Effect of the CXCR2 antagonist danirixin on symptoms and health status in COPD

To the Editor:

Approximately one-third of patients with chronic obstructive pulmonary disease (COPD) have chronic mucus hypersecretion (CMH) [1], often referred to as chronic bronchitis. Despite treatment with inhaled medications and other therapies, such as expectorants or methylxanthines, patients with CMH may continue to experience exacerbations, substantial symptom burden and poor health status [1]. CXCR2 antagonists are effective in multiple preclinical and human models of airway inflammation [2–5]. Danirixin is a competitive, reversible, oral CXCR2 antagonist that has been well tolerated in healthy subjects and in patients with influenza [6, 7]. We report the results of a 52-week Phase 2 study conducted in Germany and the USA (GSK protocol 200163; ClinicalTrials.gov identifier NCT02130193) assessing the effects of danirixin when added to standard-of-care inhaled medications in participants with symptomatic COPD. Participants with a forced expiratory volume in 1 s (FEV_1) ⩾50% of predicted normal and a history of two exacerbations in the prior 12 months, or one exacerbation and elevated plasma fibrinogen ⩾3 $mg{\cdot}mL^{-1}$, as well as a history of chronic cough and/or mucus hypersecretion on most days for at least the previous 3 months prior to screening, were eligible. Full inclusion and exclusion criteria are available online at clinicaltrials.gov. The study was approved by the Western Institutional Review Board (Puyallup, WA, USA) and the Ethikkommission I, Ärztekammer Schleswig-Holstein (Bad Segeberg, Germany). Written informed consent was obtained from all participants.

The primary end-points were respiratory symptoms at week 52 evaluated using the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) instrument recorded in an electronic diary, and the incidence of healthcare resource utilisation (HCRU)-defined COPD exacerbations. The E-RS: COPD quantifies respiratory symptom severity and yields a total score, with higher scores indicating more severe symptoms. It is suggested that a reduction of two points or more is indicative of a clinically meaningful improvement in symptoms [8]. Key secondary end-points included change from baseline in both health status (COPD assessment test (CAT) and E-RS: COPD subscale scores (breathlessness, cough and sputum, and chest symptoms)) and safety.

All randomised participants (n=93) were included in the intent-to-treat population for the primary analysis using a Bayesian repeated-measures mixed-effects model. The mean monthly E-RS: COPD score with corresponding 95% credible intervals was calculated, along with the difference between treatment groups. The number of HCRU-defined exacerbations was analysed using a Bayesian Cox model. CAT scores were summarised for each treatment group at each visit, with a clinically meaningful improvement indicated by a decrease from baseline of ⩾2 points [9].

Following screening of 127 participants, 93 were randomised to receive either oral danirixin 75 mg twice daily (n=45) or placebo (n=48), in addition to COPD standard-of-care medications (figure 1a). Decreases in the E-RS: COPD total score were observed with danirixin within 2 months of study start and were maintained through 52 weeks (figure 1b). The posterior mean total score over months 3–12 was 11.16 in the danirixin group and 12.67 in the placebo group (treatment difference −1.52 (95% CrI −4.26–+1.33)). In a *post hoc* analysis, the Bayesian probability that the true treatment difference over months 3–12 was <0 was 85%; the probability that the true treatment difference was <−1 was 65%. The improvement in E-RS: COPD scores appeared to be driven by changes in the breathlessness and cough and sputum subscales, while no change was noted in the chest symptom subscale. At week 52, CAT scores had improved by a

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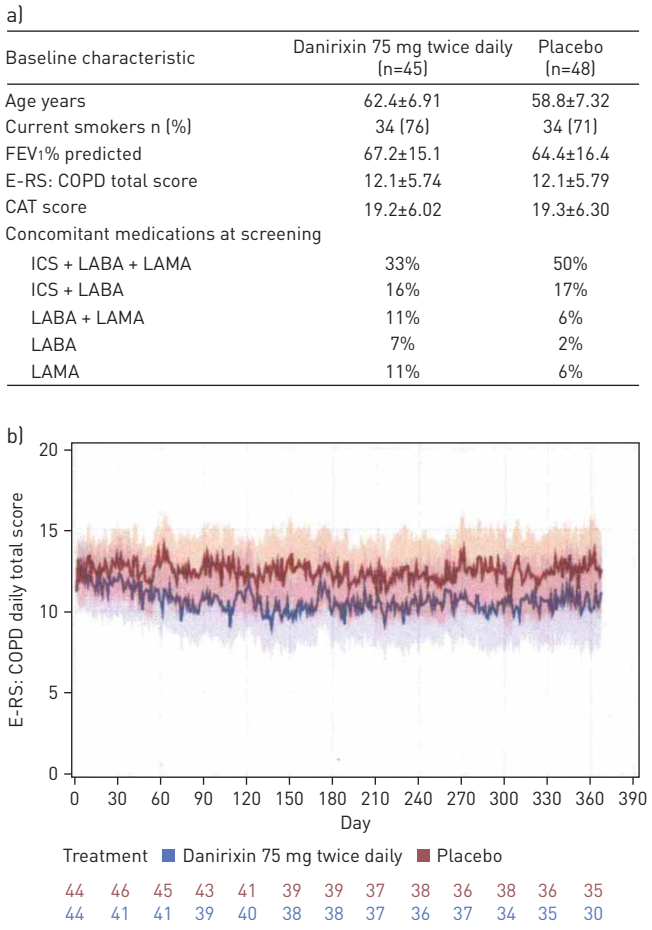
Danirixin was associated with improved respiratory symptoms and health status in patients with mild-to-moderate COPD http://ow.ly/5m6P30luwfh

Cite this article as: Lazaar AL, Miller BE, Tabberer M, *et al*. Effect of the CXCR2 antagonist danirixin on symptoms and health status in COPD. *Eur Respir J* 2018; 52: 1801020 [https://doi.org/10.1183/13993003.01020-2018].

a)

Baseline characteristic	Danirixin 75 mg twice daily (n=45)	Placebo (n=48)
Age years	62.4±6.91	58.8±7.32
Current smokers n (%)	34 (76)	34 (71)
FEV_1% predicted	67.2±15.1	64.4±16.4
E-RS: COPD total score	12.1±5.74	12.1±5.79
CAT score	19.2±6.02	19.3±6.30
Concomitant medications at screening		
ICS + LABA + LAMA	33%	50%
ICS + LABA	16%	17%
LABA + LAMA	11%	6%
LABA	7%	2%
LAMA	11%	6%



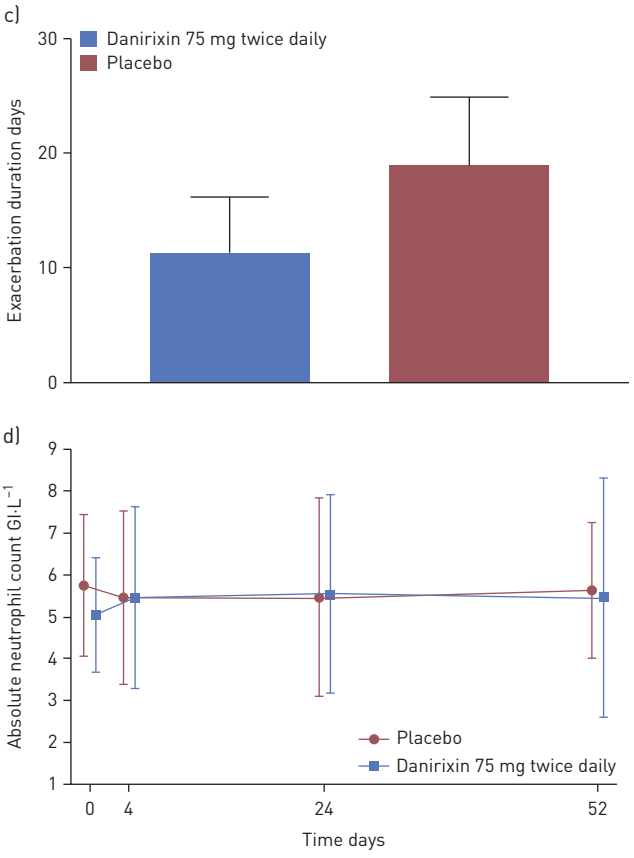


FIGURE 1 a) Patient demographics and baseline characteristics; b) daily Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease (E-RS: COPD) total score; c) mean exacerbation duration; and d) peripheral blood neutrophil counts. Data are presented as mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; CAT: COPD assessment test; ICS: inhaled corticosteroids; LABA: long-acting beta agonist; LAMA: long-acting muscarinic receptor antagonist.

mean of −2.1 points (95% CI −5.1–+1.0) in the danirixin group compared with a deterioration of +0.7 points (95% CI −1.2–+2.6) in the placebo group. In a *post hoc* analysis, the Bayesian probability that the true treatment difference at week 52 was <−1 was 90%; the probability that the true treatment difference was <−2 was 71.7%.

During the study, 21 (47%) participants receiving danirixin and 23 (48%) receiving placebo experienced at least one moderate or severe COPD exacerbation. There was no difference in the total number of HCRU-defined exacerbations in the danirixin and placebo groups (43 *versus* 39 exacerbations, respectively); however, the median reported exacerbation duration was 9 days (range 4–50) in the danirixin group and 17 days (range 4–65) in the placebo group (figure 1c).

Approximately 80% of participants in both treatment groups experienced at least one adverse event during the study, but few were drug-related (danirixin 4 (9%) *versus* placebo 7 (15%)). Diarrhoea, nausea and headache were the most common treatment-related adverse events in both groups, though reported at a lower incidence in the danirixin group. There was no difference in the number of participants with serious adverse events or withdrawals due to adverse events. A complete listing of adverse events and severe adverse events is available online at clinicaltrials.gov. No changes in blood neutrophil levels were observed with danirixin (figure 1d). The median serum C-reactive protein was 3.4 $mg{\cdot}L^{-1}$ (interquartile range 1.8–6.4) at day 1 and 4.0 $mg{\cdot}L^{-1}$ (1.6–6.7) at week 52 for the danirixin group; the corresponding values for placebo were 2.3 $mg{\cdot}L^{-1}$ (1.4–5.9) and 3.5 $mg{\cdot}L^{-1}$ (2.1–6.4), respectively.

This first-in-patient study investigated the safety and efficacy of danirixin in participants with COPD and CMH who were symptomatic, with a history of exacerbations despite receiving standard-of-care inhaled medications. Overall, participants who received danirixin demonstrated improvements in respiratory symptoms and health status compared with participants on placebo. We observed no difference in the

number of HCRU-defined exacerbations experienced by participants in the danirixin and placebo groups, although the data raise the possibility that danirixin may reduce the duration of COPD exacerbations. This should be interpreted cautiously, as the methods for determining exacerbation duration were not standardised and probably varied from observer to observer. Respiratory symptom scores improved over time starting from about 2 months of treatment and there was an improvement in health status, demonstrated by a clinically meaningful decrease in the CAT score in participants treated with danirixin. Since no differences were observed in the number of HCRU-defined exacerbations experienced between the two treatment groups, this may indicate that the changes in health status scores are not driven by effects on acute exacerbations but by an overall reduction in the burden of lung inflammation. This will be explored in larger trials. The incidence of adverse events was similar in the danirixin- and placebo-treated groups. The absence of neutropenia seen with danirixin contrasts with other CXCR2 antagonists that have been tested in asthma, bronchiectasis and COPD [10–12] and may be due to the greater reversibility of its receptor binding compared with the other CXCR2 antagonists [5, 13–15].

The current trial has limitations, notably the small number of participants. A previous study suggested that CXCR2 antagonists may have greater efficacy in current rather than former smokers [11], but as most participants in the current study were smokers, it was not possible to analyse the effect of danirixin by smoking status. Finally, there were no E-RS: COPD scores collected prior to the start of treatment.

In conclusion, this study indicates positive trends in respiratory symptoms and health status in patients with mild-to-moderate symptomatic COPD at high risk for exacerbations and support the hypothesis that danirixin may be a useful adjunct treatment.

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This study is registered at ClinicalTrials.gov with identifier NCT02130193. Within 6 months of publication, anonymised individual participant data, the annotated case report form, protocol, reporting and analysis plan, data set specifications, raw dataset, analysis-ready dataset, and clinical study report will be available for research proposals approved by an independent review committee. A data access agreement will be required. Proposals should be submitted to www.clinicalstudydatarequest.com

Received: Jan 26 2018 | Accepted after revision: Aug 02 2018

Conflict of interest: A.L. Lazaar is an employee of GlaxoSmithKline and holds stock in the company. B.E. Miller is an employee and shareholder of GSK. M. Tabberer is an employee of and holds stock in GSK. J. Yonchuk is an employee and shareholder of GSK. N. Leidy is employed by Evidera, a healthcare research firm that provides consulting and other research services to pharmaceutical, device, government and non-government organisations. In this salaried position, N. Leidy works with a variety of companies and organisations, receiving no payment or honoraria directly from these organisations for services rendered, apart from honoraria received for her advisory role on two NIH-funded programmes: PATIENTS and PCAR. Evidera is the copyright owner of the EXACT and E-RS. C. Ambery is an employee and shareholder of GSK. J. Bloomer is an employee and shareholder of GSK. H. Watz is an employee of GSK. R. Tal-Singer is an employee and shareholder of GSK.

Support statement: This study was funded by GlaxoSmithKline. Funding information for this article has been deposited with the Crossref Funder Registry.

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