Brief Report

Safety, Tolerability, and Pharmacokinetics of a New Formulation of Nemiralisib Administered via a Dry Powder Inhaler to Healthy Individuals

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ABSTRACT

Purpose: Nemiralisib, a phosphoinositide 3-kinase δ inhibitor, is being investigated as an immunomodulatory agent with anti-inflammatory properties in chronic obstructive pulmonary disease. This study evaluated the pharmacokinetic (PK) properties and safety of a new formulation of nemiralisib that contains 0.4% magnesium stearate.

Methods: In this randomized, double-blind, parallel-group study, healthy individuals received a single dose of 500 or 750 μg of nemiralisib administered via the Ellipta dry powder inhaler (DPI) (n = 6 in each treatment group). Aerodynamic particle size distribution (APSD) data comparing previous and new formulations were available before the study. Serial PK analyses for plasma exposure and safety assessments were performed during the first 24 h after dosing, with follow-up measurements on days 3 and 6 in clinic.

Findings: APSD had increases of approximately 6-fold and 2-fold in very fine particle mass and fine particle mass over the previous (Diskus) formulation. In humans, systemic exposure (AUC) was greater after inhalation of 750 versus 500 μg of nemiralisib (AUC_{0-t}: 17,200 h·pg/mL; 95% CI, 10,900−27,200 h·pg/mL and 13,100; 95% CI, 8130−21,000 h·pg/mL, respectively). A low frequency of individual adverse events and no serious adverse events were reported after both doses.

Implications: After single-dose inhalation of 500 and 750 μg of nemiralisib from the Ellipta DPI in healthy individuals, plasma PK data were well defined, and as predicted based on previous PK and APSD data, exposure was increased with the new formulation. Nemiralisib was well tolerated with no new safety issues identified. These data supported progression of nemiralisib to a Phase IIb study in patients with chronic obstructive pulmonary disease. ClinicalTrials.gov identifier: NCT03189589. (*Clin Ther.* 2019;41:1214−1220) © 2019 Published by Elsevier Inc.

Key words: chronic obstructive pulmonary disease, healthy individuals, nemiralisib, pharmacokinetic properties, tolerability.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease characterized by persistent respiratory symptoms and chronic airflow limitation caused by structural changes, narrowing of the small airways, and destruction of the lung parenchyma.[1] Neutrophils play a key role in the inflammatory processes in COPD, and their numbers and products correlate with COPD disease severity.[2−4] Phosphoinositide 3-kinase δ (PI3Kδ) is a lipid kinase expressed primarily in leukocytes, and PI3Kδ inhibitors are a new therapeutic target in COPD because of their potential to reduce markers of inflammation and correct aberrant neutrophil migration, thereby potentially reducing the incidence of pathogen-induced exacerbations.[3,4]

Accepted for publication April 5, 2019
https://doi.org/10.1016/j.clinthera.2019.04.008
0149-2918/$ - see front matter

Nemiralisib is a potent and highly selective PI3Kδ inhibitor that is being investigated as an immunomodulatory agent with anti-inflammatory properties in COPD.[5,6] Nemiralisib has been well tolerated in studies of healthy volunteers that have tested a range of doses and inhaled formulations, including studies with both the Diskus[7] and Ellipta (GlaxoSmithKline, Hertfordshire, United Kingdom) dry powder inhalers (DPIs).[8] In patients with stable COPD, 14 days of treatment with nemiralisib suppressed sputum interleukin 8 and 6 levels, consistent with the known anti-inflammatory activity of a PI3Kδ inhibitor.[6] In a 3-month study of patients with an acute exacerbation, the addition of nemiralisib to usual care resulted in an improvement in change from baseline in lung function parameters measured by high-resolution computed tomography compared with placebo.[9] In studies of patients with COPD, nemiralisib administered via the Diskus DPI was generally well tolerated; however, the occurrence of short postinhalation cough was observed.[6,9]

As part of the continued clinical development of nemiralisib, this study aimed to assess the safety and pharmacokinetic (PK) properties of a new formulation of nemiralisib administered via the Ellipta DPI in healthy individuals. The new formulation contains 0.4% magnesium stearate as the stabilizing excipient compared with 0.6% in the previous Ellipta formulation.[8] An additional objective was to use data derived from this study to provide information about the expected PK profile and systemic exposure in patients to be recruited to a Phase IIb study in COPD.

METHODS

Participants and Study Design

Participants were healthy men or women, aged 18−75 years old with normal spirometry, weight ≥50 kg, and body mass index of 18.0 to 35.0 kg/m^2. Participants with a current or recent history of asthma; patients with cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, or neurologic disorders; and smokers or those with a history of smoking (in the last 6 months and a total pack-year history >5 years) were excluded. Participants were also required to refrain from use of over-the-counter or prescription medications within 7 days before dosing and live vaccines within 1 month of dosing or during the study. Full eligibility criteria are available on ClinicalTrials.gov. Written informed consent was obtained from all participants before any study procedures, and the study was approved by the Wales Research Ethics Committee (protocol study number: 207674).

This was a randomized, double-blind, parallel group, single-dose, Phase 1 study conducted in 1 centre in the United Kingdom between June and July 2017. After a screening visit up to 28 days before day 1, participants were admitted to the study clinic on day −1 and dosed on day 1. After 24-h postdose assessments and clinical review on day 2, participants were discharged and returned to clinic on days 3 and 6 for further assessments (tolerability and medication review and PK sampling) and then received a follow-up telephone call at 10 to 12 days after dosing. Participants received a single dose of 500 or 750 μg of nemiralisib administered via the Ellipta DPI in a 1:1 ratio. Participants were assigned a unique randomization number in ascending numerical order using the Interactive Web Response System, according to the randomization schedule generated before the study by the Clinical Statistics Department of GlaxoSmithKline. Both treatments looked identical to maintain the treatment blind.

Outcome Measures

PK Profile

The primary outcome was the PK profile after single-dose nemiralisib administration. PK blood samples were collected before dosing and 5 min and 0.5, 2, 6, and 12 h after dosing on day 1; 24 h after dosing on day 2; 48 h after dosing on day 3, and 120 h after dosing on day 6. Samples were collected into K3-EDTA tubes and centrifuged at 1500*g* and +4°C for 10 min. The plasma was stored at −20°C before shipment for analysis to Aptuit (Verona, Italy). Plasma samples were analyzed for nemiralisib concentrations using a validated analytical method based on protein precipitation using acetonitrile that contained [$^2H_7$]-nemiralisib as an internal standard, followed by TurboIonSpray (SCIEX, Concord, Ontario, Canada) LC-MS/MS analysis. The lower limit of quantitation was 20 pg/mL using a 50-μL aliquot of human plasma with a higher limit of quantitation of 10,000 pg/mL. A 3-μL aliquot of extracted sample was injected onto an LC system that consisted of a 50 × 2.1-mm internal diameter Agilent Zorbax SB-CN 5-μm column (Agilent Technologies Inc, Santa Clara, California)

and a Water Acquity UPLC chromatography system (Waters Corp, Milford, MA). Mobile phases of 10 mM ammonium formate and acetonitrile at a flow rate of 0.8 mL/min and a column temperature of 40°C were used to elute nemiralisib at a typical retention time of 0.9 min.

Safety and Tolerability

Adverse events (AEs) were monitored from dosing on day 1 through to the follow-up call. Vital signs were measured and 12-lead ECGs were performed at screening and on day 1 before dosing; at 5 min (ECG only), 1 h (vital signs only), and 6 h after dosing; and on day 2 before discharge. Routine laboratory tests were assessed at screening and on day −1 before dosing. Spirometry (forced expiratory volume in 1 s and forced vital capacity) was performed at screening and on day 1 before dosing and 30 min after dosing.

Aerodynamic Particle Size Distribution

To examine the expected PK profile and systemic exposure in patients to be recruited to a Phase IIb study, an assessment of the aerodynamic particle size distribution (APSD) of 100 and 500 μg of nemiralisib delivered from the Ellipta DPI (0.6% and 0.4% magnesium stearate formulations) and Diskus DPI and 750 μg from the Ellipta (0.4% formulation) was performed. Next generation impaction (NGI) at an airflow rate of 60 L/min was used to test a composite sample of 10 blisters (Diskus) or 6 blisters (Ellipta), taken from each of 4 replicate inhalers. Analysis of the sample was performed by reversed-phase gradient HPLC with UV detection. The generated APSD data were used to calculate fine particle mass (FPM) (NGI stages 3, 4, and 5) and very fine particle mass (vFPM) (NGI stages 6 and 7, filter and external filter). Results were expressed in terms of the percentage of the mass found on the various stages and filters relative to the label claim (percentage of label claims of nominal dose).

PK Parameter Definitions and Statistical Analysis

No formal hypotheses were tested. Assuming the variability was similar to that observed previously using the Ellipta DPI with 0.6% magnesium stearate,[10] the sample size of 12 individuals (6 in each treatment group) was estimated to provide sufficient precision around the estimates of C_{max} and AUC to obtain a preliminary assessment of the PK properties of nemiralisib administered via the Ellipta DPI with 0.4% magnesium stearate. Plasma nemiralisib concentration-time data were analyzed by a standard noncompartmental analysis model using the software package Phoenix WinNonlin Pro. The following PK parameters were derived: AUC_{0-24}, AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{½}$, and trough concentration at 24 h after a single dose. Summary statistics are also presented (median, range, geometric mean with associated 95% CI, and between-subject CV). All safety data were summarized.

RESULTS

Participants

Nineteen participants were screened for the study of whom 12 were randomized to treatment and completed all assessments, 6 in each of the 500 and 750 μg of nemiralisib groups as planned. Of the 7 participants who failed the screening, 6 failed to meet all inclusion and exclusion criteria and 1 withdrew consent. All participants were male, and the mean age per group was 54 (range, 45−59) years in the 500 μg of nemiralisib group and 43 (range, 31−60) years in the 750 μg of nemiralisib group.

PK Properties

Nemiralisib was absorbed rapidly into plasma after single-dose administration of 500 and 750 μg of nemiralisib from the Ellipta DPI (median T_{max} of 0.08 h after both doses) (Table I). Plasma concentration-time profiles were visually similar for both the 500- and 750-μg doses, and plasma concentrations were still measurable at 120 h after dosing following both treatments (Fig. 1). After attainment of C_{max}, plasma concentrations decreased rapidly until approximately 2 h after dosing; thereafter, a slower decrease in nemiralisib plasma concentrations was observed.

Systemic exposure in terms of AUC was greater after inhalation of the 750-μg dose compared with the 500-μg dose (Table I). Geometric mean C_{max} was lower after the 750-μg dose versus the 500-μg dose. Exclusion of one outlying C_{max} measurement for one participant from the summary statistics resulted in a geometric mean C_{max} of 2000 pg/mL, which was similar to the geometric mean of 2030 pg/mL for the 500-μg dose. The $t_{1/2}$ values were comparable after both doses of nemiralisib, with estimates of 43.8 and 38.3 h following the 500-μg and 750-μg doses, respectively. Between-participant CV in the extent of

Table I. Summary of nemiralisib pharmacokinetic parameters.

Parameter	Nemiralisib 500 μg (n = 6)	Nemiralisib 750 μg (n = 6)
$C_{max,}$ pg/mL		
Geometric mean (95% CI)	2030 (1320–3130)	1630 (847–3120)
Between-subject CV, %	43	69
Trough concentration at 24 h after a single dose, pg/mL		
Geometric mean (95% CI)	166 (120–228)	240 (174–331)
Between-subject CV, %	31	31
$T_{max,,}$ median (range), h	0.08 (0.08–0.10)	0.08 (0.07–0.08)
AUC_{0-t}, h•pg/mL		
Geometric mean (95% CI)	13,100 (8130–21,000)	17,200 (10,900–27,200)
Between-subject CV, %	48	46
AUC_{0-24}, h•pg/mL		
Geometric mean (95% CI)	5810 (4310–7820)	8030 (5460–11,800)
Between-subject CV, %	29	38
$AUC_{0-\infty}$, h•pg/mL*		
Geometric mean (95% CI)	19,000 (13,900–26,100)	22,600 (16,000–32,000)
Between-subject CV, %	20	28
$t_{1/2}$, h*		
Geometric mean (95% CI)	43.8 (39.8–48.3)	38.3 (30.0–48.9)
Between-subject CV, %	6	20

* Sample sizes are 4 and 5 for the nemiralisib 500 μg and nemiralisib 750 μg groups, respectively.

systemic exposure to nemiralisib was generally low to moderate after administration of the 500-μg and 750-μg doses (Table I).

Safety and Tolerability

A total of 9 AEs was reported by 6 participants during the study, 3 from each treatment group. The most frequently reported AE was fatigue, which was reported in 2 participants (17%), both after inhalation of 750 μg of nemiralisib. Other AEs (catheter site inflammation, headache, somnolence, constipation, limb injury, musculoskeletal stiffness, and cough) were reported in 1 participant each. The AEs of headache and cough, reported by 1

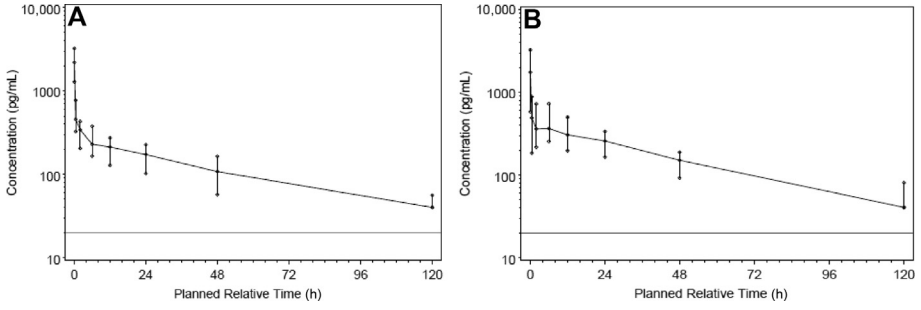

Fig. 1. Median (range) nemiralisib plasma concentration-time plot (semi-log) after single-dose administration with 500 μg of nemiralisib (A) or 750 μg of nemiralisib (B).

participant after inhalation of 750 μg, were considered by the investigator to be drug related.

There were no serious AEs, deaths or other significant AEs, including paradoxical bronchospasm, reported during the study. There were also no clinically significant abnormalities reported for vital signs, ECG, or any laboratory measurements.

In Vitro Analysis of Formulation

Respirable mass was highest for the Ellipta formulation that contained magnesium stearate 0.4% followed by the Ellipta formulation that contained magnesium stearate 0.6% and then the Diskus (Table II). APSD data for each device and dose strength (including 100 μg data used in the Ellipta formulation that contained magnesium stearate 0.6%) was used to calculate the change in *in vitro* performance to predict the change in clinical exposure to the new formulation. Differences in plasma exposure data among the different formulations correlated well with changes in respirable mass data (based on a 500-μg dose level),

Table II. Comparison of aerodynamic particle size distribution data for nemiralisib inhalation powder products and summary of pharmacokinetic parameters with *in vitro* prediction.*

Variable	Diskus	Ellipta (0.6% Magnesium Stearate)	Ellipta (0.4% Magnesium Stearate)	Fold Change From Diskus to Ellipta (0.4% Magnesium Stearate)	
				In Vivo	*In Vitro Prediction*†
Aerodynamic particle size distribution data, % of label claims					
100 μg					
FPM	23	25.8	41.7	—	—
VFPM	1	3.5	5.3	—	—
FPM and VFPM	24	29.3	47.0	—	—
500 μg					
FPM	26	31.9	46.2	—	—
VFPM	1	5.0	5.8	—	—
FPM and VFPM	27	36.9	52.0	—	—
750 μg					
FPM	—	—	40.0	—	—
VFPM	—	—	4.6	—	—
FPM and VFPM	—	—	44.6	—	—
Summary of pharmacokinetic parameters (geometric mean presented) with *in vitro* prediction (based on a 500-μg dose)					
C_{max}, pg/mL‡	250	998	2030	8.1	6
AUC_{0-24}, h•pg/mL‡	2763	4250	5810	2.1	1.9
Trough concentration at 24 h (day 1), pg/mL‡	97	118	166	1.7	1.7

FPM = fine particle mass; VFPM = very fine particle mass.

* Formulations were as follows: Diskus: nemiralisib and lactose monohydrate; Ellipta (0.6% magnesium stearate): nemiralisib, 0.6% magnesium stearate, and lactose monohydrate; and Ellipta (0.4% magnesium stearate): nemiralisib, 0.4% magnesium stearate, and lactose monohydrate.

† On the basis of the 500-μg dose data or for Phase I Ellipta, this was based on linear extrapolation of the 200-μg dose (2 × 100 μg).

‡ *In vitro* predictions based on ratios of VFPM (C_{max}), VFPM plus FPM (AUC), and FPM(trough concentration at 24 h).

as indicated by the close match between *in vitro* prediction and *in vivo* performance data (Table II).

The magnitude of change *in vivo* (plasma exposure data) from the Diskus to the Ellipta magnesium stearate 0.4% product was 8-fold with respect to C_{max} and approximately 2-fold with respect to AUC_{0-24} and trough concentration at 24 h compared with *in vitro* predictions of 6-fold (based on vFPM) and 2-fold (based on FPM plus vFPM and FPM).

DISCUSSION

Nemiralisib is currently being evaluated as a potential new immunomodulatory therapy in COPD, and this study represents a step in its clinical development by being the first study to assess the PK properties, safety and tolerability of a new formulation that contains magnesium stearate 0.4% for delivery via the Ellipta DPI. Healthy participants were considered appropriate to assess the new formulation because previous studies assessing device and formulation have been conducted in healthy populations and no significant differences in the PK profiles have been observed between healthy participants and patients with COPD.[6,8]

In this study, systemic exposure of nemiralisib was higher after inhalation of the 750-µg versus 500-µg dose, when measured by AUC parameters; however, geometric mean maximum plasma concentration of nemiralisib as measured by C_{max} was lower after the 750-µg dose (Table I). This finding may be attributed to the lower observed C_{max} value for 1 participant dosed with 750 µg, which appeared to be an outlier, and exclusion of which resulted in similar geometric mean C_{max} values with respect to both inhaled doses. Another explanation could be the slightly lower level of vFPM with the 750-µg dose compared with the 500-µg dose (4.6% compared with 5.8% of label claims of nominal dose) (Table II). The rapid absorption of nemiralisib and a t½ of approximately 40 h observed after both the 500- and 750-µg doses compare well with data in prior studies with the Diskus device and with the Ellipta DPI formulation that contains 0.6% magnesium stearate.[6,8]

After the change in nemiralisib formulation compared with previous studies,[6,8] it was anticipated that the PK profile would be affected. The magnitude of the change in the observed exposure in humans closely matched the magnitude of change in APSD data in terms of the change in FPM and vFPM. The change in C_{max} was correlated with the change in vFPM, and AUC and trough concentration at 24 h after single dose were correlated with the FPM plus vFPM and FPM fractions, respectively. We hypothesized that the smaller sized particles (vFPM) are being deposited deeper in the lungs down to the alveolar barrier level, where they are likely transported much more rapidly across this cell layer, and hence the increase in vFPM contributed to an increase to C_{max}. Particles deposited higher up the bronchial tree tend to be larger and have more impact on exposure over time (therefore, increases in vFPM plus FPM and FPM contributed to increases in AUC and trough concentration at 24 h). By using the experience gained from the development of nemiralisib in terms of *in vitro* respirable mass data (APSD) and observed PK parameters, the increased systemic exposure observed in this study was correctly predicted and will help in understanding the likely exposure in patients of the new formulation.

Nemiralisib was well tolerated in this study with a low frequency of reported AEs in both treatment groups, none of which were assessed as serious AEs. Short post-inhalation cough, the most commonly reported AE in patient studies using the Diskus inhaler and nemiralisib formulation that contained no magnesium stearate,[6,9] was reported by 1 participant only in the 750-µg group. Because 750 µg is the highest dose being investigated in the Phase IIb dose-ranging patient study (in patients with acutely exacerbating COPD), this provides some, albeit limited, reassurance that the new formulation of nemiralisib delivered via the Ellipta DPI is not expected to produce any new safety and tolerability concerns. Importantly, it is expected that systemic exposures will remain within previously documented safe systemic exposure limits[11] (in terms of maximum exposures and that being targeted for efficacy).

In conclusion, after single-dose inhalation of 500 and 750 µg of nemiralisib from the Ellipta DPI in healthy individuals, plasma PK data were well defined. Moreover, these data were consistent with the inhalation profile and deposition characteristics observed during nemiralisib's product development and in line with changes to the drug formulation. Nemiralisib was well tolerated with no new safety issues identified. These data supported the progression of nemiralisib to a Phase IIb study in patients with COPD.

FUNDING SOURCES

This study was funded by GlaxoSmithKline, which was involved in the study design; in the collection, analysis, and interpretation of data; and in the writing of the manuscript. Ellipta is owned by or licensed to the GlaxoSmithKline group of companies.

CONFLICTS OF INTEREST

Robert Wilson, Alison Templeton, Claudia Leemereise, Rhean Eames, and Edith M. Hessel are GlaxoSmithKline employees and all hold GlaxoSmithKline shares, except for Claudia Leemereise. Edith M. Hessel is named on patents for compound GSK2269557 (nemiralisib). Edward Banha-Hall is a National Health Service employee who is seconded to GlaxoSmithKline for 50% of his time. Information on GlaxoSmithKline's data sharing commitments and requesting access can be found at https://www.clinicalstudydatarequest.com. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

ACKNOWLEDGMENTS

We thank Alan Paul and Christopher Jones (Product Development & Supply, GlaxoSmithKline) for providing the aerodynamic particle size distribution data analysis and for reviewing the manuscript. Editorial support was provided by Kate Hollingworth of Continuous Improvement Ltd and funded by GlaxoSmithKline.

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