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ARTICLE

Phase I and scintigraphy studies to evaluate safety, tolerability, pharmacokinetics, and lung deposition of inhaled GDC-0214 in healthy volunteers

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Abstract

Several inflammatory cytokines that promote inflammation and pathogenesis in asthma signal through the Janus kinase 1 (JAK1) pathway. This phase I, randomized, placebo-controlled trial assessed the pharmacokinetics and safety of single and multiple ascending doses up to 15 mg twice daily for 14 days of a JAK1 inhibitor, GDC-0214, in healthy volunteers (HVs; $n = 66$). Doses were administered with a dry powder, capsule-based inhaler. An accompanying open-label gamma scintigraphy study in HVs examined the lung deposition of a single dose of inhaled Technetium-99m (^{99m}Tc)-radiolabeled GDC-0214. GDC-0214 plasma concentrations were linear and approximately dose-proportional after both single and multiple doses. Peak plasma concentrations occurred at 15–30 min after dosing. The mean apparent elimination half-life ranged from 32 to 56 h across all single and multiple dose cohorts. After single and multiple doses, all adverse events were mild or moderate, and none led to treatment withdrawal. There was no clear evidence of systemic toxicity due to JAK1 inhibition, and systemic exposure was low, with plasma concentrations at least 15-fold less than the plasma protein binding-corrected IC50 of JAK1 at the highest dose. Scintigraphy showed that approximately 50% of the emitted dose of radiolabeled GDC-0214 was deposited in the lungs and was distributed well to the peripheral airways. ^{99m}Tc-radiolabeled GDC-0214 (1 mg) exhibited a mean plasma C_{max} similar to that observed in phase I at the same dose level. Overall, inhaled GDC-0214 exhibited pharmacokinetic properties favorable for inhaled administration.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Many factors drive asthma pathogenesis, including several cytokines that signal through the Janus kinase 1 (JAK1) pathway. Inhibition of JAK1 is a possible

target for asthma treatments, but previous studies show oral JAK1 inhibitors lead to increased risk of severe infections, malignancy and cardiovascular events.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study investigated the safety, pharmacokinetics, and lung deposition of GDC-0214, an inhaled JAK1 inhibitor designed to target the lungs.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Inhaled delivery of a JAK inhibitor for 14 days exhibited low systemic exposure, leading to few adverse events and limited systemic toxicity, while demonstrating high deposition in the lungs.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Local pulmonary application of JAK inhibitors may be an effective treatment for asthma with limited systemic risks.

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways with approximately 350 million people affected worldwide.[1,2] Clinically, patients may present with cough, wheezing, and dyspnea, and exhibit variable airflow obstruction, airway inflammation, mucus hypersecretion, and subepithelial fibrosis.[3] Despite the development of effective controller therapies, such as inhaled corticosteroids, long-acting β-agonists, and other controller medications, a substantial proportion of patients continue to have uncontrolled or poorly controlled asthma.[3-8]

Advances in understanding the underlying biology have identified different asthma subtypes. One important mechanism is Type 2 inflammation driven by multiple Type 2 cytokines, such as interleukin (IL)-13, IL-4, IL-5, and thymic stromal lymphopoietin.[9] Inhibition of each of these Janus kinase 1 (JAK1)-associated cytokine pathways has shown clinical efficacy in asthma.[10-13] Many other JAK1-associated inflammatory cytokines, including IL-9, IL-6, and interferons, may also participate in asthma pathogenesis.[9,14,15] As shown in preclinical studies of other inhaled JAK inhibitors,[16] targeting a JAK1 inhibitor to the lung by inhalation may simultaneously inhibit these inflammatory pathways and decrease systemic toxicities associated with oral administration.

GDC-0214 is a small molecule inhibitor of JAK1 being developed for the inhaled treatment of asthma. GDC-0214 is a potent inhibitor of JAK1 and is highly selective for JAK family kinases.[17] In a rat model of asthma, GDC-0214 was retained in the lung with inhalation dosing and suppressed eosinophil recruitment, with no evidence of activity outside the lung.[18] The proof-of-activity portion of the current study that examined GDC-0214 administration in patients with mild asthma has been previously described, and showed that inhaled GDC-0214 reduced fractional exhaled nitric oxide (FeNO), a biomarker of airway inflammation, and exhibited low systemic exposure and few safety concerns.[17]

This phase I study assessed the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics after single and multiple inhaled doses of GDC-0214 in healthy volunteers. To better understand the extent of inhaled GDC-0214 exposure in the lung, we used clinical gamma scintigraphy in healthy subjects to directly evaluate the lung deposition and distribution of Technetium-99m (^{99m}Tc)-radiolabeled GDC-0214.

METHODS

Study design

This phase I randomized, investigator- and subject-blinded study evaluated the safety, tolerability, PK, and pharmacodynamics of single and multiple ascending doses of inhaled GDC-0214 in healthy volunteers (HVs). A third part of the study, which examined GDC-0214 proof of activity (fractional exhaled nitric oxide (FeNO) level as the primary marker) in patients with mild asthma, has been reported separately.[17] The study was conducted at two clinical research units (CRUs) in New Zealand.

Part A, the single ascending-dose (SAD) phase, consisted of five sequential cohorts receiving placebo or single GDC-0214 doses of 0.15, 0.5, 1.5, 5, or 15 mg. Smaller-sized (3 active: 2 placebo) cohorts are planned for the first two cohorts (0.15 and 0.5 mg) in Part A because these doses are below the anticipated therapeutic dose range of 1.3–7.7 mg q.d., and therefore, limited pharmacologic activity

is expected. All following cohorts in Part A enrolled 8 participants each (6 active: 2 placebo). All participants resided at the CRU for a minimum of 72 h after dosing (Day −1 to Day 4). Participants returned for regularly scheduled follow-up visits through Day 15.

Part B, the multiple ascending-dose (MAD) phase, consisted of four sequential cohorts, each with 8 participants (6 active: 2 placebo) receiving placebo or GDC-0214 doses of 1 mg daily (q.d.), 3 mg q.d., 10 mg q.d., or 15 mg twice daily (b.i.d.) for 14 days. All participants resided at the CRU during the 14-day treatment period until 24 hours after completing the last dose (Day −1 to Day 15). Participants then returned for regularly scheduled follow-up visits through Day 42.

The study was registered in the Australian New Zealand Clinical Trials Registry (ACTRN12617001227381), approved by Health and Disability Ethics Committee, New Zealand (19/STH/60), and Part A and Part B of the study were conducted at the Christchurch Clinical Studies Trust (CCST; now New Zealand Clinical Research (NZCR), Christchurch, New Zealand). Part C (proof of activity) of the study was conducted at the Medical Research Institute of New Zealand (Wellington, New Zealand) and results were published elsewhere.[17] The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference for Harmonisation (ICH) E6 guidelines for Good Clinical Practice (GCP). All patients provided written informed consent before participation in the study.

Participants

Eligible participants were HVs, 18–65 years old, with a body mass index (BMI) of 18–37 kg/m^2 and a weight of 50–120 kg, and in good health as determined by no clinically significant findings from medical history, 12-lead electrocardiogram (ECG), and vital signs. Participants were required to have a forced expiratory volume in 1 s (FEV_1) of >70% predicted at screening and pre-randomization (Day 1) and a forced vital capacity (FVC) of >2.0 L by spirometry at screening. Participants must also have demonstrated sufficient inspiratory effort using the inhaler training device and demonstrated correct use of the dry powder inhaler (DPI) using a placebo capsule. Additional exclusion criteria and randomization and blinding information are provided in the Methods S1.

Drug formulation and administration

GDC-0214 (Genentech, Inc.) was supplied as formulated capsules for inhalation in doses of 50, 250, and 1000 μg. Placebo-formulated capsules for inhalation were supplied in the same packaging configuration. All active and placebo doses were administered via oral inhalation using the Plastiape RS01 DPI (high resistance variant – 60 L/min at 4 kPa). Capsules were loaded into DPIs by an unblinded site pharmacist. Each dose, which required a minimum of two successful inhalations from one or more capsules, was delivered over 15 (±5) min. For cohorts that required 10 or more capsules, subjects were given up to a maximum of 30 min to complete dosing.

Outcomes and assessments

PK outcomes were the plasma concentrations following single and multiple ascending doses of GDC-0214. Plasma concentration is a commonly used surrogate to determine the lung PK profile for inhaled therapeutics.[19] In Part A, PK blood samples were collected on Day 1 (pre-dose, 5 min, 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 8 h, and 12 h post-dose), Day 2 (24 h and 36 h post-dose), Day 3, Day 4, and at the Days 6, 10, and 15 clinic visits. In Part B, PK blood samples were collected on Day 1 (same as Part A), pre-dose on Days 2, 3, 4, 6, 8, and 11, Day 14 (same schedule as Part A and Day 1), and on Days 15 (24 h post-dose), 16 (48 h post-dose), 17 (72 h post-dose), and during clinic visits on Days 21, 28, 35, and 42 (study completion/early termination). Because the goal of inhaled therapy is to minimize systemic exposure, a highly sensitive assay for GDC-0214 was developed to measure the concentration in human plasma. This high-performance liquid chromatography (HPLC) with tandem mass spectrometry assay (lower limit of quantification: 10 pg/mL) was fully validated with the desired sensitivity and specificity as recommended by Food and Drug Administration (FDA) Bioanalytical Method Validation Guidance (2018).[20] Detailed PK assay methods are included in the Methods S1.

The primary safety outcomes were the frequency and severity of adverse events (AEs), and the change from baseline in vital signs, ECG, laboratory tests, and spirometry. Laboratory tests included monitoring for JAK-specific toxicity, particularly blood reticulocyte counts, lymphocyte subsets, and fasting lipids.

Spirometry

All pulmonary function testing was conducted in accordance with the 2005 American Thoracic Society (ATS) – European Respiratory Society Consensus Statement.[21] Spirometry was performed at approximately the same time of day (±2 h) for each visit.

Statistical methods

Sample size determination

A sample size of 3 to 6 HVs treated with GDC-0214 in each dose level was selected. This sample size is historically consistent with similar SAD/MAD studies and is sufficient to provide a preliminary assessment of the interindividual variability in PK parameters.

Analysis populations

The safety analysis population included all HVs in Parts A and B who received at least one dose of study drug, with subjects grouped according to treatment received. The PK analysis population included participants with sufficient data to enable estimation of key parameters (e.g., area under the curve [AUC], maximum plasma concentration [C_{max}], time to C_{max} [t_{max}], and terminal elimination half-life [$t_{1/2}$]), with subjects grouped according to treatment received.

Scintigraphy

Gamma scintigraphy (EudraCT: 2019-002630-36) was performed using an open-label, uncontrolled, non-randomized design to investigate the deposition of inhaled Technetium-99m (^{99m}Tc)-radiolabeled GDC-0214. The study enrolled 12 HVs; each HV received a single dose of 1 mg radiolabeled GDC-0214. Eligibility criteria were similar to the SAD/MAD portion of the Phase I study.

^{99m}Tc was surface-associated with GDC-0214 powder and blended with lactose carrier in small-scale batches manufactured on each dosing day. The content uniformity of the blends was assessed by validated HPLC analysis. The radiolabeled formulation was accurately dispensed into capsules (1 mg GDC-0214 per capsule) and the aerodynamic particle size distribution (APSD) was measured using a Next Generation Impactor (NGI). GDC-0214 was quantified by validated HPLC analysis and ^{99m}Tc was determined by gamma scintigraphy. Validation batches demonstrated that ^{99m}Tc was an accurate surrogate for the GDC-0214. The key aerosol characteristics of the ^{99m}Tc-radiolabeled GDC-0214 formulations, that is, fine particle fraction, fine particle dose, mass median aerodynamic diameter (MMAD), and geometric standard deviation (GSD), were similar to the phase I product.

Subjects in the scintigraphy study were trained using the In-Check Dial (Clement Clarke) at the medium resistance setting, equivalent to ≥60 L/min inspiratory flow. Prior to dosing procedures, subjects inhaled Krypton-81m (^{81m}Kr) gas to enable accurate determination of the ventilated area of their lungs. Subjects also underwent a transmission scan (Cobalt-57) of their thorax/abdomen and head/neck to enable regional tissue attenuation correction factors to be derived. All radioactive counts were corrected, where appropriate, for radioactive decay, background radiation, and tissue attenuation.

Total intrapulmonary drug deposition of GDC-0214 was expressed as the percentage of the emitted dose. The emitted dose was calculated as the sum of corrected radioactive counts detected in the lungs and extrathoracic regions (i.e., oropharynx, mouthwash, stomach, and exhalation filter). Distribution of the drug within the lung was evaluated using the central and peripheral intrapulmonary GDC-0214 distribution, expressed as the penetration index [PI], defined as the normalized outer lung to inner lung [O/I] deposition ratio,[22] and the standardized central to peripheral ratio [sC/P]. See Supplement for additional scintigraphy Methods S1.

The scintigraphy study protocol was reviewed and approved by a Research Ethics Committee (Wales Research Ethics Committee 2 Cardiff) before the start of any study procedures. The study was performed in accordance with the Declaration of Helsinki, the Association of the British Pharmaceutical Industry Guidelines for Phase I Trials (2018), the ICH Guideline for Good Clinical Practice E6 (R2), the Medicines for Human Use (Clinical Trials) Regulations 2004, and any applicable local standard operating procedures. All participants provided written, informed consent.

RESULTS

Participant characteristics

The study randomized a total of 66 HVs (34 to Part A, 32 to Part B) from December 11, 2017 through August 23, 2018. All HVs received the study drug or placebo as planned and completed the study, including follow-up. All HVs received at least one dose of study drug or placebo.

In Part A, the mean age was 27.1 years (range: 18–56 years), and the mean (SD) BMI: 26.7 kg/m^2 (4.98 kg/m^2) at baseline (Table 1). A higher percentage of participants were female (58.8%), the majority were White (85.3%), and not Hispanic/Latino (94.1%). The baseline mean FEV_1 was 3.7 L (range: 2.1–5.4 L).

In Part B, the mean age of the HVs was 26.7 years (range: 18–44 years), with a mean (SD) BMI of 25.6 kg/m^2 (3.56 kg/m^2) at baseline (Table 1). A higher percentage of HVs were male (65.6%), and the majority of the HVs were White (87.5%) and were ethnically not Hispanic/Latino

TABLE 1 Demographics and baseline characteristics

Part A (SAD)	Placebo ($n = 10$)	0.15 mg ($n = 3$)	0.5 mg ($n = 3$)	1.5 mg ($n = 6$)	5 mg ($n = 6$)	15 mg ($n = 6$)	All HVs ($N = 34$)
Age, y, mean (SD)	32.2 (11.6)	29.0 (6.1)	21.7 (1.2)	21.5 (2.7)	27.2 (8.9)	25.7 (7.2)	27.1 (8.8)
Male	5 (50.0%)	2 (66.7%)	1 (33.3%)	3 (50.0%)	2 (33.3%)	1 (16.7%)	14 (41.2%)
Female	5 (50.0%)	1 (33.3%)	2 (66.7%)	3 (50.0%)	4 (66.7%)	5 (83.3%)	20 (58.8%)
Ethnicity, not Hispanic or Latino	9 (90.0%)	3 (100%)	3 (100%)	6 (100%)	6 (100%)	5 (83.3%)	32 (94.1%)
Race							
Black or African American	0	1 (33.3%)	0	0	0	0	1 (2.9%)
Native Hawaiian or other Pacific Islander	1 (10.0%)	0	1 (33.3%)	0	0	1 (16.7%)	3 (8.8%)
White	9 (90.0%)	2 (66.7%)	2 (66.7%)	6 (100%)	6 (100%)	4 (66.7%)	29 (85.3%)
Multiple	0	0	0	0	0	1 (16.7%)	1 (2.9%)
BMI (kg/m^2) at baseline, mean (SD)	27.09 (5.43)	26.35 (7.36)	26.62 (6.79)	27.97 (5.38)	26.64 (4.64)	24.76 (3.64)	26.65 (4.98)
Baseline FEV_1 (L) (pre-dose), mean (SD)	3.74 (1.05)	3.57 (0.67)	3.59 (1.03)	3.71 (0.93)	3.99 (0.86)	3.42 (0.57)	3.70 (0.85)

Part B (MAD)	Placebo ($n = 8$)	1 mg q.d. ($n = 6$)	3 mg q.d. ($n = 6$)	10 mg q.d. ($n = 6$)	15 mg b.i.d. ($n = 6$)	All HVs ($N = 32$)
Age, y, mean (SD)	31.0 (6.8)	23.0 (4.1)	27.8 (10.5)	25.5 (5.5)	24.5 (5.2)	26.7 (7.0)
Male	5 (62.5%)	6 (100%)	5 (83.3%)	4 (66.7%)	1 (16.7%)	21 (65.6%)
Female	3 (37.5%)	0	1 (16.7%)	2 (33.3%)	5 (83.3%)	11 (34.4%)
Ethnicity, not Hispanic or Latino	6 (75.0%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	30 (93.8%)
Race						
Asian	0	1 (16.7%)	0	0	0	1 (3.1%)
Black or African American	0	0	0	0	1 (16.7%)	1 (3.1%)
Native Hawaiian or other Pacific Islander	0	0	1 (16.7%)	0	0	1 (3.1%)
White	7 (87.5%)	5 (83.3%)	5 (83.3%)	6 (100%)	5 (83.3%)	28 (87.5%)
Unknown	1 (12.5%)	0	0	0	0	1 (3.1%)
BMI (kg/m^2) at baseline, mean (SD)	24.74 (2.29)	25.93 (3.49)	25.93 (4.37)	27.11 (5.22)	24.56 (2.67)	25.60 (3.56)
Baseline FEV_1 (L) (pre-dose), mean (SD)	3.80 (0.75)	4.53 (0.39)	3.96 (0.80)	4.07 (0.32)	3.78 (1.08)	4.01 (0.73)

Abbreviations: b.i.d., twice a day; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; HV, healthy volunteer; MAD, multiple ascending-dose phase; q.d., once a day; SAD, single ascending-dose phase; SD, standard deviation.

(93.8%). The mean FEV_1 at baseline was 4.0 L (range: 2.9–5.9 L).

Pharmacokinetics

Following single inhalation of GDC-0214, a rapid initial peak and decline were observed, followed by a longer terminal phase (Figure 1a). Peak plasma concentrations were reached between 15 and 30 min post-dose. The mean peak C_{max} and systemic exposures (AUC from time 0 to infinity, $AUC_{0-\infty}$) both increased in an approximately dose-proportional manner across cohorts (Table 2). Mean $t_{1/2}$ values were similar across all dose levels and ranged from 36.5 to 39.7 h. The mean CL/F and apparent volume of distribution (V_z/F) values ranged from 149–227 L/h and from 7740–12,600 L, respectively.

Following 14 days of dosing at 1 mg q.d., 3 mg q.d., 10 mg q.d., and 15 mg b.i.d., steady-state concentrations were achieved by Day 6 of q.d. or b.i.d. dosing, consistent with the approximately 40-h apparent $t_{1/2}$ (Figure 1b). The mean $t_{1/2}$ values were similar across the first three cohorts (1 mg, 3 mg, and 10 mg q.d.) and ranged from 32.0 to 40.8 h (Table 3). The 15-mg b.i.d. cohort had a longer mean half-life of 56.7 h because GDC-0214 plasma concentrations were detectable up to Day 42 (28 days after the last dose) in 2 of the 6 active subjects. The accumulation ratio (AR) based on the trough concentration (C_{min}, minimum concentration under steady-state conditions within a dosing interval), estimated as $C_{min,\ Day\ 14}/C_{min,\ Day\ 1}$ was approximately 2 to 3 two to three for both q.d. and b.i.d. cohorts. The C_{max} and AUC during one dosing interval (AUC_{tau}) both increased in an approximately dose-proportional manner across the three MAD q.d. cohorts. Overall, systemic exposure was low, with plasma concentrations (total) at least 15-fold less than the plasma protein binding-corrected cellular 50% inhibitory concentration of JAK1 of 97,000 pg/mL at the highest dose.[17]

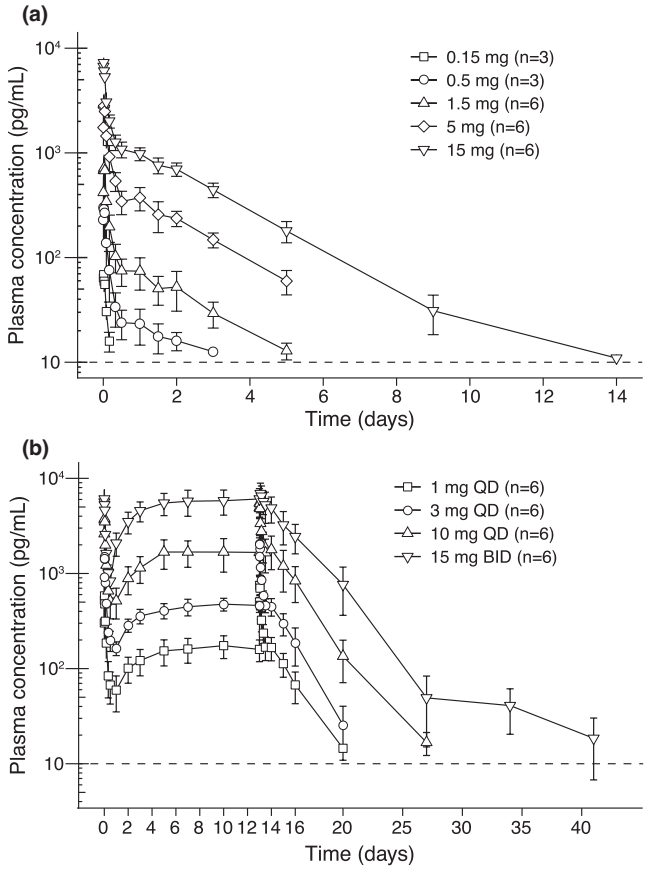

FIGURE 1 GDC-0214 plasma concentration-time profiles in the (a) single ascending-dose (SAD) and (b) multiple ascending-dose (MAD) phases

Safety

GDC-0214 was safe and well tolerated up to a single dose of 15 mg or multiple doses up to 15 mg b.i.d. for 14 days. All adverse events were mild or moderate. There were no deaths, no serious adverse events, or events leading to treatment withdrawal. The only event seen in three or more volunteers in Part A was upper respiratory tract infection, which was reported by 1 volunteer (10%) in the placebo group and 3 volunteers (50%) in the 1.5 mg group (Table 4; Table S1). The only AEs reported in three or more volunteers in Part B were upper respiratory tract infection, headache, and cough (Table 4; Table S2).

There were no clinically relevant changes in laboratory parameters, ECGs, or vital signs. Compared to placebo, we observed no significant changes in CD4T cells, CD8T cells, or B cells in GDC-0214-treated cohorts. There were also no significant changes from baseline in levels of NK cells, reticulocytes, or low-density lipoprotein cholesterol that would have indicated systemic effects resulting from JAK1 inhibition (Table S3).

Scintigraphy

Twelve healthy men (29–49 years old) were enrolled into the scintigraphy study (Table S4). Of the emitted dose (i.e., dose emitted from the device mouthpiece) of 1 mg radiolabeled GDC-0214, 50.13% (13.84%) mean (CV%) was deposited in the lungs, and 49.13% (14.41%) impacted in the mouth/oropharynx and was subsequently swallowed. A small fraction of the drug (0.74%, CV% of 73.58%) was exhaled after the breath-hold. Subjects were able to use the RS01 device to consistently deliver a high fraction of the emitted dose to the lungs. Capsule emptying was efficient and reproducible with a mean emitted dose of

TABLE 2 GDC-0214 plasma pharmacokinetic parameters in the single ascending-dose phase (Part A)

Treatment	Statistic	C_{max} (pg/mL)	T_{max}[a] (h)	AUC_{inf} (pg.h/mL)	$T_{1/2}$ (h)	V_z/F (L)	CL/F (L/h)
0.15 mg	*N*	3	3	3	3	3	3
	Mean	70.2	0.283	NE	NE	NE	NE
	SD	4.48	(0.117–0.533)	NE	NE	NE	NE
	CV%	6.4	67.4	NE	NE	NE	NE
0.5 mg	*N*	3	3	3	3	3	3
	Mean	301	0.267	2458	37.3	12264	227
	SD	147	(0.267–0.317)	883	3.32	5719	98431
	CV%	48.9	10.2	35.9	8.9	46.6	43.4
1.5 mg	*N*	6	6	6	6	6	6
	Mean	763	0.517	7320	38.7	12620	220
	SD	228	(0.267–1.03)	1934	4.84	5757	69
	CV%	29.8	48.2	26.4	12.5	45.6	31.5
5 mg	*N*	6	6	6	6	6	6
	Mean	2883	0.458	34727	36.5	7744	149
	SD	782	(0.333–0.600)	5967	5.74	1588	32
	CV%	27.1	30.4	17.2	15.7	20.5	21.6
15 mg	*N*	6	6	6	6	6	6
	Mean	7270	0.500	96038	39.7	9116	158
	SD	863	(0.500–0.583)	11150	10.6	3118	19
	CV%	11.9	6.6	11.6	26.8	34.2	12.1

Abbreviations: AUC_{inf}, area under concentration–time curve from Time 0 to infinity; CL/F, apparent clearance; C_{max}, maximum plasma concentration observed; CV%, percentage coefficient of variation; N, number of healthy volunteers; NE, not evaluable; SD, standard deviation; $T_{1/2}$, half-life (time for the drug in the body to be reduced by one-half); T_{max}, time to maximum concentration; V_z/F, apparent volume of distribution.

[a]Presented as median (range) instead of arithmetic mean (SD).

approximately 81% (Figure 2a, Table S5). Thus, the calculated mean dose of ^{99m}Tc-radiolabeled GDC-0214 deposited in the lungs was approximately 0.41 mg from a single capsule (1 mg). The mean PI (penetration index), an indicator of regional distribution of drug within the lungs, normalized for ^{81m}Kr gas distribution, was 0.76 (30.47%) (Figure 2b). A value close to 1 indicates that the drug was homogeneously deposited throughout the lungs. The mean value of 0.76 (30.47%) observed in this study indicates good penetration of the drug into the outer lung region. The mean sC/P ratio (C/P standardized for ^{81m}Kr gas distribution) was 1.52 (54.41%). The central and peripheral regions for this ratio differ from the outer:inner regions used for the PI calculation. However, sC/P is approximately the inverse of the PI; thus a value greater than 1 describes more central drug deposition. The mean sC/P of 1.52 (54.41%) shows that the drug tended to be more centrally deposited, but still achieved penetration into the peripheral lung region.

Radiolabeled GDC-0214 in the scintigraphy study showed a consistent PK profile (15 min to 4 h post-dose) compared to that in the phase I study (Figure 2c). The overall PK variability in the scintigraphy study is slightly less than in the phase I study, likely due to the sample size differences ($n = 12$, scintigraphy vs. $n = 6$ active, phase I cohort). Radiolabeled GDC-0214 was well tolerated; no new safety signals were identified. Two AEs were reported; neither was related to GDC-0214.

DISCUSSION

To our knowledge, this is the first report evaluating the PK, safety, and lung deposition of an inhaled small molecule JAK inhibitor in healthy subjects. This route of administration drives direct lung exposure, which may maximize the potential of a drug to reach all areas of the lung over a sustained period at lower doses than other routes of administration, while minimizing systemic side effects known to be associated with oral administration.[23,24] However, inhalation delivery presents some inherent challenges for determining the source of the plasma concentrations of a drug (i.e., the plasma profile is a mix of inhaled drug that passes through the lung into the

TABLE 3 GDC-0214 plasma pharmacokinetic parameters in the multiple ascending-dose phase (Part B)

Treatment	Statistic	First dose (Day 1)		AUC_{tau}, Day1 (pg.h/mL)	Steady-state (Day 14)						
		C_{max}, Day 1 (pg/mL)	C_{min}, Day 1 (pg/mL)		C_{max}, Day 14 (pg/mL)	C_{min}, Day 14 (pg/mL)	$AUC_{tau,\ Day14}$ (pg.h/mL)	$t_{1/2}$ (h)	AR (C_{min})	AR (C_{max})	AR (AUC_{tau})
1 mg q.d.	N	6	6	6	6	6	6	6	6	6	6
	Mean	581	59.4	2910	810	167	5969	38.5	3.0	1.5	2.19
	SD	262	24.3	1130	221	45.8	1493	3.79	0.96	0.584	0.671
	CV%	45.1	41.0	39.0	27.3	27.5	25.0	9.8	32.0	38.9	30.7
3 mg q.d.	N	6	6	6	6	6	6	5	6	6	6
	Mean	1510	164	8080	2115	450	15,794	32.0	2.79	1.36	1.97
	SD	375	26.9	924	455	94.2	1490	4.13	0.69	0.166	0.254
	CV%	24.8	16.4	11.4	21.5	20.9	9.4	12.9	24.6	12.2	12.9
10 mg q.d.	N	6	6	6	6	6	6	6	6	6	6
	Mean	3770	517	21,300	5982	1780	52,824	40.8	3.47	1.64	2.48
	SD	1530	184	5870	1536	688	18,416	6.83	0.74	0.661	0.714
	CV%	40.7	35.7	27.5	25.7	38.6	34.9	16.8	21.2	40.2	28.8
15 mg b.i.d.	N	6	6	6	6	6	6	6	6	6	6
	Mean	6080	2090	39,500	12,423	5260	79,907	56.9	2.49	2.02	2.01
	SD	1520	572	9790	4184	1900	22608	13.7	0.37	0.435	0.171
	CV%	25.1	27.4	24.8	33.7	36.1	28.3	24.1	14.7	21.6	8.5

Abbreviations: AR, accumulation ratio; AUC_{tau}, area under concentration–time curve during one dosing interval; b.i.d., twice a day; C_{max}, maximum plasma concentration observed; C_{min}, minimum plasma concentration observed under steady-state conditions within a dosing interval; CV%, percentage coefficient of variation; N, number of healthy volunteers; q.d., once a day; SD, standard deviation; $T_{1/2}$, half-life (time for the drug in the body to be reduced by one-half).

Note One healthy volunteer in the 3 mg q.d. cohort had detectable concentration at Day 42 while the previous two concentrations on Day 28 and Day 35 had fallen below the lower limit of quantitation. This data point was likely due to sample contamination. Therefore, the mean and SD values for the 3 mg dose group at study Day 42 were not included in the mean half-life calculation.

TABLE 4 Summary of adverse effects (AEs) and most common AEs in the single ascending-dose and multiple ascending-dose phases

Part A (SAD)	Placebo ($n = 10$)	0.15 mg ($n = 3$)	0.5 mg ($n = 3$)	1.5 mg ($n = 6$)	5 mg ($n = 6$)	15 mg ($n = 6$)	All HVs ($N = 34$)
Total number of participants with at least one AE	5 (50.0%)	1 (33.3%)	2 (66.7%)	3 (50.0%)	2 (33.3%)	4 (66.7%)	17 (50.0%)
Total number of AEs	9	1	3	5	2	4	24
Total number of deaths	0	0	0	0	0	0	0
Total number of participants withdrawn from study due to an AE	0	0	0	0	0	0	0
Serious AE	0	0	0	0	0	0	0
AE leading to withdrawal from treatment	0	0	0	0	0	0	0
Related AE	3 (30.0%)	0	0	1 (16.7%)	0	1 (16.7%)	5 (14.7%)
MedDRA preferred term (in ≥3 participants)							
Upper respiratory tract infection	1 (10.0%)	0	0	3 (50.0%)	0	0	4 (11.8%)

Part B (MAD)	Placebo ($n = 8$)	1 mg q.d. ($n = 6$)	3 mg q.d. ($n = 6$)	10 mg q.d. ($n = 6$)	15 mg b.i.d. ($n = 6$)	All HVs ($N = 32$)
Total number of participants with at least one AE	5 (62.5%)	6 (100%)	4 (66.7%)	6 (100%)	4 (66.7%)	25 (78.1%)
Total number of AEs	16	6	11	13	8	54
Total number of deaths	0	0	0	0	0	0
Total number of participants withdrawn from study due to an AE	0	0	0	0	0	0
Serious AE	0	0	0	0	0	0
Related serious AE	0	0	0	0	0	0
AE leading to withdrawal from treatment	0	0	0	0	0	0
Related AE	1 (12.5%)	0	1 (16.7%)	0	0	2 (6.3%)
MedDRA preferred term (in ≥3 participants)						
Upper respiratory tract infection	3 (37.5%)	2 (33.3%)	3 (50.0%)	2 (33.3%)	0	10 (31.3%)
Headache	3 (37.5%)	1 (16.7%)	2 (33.3%)	0	2 (33.3%)	8 (25.0%)
Cough	2 (25.0%)	0	1 (16.7%)	0	0	3 (9.4%)

Abbreviations: AE, adverse effect; b.i.d., twice a day; HV, healthy volunteer; MAD, multiple ascending-dose phase; q.d., once a day; SAD, multiple ascending-dose phase.

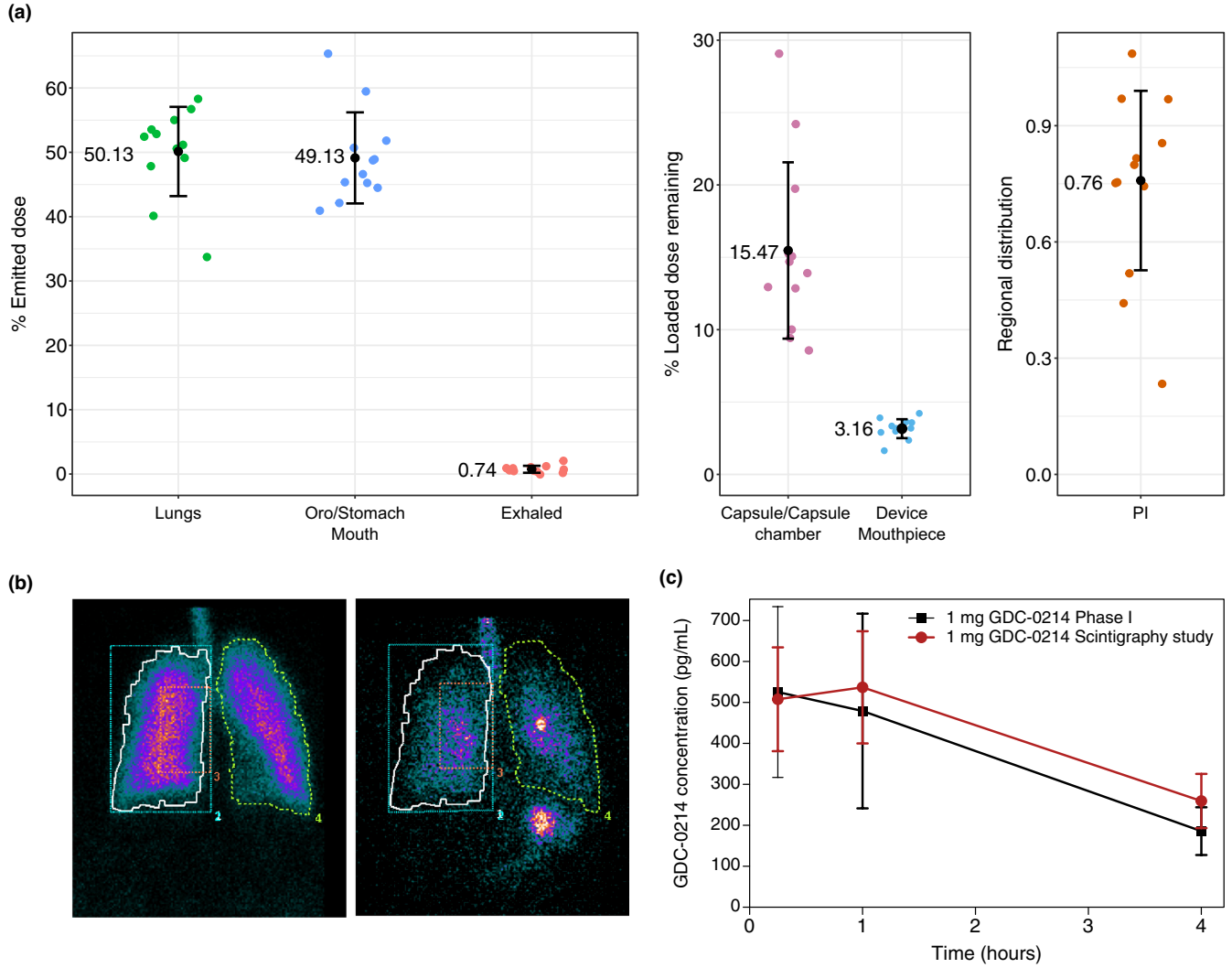

FIGURE 2 (a) Deposition (% of emitted dose) of GDC-0214 in the lungs and extrathoracic regions, and the amount of GDC-0214 remaining in the device mouthpiece and capsule/capsule chamber (% of loaded dose). Oro, oropharyngeal; PI, penetration index (ventilation-corrected outer/inner distribution ratio). (b) Representative image of GDC-0214 deposition in a healthy volunteer, showing anterior views of the ^{81m}Kr gas ventilation image (left panel) and the deposition image (right panel). Lung margins derived from the ^{81m}Kr gas are shown; white and green lines indicate regions of interest (ROIs) drawn around the boundary of the lungs; the outer and inner ROIs are shown around the right lung. Blue region, outer lung ROI; red/orange region, inner lung ROI. Right panel also shows an additional area of radioactivity in the stomach below the left lung, indicating where some of the drug was deposited in the mouth and then swallowed. (c) GDC-0214 (1 mg dose) plasma concentration–time profile in healthy volunteers in Part B and the scintigraphy study

systemic circulation and swallowed drug that is absorbed through the gastrointestinal tract) and determining the amount of drug that is delivered to the lung.

Several approaches could help deconvolute the source of plasma concentration, including administration of oral drug to help determine bioavailability, administration of intravenous drug to obtain the systemic clearance, and the use of charcoal block.[25] A charcoal block study administers charcoal suspension at various intervals to eliminate the enteral absorption of the proportion of inhaled drug which may be swallowed, so systemic concentration reflects only that fraction of the drug that is absorbed from the respiratory tract. GDC-0214 was designed to optimize lung retention and have minimal oral bioavailability. Given these properties, a charcoal block study would have likely resulted in a similar concentration–time profile as was observed in the current study. Furthermore, a study with oral GDC-0214 would have resulted in low, or possibly even undetectable, plasma concentrations; therefore, we did not further consider either approach. While we did consider a study with intravenous GDC-0214 to determine the systemic clearance, we ultimately chose a different approach because the observed PK profiles of GDC-0214 in the phase I study were consistent with what was predicted by the physiologically based pharmacokinetic (PBPK) model (M.R. Durk, 2016, unpublished data),

which assumed the systemic clearance is close to the liver blood flow.

None of the above approaches addresses the key question of whether and how much drug was delivered to the lung. To address this question, we took a two-pronged approach. First, in patients with mild asthma, we evaluated the reduction in the fraction of exhaled nitric oxide (FeNO), a biomarker indicative of inhibition in the IL-13/4 pathway, which is mediated by JAK inhibition. As previously reported, we observed dose-dependent decreases in FeNO, indicating successful JAK inhibition in the lung.[17] Second, because we could not measure PK directly in the lung in humans, we directly evaluated the lung deposition of GDC-0214 using scintigraphy. With this technique, we found efficient deposition (approximately 50% of emitted dose) of radiolabeled GDC-0214 in the lung, with the mean PI value suggesting that GDC-0214 distributes well to the peripheral airways.

The mean percent lung deposition of GDC-0214 compares favorably with other scintigraphic assessments of passive DPI devices using conventional micronised API/lactose blends. Brand et al. investigated the Handihaler capsule DPI and found that in HVs approximately 43% of the emitted dose of tiotropium was delivered to the lungs.[26] In HVs receiving a formulation of beclometasone dipropionate/formoterol fumarate delivered via the NEXThaler multidose DPI, Virchow et al. reported a mean lung deposition of 55% of the emitted drug.[27] Newman et al. determined a mean emitted lung dose of approximately 35% of aclidinium bromide delivered via the Genuair multidose DPI in HVs.[28] Warren et al. investigated lung deposition from two multidose devices delivering budesonide to HVs.[29] The Clickhaler delivered a mean emitted dose to the lungs of 29% while for the Turbuhaler the mean emitted lung dose was 18%.

The lack of standardized methods hampers comparison of regional lung deposition patterns for data generated by different investigator sites. The publication of standardized techniques by the International Society for Aerosols in Medicine (ISAM) Regulatory Affairs Networking Group is intended to address this issue.[22] In accordance with this guidance, we have reported the current distribution data in terms of PI as well as sC/P. We can directly compare our data with sC/P data published by Warren et al.[29,30] For the Clickhaler and Turbuhaler, the mean sC/P values were 1.9 and 2.3, respectively, at corresponding measured mean inspiratory flow rates of 50.9 and 47.0 L/min.[29] The sC/P of 1.52 in this study indicates a more homogeneous dispersion than either the Clickhaler or Turbuhaler.

Given the comparable APSD of the formulations used in the phase I and scintigraphy studies, as expected, the plasma PK profile observed in the scintigraphy study was similar to the phase I study cohort that received the same dose. These results further confirmed the consistency of the drug material characteristics in both studies, and the overall and regional lung deposition results in the scintigraphy study are representative of those in the phase I study. Taken together, the efficient lung deposition and PK characteristics of GDC-0214 both contribute to the clear FeNO reductions observed in the GDC-0214 phase I proof-of-activity study.[17]

Inhaled GDC-0214 was safe and well tolerated in HVs receiving single doses of up to 15 mg and multiple doses up to 15 mg for 14 days. The study demonstrated high pulmonary deposition and low systemic exposure. The JAK pathway participates in both hematopoiesis[31] and lipid metabolism.[32-34] While they have been approved as therapeutics for rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis, oral JAK inhibitors have led to alterations in the levels of lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids.[35] A recent study with the oral JAK inhibitor tofacitinib has reported an increased risk of all-cause mortality, including sudden cardiovascular (CV) death relative to patients on tumor necrosis factor inhibitors, in older patients with CV risk factors.[36] We therefore looked for evidence of systemic JAK inhibition that could pose a potential safety risk. At doses up to 15 mg b.i.d. for 10 days, we did not observe clear changes in lymphocyte subsets (e.g., natural killer (NK) cells) or lipids despite close monitoring. While these findings are reassuring, the short duration and small sample size of this study does not entirely preclude the possibility of some systemic JAK inhibition. Although the low plasma exposure to GDC-0214 compared to the plasma protein binding-corrected cellular JAK1 IC50 would predict low systemic JAK inhibitory activity, we did not perform ex vivo stimulation assays that would have identified such activity.[37,38] Thus, although pulmonary delivery is expected to minimize risks of systemic JAK inhibition, including increases in cholesterol and thrombosis, longer-term trials would be needed to demonstrate this.

Upper respiratory tract infection was the most common AE reported, but was Grade 1 or Grade 2, non-serious, and occurred in similar proportions between patients treated with GDC-0214 and placebo. As in patients with mild asthma,[17] the incidence and intensity of AEs was low and comparable to placebo. We observed no apparent dose–response pattern in AEs and found no concerning safety signals that would have suggested systemic toxicity deriving from JAK1 inhibition.

The generalizability of our PK and scintigraphy findings may be limited by the fact that our results represent drug administration under ideal conditions where the drug was prepared by a trained pharmacist and administered in the clinic under direct observation. In the real world, exposure may vary depending on patients'

ability to perform these steps in adherence with the user instructions.

In summary, GDC-0214 exhibited approximately linear and dose-proportional pharmacokinetics, achieved a low overall systemic exposure compared with other oral JAK inhibitors, achieved an approximately 50% lung-deposited dose in the scintigraphy study, and had an overall favorable safety profile with no short-term evidence of systemic JAK inhibition. Previous work has shown the dose-dependent reduction of FeNO in mild asthma patients, but further studies would be required to determine whether this would translate into more clinically meaningful endpoints such as an improvement in FEV_1 or a reduction in exacerbations.

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CONFLICT OF INTEREST

R.Z., H.C., J.G., G.S., M.R.D., Y.Z., L.C., J.R.K, S.V., O.H., A.E., and R.O. are employees of Genentech, Inc. and own Roche stock and options. F.C. was an employee of Genentech, Inc. at the time this work was performed and is currently an employee and stockholder of AbbVie. S.W. and G.T. are employees and shareholders of Cardiff Scintigraphics, Ltd. C.W. owns stock in NZCR (CCST).

AUTHOR CONTRIBUTIONS

R.Z., J.G., S.W., and R.O. wrote the manuscript. R.Z., H.C., J.G., F.C., M.R.D., J.R.K., S.W., G.T., A.E., and R.O. designed the research. R.Z., J.G., L.C., S.W., and G.T. performed the research. R.Z., H.C., J.G., G.S., M.R.D., Y.Z., J.R.K., S.V., S.W., G.T. O.H., and C.W. analyzed the data. L.C., S.W., and G.T. contributed new analytical tools.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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