Examples of inorganic bases include hydroxides, carbonates, and bicarbonates of alkali and alkaline earth metals. Examples of alkali and alkaline earth metal hydroxides include lithium hydroxide, sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, and barium hydroxide. Examples of alkali and alkaline earth metal carbonates include sodium carbonate, potassium carbonate, calcium carbonate, and magnesium carbonate. Examples of alkali metal bicarbonates include sodium bicarbonate and potassium bicarbonate. Examples of organic bases include N,N-diisopropylethylamine, triethylamine, triisopropylamine, N,N-2-trimethyl-2-propanamine, N-methylmorpholine, 4-dimethylaminopyridine, 2,6-di-tert-butyl-4-dimethylaminopyridine, 1,4-diazabicyclo[2.2.2]octane, and 1,8-diazabicyclo[5.4.0]undec-7-ene. In an embodiment of the present invention, the base used is sodium hydroxide.

The solvents may be selected from the group consisting of hydrocarbons, alcohols, ethers, chlorinated hydrocarbons, carboxylic acids, ketones, amides, sulphoxides, water,

and mixtures thereof. Examples of hydrocarbons include benzene, toluene, and xylene. Examples of alcohols include methanol, ethanol, 1-propanol, 1-butanol, and 2-butanol. Examples of ethers include diethyl ether, ethyl methyl ether, di-isopropyl ether, tetrahydrofuran, and 1,4-dioxane. Examples of chlorinated hydrocarbons include dichloromethane and chloroform. Examples of carboxylic acids include formic acid, acetic acid, and propionic acid. Examples of ketones include acetone, dimethyl ketone, ethyl methyl ketone, and methyl iso-butyl ketone. Examples of amides include N,N-dimethylformamide and N,N-dimethylacetamide. Examples of sulphoxides include dimethyl sulphoxide and diethyl sulphoxide. In an embodiment of the present invention, a mixture of methanol and tetrahydrofuran is used.

In an embodiment of the present invention, the partial recovery of the solvent(s) from the reaction mixture is carried out at a temperature of about 40°C to about 50°C under reduced pressure.

In another embodiment of the present invention, a mixture of acetonitrile and water in a 1:2 ratio is used for washing.

Isolation of the crystalline form of baricitinib may be carried out by concentration, precipitation, cooling, filtration, centrifugation, or combinations thereof, followed by drying. Drying may be carried out using any suitable method such as drying under reduced pressure, air drying, or vacuum tray drying. Drying may be carried out at a temperature of about 35°C to about 50°C for about 10 hours to about 2 days.

In an embodiment of the present invention, the isolation of the crystalline form of baricitinib is carried out by filtration followed by drying at a temperature of about 35°C to about 50°C for about 24 hours.

The crystalline form of baricitinib is a highly pure, easy to filter, free-flowing solid. The crystalline form of baricitinib has good thermodynamic stability, good solubility, residual solvent content in compliance with the ICH guidelines, prolonged shelf life, and good bioavailability.

The crystalline form of baricitinib may be administered as part of a pharmaceutical composition for the treatment of JAK-associated diseases, including inflammatory diseases, autoimmune disorders, diabetic nephropathy, and cancer. Accordingly, in a further aspect of the present invention, there is provided a pharmaceutical composition

comprising the crystalline form of baricitinib and one or more pharmaceutically acceptable carriers, diluents, or excipients, and optionally other therapeutic ingredients.

In the foregoing section, embodiments are described by way of an example to illustrate the process of the present invention. However, this is not intended in any way to limit the scope of the present invention. Several variants of the example would be evident to persons ordinarily skilled in the art which are within the scope of the present invention.

Methods

The X-ray powder diffraction patterns were recorded using a PANalytical® Expert PRO with X'celerator® as the detector, 0.02 as step size, and 3-40° 2θ as range using CuKα radiation.

The DSC thermogram was recorded using a Mettler Toledo® DSC 821e instrument.

The TGA was recorded using a TA Instruments® Q500.

The IR spectrum was recorded using a Perkin Elmer® Spectrum One FT-IR spectrometer.

Example: Preparation of crystalline form of baricitinib

(4-(1-(3-(Cyanomethyl)-1-(ethylsulfonyl)azetidin-3-yl)-1H-pyrazol-4-yl)-7H-pyrrolo [2,3-d]pyrimidin-7-yl)methyl pivalate (8 g), methanol (40 mL), tetrahydrofuran (160 mL), and 1M sodium hydroxide (18.4 mL) were added into a reaction vessel at 20°C to 25°C. The reaction mixture was stirred for 3 hours. Progress of the reaction was monitored by thin layer chromatography. On completion, the reaction mixture was quenched with water (80 mL). The pH was adjusted to 7.0 to 7.5 by adding 1N hydrochloric acid. Half of the solvent was recovered at a temperature of 40°C to 50°C. The reaction mixture was stirred at 20°C to 25°C for 18 hours, and then cooled to 5°C to 10°C. The solids were filtered, washed with a mixture of acetonitrile (50 mL) and water (100 mL), and then dried at 40°C to 50°C under reduced pressure for 24 hours to obtain the crystalline form of baricitinib.

Yield: 70%

We claim:

1. A crystalline form of baricitinib characterized by an X-ray Powder Diffraction (XRPD) pattern having peaks at d-spacings of 5.31, 4.65, 3.52, and 3.48 Å.

2. The crystalline form of baricitinib according to claim 1, further characterized by an XRPD pattern having peaks at d-spacings of 7.06, 5.91, 5.75, 5.43, and 2.98 Å.

3. The crystalline form of baricitinib according to claim 1, characterized by an XRPD pattern substantially as depicted in Figure 1.

4. The crystalline form of baricitinib according to claim 1, characterized by a Differential Scanning Calorimetry (DSC) thermogram having endotherms at about 180.63°C and about 207.98°C.

5. The crystalline form of baricitinib according to claim 1, characterized by a DSC thermogram substantially as depicted in Figure 2.

6. The crystalline form of baricitinib according to claim 1, having a water content of about 3%, as determined by Thermogravimetric Analysis (TGA).

7. The crystalline form of baricitinib according to claim 1, characterized by a TGA substantially as depicted in Figure 3.

8. The crystalline form of baricitinib according to claim 1, characterized by an Infra-red (IR) spectrum substantially as depicted in Figure 4.

9. A process for the preparation of the crystalline form of baricitinib according to claim 1 comprising the steps of:

i) reacting (4-(1-(3-(cyanomethyl)-1-(ethylsulfonyl)azetidin-3-yl)-1H-pyrazol-4-yl)-7H-pyrrolo [2,3-d]pyrimidin-7-yl)methyl pivalate with a base in the presence of one or more solvents;

ii) partially recovering the solvent(s) from the reaction mixture;

iii) stirring the reaction mixture;

iv) filtering a solid obtained from the reaction mixture;

v) washing the solid with a mixture of acetonitrile and water; and

vi) drying the solid.

10. The process according to claim 9, wherein the base is selected from the group consisting of inorganic and organic bases.

11. The process according to claim 10, wherein the inorganic base is selected from the group consisting of hydroxides, carbonates, and bicarbonates of alkali or alkaline earth metals.

12. The process according to claim 11, wherein the inorganic base is sodium hydroxide.

13. The process according to claim 9, wherein the one or more solvents used in step i) is selected from the group consisting of hydrocarbons, alcohols, ethers, chlorinated hydrocarbons, carboxylic acids, ketones, amides, sulphoxides, water, and mixtures thereof.

14. The process according to claim 13, wherein the solvent is a mixture of methanol and tetrahydrofuran.

15. The process according to claim 9, wherein the partial recovery of the solvent(s) is carried out at a temperature of about 35°C to 60°C.

16. The process according to claim 9, wherein the washing is carried out with a mixture of acetonitrile and water in a 1:2 ratio.

17. The process according to claim 9, wherein the drying is carried out at a temperature of 35°C to 50°C.

18. A pharmaceutical composition comprising the crystalline form of baricitinib according to claim 1, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

19. Use of the crystalline form of baricitinib according to claim 1 for the treatment of JAK-associated diseases.

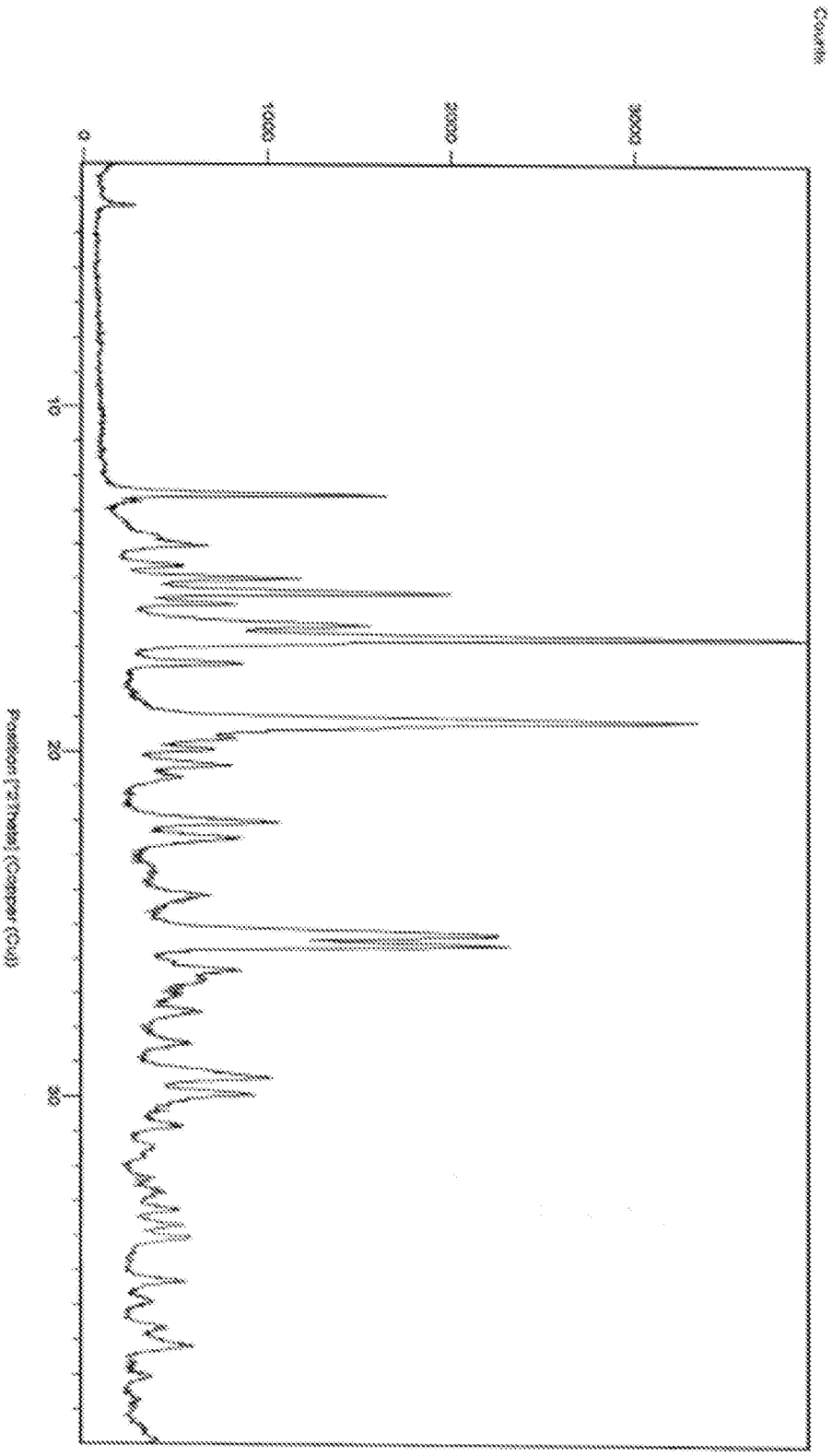


FIGURE 1: X-RAY POWDER DIFFRACTION (XRPD) PATTERN OF THE CRYSTALLINE FORM OF BARICITINIB.

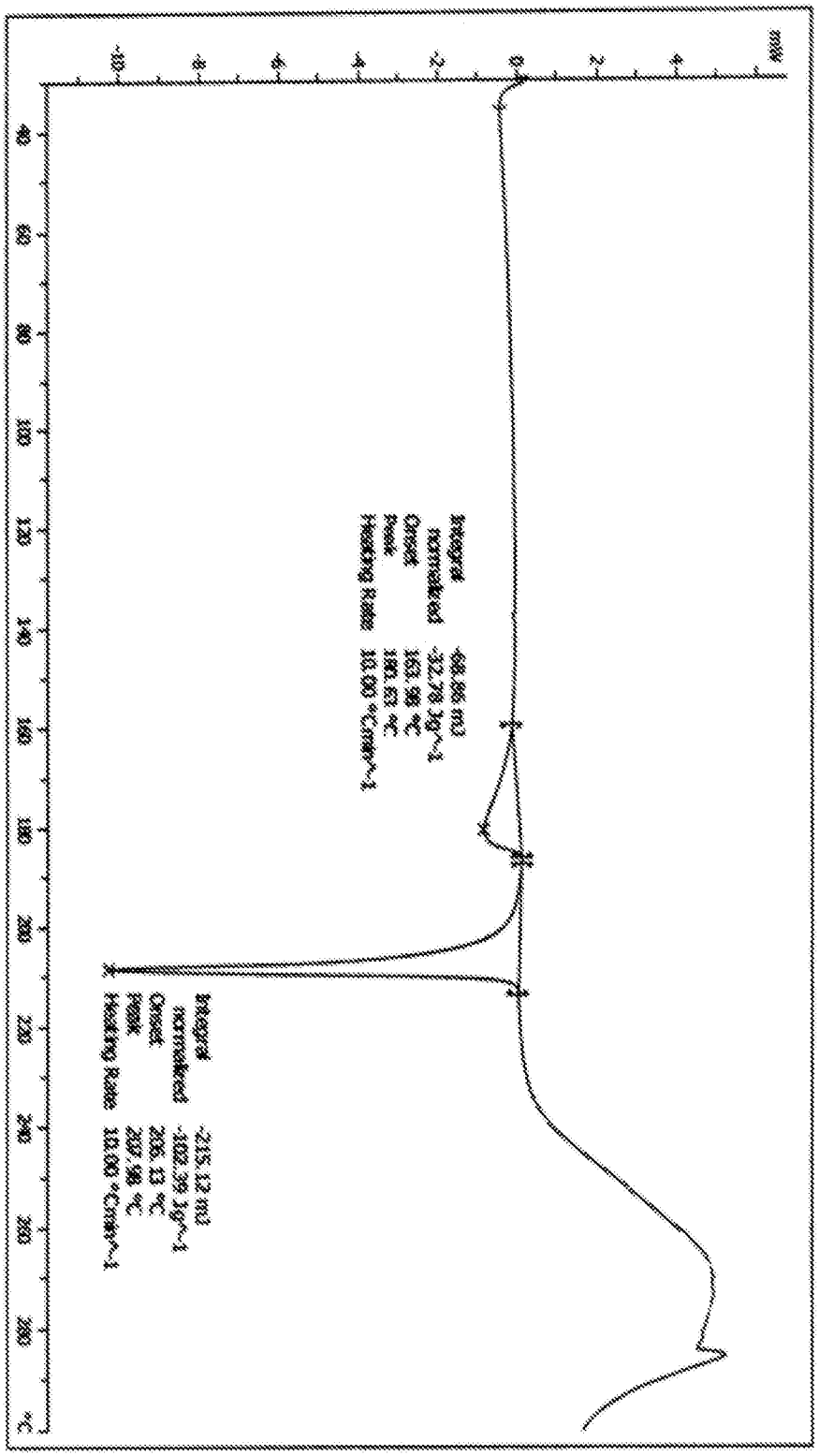


FIGURE 2: DIFFERENTIAL SCANNING CALORIMETRY (DSC) THERMOGRAM OF THE CRYSTALLINE FORM OF BARICITINIB.

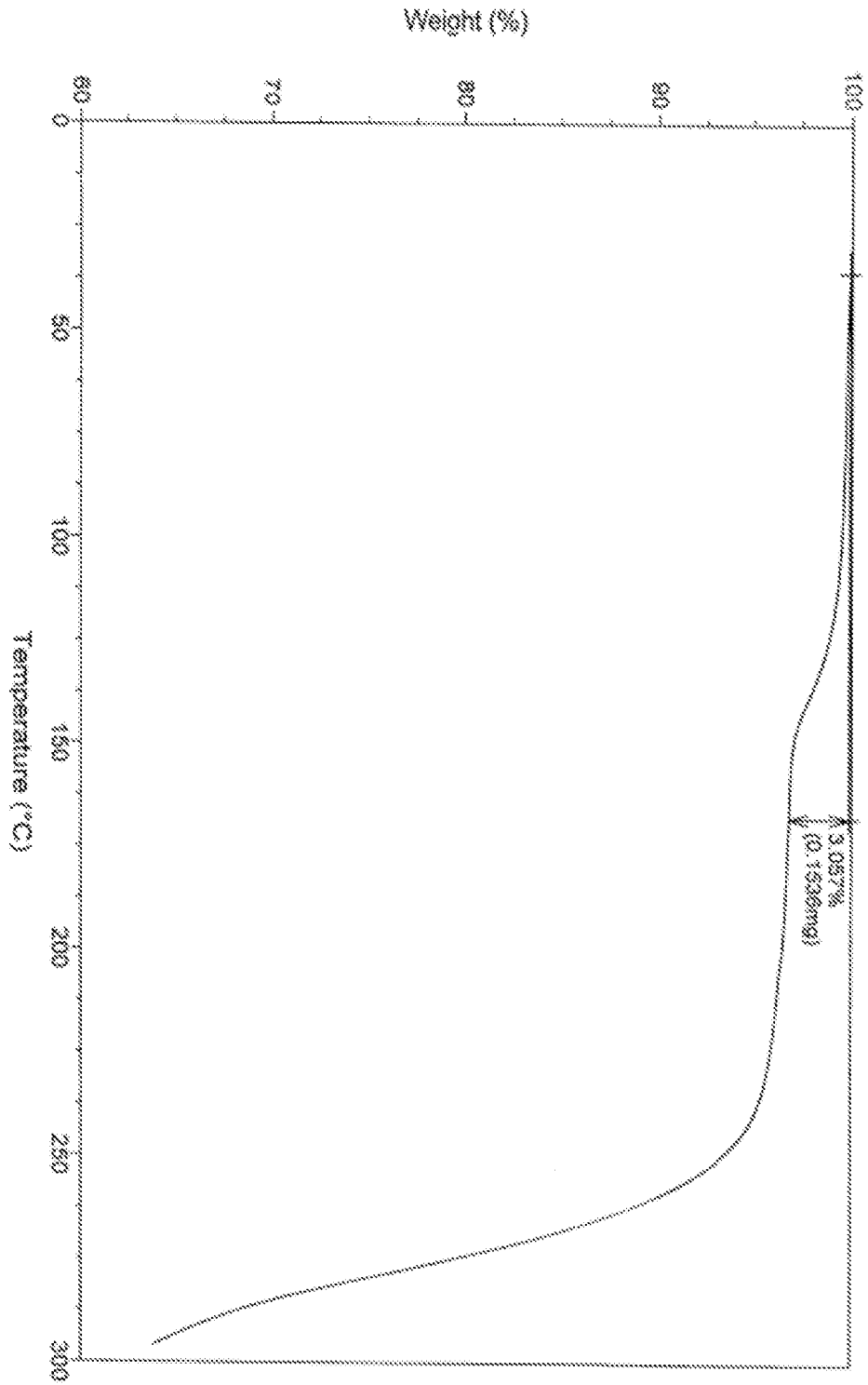


FIGURE 3: THERMOGRAVIMETRIC ANALYSIS (TGA) OF THE CRYSTALLINE FORM OF BARICITINIB.

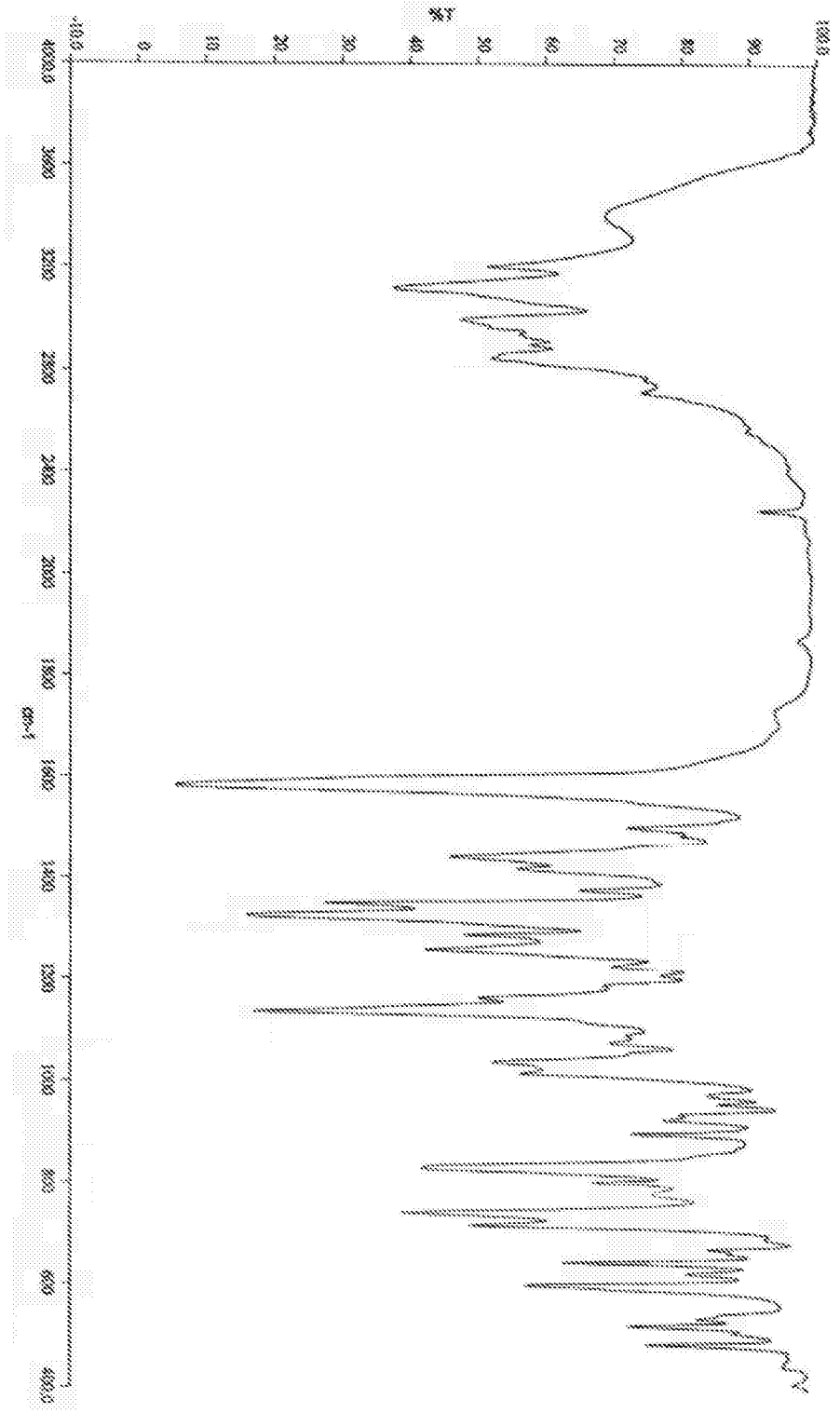


FIGURE 4: INFRA-RED (IR) SPECTRUM OF THE CRYSTALLINE FORM OF BARICITINIB.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 15/53123

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/42 (2015.01)
CPC - C07D 471/04; C07D 487/04; A61K 31/437
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)
IPC(8): A01N 43/42 (2015.01)
CPC: C07D 471/04; C07D 487/04; A61K 31/437

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/303 (key word limited; see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar
Search terms used: crystalline baricitinib, X-ray Powder Diffraction (XRPD) pattern

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/0233903 A1 (Rodgers et al.) 17 September 2009 (17.09.2009); para [0157]-[0159], [0257]	1-19
A	WO 2014/028756 A1 (Tung) 20 February 2014 (20.02.2014); para [13] and [42]	1-19

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"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
15 July 2015 (15.07.2015)	30 JUL 2015
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: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)