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(54) Title: ACID ADDITION SALTS OF FILGOTINIB

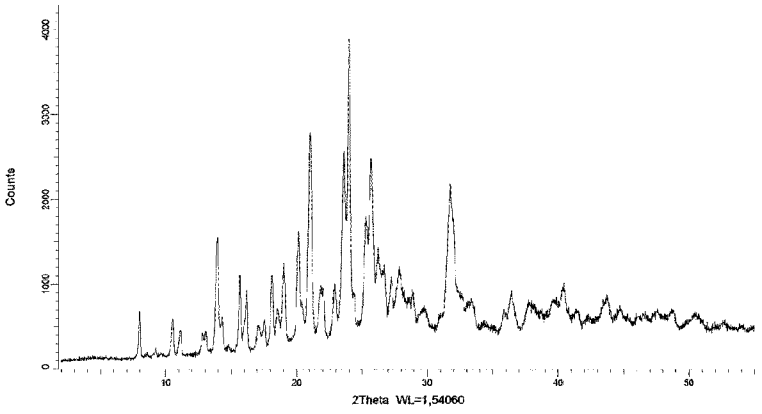

Figure 1: XRD- diffractogram of filgoftinib hydrochloride Form E

(57) Abstract: The present invention relates to filgotinib hydrochloride acid addition salt, its polymorphs, a method of preparing the same as well as a pharmaceutical composition comprising the same.

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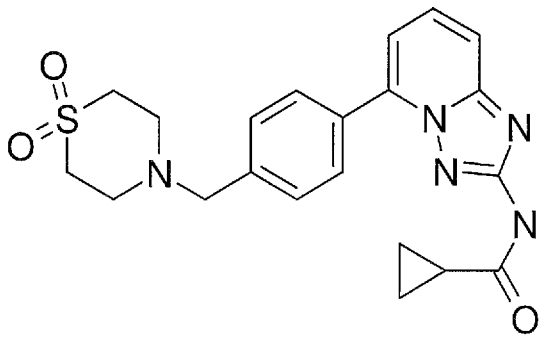
Acid Addition Salts of Filgotinib

The present invention relates to filgotinib acid addition salts, their polymorphs, a method of preparing the same as well as a pharmaceutical composition comprising the same.

The IUPAC name of filgotinib is N-[5-[4-[(1,1-dioxo-1,4-thiazinan-4-yl)methyl]phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide.

Filgotinib is represented by the following chemical structure according to Formula (I):



Formula (I)

Filgotinib (also known as GLPG-0634 or N-(5-(4-((1,1-dioxothiomorpholino)methyl) phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropane-carboxamide) is an orally available, selective inhibitor of JAK1 (Janus kinase 1) being developed by Galapagos for the treatment of rheumatoid arthritis and potentially other inflammatory diseases.

JAKs are critical components of signaling mechanisms utilized by a number of cytokines and growth factors, including those that are elevated in rheumatoid arthritis patients. Other non-selective JAK inhibitors have shown long-term efficacy in rheumatoid arthritis trials with an early onset of action. Contrary to baricitinib and ruxolitinib, which are mixed JAK1 and JAK2 inhibitors, and

tofacitinib, which is a specific JAK3 inhibitor, filgotinib was developed to specifically target JAK1.

The active pharmaceutical ingredient filgotinib is known from WO 2010/149769 A1. Similar synthetic routes for obtaining derivatives of filgotinib are also described in WO 2010/010190 A1.

Filgotinib in form of the free base is practically insoluble. One option to enhance the solubility is the formation of a filgotinib base or acid addition salt.

WO 2010/149769 generally refers to certain filgotinib acid addition salts. However, said document describes neither a method for their preparation nor any properties nor polymorphs thereof. It additionally turned out that some of the described filgotinib acid addition salts do not seem to be enabled. In particular the formation of filgotinib acid addition salt could not be observed in case that the acid was fumaric acid, tartaric acid, maleic acid or oxalic acid.

Additionally, due to necessary preparation methods several filgotinib acid addition salts contain an unacceptably high residual content. However, according to FDA regulations any solvent is only acceptable to a certain concentration. These concentrations depend on the solvent and can be low or very low. For example, according to FDA regulations, dichloromethane, dioxane and ethanol are only allowable in amounts of 600 ppm, 380 ppm and 5000 ppm respectively. These values are difficult to achieve since employing conventional drying methods, like drying at elevated temperatures with and without vacuum, did not lead to pharmaceutically acceptable solvent levels and/or drug purity levels.

Consequently, there is still a need for filgotinib acid addition salts which are present in a pure and/or stable form.

Hence, it was an object of the present invention to overcome the drawbacks of the above-mentioned prior art.

Additionally filgotinib acid addition salts should be provided in a form which is easy to prepare.

Further, a form of filgotinib addition salt having a residual solvent content within pharmaceutically acceptable limits should be provided.

According to the present invention, the above objectives are unexpectedly achieved. Filgotinib acid addition salt, preferably filgotinib hydrochloride and filgotinib sulfate and the corresponding polymorphs thereof, the process of their preparation and pharmaceutical compositions comprising said filgotinib acid addition salts are provided.

Filgotinib acid addition salt, preferably filgotinib hydrochloride and filgotinib sulfate, might be present in different polymorphic forms or mixtures thereof.

The filgotinib acid addition salts of the present invention can be preferably present in crystalline form.

A crystal form may be referred to herein as being characterized by data selected from two or more different data groupings, for example by a powder XRD pattern having a group of specific peaks or by a powder XRD pattern as shown in a figure depicting a diffractogram or by "a combination thereof" (or "combinations thereof" or "any combination thereof"). These expressions, e.g. "any combination thereof", contemplate that the skilled person may characterize a crystal form using any combination of the recited characteristic analytical data. For example, the skilled person may characterize a crystal form using a group of three, four or five characteristic powder XRD peaks and supplement that characterization with one or more additional feature(s) observed in the powder X-ray diffractogram, e.g., an additional peak, a characteristic peak shape, a peak intensity or even the absence of a peak at some position in the powder XRD pattern. Alternatively, the skilled person may in some instances characterize a crystal form using a group of three, four or five characteristic powder XRD peaks and supplement that characterization

with one or more additional feature(s) observed using another analytical method, for example using one or more characteristic peaks in a solid state IR spectrum, solid state NMR or characteristics of the DSC thermogram of the crystal form that is being characterized.

Unless indicated otherwise, XRPD peaks are recorded using copper $K\alpha_1/K\alpha_2$ radiation with a wavelength 1.5406 Å (weighted mean of Cu $K\alpha_1$ and Cu $K\alpha_2$). Further, unless indicated otherwise, XRPD peaks are reported as degrees 2θ values with a standard error of ± 0.2 degrees 2θ.

A crystal form may be referred to herein as being characterized by graphical data "as depicted in" a particular figure. Such data include for example powder X-ray diffractograms. The skilled person will understand that such graphical representations of data may be subject to small variations, e.g. in peak relative intensities and peak positions due to factors such as variations in instrument response and variations in sample concentration and purity, which are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the figures herein with graphical data generated for an unknown crystal form and confirm whether the two sets of graphical data characterize the same crystal form or two different crystal forms.

Thus, the subject of the present invention is filgotinib hydrochloride having characteristic X-ray powder diffraction peaks at 8.0, 10.5, 20.1, 24.0 and 25.7 degrees 2θ (± 0.2 degrees 2θ). That form of filgotinib hydrochloride is hereinafter referred to as polymorphic Form E of filgotinib hydrochloride.

In a preferred embodiment the filgotinib hydrochloride Form E can be characterized by one or more further XRPD diffraction peak(s) at 13.9, 18.1, 19.0, 21.1 and/or 23.6 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present invention filgotinib hydrochloride Form E can be characterized by the XRPD diffraction peak(s) at

degrees 2θ ± 0.2 degrees 2θ (intensity %): 8.0 (16), 8.6 (2), 9.2 (3), 10.5 (12), 11.1 (8), 12.8 (6), 13.0 (7), 13.9 (38), 14.3 (11), 14.8 (2), 15.7 (26), 16.2 (19), 17.1 (7), 17.5 (8), 18.1 (23), 18.6 (11), 19.0 (27), 20.1 (34), 20.4 (12), 21.1 (70), 21.9 (15), 22.9 (17), 23.6 (62), 24.0 (100), 24.3 (12), 25.3 (35), 25.7 (57), 26.2 (25), 26.6 (17), 27.2 (15), 27.8 (17), 28.9 (11), 29.8 (6), 31.1 (4), 31.8 (45), 32.6 (12), 33.4 (10), 35.9 (6), 36.4 (12), 37.8 (8), 38.7 (5), 39.6 (8), 40.4 (12), 41.4 (5), 42.3 (4), 43.7 (8), 44.7 (4), 46.4 (3), 47.6 (4) and 48.7 (5).

An XRPD diffraction pattern of filgotinib hydrochloride Form E is shown in Figure 1.

Alternatively preferred, filgotinib hydrochloride Form E can be characterized by an FT-IR spectrum showing peaks at the following wave numbers: 3446, 3354, 3097, 2974, 2895, 2798, 2654, 2480, 2374, 1705, 1647, 1591, 1564, 1522, 1504, 1458, 1446, 1425, 1416, 1396, 1348, 1317, 1284, 1254, 1213, 1192, 1153, 1132, 1090, 1066, 1028, 1014, 953, 935, 914, 881, 862, 837, 822, 795, 769, 744, 737, 714, 675, 648, 634, 621.

In a further preferred embodiment of the invention filgotinib hydrochloride, in particular Form E of filgotinib hydrochloride, has a residual solvent content within pharmaceutically acceptable limits.

In the present application residual solvent content within pharmaceutically acceptable limits refers to a concentration limit (in ppm) of the corresponding solvent.

Concentration limits for solvents can be found in Guidance for Industry, Q3C-Tables and List, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), February 2012, ICH, Revision 2.

The solvents are categorized into three classes.

Class 1 relates to solvents that should be avoided in pharmaceutical products, such as carbon tetrachloride.

Solvent	Concentration Limit (ppm)	Concern
Benzene	**2**	**Carcinogen**
Carbon tetrachloride	**4**	**Toxic and environmental hazard**
1,2-Dichloroethane	**5**	**Toxic**
1,1-Dichloroethene	**8**	**Toxic**
1,1,1-Trichloroethane	**1,500**	**Environmental hazard**

Table 1: Class 1 solvents and their concentration limits

Class 2 relates to solvents that should be limited in pharmaceutical products because of their inherent toxicity.

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3,880
Cumene	0.7	70
1,2-Dichloroethene	18.7	1,870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1,090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethyleneglycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3,000
2-Methoxyethanol	0.5	50
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1,180
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene[1]	21.7	2,170

[1]Usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethyl benzene.

Table 2: Class 2 solvents and their concentration limits

Class 3 relates to solvents which should be limited by GMP or other quality-based requirements. These solvents should be present in an amount below 5000 ppm.

Acetic acid	**Heptane**
Acetone	**Isobutyl acetate**
Anisole	**Isopropyl acetate**
1-Butanol	**Methyl acetate**
2-Butanol	**3-Methyl-1-butanol**
Butyl acetate	**Methylethyl ketone**
***tert*-Butylmethyl ether**	**Methylisobutyl ketone**
Dimethyl sulfoxide	**2-Methyl-1-propanol**
Ethanol	**Pentane**
Ethyl acetate	**1-Pentanol**
Ethyl ether	**1-Propanol**
Ethyl formate	**2-Propanol**
Formic acid	**Propyl acetate**

Table 3: Class 3 solvents having a concentration limit of 5000 ppm.

Filgotinib hydrochloride Form E is easily available from the synthesis without the need of a time-consuming and cost-intensive purification step.

Additionally, filgotinib hydrochloride Form E contains an amount of residual organic solvent(s) so small that the compound meets the requirements of the FDA regulations.

A further subject of the present invention is a process for preparing filgotinib hydrochloride according to the present invention, in particular filgotinib hydrochloride Form E, characterized by the following steps:

a) providing filgotinib
b) suspending filgotinib from step a) in aqueous hydrochloric acid
c) isolating filgotinib hydrochloride Form E.

In step a) filgotinib, preferably filgotinib in form of its free base, is provided. Filgotinib in form of its free base also refers to polymorphs, solvates and hydrates thereof.

Filgotinib free base can for example be prepared by reacting cyclopropane carboxylic acid [5-(4-bromomethyl-phenyl)-[1,2,4]triazolo[1,5a]pyridine-2yl]-amide with thiomorpholine dioxide until the completion of the reaction and the evaporation of the solvent. Up to this point the reaction steps are carried out as described for example in WO 2010/149769. However, contrary to said prior art, the resulting substance was suspended in an organic solvent or a mixture of organic solvents. After optionally heating and subsequently cooling the mixture, the organic solvent or the mixture of organic solvents is evaporated. Then the resulting substance is suspended in an organic solvent or a mixture of organic solvents once more. Again, after optionally heating and cooling the mixture, the product is filtered off and dried.

Examples of organic solvents are methanol, ethanol, isopropanol, acetone, ethylacetate, dichloromethane, trichloromethane, dioxane, tetrahydrofurane, acetonitrile, diethylether and *tert*-butyl methyl ether.

In a preferred embodiment the first and second suspending steps of the substance are carried out in a mixture of organic solvents, in particular in a mixture of dichloromethane and methanol, more specifically in a mixture of dichloromethane and methanol with a volume ratio of 1:1 to 5:1.

It is further preferred that the suspension is subjected to a mechanical movement such as stirring.

Further, in the first optional heating and cooling step the reaction mixture is heated from 23°C (ambient temperature) to an elevated temperature, preferably to the boiling point of the organic solvent or the mixture of the organic solvents and then cooled down to preferably 23°C (ambient temperature) again.

The conditions of the second optional heating and cooling step preferably correspond to the ones as mentioned above.

The step of drying can preferably be carried out at a temperature of 23°C to 70°C, preferably 30°C to 60°C. Alternatively or additionally the drying can preferably be carried out under reduced pressure of 1 to 500 mbar, in particular 10 to 100 mbar.

In step b) the filgotinib from step a) is suspended in aqueous hydrochloric acid. It is preferred that the hydrochloric acid is from 8% HCl_{aq} to 32% HCl_{aq}, more preferably from 10% HCl_{aq} to 28% HCl_{aq}, in particular from 12% HCl_{aq} to 24% HCl_{aq}.

It is further preferred that the suspension is subjected to a mechanical movement such as stirring.

In a preferred embodiment step b) includes stirring for 1 to 24 hours, preferably 2 to 20 hours, in particular 4 to 16 hours. Further, the stirring can be carried out at temperatures of 10 to 60°C, preferably 15 to 55°C, in particular 20° to 50°C.

Step c) of isolating filgotinib hydrochloride can preferably comprise cooling the suspension of step b), preferably to a temperature of 0°C to 20°C, more preferably 2°C to 15°C, in particular 3°C to 10°C.

Further in step c) isolating of filgotinib hydrochloride Form E can preferably be carried out by filtering off the solid. Further, filgotinib hydrochloride Form E can preferably be washed, preferably with half concentrated hydrochloric acid. Subsequently, the filgotinib hydrochloride can preferably be dried. Drying can

preferably be carried out at a temperature of 23°C to 70°C, preferably 30°C to 60°C. Alternatively or additionally the drying can preferably be carried out under reduced pressure of from 1 to 500 mbar, in particular 3 to 45 mbar.

As can seen from the above, isolating filgotinib hydrochloride, in particular filgotinib hydrochloride Form E is easily accessible by a process without the use of complex, time and cost intensive process steps.

An alternative particularly preferred process for preparing filgotinib hydrochloride according to the present invention, in particular filgotinib hydrochloride Form E, is characterized by the following steps:

a') dissolving filgotinib in an organic solvent
b') adding aqueous hydrochloric acid to the solution of step a')
c') isolating filgotinib hydrochloride Form E.

In step a') filgotinib, preferably filgotinib in form of its free base, is dissolved, preferably completely dissolved, in an organic solvent or in a mixture of organic solvents. Filgotinib in form of its free base also refers to polymorphs, solvates and hydrates thereof.

Examples of organic solvent correspond to the ones mentioned above, wherein in the present process water is not considered as organic solvent.

It is further preferred that step a') is carried out under mechanical movement such as stirring.

In step b') aqueous hydrochloric acid can be preferably added to the solution from step a').It is preferred that the hydrochloric acid is from 8% HCl_{aq} to 32% HCl_{aq}, more preferably from 10% HCl_{aq} to 28% HCl_{aq}, in particular from 12% HCl_{aq} to 24% HCl_{aq}.

It is further preferred that while adding aqueous hydrochloric acid to the solution of step a') the suspension is subjected to a mechanical movement such as stirring.

In a preferred embodiment step b') includes further stirring for 1 to 24 hours, preferably 2 to 20 hours, in particular 4 to 16 hours. Further, the stirring can be carried out at temperatures from 10 to 60°C, preferably 15 to 55°C, in particular 20° to 50°C.

Step c') of isolating filgotinib hydrochloride Form E can preferably comprise cooling the mixture of step b'), preferably to a temperature of 0°C to 27°C, more preferably 5°C to 25°C, in particular 15°C to 23°C.

Further, in step c') the isolating of filgotinib hydrochloride Form E can preferably be carried out by filtering off the solid. Further, filgotinib hydrochloride Form E can preferably be washed, preferably with half concentrated aqueous hydrochloric acid. Subsequently, the filgotinib hydrochloride Form E can preferably be dried. Drying can preferably be carried out at a temperature of 23°C to 70°C, preferably 30°C to 60°C. Alternatively or additionally the drying can preferably be carried out under reduced pressure of 1 to 500 mbar, in particular 3 to 45 mbar.

As can seen from the above, isolating filgotinib hydrochloride is easily accessible by a process without the use of complex, time and cost intensive process steps.

A further subject of the present invention is filgotinib hydrochloride having characteristic X-ray powder diffraction peaks at 21.4, 21.7, 22.9, 24.3 and/or 25.1 degrees 2θ (± 0.2 degrees 2θ). This form of filgotinib hydrochloride is hereinafter referred to as polymorphic Form F of filgotinib hydrochloride.

In a preferred embodiment the filgotinib hydrochloride Form F can be characterized by one or more further XRPD diffraction peak(s) at 12.2, 13.4, 13.8, 18.7 and/or 20.6 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present invention filgotinib hydrochloride Form A can be characterized by the XRPD diffraction peak(s) at degrees 2θ ± 0.2 degrees 2θ: 6.7, 7.6, 8.5, 9.3, 9.7, 10.6, 11.5, 12.2, 13.1, 13.4, 13.8, 14.0, 15.5, 16.0, 16.6, 17.0, 17.4, 17.8, 18.0, 18.7, 19.3, 19.7, 20.3, 20.6, 21.0, 21.4, 21.7, 21.9, 22.6, 22.9, 23.3, 24.3, 25.1, 25.7, 25.9, 26.6, 26.9, 27.2, 27.9, 28.2, 29.0, 29.8, 30.3, 30.6, 31.1, 31.6, 32.2, 33.1, 33.8, 34.4, 34.7, 35.1, 36.6, 37.0, 37.5, 38.5, 39.3, 39.8, 41.1, 42.0, 42.5, 43.6, 44.3, 44.9, 46.7, 48.2, 48.8, 49.8, 50.2, 51.3, 51.8, 52.6, 53.4, 54.9.

An XRPD diffraction pattern of filgotinib hydrochloride Form F is shown in Figure 2.

Filgotinib hydrochloride Form F can for example be prepared by exposing filgotinib hydrochloride Form E to 40°C in a closed glass vial for four weeks. The product completely transformed in to filgotinib hydrochloride Form F.

Alternatively, filgotinib hydrochloride Form F can for example be prepared by exposing filgotinib hydrochloride Form E to 40°C and 75% relative humidity in an open glass vial for weeks. The product completely transformed in to filgotinib hydrochloride Form F.

A further subject of the present invention is filgotinib hydrochloride having characteristic X-ray powder diffraction peaks at 14.9, 19.4, 19.9, 24.8 and 28.3 degrees 2θ (± 0.2 degrees 2θ). This form of filgotinib hydrochloride is hereinafter referred to as polymorphic Form A of filgotinib hydrochloride.

In a preferred embodiment the filgotinib hydrochloride Form A can be characterized by one or more further XRPD diffraction peak(s) at 7.1, 9.6, 14.3, 18.6 and/or 26.2 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present invention filgotinib hydrochloride Form A can be characterized by the XRPD diffraction peak(s) at

degrees 2θ ± 0.2 degrees 2θ (intensity %): 7.1 (19), 9.6 (100), 13.2 (11), 13.9 (8), 14.3 (28), 14.9 (10), 15.6 (24), 15.9 (13), 16.2 (9), 16.8 (6), 17.2 (10), 18.6 (35), 19.4 (64), 19.9 (42), 20.4 (12), 20.5 (13), 21.4 (8), 22.4 (7), 22.6 (5), 23.5 (2), 24.3 (26), 24.8 (33), 26.2 (68), 26.7 (47), 27.2 (17), 28.3 (35), 29.4 (10), 30.0 (8), 30.8 (16), 31.5 (13), 33.0 (9), 33.5 (16), 34.1 (3), 36.2 (8), 37.0 (10), 39.1 (7), 40.4 (5), 41.3 (6), 43.1 (7), 44.9 (2), 47.6 (8), 49.8 (6) and 51.7 (3).

Alternatively preferred, filgotinib hydrochloride Form A can be characterized by an FT-IR spectrum showing peaks at the following wave numbers: 3090, 2987, 2943, 2845, 2777, 2436, 2378, 1693, 1647, 1599, 1572, 1524, 1502, 1470, 1454, 1425, 1396, 1350, 1335, 1298, 1282, 1244, 1213, 1169, 1126, 1120, 1066, 1030, 1012, 980, 951, 935, 916, 895, 870, 841, 816, 783, 754, 735, 719, 704, 681, 671, 654, 644, 633, 623, 604.

Filgotinib hydrochloride Form A can for example be prepared by the following steps:

a_A) dissolving filgotinib in organic solvent

b_A) adding aqueous hydrochloric acid

c_A) isolating filgotinib hydrochloride Form A

A further subject of the present invention is filgotinib hydrochloride having characteristic X-ray powder diffraction peaks at 13.7, 16.2, 22.3, 23.2 and 25.5 degrees 2θ (± 0.2 degrees 2θ). This form of filgotinib hydrochloride can be considered as polymorphic Form B of filgotinib hydrochloride.

In a preferred embodiment the filgotinib hydrochloride Form B can be characterized by one or more further XRPD diffraction peak(s) at 12.0, 13.2, 15.5, 18.1 and/or 21.1 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present invention filgotinib hydrochloride Form B can be characterized by the XRPD diffraction peak(s) at

degrees 2θ ± 0.2 degrees 2θ (intensity %): 9.6 (17), 12.0 (55), 13.2 (51), 13.7 (34), 14.3 (32), 15.5 (45), 16.2 (21), 18.1 (52), 21.1 (59), 22.3 (100), 23.2 (99), 23.7 (64), 24.8 (46), 25.5 (81), 26.6 (74), 27.4 (81), 28.7 (29) and 33.5 (31).

Alternatively preferred, filgotinib hydrochloride Form B can be characterized by an FT-IR spectrum showing peaks at the following wave numbers: 3084, 2978, 2922, 2482, 1693, 1649, 1633, 1595, 1560, 1522, 1500, 1473, 1448, 1396, 1356, 1311, 1277, 1250, 1184, 1167, 1130, 1063, 1026, 953, 912, 866, 839, 820, 785, 735, 715, 675, 633.

Filgotinib hydrochloride Form B can for example be prepared by the following steps:

a_B) dissolving filgotinib in a mixture of organic solvents

b_B) adding aqueous hydrochloric acid

c_B) isolating filgotinib hydrochloride Form B

A further subject of the present invention is filgotinib hydrochloride having characteristic X-ray powder diffraction peaks at 8.8, 11.0, 17.7, 21.7 and 22.5 degrees 2θ (± 0.2 degrees 2θ). This filgotinib hydrochloride can be considered as polymorphic Form C of filgotinib hydrochloride.

In a preferred embodiment the filgotinib hydrochloride Form C can be characterized by one or more further XRPD diffraction peak(s) at 7.1, 9.5, 16.3, 21.4 and/or 27.6 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present invention filgotinib hydrochloride Form C can be characterized by the XRPD diffraction peak(s) at degrees 2θ ± 0.2 degrees 2θ (intensity %): 7.1 (38), 7.4 (6), 8.8 (7), 9.5 (13), 11.0 (46), 14.2 (7), 15.0 (4), 15.5 (8), 16.3 (13), 17.3 (21), 17.7 (38), 17.8 (31), 18.6 (11), 19.5 (15), 19.8 (19), 21.4 (100), 21.7 (48), 22.5 (22), 23.3 (7), 23.9 (15), 26.0

(31), 27.6 (45), 28.6 (16), 29.9 (25), 30.9 (10), 32.5 (6), 33.4 (5), 35.4 (10), 37.8 (9), 39.8 (8) and 42.1(3).

Alternatively preferred, filgotinib hydrochloride Form C can be characterized by an FT-IR spectrum showing peaks at the following wave numbers: 3649, 3390, 3091, 3016, 2980, 2928, 2609, 2519, 2386, 2108, 1691, 1647, 1595, 1566, 1522, 1514, 1502, 1444, 1392, 1342, 1313, 1277, 1250, 1184, 1159, 1132, 1068, 1059, 1026, 953, 912, 877, 866, 841, 818, 783, 733, 715, 677, 648, 633, 621.

Filgotinib hydrochloride Form C can for example be prepared by the following steps:

a_C) dissolving filgotinib in a mixture of organic solvents
b_C) heating the mixture to reflux
c_C) adding hydrochloric acid in organic solvent
d_C) isolating filgotinib hydrochloride Form C

A further subject of the present invention is filgotinib hydrochloride having characteristic X-ray powder diffraction peaks at 7.6, 10.4, 10.8, 15.8 and 17.4 degrees 2θ (± 0.2 degrees 2θ). This form of filgotinib hydrochloride can be considered as polymorphic Form D of filgotinib hydrochloride.

In a preferred embodiment the filgotinib hydrochloride Form D can be characterized by one or more further XRPD diffraction peak(s) at 12.0, 18.1, 21.4, 24.2 and/or 27.5 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present invention filgotinib hydrochloride Form D can be characterized by the XRPD diffraction peak(s) at degrees 2θ ± 0.2 degrees 2θ (intensity %): 7.6 (22), 8.5 (1), 10.4 (11), 10.8 (27), 12.0 (25), 12.5 (4), 14.0 (2), 14.4 (6), 15.8 (24), 17.4 (50), 18.1 (22), 19.1 (3), 19.6 (4), 21.4 (100), 22.2 (13), 22.9 (3), 23.7 (16), 24.2 (38), 25.1 (18), 26.3 (7), 26.5 (10), 27.5 (26), 28.4 (17), 29.3 (13), 30.0 (13), 31.0 (11), 31.5 (11), 31.8 (7), 32.9

(6), 33.8 (6), 34.6 (8), 35.9 (8), 36.9 (4), 38.3 (10), 39.0 (17), 42.2 (6), 42.8 (6), 44.3 (4), 45.5 (2), 47.1 (6), 49.9 (4), 51.5 (4) and 53.8 (3).

Alternatively preferred, filgotinib hydrochloride Form D can be characterized by an FT-IR spectrum showing peaks at the following wave numbers: 3429, 3093, 2978, 2924, 2891, 2656, 2605, 2499, 2118, 1695, 1647, 1597, 1566, 1522, 1502, 1446, 1394, 1340, 1311, 1275, 1246, 1188, 1167, 1134, 1061, 1026, 951, 912, 866, 841, 820, 783, 737, 717, 708, 677, 648, 633.

Filgotinib hydrochloride Form D can for example be prepared by the following steps:

a_D) dissolving filgotinib in an organic solvent and heating the solution

b_D) adding hydrochloric acid in organic solvent

c_D) isolating filgotinib hydrochloride Form D

A further aspect of the present invention is filgotinib in form of filgotinib sulfuric acid addition salts, in particular specific polymorphs of filgotinib sulfate.

Thus, a further subject of the present invention is filgotinib sulfate having characteristic X-ray powder diffraction peaks at 11.5, 18.0, 21.3, 22.1 and 23.5 degrees 2θ (± 0.2 degrees 2θ). This filgotinib sulfate can be considered as polymorphic Form S1 of filgotinib sulfate.

In a preferred embodiment the filgotinib sulfate Form S1 can be characterized by one or more further XRPD diffraction peak(s) at 15.8, 19.0, 19.2, 19.7 and/or 21.8 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present invention filgotinib sulfate Form S1 can be characterized by the XRPD diffraction peak(s) at degrees 2θ ± 0.2 degrees 2θ (intensity %): 7.9 (3), 8.8 (4), 11.0 (5), 11.3 (7), 11.5 (16), 11.9 (4), 12.9 (3), 13.1 (3), 14.3 (2), 15.8 (9), 18.0 (27), 19.0 (16), 19.2 (24), 19.7 (37), 20.2 (10), 20.9 (5), 21.3 (21), 21.8 (64), 22.1 (100), 23.5 (30), 23.8 (22), 24.3

(19), 24.7 (10), 25.0 (6), 25.6 (15), 26.5 (13), 27.0 (2), 28.6 (4), 29.1 (8), 29.4 (10), 30.3 (5), 30.7 (6), 31.1 (4), 31.9 (9), 32.2 (3), 33.2 (3), 33.4 (4), 34.5 (3), 35.5 (4), 36.2 (2), 37.1 (2), 38.9 (3), 39.7 (4) and 40.6 (5).

Alternatively preferred, filgotinib sulfate Form S1 can be characterized by an FT-IR spectrum showing peaks at the following wave numbers: 3103, 2982, 2935, 2735, 2580, 1703, 1647, 1601, 1529, 1510, 1452, 1394, 1315, 1196, 1163, 1132, 1045, 1020, 953, 910, 849, 835, 795, 766, 735, 714, 677, 606.

It turned out that filgotinib sulfate, in particular filgotinib sulfate Form S1, shows an improved solubility not only compared to filgotinib free base but also with regard to filgotinib sulfonates.

Further, filgotinib sulfate, in particular filgotinib sulfate Form S1, shows an advantageous hygroscopicity.

Filgotinib sulfate Form S1 can for example be prepared by the following steps:

l) dissolving filgotinib in organic solvent
m) adding sulfuric acid
n) isolating filgotinib sulfate Form S1

In step l) filgotinib, preferably filgotinib in form of its free base, is dissolved, preferably completely dissolved, in an organic solvent or in a mixture of organic solvents. Filgotinib in form of its free base also refers to polymorphs, solvates and hydrates thereof.

Examples of organic solvents are methanol, ethanol, isopropanol, acetone, ethylacetate, dichloromethane, trichloromethane, dioxane, tetrahydrofurane, acetonitrile, diethylether and *tert*-butyl methyl ether. A preferred organic solvent is dichloromethane. Water is preferably not considered as organic solvent.

It is further preferred that step l) is carried out under mechanical movement such as stirring.

In step m) sulfuric acid can preferably be added to the solution from step l).

It is further preferred that while adding the solution of step l) the suspension is subjected to a mechanical movement such as stirring.

In a further preferred embodiment a second organic solvent can be added after the addition of sulfuric acid. Examples of the second organic solvent correspond to the organic solvents mentioned above. In a preferred embodiment the second organic solvent is isopropanol.

In a preferred embodiment step m) includes further stirring for 1 to 24 hours, preferably 2 to 20 hours, in particular 4 to 16 hours.

Step n) of isolating filgotinib sulfate Form S1 can preferably comprise cooling the mixture of step m), preferably to a temperature of 0°C to 27°C, more preferably 5°C to 25°C, in particular 15°C to 23°C.

Further, in step n) isolating filgotinib sulfate Form S1 can preferably be carried out by filtering off the solid. Further, filgotinib sulfate Form S1 can preferably be washed, preferably with dichloromethane. Subsequently, the filgotinib sulfate Form S1 can preferably be dried. Drying can preferably be carried out at a temperature of 23°C to 70°C, preferably of 30°C to 60°C. Alternatively or additionally the drying can preferably be carried out under reduced pressure of 1 to 500 mbar, in particular 3 to 45 mbar.

As can be seen from the above, filgotinib sulfate is easily accessible by a process without the use of complex, time and cost intensive process steps.

A further subject of the present invention is filgotinib sulfate having characteristic X-ray powder diffraction peaks at 4.5, 6.0, 11.4, 16.7 and 22.6 degrees 2θ (± 0.2 degrees 2θ). This filgotinib sulfate can be considered as polymorphic Form S2 of filgotinib sulfate.

In a preferred embodiment the filgotinib sulfate Form S2 can be characterized by one or more further XRPD diffraction peak(s) at 10.5, 15.8, 19.3, 20.9 and/or 25.6 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present invention filgotinib sulfate Form S2 can be characterized by the XRPD diffraction peak(s) at degrees 2θ ± 0.2 degrees 2θ (intensity %): 4.5 (10), 6.0 (12), 6.5 (1), 9.0 (2), 9.5 (5), 10.5 (27), 11.4 (20), 12.0 (55), 12.4 (2), 12.8 (5), 13.1 (1), 13.4 (8), 14.0 (9), 14.5 (6), 15.2 (3), 15.8 (27), 15.9 (32), 16.0 (35), 16.7 (16), 17.5 (8), 18.1 (7), 18.4 (3), 19.2 (29), 19.3 (39), 19.6 (44), 19.8 (54), 20.2 (31), 20.6 (24), 20.8 (69), 20.9 (90), 21.1 (48), 21.4 (10), 21.9 (25), 22.2 (32), 22.6 (100), 22.8 (34), 23.1 (22), 23.4 (14), 23.8 (30), 24.1 (30), 24.2 (44), 24.9 (20), 25.1 (33), 25.6 (88), 26.0 (18), 26.4 (5), 27.3 (12), 27.5 (15), 27.8 (9), 28.2 (13), 28.8 (8), 29.3 (16), 29.9 (11), 30.2 (16), 30.6 (7), 30.8 (11), 31.3 (12), 31.6 (20), 32.2 (11), 32.5 (4), 33.0 (10), 33.5 (6), 33.7 (6), 34.2 (5), 34.8 (4), 35.4 (8), 35.6 (8), 36.5 (2), 37.3 (6), 37.9 (6), 38.4 (5), 39.0 (4), 39.6 (9), 40.3 (4), 41.0 (7), 41.6 (5), 42.6 (9), 43.4 (3), 43.7 (4), 44.5 (7), 45.3 (10), 46.2 (3), 46.9 (4), 47.8 (6) and 48.4 (2).

Alternatively preferred, filgotinib sulfate Form S2 can be characterized by an FT-IR spectrum showing peaks at the following wave numbers: 3421, 3205, 3109, 3010, 2985, 2935, 2602, 2118, 1703, 1647, 1597, 1570, 1506, 1460, 1446, 1402, 1392, 1331, 1309, 1230, 1200, 1155, 1132, 1068, 1045, 1018, 953, 912, 866, 847, 796, 785, 731, 710, 683, 633.

Filgotinib sulfate Form S2 can for example be prepared by the following steps:

l_{S2}) dissolving filgotinib in organic solvent

m_{S2}) warming the solution of step l_{S2})

n_{S2}) adding a second organic solvent

o_{S2}) adding sulfuric acid

p_{S2}) isolating filgotinib sulfuric acid addition salt Form S2

A further subject of the present invention is filgotinib sulfate having characteristic X-ray powder diffraction peaks at 8.4, 12.1, 14.9, 16.9 and 20.0 degrees 2θ (± 0.2 degrees 2θ). This filgotinib sulfate can be considered as polymorphic Form S3 of filgotinib sulfate.

In a preferred embodiment the filgotinib sulfate Form S3 can be characterized by one or more further XRPD diffraction peak(s) at 9.9, 10.4, 20.9, 22.3 and/or 26.0 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present invention filgotinib sulfate Form S3 can be characterized by the XRPD diffraction peak(s) at degrees 2θ ± 0.2 degrees 2θ (intensity %): 5.0 (4), 8.4 (71), 9.1 (8), 9.9 (30), 10.4 (36), 12.1 (100), 13.6 (14), 14.9 (14), 15.2 (8), 15.6 (5), 16.9 (30), 18.3 (7), 18.8 (8), 20.0 (37), 20.9 (38), 22.3 (37), 22.7 (18), 24.2 (26), 25.3 (21), 26.0 (45), 26.6 (10), 27.7 (19), 28.2 (22), 29.1 (8), 29.6 (8), 30.1 (2), 30.9 (8), 31.5 (7), 32.3 (10), 34.2 (4), 34.9 (6), 35.2 (7), 37.0 (7), 37.6 (3), 38.6 (2), 40.6 (8), 41.6 (7) and 42.6 (7).

Alternatively preferred, filgotinib sulfate Form S3 can be characterized by an FT-IR spectrum showing peaks at the following wave numbers: 2983, 2928, 1695, 1649, 1595, 1576, 1525, 1502, 1452, 1394, 1356, 1302, 1271, 1169, 1122, 1074, 1024, 953, 781, 733.

Filgotinib sulfate Form S3 can be for example be prepared by the following steps:

l_{S3}) suspending filgotinib in organic solvent

m_{S3}) warming the solution of step l_{S3})

n_{S3}) adding a second organic solvent

o_{S3}) adding sulfuric acid

p_{S3}) precipitating raw product

q_{S3}) optionally adding water

r_{S3}) isolating filgotinib sulfate Form S3

Step q_{S3}) can preferably be carried out in a humidity chamber. Alternatively, step q_{S3}) can preferably be conducted by applying DVS (dynamic vapour sorption) to the raw product of step p_{S3}, wherein the DVS can preferably be characterized by the differing humidities as follows:

$$40\% \rightarrow 0\% \rightarrow 75\% \rightarrow 95\% \rightarrow 0\% \rightarrow 40\%$$

A further subject of the present invention is filgotinib sulfate having characteristic X-ray powder diffraction peaks at 5.1, 10.1, 13.0, 15.4 and 17.1 degrees 2θ (± 0.2 degrees 2θ). This filgotinib sulfate can be considered as polymorphic Form S4 of filgotinib sulfate.

In a preferred embodiment the filgotinib sulfate Form S4 can be characterized by one or more further XRPD diffraction peak(s) at 11.0, 18.8, 19.7, 22.3 and/or 25.6 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present invention filgotinib sulfate Form S4 can be characterized by the XRPD diffraction peak(s) at degrees 2θ ± 0.2 degrees 2θ (intensity %): 5.1 (49), 9.2 (13), 10.1 (45), 10.3 (17), 11.0 (55), 11.4 (2), 12.0 (3), 13.0 (20), 13.7 (9), 15.4 (29), 15.8 (13), 16.0 (8), 17.1 (27), 18.8 (83), 19.1 (26), 19.7 (100), 21.1 (3), 22.3 (53), 22.8 (27), 23.6 (15), 24.8 (24), 25.6 (56), 26.1 (54), 27.5 (24), 27.8 (35), 28.2 (17), 28.9 (13), 29.2 (13), 30.6 (17), 31.2 (14), 31.8 (7), 32.5 (4), 33.5 (17), 35.0 (3), 36.8 (7), 38.2 (3), 38.7 (3), 39.7 (4), 40.4 (4), 41.2 (9), 41.6 (9), 42.3 (7), 44.3 (4) and 45.6 (6).

Alternatively preferred, filgotinib sulfate Form S4 can be characterized by an FT-IR spectrum showing peaks at the following wave numbers: 2983, 2929, 1695,

1649, 1595, 1574, 1502, 1454, 1394, 1354, 1304, 1271, 1165, 1126, 1024, 953, 843, 818, 781, 733, 717, 708, 683.

Filgotinib sulfate Form S4 can for example be prepared by the following steps:

l_{S4}) suspending filgotinib in organic solvent

m_{S4}) warming the solution of step l_{S4})

n_{S4}) adding a second organic solvent

o_{S4}) adding aqueous sulfuric acid

p_{S4}) optionally adding water

q_{S4}) isolating filgotinib sulfate Form S4

The present filgotinib sulfate polymorphic forms show a superior solubility, compared with filgotinib and even with the corresponding filgotinib sulfonic acid addition salts.

Further, the present filgotinib sulfate shows a low polymorphism, which is advantageous in view of the regulations for pharmaceutical products.

In addition, the present filgotinib sulfates, in particular Form S3 and S4, can be provided essentially free of residual organic solvent. Essentially free of residual organic solvent describes that the corresponding filgotinib sulfate contains an amount of residual organic solvent which is significantly below the concentration limit of an organic solvent as mentioned above with regard to the Guidance for Industry, Q3C-Tables and List.

Examples of organic solvents being referred to as residual organic solvents as well as organic solvents used in the preparation of the above-mentioned filgotinib sulfate polymorphs can be methanol, ethanol, isopropanol, acetone, ethylacetate, dichloromethane, trichloromethane, dioxane, tetrahydrofurane, acetonitrile, diethylether and *tert*-butyl methyl ether, preferably dichloromethane, methanol and a mixture of dichloromethane and methanol.

The present invention furthermore relates to pharmaceutical compositions comprising the compounds of the invention, in particular filgotinib hydrochloride Form E and Form F. The parmaceutical formulation can preferebly be further processed to an oral doasage form, such as a capsule or tablet.

The present pharmaceutical composition and/or the oral dosage form of the present invention can be prepared by the methods well known to a person skilled in the art such as dry and wet granulation and direct compresion.

The pharmaceutical composition can additionally contain one or more pharmaceutically acceptable excipient(s), such as fillers, binders, glidants, disintegrants, lubricants, flow regulating agents and release agents. Suitable excipients are for example disclosed in "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", published by H.P. Fielder, 4th Edition and "Handbook of Pharmaceutical Excipients", 3rd Edition, published by A.H. Kibbe, American Pharmaceutical Association, Washington, USA, and Pharmaceutical Press, London.

The term filler generally means substances which serve to form the body of the tablet in the case of tablets with small amounts of active agent (e.g. less than 60% by weight). This means that fillers "dilute" the active agent(s) in order to produce an adequate tablet compression mixture. The normal purpose of fillers therefore is to obtain a suitable tablet size. Examples of preferred fillers are lactose, lactose derivatives, starch, starch derivatives, treated starch, chitin, cellulose and derivatives thereof, calcium phosphate, calcium hydrogen phosphate, sucrose, calcium carbonate, magnesium carbonate, magnesium oxide, maltodextrin, calcium sulphate, dextrates, dextrin and/or dextrose, hydrogenated vegetable oil. Fillers can be present in an amount of 0 to 80% by weight, preferably in an amount of 10 to 60% by weight of the total weight of the composition.

A binder is generally a substance which is capable of increasing the strength of the resulting dosage form, especially the resulting tablets. Suitable binders are for

example polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, hydroxyethyl cellulose, sugars, dextran, corn starch. Binders can be present in an amount of 0 to 30% by weight, preferably in an amount of 2 to 15% by weight of the total weight of the composition.

Glidants can be used to improve the flowability. Suitable glidants are for example alkaline earth metal salts of fatty acids, like stearic acid. The glidant can be present for example in an amount of 0 to 2% by weight, preferably in an amount of 0.5 to 1.5% by weight of the total weight of the composition.

Disintegrants are compounds which enhance the ability of the dosage form, preferably the ability of the tablet, to break into smaller fragments when in contact with a liquid, preferably water. Suitable disintegrants are for example croscarmellose sodium, sodium carboxymethyl starch, crosslinked polyvinylpyrrolidone (crospovidone), sodium carboxymethylglycolate (such as Explotab) and sodium bicarbonate. The disintegrant can be present in an amount of 0 to 20% by weight, preferably in an amount of 1 to 15% by weight of the total weight of the composition.

A suitable flow regulating agent is for example colloidal silica. The flow regulating agent can be present in an amount of 0 to 8% by weight, preferably in an amount of 0.1 to 3% by weight of the total weight of this composition.

A suitable release agent is for example talcum. The release agent can be present in an amount of 0 to 5% by weight, preferably in an amount of 0.5 to 3% by weight of the total weight of the composition.

It is further preferred that the pharmaceutical composition is processed into an oral dosage form. The oral dosage form, preferably a tablet or a capsule, more preferably a tablet, can preferably be coated, preferably film coated.

In the present invention the following three types of film coatings are possible:

- film coating without affecting the release of the active ingredient,
- gastric juice-resistant film coatings,
- retard film coatings.

Generally, film coatings can be prepared by using film-forming agents such as waxes, cellulose derivatives, poly(meth)acrylate, polyvinylpyrrolidone, polyvinyl acetate phthalate, and/or shellac or natural rubbers such as carrageenan.

It is preferred that the present tablet is coated with a gastric juice-resistant film coating. Alternatively, a capsule comprising a gastric juice-resistant film coating can be used.

The gastric juice-resistant film coating preferably is a film coating being stable in the pH range of about 0.7 to 3.0, which is supposed to be the pH-value of human gastric juice found in the stomach. However, in an environment with a pH value of 5 to 9, which is supposed to be present in the (small) intestine of the human body, the gastric juice-resistant film coating preferably dissolves and the drug can be released.

The gastric juice-resistant film coating (often also referred to as enteric coating) can comprise film-forming agents, for example fats, fatty acids, waxes, alginates, shellac, polyvinyl acetate phthalate, cellulose derivatives such as carboxy methyl ethyl cellulose, cellulose acetate succinate, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, cellulose acetate trimellitate, and meth(acrylic)acid copolymers such as methyl acrylate-methacrylic acid copolymers, methyl methacrylate-methacrylic acid copolymers, Eudragits (for example Eudragit® L30D, Eudragit® L, Eudragit® S).

The coating is preferably free of active ingredient. It is further preferred that the thickness of the coating is usually 10 µm to 2 mm, preferably from 50 to 500 µm.

The preferred coating may comprise a film-forming agent and one or more of the following: lubricant, surfactant, glidant, pigment and water.

The preferred coating according to an embodiment of the present invention can comprise, along with the film-forming agent, e.g. stearic acid as lubricant for plasticizing and dissolving the polymer, sodium lauryl sulfate as a surfactant for wetting and dispersing, talc as glidant, iron oxide yellow and/or titanium oxide as pigment(s) and optionally purified water.

In a preferred embodiment the pharmaceutical composition can be administered one to three times a day, preferably once or twice a day, more preferably once a day.

The present invention further relates to the use of the present compound, in particular filgotinib hydrochloride Form E and Form F, for preparing a pharmaceutical preparation for the treatment of patients with rheumatoid arthritis and other inflammatory diseases.

Experimental part

Analytical Methods

^{1}H-NMR Spectroscopy

Instrument: Varian Mercury 400 Plus NMR Spectrometer, Oxford AS, 400 MHz.

HPLC/UV

Method A:

Instrument:	HP1200
Injection volume:	5 µl
Solvent A:	acetonitrile

Solvent B: 0.01M KH_2PO_4, pH = 2.3

Flow: 1.5 ml/min

Temperature: RT

Column: Supelco C18, 150 * 4.6 mm, 5 µm

time [min]	solvent B [%]
0.00	75
8.00	40
13.00	40
14.00	75
17.00	75

Method B:

Method B corresponds to Method A, wherein the injection volume is amended to be 2 µl and the following solvent gradient profile

time [min]	solvent B [%]
0.00	75
8.00	500
13.00	40
14.00	75
17.00	75

Method C:

Method C corresponds to Method A, wherein the flow is amended to be 1 ml/min and the following solvent gradient profile

time [min]	solvent B [%]
0.00	85
4.00	60
8.00	50
10.00	30
12.00	30
13.00	85
17.00	85

X-Ray Powder Diffraction (XRPD)

The sample was analyzed on a D8 Advance X-ray powder diffractometer (Bruker-AXS, Karlsruhe, Germany). The sample holder was rotated in a plane parallel to its surface at 20 rpm during the measurement. Further conditions for the measurements are summarized in the table below. The raw data were analyzed with the program EVA (Bruker-AXS, Germany). The samples were layered onto a silicon specimen holder.

	standard measurement
Radiation	Cu $K_{\alpha 1/2}$ (λ=1.5406 Å)
Source	38 kV / 40 mA
Detector	Vantec
detector slit	Variable
divergence slit	v6
antiscattering slit	v6
2θ range / °	$2 \leq 2\theta \leq 55$
step size / °	0.017

Fourier Transform (FT) Infrared (IR) Spectroscopy

Instrument: Thermo Nicolet, Avatar 330 FT-IR. Smart Endurance Diamond-ATR.

Software: Omnic Vers. 6.1a. The sample was measured in solid form by placing the sample in the sample holder and directly carrying out the measurement.

Differential Scanning Calorimetry (DSC)

Instrument:	Mettler Toledo DSC 822E coupled with a Mettler Toledo Gas-Flow-Controller TS0800GC1 (Mettler-Toledo GmbH, Gießen, Germany)
Aluminium crucible:	40 µL
Lid:	Perforated
Temperature range:	30°C to 350°C
Heating rate:	10°C/ min
Nitrogen flush:	50 mL / min
Software:	STARe Version. 8.10
Interpretation:	Endothermic modus

Thermogravimetric Analysis (TGA)

Apparatus:	Mettler Toledo TGA/DSC1 (Mettler-Toledo GmbH, Gießen, Germany)
Aluminium crucible:	40 µL (open)
Temperature range:	25°C to 400°C
Heating rate:	10°C/ min
Nitrogen flush:	50 mL / min
Software:	STARe Version. 11.00

Solubility Determination in Aqueous Solvents

75 mg (exactly weighed) test substance was weighed into a glass vial, followed by addition of 3 ml solvent (corresponding buffer system at various pH). A stirring bar was added, the vial was fixed in a block heater at 37°C and the suspension was stirred with approx. 250 rpm. After 15 min and 1 h, samples were withdrawn,

filtered through a 0.2 µm disposable filter, 50 µl of the clear filtrate were diluted with 950 µl DMSO and 2 µl thereof were analyzed by HPLC/UV.

Hygroscopicity

Vapour sorption experiments were performed in the instrument SPSx-1µ (Projekt Messtechnik, Ulm, Germany) at a temperature of 25°C and the humidity cycles as shown below.

Humidity cycle conditions

Cycle	rel. humidity (% RH)		Number of
no.	start value	end value	steps
1	40	0	4
2	5	65	6
3	75	75	1*
4	85	95	1
5	90	0	9
6	5	35	3

*kept constant for 24 hours

Determination of residual solvents by Headspace GC

Sample preparation

Samples were dissolved in 1 ml dimethyl sulfoxide to a final concentration of 50 mg/ml. Calibration was realized with samples containing the solvent of interest in the concentration recommended by ICH guidelines (380 ppm for 1,4-dioxane, 600 ppm dichloromethane, 5000 ppm for ethanol and 3000 ppm for methanol).

Instrument settings

Instrument:	G1888 Network Headspace Sampler coupled with a 7890A GC-System from Agilent Technologies

Column settings	
Column:	HP-624
Column length (i.d.):	30 m (0.25 mm)
Film thickness	1.4 µm
Carrier gas (flow):	He (1.0 ml/min)

Injector settings	
Injector temp.:	220°C
Split:	10:1

Detector settings:	
transfer line	280°C
MS source:	230°C
MS Quadrupole:	150°C
Ionization:	EI+
Detection mode:	Scan (m/z 20 - 300)

Identification by EI spectrum and retention time:

1,4-dioxane:	14.3 min
dichloromethane:	6.8 min
ethanol:	5.2 min
methanol:	4.0 min

Temperature program:	
Initial:	35°C (5 min isotherm)
Rate:	5°C/min
Final:	190°C (9.4 min isotherm)
Total run time:	45.4 min

Headspace settings:	
Oven temp.:	70°C
Loop temp.:	100°C
Transfer temp.:	120°C
Injection loop:	1 ml
vial pressure:	13.5 psi
vial equilibration time:	15 min
pressurize time:	0.2 min
loop fill time:	0.2 min
loop equilibration time:	0.1 min
injection time:	0.5 min
sequence purge time:	20 min

EXAMPLES

Example 1:

N-[5-[4-[(1,1-dioxido-4-thiomorpholinyl)methyl] phenyl] [1,2,4]triazolo[1,5-a]pyridin-2-yl]-cyclopropanecarboxamide (filgotinib free base)

[5-(4-bromomethyl-phenyl)-1,2,4]triazolo[1,5-a]pyridine-2-yl]amide (9 g; 24 mmol) was dissolved in a mixture of methanol (15 ml) and dichloromethane (75 ml). Diisopropylethylamine (8.25 ml; 48.5 mmol) was added. Thiomorpholine dioxide (3.61 g; 26.7 mmol) was added in one portion. The mixture was stirred over night at 23°C. After completion of the reaction the solvent was evaporated. The grey compound was suspended in a mixture of ethyl acetate (100 ml) and

methanol (10 ml) and stirred for 2 hours at 23°C. The product was filtered off and dried under vacuum at 17 mbar and 50°C for 3 hours.

Yield:	9.53 g (92% of theory)
purity (HPLC/UV, method A, t_r= 2.2 min, λ=230 nm):	98.6%
^{1}H-NMR (400 MHz, DMSO-d_6) [δ ppm]	0.74 - 0.86 (m, 4 H) 2.01 (br. s., 1 H) 2.91 (s, 4 H) 3.10 - 3.15 (m, 4 H) 3.75 (s, 2 H) 7.27 (dd, J=6.26, 1.56 Hz, 1 H)7.50 (d, J=8.21 Hz, 2 H) 7.65 - 7.71 (m, 2 H) 7.97 (d, J=8.21 Hz, 2 H) 11.02 (br. s., 1 H)
FT-IR (ATR) [cm^{-1}]	3288, 3230, 3188, 3088, 3057, 3003, 2935, 2843, 2820, 1699, 1635, 1576, 1552, 1525, 1495, 1398, 1369, 1333, 1321, 1298, 1269, 1215, 1186, 1157, 1126, 1113, 1084, 1053, 1038, 1020, 978, 962, 941, 891, 862, 854, 822, 779, 729, 677, 656, 631, 625, 615
XRPD	1st priority reflections 7.1, 8.1, 10.8, 18.4, 27.3°2θ 2nd priority reflections 14.2, 16.2, 17.2, 19.8, 25.2°2θ
DSC	endotherms (onset T):214°C; 319°C (br.)
residual solvent content	0.5.-2% (dichloromethane)

Example 1'

N-[5-[4-[(1,1-dioxido-4-thiomorpholinyl)methyl] phenyl] [1,2,4]triazolo[1,5-a]pyridin-2-yl]-cyclopropanecarboxamide (filgotinib free base)

[5-(4-bromomethyl-phenyl)-1,2,4]triazolo[1,5-a]pyridine-2-yl]amide (25 g; 67.3 mmol) was dissolved in a mixture of methanol (52 ml) and dichloromethane (260 ml). Diisopropylethylamine (23 ml) was added. Thiomorpholine dioxide (10.1 g; 74.1 mmol) was added in one portion. The mixture was stirred over night at 23°C. After completion of the reaction the solvent was evaporated. The grey compound was suspended in a mixture of dichloromethane (180 ml) and methanol (80 ml) and stirred under reflux and nitrogen atmosphere for 30 minutes. The

reaction mixture was slowly cooled to 23°C under stirring. At about 40°C the product began to precipitate. After about one hour at 23°C, a white to off-white thick suspension was formed. Stirring was continued overnight under nitrogen atmosphere at 23°C. The solvent was evaporated at 43°C and to the grey solid was added a mixture of dichloromethane (200 ml) and methanol (80 ml). The suspension was heated to reflux and kept at this temperature for 1.5 hours (suspension became solution), then heating was turned off and the flask was left in the cooling oil bath and stirring was continued overnight. The product was filtered off and washed with 50 ml dichloromethane and dried over night at 40°C and 7 mbar (crop I; 18.07 g).

The mother liquor was evaporated and the remaining grey solid was suspended in ethanol (100 ml) and water (20 ml), heated to reflux and cooled slowly to room temperature. The product was filtered off and suspended in acetone (50 ml), stirring was performed for 30 minutes, then the product was filtered off and dried at 40°C at 7 mbar overnight to yield the product as a brownish solid (7.05 g)

Yield:	25.12 g (64%)
purity (HPLC/UV, method B t_r= 2.2 min, λ=230 nm):	99.0% (crop I), 98.8% (crop II)
FT-IR (ATR) [cm^{-1}] (crop I):	3228, 3132, 3082, 3003, 2918, 2829, 1666, 1637, 1556, 1525, 1510, 1466, 1444, 1414, 1381, 1356, 1342, 1319, 1290, 1267, 1248, 1190, 1167, 1155, 1128, 1107, 1076, 1047, 1022, 953, 924, 852, 795, 727, 687, 661, 634
XRPD (crop I same as crop II)	1st priority reflections 9.2, 10.2, 21.0, 22.9, 29.5°2θ 2nd priority reflections 12.9, 14.1, 16.5, 18.8, 24.3°2θ
DSC (crop I)	endotherms (onset T): 235°C; 327°C (br.)
residual solvent content	0.5-2% (dichloromethane)

Example 2: Filgotinib hydrochloride Form E

In a 10 l glass reactor, 100 g (235 mmol) filgotinib base were mixed with 8 l dichloromethane. While stirring the suspension at 24°C (230 rpm), 52 ml (517 mmol) 32% aqueous HCl were added dropwise within 5 minutes. A white precipitate was formed and the mixture was stirred over night at 23°C.The white product was filtered off and washed with 3 l dichloromethane and dried for two days at 50°C / 10 mbar.

Name:	Filgotinib hydrochloride Form E
Yield:	112.5 g
Purity (HPLC/UV, method B, t_r= 2.4 min, λ=230 nm)	> 99.9%

Example 2': Filgotinib hydrochloride Form E

Filgotinib base, 2.5 g (5.9 mmol) was suspended in a mixture of 32% HCl_{aq} (8.5 ml) and water (8.5 ml) and stirred over 4.5 hours at 45°C. The reaction mixture was cooled to 23°C, stirring was continued over night. The mixture was cooled to 5°C and stirred for approx. 2 hours. The solid was filtrated off, washed with a mixture of 32% HCl_{aq} (1.5 ml) and water (1.5 ml) and dried under vacuum at 50°C/6 mbar over night.

Name:	Filgotinib hydrochloride Form E
Yield:	2.51 g
Purity (HPLC/UV, method B, t_r= 2.4 min, λ=230 nm)	99.5%

The obtained filgotinib hydrodrochloride Form E was free of dichloromethane (residual solvent).

The following data is identical in Examples 2 and 2'

^{1}H NMR (400 MHz, DMSO-d_6) [δ ppm]	0.77 - 0.92 (m, 4 H) 2.02 (br. s., 1 H) 3.67 (br. s., 8 H) 4.58 (s, 2 H) 5.11 - 5.94 (m, 4 H) 7.45 (dd, J=7.23, 1.37 Hz, 1 H) 7.74 - 7.79 (m, 1 H) 7.87 (s, 3 H) 8.10 (d, J=8.60 Hz, 2 H) 11.52 (br. s., 1 H) 12.08 - 13.24 (m, 1 H)
FT-IR (ATR) [cm^{-1}]:	3446, 3348, 3097, 2974, 2895, 2798, 2654 2480, 2374, 1705, 1647, 1591, 1564, 1522, 1504, 1458, 1446, 1425, 1416, 1396, 1348, 1317, 1284, 1254, 1213, 1192, 1153, 1132, 1090, 1066, 1028, 953, 935, 914, 881, 862, 837, 822, 795, 769, 744, 737, 714, 675, 648, 634, 621
XRPD	1st priority reflections 8.0, 10.5, 20.1, 24.0, 25.7 2nd priority reflections 13.9, 18.1, 19.0, 21.1, 23.6
DSC	endotherms: 30-140°C (br.) peak at 106°C, 140-240°C (br.) peak at 205°C, 240-380°C peaks at 270, 293 and 300°C

Example 3: Filgotinib hydrochloride Form F

Filgotinib hydrochloride Form E was exposed to 40°C in a closed glass vial for 4 weeks. The product completely transformed into Form F.

Example 3': Filgotinib hydrochloride Form F

Filgotinib hydrochloride Form E was exposed to 40°C and 75% relative humidity in an open glass vial for 4 weeks. The product completely transformed into Form F.

The filgotinib hydrodrochloride Form F was free of dichloromethane (residual solvent).

Example 4: Filgotinib hydrochloride Form A

In a 500 ml round bottom flask, 5.8 g (13.6 mmol) filgotinib were dissolved in 465 ml dichloromethane. While stirring at 23°C, 2.95 ml (30 mmol) 32% aqueous HCl was added dropwise within 15 minutes. A white precipitate was formed and the mixture was stirred over night at 23°C. The white product was filtered off and washed with 150 ml dichloromethane and dried for 4 hours at 50°C / 27 mbar.

Name	Filgotinib hydrochloride Form A
Yield:	5.4 g (86% of theory)
purity (HPLC/UV, method B, t_r= 2.3 min, λ=230 nm):	98.9%
^{1}H NMR (400 MHz, DMSO-d_6) [δ ppm]	0.81 - 0.91 (m, 4 H) 2.02 (br. s., 1 H) 3.67 (br. s., 8 H) 4.60 (s, 2 H) 7.47 (dd, *J*=7.43, 1.17 Hz, 1 H) 7.77 - 7.80 (m, 1 H) 7.84 - 7.89 (m, 3 H) 8.08 (d, *J*=8.21 Hz, 2 H) 8.93 - 10.51 (m, 1 H) 11.68 (br. s., 1 H)
FT-IR (ATR) [cm^{-1}]:	3090, 2987, 2943, 2845, 2777, 2436, 2378, 1693, 1647, 1599, 1572, 1524, 1502, 1470, 1454, 1425, 1396, 1350, 1335, 1298, 1282, 1244, 1213, 1169, 1126, 1120, 1066, 1030, 1012, 980, 951, 935, 916, 895, 870, 841, 816, 783, 754, 735, 719, 704, 681, 671, 654, 644, 633, 623, 604
XRPD	1st priority reflections 14.9, 19.4, 19.9, 24.8, 28.3 2nd priority reflections 7.1, 9.6, 14.3, 18.6, 26.2
DSC	endotherms: 65°C (br.), 200°C (br.), 257°C (br.) exotherms: 245°C (br.)

The obtained filgotinib hydrodrochloride Form A was free of dichloromethane (residual solvent)

Example 5: Filgotinib hydrochloride Form B

In a 250 ml round bottom flask, 2.0 g (4.7 mmol) filgotinib base were dissolved in a mixture of 160 ml dichloromethane and 4 ml methanol. While stirring at room temperature, 1 ml (10.3 mmol) 32% aqueous HCl was added dropwise within 3 minutes. A white precipitate was formed and the mixture was stirred over night at 23°C. The white product was filtered off and washed with 40 ml dichloromethane and dried for four days at 50°C / 7 mbar.

Name	Filgotinib hydrochloride Form B
Yield:	2.13 g (98% of theory)
purity (HPLC/UV, method B, t_r= 2.2 min, λ=230 nm):	98.3%
^{1}H NMR (400 MHz, DMSO-d_6) [δ ppm]	0.76 - 0.88 (m, 4 H) 2.01 (br. s., 1 H) 3.63 (br. s., 8 H) 4.53 (br. s., 2 H) 4.85 (br. s., 2 H) 7.37 (dd, *J*=6.84, 1.76 Hz, 1 H) 7.71 - 7.79 (m, 2 H) 7.82 (d, *J*=8.21 Hz, 2 H) 8.10 (d, *J*=8.60 Hz, 2 H) 11.25 (br. s., 1 H)
FT-IR (ATR) [cm^{-1}]:	3084, 2978, 2922, 2482, 1693, 1649, 1633, 1595, 1560, 1522, 1500, 1473, 1448, 1396, 1356, 1311, 1277, 1250, 1184, 1167, 1130, 1063, 1026, 953, 912, 866, 839, 820, 785, 735, 715, 675, 633
XRPD	1st priority reflections 13.7, 16.2, 22.3, 23.2, 25.5 2nd priority reflections 12.0, 13.2, 15.5, 18.1, 21.1

The obtained dichloromethane (residual solvent) content of filgotinib hydrochloride Form B was 512 ppm.

Example 6: Filgotinib hydrochloride Form C

In a 100 ml round botton flask 0.5 g (1.18 mmol) filgotinib base were dissolved in a mixture of 40 ml dichloromethane and 2 ml isopropyl alcohol and the mixture

was heated to reflux (approx. 37°C). While maintaining reflux condtions, 1.14 ml (1.4 mmol) 1.25 M HCl in isopropyl alcohol were added dropwise. After completion, the mixture was stirred under reflux for another 40 min, then allowed to cool to 23°C and stirred over night at 23C. The white product was filtered off, washed with 10 ml dichloromethane and dried for 0.5 h at 50°C / 20 mbar. The mother liqour was filtrated with a glass microfibre filter and washed with dichloromethane (10 ml). The combined crops were dried for two days at 40°C and 8 mbar.

Name	Filgotinib hydrochloride Form C
Yield:	0.32 g (59% of theory)
purity (HPLC/UV,method B, t_r= 2.3 min, λ=254 nm):	98.8%
^{1}H NMR (400 MHz, DMSO-d_6) [δ ppm]	0.78 - 0.89 (m, 4 H) 2.01 (br. s., 1 H) 3.66 (br. s., 8 H) 4.57 (s, 2 H) 5.74 (s, 0.17 H (dichloromethane)) 7.18 (br. s, 2 H) 7.42 (dd, *J*=7.23, 1.37 Hz, 1 H) 7.74 - 7.89 (m, 4 H) 8.10 (d, *J*=8.21 Hz, 2 H) 11.44 (br. s., 1 H)
FT-IR (ATR) [cm^{-1}]:	3649, 3390, 3091, 3016, 2980, 2928, 2609, 2519, 2386, 2108, 1691, 1647, 1595, 1566, 1522, 1514, 1502, 1444, 1392, 1342, 1313, 1277, 1250, 1184, 1159, 1132, 1068, 1059, 1026, 953, 912, 877, 866, 841, 818, 783, 733, 715, 677, 648, 633, 621
XRPD	1st priority reflections 8.8, 11.0, 17.7, 21.7, 22.5 2nd priority reflections 7.1, 9.5, 16.3, 21.4, 27.6
DSC	endotherms: 32°C (br.), 85°C (br.), 180°C (br.), 213°C (br.), 201°C (br.)

Example 7: Filgotinib hydrochloride Form D

In a 100 ml round bottom flask, 0.5 g (1.18 mmol) filgotinib base were dissolved in 250 ml 1,4-dioxane and the solution was heated to 85°C. While maintaining this

temperature, 0.65 ml (2.6 mmol) 4 M HCl in 1,4-dioxane were added dropwise within 5 min. After completion, the mixture was stirred at 85°C for another 60 min, then allowed to cool to room temperature and stirred over night at 23°C. The white product was filtered off, washed with 20 ml 1,4-dioxane and dried over night at 50°C / 7 mbar and for another two days at 70°C / 8 mbar.

Name	Filgotinib hydrochloride, Form D
Yield:	0.5 g (92% of theory)
purity (HPLC/UV, method B, t_r= 2.3 min, λ=230 nm):	99.7%
^{1}H NMR (400 MHz, DMSO-d_6) [δ ppm]	0.71 - 0.89 (m, 4 H) 2.01 (br. s., 1 H) 3.34 - 4.02 (m, 8 H (dioxane included) 4.56 (s, 2 H) 6.41 - 7.27 (m, 2 H) 7.41 (dd, *J*=7.04, 1.56 Hz, 1 H) 7.71 - 7.81 (m, 2 H) 7.84 (d, *J*=8.21 Hz, 2 H) 8.10 (d, *J*=8.21 Hz, 2 H) 11.38 (br. s., 1 H)
FT-IR (ATR) [cm^{-1}]:	3429, 3093, 2978, 2924, 2891, 2656, 2605, 2499, 2118, 1695, 1647, 1597, 1566, 1522, 1502, 1446, 1394, 1340, 1311, 1275, 1246, 1188, 1167, 1134, 1061, 1026, 951, 912, 866, 841, 820, 783, 737, 717, 708, 677, 648, 633
XRPD	1st priority reflections 7.6, 10.4, 10.8, 15.8, 17.4 2nd priority reflections 12.0, 18.1, 21.4, 24.2, 27.5
DSC	endotherms: 32°C (br.), 152°C (br.), 185°C (br.), 237°C (br.)

Example 8: Filgotinib sulfate Form S1

0.5 g (0.12 mmol) filgotinib base were dissolved in 40 ml dichloromethane. At 23°C sulfuric acid (0.07 ml) was added in one portion into this solution. A syrupy residue was formed. Isopropyl alcohol (2 ml) was added. The reaction mixture was stirred over night at 23°C, forming a white precipiate. The product was filtered off, washed with dichloromethane (10 ml) and dried for 2.5 hours at 50°C / 20 mbar.

Name	Filgotinib sulfate, Form S1
Yield:	0.67 g (92% of theory)
purity (HPLC/UV, method A, t_r= 2.2 min, λ=230 nm):	91%
^{1}H NMR (400 MHz, DMSO-d_6) [δ ppm]	0.78 - 0.89 (m, 4 H) 1.02 (d, *J*=6.26 Hz, 0.12 H) 1.10 (d, *J*=6.26 Hz, 0.04 H) 2.44 - 2.48 (s, 1 H) 3.57 - 3.63 (m, 4 H) 3.63 - 3.72 (m, 4 H) 4.56 (s, 2 H) 5.73 (s, 0.1 H (DCM)) 7.45 (dd, *J*=7.43, 1.17 Hz, 1 H) 7.55 (dd, *J*=7.63, 1.37 Hz, 0.15 H) 7.72 - 7.76 (m, 3 H) 7.77 - 7.79 (m, 1 H) 7.82 - 7.88 (m, 1 H) 7.95 - 8.05 (m, 1.2 H) 8.07-8.14 (m, 1 H)
FT-IR (ATR) [cm^{-1}]:	3103, 2982, 2935, 2735, 2580, 1703, 1647, 1601, 1529, 1510, 1452, 1394, 1315, 1196, 1163, 1132, 1045, 1020, 953, 910, 849, 835, 795, 766, 735, 714, 677, 606
XRPD	1st priority reflections: 11.5, 18.0, 21.3, 22.1, 23.5 2nd priority reflections 15.8, 19.0, 19.2, 19.7, 21.8
DSC	br. endotherm (30-120°C); br. endotherm (200-320°C) with peaks at 264, 288 and 299°C

Example 9: Filgotinib sulfate Form S2

0.5 g (0.12 mmol) filgotinib base were added to 40 ml dichloromethane and heated to reflux (approx. 35°C). 2 ml methanol were added and 0.4 ml sulfuric acid (30% aqueous solution) were added dropwise at this temperature. The reaction mixture was stirred for 30 min. at 35°C; during stirring a white precipate was formed. Then the reaction mixture was slowly cooled down to 23°C under stirring. The product was filtered off, washed with 10 ml dichloromethane and dried over night at 50°C / 8 mbar.

Name	Filgotinib sulfate, Form S2
Yield:	0.74 g (100% of theory)
purity (HPLC/UV, method B, t_r= 2.2 min, λ=230 nm):	97.5%
^{1}H NMR (400 MHz, DMSO-d_6) [δ ppm]	0.83 - 0.91 (m, 4 H) 1.17 - 1.29 (m, 0.03 H (imp.)) 2.00 (br. s., 1 H) 3.15 (s, 0.27 H (imp.)) 3.37 (s, 0.3 H (imp.)) 3.60 (m, 4 H) 3.69 (m, 4 H) 4.59 (s, 2 H) 5.73 (m, 0.06 H (imp.)) 6.85 - 7.40 (br. s, 8 H) 7.49 (dd, J=7.43, 1.17 Hz, 2 H) 7.56 - 7.63 (m, 1 H) 7.70 - 7.83 (m, 4 H) 7.84 - 7.95 (m, 1 H) 7.97 - 8.06 (m, 0.23 H (imp.)) 8.10 (d, J=8.21 Hz, 2 H) 11.67 (br. s., 1 H)
FT-IR (ATR) [cm^{-1}]:	3421, 3205, 3109, 3010, 2985, 2935, 2602, 2118, 1703, 1647, 1597, 1570, 1506, 1460, 1446, 1402, 1392, 1331, 1309, 1230, 1200, 1155, 1132, 1068, 1045, 1018, 953, 912, 866, 847, 796, 785, 731, 710, 683, 633
XRPD	1st priority reflections 4.5, 6.0, 11.4, 16.7, 22.6 2nd priority reflections 10.5, 15.8, 19.3, 20.9, 25.6
DSC	br. endotherm (30-120°C); br. endotherm (240-320°C) with peaks at 267, 283 and 300°C;

Example 10: Filgotinib sulfate Form S3

2.0 g (4.7 mmol) filgotinib base were added to 80 ml dichloromethane and heated to reflux. 10 drops of methanol were added. The compound was nearly dissolved. While maintaining this temperature, 1.0 ml sulfuric acid (30% aqueous solution) was added dropwise and stirring was continued for 75 minutes. Then the reaction mixture was slowly cooled down to 23°C and stirred over night. The product was filtered off, washed with 30 ml dichloromethane and dried for 5 hours at 50°C/20 mbar. The white product was put into a humidity chamber at 50°C and 100% humidity over night. The obtained solid (white compound) was dried for 7.5 hours

at 50°C/7 mbar. Further, the solid was suspended in 10 ml water. Additional water was added after approximately 15 minutes and stirring was continued over 3.5 hours. The product was filtrated off and died at 50 °C/8mbar overnight. Further, the solid was exposed to a cycle of differing degrees of humidity as shown below:

40% → 0% → 75% → 75% → 95% → 0% → 40%

Name	Filgotinib sulfate, Form S3
purity (HPLC/UV, method B, t_r= 2.3 min, λ=230 nm):	97.5%
^{1}H NMR (400 MHz, DMSO-d_6) [δ ppm]	0.79 - 0.87 (m, 4 H) 2.00 (br. s., 1 H) 3.54 (br. s., 5 H) 3.63 (br. s., 5 H) 4.51 (s, 2 H) 5.74 (s, 0.07 H (DCM)) 7.40 (dd, J=7.04, 1.56 Hz, 1 H) 7.69 - 7.74 (m, 3 H) 7.75 (d, J=1.56 Hz, 1 H) 7.77 - 7.83 (m, 1 H) 8.11 (d, J=8.21 Hz, 2 H) 8.54 - 9.41 (m, 4 H) 11.31 (br. s., 1 H)
FT-IR (ATR) [cm^{-1}]:	2983, 2928, 1695, 1649, 1595, 1576, 1525, 1502, 1452, 1394, 1356, 1302, 1271, 1169, 1122, 1074, 1024, 953, 781, 733
XRPD	1st priority reflections 8.4, 12.1, 14.9, 16.9, 20.0 2nd priority reflections 9.9, 10.4, 20.9, 22.3, 26.0

The obtained filgotinib sulfate Form S3 was free of dichloromethane (residual solvent).

Example 11: Filgotinib sulfate Form S4

A mixture of 4.0 g (9.4 mmol) filgotinib base and 160 ml dichloromethane was heated to reflux and 1 ml methanol was added. While maintaining this temperature, 2.0 ml sulfuric acid (30% aqueous solution) were added dropwise. Precipitation of a solid was observed. Stirring at reflux was continued for 80 minutes. Then, the reaction mixture was slowly cooled down to 23°C and stirred over night. The white

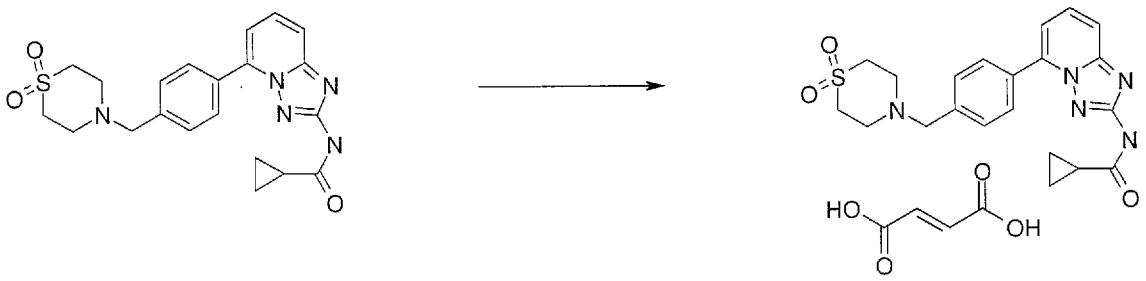
product was filtered off, washed with 80 ml dichloromethane and dried at 50°C / 20 mbar for two days. To this product 27 ml water were added and the mixture was stirred for 15 minutes. Thereafter, another 27 ml water were added and stirring was continued for 3 hours, the product was filtered off and dried over night at 50°C.

Name	Filgotinib sulfate, Form S4
Yield:	3.89 g (79% of theory)
purity (HPLC/UV, method B, t_r= 2.4 min, λ=230 nm)	97.4%
^{1}H NMR (400 MHz, DMSO-d_6) [δ ppm]	0.78 - 0.86 (m, 4 H) 1.89 - 2.10 (m, 1 H) 3.53 (d, *J*=16.03 Hz, 8 H) 4.43 (br. s., 2 H) 7.36 (dd, *J*=6.65, 1.56 Hz, 1 H) 7.69 (d, *J*=8.60 Hz, 2 H) 7.71 - 7.79 (m, 2 H) 8.10 (d, *J*=8.21 Hz, 2 H) 11.20 (br. s., 1 H)
FT-IR (ATR) [cm^{-1}]:	2983, 2929, 1695, 1649, 1595, 1574, 1502, 1454, 1394, 1354, 1304, 1271, 1165, 1126, 1024, 953, 843, 818, 781, 733, 717, 708, 683
XRPD	1st priority reflections 5.1, 10.1, 13.0, 15.4, 17.1 2nd priority reflections 11.0, 18.8, 19.7, 22.3, 25.6

The obtained filgotinib sulfate Form S3 was free of dichloromethane (residual solvent).

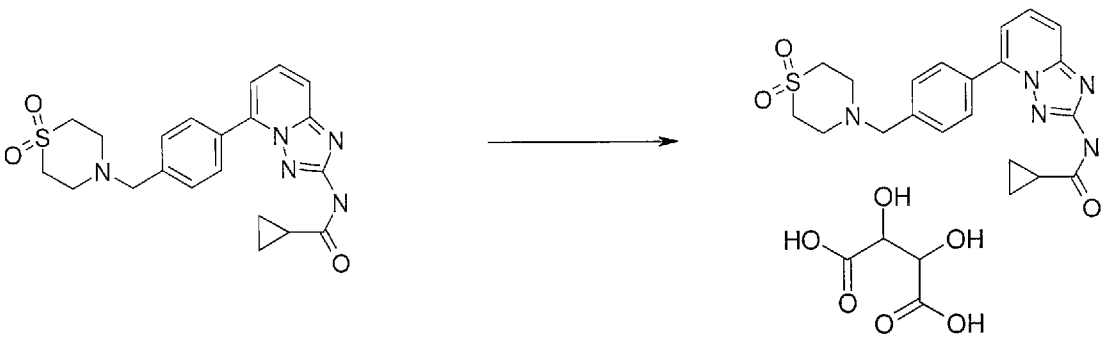
Reference Examples

Reference Example 1: Filgotinib fumarate



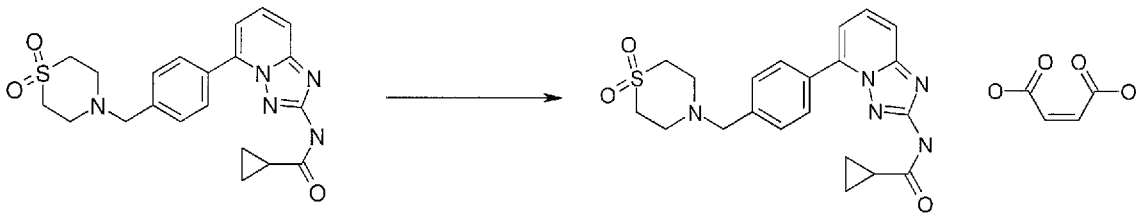
Filgotinib free base (0.5 g) was dissolved in dichloromethane (13 ml) and methanol (2 ml) at room temperature and heated to reflux. Fumaric acid (0.15 g) was dissolved in dichloromethane (17 ml) and methanol (3 ml). The acid solution was dropped into the solution of filgotinib and stirred for 1 hour at reflux temperature, then cooled to 23°C. The reaction mixture was stirred over night, no salt formation could be observed.

Reference Example 2: Filgotinib tartrate



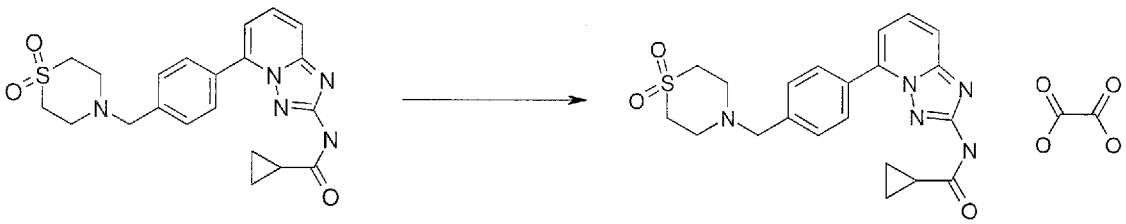
Filgotinib free base (0.5 g) was dissolved in dichloromethane (13 ml) and methanol (2 ml). D-tartaric acid (0.19 g) was dissolved in dichloromethane (17 ml) and methanol (3 ml). The acid solution was dropped into the solution of filgotinib at 50°C. The reaction mixture was stirred for 1 hour and then slowly cooled to 23°C. The reaction mixture was stirred for 3 days, no salt formation could be observed.

Reference Example 3: Filgotinib maleate:



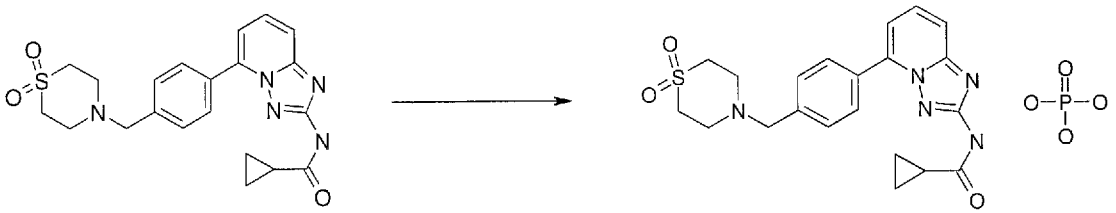
Filgotinib free base (0.5 g) was dissolved at room temperature in dichloromethane (18 ml) and methanol (2 ml) and heated to reflux. Maleic acid (0.47 g) was dissolved in dichloromethane (12 ml) and methanol (2 ml). The acid solution was dropped into the solution of the starting material; stirring was continued for 1 hour at reflux temperature. The reaction mixture was cooled to 23°C. The reaction mixture was left stirring over night, no salt formation could be observed.

Reference Example 4: Filgotinib oxalate



Filgotinib free base (0.5 g) was dissolved in dichloromethane (18 ml) and methanol (2 ml), the reaction mixture was heated to reflux. Oxalic acid (0.12 g) was dissolved in dichloromethane (4.5 ml) and methanol (0.5 ml), the acid solution was dropped into the solution of the starting material and stirred for 1 hour at reflux temperature, then cooled to 23°C. The reaction mixture was stirred over night. No salt formation could be observed.

Reference Example 5: Filgotinib phosphate



a) Filgotinib free base (0.5 g) was dissolved in dichloromethane (40 ml). Phosphoric acid (85%, 0.1 ml) was dropped into this solution at room temperature. The reaction mixture was stirred over night. A syrupy residue was formed, the solvent was decanted off and the substance was dried by evaporating (0.32 g). The solid was milled in a mortar. After storage for 4 days in a closed vial, the solid substance transformed into a syrupy substance by water uptake. In the present case the salt formation was successful, but the corresponding salt is highly instable due to its high hygroscopy and thus not applicable for a pharmaceutical formulation.

b) Filgotinib free base (0.5 g) was dissolved in dioxane (250 ml) at 73°C. Phosphoric acid (anhydrous) (0.254 g) was dissolved in dioxane (20 ml) and added dropwise within 10 min into the solution of the starting material. The reaction mixture was stirred for 45 minutes at 80°C, slowly cooled to 23°C. After stirring over night, the beige product was filtered off and washed with dioxane (20 ml). The solid, filtrated product transformed into a syrupy substance shortly after filtration. Again, in the present case the salt formation was successful, but the corresponding salt is highly instable due to its high hygroscopy and thus not applicable for a pharmaceutical formulation.

Claims:

1. Crystalline filgotinib hydrochloric acid addition salt.

2. Crystalline filgotinib acid addition salt according to claim 1 having a residual solvent content within pharmaceutically acceptable limits.

3. Filgotinib hydrochloride according to claims 1 or 2 having characteristic X-ray powder diffraction peaks at 8.0, 10.5, 20.1, 24.0 and 25.7 degrees 2θ (± 0.2 degrees 2θ).

4. Filgotinib hydrochloride according to claims 1 to 3 having one or more further characteristic X-ray powder diffraction peak(s) at 13.9, 18.1, 19.0, 21.1 and/or 23.6 degrees 2θ (± 0.2 degrees 2θ).

5. Filgotinib hydrochloride according to claims 1 to 4 having characteristic X-ray powder diffraction peaks at 8.0, 8.6, 9.2, 10.5, 11.1, 12.8, 13.0, 13.9, 14.3, 14.8, 15.7, 16.2, 17.1, 17.5, 18.1, 18.6, 19.0, 20.1, 20.4, 21.1, 21.9, 22.9, 23.6, 24.0, 24.3, 25.3, 25.7, 26.2, 26.6, 27.2, 27.8, 28.9, 29.8, 31.1, 31.8, 32.6, 33.4, 35.9, 36.4, 37.8, 38.7, 39.6, 40.4, 41.4, 42.3, 43.7, 44.7, 46.4, 47.6 and 48.7.

6. Process for preparing filgotinib hydrochloride according to any one of claims 1 to 5, characterized by the following steps:

a) providing filgotinib
b) suspending filgotinib from step a) in aqueous hydrochloric acid
c) isolating filgotinib hydrochloride.

7. Filgotinib hydrochloride according to claims 1 or 2 having characteristic X-ray powder diffraction peaks at 21.4, 21.7, 22.9, 24.3 and/or 25.1 degrees 2θ (± 0.2 degrees 2θ).

8. Filgotinib hydrochloride according to claims 1 or 2 and 7 having one or more further characteristic X-ray powder diffraction peak(s) at 12.2, 13.4, 13.8, 18.7 and/or 20.6 degrees 2θ (± 0.2 degrees 2θ).

9. Filgotinib hydrochloride according to claims 1 or 2 and 7 to 8 having characteristic X-ray powder diffraction peaks at 6.7, 7.6, 8.5, 9.3, 9.7, 10.6, 11.5, 12.2, 13.1, 13.4, 13.8, 14.0, 15.5, 16.0, 16.6, 17.0, 17.4, 17.8, 18.0, 18.7, 19.3, 19.7, 20.3, 20.6, 21.0, 21.4, 21.7, 21.9, 22.6, 22.9, 23.3, 24.3, 25.1, 25.7, 25.9, 26.6, 26.9, 27.2, 27.9, 28.2, 29.0, 29.8, 30.3, 30.6, 31.1, 31.6, 32.2, 33.1, 33.8, 34.4, 34.7, 35.1, 36.6, 37.0, 37.5, 38.5, 39.3, 39.8, 41.1, 42.0, 42.5, 43.6, 44.3, 44.9, 46.7, 48.2, 48.8, 49.8, 50.2, 51.3, 51.8, 52.6, 53.4, 54.9.

10. Pharmaceutical composition comprising filgotinib hydrochloride according to any one of claims 1 to 9.

11. Pharmaceutical composition according to claim 10, wherein the pharmaceutical composition is a solid oral dosage form.

12. Compound according to any one of claims 1 to 9 for use in the treatment of systemic diseases, autoimmune diseases or inflammatory diseases, preferably for the use in the treatment of multiple sclerosis, rheumatoid arthritis or psoriasis.

13. Method for treating and/or preventing systemic diseases, autoimmune diseases and/or inflammatory diseases, preferably multiple sclerosis, rheumatoid arthritis, or psoriasis, in particular multiple sclerosis, comprising administering to a subject in need thereof a therapeutically effective amount of the compound according to any one of claims 1 to 5 or claims 7 to 9 or the pharmaceutical composition according to claims 10 or 11.

Figures

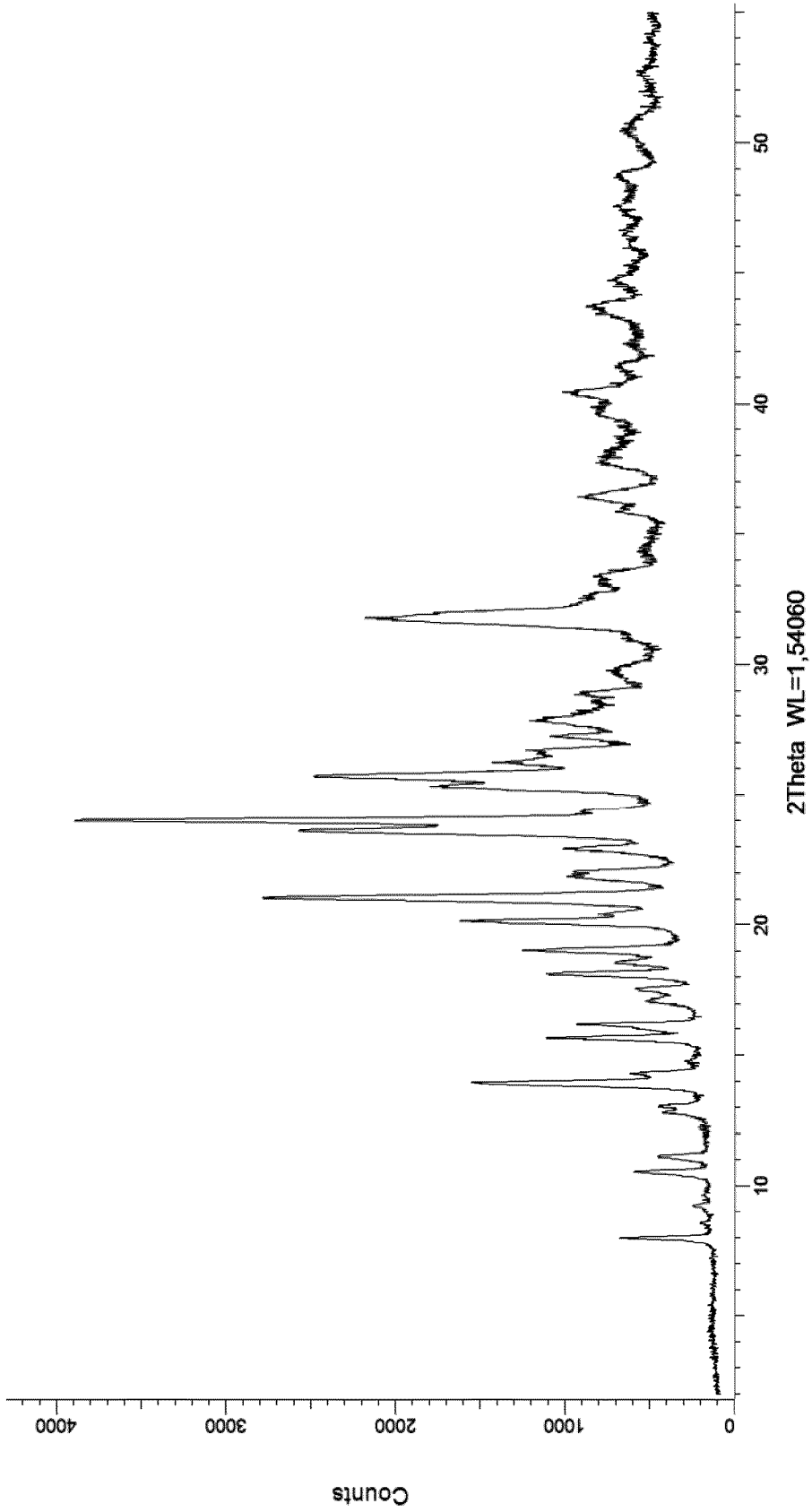


Figure 1: XRD- diffractogram of filgoftinib hydrochloride Form E

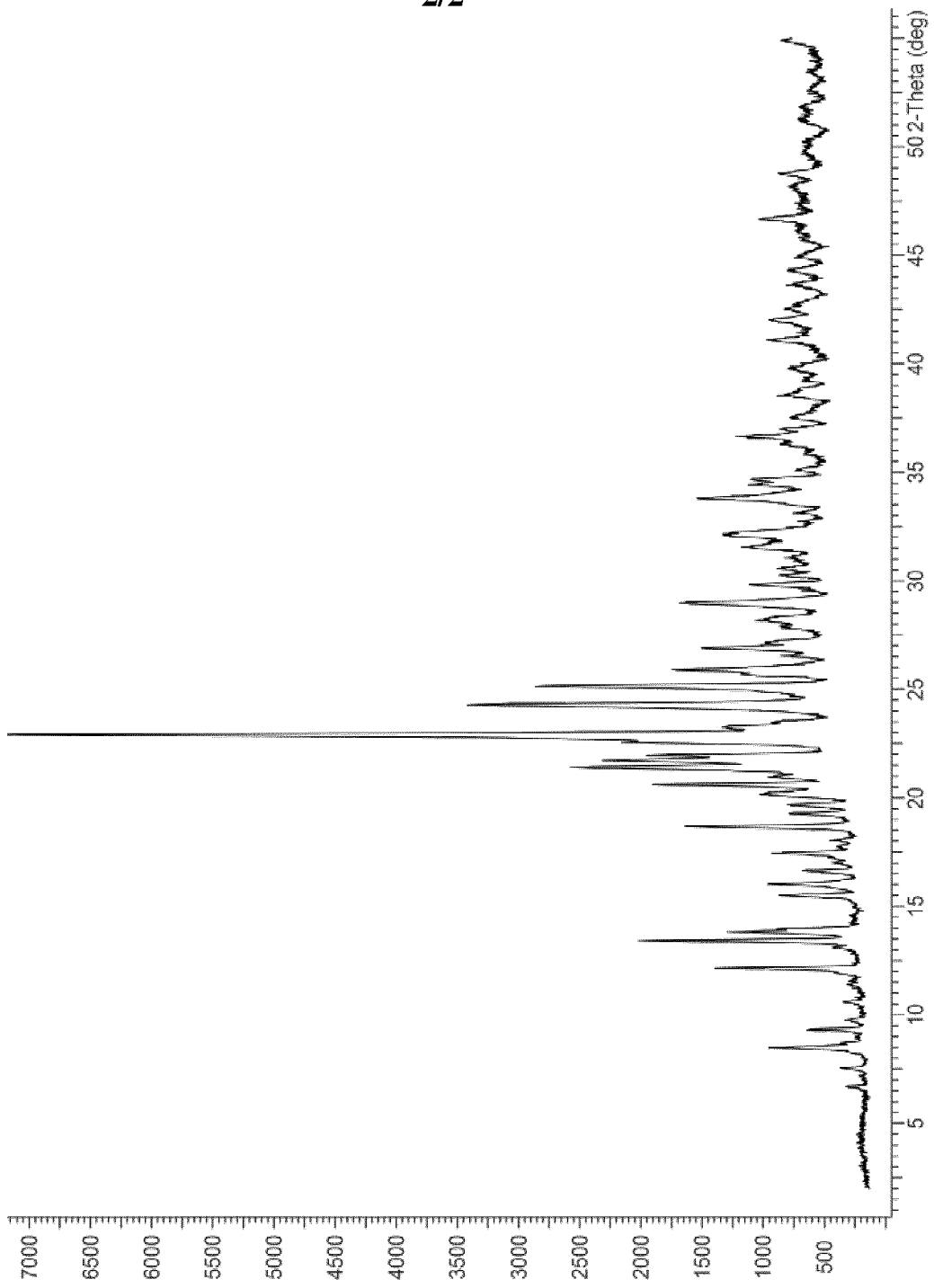


Figure 2: XRD-diffractogram of filgotinib hydrochloride Form F

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/063151

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/43 A61P19/02
ADD.

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)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/149769 A1 (GALAPAGOS NV [BE]) 29 December 2010 (2010-12-29) page 1, line [0001] page 6, line 29, paragraph [0033] page 26, paragraph [00127]; compound 1 page 28, paragraph [00131]; compound 1 page 33, paragraph [00149]; table IIIA page 35, paragraph [00156]; compound 1 page 36, paragraph [00163]; table IIIC claims 1,2,6 -----	1-13

☐ 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

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"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 2016	27/07/2016

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/063151

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