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Early View

Research letter

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

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

Aili L. Lazaar[1], Bruce E. Miller[1], Maggie Tabberer[2], John Yonchuk[1], Nancy Leidy[3], Claire Ambery[2], Jackie Bloomer[4], Henrik Watz[5] and Ruth Tal-Singer[1]

Affiliations:

[1]GSK, Collegeville, PA (USA), [2]GSK, Stockley Park (UK), [3]Evidera, Bethesda, MD (USA), [4]GSK, Ware (UK), [5]Pulmonary Research Institute Lungen Clinic Grosshansdorf, Airway Research Center North (ARCN), German Center for Lung Research (DZL), Grosshansdorf (Germany).

Correspondence: Aili Lazaar, 1250 S. Collegeville Road, Collegeville, PA 19426 USA.

E-mail: aili.l.lazaar@gsk.com

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 an $FEV_1 \geq 50\%$ 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 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 b.i.d. (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 to 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 mean of –2.1 points (95% CI: –5.1 to 1.0) in the danirixin group compared with a deterioration of +0.7 points (95% CI: –1.2 to 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 participants receiving danirixin (47%) and 23 receiving placebo (48%) 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 (AE) 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 AEs in both groups, though reported at a lower incidence in the danirixin group. There was no difference in the number of participants with serious AEs (SAEs) or withdrawals due to AEs. A complete listing of AEs and SAEs 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 [IQR] 1.8–6.4) at day 1 and 4.0 $mg \cdot L^{-1}$ (IQR 1.6–6.7) at week 52 for the danirixin group; the corresponding values for placebo were 2.3 $mg \cdot L^{-1}$ (IQR 1.4–5.9) and 3.5 $mg \cdot L^{-1}$ (IQR 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.

Data Sharing Statement:
Information on GSK's data sharing commitments and requesting access to anonymized individual participant data and associated documents can be found at www.clinicalstudydatarequest.com.

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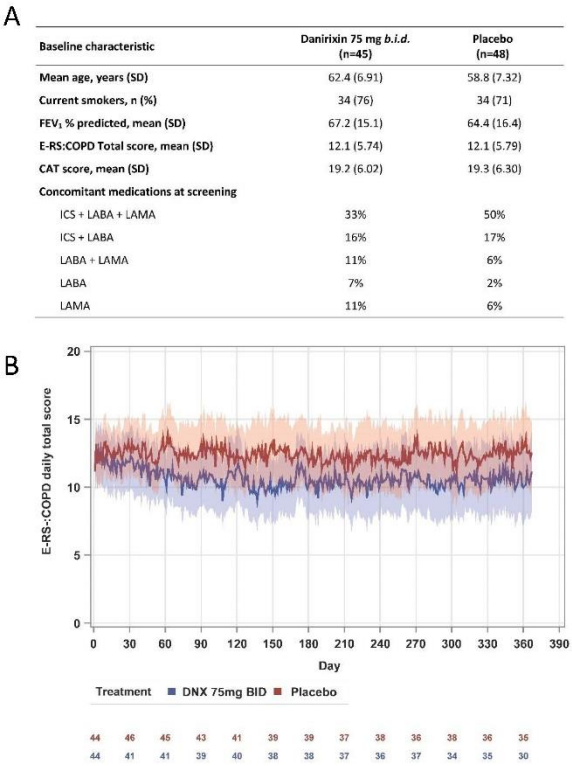
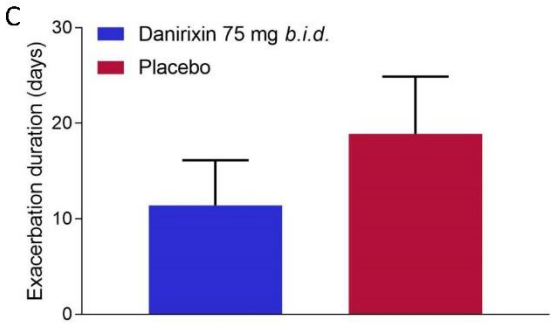
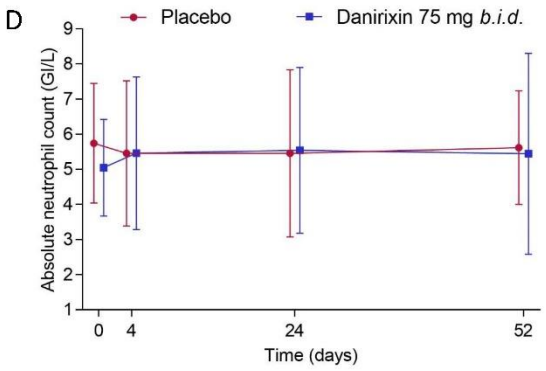
FIGURE

A

Baseline characteristic	Danirixin 75 mg *b.i.d.* (n=45)	Placebo (n=48)
Mean age, years (SD)	62.4 (6.91)	58.8 (7.32)
Current smokers, n (%)	34 (76)	34 (71)
FEV$_1$ % predicted, mean (SD)	67.2 (15.1)	64.4 (16.4)
E-RS:COPD Total score, mean (SD)	12.1 (5.74)	12.1 (5.79)
CAT score, mean (SD)	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%







A. Patient demographics and baseline characteristics; B. Daily E-RS: COPD total score; C. Mean exacerbation duration; D. Peripheral blood neutrophil counts.