

**Cross-Reference to Related Application**

This application claims priority to and the benefit of UK Patent Application No. 2316063.3, filed October 20, 2023. The entire contents of this application are hereby incorporated by reference herein.

**Field**

The present disclosure relates to methods of treatment or prophylaxis of diseases and conditions in which inhibition of JAK1 function is of therapeutic significance.

**Background**

The JAK (Janus-associated kinase) family includes three receptor bound tyrosine kinases, JAK1, JAK2 and JAK3, and a non-receptor bound member, Tyk2, which all play a critical role in cytokine and growth factor mediated signal transduction (Schindler C 1995). JAK1 interacts with, among others, the receptors of type I interferon (e.g., IFN $\alpha$ ), type II interferon (e.g., IFN $\gamma$ ), the common gamma chain  $\gamma_c$  (e.g., IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21), and the interleukin-6 family (IL-10, IL-13 and IL-22) (O'Shea 2013). After these cytokines bind to their receptors, receptor oligomerization occurs, resulting in the cytoplasmic tails of associated JAK kinases moving into proximity and facilitating the trans-phosphorylation and activation of tyrosine residues on the JAK kinase. Phosphorylated JAK kinases bind and activate various Signal Transducer and Activator of Transcription (STAT) proteins. These STAT proteins then dimerize and translocate to the nucleus where they function as both signalling molecules and transcription factors and ultimately bind to specific DNA sequences present in the promoters of cytokine-responsive genes (Leonard 2000). Various immunodeficiency and autoimmune diseases such as allergies, asthma, alopecia areata, transplant (allograft) rejection, rheumatoid arthritis, amyotrophic lateral sclerosis and multiple sclerosis, and solid and hematologic cancers result from signalling disruption in the JAK/STAT pathway. See for example, Frank 1999, Vijayakrishnan 2011 and Laurence 2012, O'Shea 2013, Ghoreschi 2014, Clark 2014, Ashino 2014 and Herrera 2015.

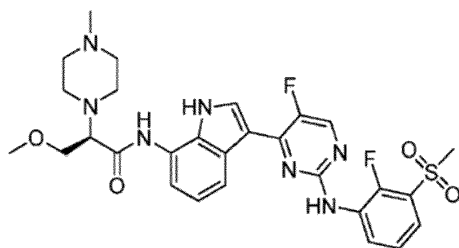
An important element of JAK1 is the ability to pair with other JAK kinases at the intracellular domains of different subunits of the receptor. For example, JAK3 associates with the common gamma chain ( $\gamma_c$ ) of the various cytokine receptors and pairs with JAK1 (Pesu 2008). It has been indicated that JAK1 is dominant over JAK3, and inhibition of JAK1 is sufficient to inactivate signalling through the common gamma chain despite JAK3 activity (Haan 2011). Thus, selective inhibition of JAK1 may be sufficient to treat a number of inflammatory and autoimmune diseases associated with cytokine signalling via the JAK1/JAK3-STAT pathway.

Examples of JAK1 related disorders include, for example, leukaemia, lymphoma, transplant rejection (e.g., pancreas islet transplant rejection, bone marrow transplant applications (e.g., graft-versus-host disease)) and autoimmune/inflammatory diseases (e.g., Type 1 diabetes, allergic reactions, lupus, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial

spondyloarthritis, psoriasis, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease (COPD), vitiligo and alopecia areata.

Asthma is a heterogenous disease, usually characterised by chronic airway inflammation and bronchial hyperreactivity. It is defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity together with variable expiratory airflow obstruction. The JAK1-STAT6 pathway is a particularly attractive target in context of T2 asthma, as the key T2 cytokines, IL-4 and IL-13 activate JAK1, which in turn phosphorylates STAT6 leading to initiation of T2 inflammatory processes including eosinophil recruitment and activation, antibody class switching to immunoglobulin E production, goblet cell hyperplasia and mucus hypersecretion, and airway hyperreactivity and remodelling.

Examples of compounds that possess selective JAK1 inhibition are taught in WO2018/134213, including ((*R*)-*N*-(3-(5-fluoro-2-(2-fluoro-3-(methylsulfonyl)phenylamino)pyrimidin-4-yl)-1*H*-indol-7-yl)-3-methoxy-2-(4-methylpiperazin-1-yl)propanamide with the structure shown below, referred to as a "Compound of Formula I" or "Compound 1."



(I).

WO2018/134213, US2019/367490A1 and US2021/188821A1, the contents of which are hereby incorporated by reference in their entirety, describe additional JAK inhibiting compounds, including various salts of (*R*)-*N*-(3-(5-fluoro-2-(2-fluoro-3-(methylsulfonyl)phenylamino)pyrimidin-4-yl)-1*H*-indol-7-yl)-3-methoxy-2-(4-methylpiperazin-1-yl)propanamide. The synthesis of Compound 1 is described in WO2018/134213 (example 35) and Pithani 2023.

WO2020/016302 and US2020/062737A1, the contents of which are hereby incorporated by reference in their entirety, disclose a xinafoate salt of Compound 1 and a process for preparing said salt.

JAK inhibitors have immunosuppressive properties. The potential risks associated with the administration of Compound 1 are based on non-clinical studies and approved drugs with a similar mechanism of action (i.e., oral JAK inhibitors). In the non-clinical studies, high doses of Compound 1 decreased lymphocyte and eosinophil counts in rats, but only at systemic exposures greater than those expected in humans. Orally administered JAK inhibitors (mainly indicated for rheumatoid arthritis) are associated with various infections such as pneumonia, herpes zoster, urinary tract infections and skin or soft-tissue infections. The risk of pneumonia and herpes zoster has been identified as common adverse reactions for most of the oral JAK inhibitors (tofacitinib). For JAK inhibitors, based on their anti-inflammatory properties, there is a potential risk of adversely influencing the antiviral response. In addition, patients with low absolute

lymphocyte count have an increased risk for serious infections. (Van Vollenhoven 2019). Further, in 2021, the FDA issued a Black Box warning for three oral JAK inhibitors, tofacitinib, baricitinib and upadacitinib in respect to an increased risk of serious heart-related events such as heart attack, stroke, cancer, blood clots and death.

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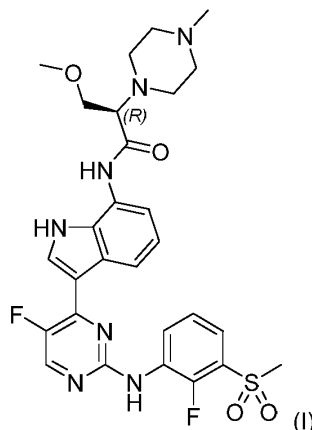
Compound 1 is being developed for the treatment of asthma via inhaled delivery, to maximise local efficacy in the lung. Systemic exposure of Compound 1 is lower than with oral JAK inhibitors, which may lead to a significantly improved safety profile compared to oral JAK inhibitors. To deliver Compound 1 to patients, dosing regimens need to be developed with the aim of providing an efficacious treatment with an improved safety profile, compared with currently approved JAK1 inhibitors.

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### Summary

In some embodiments, disclosed is a method of treatment or prophylaxis of a disease or condition in which inhibition of JAK1 is beneficial, comprising administering to a subject in need thereof, a Compound of Formula (I) (also referred to as Compound 1):

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or a pharmaceutically acceptable salt thereof, in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base.

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In some embodiments, disclosed is a method of treatment or prophylaxis of a disease or condition in which inhibition of JAK1 is beneficial, comprising administering to a subject Compound 1 in a delivered dose of from 0.4 mg to 3.1 mg of the free base twice per day, wherein Compound 1 may be in the form of a pharmaceutically acceptable salt.

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In some embodiments, disclosed is Compound 1, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of a disease or condition in which inhibition of JAK1 is beneficial, wherein said treatment comprises the administration of Compound 1 in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base to said subject.

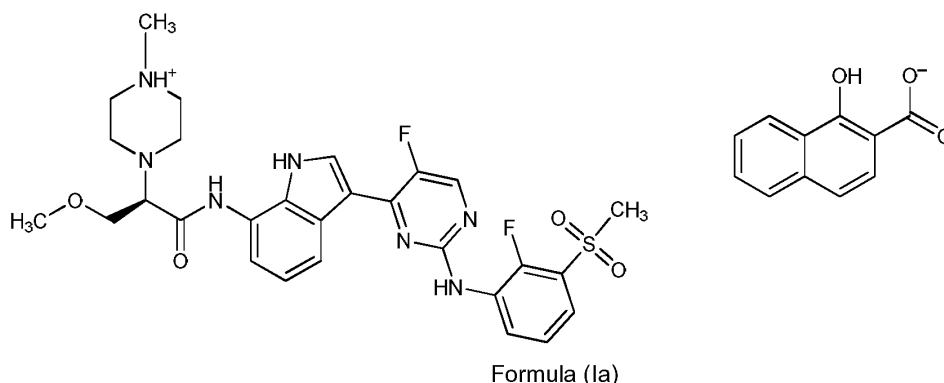
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In some embodiments, disclosed is Compound 1, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of a disease or condition in which inhibition of JAK1 is beneficial, wherein

said treatment comprises the administration of Compound 1 in a delivered dose of from 0.4 mg to 3.1 mg of the free base twice per day to said subject.

In some embodiments, disclosed is the use of a Compound of Formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment or prophylaxis of a disease or condition in which inhibition of JAK1 is beneficial, wherein said treatment comprises administering to the patient a Compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base.

In some embodiments, disclosed is the use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a delivered dose of from 0.4 to 3.1 mg of the free base twice per day. In at least one embodiment, the present disclosure includes Compound 1 prepared as a xinafoate (1-hydroxy-2-naphthoate) salt (Formula (Ia)):



4-((2*R*)-1-[(3-{5-fluoro-2-[2-fluoro-3-(methanesulfonyl)anilino]pyrimidin-4-yl}-1*H*-indol-7-yl)amino]-3-methoxy-1-oxopropan-2-yl)-1-methylpiperazin-1-ium; 1-hydroxynaphthalene-2-carboxylate.

In some embodiments Compound 1 is administered in a daily delivered dose of 0.8 mg, 1.8 mg, 2.8 mg or 6.0 mg of the free base.

In some embodiments Compound 1 is administered in a delivered dose of 1.4 mg twice per day, 0.9 mg twice per day, 0.4 mg twice per day or 3.0 mg twice per day of the free base.

In some embodiments the Compound of Formula (I) is administered as the xinafoate salt in a daily delivered dose of from 1.05 mg to 8.14 mg of the xinafoate salt.

In some embodiments the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 1.84 mg, 1.18 mg, 0.53 mg or 3.94 mg of the xinafoate salt twice per day.

In some embodiments the disease or condition in which inhibition of JAK1 is beneficial is selected from type 1 diabetes, lupus, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic

arthritis, axial spondyloarthritis, psoriasis, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, COPD, vitiligo and alopecia areata.

5 In some embodiments the disease or condition in which inhibition of JAK1 is beneficial is COPD or asthma. In some embodiments the disease or condition in which inhibition of JAK1 is beneficial is COPD. In some embodiments the disease or condition in which inhibition of JAK1 is beneficial is asthma.

10 In some embodiments, disclosed is a kit for use in a method of treatment or prophylaxis of a disease or condition in which inhibition of JAK1 is beneficial, the kit comprising an inhaler which delivers the Compound of Formula (I) in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base, wherein the Compound of Formula (I) may be the form of a pharmaceutically acceptable salt. In some embodiments the inhaler is a dry powder inhaler or a metered dose inhaler.

15 In some embodiments, disclosed is inhaler which is configured to deliver the Compound of Formula (I), in a delivered dose of from 0.4 mg to 3.1 mg of the free base, wherein the Compound of Formula (I) may be the form of a pharmaceutically acceptable salt. In some embodiments the inhaler is a dry powder inhaler or a metered dose inhaler.

20 In a phase 1 study, described in more detail below, it was surprisingly found that no major safety and tolerability concerns were identified in doses up to the highest dose given. There were no serious adverse events reported and no deaths in this part of the study. Overall, all reported adverse events were considered by the Investigator to be mild or moderate in intensity, except for one adverse event which was considered to be of severe intensity.

25 A 50% reduction in the lung inflammation biomarker fractional exhaled nitric oxide (FeNO), versus placebo in participants with mild asthma has been found for both the 1.4 mg and 3.0 mg twice a day dosage. The FeNO data also demonstrates a good effect both before and after dosing, demonstrating that there is 24-hour coverage using the twice daily regime.

30 The 1.4 mg twice a day (BID) dose has been found to be safe and well-tolerated and resulted in approximately 50% reduction in the lung inflammation biomarker FeNO versus placebo in participants with mild asthma. A reduction in FeNO of this magnitude is regarded as a good indication of likely clinical efficacy.

35 The present disclosure includes the combination of the aspects and certain features described except where such a combination is clearly impermissible or expressly avoided.

### **Summary of the Figures**

40 **Figure 1.** shows PK data, geometric mean plasma concentration (nmol/L) of Compound 1 verses time, for phase 1 - part 1a (single ascending dose) of the clinical trial of 7 different dosages administered at day 1.

**Figure 2.** shows PK data, geometric mean plasma concentration (nmol/L) of Compound 1 verses time, for phase 1 - part 1b of the clinical trial of 2 different dosages – 0.3 mg IV and 1mg oral administered at day 1.

**Figures 3 & 4.** show PK data, geometric mean plasma concentration (nmol/L) of Compound 1 verses time, for phase 1 – part 2 (multiple ascending dose, twice a day) of the clinical trial of 3 different dosages – 0.4 mg, 1.4 mg and 3 mg all administered as a dry powder inhaler (DPI) at day 1 (Fig. 3) and at day 7 (Fig. 4).

**Figure 5.** shows the PK data, geometric mean plasma concentration (nmol/L) of Compound 1 verses time, for phase 1 part 3 of the clinical trial following single doses of 1.4 mg and 3 mg of Compound 1 as a dry powder inhaler in patients with mild asthma at day 1.

**Figure 6.** shows the PK data geometric mean plasma concentration (nmol/L) of Compound 1 verses time, for phase 1 part 3 following multiple BID doses of 1.4 mg and 3 mg of Compound 1 as a dry powder inhaler in patients with mild asthma at day 10.

**Figure 7.** shows the FeNO relative change from baseline in 2 hours post-morning dose of Compound 1 (a plot of MMRM analysis by time-point, Part 3, Safety analysis set) of 1.4 mg and 3 mg BID.

**Figure 8.** shows a graphical representation of the Phase 1 (Part 1a (SAD) and Part1b (oral and IV)) clinical trial.

**Figure 9.** shows a graphical representation of the Phase 1 Part 2 clinical trial.

**Figure 10.** shows a graphical representation of the Phase 1 Part 3 clinical trial.

### ***Detailed Description***

Aspects and embodiments will now be discussed with reference to the accompanying figures. Further aspects and embodiments will be apparent to those skilled in the art. All documents mentioned in this text are incorporated herein by reference.

### ***Salt***

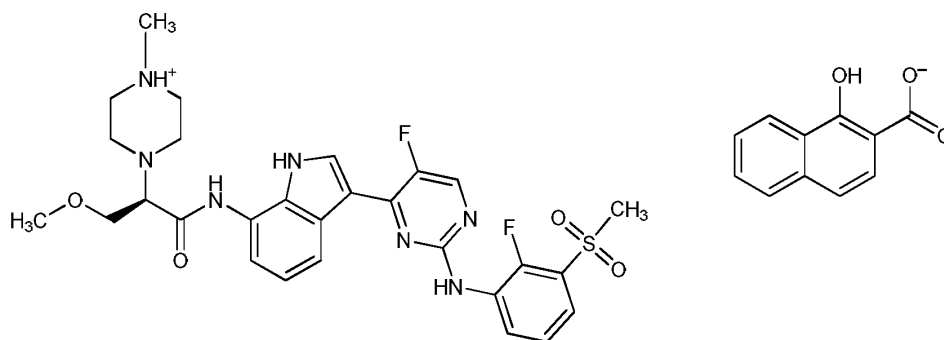
In some embodiments, a free base Compound 1 is administered to a subject. In some embodiments, a pharmaceutically acceptable salt of Compound 1 is administered to a subject. In some embodiments, crystalline Compound 1 or a pharmaceutically acceptable salt of Compound 1 is administered to a subject.

The language "pharmaceutically acceptable salt" includes acid addition salts that retain the biological effectiveness and properties of Compound 1. Pharmaceutically acceptable salts can be formed with inorganic acids or organic acids, such as acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlorotheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, palmoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, subsalicylate, tartrate, tosylate and trifluoroacetate salts. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid,

phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, trifluoroacetic acid, sulfosalicylic acid, and the like.

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In some embodiments Compound 1 is administered as the xinafoate (1-hydroxy-2-naphthoic acid) salt (Formula (Ia)):



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Formula (Ia).

4-((2*R*)-1-[(3-{5-fluoro-2-[2-fluoro-3-(methanesulfonyl)anilino]pyrimidin-4-yl}-1*H*-indol-7-yl)amino]-3-methoxy-1-oxopropan-2-yl)-1-methylpiperazin-1-ium; 1-hydroxynaphthalene-2-carboxylate.

#### Pharmaceutical compositions

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The present disclosure includes, in at least one embodiment, pharmaceutical compositions comprising Compound 1 and a pharmaceutically acceptable excipient, carrier or diluent.

The language "pharmaceutically acceptable excipient, carrier or diluent" includes compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for

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use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable excipients, carriers, and diluents are well known in the art and any selection of actual pharmaceutically acceptable excipients, carriers, and diluents depend on the intended use and method of administration of the pharmaceutical composition.

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Compositions for administration by inhalation and/or insufflation may be in the form of a conventional pressurized aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active

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ingredient. For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

A nebulizer is a drug delivery device used to administer medication in the form of a mist inhaled into the lungs. Different types of nebulizers are known to the skilled person and include jet nebulizers, ultrasonic wave nebulizers and vibrating mesh technology. Some nebulizers provide a continuous flow of nebulized solution, i.e. they will provide continuous nebulization over a long period of time, regardless of whether the subject inhales from it or not, while others are breath-actuated, i.e. the subject only gets some dose when they inhale from it.

A non-pressurised metered-dose inhaler (MDI), also known as a soft mist inhaler, is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of liquid aerosolized medicine. Such a metered-dose inhaler commonly consists of three major components; a canister which comprises the formulation to be administered, a metering valve, which allows a metered quantity of the formulation to be dispensed with each actuation, and an actuator (or mouthpiece) which allows the patient to operate the device and directs the liquid aerosol into the patient's lungs.

A dry powder inhaler (DPI) delivers medication to the lungs in the form of a dry powder. DPIs are commonly used to treat diseases or conditions where topical application to the lungs is beneficial, for example in the treatment of respiratory diseases such as asthma and COPD, although DPIs can also be used to administer medication for other diseases. Examples of DPI devices include the TURBUHALER, GENUAIR and DISKUS.

In some embodiments Compound 1 is administered as an inhaled aerosol dosage form. In some embodiments Compound 1 is administered as a dry powder. In some embodiments Compound 1 is administered using a metered dose inhaler. In some embodiments Compound 1 is administered using a dry powder inhaler.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990. Depending on, for instance, potency and physical characteristics of Compound 1 and pharmaceutically acceptable salts thereof (i.e., active ingredient), pharmaceutical compositions that may be mentioned include those in which the active ingredient is present in at least 1% (or at least 10%, at least 30% or at least 50%) by weight.

#### *Dose*

In some embodiments, Compound 1 or a pharmaceutically acceptable salt thereof is administered orally. In some embodiments Compound 1, or a pharmaceutically acceptable salt thereof is administered by inhalation and/or insufflation. In some embodiments Compound 1 is in the form of a conventional pressurized aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets.

Compound 1 can be delivered to the lungs as a free base (i.e. the active drug) or as a pharmaceutically acceptable salt. The amounts of the free base and the salt will differ slightly, but the same amount of the active ingredient will be delivered from the aerosol.

- 5 The dosages that are referred to are the amount of the active ingredient which is dispensed from the conventional pressurized aerosol. The amount of active ingredient which reaches the lungs can vary due to a number of different factors such as mechanical barriers including the impaction of inhaled drug particles in the mouth and nose, impaction losses in large airways which can restrict delivery to the peripheral lung regions, effects of disease such as airway narrowing, mucus hypersecretion and mucus  
10 plugging and removal of the drug by lung mucociliary clearance.

- As used herein "local exposure" means there are sufficient levels of the of the inhaled Compound 1 present in the lung to interact with the target in the lung. This may occur without detectable target engagement in the blood or measurable concentrations of Compound 1 in the blood or serum. As inhaled dose levels  
15 increase, the level of lung target engagement may increase, and this may also be associated with substantive inhibition of target engagement in the blood and measurable concentrations of Compound 1 in the blood or serum. The term "local lung exposure" refers to the lung concentration of the inhaled Compound 1 that is responsible for its lung target engagement. The reduction of fractional nitric oxide concentration in exhaled breath (FeNO) may be used to determine whether sufficient "local exposure" is  
20 achieved. In some other cases, in particular if the subject is human, since direct measurement of the amount of Compound 1 that remains in the lung is difficult, determination of "local exposure" or "local lung exposure" may be carried out indirectly by determining the amount of Compound 1 that enters the circulatory system.

- 25 In some embodiments Compound 1, is administered to the subject at least once per day. In some embodiments, Compound 1 may be administered to the subject once daily. In some embodiments, Compound 1, may be administered to the subject twice daily.

- In some embodiments Compound 1 is administered to the subject continuously. In some embodiments  
30 Compound 1 is administered to the subject twice a day continuously. In some embodiments Compound 1 is used as a long-term maintenance medicine.

- In some embodiments Compound 1 is administered twice a day at any time of day. In some embodiments Compound 1 is administered at any time of day or night as the subject feels is needed in response to  
35 symptoms. In some embodiments Compound 1 is administered once in the evening and once in the morning. In some embodiments Compound 1 is administered as one inhalation in the morning and one inhalation in the evening. In some embodiments Compound 1 is administered as 2 inhalations either in the morning or evening.

- 40 In some embodiments, the dosages are spaced from 10 to 14 hours. In some embodiments, the dosages are spaced from 11 hours 30 minutes to 12 hours 30 minutes.

In the methods for treating asthma disclosed herein, the delivered dose of Compound 1 is from about 0.8 to about 6.2 mg of the free base per day. The amount of the free base is the amount of active drug i.e. the amount of the active product ingredient (API). A “delivered dose” refers to the dose of Compound 1 that is delivered to a subject, i.e. the dose that comes out or is administered from an inhalation device when applying the device.

In some embodiments Compound 1 is administered in a daily delivered dose of from about 0.8 mg to about 6.2 mg of the free base. In some embodiments Compound 1 is administered in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base in the form of a pharmaceutically acceptable salt. In some embodiments the daily delivered dose may therefore be 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, 1.6 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2.0 mg, 2.1 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.5 mg, 2.6 mg, 2.7 mg, 2.8 mg, 2.9 mg, 3.0 mg, 3.1 mg, 3.2 mg, 3.4 mg, 3.5 mg, 3.6 mg, 3.7 mg, 3.8 mg, 3.9 mg, 4.0 mg, 4.1 mg, 4.2 mg, 4.3 mg, 4.4 mg, 4.5 mg, 4.6 mg, 4.7 mg, 4.8 mg, 4.9 mg, 5.0 mg, 5.1 mg, 5.2 mg, 5.3 mg, 5.4 mg, 5.5 mg, 5.6 mg, 5.7 mg, 5.8 mg, 5.9 mg, 6.0 mg, 6.1 mg or 6.2 mg per day. These dosages refer to the delivered dose of the free base.

In some embodiments the daily delivered dose may be at least 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, 1.6 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2.0 mg, 2.1 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.5 mg, 2.6 mg, 2.7 mg, 2.8 mg, 2.9 mg, 3.0 mg, 3.1 mg, 3.2 mg, 3.4 mg, 3.5 mg, 3.6 mg, 3.7 mg, 3.8 mg, 3.9 mg, 4.0 mg, 4.1 mg, 4.2 mg, 4.3 mg, 4.4 mg, 4.5 mg, 4.6 mg, 4.7 mg, 4.8 mg, 4.9 mg, 5.0 mg, 5.1 mg, 5.2 mg, 5.3 mg, 5.4 mg or 5.5 mg of the free base per day.

In some embodiments Compound 1 is administered in a daily delivered dose of up to 6.2 mg, 6.1 mg, 6.0mg, 5.9 mg, 5.8 mg, 5.7mg, 5.6 mg, 5.5 mg, 5.4 mg, 5.3 mg, 5.2 mg, 5.1 mg, 5.0 mg, 4.9 mg, 4.8 mg, 4.7 mg, 4.6 mg, 4.5 mg, 4.4 mg, 4.3 mg, 4.2 mg, 4.1 mg, 4.0 mg, 3.9 mg, 3.8 mg, 3.7 mg, 3.6 mg, 3.5 mg, 3.4 mg, 3.3 mg, 3.2 mg, 3.1 mg, 3.0 mg, 2.9 mg, 2.8 mg, 2.7 mg, 2.6 mg, 2.5 mg, 2.4 mg, 2.3 mg, 2.2 mg, 2.1 mg, 2.0 mg, 1.9 mg, 1.8 mg, 1.7 mg, 1.6 mg, 1.5 mg, 1.4 mg, 1.3 mg, 1.2 mg, 1.1 mg or 1.0 mg of the free base per day.

In some embodiments Compound 1 is administered in a daily delivered dose of from 2.6 to 3.0mg, from 1.6 to 2.0 mg, from 0.6 to 1.0 mg or from 5.8 to 6.2 mg of the free base. In some embodiments Compound 1 is administered in a daily delivered dose of 2.8 mg of the free base. In some embodiments Compound 1 is administered in a daily delivered dose of 1.8 mg of the free base. In some embodiments Compound 1 is administered in a daily delivered dose of 0.8 mg of the free base. In some embodiments Compound 1 is administered in a daily delivered dose of 6.0 mg of the free base.

In some embodiments, Compound 1 is administered twice a day (bid), bid is an abbreviation meaning two times a day and is commonly used in drug dosing instructions.

In some embodiments Compound 1 is administered in a delivered dose of from 0.4 to 3.1 mg of the free base twice per day. In some embodiments Compound 1 is administered in a delivered dose of 0.4 mg twice per day, 0.45 mg twice per day, 0.5 mg twice per day, 0.6 mg twice per day, 0.65 mg twice per day, 0.7 mg twice per day, 0.75 mg twice per day, 0.8 mg twice per day, 0.85 mg twice per day, 0.9 mg twice per day, 0.95 mg twice per day, 1.0 mg twice per day, 1.05 mg twice per day, 1.1 mg twice per day, 1.15 mg twice per day, 1.2 mg twice per day, 1.25 mg twice per day, 1.3 mg twice per day, 1.35 mg twice per day, 1.4 mg twice per day, 1.45 mg twice per day, 1.5 mg twice per day, 1.55 mg twice per day, 1.6 mg twice per day, 1.65 mg twice per day, 1.7 mg twice per day, 1.75 mg twice per day, 1.8 mg twice per day, 1.85 mg twice per day, 1.9 mg twice per day, 2.0 mg twice per day, 2.05 mg twice per day, 2.1 mg twice per day, 2.15 mg twice per day, 2.2 mg twice per day, 2.25 mg twice per day, 2.3 mg twice per day, 2.35 mg twice per day, 2.4 mg twice per day, 2.45 mg twice per day, 2.5 mg twice per day, 2.55 mg twice per day, 2.6 mg twice per day, 2.7 mg twice per day, 2.75 mg twice per day, 2.8 mg twice per day, 2.85 mg twice per day, 2.9 mg twice per day, 2.95 mg twice per day, 3.0 mg twice per day, 3.05 mg twice per day or 3.1 mg twice per day. These dosages refer to the dose of the free base.

In some embodiments Compound 1 is administered in a delivered dose of at least 0.4 mg twice per day, 0.45 mg twice per day, 0.5 mg twice per day, 0.6 mg twice per day, 0.65 mg twice per day, 0.7 mg twice per day, 0.75 mg twice per day, 0.8 mg twice per day, 0.85 mg twice per day, 0.9 mg twice per day, 0.95 mg twice per day, 1.0 mg twice per day, 1.05 mg twice per day, 1.1 mg twice per day, 1.15 mg twice per day, 1.2 mg twice per day, 1.25 mg twice per day, 1.3 mg twice per day, 1.35 mg twice per day, 1.4 mg twice per day, 1.45 mg twice per day, 1.5 mg twice per day, 1.55 mg twice per day, 1.6 mg twice per day, 1.65 mg twice per day, 1.7 mg twice per day, 1.75 mg twice per day, 1.8 mg twice per day, 1.85 mg twice per day, 1.9 mg twice per day, 2.0 mg twice per day, 2.05 mg twice per day, 2.1 mg twice per day, 2.15 mg twice per day, 2.2 mg twice per day, 2.25 mg twice per day, 2.3 mg twice per day, 2.35 mg twice per day, 2.4 mg twice per day, 2.45 mg twice per day, 2.5 mg twice per day, 2.55 mg twice per day, 2.6 mg twice per day, 2.7 mg twice per day or 2.75 mg twice per day. These dosages refer to the dose of the free base.

In some embodiments Compound 1 is administered in a delivered dose of up to 3.1 mg twice per day, 3.05 mg twice per day, 3.0 mg twice per day, 2.95 mg twice per day, 2.9 mg twice per day, 2.85 mg twice per day, 2.8 mg twice per day, 2.75 mg twice per day, 2.7 mg twice per day, 2.65 mg twice per day, 2.6 mg twice per day, 2.55 mg twice per day, 2.5 mg twice per day, 2.45 mg twice per day, 2.4 mg twice per day, 2.35 mg twice per day, 2.3 mg twice per day, 2.25 mg twice per day, 2.2 mg twice per day, 2.15 mg twice per day, 2.1 mg twice per day, 2.05 mg twice per day, 2.0 mg twice per day, 1.95 mg twice per day, 1.9 mg twice per day, 1.85 mg twice per day, 1.8 mg twice per day, 1.75 mg twice per day, 1.7 mg twice per day, 1.65 mg twice per day, 1.6 mg twice per day, 1.55 mg twice per day, 1.5 mg twice per day, 1.45 mg twice per day, 1.4 mg twice per day, 1.35 mg twice per day, 1.3 mg twice per day, 1.25 mg twice per day, 1.2 mg twice per day, 1.15 mg twice per day, 1.1 mg twice per day, 1.05 mg twice per day, 1.0 mg twice per day, 0.95 mg twice per day, 0.9 mg twice per day, 0.85 mg twice per day, 0.8 mg twice per day, 0.75 mg twice per day, 0.7 mg twice per day, 0.65 mg twice per day, 0.6 mg twice per day, 0.55 mg twice per day, or 0.5 mg twice per day. These dosages refer to the dose of the free base. In some

embodiments the above dosages of the active drug are provided in the form of a pharmaceutically acceptable salt. In some embodiments the pharmaceutically acceptable salt in which the dosages are delivered is the xinafoate salt.

- 5 In some embodiments Compound 1 is administered in a delivered dose of from 1.3 to 1.5 mg of the free base twice per day. In some embodiments Compound 1 is administered in a delivered dose of from 0.8 to 1.0 mg of the free base twice per day. In some embodiments Compound 1 is administered in a delivered dose of from 1.0 mg to 1.3 mg of the free base twice per day. In some embodiments Compound 1 is administered in a delivered dose of from 0.3 to 0.5 mg of the free base twice per day. In
- 10 some embodiments Compound 1 is administered in a delivered dose of from 0.5 to 0.8 mg of the free base twice per day. In some embodiments Compound 1 is administered in a delivered dose of from 1.5 to 1.8 mg of the free base twice per day. In some embodiments Compound 1 is administered in a delivered dose of from 1.8 to 2.1 mg of the free base twice per day. In some embodiments Compound 1 is administered in a delivered dose of from 2.1 to 2.4 mg of the free base twice per day. In some
- 15 embodiments Compound 1 is administered in a delivered dose of from 2.4 to 2.7 mg of the free base twice per day. In some embodiments Compound 1 is administered in a delivered dose of from 2.7 to 2.9 mg of the free base twice per day. In some embodiments Compound 1 is administered in a delivered dose of from 2.9 to 3.1 mg of the free base twice per day. In some embodiments Compound 1 is administered in a delivered dose of 1.4 mg of the free base twice per day.
- 20 In some embodiments Compound 1 is administered in a delivered dose of 0.9 mg of the free base twice per day. In some embodiments Compound 1 is administered in a delivered dose of 0.4 mg of the free base twice per day. In some embodiments Compound 1 is administered in a delivered dose of 3.0 mg of the free base twice per day.

- 25 In some embodiments the above dosages of the active drug are provided in the form of a pharmaceutically acceptable salt. In some embodiments the pharmaceutically acceptable salt in which the dosages are delivered is the xinafoate salt.

- 30 In some embodiments Compound 1 is administered in a delivered dose of from about 0.4 to about 3.0 mg of the active drug twice per day in the form of a pharmaceutically acceptable salt. In some embodiments the pharmaceutically acceptable salt is the xinafoate salt.

- 35 In some embodiments the above dosages of the active drug are provided in the form of a pharmaceutically acceptable salt. In some embodiments the pharmaceutically acceptable salt in which the dosages are delivered is the xinafoate salt.

- 40 In some embodiments Compound 1 is administered as the xinafoate salt in a daily delivered dose of from 1.05 mg to 8.14 mg of the xinafoate salt. In some embodiments Compound 1, is administered in a delivered dose of from about 1.69-1.99 mg of the xinafoate salt twice per day. In some embodiments Compound 1 is administered in a delivered dose of 1.84 mg of the xinafoate salt twice per day. In some embodiments Compound 1 is administered in a delivered dose of from about 1.03 to 1.33 mg xinafoate

salt twice per day. In some embodiments Compound 1 is administered in a delivered dose of 1.18 mg xinafoate salt twice per day. In some embodiments the xinafoate salt of Compound 1, is administered in a delivered dose of from about 0.38 to 0.68 mg xinafoate salt twice per day. In some embodiments the xinafoate salt of Compound 1, is administered in a delivered dose of 0.53 mg xinafoate salt twice per day.

5 In some embodiments Compound 1, is administered in a delivered dose of from about 3.7 to 4.1 mg xinafoate salt twice per day. In some embodiments Compound 1, is administered in a delivered dose of 3.94 mg xinafoate salt twice per day.

The weight equivalent of Compound 1 as a free base in a 1.84 mg of the xinafoate salt is calculated at about 1.4 mg (that is, about 76% of the weight of Compound 1 xinafoate corresponds to the free base, with the remaining about 24% of the weight corresponding to the salt).

10

The weight equivalent of Compound 1 as a free base in a 1.18 mg of the xinafoate salt is calculated at about 0.9 mg (that is, about 76% of the weight of Compound 1 xinafoate corresponds to the free base, with the remaining about 24% of the weight corresponding to the salt).

15

The weight equivalent of Compound 1 as a free base in a 0.53 mg of the xinafoate salt is calculated at about 0.4 mg (that is, about 76% of the weight of Compound 1 xinafoate corresponds to the free base, with the remaining about 24% of the weight corresponding to the salt).

20

The weight equivalent of Compound 1 as a free base in a 3.94 mg of the xinafoate salt is calculated at about 3.0 mg (that is, about 76% of the weight of Compound 1 xinafoate corresponds to the free base, with the remaining about 24% of the weight corresponding to the salt).

25 In some embodiments the dosages listed are for a dry powder inhaler.

In some embodiments the dosages listed are the unit dose dispensed from the inhaler. These are therefore the delivered dosages from the inhaler. In some embodiments the dosages listed are the delivered dose from the dry powder inhaler.

30

#### *Methods*

The language "treat," "treating" and "treatment" includes the inhibition of JAK1 in a subject, amelioration of one or more symptoms of diseases or conditions in which inhibition of JAK1 is beneficial in a subject, or the slowing or delaying of progression of diseases or conditions in which inhibition of JAK1 is beneficial in a subject.

35

The language "prophylaxis" includes the inhibition of JAK1 in a subject to prevent or protect against a disease or condition in which inhibition of JAK1 is beneficial.

40 The language "inhibit", "inhibition" or "inhibiting" includes a decrease in the baseline activity of a biological activity or process.

The term "subject" means human. In some embodiments, the subject is suffering from diseases or conditions in which inhibition of JAK1 is beneficial.

5 In some embodiments, Compound 1 or a pharmaceutically acceptable salt thereof are administered in a treatment cycle. In some embodiments, Compound 1 or a pharmaceutically acceptable salt thereof is continuously administered in the treatment cycle.

10 The term "continuous" or "continuously" refers to administration of a therapeutic agent, e.g. Compound 1, at regular intervals without stopping or interruption, i.e., no void day. By "void day", it is meant a day when a therapeutic agent is not administered.

A "cycle", "treatment cycle" or "dosing schedule", as used herein, refers to a period of treatment that is repeated on a regular schedule. For example, the treatment can be given for one week, two weeks, or three weeks wherein Compound 1 is administered. In some embodiments, a treatment cycle is about 1  
15 week to about 3 months. In some embodiments, a treatment cycle is about 5 days to about 1 month. In some embodiments, a treatment cycle is about 1 week to about 3 weeks. In some embodiments, a treatment cycle is about 1 week, about 10 days, about 2 weeks, about 3 weeks, about 4 weeks, about 2 months, or about 3 months.

20 Phosphorylation of STAT6 in the CD3+ T cell population may be used as a marker for systemic exposure of Compound 1. Determination of STAT6 phosphorylation (pSTAT6) may be carried out by any suitable method known to a person skilled in the art. For example, following administration of Compound 1 to the subject, whole blood may be collected from the subject, stimulated with IL-4 and pSTAT6 in the CD3+ T cell subpopulation assessed using fluorescence-activated cell sorting (FACS). Inhibition of IL-4 stimulated  
25 STAT6 phosphorylation in CD3+ T cells following administration of Compound 1 to the subject indicates systemic exposure of Compound 1. The percentage inhibition of IL-4 stimulated STAT6 phosphorylation in CD3+ T cells by Compound 1 may, for example, be determined relative to a control subject who has not been administered any Compound 1. This may be the same subject (with IL-4 stimulated STAT6 phosphorylation in CD3+ T cells being assessed prior to administration of a Compound 1) or in a different  
30 subject who has not been administered any Compound 1.

Fractional nitric oxide concentration in exhaled breath (FeNO) may be used as a marker to determine the effectiveness of Compound 1 in treating asthma. The person skilled in the art would readily be able to measure FeNO using known techniques, for example a FeNO test is conducted by breathing out slowly and steadily into the mouthpiece attached to a hand-held monitor. The reading shows up on the monitor,  
35 with the result of the FeNO test showing how inflamed the airways are. A commonly used FeNO test is the American Thoracic Society (ATS) 2005 test.

The percentage reduction of FeNO by Compound 1 may, for example, be determined relative to a control subject who has not been administered any Compound 1. This may be the same subject (with FeNO being  
40 assessed prior to administration of Compound 1) or in a different subject who has not been administered any Compound 1. A placebo may have been administered to this different subject.

In some embodiments Compound 1 is used in the treatment of JAK1 related disorders. JAK1 related disorders include, for example, Type 1 diabetes, lupus, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriasis, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, COPD, vitiligo and alopecia areata.

In some embodiments the JAK1 related disorder to be treated is asthma. In some embodiments the JAK1 related disorder to be treated is mild asthma. In some embodiments the asthma is mild and in patients with elevated FeNO.

10

In some embodiments the JAK1 related disorder to be treated is COPD.

In some embodiments Compound 1 is used for the treatment of asthmatics that are symptomatic despite treatment with medium-high dose ICS-LABA.

15

In some embodiments, disclosed is a method of treatment or prophylaxis of asthma, comprising administering to a subject Compound 1 in a daily delivered dose of 0.8 mg to 6.2 mg of the free base wherein Compound 1 may be in the form of a pharmaceutically acceptable salt.

In some embodiments, disclosed is Compound 1, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of asthma, wherein said treatment comprises the administration of Compound 1 in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base, to said subject. In some embodiments, disclosed is the use of Compound 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment or prophylaxis of asthma, wherein said treatment comprises administering to the patient Compound 1 in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base.

25

In some embodiments, disclosed is a method of treatment or prophylaxis of COPD, comprising administering to a subject Compound 1 in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base, wherein Compound 1 may be in the form of a pharmaceutically acceptable salt.

30

In some embodiments, disclosed is Compound 1, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of COPD, wherein said treatment comprises the administration of Compound 1 in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base, to said subject.

In some embodiments, disclosed is the use of Compound 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment or prophylaxis of COPD, wherein said treatment comprises administering to the patient Compound 1 in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base.

35

#### 40 **Preclinical studies**

Safety and tolerability information from preclinical toxicology studies is summarised below:

Inhalation administration of Compound 1 xinafoate has been tolerated in toxicology studies in the rat (up to 6-months) and dog (up to 9-months). In the rat, reductions in respiratory rate and tidal volume have been observed, however these changes were not observed in the dog. Pathological changes consistent with irritation have been observed in the respiratory tract, but at dose levels greater than those to be used clinically. Infections were detected in several dogs at the highest dose level tested in the 9-month toxicology study, however no infections occurred at the lower dose levels, at which achieved systemic exposures were greater than those expected clinically.

\*\*\*

## 10 **Examples**

### EXAMPLE 1 – Phase 1 clinical trial part 1a and 1b

#### *Phase 1*

The study investigated the safety and preliminary clinical efficacy of Compound 1 in patients with asthma. Part 1 was a first in human clinical study and assessed the safety and tolerability, as well as the single dose pharmacokinetics (PK) of inhaled Compound 1 in healthy volunteers. A total of 54 healthy participants were exposed to Compound 1 at doses from 0.3 to 6 mg as single doses and 18 healthy participants at doses from 0.4 to 3 mg BID as multiple doses. In these healthy participants, Compound 1 was found to be safe and well-tolerated. Figures 8 shows a graphical representation of the Phase 1 (Part 1a (SAD) and Part1b (oral and IV)) clinical trial, in which the following abbreviations are used: DPI - Dry Powder Inhaler, IV - Intravenous, PO - oral, SAD - single ascending dose, SRC - Safety Review Committee.

#### *Part 1a*

Part 1a includes a single dose administration at ascending dose with a dry powder inhaler formulation of Compound 1. Seven dose levels (0.025 mg, 0.1 mg, 0.3 mg, 1 mg, 2 mg, 4 mg, and 6 mg) of Compound 1 were investigated. Dosing for each ascending dose cohort proceeded with 2 subjects in a sentinel sub-cohort, such that 1 subject received Compound 1 and one subject received placebo. Subjects received a single inhaled dose of Compound 1 or the corresponding placebo on Day 1.

30

Summary of adverse events (AEs) for part 1a:

- Headache (10 events) was the most frequently reported AE for subjects who were administered Compound 1.
- The number of events reported for the other AEs were all less than 3.
- 35 ▪ The number of events for AEs reported for subjects who were administered placebo were all less than 3. There were no deaths or SAEs reported.
- At least 1 AE was reported across 23 (53.5%) subjects who were administered Compound 1 and for 7 (50.0%) subjects who were administered placebo.
- Overall, all reported AEs were considered by the Investigator to be mild or moderate in intensity, except for an AE of syncope experience by one subject on Day 11 that was considered by the Investigator to be of severe intensity. The subject was administered 0.3 mg of Compound 1.
- 40

Part 1b

In part 1b Compound 1 was administered as a single intravenous (IV) or per os (PO) oral dose to two different cohorts of healthy volunteers. The main purpose was to compare the PK between IV, oral and inhaled administration. Part 1b is an open-label, single-dose study, consisting of 2 dose cohorts. Subjects received either a single intravenous (IV) (0.3 mg) or oral (PO [per os]) (1 mg) dose of Compound 1 on Day 1. Dosing for IV and PO cohorts were proceeded by a sentinel subject.

Dose in Intravenous and Oral Cohort(s)

The dose for the IV cohort was 0.3 mg. The IV dose was selected based on PK predictions (from pre-clinical PK) that the dose was high enough to allow for quantification of plasma Compound 1 levels 24 hours after dosing. The dose was also selected to be low enough not to exceed the pre-defined exposure safety limits. The predicted exposure for the single IV dose is well below the maximum allowed exposure (1.7% of Cmax, 1.2% of AUC(0-24)).

The dose for the PO cohort was 1 mg. The PO dose was selected based on PK predictions (from pre-clinical PK) that the dose was high enough to allow for quantification of plasma Compound 1 levels 24 hours after dosing. The dose was also selected to be low enough not to exceed the pre-defined exposure safety limits. The predicted exposure for the single PO dose is well below the maximum allowed exposure (3.2% of Cmax, 3.1% of AUC(0-24)).

Summary of adverse events for part 1b

- There were no deaths or SAEs reported.
- Slightly more AEs (5 AEs) were reported for the subjects who were administered Compound 1 0.3 mg IV than the subject who was administered Compound 1, 1 mg PO (2 AEs).
- Overall, all reported AEs were considered by the Investigator to be mild or moderate in intensity.

**Objectives and outcome measures - Part 1a**

Table 1 – Phase 1 Part 1a primary objectives and outcome measures

| Primary Objective                                                                                                                    | Outcome Measures                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| To assess the safety and tolerability of Compound 1 following inhaled administration of single ascending doses to healthy volunteers | <ul style="list-style-type: none"><li>• Incidence of Adverse Events,</li><li>• Vital signs (supine Blood Pressure, pulse, respiratory rate, and body temperature),</li><li>• 12-lead Electrocardiograms (ECG),</li><li>• 12-lead Digital electrocardiogram (dECG),</li><li>• Telemetry,</li><li>• Physical examination,</li><li>• Laboratory assessments (hematology, clinical chemistry, and urinalysis),</li><li>• Spirometry,</li><li>• End-tidal CO<sub>2</sub>,</li></ul> |

|  |                                                                                                                                                                    |
|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <ul style="list-style-type: none"> <li>• Capillary blood gas, and</li> <li>• Oxygen saturation SpO<sub>2</sub> (Peripheral capillary oxygen saturation)</li> </ul> |
|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Table 2 - Phase 1 Part 1a secondary objectives and outcome measures

| Secondary Objectives                                                                                                 | Outcome Measures                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| To characterize the plasma PK of Compound 1 following inhaled administration of single ascending doses of Compound 1 | <p>PK concentrations and PK parameters:</p> <ul style="list-style-type: none"> <li>• C<sub>max</sub> (Maximum observed plasma concentration),</li> <li>• T<sub>max</sub> (Time to reach maximum observed concentration following drug administration),</li> <li>• <math>\lambda_z</math> (Terminal elimination rate constant, estimated from linear regression of the terminal part of the log concentration versus time curve),</li> <li>• <math>t_{1/2\lambda_z}</math> (Half-life associated with terminal slope (<math>\lambda_z</math>) of a semi logarithmic concentration-time curve),</li> <li>• Partial area under the plasma concentration-time curve from time 0 to 12 hours AUC(0-12),</li> <li>• Partial area under the plasma concentration- time curve from time 0 to 24 hours AUC(0-24),</li> <li>• Area under the plasma concentration curve from zero to the last quantifiable concentration AUC<sub>last</sub>,</li> <li>• Area under plasma concentration-time curve from zero to infinity (AUC<sub>inf</sub>) represents the total drug exposure across time,</li> <li>• CL/F: Apparent total body clearance of drug from plasma after extravascular administration;</li> <li>• Volume of distribution (apparent) at steady state following extravascular administration (based on terminal phase) V<sub>z</sub>/F,</li> <li>• AUC<sub>last</sub>/D- Dose normalized AUC<sub>last</sub>, derived by AUC<sub>last</sub> divided by the dose administered,</li> <li>• AUC<sub>inf</sub>/D - Dose normalized AUC<sub>inf</sub>, derived by AUC<sub>inf</sub> divided by the dose administered,</li> <li>• C<sub>max</sub>/D Dose normalized C<sub>max</sub> derived by C<sub>max</sub> divided by the dose administered,</li> <li>• Time of last observed (quantifiable) concentration (t<sub>last</sub>)</li> </ul> |

Table 3 – Phase 1 Part 1a Exploratory Objectives and outcome measures

| Exploratory Objectives                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Outcome Measures                                                                                                                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| To investigate Ig (immunoglobulin) concentrations                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Total Ig (immunoglobulin), total IgE (Immunoglobulin E)                                                                                                  |
| To assess the taste of Compound 1 following inhaled administration of single ascending doses to healthy volunteers                                                                                                                                                                                                                                                                                                                                                                                        | Standardized taste questionnaire                                                                                                                         |
| An Exposure Response (E-R) analysis may be conducted of Heart Rate corrected QT (ECG interval measured from the onset of the QRS complex to the end of the T wave) data from this study alone or in combination with other studies as appropriate, with a pre-specified workflow described in a separate technical document, for the QTc (QT interval corrected for heart rate) parameter, as part of the cardiac safety evaluation and with the intention to obtain a TQT (Thorough QT) study substitute | Dynamic Electrocardiograms dECGs                                                                                                                         |
| To evaluate systemic target engagement                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Peripheral Interleukin-4 (IL-4) induced STAT6 (Signal transducer and activator of transcription 6) phosphorylation                                       |
| To investigate the presence of metabolites of Compound 1 in plasma                                                                                                                                                                                                                                                                                                                                                                                                                                        | Analyze plasma samples for the presence of any metabolites. Results will be used to guide future investigations of exposure to metabolites of Compound 1 |
| To evaluate the effect of Compound 1 on cough frequency in healthy volunteers when compared with placebo                                                                                                                                                                                                                                                                                                                                                                                                  | Cough frequency monitoring                                                                                                                               |

## Part 1b

Table 4 – Phase 1 Part 1b (IV or PO dose) primary objectives and outcome measures

| Primary Objective                                                                                                     | Outcome Measures                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| To characterize the plasma PK of Compound 1 following IV and PO administration of a single dose to healthy volunteers | PK concentrations and PK parameters: <ul style="list-style-type: none"> <li>• C<sub>max</sub> (Maximum observed plasma concentration),</li> <li>• T<sub>max</sub> (Time to reach maximum observed concentration following drug administration),</li> <li>• λ<sub>z</sub> (Terminal elimination rate constant, estimated from linear regression of the terminal part of the log concentration versus time curve),</li> <li>• t<sub>1/2</sub>λ<sub>z</sub> (Half-life associated with terminal slope (λ<sub>z</sub>) of a semi logarithmic concentration-time curve),</li> </ul> |

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <ul style="list-style-type: none"> <li>• Partial area under the plasma concentration-time curve from time 0 to 12 hours AUC(0-12),</li> <li>• Partial area under the plasma concentration- time curve from time 0 to 24 hours AUC(0-24),</li> <li>• Area under the plasma concentration curve from zero to the last quantifiable concentration AUClast,</li> <li>• Area under plasma concentration-time curve from zero to infinity (AUCinf) represents the total drug exposure across time,</li> <li>• CL/F: Apparent total body clearance of drug from plasma after extravascular administration; CL: Total body clearance of drug from plasma after intravascular administration,</li> <li>• CL: Total body clearance of drug from plasma after intravascular administration,</li> <li>• Volume of distribution (apparent) at steady state following extravascular administration (based on terminal phase) <math>V_z/F</math>,</li> <li>• <math>V_z</math>: Volume of distribution following intravascular administration (based on terminal phase)</li> <li>• AUClast/D- Dose normalized AUClast, derived by AUClast divided by the dose administered,</li> <li>• AUCinf/D - Dose normalized AUCinf, derived by AUCinf divided by the dose administered,</li> <li>• <math>C_{max}/D</math> Dose normalized <math>C_{max}</math> derived by <math>C_{max}</math> divided by the dose administered,</li> <li>• Time of last observed (quantifiable) concentration (tlast)</li> </ul> |
|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Table 5 – Phase 1 Part 1b (IV or PO dose) secondary objectives and outcome measures

| Secondary Objectives                                                                                                          | Outcome Measures                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| To assess the safety and tolerability of Compound 1 following IV and PO administration of a single dose to healthy volunteers | <ul style="list-style-type: none"> <li>• Incidence of Adverse Events,</li> <li>• Vital signs (supine blood pressure, pulse, respiratory rate, and body temperature),</li> <li>• 12-lead electrocardiograms (ECG),</li> <li>• 12-lead digital electrocardiogram dECG,</li> <li>• Telemetry,</li> <li>• Physical examination,</li> <li>• Laboratory assessments (hematology, clinical chemistry, and urinalysis),</li> <li>• End-tidal CO<sub>2</sub>,</li> </ul> |

|                                                                                                            |                                                                                                                                                                                                                                                                                                    |
|------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| To assess renal clearance of Compound 1 following IV administration of a single dose to healthy volunteers | Where possible the following PK parameters will be assessed: CLR (Renal clearance of drug from plasma), fe(t1-t2) - Cumulative percentage of dose excreted unchanged in urine from time t1 to time t2, Ae(t1-t2) - Cumulative amount of unchanged drug excreted into urine from time t1 to time t2 |
|------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Table 6 – Phase 1 Part 1b (IV or PO dose) Exploratory Objectives and outcome measures

| Exploratory Objectives                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Outcome Measures                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| To investigate Ig concentrations                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Total Ig (immunoglobulin), total IgE (Immunoglobulin E) |
| An Exposure Response (E-R) analysis may be conducted of Heart Rate corrected QT (ECG interval measured from the onset of the QRS complex to the end of the T wave) data from this study alone or in combination with other studies as appropriate, with a pre-specified workflow described in a separate technical document, for the QTc (QT interval corrected for heart rate) parameter, as part of the cardiac safety evaluation and with the intention to obtain a TQT (Thorough QT) study substitute | Dynamic electrocardiograms dECGs                        |

PK data for Part 1a

- 5
- It was found that Compound 1 was rapidly absorbed following single doses with median tmax ranging from 0.07 to 0.14 hours post dose. Following Cmax, plasma concentrations declined rapidly to 0.5-hour post dose. The t1/2λz was consistent ranging from 28.6 to 31.0 hours. There was no dose-dependent effect on PK across the 1 to 6 mg dose range. It was also found that between-subject variability based on geometric CV ranged from 21.0 to 79.0 % for Cmax and 13.0 to 45.1 % for AUC(0-24).

10

The PK data for part 1a is shown in Table 7:

Table 7 - PK day 1 data for part 1a of the study.

| PK Day 1                            |                                   | Compound 1 DPI Dose                    |                                       |                                     |                                     |
|-------------------------------------|-----------------------------------|----------------------------------------|---------------------------------------|-------------------------------------|-------------------------------------|
| Parameter (Units)                   | Statistic                         | 0.025 mg (N = 6)                       | 0.1 mg (N = 6)                        | 0.3 mg (N = 7)                      | 1 mg (N = 6)                        |
| AUCinf (h*nmol/L)                   | Geomean (CV%)<br>Min - Max<br>[n] | NC<br>NC                               | 3.656 (17.73)<br>2.87 - 4.64<br>[6]   | 17.17 (15.53)<br>14.0 - 20.9<br>[7] | 73.15 (16.95)<br>60.0-90.6<br>[6]   |
| AUC(0-12) (h*nmol/L)                | Geomean (CV%)<br>Min - Max<br>[n] | NC<br>NC                               | 1.612 (14.29)<br>1.38 - 1.95<br>[6]   | 5.107 (15.18)<br>4.07 - 6.28<br>[7] | 18.48 (32.30)<br>13.3 - 28.4<br>[6] |
| AUC(0-24) (h*nmol/L)                | Geomean (CV%)<br>Min - Max<br>[n] | NC<br>NC                               | 2.521 (14.78)<br>2.08 - 3.02<br>[6]   | 8.359 (14.10)<br>6.91 - 9.88<br>[7] | 31.06 (30.11)<br>22.8 - 46.6<br>[6] |
| AUClast (h*nmol/L)                  | Geomean (CV%)<br>Min - Max<br>[n] | NC<br>NC                               | 1.474 (31.17)<br>1.02 - 2.38<br>[6]   | 12.40 (15.69)<br>10.3 -15.3<br>[7]  | 60.09 (24.02)<br>45.1 - 79.5<br>[6] |
| Cmax (nmol/L)                       | Geomean (CV%)<br>Min - Max<br>[n] | 0.2015 (23.19)<br>0.164 - 0.253<br>[4] | 0.6519 (36.18)<br>0.394 - 1.11<br>[6] | 2.205 (79.04)<br>1.33 - 7.23<br>[7] | 4.979 (48.45)<br>2.25 - 7.87<br>[6] |
| tmax (h)                            | Median<br>Min - Max<br>[n]        | 0.08<br>0.07 - 0.08<br>[4]             | 0.08<br>0.07 - 0.10<br>[6]            | 0.08<br>0.07 - 0.13<br>[7]          | 0.08<br>0.05 - 0.10<br>[6]          |
| t <sub>1/2</sub> λ <sub>z</sub> (h) | Geomean (CV%)<br>Min - Max<br>[n] | NC<br>NC                               | 13.62 (13.75)<br>11.2 - 15.9<br>[6]   | 25.12 (13.39)<br>19.2 - 29.0<br>[7] | 31.03 (25.63)<br>22.5 - 43.4<br>[6] |
| CL/F (L/h)                          | Geomean (CV%)<br>Min - Max<br>[n] | NC<br>NC                               | 45.62 (17.73)<br>35.9 - 58.2<br>[6]   | 29.15 (15.53)<br>23.9 - 35.8<br>[7] | 22.80 (16.95)<br>18.4 - 27.8<br>[6] |
| VzF (L)                             | Geomean (CV%)<br>Min Max [n]      | NC<br>NC                               | 896.6 (12.80)<br>739 - 1080<br>[6]    | 1056 (13.85)<br>901 - 1320<br>[7]   | 1020 (39.12)<br>597 - 1430<br>[6]   |

| PK Day 1                            |                                   | Compound 1 DPI Dose                 |                                     |                                     |
|-------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Parameter (Units)                   | Statistic                         | 2 mg (N = 6)                        | 4 mg (N = 6)                        | 6 mg (N = 6)                        |
| AUCinf (h*nmol/L)                   | Geomean (CV%)<br>Min - Max<br>[n] | 123.6 (42.81)<br>67.6 - 183<br>[6]  | 254.1 (25.74)<br>193 - 349<br>[6]   | 355.1 (22.20)<br>244 - 450<br>[6]   |
| AUC(0-12) (h*nmol/L)                | Geomean (CV%)<br>Min - Max<br>[n] | 31.86 (48.98)<br>13.8 - 46.6<br>[6] | 67.66 (23.12)<br>49.3 - 85.7<br>[6] | 104.2 (9.221)<br>91.6 - 119<br>[6]  |
| AUC(0-24) (h*nmol/L)                | Geomean (CV%)<br>Min - Max<br>[n] | 53.88 (45.11)<br>25.1 - 77.6<br>[6] | 114.6 (21.85)<br>85.8 - 147<br>[6]  | 172.0 (13.03)<br>138 - 202<br>[6]   |
| AUClast (h*nmol/L)                  | Geomean (CV%)<br>Min - Max<br>[n] | 116.6 (44.41)<br>61.6 - 173<br>[6]  | 243.7 (24.47)<br>188 - 324<br>[6]   | 343.0 (20.87)<br>239 - 422<br>[6]   |
| Cmax (nmol/L)                       | Geomean (CV%)<br>Min - Max<br>[n] | 10.48 (58.51)<br>3.69 - 17.6<br>[6] | 18.78 (46.55)<br>11.3 - 31.5<br>[6] | 21.09 (20.95)<br>16.6 - 25.6<br>[6] |
| tmax (h)                            | Median<br>Min - Max<br>[n]        | 0.07<br>0.05 - 0.10<br>[6]          | 0.12<br>0.10 - 0.12<br>[6]          | 0.14<br>0.10 - 0.28<br>[6]          |
| t <sub>1/2</sub> λ <sub>z</sub> (h) | Geomean (CV%)<br>Min - Max<br>[n] | 31.01 (13.38)<br>23.7 - 33.7<br>[6] | 29.15 (21.48)<br>21.7 - 37.9<br>[6] | 28.62 (14.17)<br>24.9 - 35.1<br>[6] |
| CL/F (L/h)                          | Geomean (CV%)<br>Min - Max        | 26.98 (42.81)<br>18.3 - 49.3        | 26.25 (25.74)<br>19.1 - 34.6        | 28.17 (22.20)<br>22.2 - 41.1        |

|                      | [n]                          | [6]                               | [6]                               | [6]                               |
|----------------------|------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| V <sub>z</sub> F (L) | Geomean (CV%)<br>Min Max [n] | 1207 (39.68)<br>849 - 2390<br>[6] | 1104 (20.78)<br>869 - 1520<br>[6] | 1163 (14.67)<br>973 - 1480<br>[6] |

SAD: Single ascending dose; DPI: Dry powder inhaler; N: Number of subjects in the pharmacokinetic set; n: Number of subjects in analysis; Geoman: geometric mean; Max: Maximum; Min: Minimum; CV: geometric coefficient of variance (%); NC: Not Calculated

- 5 This data is also represented in Figure 1, in which:

| Dose   | 0.1 mg | 0.3 mg | 1 mg | 2 mg | 4 mg | 6mg |
|--------|--------|--------|------|------|------|-----|
| Symbol | ●      | ○      | I    | □    | ▽    | ★   |

#### PK data for Part 1b

- It was found that following 0.3 mg IV and 1 mg oral dosing, the geometric mean  $t_{1/2\lambda z}$  of Compound 1 was 23.8 and 30.6 hours, respectively. In the IV cohort, 3/6  $t_{1/2\lambda z}$  values and all the  $t_{1/2\lambda z}$  values in the oral cohort were calculated over a period of < 3x the resultant half-life, hence the terminal phase may not be fully characterized in these cohorts. Despite the different PK collection timepoints, the geometric mean  $t_{1/2\lambda z}$  values were similar between the IV, oral and inhaled (Part 1a SAD1 to 6 mg range: 28.6 to 31.0 hours) cohorts, indicating consistent rates of Compound 1 elimination for the three dose routes. The estimated probable oral bioavailability of Compound 1 based on geometric mean AUC<sub>inf</sub> values was 36.0%. Between-subject variability based on geometric CV following IV and oral dosing was 42.9 and 44.1 % for C<sub>max</sub>, respectively, and 17.4 and 38.1 % for AUC(0-24), respectively.
- Excretion as Compound 1 in urine was low following a single IV dose of 0.3 mg Compound 1, with the arithmetic mean percentage of dose excreted [fe(0-48)] at 8.25 % and an arithmetic mean CLR of 1.77 L/h.

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The PK data for part 1b is shown in the tables 8 and 9 below.

Table 8 – PK day 1 data for part 1b

| PK Day 1                       |                                 | Compound 1 Dose                     |                                       |
|--------------------------------|---------------------------------|-------------------------------------|---------------------------------------|
| Parameter (Units)              | Statistic                       | 0.3 mg IV (N=6)                     | 1 mg Oral (N = 6)                     |
| AUC <sub>inf</sub> (h*nmol/L)  | Geomean (CV%)<br>Min-Max<br>[n] | 30.80 (12.29)<br>25.3 - 36.7<br>[6] | 36.98 (33.70)<br>21.9 – 50.5<br>[6]   |
| AUC(0-12) (h*nmol/L)           | Geomean (CV%)<br>Min-Max<br>[n] | 11.14 (18.77)<br>8.41 - 14.2<br>[6] | 8.310 (43.98)<br>4.90 – 13.8<br>[6]   |
| AUC(0-24) (h*nmol/L)           | Geomean (CV%)<br>Min-Max<br>[n] | 16.49 (17.37)<br>13.0 – 20.3<br>[6] | 14.86 (38.12)<br>9.37 – 23.1<br>[6]   |
| AUC <sub>last</sub> (h*nmol/L) | Geomean (CV%)<br>Min-Max<br>[n] | 23.35 (14.82)<br>19.7 – 28.9<br>[6] | 26.66 (39.04)<br>15.1 – 40.0<br>[6]   |
| C <sub>max</sub> (nmol/L)      | Geomean (CV%)<br>Min-Max<br>[n] | 7.577 (42.88)<br>3.50 – 11.1<br>[6] | 0.8609 (44.07)<br>0.554 – 1.48<br>[6] |
| t <sub>max</sub>               | Geomean (CV%)                   | 0.33                                | 4.51                                  |

|                                     |                |                    |                    |
|-------------------------------------|----------------|--------------------|--------------------|
| (h)                                 | Min-Max<br>[n] | 0.27 – 0.37<br>[6] | 1.48 – 8.00<br>[6] |
| $t_{1/2\lambda z}$                  | Geomean (CV%)  | 23.78 (24.73)      | 30.59 (39.82)      |
| (h)                                 | Min-Max<br>[n] | 18.3 – 32.4<br>[6] | 22.3 – 65.1<br>[6] |
| CL/F or CL                          | Geomean (CV%)  | 16.24 (12.29)      | 45.10 (33.70)      |
| (L/h)                               | Min-Max<br>[n] | 13.6 – 19.8<br>[6] | 33.0 – 76.2<br>[6] |
| V <sub>z</sub> /F or V <sub>z</sub> | Geomean (CV%)  | 557.2 (26.40)      | 1990 (43.18)       |
| (L)                                 | Min-Max<br>[n] | 414 – 761<br>[6]   | 1180 – 3100<br>[6] |

DPI: Dry Powder inhaler; IV: Intravenous; N: Number of subjects in the pharmacokinetic analysis set; n: Number of subjects included in analysis; Geomean: geometric mean; Max: Maximum; Min: Minimum; CV: geometric coefficient of variance (%)

5 This day 1 data is also represented in Figure 2, in which:

|        |        |      |
|--------|--------|------|
| Dose   | 0.3 mg | 1 mg |
| Symbol | ○      | I    |

Excretion as Compound 1 in urine was low following a single IV dose of 0.3 mg Compound 1, with the arithmetic mean percentage of dose excreted [fe(0-48)] at 8.25 % and an arithmetic mean CLR of 1.77 L/h.

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Table 9 - PK day 1 data for part 1b

| Parameter (Units)  | Statistic            | 0.3mg IV Compound 1 (N = 6) |
|--------------------|----------------------|-----------------------------|
| fe(0-48) (%)       | Arithmetic mean (SD) | 8.249 (1.710)               |
|                    | Geometric mean (CV%) | 8.087 (22.73)               |
|                    | Min-Max [n]          | 5.54-10.1 [6]               |
| CLR(0-48)<br>(L/h) | Arithmetic mean (SD) | 1.773 (0.4245)              |
|                    | Geometric mean (CV%) | 1.735 (22.47)               |
|                    | Min-Max [n]          | 1.41-2.51 [6]               |

IV: Intravenous; N: Number of subjects in the pharmacokinetic analysis set; n: Number of subjects included in the analysis; SD: standard deviation; CV: geometric coefficient of variance (%); Max: Maximum; min: Minimum

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EXAMPLE 2 - Phase 1 clinical trial part 2 and 3

Phase 1 clinical trial Part 2

Part 2 (multiple ascending dose [MAD]) started when at least 4 cohorts in Part 1a (SAD) have been completed. In Part 2 (MAD), Compound 1 was administered at multiple doses (twice daily [BID], 7 days) to healthy volunteers. In Part 2 of the study, safety, tolerability, and multiple-dose PK will be examined. The multiple-dose administration will be performed with DPI-formulated Compound 1. Part 2 was a randomized, single-blind, placebo-controlled, multiple ascending dose (MAD), sequential group design. Three dose levels (0.4 mg, 1.4 mg, and 3 mg) of Compound 1 were investigated. Dosing for each ascending dose cohort proceeded with 2 subjects in a sentinel sub-cohort, such that 1 subject received

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Compound 1 and one subject received placebo. Subjects received twice daily (BID) inhaled doses of Compound 1 or placebo on Day 1 to Day 6 (12 hour [± 30 min] intervals between doses), and a single inhaled dose on Day 7.

5 Figure 9 shows a graphical representation of the Phase 1 Part 2 clinical trial, in which  $N = x(y+z)$  represents the number of healthy volunteers where x is the total, y is the numbered administered Compound 1, z is the number administered the placebo. The following abbreviations are used in Figure 9: DPI - Dry Powder Inhaler, IV - Intravenous, PO - oral , MAD – multiple ascending dose, SRC - Safety Review Committee.

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Table 10 – Part 2 Primary objective and outcome measures

| Primary Objective                                                                                                                      | Outcome Measures                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| To assess the safety and tolerability of Compound 1 following inhaled administration of multiple ascending doses to healthy volunteers | <ul style="list-style-type: none"><li>• Incidence of Adverse Events,</li><li>• Vital signs (supine blood pressure, pulse, respiratory rate, and body temperature),</li><li>• 12-lead electrocardiograms (ECG),</li><li>• 12-lead digital electrocardiogram dECG,</li><li>• Telemetry,</li><li>• Physical examination,</li><li>• Laboratory assessments (hematology, clinical chemistry, and urinalysis),</li><li>• Spirometry,</li><li>• Capillary blood gas, and oxygen saturation SpO2 (peripheral capillary oxygen saturation)</li></ul> |

Table 11 - Phase 1 Part 2 Secondary objective and outcome measures

| Secondary Objectives                                                                                                           | Outcome Measures                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|--------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| To characterize the plasma PK of Compound 1 following inhaled administration of multiple ascending doses to healthy volunteers | <p>PK concentrations and PK parameters:</p> <ul style="list-style-type: none"> <li>• C<sub>max</sub> (Maximum observed plasma concentration),</li> <li>• T<sub>max</sub> (Time to reach maximum observed concentration following drug administration),</li> <li>• λ<sub>z</sub> (Terminal elimination rate constant, estimated from linear regression of the terminal part of the log concentration versus time curve),</li> <li>• t<sub>1/2</sub>λ<sub>z</sub> (Half-life associated with terminal slope (λ<sub>z</sub>) of a semi logarithmic concentration-time curve),</li> <li>• Partial area under the plasma concentration- time curve from time 0 to 24 hours AUC(0-24),</li> <li>• AUC<sub>τ</sub> - Area under plasma concentration-time curve in the dose interval</li> <li>• Area under the plasma concentration curve from zero to the last quantifiable concentration AUC<sub>last</sub>,</li> <li>• CL/F: Apparent total body clearance of drug from plasma after extravascular administration;</li> <li>• Volume of distribution (apparent) at steady state following extravascular administration (based on terminal phase) V<sub>z</sub>/F,</li> <li>• AUC<sub>last</sub>/D- Dose normalized AUC<sub>last</sub>, derived by AUC<sub>last</sub> divided by the dose administered,</li> <li>• AUC<sub>τ</sub>/D - Dose normalized AUC<sub>τ</sub>, derived by AUC<sub>τ</sub> divided by the dose administered,</li> <li>• C<sub>max</sub>/D Dose normalized C<sub>max</sub> derived by C<sub>max</sub> divided by the dose administered,</li> <li>• R<sub>ac</sub> AUC -Accumulation ratio for AUC<sub>τ</sub>;</li> <li>• R<sub>ac</sub> C<sub>max</sub> - Accumulation ratio for C<sub>max</sub></li> <li>• Time of last observed (quantifiable) concentration (t<sub>last</sub>)</li> </ul> |
| To evaluate the effect of Compound 1 on cough severity in healthy volunteers when compared with placebo                        | Cough severity self-assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

Table 12 - Phase 1 Part 2 Exploratory objective and outcome measures

| Exploratory Objectives                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Outcome Measures                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| To investigate Ig concentrations                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Total Ig (immunoglobulin), total IgE (Immunoglobulin E)                                |
| An Exposure Response (E-R) analysis may be conducted of HR corrected QT (ECG interval measured from the onset of the QRS complex to the end of the T wave) data from this study alone or in combination with other studies as appropriate, with a pre-specified workflow described in a separate technical document, for the QTc (QT interval corrected for heart rate) parameter, as part of the cardiac safety evaluation and with the intention to obtain a TQT (Thorough QT) study substitute | Dynamic electrocardiograms dECGs                                                       |
| To investigate the presence of metabolites of Compound 1 in plasma and urine                                                                                                                                                                                                                                                                                                                                                                                                                      | Analyze plasma and urine samples at steady state for the presence of any metabolites.. |
| To quantify 4-beta-OH-cholesterol in plasma                                                                                                                                                                                                                                                                                                                                                                                                                                                       | As a marker for induction of CYP3A4 following repeated dosing of Compound 1            |
| To evaluate the effect of Compound 1 on cough frequency in healthy volunteers when compared with placebo                                                                                                                                                                                                                                                                                                                                                                                          | Cough frequency monitoring                                                             |
| To evaluate the feasibility and subject acceptability of finger prick self-sampling for Compound 1 safety and PK concentrations (optional)                                                                                                                                                                                                                                                                                                                                                        | TDL Tinies Self-collection sampling                                                    |

## Summary of adverse events for part 2:

- There were no deaths or SAEs reported.
- 5 • At least 1 AE was reported across 13 (72.2%) subjects who were administered Compound 1 and for 5 (83.3%) subjects who were administered placebo.
- Overall, all reported AEs were considered by the Investigator to be mild or moderate in intensity.
- For subjects who were administered Compound 1, most AEs were reported for the SOC Nervous System Disorders (9 AEs) and Respiratory, Thoracic and Mediastinal Disorders (8 AEs).
- 10 • The most common reported AEs for subject who were administered Compound 1 were dizziness and cough (4 AEs each).
- For subjects who were administered placebo, most AEs were reported for the SOC Nervous System Disorders (3 AEs).
- 15 • The most frequently reported AEs for subject who were administered placebo was dizziness (2 AEs).

- AEs reported for 11 (61.1%) subjects who were administered Compound 1 and for 4 (66.7%) subjects who were administered placebo were assessed by the Investigator to be possibly related to the IMP.
- The AEs assessed by the Investigator as possibly related to IMP that were reported for one or more subjects in different cohorts, were:
  - Dizziness (reported for 2 [33.3%] subjects each who was administered Compound 1 0.4 mg and 3 mg, and 1 [16.7%] subject who was administered placebo).
  - Headache (reported for 1 [16.7%] subject each who was administered Compound 1 0.4 mg and 3mg and 1 [16.7%] subject who was administered placebo).
  - Cough (reported for 2 [33.3%] subjects who were administered Compound 1 3 mg and 1 [16.7%] subject who was administered placebo).
  - Fatigue (reported for 2 [33.3%] subjects who were administered Compound 1 0.4 mg, 1 [16.7%] subject who was administered Compound 1 1.4 mg and 1 [16.7%] subject who was administered placebo).

*PK data for Part 2*

The PK data for part 2, following single doses of Compound 1 from 0.4 to 3 mg in a dry powder inhaler on Day 1 is shown in Figure 3, in which:

| Dose   | 0.4 mg | 1.4 mg | 3 mg |
|--------|--------|--------|------|
| Symbol | +      | #      | △    |

This is consistent with Part 1a, Compound 1 was rapidly absorbed with median tmax ranging from 0.08 to 0.10 hour post dose following single doses of from 0.4 to 3 mg DPI Compound 1 on Day 1.

The PK data for part 2, day 7, following multiple BID doses of Compound 1 from 0.4 to 3 mg in a dry powder inhaler is shown in Figure 4, in which:

| Dose   | 0.4 mg | 1.4 mg | 3 mg |
|--------|--------|--------|------|
| Symbol | +      | #      | △    |

This is consistent with the single dose profiles on PK Day 1, Compound 1 was rapidly absorbed with median tmax ranging from 0.08 to 0.12 hour post dose following multiple BID doses of from 0.4 to 3 mg DPI Compound 1. After multiple doses, on Day 7, quantifiable Compound 1 concentrations were observed up to the last 144-hour post dose timepoint for all except one subject (0.4 mg BID cohort).

Phase 1 clinical trial part 3

Part 3 of the study was a randomized, single-blind, placebo-controlled, multiple dose, PK and PD study in patients with mild asthma. Two dose levels (1.4 mg and 3 mg) of Compound 1 were investigated. Subjects received BID inhaled doses of Compound 1 or placebo on Day 1 to Day 9 (12 hour intervals between doses), and a single inhaled dose on Day 10.

Figure 10 shows a graphical representation of the Phase 1 Part 3 clinical trial, in which the following abbreviations are used: BID - Twice daily; MAD - Multiple ascending dose; PoM - proof of mechanism; SRC - Safety Review Committee.

Table 13 – Phase 1 part 3 primary objective and outcome measures

| Primary Objective                                                                                                                                 | Outcome Measures                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| To assess the safety and tolerability of Compound 1 following inhaled DPI administration of multiple ascending doses to patients with mild asthma | <ul style="list-style-type: none"> <li>• Incidence of Adverse Events,</li> <li>• Vital signs (supine blood pressure, pulse, respiratory rate, and body temperature),</li> <li>• 12-lead electrocardiograms (ECG),</li> <li>• 12-lead digital electrocardiogram dECG,</li> <li>• Telemetry,</li> <li>• Physical examination,</li> <li>• Laboratory assessments (hematology, clinical chemistry, and urinalysis),</li> <li>• Spirometry,</li> <li>• Capillary blood gas, and oxygen saturation SpO<sub>2</sub> (Peripheral capillary oxygen saturation)</li> </ul> |

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Table 14 – Phase 1 part 3 secondary objective and outcome measures

| Secondary Objectives                                                                                                                 | Outcome Measures                                                                                                                                                                                                                                                                                                                 |
|--------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| To characterize the plasma PK of Compound 1 following inhaled DPI administration of multiple ascending doses to patients with asthma | PK concentrations and PK parameters such as: <ul style="list-style-type: none"> <li>• C<sub>max</sub> (Maximum observed plasma concentration),</li> <li>• AUC – Area under plasma concentration versus time after dosing</li> <li>• AUC<sub>T</sub> - Area under plasma concentration-time curve in the dose interval</li> </ul> |
| To evaluate the effect of Compound 1 on cough severity in patients with mild asthma                                                  | Cough severity self-assessment (VAS)                                                                                                                                                                                                                                                                                             |
| To evaluate anti-inflammatory effect in patients with mild asthma                                                                    | Change from baseline in 2 hours post-morning dose FeNO levels on Days 1 to 10<br>Change from baseline in pre-morning dose (Days 1 to 9 and 10) and pre-evening dose FeNO levels on Days 1 to 9                                                                                                                                   |

Table 15 – Phase 1 part 3 secondary objective and outcome measures

| Exploratory Objectives                                                                                                                                                                                                                                                                                                                | Outcome Measures                                                                                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| To investigate Ig concentrations                                                                                                                                                                                                                                                                                                      | Total Ig (Immunoglobulin), total IgE (Immunoglobulin E), and specific IgE                                       |
| An E-R analysis may be conducted of HR corrected QT data from this study alone or in combination with other studies as appropriate, with a pre-specified workflow described in a separate technical document, for the QTc parameter, as part of the cardiac safety evaluation and with the intention to obtain a TQT study substitute | dECGs (igital electrocardiogram)                                                                                |
| To evaluate systemic target engagement                                                                                                                                                                                                                                                                                                | Peripheral IL-4 induced STAT6 phosphorylation (Signal transducer and activator of transcription 6)              |
| To assess plasma protein and upper airway tissue biomarkers associated with asthma and the JAK1 pathway                                                                                                                                                                                                                               | Protein biomarkers in plasma (e.g. EDN (Eosinophil-derived neurotoxin), CCL17 (Chemokine (C-C motif ligand 17)) |
|                                                                                                                                                                                                                                                                                                                                       | Protein biomarkers in nasal lining fluid (Type 2 and non-Type 2) using nasosorption                             |

PK data for Part 3

5 The PK data for part 3 following single doses of 1.4 and 3 mg of Compound 1 in a DPI in patients with mild asthma at day 1 is shown in Figure 5, in which

|        |        |      |
|--------|--------|------|
| Dose   | 1.4 mg | 3 mg |
| Symbol | #      | △    |

This is consistent with Part 1a and 2, Compound 1 was rapidly absorbed with t<sub>max</sub> at 0.07 and 0.08 hour post dose following single doses of 1.4 and 3 mg of Compound 1 in a DPI, in patients with mild asthma.

10 The PK data for part 3, day 10 following multiple BID doses of 1.4 and 3 mg of Compound 1 in a DPI, in patients with mild asthma is shown in Figure 6, in which

|        |        |      |
|--------|--------|------|
| Dose   | 1.4 mg | 3 mg |
| Symbol | #      | △    |

15 The t<sub>1/2</sub> following multiple BID dosing was consistent between healthy volunteers and patients, with geometric mean values ranging from 37.2 to 39.0 hours in Part 2 and 36.9 and 44.7 hours in Part 3. In general, patients appeared to show lower exposure to Compound 1 compared to healthy volunteers. Geometric mean C<sub>max</sub> was 35% lower in patients from a single 3 mg dose and 27% and 32% lower following multiple doses of 1.4 and 3 mg BID, respectively. In contrast, at 1.4 mg on Day 1, patients showed 34% higher geometric mean C<sub>max</sub> than healthy volunteers, however, between-subject

variabilities in Cmax were exceptionally high (58.1 to 80.7 % geometric CV) for the 1.4 and 3 mg cohorts in Parts 2 and 3 on PK Day 1.

- Geometric mean AUC was also lower in patients compared to volunteers but to a lesser extent by 12% and 26% from single dose and by 7% and 18% following multiple dosing at 1.4 and 3 mg BID, respectively.

The PK data for the single dose for parts 2 and 3 is shown in the table below:

Table 16 – PK data for the single dose for parts 2 and 3

| <b>PK Day 1</b>                          |               | <b>Part 2 Healthy Volunteers<br/>DPI Compound 1</b> |                |               |
|------------------------------------------|---------------|-----------------------------------------------------|----------------|---------------|
| Parameter (Units)                        | Statistic     | 0.4 mg (N = 6)                                      | 1.4 mg (N = 6) | 3 mg (N = 6)  |
| AUC <sub>τ</sub><br>(h*nmol/L)           | Geomean (CV%) | 5.230 (37.09)                                       | 29.18 (35.41)  | 60.52 (20.89) |
|                                          | Min-Max       | 2.83 – 7.53                                         | 21.3 – 47.6    | 40.1 – 71.3   |
|                                          | [n]           | [6]                                                 | [6]            | [6]           |
| AUC <sub>clast</sub><br>(h*nmol/L)       | Geomean (CV%) | 5.174 (36.99)                                       | 29.04 (35.18)  | 59.48 (20.36) |
|                                          | Min-Max       | 2.80 – 7.45                                         | 21.2 – 47.0    | 39.6 – 68.1   |
|                                          | [n]           | [6]                                                 | [6]            | [6]           |
| Cmax<br>(nmol/L)                         | Geomean (CV%) | 2.922 (56.34)                                       | 7.030 (80.67)  | 20.15 (78.69) |
|                                          | Min-Max       | 1.61 – 6.37                                         | 3.72 – 18.6    | 7.14 – 48.3   |
|                                          | [n]           | [6]                                                 | [6]            | [6]           |
| tmax<br>(h)                              | Geomean (CV%) | 0.08                                                | 0.10           | 0.09          |
|                                          | Min-Max       | 0.07 – 0.13                                         | 0.07 – 0.12    | 0.08 – 0.13   |
|                                          | [n]           | [6]                                                 | [6]            | [6]           |
| AUC <sub>τ</sub> /D<br>(h*nmol/L/mg)     | Geomean (CV%) | 13.07 (37.09)                                       | 20.85 (35.41)  | 20.17 (20.89) |
|                                          | Min-Max       | 7.07 – 18.8                                         | 15.2 – 34.0    | 13.4 – 23.8   |
|                                          | [n]           | [6]                                                 | [6]            | [6]           |
| AUC <sub>clast</sub> /D<br>(h*nmol/L/mg) | Geomean (CV%) | 12.93 (36.99)                                       | 20.74 (35.18)  | 19.83 (20.36) |
|                                          | Min-Max       | 7.00 – 18.6                                         | 15.1 – 33.6    | 13.2 – 22.7   |
|                                          | [n]           | [6]                                                 | [6]            | [6]           |
| Cmax/D<br>(nmol/L/mg)                    | Geomean (CV%) | 7.304 (56.34)                                       | 5.022 (80.67)  | 6.716 (78.69) |
|                                          | Min-Max       | 4.01 – 15.9                                         | 2.66 – 13.3    | 2.38-16.1     |
|                                          | [n]           | [6]                                                 | [6]            | [6]           |

| <b>PK Day 1</b>                      |               | <b>Part 3 Patients<br/>DPI Compound 1</b> |               |
|--------------------------------------|---------------|-------------------------------------------|---------------|
| Parameter (Units)                    | Statistic     | 1.4 mg (N=6)                              | 3 mg (N=7)    |
| AUC <sub>τ</sub><br>(h*nmol/L)       | Geomean (CV%) | 25.54 (24.53)                             | 44.90 (20.06) |
|                                      | Min-Max       | 17.9 – 34.9                               | 35.7 – 65.0   |
|                                      | [n]           | [6]                                       | [7]           |
| AUC <sub>clast</sub><br>(h*nmol/L)   | Geomean (CV%) | 25.53 (24.17)                             | 44.89 (19.72) |
|                                      | Min-Max       | 18.0 – 34.9                               | 36.0 – 64.8   |
|                                      | [n]           | [6]                                       | [7]           |
| Cmax<br>(nmol/L)                     | Geomean (CV%) | 9.399 (59.41)                             | 13.07 (58.06) |
|                                      | Min-Max       | 4.88 – 17.7                               | 6.42 – 34.6   |
|                                      | [n]           | [6]                                       | [7]           |
| tmax<br>(h)                          | Geomean (CV%) | 0.07                                      | 0.08          |
|                                      | Min-Max       | 0.05 – 0.08                               | 0.07 – 0.13   |
|                                      | [n]           | [6]                                       | [7]           |
| AUC <sub>τ</sub> /D<br>(h*nmol/L/mg) | Geomean (CV%) | 18.24 (24.53)                             | 14.97 (20.06) |
|                                      | Min-Max       | 12.8 – 24.9                               | 11.9 -21.6    |
|                                      | [n]           | [6]                                       | [7]           |
| AUC <sub>clast</sub> /D              | Geomean (CV%) | 18.24 (24.17)                             | 14.96 (19.72) |

|                     |                                         |                                     |                                     |
|---------------------|-----------------------------------------|-------------------------------------|-------------------------------------|
| (h*nmol/L/mg)       | Min-Max<br>[n]                          | 12.9 – 25.0<br>[6]                  | 12.0 – 21.6<br>[7]                  |
| C <sub>max</sub> /D | Geomean (CV%)<br>Min-Max<br>(nmol/L/mg) | 6.714 (59.41)<br>3.48 – 12.7<br>[6] | 4.356 (58.06)<br>2.14 – 11.5<br>[7] |

MAD: Multiple ascending dose; DPI: Dry powder inhaler; N: Number of subjects in the pharmacokinetic analysis set; n: Number of subjects included in analysis; Geomean: geometric mean; Max: Maximum; Min: Minimum; CV: geometric coefficient of variance (%)

- 5 The PK data for the multiple doses for parts 2 and 3 is shown in the table below:

Table 17 – PK data for the multiple dose for parts 2 and 3.

| PK Day 7 and 10*                        |                                 | Part 2 Healthy Volunteers<br>DPI Compound 1 |                                     |                                     |
|-----------------------------------------|---------------------------------|---------------------------------------------|-------------------------------------|-------------------------------------|
| Parameter<br>(Units)                    | Statistic                       | 0.4 mg BID<br>(N = 6)                       | 1.4 mg BID<br>(N = 6)               | 3 mg BID<br>(N = 6)                 |
| AUC <sub>τ</sub><br>(h*nmol/L)          | Geomean (CV%)<br>Min-Max<br>[n] | 24.50 (21.01)<br>18.2 – 30.9<br>[6]         | 118.3 (23.32)<br>86.9 – 158<br>[6]  | 235.5 (22.55)<br>165 – 295<br>[6]   |
| AUC <sub>last</sub><br>(h*nmol/L)       | Geomean (CV%)<br>Min-Max<br>[n] | 98.58 (38.08)<br>52.0 – 135<br>[6]          | 499.8 (43.07)<br>315 – 847<br>[6]   | 987.9 (38.60)<br>608 – 1540<br>[6]  |
| C <sub>max</sub><br>(nmol/L)            | Geomean (CV%)<br>Min-Max<br>[n] | 5.366 (30.81)<br>3.90 – 8.52<br>[6]         | 19.92 (16.41)<br>16.5 – 26.0<br>[6] | 41.98 (23.94)<br>30.8 – 60.7<br>[6] |
| t <sub>max</sub><br>(h)                 | Geomean (CV%)<br>Min-Max<br>[n] | 0.08<br>0.07 – 0.12<br>[6]                  | 0.08<br>0.07 – 0.10<br>[6]          | 0.12<br>0.07 – 0.15<br>[6]          |
| t <sub>1/2λz</sub><br>(h)               | Geomean (CV%)<br>Min-Max<br>[n] | 38.95 (21.24)<br>28.8 – 54.5<br>[6]         | 37.17 (19.46)<br>29.5 – 50.3<br>[6] | 38.51 (19.22)<br>31.7 – 52.9<br>[6] |
| CL/F<br>(L/h)                           | Geomean (CV%)<br>Min-Max<br>[n] | 27.22 (21.01)<br>21.6 – 36.7<br>[6]         | 19.74 (23.32)<br>14.7 – 26.9<br>[6] | 21.25 (22.55)<br>16.9 – 30.3<br>[6] |
| V <sub>z</sub> /F<br>(L)                | Geomean (CV%)<br>Min-Max<br>[n] | 1530 (24.44)<br>1190 – 2100<br>[6]          | 1059 (10.50)<br>866 – 1150<br>[6]   | 1180 (13.06)<br>987 – 1420<br>[6]   |
| Rac AUC                                 | Geomean (CV%)<br>Min-Max<br>[n] | 4.685 (34.36)<br>3.44 – 8.83<br>[6]         | 4.052 (34.92)<br>2.27 – 6.46<br>[6] | 3.891 (15.49)<br>3.18 – 4.59<br>[6] |
| Rac C <sub>max</sub>                    | Geomean (CV%)<br>Min-Max<br>[n] | 1.837 (46.49)<br>0.911 – 2.87<br>[6]        | 2.834 (76.38)<br>1.37 – 5.42<br>[6] | 2.084 (53.72)<br>1.26 – 4.95<br>[6] |
| AUC <sub>τ</sub> /D<br>(h*nmol/L/mg)    | Geomean (CV%)<br>Min-Max<br>[n] | 61.25 (21.01)<br>45.4 – 77.3<br>[6]         | 84.47 (23.32)<br>62.1 – 113<br>[6]  | 78.48 (22.55)<br>55.0 – 98.5<br>[6] |
| AUC <sub>last</sub> /D<br>(h*nmol/L/mg) | Geomean (CV%)<br>Min-Max<br>[n] | 246.4 (38.08)<br>130 – 338<br>[6]           | 357.0 (43.07)<br>225 – 605<br>[6]   | 329.3 (38.60)<br>203 – 513<br>[6]   |
| C <sub>max</sub> /D<br>(nmol/L/mg)      | Geomean (CV%)<br>Min-Max<br>[n] | 13.41 (30.81)<br>9.75 – 21.3<br>[6]         | 14.23 (16.41)<br>11.8 – 18.6<br>[6] | 13.99 (23.94)<br>10.3 – 20.2<br>[6] |

| <i>PK Day 7 and 10*</i>                 |                                 | <i>Part 3 Patients<br/>DPI Compound 1</i> |                                     |
|-----------------------------------------|---------------------------------|-------------------------------------------|-------------------------------------|
| <b>Parameter<br/>(Units)</b>            | <b>Statistic</b>                | <b>1.4 mg BID<br/>(N = 6)</b>             | <b>3 mg BID<br/>(N = 7)</b>         |
| AUC <sub>τ</sub><br>(h*nmol/L)          | Geomean (CV%)<br>Min-Max<br>[n] | 110.1 (10.26)<br>93.7 – 125<br>[6]        | 192.1 (25.65)<br>141 – 251<br>[6]   |
| AUC <sub>last</sub><br>(h*nmol/L)       | Geomean (CV%)<br>Min-Max<br>[n] | 479.8 (26.81)<br>355 – 689<br>[6]         | 948.6 (32.74)<br>678 – 1410<br>[6]  |
| C <sub>max</sub><br>(nmol/L)            | Geomean (CV%)<br>Min-Max<br>[n] | 14.64 (19.51)<br>11.3 – 19.6<br>[6]       | 28.37 (28.22)<br>20.2 – 46.5<br>[6] |
| t <sub>max</sub><br>(h)                 | Geomean (CV%)<br>Min-Max<br>[n] | 0.08<br>0.07 – 0.42<br>[6]                | 0.08<br>0.05 – 0.13<br>[6]          |
| t <sub>1/2λz</sub><br>(h)               | Geomean (CV%)<br>Min-Max<br>[n] | 36.90 (22.08)<br>29.4 – 49.9<br>[6]       | 44.73 (21.07)<br>32.4 – 60.7<br>[6] |
| CL/F<br>(L/h)                           | Geomean (CV%)<br>Min-Max<br>[n] | 21.20 (10.26)<br>18.7 – 24.9<br>[6]       | 26.05 (25.65)<br>19.9 – 35.4<br>[6] |
| V <sub>z</sub> /F<br>(L)                | Geomean (CV%)<br>Min-Max<br>[n] | 1129 (14.72)<br>910 – 1340<br>[6]         | 1681 (34.29)<br>934 – 2320<br>[6]   |
| Rac AUC                                 | Geomean (CV%)<br>Min-Max<br>[n] | 4.311 (30.22)<br>3.09 – 6.73<br>[6]       | 4.226 (18.23)<br>3.32 – 5.52<br>[6] |
| Rac C <sub>max</sub>                    | Geomean (CV%)<br>Min-Max<br>[n] | 1.557 (58.01)<br>0.637 – 2.71<br>[6]      | 2.108 (39.22)<br>1.34 – 3.51<br>[6] |
| AUC <sub>τ</sub> /D<br>(h*nmol/L/mg)    | Geomean (CV%)<br>Min-Max<br>[n] | 78.66 (10.26)<br>66.9 – 89.2<br>[6]       | 64.02 (25.65)<br>47.1 – 83.6<br>[6] |
| AUC <sub>last</sub> /D<br>(h*nmol/L/mg) | Geomean (CV%)<br>Min-Max<br>[n] | 342.7 (26.81)<br>254 – 492<br>[6]         | 316.2 (32.74)<br>226 – 469<br>[6]   |
| C <sub>max</sub> /D<br>(nmol/L/mg)      | Geomean (CV%)<br>Min-Max<br>[n] | 10.45 (19.51)<br>8.06 – 14.0<br>[6]       | 9.456 (28.22)<br>6.74 – 15.5<br>[6] |

MAD: Multiple ascending dose; DPI: Dry powder inhaler; N: Number of subjects in the pharmacokinetic analysis set; n: Number of subjects included in analysis; Geomean: Geometric mean; Max: Maximum; Min: Minimum; CV: geometric coefficient of variance (%); NA: Not Applicable; NC: Not Calculated

5 \* PK Day 7 for Part 2 and PK Day 10 for Part 3

Accumulation of systemic Compound 1 with multiple dosing was apparent in healthy volunteers, with geometric mean Rac AUC and Rac C<sub>max</sub> ranging from 3.89 to 4.69 and 1.84 to 2.83, respectively.

10 Similar extent of accumulation was determined in patients administrated at 1.4 and 3 mg Compound 1 (geometric mean: RacAUC of 4.31 and 4.23; RacC<sub>max</sub> of 1.56 and 2.11, respectively).

Steady state was achieved after approximately 6 days of BID dosing based on the geometric mean and individual trough concentrations. This was consistent across the dose levels and between the healthy volunteers and patients.

Between-subject variability in exposure was largely consistent across the 0.4 to 1.4 mg BID dose range with no marked difference between healthy volunteers and patients. The geometric CV ranged from 56.3 to 80.7 % for C<sub>max</sub> and 20.1 to 37.1 % for AUC<sub>τ</sub> following a single dose. Variability was lower following multiple dosing, with geometric CV ranging from 16.4 to 30.8 % for C<sub>max</sub> and 10.3 to 25.7 % for AUC<sub>τ</sub>. A summary of the PK data for parts 2 and 3 is shown in the table below:

| Analysis Visit     | Parameter (Units)           | Part 2 – Healthy Volunteers |                                                   | Part 3 - Patients |                                                   |
|--------------------|-----------------------------|-----------------------------|---------------------------------------------------|-------------------|---------------------------------------------------|
|                    |                             | n                           | Compound 1 DPI<br>Doses: 0.4, 1.4 and 3<br>mg BID | n                 | Compound 1 DPI<br>Doses: 0.4, 1.4 and 3<br>mg BID |
|                    |                             |                             | Slope Estimate (95%<br>CI)                        |                   | Slope Estimate (95%<br>CI)                        |
| PK Day 1           | C <sub>max</sub> (nmol/L)   | 18                          | 0.9329 (0.5436, 1.322)                            | 13                | 0.4324 (-0.4416, 1.306)                           |
|                    | AUC <sub>τ</sub> (h*nmol/L) | 18                          | 1.231 (1.041, 1.421)                              | 13                | 0.7402 (0.3879, 1.092)                            |
| PK Day 7 or<br>10* | C <sub>max</sub> (nmol/L)   | 18                          | 1.024 (0.8834, 1.164)                             | 12                | 0.8684 (0.4655, 1.271)                            |
|                    | AUC <sub>τ</sub> (h*nmol/L) | 18                          | 1.136 (0.9985, 1.274)                             | 12                | 0.7300 (0.4049, 1.055)                            |

MAD: Multiple ascending dose; DPI: Dry powder inhaler; n: number of data points used in regression; CI: Confidence Interval.

\* PK Day 7 for Part 2 and PK Day 10 for Part 3

Model: The linear model used was  $\log(Y) = \text{intercept} + \text{slope} * \log(\text{dose})$ , where Y is the parameter estimate; the natural logarithm has been used. Exponentiation of both sides of this equation produces the usual form of the powder model:  $Y = \exp(\text{intercept}) * (\text{dose})^{\text{slope}}$ . The slope parameter is obtained using ordinary least-squares.

This shows that over the 0.4 to 3 mg BID dose range in healthy volunteers, increases in C<sub>max</sub> and AUC<sub>τ</sub> were approximately proportional to dose.

Fractional Exhaled Nitric Oxide data from phase 1 part 3 of the clinical trial

The Fractional Exhaled Nitric Oxide data from phase 1 part 3 of the clinical trial is shown in the tables below.

Table 18  
(FeNO, relative change from baseline in 2 hours post-morning dose (Days 1 to 10), linear mixed model with observed cases: Part 3 (BID MAD) (safety analysis set)):

|                 |                    |                        |   |   | Relative change from baseline <sup>a</sup> |                |                                         |                          |                      |         |
|-----------------|--------------------|------------------------|---|---|--------------------------------------------|----------------|-----------------------------------------|--------------------------|----------------------|---------|
| Variable (unit) | Scheduled day/time | Treatment              | N | n | Geometric LS means                         | 90% CI         | Comparison                              | Geometric LS means ratio | 90% CI of difference | p-Value |
| FeNO (ppth)     | Up to Day 10       | Pooled placebo         | 4 | 4 | 0.979                                      | (0.478, 2.006) |                                         |                          |                      |         |
|                 |                    | Compound 1, 1.4 mg DPI | 6 | 6 | 0.461                                      | (0.228, 0.931) | Compound 1, 1.4mg DPI vs pooled placebo | 0.471                    | (0.334, 0.663)       | 0.002   |
|                 |                    | Compound 1, 3mg DPI    | 7 | 7 | 0.465                                      | (0.231, 0.938) | Compound 1, 3mg DPI vs pooled placebo   | 0.475                    | (0.335, 0.674)       | 0.002   |

<sup>a</sup> The baseline for FeNO analysis will be the average FeNO measurement on Day -2 and Day -1 corresponding to the analyzed endpoint.

Results based on MMRM using all post-baseline 2 hours post-dose FeNO assessments. Analyses will be performed on the log-transformed FeNO data to normalize the skewed distribution of this endpoint with log-transformed relative change from baseline as the primary dependent variable, treatment, visit and treatment-by-visit interaction as fixed effects and random effect for subject and log-transformed baseline FeNO a covariate.

BID, twice daily; CI, Confidence interval; DPI, dry powder inhaler; LS, least-squares; MAD, multiple ascending dose; MMRM, Mixed effect model of repeated measures; n, number of data points included in the analysis; N, number of subjects in the safety analysis set.

Table 19 (FeNO, Relative change from baseline in pre-morning dose (Days 1 to 10), linear mixed model with observed cases: Part 3 (BID MAD (safety analysis set):

| Variable<br>(unit) | Scheduled<br>day/time | Treatment                    | N | n | Relative change from baseline <sup>a</sup> |                   |                                                     |                                |                         |             |
|--------------------|-----------------------|------------------------------|---|---|--------------------------------------------|-------------------|-----------------------------------------------------|--------------------------------|-------------------------|-------------|
|                    |                       |                              |   |   | Geometric<br>LS means                      | 90% CI            | Comparison                                          | Geometric<br>LS means<br>ratio | 90% CI of<br>difference | p-<br>Value |
| FeNO<br>(ppth)     | Up to Day<br>10       | Pooled<br>placebo            | 4 | 4 | 0.927                                      | (0.504,<br>1.704) |                                                     |                                |                         |             |
|                    |                       | Compound<br>1, 1.4 mg<br>DPI | 6 | 6 | 0.453                                      | (0.250,<br>0.822) | Compound<br>1, 1.4mg<br>DPI vs<br>pooled<br>placebo | 0.489                          | (0.360,<br>0.665)       | 0.001       |
|                    |                       | Compound<br>1, 3mg DPI       | 7 | 7 | 0.391                                      | (0.216,<br>0.708) | Compound<br>1, 3mg DPI<br>vs pooled<br>placebo      | 0.422                          | (0.308,<br>0.577)       | <0.001      |

- 5     <sup>a</sup>     The baseline for FeNO analysis will be the average FeNO measurement on Day -2 and Day -1 corresponding to the analyzed endpoint.

Results based on MMRM using all post-baseline 2 hours post-dose FeNO assessments. Analyses will be performed on the log-transformed FeNO data to normalize the skewed distribution of this endpoint with log-transformed relative change from baseline as the primary dependent variable, treatment, visit and treatment-by-visit interaction as fixed effects and random effect for subject and log-transformed baseline FeNO a covariate.

10     BID, twice daily; CI, Confidence interval; DPI, dry powder inhaler; LS, least-squares; MAD, multiple ascending dose; MMRM, Mixed effect model of repeated measures; n, number of data points included in the analysis; N, number of subjects in the safety analysis set.

Table 20 ((FeNO, Relative change from baseline in pre-evening dose (Days 1 to 9), linear mixed model with observed cases: Part 3 (BID MAD (safety analysis set):

|                 |                    |                        |   |   | Relative change from baseline <sup>a</sup> |                |                                         |                          |                      |         |
|-----------------|--------------------|------------------------|---|---|--------------------------------------------|----------------|-----------------------------------------|--------------------------|----------------------|---------|
| Variable (unit) | Scheduled day/time | Treatment              | N | n | Geometric LS means                         | 90% CI         | Comparison                              | Geometric LS means ratio | 90% CI of difference | p-Value |
| FeNO (ppth)     | Up to Day 10       | Pooled placebo         | 4 | 4 | 0.914                                      | (0.708, 1.179) |                                         |                          |                      |         |
|                 |                    | Compound 1, 1.4 mg DPI | 6 | 6 | 0.419                                      | (0.338, 0.518) | Compound 1, 1.4mg DPI vs pooled placebo | 0.458                    | (0.331, 0.635)       | <0.001  |
|                 |                    | Compound 1, 3mg DPI    | 7 | 7 | 0.360                                      | (0.295, 0.441) | Compound 1, 3mg DPI vs pooled placebo   | 0.394                    | (0.283, 0.549)       | <0.001  |

<sup>a</sup> [a] The baseline for FeNO analysis will be the average FeNO measurement on Day -2 and Day -1 corresponding to the analyzed endpoint.

Results based on MMRM using all post-baseline 2 hours post-dose FeNO assessments. Analyses will be performed on the log-transformed FeNO data to normalize the skewed distribution of this endpoint with log-transformed relative change from baseline as the primary dependent variable, treatment, visit and treatment-by-visit interaction as fixed effects and random effect for subject and log-transformed baseline FeNO a covariate.

BID, twice daily; CI, Confidence interval; DPI, dry powder inhaler; LS, least-squares; MAD, multiple ascending dose; MMRM, Mixed effect model of repeated measures; n, number of data points included in the analysis; N, number of subjects in the safety analysis set.

Figure 7 shows the FeNO relative change from baseline in 2 hours post-morning dose (a plot of MMRM analysis by time-point, Part 3, Safety analysis set). In Figure 7:

| Dose   | Placebo | 1.4 mg | 4 mg |
|--------|---------|--------|------|
| Symbol | ○       | ★      | △    |

This shows that when compared with placebo, both 1.4 mg Compound 1 and 3 mg Compound 1 showed significant changes from baseline for relative FeNO levels 2 hours post-morning dose on Days 1 to 10 (p value = 0.002). Similarly, when compared with placebo, changes from baseline in pre-morning dose (Days 1 to 9 and 10) and pre-evening dose FeNO levels on days 1 to 9 indicated a high significance (p value ≤ 0.001).

This data demonstrates an approximately 50% reduction in the lung inflammation biomarker FeNO versus placebo in participants with mild asthma in both the 1.4 mg and 3.0 mg twice a day. This data also

demonstrates a good effect both before and after dosing demonstrating that there is 24-hour coverage using the twice daily regime.

EXAMPLE 3 - Phase 2a clinical trial

- 5 Phase 2a of the clinical trial is to be completed.

**Overall Design Synopsis:**

- 10 This is a Phase 2a, multicentre, randomised, placebo-controlled, double-blind, parallel-group study designed to evaluate the efficacy, safety and PK of Compound 1 administered BID using the SD3FL dry-powder inhaler at one dose level over a 12-week Treatment period in adult participants with uncontrolled moderate-to-severe asthma. This study will include around 150 study sites globally.

- 15 Approximately 320 participants, with uncontrolled asthma despite receiving treatment with medium or high dose ICS-LABA at screening and at Visit 3 (Asthma Control Questionnaire-6 score  $\geq 1.5$ ) will be randomly assigned in a 1:1 ratio to 1 of the 2 treatment arms (Compound 1 1.4 mg BID or placebo). To ensure balance between the treatment arms, randomisation will be stratified based on participant's ICS dose level at Visit 1 (medium, high) and region. Compound 1, 1.4 mg and placebo will be administered BID using the SD3FL inhaler, also known and marketed as GENUAIR® in the Europe and PRESSAIR® in the United States.

20

**Patients**

- 25 Approximately 320 participants with uncontrolled asthma despite receiving treatment with medium or high dose ICS-LABA (inhaled corticosteroid-long-acting beta-agonist) at screening and at Visit 3 (ACQ-6 score  $\geq 1.5$ ) will be randomly assigned in a 1:1 ratio to 1 of the 2 treatment arms (Compound 1, 1.4 mg BID or placebo). This may be adjusted up to approximately 385 participants following a planned IA. To ensure balance between the treatment arms, randomisation will be stratified based on participant's ICS dose level at Visit 1 (medium, high) and region. In addition, it will be ensured that at least 40% of participants have a FeNO value  $\geq 25$  ppb at Visit 3 and that at least 30% of participants randomised in the study have a documented history of  $\geq 2$  severe asthma exacerbations within 1 year prior to Visit 1.

30 **Core inclusion criteria**

- 1 Participant must be 18 to 80 years of age inclusive, at the time of signing the informed consent.
- 2 Participants treated with medium-high dose ICS combination with LABA at a stable dose for at least 3 months prior to Visit 1 (the ICS can be contained within an ICS-LABA fixed dose combination product).
- 35 – Treatment with additional asthma controller therapies (e.g., LAMA, LTRA) at a stable dose  $\geq 3$  months prior to Visit 1 is allowed. Treatment with maintenance systemic corticosteroids (oral or injectable) is not allowed.
- 3 A documented history of  $\geq 1$  severe asthma exacerbation within 1 year prior to Visit 1.  
A severe asthma exacerbation is defined as a worsening of asthma that leads to any of the following:

- Use of systemic corticosteroids for at least 3 consecutive days to treat symptoms of asthma worsening (a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids).
- An emergency room visit (defined as evaluation and treatment for < 24 hours in an emergency department) due to asthma that required systemic corticosteroids (as per the above).
- An inpatient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for  $\geq 24$  hours) due to asthma.

Acceptable documentation of a severe asthma exacerbation in this protocol is:

- Documented prescription of systemic corticosteroids for at least 3 days to treat asthma worsening (a single depo-injectable dose of corticosteroids will be considered equivalent to 3-day bolus/burst of systemic corticosteroids). In participants with an established self-management plan, documented filling of a prescription will be considered adequate.
  - Clinic visit or consultation (primary or specialised HCP) notes providing evidence of  $\geq 1$  exacerbation in the previous 12 months prior to enrolment.
  - Emergency room/hospital records that the participant attended an emergency room visit (defined as evaluation and treatment for < 24 hours in an emergency department) due to asthma that required systemic corticosteroids (as per the above).
  - Discharge summaries from hospital, emergency room or urgent care facility indicating that a participant was hospitalised (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for  $\geq 24$  hours) due to asthma.
- 4 Morning pre-BD FEV1 between  $\geq 40\%$  and  $\leq 90\%$  predicted at Visit 1 and Visit 3 (pre-randomisation).
- 5 Able to perform acceptable lung function testing for FEV1 according to ATS/ERS 2019 acceptability criteria.
- 25 6 Documented evidence of asthma as demonstrated by any of the following in the 10 years up to or including Visit 1:
- Post-BD reversibility of FEV1  $\geq 12\%$  and  $\geq 200$  mL, or
  - Average daily variability of PEF  $> 10\%$  over a 2-week period, or
  - Variability of FEV1  $> 12\%$  and 200 mL between any 2 clinical visits, or
  - Positive bronchial challenge test (a positive test is defined as a fall in FEV1 from pre-challenge of  $\geq 20\%$  with standard doses of methacholine or histamine, or  $\geq 15\%$  with standardised hyperventilation, hypertonic saline, or mannitol challenge), or
  - Positive exercise challenge test (a positive test is defined as a fall in FEV1 of  $> 10\%$  and  $> 200$  mL from pre-challenge), or
  - A FeNO test with a value of  $\geq 40$  ppb despite confirmed ICS maintenance therapy.

If documentation is not available to support any of these diagnostic criteria, and if in the opinion of the investigator the clinical diagnosis of asthma is still considered likely, the investigation and confirmation of an average daily variability of PEF  $> 10\%$  over a 2-week period can also be considered as confirmatory of the diagnosis of asthma if undertaken during the period of screening and run-in.

- 40 7 An ACQ-6 score  $\geq 1.5$  at Visit 1 and at Visit 3 (pre-randomisation).

- 8 Able and willing to comply with the requirements of the CSP including ability to read, write, be fluent in the translated language of all participants facing questionnaires used at the study site, and use electronic devices, e.g., ePRO device and spirometer.
- 9 Body weight of  $\geq 40$  kg and body mass index of  $< 35$  kg/m<sup>2</sup>.
- 5 10 Male and/or female
- Contraceptive use by females should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. There are no restrictions on male participants or their female partners.
- Females not of childbearing potential are defined as females who are either permanently sterilised
- 10 (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. The following age-specific requirements apply:
- Females  $< 50$  years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle-stimulating hormone levels in the postmenopausal range.
  - 15 – Females  $\geq 50$  years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
  - All FOCBP who are sexually active with a non-sterilised male partner must agree to use one highly effective method of birth control, as defined below, for a minimum of 3 months prior to Visit 1 and throughout entire duration of the study, and for 1 month after the last dose of IMP.
  - 20 Cessation of contraception after this point should be discussed with a responsible physician. A highly effective method of contraception is defined as one that can achieve a failure rate of  $< 1\%$  per year when used consistently and correctly.
  - The following are not acceptable methods of contraception: Periodic abstinence (calendar, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea. Female
  - 25 condom and male condom should not be used together.
  - All FOCBP must have a negative serum pregnancy test result at Visit 1.
  - Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual
  - 30 intercourse during the entire period of risk associated with the IMP), a vasectomised partner, IMPLANON, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, DEPO-PROVERA injections, oral contraceptive, and EVRA PATCH, XULANE or NUVARING.
  - 11 Capable of giving signed informed consent prior to any study-specific procedures.
  - 12 Provision of signed and dated written Optional Genetic Research Information informed consent
  - 35 prior to collection of samples for optional genetic research that supports the Genomic Initiative.

#### Randomisation Inclusion Criteria

At the end of the Run-in period (Visit 3), participants must fulfil the following additional criteria in order to be randomised into the study and enter the Treatment period:

- 40 1 Pre-BD FEV1 between  $\geq 40\%$  and  $\leq 90\%$  predicted (pre-randomisation).

- 2 A pre-BD/pre-IMP dose FEV1 at Visit 3 that has not increased or decreased by 20% or more from the pre-BD FEV1 recorded at Visit 1 and at Visit 2.
- 3 An ACQ-6 score of  $\geq 1.5$  (pre-randomisation).
- 4 At least 80% compliance with usual asthma background medication during Run-in period (from
- 5 Visit 2 to Visit 3) based on the daily asthma ePROs.
- 5 Minimum 80% compliance with daily eCOA assessments. Compliance is defined as completing the daily ePRO questions and PEF measurement (morning and evening) at least 80% of the time during the Run-in period and during the 14 days preceding Visit 3.
- 6 For female participants, a negative urine pregnancy test prior to administration of IMP
- 10 (randomisation).

### Core exclusion criteria

#### *Medical Conditions*

- 1 A severe asthma exacerbation within 8 weeks of prior to randomisation.
- 15 2 History of herpes zoster reactivation e.g., shingles.
- 3 Participants with a significant COVID-19 illness within 6 months of enrolment:
  - Participants with a diagnosis of COVID-19 pneumonia based on radiological assessment.
  - Participants with a diagnosis of COVID-19 requiring hospitalisation and/or oxygen supplementation therapy.
- 20 4 Clinically important pulmonary disease other than asthma e.g., active lung infection, COPD, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, history or planned lung lobectomy, alpha-1 anti-trypsin deficiency, primary ciliary dyskinesia, Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis and hyper-eosinophilic syndrome.
- 25 5 Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that is not stable in the opinion of the investigator and could:
  - affect the safety of the participant throughout the study,
  - influence the findings of the study or the interpretation, or
  - 30 – impede the participant's ability to complete the entire duration of study.
- 6 Any clinically significant cardiac or cerebrovascular disease:
  - Unstable angina, acute coronary syndrome (acute myocardial infarction, unstable angina), coronary intervention with percutaneous coronary intervention/coronary artery bypass surgery or stroke within 6 months of Visit 1.
  - 35 – Heart failure, New York Heart Association, Classes II to IV.
  - Systemic hypertension, except if well-controlled using 2 or fewer medications and stable for at least 6 months.
  - Untreated high degree atrioventricular block (second – third degree atrioventricular block)/significant sinus node dysfunction/pause or therapy requiring tachyarrhythmia.
  - 40 Participants with atrial fibrillation or flutter and optimally controlled ventricular rate at resting < 100 bpm might be included as judged by the investigator.

- History or family history of long QT-syndrome or sudden cardiac death with age < 40 years old.
  - History of QT prolongation associated with other medications that required discontinuation of that medication.
  - Hypertrophic cardiomyopathy or clinically significant valvular heart disease.
  - 5     – Pulmonary arterial hypertension, either idiopathic or due to connective tissue or thromboembolic disease.
  - 7     History of venous thromboembolism.
  - 8     Participants who, as judged by the investigator, have evidence of active TB, either treated or untreated, or latent TB without completion of an appropriate course of treatment or appropriate
  - 10    ongoing prophylactic treatment. Evaluation will be according to the local standard of care as determined by local guidelines and may consist of history and physical examinations, chest X-ray, or TB test (e.g., purified protein derivative or QuantiFERON® test).
  - 9     Participants with a recent history of, or who have a positive test for, infective hepatitis or unexplained jaundice, or participants who have been treated for hepatitis B, hepatitis C, or HIV. Any of the
  - 15    following would exclude the participant from the study:
    - Participants positive for hepatitis C antibody.
    - Participants positive for hepatitis B virus surface antigen.
    - Participants positive for hepatitis B virus core antibody.
    - Participants with history of infection or positivity of HIV.
  - 20    Note: Participants with a history of hepatitis B vaccination without a history of hepatitis B are permitted. If vaccinated participants test positive for hepatitis B antibody, a confirmatory PCR test will be performed.
  - 10    Current or prior history of alcohol or drug abuse (including marijuana), as judged by the investigator. Positive drug screening result that cannot be justified by participant's medical history and its relevant treatment (over-the-counter product or a valid prescription), or history of or current alcohol or drug
  - 25    abuse (including marijuana and marijuana-containing valid prescriptions), as judged by the investigator.
  - 11    History of malignancy other than superficial basal cell carcinoma.
- Prior/Concomitant Therapy*
- 12    Treatment with systemic corticosteroid (short-term or maintenance) use within 4 weeks (oral) or
  - 30    8 weeks (intramuscular) before Visit 1.
  - 13    Any immunosuppressive therapy (including hydroxychloroquine, methotrexate, cyclosporine and tacrolimus) within 12 weeks prior to Visit 1.
  - 14    Treatment with marketed biologics including benralizumab, mepolizumab, reslizumab, omalizumab, dupilumab and tezepelumab within 6 months of Visit 1 or 5 half-lives, whichever is longer.
  - 35    15    Inhaled corticosteroid plus fast-acting  $\beta_2$  agonist as a reliever (e.g., Symbicort, Fostair, or Airsupra Maintenance and Reliever Treatment) is not allowed 15 days prior to Visit 1, during Screening/Run-in and throughout the Treatment period and preferably 1 week after the last dose of IMP.
  - 16    Live, attenuated, or mRNA vaccines within 4 weeks of Visit 1.
  - 17    Immunoglobulin or blood products within 4 weeks of Visit 1.

- 18 Any immunotherapy within 6 months of Visit 1, except for stable maintenance dose allergen-specific immunotherapy started at least 4 weeks prior to Visit 1 and expected to continue through to the end of the Follow-up period.

*Prior/Concurrent Clinical Study Experience*

- 5 19 Concurrent enrolment in another clinical study.
- 20 Participant treated with any investigational drug within 4 months (or 5 half-lives, whichever is longer) prior to Visit 1.
- 21 Participants with a known hypersensitivity to Compound 1 or any of the excipients of the product.

*Diagnostic Assessments*

- 10 22 Abnormal findings identified on physical examination, ECG, or laboratory testing include, but are not limited to:
- ALT or AST  $\geq 1.5 \times$  ULN.
  - TBL  $\geq$  ULN (unless due to known Gilbert's disease).
  - Evidence of chronic liver disease.
- 15 – Abnormal vital signs, after 5 minutes of supine or sitting rest (confirmed by 1 controlled measurement), defined as any of the following:
- Systolic BP  $< 80$  mmHg or  $\geq 150$  mmHg.
  - Diastolic BP  $< 50$  mmHg or  $\geq 95$  mmHg.
  - Pulse  $< 50$  bpm or  $> 100$  bpm.
- 20 – Signs of pulmonary oedema or volume overload.
- Any clinically significant rhythm, conduction, or morphology abnormalities in the ECG including but not limited to QTcF  $> 450$  ms.

- In addition, any other clinically relevant abnormal findings on physical examination or laboratory testing including haematology, coagulation, serum chemistry, urinalysis, or ECG between Visit 1 and Visit 3
- 25 (randomisation), that in the opinion of the investigator or medical monitor might compromise the safety of the participant in the study or interfere with evaluation of the IMP.

*Other Exclusions*

- 23 For female participants only – currently pregnant (confirmed with positive pregnancy test) or breast-feeding.
- 30 24 Current smokers or participants with smoking history  $\geq 10$  pack-years.
- Note: Pack-years are calculated as average number of cigarettes per day  $\times$  number of years/20. For example, 1 pack year = 20 cigarettes smoked per day for 1 year or 10 cigarettes per day for 2 years.
  - Smokers with smoking history of  $< 10$  pack-years or users of vaping or e-cigarettes, must have
- 35 stopped at least 6 months prior to Visit 1.
- 25 Participants with a known long-term exposure to occupational asbestos, silica, radon, heavy metals, and polycyclic aromatic hydrocarbons.
- 26 Positive family history of lung cancer (decision on enrolling participants with positive family history of lung cancer will be made on a case-by-case basis by the investigator in consultation with the medical
- 40 monitor).

- 27 Positive urine cotinine test or exhaled carbon monoxide test at Visit 1 and at any timepoint throughout the study.
- 28 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
- 5 29 Judgement by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.
- 30 Donation of blood ( $\geq 450$  mL) within 3 months or donation of plasma within 14 days before Visit 1.
- 31 Major surgery within 8 weeks prior to Visit 1, or planned inpatient surgery, major dental procedure or hospitalisation during Screening, Treatment, or Follow-up periods.

10

**Dose**

The tested dosages are 1.4 mg twice per day, 0.9 mg twice per day and 0.4 mg twice per day. The tested daily dosages are therefore 0.8 mg, 1.8 mg or 2.8 mg.

- 15 The proposed dose regimen, 1.4 mg BID (2.8 mg/day) is based on the observed safety and efficacy biomarker data from the Phase 1 study (D8210C00001). In the Phase 1 study (D8210C00001), a 1.4 mg BID dose was found to be safe and well-tolerated and resulted in approximately 50% reduction in the lung inflammation biomarker FeNO versus placebo in participants with mild asthma. A reduction in FeNO of this magnitude is regarded as a good indication of likely clinical efficacy.

20

The term dose refers to the device delivered dose of Compound 1. The dose selection is based on target engagement (FeNO level) and safety data from the Phase 1 study (D8210C00001).

- Therefore, the 1.4 mg BID dose was considered to provide the optimal risk/benefit profile to evaluate in further clinical development based on the data available.
- 25

*Table 21 – Phase 2 primary objectives, endpoints and estimands.*

| Primary Objectives                                                                                                                                  | Endpoints and Estimand                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| To evaluate the clinical efficacy of Compound 1 1.4 mg BID as compared to placebo in adult participants with moderate-to-severe uncontrolled asthma | <p><b>Population:</b> Analysis will include participants randomised to either placebo or Compound 1, 1.4 mg BID arms.</p> <p><b>Endpoint:</b> Time to first CompEx (composite endpoint for exacerbation) event.</p> <p><b>Population-level summary measure:</b> Hazard ratio, survival estimates by Kaplan-Meier estimator.</p> <p><b>Strategy of intercurrent events:</b></p> <p><u>Primary estimand:</u> While on treatment – if an intercurrent event occurs before first CompEx event, the participant will be censored at the time of intercurrent event.</p> <p><u>Supportive estimand:</u> Treatment policy (reflects ITT - intent-to-treat principle) – after intercurrent event,</p> |

| Primary Objectives | Endpoints and Estimand                                                                                                                                                                  |
|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                    | participants remain in the study so that the endpoint could be studied until Week 12. Treatment policy strategy used to estimate the efficacy of Compound 1 in “real world” conditions. |

Table 22 – Phase 2 secondary objectives, endpoints and estimands.

| Secondary Objectives                                                                                                                                | Endpoints and Estimand                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| To evaluate the clinical efficacy of Compound 1 1.4 mg BID as compared to placebo in adult participants with moderate-to-severe uncontrolled asthma | <p><b>Population:</b> Analysis will include participants randomised to either placebo or Compound 1, 1.4 mg BID arms.</p> <p><b>Endpoints**:</b> Change from baseline in:</p> <ol style="list-style-type: none"> <li>1 Pre-BD FEV1 (forced expiratory volume in 1 second) at Week 4 and Week 12</li> <li>2 CAAT (chronic airways assessment test) at Week 4 and Week 12</li> <li>3 ACQ-6 (asthma control questionnaire-6) at Week 4 and Week 12</li> <li>4 Average morning and average evening PEF (peak expiratory flow) at Week 4 and Week 12, and average over the 12-week Treatment period</li> <li>5 Daily asthma symptom score (total, daytime, and night-time) at Week 4 and Week 12</li> </ol> <p><b>Population-level summary measure:</b> Average change from baseline.</p> <p><b>Strategy for intercurrent events:</b> Same as for primary objectives.</p> |
|                                                                                                                                                     | <p><b>Population:</b> Analysis will include participants randomised to either placebo or Compound 1 1.4 mg BID arms.</p> <p><b>Endpoints:</b></p> <ol style="list-style-type: none"> <li>1 Time to first CompEx (composite endpoint for exacerbation) acute worsening event</li> <li>2 CompEx (composite endpoint for exacerbation) event rate</li> <li>3 CompEx (composite endpoint for exacerbation) acute worsening event rate</li> </ol> <p><b>Population-level summary measure:</b></p> <ol style="list-style-type: none"> <li>1 Hazard ratio, survival estimates by Kaplan-Meier estimator</li> <li>2 (a) Percentage of participants with at least 1 event<br/>(b) Event rate normalised on study follow-up duration (12 weeks)</li> <li>3 (a) Percentage of participants with at least 1 event</li> </ol>                                                     |

| Secondary Objectives                                                                                                                              | Endpoints and Estimand                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                   | (b) Event rate normalised on study follow-up duration<br>(12 weeks)<br><b>Strategy for intercurrent events:</b> <ol style="list-style-type: none"> <li>1 While on treatment</li> <li>2 Treatment policy</li> <li>3 Treatment policy</li> </ol>                                                                                                                                               |
| To evaluate the effect of Compound 1 on airway inflammation as measured by FeNO                                                                   | <b>Population:</b> Analysis will include participants randomised to either placebo or Compound 1 1.4 mg BID arms.<br><b>Endpoint**:</b> Change from baseline in FeNO at Week 4 and Week 12.<br><b>Population-level summary measure:</b> Average change from baseline to Week 4 and Week 12.<br><b>Strategy for intercurrent events:</b> Same as for the primary objectives.                  |
| To evaluate the effect of Compound 1 1.4 mg BID on cough as compared to placebo in adult participants with moderate-to-severe uncontrolled asthma | <b>Population:</b> Analysis will include participants randomised to either placebo or Compound 1 1.4 mg BID arms.<br><b>Endpoints**:</b> Change from baseline in cough severity at Week 4, Week 12, and over the Treatment period.<br><b>Population-level summary measure:</b> Average change from baseline.<br><b>Strategy for intercurrent events:</b> Same as for the primary objectives. |
| To evaluate the PK of Compound 1 in all participants after 4 weeks and 12 weeks dosing                                                            | <b>Population:</b> All participants who had received at least 1 dose of Compound 1, and who had at least one measurable PK sample after first dose.<br><b>Endpoint**:</b> Compound 1 plasma concentration pre- and post-dose at Week 4, pre-dose at Week 12.<br><b>Population-level summary measure:</b> Summary statistics<br><b>Strategy for intercurrent events:</b> While on treatment   |

\*\* Timepoints included in the estimands refers to: Baseline = V3 (Day 1); Week 4 = V5

(29 days  $\pm$  3 days); Week 12 = V7 (85 days  $\pm$  3 days).

Intercurrent events are events occurring after treatment initiation (e.g., discontinuation of IMP, terminal events such as death) that affect either the measurement or interpretation of the summary measure

5 (e.g., hazard ratio) associated with the clinical question of interest.

Table 23 – Phase 2 safety objectives, endpoints and estimands.

| Secondary Objectives                                                    | Endpoints and Estimand                                                                                                |
|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| To assess the safety and tolerability of Compound 1 1.4 mg BID in adult | <b>Population:</b> Analysis will include all participants randomised to either placebo or Compound 1 1.4 mg BID arms. |

| Secondary Objectives                                     | Endpoints and Estimand                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| participants with moderate-to-severe uncontrolled asthma | <p><b>Endpoint:</b> Safety and tolerability evaluations using all Adverse Events, vital sign measures, clinical laboratory assessments, ECG (electrocardiogram).</p> <p><b>Population-level summary measure:</b> Descriptive statistics including absolute counts and frequencies.</p> <p><b>Strategy for intercurrent events:</b></p> <p><u>Primary estimand:</u> While on treatment – if an intercurrent event occurs, after the safety follow-up, any subsequent safety data will not be taken into consideration in the safety evaluation.</p> <p><u>Supportive estimand:</u> Treatment policy – if an intercurrent event occurs, participants remain in the study and any safety data until Week 12 plus safety follow-up will be taken into consideration in the safety evaluation.</p> |

Table 24 Pharmacokinetic Parameters

| Parameter                    | Explanation                                                                                                                                      |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| C <sub>max</sub>             | Maximum observed plasma concentration                                                                                                            |
| t <sub>max</sub>             | Time to reach maximum observed concentration following drug administration                                                                       |
| $\lambda_z$                  | Terminal elimination rate constant, estimated from linear regression of the terminal part of the log concentration versus time curve             |
| t <sub>1/2</sub> $\lambda_z$ | Half-life associated with terminal slope ( $\lambda_z$ ) of a semi-logarithmic concentration-time curve                                          |
| AUC(0-12)                    | Partial area under the plasma concentration-time curve from time 0 to 12 hours                                                                   |
| AUC(0-24)                    | Partial area under the plasma concentration-time curve from time 0 to 24 hours                                                                   |
| AUC <sub>last</sub>          | Area under the plasma concentration-curve from zero to the last quantifiable concentration                                                       |
| AUC <sub>inf</sub>           | Area under plasma concentration-time curve from zero to infinity                                                                                 |
| CL/F                         | Apparent total body clearance of drug from plasma after extravascular administration (Inhaled and PO Cohorts only)                               |
| CL                           | Total body clearance of drug from plasma after intravascular administration (IV Cohort only)                                                     |
| V <sub>z</sub> /F            | Volume of distribution (apparent) at steady state following extravascular administration (based on terminal phase) (Inhaled and PO Cohorts only) |
| V <sub>z</sub>               | Volume of distribution following intravascular administration (based on terminal phase) (IV Cohort only)                                         |
| AUC <sub>last</sub> /D       | Dose normalized AUC <sub>last</sub> , derived by AUC <sub>last</sub> divided by the dose administered                                            |
| AUC <sub>inf</sub> /D        | Dose normalized AUC <sub>inf</sub> , derived by AUC <sub>inf</sub> divided by the dose administered                                              |

|                                     |                                                                                                                                 |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| C <sub>max</sub> /D                 | Dose normalized C <sub>max</sub> , derived by C <sub>max</sub> divided by the dose administered                                 |
| t <sub>last</sub>                   | Time of last observed (quantifiable) concentration                                                                              |
| AUC <sub>τ</sub>                    | Area under plasma concentration-time curve in the dose interval                                                                 |
| Rac AUC                             | Accumulation ratio for AUC <sub>τ</sub> (reported against Day 7 [Part 2] or Day 10 [Part 3])                                    |
| Rac C <sub>max</sub>                | Accumulation ratio for C <sub>max</sub> (reported against Day 7 [Part 2] or Day 10 [Part 3])                                    |
| t <sub>last</sub>                   | Time of last observed (quantifiable) concentration                                                                              |
| λ <sub>z</sub> lower                | Lower (earlier) t used for λ <sub>z</sub> determination                                                                         |
| λ <sub>z</sub> upper                | Upper (later) t used for λ <sub>z</sub> determination                                                                           |
| λ <sub>z</sub> N                    | Number of data points used for λ <sub>z</sub> determination                                                                     |
| λ <sub>z</sub> span ratio           | Time period over which λ <sub>z</sub> was determined as ratio of t <sub>1/2</sub> /λ <sub>z</sub>                               |
| Rsq                                 | Statistical measure of fit for the regression used for λ <sub>z</sub> determination                                             |
| Rsq adj                             | Statistical measure of fit for the regression used for λ <sub>z</sub> determination adjusted for the number of used data points |
| AUC <sub>extr</sub>                 | Extrapolated area under the curve from t <sub>last</sub> to infinity, expressed as percentage of AUC <sub>inf</sub>             |
| Ae(t <sub>1</sub> -t <sub>2</sub> ) | Cumulative amount of unchanged drug excreted into urine from time t <sub>1</sub> to time t <sub>2</sub>                         |
| fe(t <sub>1</sub> -t <sub>2</sub> ) | Cumulative percentage of dose excreted unchanged in urine from time t <sub>1</sub> to time t <sub>2</sub>                       |
| CLR                                 | Renal clearance of drug from plasma                                                                                             |

**References**

Several publications are cited above. Full citations for these references are provided below. The entirety of each of these references is incorporated herein.

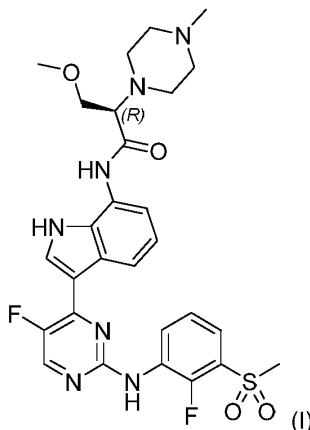
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For standard molecular biology techniques, see Sambrook, J., Russel, D.W. *Molecular Cloning, A Laboratory Manual*. 3 ed. 2001, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press

**Statements:**

1. A method of treatment or prophylaxis of a disease or condition in which inhibition of JAK1 is beneficial, comprising administering to a subject in need thereof, a Compound of Formula (I):



5 or a pharmaceutically acceptable salt thereof, in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base.

2. The method according to statement 1, wherein the disease or condition in which inhibition of JAK1 is beneficial is selected from type 1 diabetes, lupus, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriasis, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease (COPD), vitiligo and alopecia areata.

3. The method according to statement 2, wherein the disease or condition in which inhibition of JAK1 is beneficial is asthma.

4. The method according to statement 2, wherein the disease or condition in which inhibition of JAK1 is beneficial is COPD.

5. The method according to any one of statements 1 to 4, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of at least 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, 1.6 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2.0 mg, 2.1 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.5 mg, 2.6 mg, 2.7 mg, 2.8 mg, 2.9 mg, 3.0 mg, 3.1 mg, 3.2 mg, 3.4 mg, 3.5 mg, 3.6 mg, 3.7 mg, 3.8 mg, 3.9 mg, 4.0 mg, 4.1 mg, 4.2 mg, 4.3 mg, 4.4 mg, 4.5 mg, 4.6 mg, 4.7 mg, 4.8 mg, 4.9 mg, 5.0 mg, 5.1 mg, 5.2 mg, 5.3 mg, 5.4 mg or 5.5 mg per day of the free base.

6. The method according to any one of statements 1 to 4, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of up to 6.2 mg, 6.1 mg, 6.0 mg, 5.9 mg, 5.8 mg, 5.7 mg, 5.6 mg, 5.5 mg, 5.4 mg, 5.3 mg, 5.2 mg, 5.1 mg, 5.0 mg, 4.9 mg, 4.8 mg, 4.7 mg, 4.6 mg, 4.5 mg, 4.4 mg, 4.3 mg, 4.2 mg, 4.1 mg, 4.0 mg, 3.9 mg, 3.8 mg, 3.7 mg, 3.6 mg, 3.5 mg, 3.4 mg, 3.3 mg, 3.2 mg, 3.1 mg, 3.0 mg, 2.9 mg, 2.8 mg, 2.7 mg, 2.6 mg, 2.5 mg, 2.4 mg, 2.3 mg, 2.2 mg, 2.1 mg, 2.0 mg, 1.9 mg, 1.8 mg, 1.7 mg, 1.6 mg, 1.5 mg, 1.4 mg, 1.3 mg, 1.2 mg, 1.1 mg, 1.0 mg, 0.9 mg, 0.8 mg, 0.7 mg, 0.6 mg, 0.5 mg, 0.4 mg, 0.3 mg, 0.2 mg, 0.1 mg, 0.05 mg or 0.01 mg per day of the free base.

mg, 2.1 mg, 2.0 mg, 1.9 mg, 1.8 mg, 1.7 mg, 1.6 mg, 1.5 mg, 1.4 mg, 1.3 mg, 1.2 mg, 1.1 mg or 1.0 mg per day of the free base.

7. The method according to any one of statements 1 to 6, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered in a daily delivered dose of 2.8 mg of the free base.

8. The method according to any one of statements 1 to 6, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered in a daily delivered dose of 1.8 mg of the free base.

9. The method according to any one of statements 1 to 6, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered in a daily delivered dose of 0.8 mg of the free base.

10. The method according to any one of statements 1 to 6, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered in a daily delivered dose of 6.0 mg of the free base.

11. The method according to any one of statements 1 to 10, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered at a delivered dose of from 0.4 to 3.1 mg of the free base twice per day.

12. The method according to any one of statements 1 to 11, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered in a delivered dose of at least 0.4 mg twice per day, 0.45 mg twice per day, 0.5 mg twice per day, 0.6 mg twice per day, 0.65 mg twice per day, 0.7 mg twice per day, 0.75 mg twice per day, 0.8 mg twice per day, 0.85 mg twice per day, 0.9 mg twice per day, 0.95 mg twice per day, 1.0 mg twice per day, 1.05 mg twice per day, 1.1 mg twice per day, 1.15 mg twice per day, 1.2 mg twice per day, 1.25 mg twice per day, 1.3 mg twice per day, 1.35 mg twice per day, 1.4 mg twice per day, 1.45 mg twice per day, 1.5 mg twice per day, 1.55 mg twice per day, 1.6 mg twice per day, 1.65 mg twice per day, 1.7 mg twice per day, 1.75 mg twice per day, 1.8 mg twice per day, 1.85 mg twice per day, 1.9 mg twice per day, 2.0 mg twice per day, 2.05 mg twice per day, 2.1 mg twice per day, 2.15 mg twice per day, 2.2 mg twice per day, 2.25 mg twice per day, 2.3 mg twice per day, 2.35 mg twice per day, 2.4 mg twice per day, 2.45 mg twice per day, 2.5 mg twice per day, 2.55 mg twice per day, 2.6 mg twice per day, 2.7 mg twice per day or 2.75 mg twice per day of the free base.

13. The method according to any one of statements 1 to 11, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered in a delivered dose of up to 3.1 mg twice per day, 3.05 mg twice per day, 3.0 mg twice per day, 2.95 mg twice per day, 2.9 mg twice per day, 2.85 mg twice per day, 2.8 mg twice per day, 2.75 mg twice per day, 2.7 mg twice per day, 2.65 mg twice per day, 2.6 mg twice per day, 2.55 mg twice per day, 2.5 mg twice per day, 2.45 mg twice per

- day, 2.4 mg twice per day, 2.35 mg twice per day, 2.3 mg twice per day, 2.25 mg twice per day, 2.2 mg twice per day, 2.15 mg twice per day, 2.1 mg twice per day, 2.05 mg twice per day, 2.0 mg twice per day, 1.95 mg twice per day, 1.9 mg twice per day, 1.85 mg twice per day, 1.8 mg twice per day, 1.75 mg twice per day, 1.7 mg twice per day, 1.65 mg twice per day, 1.6 mg twice per day, 1.55 mg twice per day, 1.5 mg twice per day, 1.45 mg twice per day, 1.4 mg twice per day, 1.35 mg twice per day, 1.3 mg twice per day, 1.25 mg twice per day, 1.2 mg twice per day, 1.15 mg twice per day, 1.1 mg twice per day, 1.05 mg twice per day, 1.0 mg twice per day, 0.95 mg twice per day, 0.9 mg twice per day, 0.85 mg twice per day, 0.8 mg twice per day, 0.75 mg twice per day, 0.7 mg twice per day, 0.65 mg twice per day, 0.6 mg twice per day, 0.55 mg twice per day, or 0.5 mg twice per day of the free base.
- 10 14. The method according to any one of statements 1 to 13, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered in a delivered dose of 1.4 mg of the free base twice per day.
- 15 15. The method according to any one of statements 1 to 13, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered in a delivered dose of 0.9 mg of the free base twice per day.
- 20 16. The method according to any one of statements 1 to 11, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered in a delivered dose of 0.4 mg of the free base twice per day.
- 25 17. The method according to any one of statements 1 to 11, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered in a delivered dose of 3.0 mg of the free base twice per day.
- 30 18. The method according to any one of statements 1 to 17, wherein the Compound of Formula (I) is administered as a pharmaceutically acceptable salt.
- 35 19. The method according to statement 18, wherein the Compound of Formula (I) is administered as the xinafoate salt.
20. The method according to any one of statements 1 to 4 or 19, wherein the Compound of Formula (I) is administered as the xinafoate salt in a daily delivered dose of from 1.05 mg to 8.14 mg of the xinafoate salt.
21. The method according to statement 20, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 1.84 mg of the xinafoate salt twice per day.
- 40 22. The method according to statement 20, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 1.18 mg xinafoate salt twice per day.

23. The method according to statement 20, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 0.53 mg xinafoate salt twice per day.
- 5 24. The method according to statement 20, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 3.94 mg xinafoate salt twice per day.
25. The method according to any one of statements 11 to 19 or 21 to 24, wherein the dosages are spaced from 10 to 14 hours.
- 10 26. The method according to statement 25, wherein the dosages are spaced from 11 hours 30 minutes and 12 hours 30 minutes.
27. The method according to any one of statements 1 to 26, wherein the Compound of Formula (I) or  
15 pharmaceutically acceptable salt thereof is administered orally.
28. The method according to any one of statements 1 to 26, wherein the Compound of Formula (I) or pharmaceutically acceptable salt thereof is administered in an inhaled aerosol dosage form.
- 20 29. The method according to any one of statements 1 to 26, wherein the Compound of Formula (I) or pharmaceutically acceptable salt thereof is administered via a dry powder inhaler.
30. The method according to any one of statements 1 to 26, wherein the Compound of Formula (I) or pharmaceutically acceptable salt thereof is administered via a pressurised metered dose inhaler.
- 25 31. A Compound of Formula (I) or a pharmaceutically acceptable salt thereof as defined in statement 1, for use in the treatment or prophylaxis of a disease or condition in which inhibition of JAK1 is beneficial, wherein said treatment comprises the administration of the Compound of Formula (I) or pharmaceutically acceptable salt thereof, in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base to a subject.
- 30 32. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to statement 31, wherein the disease or condition in which inhibition of JAK1 is beneficial is selected from type 1 diabetes, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, COPD, vitiligo and alopecia areata.
- 35 33. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to statement 32, wherein the disease or condition in which inhibition of JAK1 is beneficial is asthma.
- 40 34. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to statement 32, wherein the disease or condition in which inhibition of JAK1 is beneficial is COPD.

35. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of statements 31 to 34, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered in a daily delivered dose of at least 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, 1.6 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2.0 mg, 2.1 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.5 mg, 2.6 mg, 2.7 mg, 2.8 mg, 2.9 mg, 3.0 mg, 3.1 mg, 3.2 mg, 3.4 mg, 3.5 mg, 3.6 mg, 3.7 mg, 3.8 mg, 3.9 mg, 4.0 mg, 4.1 mg, 4.2 mg, 4.3 mg, 4.4 mg, 4.5 mg, 4.6 mg, 4.7 mg, 4.8 mg, 4.9 mg, 5.0 mg, 5.1 mg, 5.2 mg, 5.3 mg, 5.4 mg or 5.5 mg per day of the free base.

36. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of statements 31 to 34, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of up to 6.2 mg, 6.1 mg, 6.0 mg, 5.9 mg, 5.8 mg, 5.7 mg, 5.6 mg, 5.5 mg, 5.4 mg, 5.3 mg, 5.2 mg, 5.1 mg, 5.0 mg, 4.9 mg, 4.8 mg, 4.7 mg, 4.6 mg, 4.5 mg, 4.4 mg, 4.3 mg, 4.2 mg, 4.1 mg, 4.0 mg, 3.9 mg, 3.8 mg, 3.7 mg, 3.6 mg, 3.5 mg, 3.4 mg, 3.3 mg, 3.2 mg, 3.1 mg, 3.0 mg, 2.9 mg, 2.8 mg, 2.7 mg, 2.6 mg, 2.5 mg, 2.4 mg, 2.3 mg, 2.2 mg, 2.1 mg, 2.0 mg, 1.9 mg, 1.8 mg, 1.7 mg, 1.6 mg, 1.5 mg, 1.4 mg, 1.3 mg, 1.2 mg, 1.1 mg or 1.0 mg per day of the free base.

37. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of statements 31 to 36, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of 2.8 mg of the free base.

38. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of statements 31 to 36, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of 1.8 mg of the free base.

39. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of statements 31 to 36, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of 0.8 mg of the free base.

40. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of statements 31 to 36, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of 6.0 mg of the free base.

41. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of statements 31 to 36, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a delivered dose of from 0.4 to 3.1 mg of the free base twice per day.

42. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to statement 41, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a delivered dose of at least 0.4 mg twice per day, 0.45 mg twice per day, 0.5 mg twice per day, 0.6 mg twice per day, 0.65 mg twice per day, 0.7 mg twice per day, 0.75 mg twice per day, 0.8 mg twice per day, 0.85 mg twice per day, 0.9 mg twice per day, 0.95 mg twice per day, 1.0 mg twice per day,

1.05 mg twice per day, 1.1 mg twice per day, 1.15 mg twice per day, 1.2 mg twice per day, 1.25 mg twice per day, 1.3 mg twice per day, 1.35 mg twice per day, 1.4 mg twice per day, 1.45 mg twice per day, 1.5 mg twice per day, 1.55 mg twice per day, 1.6 mg twice per day, 1.65 mg twice per day, 1.7 mg twice per day, 1.75 mg twice per day, 1.8 mg twice per day, 1.85 mg twice per day, 1.9 mg twice per day, 2.0 mg twice per day, 2.05 mg twice per day, 2.1 mg twice per day, 2.15 mg twice per day, 2.2 mg twice per day, 2.25 mg twice per day, 2.3 mg twice per day, 2.35 mg twice per day, 2.4 mg twice per day, 2.45 mg twice per day, 2.5 mg twice per day, 2.55 mg twice per day, 2.6 mg twice per day, 2.7 mg twice per day or 2.75 mg twice per day of the free base.

43. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to statement 41, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered in a delivered dose of up to 3.1 mg twice per day, 3.05 mg twice per day, 3.0 mg twice per day, 2.95 mg twice per day, 2.9 mg twice per day, 2.85 mg twice per day, 2.8 mg twice per day, 2.75 mg twice per day, 2.7 mg twice per day, 2.65 mg twice per day, 2.6 mg twice per day, 2.55 mg twice per day, 2.5 mg twice per day, 2.45 mg twice per day, 2.4 mg twice per day, 2.35 mg twice per day, 2.3 mg twice per day, 2.25 mg twice per day, 2.2 mg twice per day, 2.15 mg twice per day, 2.1 mg twice per day, 2.05 mg twice per day, 2.0 mg twice per day, 1.95 mg twice per day, 1.9 mg twice per day, 1.85 mg twice per day, 1.8 mg twice per day, 1.75 mg twice per day, 1.7 mg twice per day, 1.65 mg twice per day, 1.6 mg twice per day, 1.55 mg twice per day, 1.5 mg twice per day, 1.45 mg twice per day, 1.4 mg twice per day, 1.35 mg twice per day, 1.3 mg twice per day, 1.25 mg twice per day, 1.2 mg twice per day, 1.15 mg twice per day, 1.1 mg twice per day, 1.05 mg twice per day, 1.0 mg twice per day, 0.95 mg twice per day, 0.9 mg twice per day, 0.85 mg twice per day, 0.8 mg twice per day, 0.75 mg twice per day, 0.7 mg twice per day, 0.65 mg twice per day, 0.6 mg twice per day, 0.55 mg twice per day, or 0.5 mg twice per day of the free base.

44. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to statement 42 or statement 43, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a delivered dose of 1.4 mg of the free base twice per day.

45. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to statement 42 or statement 43, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a delivered dose of 0.9 mg of the free base twice per day.

46. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to statement 42 or statement 43, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a delivered dose of 0.4 mg of the free base twice per day.

47. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to statement 42 or statement 43, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a delivered dose of 3.0 mg of the free base twice per day.

48. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of statements 31 to 47, wherein the Compound of Formula (I) is administered as a pharmaceutically acceptable salt.
- 5 49. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to statement 48, wherein the Compound of Formula (I) is administered as the xinafoate salt.
50. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of statements 31 to 34 or 49, wherein the Compound of Formula (I) is administered as the  
10 xinafoate salt in a daily delivered dose of from 1.05 mg to 8.14 mg of the xinafoate salt.
51. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to statement 50, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 1.84 mg of the xinafoate salt twice per day.  
15
52. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to statement 50, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 1.18 mg of the xinafoate salt twice per day.
- 20 53. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to statement 50, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 0.53 mg of the xinafoate salt twice per day.
54. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to  
25 statement 50, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 3.94 mg of the xinafoate salt twice per day.
55. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of statements 34 to 40, wherein the dosages are spaced from 10 to 14 hours.  
30
56. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to statement 55, wherein the dosages are spaced from 11 hours 30 minutes to 12 hours 30 minutes.
57. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to  
35 any one of statements 31 to 56, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.
58. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of statements 31 to 56, wherein the Compound of Formula (I), or a pharmaceutically acceptable  
40 salt thereof, is administered in an inhaled aerosol dosage form.

59. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of statements 31 to 56, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered via a dry powder inhaler.
- 5 60. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of statements 31 to 56, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered via a pressurised metered dose inhaler.
61. The use of the Compound of Formula (I) as defined in statement 1, or a pharmaceutically  
10 acceptable salt thereof, in the manufacture of a medicament for use in the treatment of or prophylaxis of diseases or conditions in which inhibition of JAK1 is beneficial, wherein said treatment comprises administering to the patient of a Compound of Formula (I), or a pharmaceutically acceptable salt thereof , in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base.
- 15 62. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to statement 61, wherein the disease or condition in which inhibition of JAK1 is beneficial is selected from type 1 diabetes, lupus, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriasis, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, COPD, vitiligo and alopecia areata.
- 20 63. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to statement 62, wherein the disease or condition in which inhibition of JAK1 is beneficial is asthma.
64. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according  
25 to statement 62, wherein the disease or condition in which inhibition of JAK1 is beneficial is COPD.
65. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 64, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of at least 0.8 mg, 0.9 mg, 1.0 mg, 1.1  
30 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, 1.6 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2.0 mg, 2.1 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.5 mg, 2.6 mg, 2.7 mg, 2.8 mg, 2.9 mg, 3.0 mg, 3.1 mg, 3.2 mg, 3.4 mg, 3.5 mg, 3.6 mg, 3.7 mg, 3.8 mg, 3.9 mg, 4.0 mg, 4.1 mg, 4.2 mg, 4.3 mg , 4.4 mg, 4.5 mg, 4.6 mg, 4.7 mg, 4.8 mg, 4.9 mg, 5.0 mg, 5.1 mg, 5.2 mg, 5.3 mg , 5.4 mg or 5.5 mg of the free base per day.
- 35 66. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 64, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of up to 6.2 mg, 6.1 mg, 6.0mg, 5.9 mg, 5.8 mg, 5.7mg, 5.6 mg, 5.5 mg, 5.4 mg, 5.3 mg, 5.2 mg, 5.1 mg, 5.0 mg, 4.9 mg, 4.8 mg, 4.7 mg, 4.6 mg, 4.5 mg, 4.4 mg, 4.3 mg, 4.2 mg, 4.1 mg, 4.0 mg, 3.9 mg, 3.8 mg, 3.7 mg, 3.6 mg, 3.5 mg, 3.4 mg, 3.3 mg,  
40 3.2 mg, 3.1 mg, 3.0 mg, 2.9 mg, 2.8 mg, 2.7 mg, 2.6 mg, 2.5 mg, 2.4 mg, 2.3 mg, 2.2 mg, 2.1 mg, 2.0 mg,

1.9 mg, 1.8 mg, 1.7 mg, 1.6 mg, 1.5 mg, 1.4 mg, 1.3 mg, 1.2 mg, 1.1 mg or 1.0 mg of the free base per day.

67. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 66, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of 2.8 mg of the free base.

68. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 66, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of 1.8 mg of the free base.

69. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 66, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of 0.8 mg of the free base.

70. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 66, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of 6.0 mg of the free base.

71. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 70, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a delivered dose of from 0.4 to 3.1 mg of the free base twice per day.

72. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 71, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a delivered dose of at least 0.4 mg twice per day, 0.45 mg twice per day, 0.5 mg twice per day, 0.6 mg twice per day, 0.65 mg twice per day, 0.7 mg twice per day, 0.75 mg twice per day, 0.8 mg twice per day, 0.85 mg twice per day, 0.9 mg twice per day, 0.95 mg twice per day, 1.0 mg twice per day, 1.05 mg twice per day, 1.1 mg twice per day, 1.15 mg twice per day, 1.2 mg twice per day, 1.25 mg twice per day, 1.3 mg twice per day, 1.35 mg twice per day, 1.4 mg twice per day, 1.45 mg twice per day, 1.5 mg twice per day, 1.55 mg twice per day, 1.6 mg twice per day, 1.65 mg twice per day, 1.7 mg twice per day, 1.75 mg twice per day, 1.8 mg twice per day, 1.85 mg twice per day, 1.9 mg twice per day, 2.0 mg twice per day, 2.05 mg twice per day, 2.1 mg twice per day, 2.15 mg twice per day, 2.2 mg twice per day, 2.25 mg twice per day, 2.3 mg twice per day, 2.35 mg twice per day, 2.4 mg twice per day, 2.45 mg twice per day, 2.5 mg twice per day, 2.55 mg twice per day, 2.6 mg twice per day, 2.7 mg twice per day or 2.75 mg twice per day of the free base.

73. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 71, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, optionally in the form of a pharmaceutically acceptable salt, is administered in a

delivered dose of up to 3.1 mg twice per day, 3.05 mg twice per day, 3.0 mg twice per day, 2.95 mg twice per day, 2.9 mg twice per day, 2.85 mg twice per day, 2.8 mg twice per day, 2.75 mg twice per day, 2.7 mg twice per day, 2.65 mg twice per day, 2.6 mg twice per day, 2.55 mg twice per day, 2.5 mg twice per day, 2.45 mg twice per day, 2.4 mg twice per day, 2.35 mg twice per day, 2.3 mg twice per day, 2.25 mg twice per day, 2.2 mg twice per day, 2.15 mg twice per day, 2.1 mg twice per day, 2.05 mg twice per day, 2.0 mg twice per day, 1.95 mg twice per day, 1.9 mg twice per day, 1.85 mg twice per day, 1.8 mg twice per day, 1.75 mg twice per day, 1.7 mg twice per day, 1.65 mg twice per day, 1.6 mg twice per day, 1.55 mg twice per day, 1.5 mg twice per day, 1.45 mg twice per day, 1.4 mg twice per day, 1.35 mg twice per day, 1.3 mg twice per day, 1.25 mg twice per day, 1.2 mg twice per day, 1.15 mg twice per day, 1.1 mg twice per day, 1.05 mg twice per day, 1.0 mg twice per day, 0.95 mg twice per day, 0.9 mg twice per day, 0.85 mg twice per day, 0.8 mg twice per day, 0.75 mg twice per day, 0.7 mg twice per day, 0.65 mg twice per day, 0.6 mg twice per day, 0.55 mg twice per day, or 0.5 mg twice per day of the free base.

74. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 73, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a delivered dose of 1.4 mg of the free base twice per day.

75. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 73, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a delivered dose of 0.9 mg of the free base twice per day.

76. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 71, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a delivered dose of 0.4 mg of the free base twice per day.

77. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 71, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a delivered dose of 3.0 mg of the free base twice per day.

78. The use of the Compound of Formula (I) according to any one of statements 61 to 77, wherein the Compound of Formula (I) is administered as a pharmaceutically acceptable salt.

79. The use of the Compound of Formula (I) according to statement 78, wherein the Compound of Formula (I) is administered as the xinafoate salt.

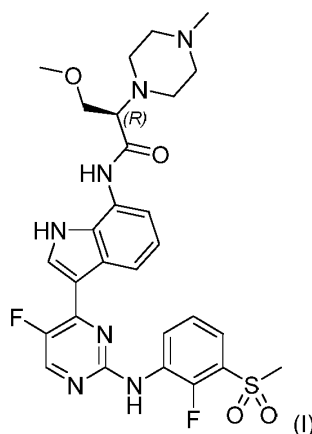
80. The use of the Compound of Formula (I) according to any one of statements 61 to 64 or 79, wherein the Compound of Formula (I) is administered as the xinafoate salt in a daily delivered dose of from 1.05 mg to 8.14 mg of the xinafoate salt.

81. The use of the Compound of Formula (I) according to statement 80, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 1.84 mg of the xinafoate salt twice per day.
- 5 82. The use of the Compound of Formula (I) according to statement 80, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 1.18 mg xinafoate salt twice per day.
83. The use of the Compound of Formula (I) according to statement 80, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 0.53 mg xinafoate salt twice per day.
- 10 84. The use of the Compound of Formula (I) according to statement 80, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 3.94 mg xinafoate salt twice per day.
85. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 71 to 79 or 81 to 84, wherein the dosages are spaced between 10 to 14 hours.
- 15 86. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to statement 85, wherein the dosages are spaced between 11 hours 30 minutes and 12 hours 30 minutes
- 20 87. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 86, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.
88. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 87, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in an inhaled aerosol dosage form.
- 25 89. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 88, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered via a dry powder inhaler.
- 30 90. The use of the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to any one of statements 61 to 88, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered via a pressurised metered dose inhaler.
- 35 91. A kit for use in method of treatment or prophylaxis of a disease or conditions in which inhibition of JAK1 is beneficial, the kit comprising an inhaler which delivers the Compound of Formula (I) in a daily delivered dose of 0.8 mg to 6.2 mg of the free base, wherein the Compound of Formula (I) may be the form of a pharmaceutically acceptable salt.
- 40 92. The kit according to statement 91, wherein the inhaler is a dry powder inhaler.

93. The kit according to statement 91, wherein the inhaler is a pressurised metered dose inhaler.
94. An inhaler which is configured to deliver the Compound of Formula (I), in a delivered dose of 0.4  
5 mg to 3.1 mg of the free base, wherein the Compound of Formula (I) may be the form of a  
pharmaceutically acceptable salt.
95. The inhaler according to statement 94, wherein the inhaler is a dry powder inhaler.
- 10 96. The inhaler according to statement 94, wherein the inhaler is a pressurised metered dose inhaler.

**Claims:**

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of a disease or  
 5 condition in which inhibition of JAK1 is beneficial, wherein said treatment comprises the administration of  
 the Compound of Formula (I) or pharmaceutically acceptable salt thereof, in a daily delivered dose of  
 from 0.8 mg to 6.2 mg of the free base to a subject.

2. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to  
 10 claim 1, wherein the disease or condition in which inhibition of JAK1 is beneficial is asthma or COPD.

3. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to  
 either claim 1 or claim 2, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt  
 thereof is administered in a daily delivered dose of at least 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3  
 15 mg, 1.4 mg, 1.5 mg, 1.6 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2.0 mg, 2.1 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.5 mg, 2.6  
 mg, 2.7 mg, 2.8 mg, 2.9 mg, 3.0 mg, 3.1 mg, 3.2 mg, 3.4 mg, 3.5 mg, 3.6 mg, 3.7 mg, 3.8 mg, 3.9 mg, 4.0  
 mg, 4.1 mg, 4.2 mg, 4.3 mg, 4.4 mg, 4.5 mg, 4.6 mg, 4.7 mg, 4.8 mg, 4.9 mg, 5.0 mg, 5.1 mg, 5.2 mg,  
 5.3 mg, 5.4 mg or 5.5 mg per day of the free base.

4. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to  
 any one of claims 1 to 3, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt  
 thereof, is administered in a daily delivered dose of up to 6.2 mg, 6.1 mg, 6.0 mg, 5.9 mg, 5.8 mg, 5.7 mg,  
 5.6 mg, 5.5 mg, 5.4 mg, 5.3 mg, 5.2 mg, 5.1 mg, 5.0 mg, 4.9 mg, 4.8 mg, 4.7 mg, 4.6 mg, 4.5 mg, 4.4 mg,  
 4.3 mg, 4.2 mg, 4.1 mg, 4.0 mg, 3.9 mg, 3.8 mg, 3.7 mg, 3.6 mg, 3.5 mg, 3.4 mg, 3.3 mg, 3.2 mg, 3.1 mg,  
 25 3.0 mg, 2.9 mg, 2.8 mg, 2.7 mg, 2.6 mg, 2.5 mg, 2.4 mg, 2.3 mg, 2.2 mg, 2.1 mg, 2.0 mg, 1.9 mg, 1.8 mg,  
 1.7 mg, 1.6 mg, 1.5 mg, 1.4 mg, 1.3 mg, 1.2 mg, 1.1 mg or 1.0 mg per day of the free base.

5. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to  
 any one of claims 1 to 4, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt  
 thereof, is administered in a daily delivered dose of one of:  
 30 (a) 2.8 mg of the free base;

- (b) 1.8 mg of the free base;
- (c) 0.8 mg of the free base; and
- (d) 6.0 mg of the free base.

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6. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of claims 1 to 4, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a delivered dose of from 0.4 to 3.1 mg of the free base twice per day.

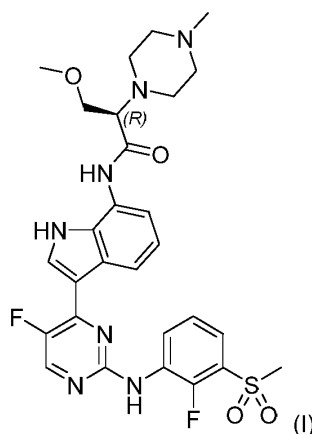
- 10 7. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to claim 6, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a delivered dose of at least 0.4 mg twice per day, 0.45 mg twice per day, 0.5 mg twice per day, 0.6 mg twice per day, 0.65 mg twice per day, 0.7 mg twice per day, 0.75 mg twice per day, 0.8 mg twice per day, 0.85 mg twice per day, 0.9 mg twice per day, 0.95 mg twice per day, 1.0 mg twice per day, 1.05 mg twice per day, 1.1 mg twice per day, 1.15 mg twice per day, 1.2 mg twice per day, 1.25 mg twice per day, 1.3 mg twice per day, 1.35 mg twice per day, 1.4 mg twice per day, 1.45 mg twice per day, 1.5 mg twice per day, 1.55 mg twice per day, 1.6 mg twice per day, 1.65 mg twice per day, 1.7 mg twice per day, 1.75 mg twice per day, 1.8 mg twice per day, 1.85 mg twice per day, 1.9 mg twice per day, 2.0 mg twice per day, 2.05 mg twice per day, 2.1 mg twice per day, 2.15 mg twice per day, 2.2 mg twice per day, 2.25 mg twice per day, 2.3 mg twice per day, 2.35 mg twice per day, 2.4 mg twice per day, 2.45 mg twice per day, 2.5 mg twice per day, 2.55 mg twice per day, 2.6 mg twice per day, 2.7 mg twice per day or 2.75 mg twice per day of the free base.

- 25 8. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to either claim 6 or claim 7, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered in a delivered dose of up to 3.1 mg twice per day, 3.05 mg twice per day, 3.0 mg twice per day, 2.95 mg twice per day, 2.9 mg twice per day, 2.85 mg twice per day, 2.8 mg twice per day, 2.75 mg twice per day, 2.7 mg twice per day, 2.65 mg twice per day, 2.6 mg twice per day, 2.55 mg twice per day, 2.5 mg twice per day, 2.45 mg twice per day, 2.4 mg twice per day, 2.35 mg twice per day, 2.3 mg twice per day, 2.25 mg twice per day, 2.2 mg twice per day, 2.15 mg twice per day, 2.1 mg twice per day, 2.05 mg twice per day, 2.0 mg twice per day, 1.95 mg twice per day, 1.9 mg twice per day, 1.85 mg twice per day, 1.8 mg twice per day, 1.75 mg twice per day, 1.7 mg twice per day, 1.65 mg twice per day, 1.6 mg twice per day, 1.55 mg twice per day, 1.5 mg twice per day, 1.45 mg twice per day, 1.4 mg twice per day, 1.35 mg twice per day, 1.3 mg twice per day, 1.25 mg twice per day, 1.2 mg twice per day, 1.15 mg twice per day, 1.1 mg twice per day, 1.05 mg twice per day, 1.0 mg twice per day, 0.95 mg twice per day, 0.9 mg twice per day, 0.85 mg twice per day, 0.8 mg twice per day, 0.75 mg twice per day, 0.7 mg twice per day, 0.65 mg twice per day, 0.6 mg twice per day, 0.55 mg twice per day, or 0.5 mg twice per day of the free base.

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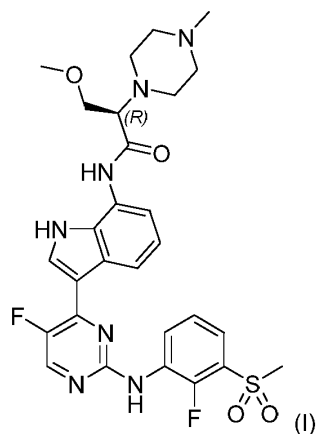
9. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to claim 7 or claim 8, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a delivered dose of one of:
- (a) 1.4 mg of the free base twice per day;
  - 5 (b) 0.9 mg of the free base twice per day;
  - (c) 0.4 mg of the free base twice per day; and
  - (d) 3.0 mg of the free base twice per day.
10. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to claim 9, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a delivered dose of 1.4 mg of the free base twice per day.
11. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of claims 1 to 10, wherein the Compound of Formula (I) is administered as a pharmaceutically acceptable salt.
12. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to claim 11, wherein the Compound of Formula (I) is administered as the xinafoate salt.
13. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of claims 1, 2 and 11, wherein the Compound of Formula (I) is administered as the xinafoate salt in a daily delivered dose of from 1.05 mg to 8.14 mg of the xinafoate salt.
14. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to claim 13, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of one of:
- (a) 1.84 mg of the xinafoate salt twice per day;
  - (b) 1.18 mg of the xinafoate salt twice per day;
  - (c) 0.53 mg of the xinafoate salt twice per day; and
  - 30 (d) 3.94 mg of the xinafoate salt twice per day.
15. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to claim 14, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 1.84 mg of the xinafoate salt twice per day.
16. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of claims 6 to 10 or claims 14 to 15, wherein the dosages are spaced from 10 to 14 hours.
17. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to claim 16, wherein the dosages are spaced from 11 hours 30 minutes to 12 hours 30 minutes.

18. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of claims 1 to 17 wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.
- 5 19. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of claims 1 to 17, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in an inhaled aerosol dosage form.
20. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to  
10 any one of claims 1 to 17, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered via a dry powder inhaler.
21. The Compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of claims 1 to 17, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt  
15 thereof, is administered via a pressurised metered dose inhaler.
22. A kit for use in a method of treatment or prophylaxis of a disease or condition in which inhibition of JAK1 is beneficial, the kit comprising an inhaler which delivers a compound of Formula (I):



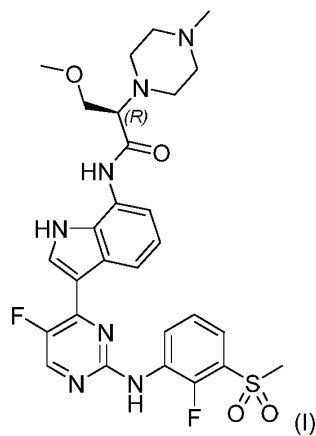
- 20 in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base, wherein the Compound of Formula (I) may be in the form of a pharmaceutically acceptable salt.
23. The kit according to claim 22, wherein the inhaler is a dry powder inhaler.
- 25 24. The kit according to claim 22, wherein the inhaler is a pressurised metered dose inhaler.
25. An inhaler which is configured to deliver a compound of Formula (I):

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in a delivered dose of 0.4 mg to 3.1 mg of the free base, wherein the Compound of Formula (I) may be the form of a pharmaceutically acceptable salt.

- 5 26. The inhaler according to claim 25, wherein the inhaler is a dry powder inhaler.
27. The inhaler according to claim 25, wherein the inhaler is a pressurised metered dose inhaler.
28. A method of treatment or prophylaxis of a disease or condition in which inhibition of JAK1 is
- 10 beneficial, comprising administering to a subject in need thereof, a Compound of Formula (I):



or a pharmaceutically acceptable salt thereof, in a daily delivered dose of from 0.8 mg to 6.2 mg of the free base.

- 15 29. The method according to claim 28, wherein the disease or condition in which inhibition of JAK1 is beneficial is selected from type 1 diabetes, lupus, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriasis, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease (COPD), vitiligo and alopecia areata.

30. The method according to claim 29, wherein the disease or condition in which inhibition of JAK1 is beneficial is asthma.
31. The method according to claim 29, wherein the disease or condition in which inhibition of JAK1 is beneficial is COPD.
32. The method according to any one of claims 28 to 31, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of at least 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, 1.6 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2.0 mg, 2.1 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.5 mg, 2.6 mg, 2.7 mg, 2.8 mg, 2.9 mg, 3.0 mg, 3.1 mg, 3.2 mg, 3.4 mg, 3.5 mg, 3.6 mg, 3.7 mg, 3.8 mg, 3.9 mg, 4.0 mg, 4.1 mg, 4.2 mg, 4.3 mg, 4.4 mg, 4.5 mg, 4.6 mg, 4.7 mg, 4.8 mg, 4.9 mg, 5.0 mg, 5.1 mg, 5.2 mg, 5.3 mg, 5.4 mg or 5.5 mg per day of the free base.
33. The method according to any one of claims 28 to 31, wherein the Compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a daily delivered dose of up to 6.2 mg, 6.1 mg, 6.0 mg, 5.9 mg, 5.8 mg, 5.7 mg, 5.6 mg, 5.5 mg, 5.4 mg, 5.3 mg, 5.2 mg, 5.1 mg, 5.0 mg, 4.9 mg, 4.8 mg, 4.7 mg, 4.6 mg, 4.5 mg, 4.4 mg, 4.3 mg, 4.2 mg, 4.1 mg, 4.0 mg, 3.9 mg, 3.8 mg, 3.7 mg, 3.6 mg, 3.5 mg, 3.4 mg, 3.3 mg, 3.2 mg, 3.1 mg, 3.0 mg, 2.9 mg, 2.8 mg, 2.7 mg, 2.6 mg, 2.5 mg, 2.4 mg, 2.3 mg, 2.2 mg, 2.1 mg, 2.0 mg, 1.9 mg, 1.8 mg, 1.7 mg, 1.6 mg, 1.5 mg, 1.4 mg, 1.3 mg, 1.2 mg, 1.1 mg or 1.0 mg per day of the free base.
34. The method according to any one of claims 28 to 33, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered in a daily delivered dose of 2.8 mg of the free base.
35. The method according to any one of claims 28 to 33, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered at a delivered dose of from 0.4 to 3.1 mg of the free base twice per day.
36. The method according to any one of claims 28 to 33, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered in a delivered dose of at least 0.4 mg twice per day, 0.45 mg twice per day, 0.5 mg twice per day, 0.6 mg twice per day, 0.65 mg twice per day, 0.7 mg twice per day, 0.75 mg twice per day, 0.8 mg twice per day, 0.85 mg twice per day, 0.9 mg twice per day, 0.95 mg twice per day, 1.0 mg twice per day, 1.05 mg twice per day, 1.1 mg twice per day, 1.15 mg twice per day, 1.2 mg twice per day, 1.25 mg twice per day, 1.3 mg twice per day, 1.35 mg twice per day, 1.4 mg twice per day, 1.45 mg twice per day, 1.5 mg twice per day, 1.55 mg twice per day, 1.6 mg twice per day, 1.65 mg twice per day, 1.7 mg twice per day, 1.75 mg twice per day, 1.8 mg twice per day, 1.85 mg twice per day, 1.9 mg twice per day, 2.0 mg twice per day, 2.05 mg twice per day, 2.1 mg twice per day, 2.15 mg twice per day, 2.2 mg twice per day, 2.25 mg twice per day, 2.3 mg twice per day, 2.35 mg twice per day, 2.4 mg twice per day, 2.45 mg twice per day, 2.5 mg twice per day, 2.55 mg twice per day, 2.6 mg twice per day, 2.7 mg twice per day or 2.75 mg twice per day of the free base.

37. The method according to any one of claims 28 to 33, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered in a delivered dose of up to 3.1 mg twice per day, 3.05 mg twice per day, 3.0 mg twice per day, 2.95 mg twice per day, 2.9 mg twice per day, 2.85 mg twice per day, 2.8 mg twice per day, 2.75 mg twice per day, 2.7 mg twice per day, 2.65 mg twice per day, 2.6 mg twice per day, 2.55 mg twice per day, 2.5 mg twice per day, 2.45 mg twice per day, 2.4 mg twice per day, 2.35 mg twice per day, 2.3 mg twice per day, 2.25 mg twice per day, 2.2 mg twice per day, 2.15 mg twice per day, 2.1 mg twice per day, 2.05 mg twice per day, 2.0 mg twice per day, 1.95 mg twice per day, 1.9 mg twice per day, 1.85 mg twice per day, 1.8 mg twice per day, 1.75 mg twice per day, 1.7 mg twice per day, 1.65 mg twice per day, 1.6 mg twice per day, 1.55 mg twice per day, 1.5 mg twice per day, 1.45 mg twice per day, 1.4 mg twice per day, 1.35 mg twice per day, 1.3 mg twice per day, 1.25 mg twice per day, 1.2 mg twice per day, 1.15 mg twice per day, 1.1 mg twice per day, 1.05 mg twice per day, 1.0 mg twice per day, 0.95 mg twice per day, 0.9 mg twice per day, 0.85 mg twice per day, 0.8 mg twice per day, 0.75 mg twice per day, 0.7 mg twice per day, 0.65 mg twice per day, 0.6 mg twice per day, 0.55 mg twice per day, or 0.5 mg twice per day of the free base.

38. The method according to any one of claims 28 to 33, wherein the Compound of Formula (I), optionally in the form of a pharmaceutically acceptable salt, is administered in a delivered dose of 1.4 mg of the free base twice per day.

39. The method according to any one of statements 28 to 38, wherein the Compound of Formula (I) is administered as a pharmaceutically acceptable salt.

40. The method according to claim 39, wherein the Compound of Formula (I) is administered as the xinafoate salt.

41. The method according to claim 40, wherein the Compound of Formula (I) is administered as the xinafoate salt in a daily delivered dose of from 1.05 mg to 8.14 mg of the xinafoate salt.

42. The method according to claim 41, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 1.84 mg of the xinafoate salt twice per day.

43. The method according to claim 41, wherein the xinafoate salt of the Compound of Formula (I), is administered in a delivered dose of 1.18 mg xinafoate salt twice per day.

44. The method according to any one of claims 35 to 38 or claims 42 to 43, wherein the dosages are spaced from 10 to 14 hours.

45. The method according to claim 44, wherein the dosages are spaced from 11 hours 30 minutes and 12 hours 30 minutes.

46. The method according to any one of claims 28 to 45, wherein the Compound of Formula (I) or pharmaceutically acceptable salt thereof is administered orally.
47. The method according to any one of claims 28 to 45, wherein the Compound of Formula (I) or pharmaceutically acceptable salt thereof is administered in an inhaled aerosol dosage form.
48. The method according to any one of claims 28 to 45, wherein the Compound of Formula (I) or pharmaceutically acceptable salt thereof is administered via a dry powder inhaler.
49. The method according to any one of claims 28 to 45, wherein the Compound of Formula (I) or pharmaceutically acceptable salt thereof is administered via a pressurised metered dose inhaler.