Safety, Tolerability, and Pharmacokinetics of Single and Repeat Doses of Nemiralisib Administered via the Ellipta Dry Powder Inhaler to Healthy Subjects

Robert Wilson, BSc[1]; Emily Jarvis, MSc[1]; Mickael Montembault, PhD[2]; J. Nicole Hamblin, DPhil[3,*]; Edith M. Hessel, PhD[3]; and Anthony Cahn, MBBS, PhD[1]

[1]GlaxoSmithKline, Stevenage, United Kingdom; [2]GlaxoSmithKline, Uxbridge, United Kingdom; and [3]Refractory Respiratory Inflammation Discovery Performance Unit, GlaxoSmithKline, Stevenage, United Kingdom

ABSTRACT

Purpose: Novel therapies to treat chronic obstructive pulmonary disease are highly desirable. The safety, tolerability, and pharmacokinetic (PK) parameters of nemiralisib, a phosphoinositide 3-kinase δ inhibitor, administered via the Ellipta dry powder inhaler (GlaxoSmithKline, Research Triangle Park, North Carolina) was evaluated, including an assessment of oral bioavailability.

Methods: This single-center, 3-part, placebo-controlled trial in 22 healthy subjects evaluated single (100 and 200 μg) and repeat (200 μg for 10 days) doses of inhaled nemiralisib in parts A (n = 12) and B (n = 12) (double-blind) and single doses of inhaled nemiralisib (200 μg) with and without charcoal block in Part C (n = 6) (open-label, 2-period, crossover). There was a minimum 14-day washout period between dosing days.

Findings: 21 subjects completed the study, mean age was similar in the three parts (A: 49 years; B: 44 years; C: 55 years). After single doses of nemiralisib, observed plasma C_{max} dropped rapidly, followed by a slower elimination phase. Near-dose proportionality was observed: mean (95% CI) plasma C_{max} and AUC_{0-24} values were 174.3 pg/mL (96.9−313.3) and 694.6 pg·h/mL (503.5−958.2) for 100 μg and 398.9 pg/mL (318.3−500.1) and 1699.6 pg·h/mL (1273.3−2268.7) for 200 μg, respectively. Repeat dosing for 10 days showed exposures ~2- to 4-fold higher than on the single dose (peak, trough, and AUC_{0-24} levels), achieving steady-state by day 6. Mean AUC_{0-24} was 2193.6 pg·h/mL and 1645.3 pg·h/mL in the absence/presence of charcoal. Two non−drug-related adverse events were observed; neither was serious or resulted in withdrawal.

Implications: Inhalation of nemiralisib was well tolerated in these healthy subjects. Plasma pharmacokinetic variables were well defined, and charcoal block data indicate that ~23% of the total systemic exposure after inhalation from Ellipta was attributable to orally absorbed drug. ClinicalTrials.gov identifier: NCT02691325. (*Clin Ther*. 2018;■:1−8) © 2018 Elsevier Inc. All rights reserved.

Key words: nemiralisib, ellipta, healthy volunteers, phramacokinetics, safety.

INTRODUCTION

Although current pharmacologic therapies in chronic obstructive pulmonary disease (COPD) are effective in reducing symptoms and decrease the risk and severity of exacerbations,[1] some patients who experience a COPD exacerbation remain susceptible to further events.[2,3] Subsequent events may be more severe and associated with worse outcomes,[4] and patients reporting frequent exacerbations typically have poor health status and a faster disease progression.[5]

Nemiralisib is a potent and highly selective inhibitor of phosphoinositide 3-kinase δ (PI3Kδ), a lipid kinase expressed exclusively in leukocytes, and is being investigated as an anti-infective and anti-inflammatory

* Current affiliation: Discovery, Charles River, Chesterford Research Park, Saffron Walden, United Kingdom.

Accepted for publication June 14, 2018.
https://doi.org/10.1016/j.clinthera.2018.06.011
0149-2918/$ - see front matter

© 2018 Elsevier Inc. All rights reserved.

agent in COPD. PI3Kδ inhibitors have the potential to improve the immune response to infection by correcting aberrant neutrophil migration and improving macrophage- and neutrophil-mediated bacterial clearance, as well as reducing inflammatory mediator release across a range of cell types, including neutrophils.[6–8] Such a treatment may benefit patients with COPD experiencing exacerbations. In healthy volunteers, nemiralisib has been well tolerated across a range of doses in both nebulized solution and as a dry powder inhalation (Diskus [GlaxoSmithKline, Research Triangle Park, North Carolina) formulation (unpublished, unrefereed poster and oral presentations). In patients with COPD exacerbations, nemiralisib 1 mg inhaled once daily for up to 84 days via the Diskus inhaler had an acceptable safety profile, supporting progression to larger studies in patients with COPD.[9] Adverse events recorded for nemiralisib in patients with COPD exacerbations include short duration postinhalation cough in 35% of patients.[9]

The aim of the present study in healthy volunteers was to assess the safety, tolerability, and pharmacokinetic (PK) parameters of inhaled nemiralisib administered for the first time via the Ellipta dry powder inhaler (DPI) (GlaxoSmithKline), with a new formulation that included an additional, stabilizing excipient, 0.6% magnesium stearate. The nemiralisib Ellipta DPI is a more efficient device compared with the nemiralisib Diskus inhaler and is the chosen device for delivery of the final drug product. The study also examined the contribution of the orally absorbed component to the plasma PK profile using a charcoal block approach. All dose levels quoted are in terms of nominal dose within the inhaler device unless otherwise stated.

SUBJECTS AND METHODS

Subjects

Healthy male or female subjects aged 20 to 75 years, with normal spirometry at screening (forced expiratory volume in 1 second and forced vital capacity $\geq$80% of predicted values), a body weight $\geq$50 kg, and a body mass index between 18 and 35 kg/m^2, were eligible. All subjects underwent medical evaluation, including medical history, physical examination, laboratory tests, and cardiac testing, to confirm eligibility. Subjects with asthma or a recent history of asthma, current or chronic history of liver disease or known hepatic/biliary abnormalities, and current smokers or subjects with a history of smoking within the last 6 months or those with a total pack year history >5 years were excluded. Full details of the inclusion/exclusion criteria can be found at ClinicalTrials.gov (NCT02691325).

The study was conducted in accordance with the guiding principles of the Declaration of Helsinki. Written informed consent was obtained from all patients, and the study was approved by Aspire Institutional Review Board, Santee, California (protocol study number 201544).

Study Design

This single-center study comprised 3 parts. Subjects could participate in >1 part providing there was at least 14 days between the last dose taken in 1 part and the first dose of the next.

Part A was a double-blind, 2-period, incomplete crossover design in which subjects received single doses of either placebo or nemiralisib 100 μg in period 1 and placebo or nemiralisib 200 μg in period 2. Twelve subjects were planned for enrollment, 10 to receive nemiralisib and 2 to receive placebo in each treatment period. Subjects were assigned to 1 of the following 3 treatment sequences in a ratio of 1:1:4: placebo followed by nemiralisib 200 μg; nemiralisib 100 μg followed by placebo; and nemiralisib 100 μg followed by nemiralisib 200 μg. There was a minimum 14-day washout between dosing days.

Part B was a double-blind, parallel-group design in which subjects received repeat doses of nemiralisib 200 μg or placebo for 10 days. Twelve subjects were planned for enrollment, 9 to receive nemiralisib and 3 to receive placebo.

Part C was an open-label, 2-period, crossover design in which 6 subjects were planned to receive single doses of nemiralisib 200 μg with ingestion of activated charcoal in 1 period and without ingestion in the other period (in each period, 3 subjects received nemiralisib with charcoal and 3 received nemiralisib without charcoal). There was a minimum 14-day washout between dosing days.

During each part of the study, treatment was inhaled as a once-daily dose from the Ellipta DPI, either as 1 inhalation (nemiralisib 100 μg or placebo) during period 1 of Part A, or as 2 inhalations (nemiralisib 100 μg or placebo) during the other study phases when nemiralisib 200 μg was evaluated. This method maintained the study blind during Parts A and B. In Part C, charcoal block suspension (5 g of activated

Download English Version:

https://daneshyari.com/en/article/10158418

Download Persian Version:

https://daneshyari.com/article/10158418

Daneshyari.com