## The novel inhaled glucocorticoid receptor agonist GW870086X protects against adenosine-induced bronchoconstriction in asthma

*To the Editor:*

Inhaled corticosteroids are first-line therapy for treatment of persistent asthma. The novel dissociated glucocorticoid GW870086X is a glucocorticoid receptor agonist with potency similar to that of fluticasone propionate in various human gene transrepression assays, which reflect the anti-inflammatory effects, but reduced activity in assays of gene transactivation, which is thought to mediate many of the adverse effects (AEs) of glucocorticoids.[1,2] The preclinical profile of these dissociated glucocorticoids suggests that there is potential for improvement in the therapeutic index beyond that of the currently available inhaled corticosteroids.[1-3] We investigated the potential anti-inflammatory activity of the novel dissociated glucocorticoid GW870086X in airway hyperresponsiveness, measured by the bronchoconstrictor response to inhaled adenosine monophosphate (AMP) in subjects with mild asthma.

Details of methods can be found in this article's Methods section in the Online Repository at www.jacionline.org. Briefly, we conducted a double-blind, placebo-controlled, 3-way cross-over study of GW870086X administered via a dry powder inhaler (Diskhaler, GlaxoSmithKline, Brentford, United Kingdom) to investigate its anti-inflammatory activity in airway responsiveness to AMP in steroid-naive subjects with mild asthma. Subjects were randomized to GW870086X (1 mg, 3 mg) or placebo administered on days 1 to 7 of each period. The AMP challenge was performed 2 hours postdosing on day 1 and at 2, 14, and 26 hours postdosing on day 7. Fractional exhaled nitric oxide (FENO) was measured on days 1 and 7. Serum osteocalcin and 24-hour urinary cortisol measurements were made on day 7.

Seventeen subjects completed the study as planned (see Table E1 in this article's Online Repository at www.jacionline.org for subjects' demographic characteristics). There was an increase in $PC_{20}$ AMP compared with placebo for GW870086X 1 mg on day 1 at 2 hours postdose and day 7 at 2 and 14 hours postdose and for GW870086X 3 mg on day 7 at 2 hours postdose (Fig 1, *A*). Estimated doubling dose differences for GW870086X 1 and 3 mg were similar across all time points, with mean doubling dose differences of 1.18 and 1.12 for 1 and 3 mg, respectively. A significant inhibitory effect of GW870086X on FENO concentrations at 2, 14, and 26 hours postdose was seen with the 1-mg dose (Fig 1, *B*). However, 3-mg data were less complete, and none were significantly different from placebo. The decrease in FENO significantly correlated with an increase in $PC_{20}$ AMP in an analysis including all the data ($r = 0.9$). There were no differences in $FEV_1$ between placebo and GW870086X on day 1 or day 7. Day 1 changes from baseline were (mean, 95% CI) 0.1 (−0.03 to 0.23), 0.16 (0.03-0.28), and 0.09 (0.04-0.22) for placebo, 1 mg, and 3 mg, respectively. There was no evidence of a reduction compared with placebo in total urinary free cortisol after 7 days of repeat dosing with GW870086X 3 mg, and this was supported by analysis of the total 24-hour urinary free cortisol parameter (Fig 2, *A*). There was no evidence of a difference from placebo in weighted mean serum osteocalcin (0-24 hours; Fig 2, *B*). Pharmacokinetic analysis of GW870086X can be found in Tables E2 and E3 in this article's Online Repository at www.jacionline.org. The pharmacokinetic disposition of GW870086X was characterized by a 2-compartment model with first-order absorption ($K_a$) and elimination. This model used ADVAN4 and TRANS4 subroutines in NONMEM library. A summary of subjects reporting AEs is presented in Table E4 in this article's Online Repository at www.jacionline.org.

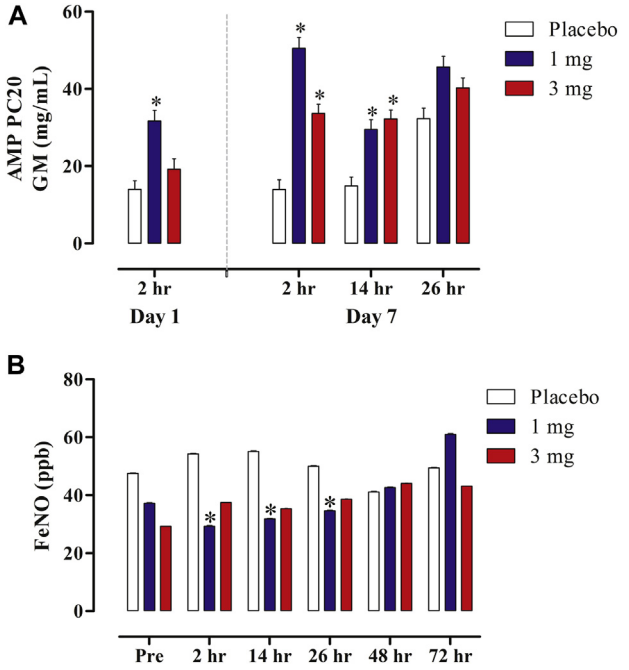


**FIG 1. A,** Effect of inhaled corticosteroids on $PC_{20}$ to inhaled AMP with GW870086X. Data are geometric mean ± geometric SEM. **P* < .05 compared with placebo. **B,** Effect of GW870086X on FENO. Data are mean ± SD. **P* < .05 difference from placebo.

GW870086X belongs to a novel class of dissociated glucocorticoids with anti-inflammatory activity and a reduced potential for AEs as it enables the glucocorticoid receptor to transrepress but has less effect on transactivation.[1,2] The anti-inflammatory actions of glucocorticoids are mainly mediated through gene transrepression, by inhibiting the action of proinflammatory transcription factors, such as NF-κB, through histone deacetylation, thereby switching off proinflammatory genes, which leads to a reduction in inflammatory proteins.[1,2] In contrast, many of the AEs of corticosteroids occur through gene transactivation[2,4,5]; a dimer of acetylated glucocorticoid receptor binds to glucocorticoid response elements in the promoter region of steroid-sensitive genes to activate (or occasionally suppress) genes (such as AE genes). In preclinical transrepression assays, GW870086X had similar or slightly less potency compared with fluticasone propionate[1] (and data on file, GlaxoSmithKline), but significantly reduced activity in transactivation assays. In the transactivation-mediated induction of liver enzymes, GW870086X induced only 30% tyrosine aminotransferase activity compared with fluticasone propionate. In the transactivation-mediated suppression of osteocalcin release, GW870086X showed less than half the suppression of osteocalcin by fluticasone propionate (30% vs 65%) (data on file, GlaxoSmithKline).

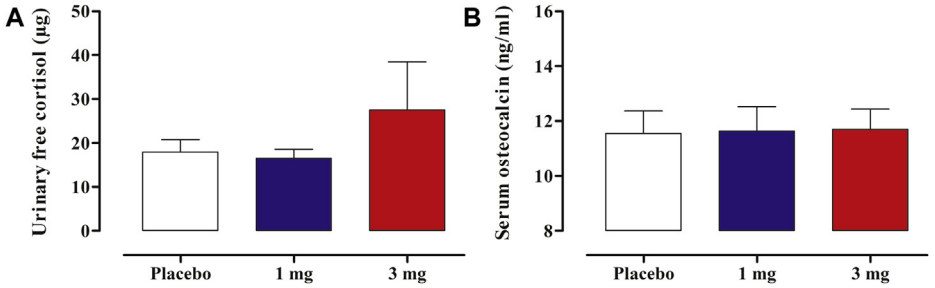


**FIG 2.** Effect of GW870086X on 24-hour urinary free cortisol on day 7 **(A)** and serum osteocalcin on day 7 **(B)**. Data are mean ± 95% CI.

In this study, we demonstrated that GW870086X inhibited the bronchoconstrictor response to inhaled AMP challenge after both a single dose and at multiple time points after repeat dosing (up to 7 days). This study achieved the primary end point of a significant reduction in the AMP challenge *versus* placebo at 2 hours on day 7. Serial challenges demonstrated a duration of effect up to 12 hours. However, at 26 hours on day 7, tolerance to inhaled AMP had occurred as shown by an increase in $PC_{20}$ on placebo.[6] We were unable to demonstrate a dose-response between the 1- and 3-mg doses perhaps because $C_{max}$ concentrations measured systemically were similar in magnitude for both doses. $C_{max}$ measurements were determined for use as a surrogate for delivery. Similar to previous studies, the AMP and FENO data suggest that GW870086X appears to follow to U-shaped response, similar to observations in previous studies.[7] There was no reduction in cortisol or osteocalcin after 7 days of repeat dosing with GW870086X. These data support the potential for reduced bone and metabolic AEs with GW870086X. The 1- and 3-mg doses were selected empirically for this study because no cortisol suppression was demonstrated in a previous study (data on file, GlaxoSmithKline) at these doses and this finding was again confirmed in the present study. The novel dissociated inhaled glucocorticoid GW870086X was well tolerated after repeated dosing with a similar incidence and intensity of reported AEs between placebo and GW870086X. No serious AEs were reported.

In conclusion, there was a significant protection against AMP challenge in subjects with asthma after single and multiple doses of GW870086X with a potential improved therapeutic index. The novel dissociated glucocorticoid concept merits further investigation in clinical studies of inflammatory lung disease with GW870086X.

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## A new case of Fas-associated death domain protein deficiency and update on treatment outcomes

*To the Editor:*

We present a new case of Fas-associated death domain protein (FADD) deficiency[1] (MIM 613759) in a 3-year-old girl of Pakistani descent. She was well until age 6 months, when she developed pneumococcal meningitis from which she recovered fully with antibiotic therapy. The family history was notable for the death of 2 male siblings from pneumococcal meningitis in infancy, while another female sibling had died at age 4 months from congenital cardiac abnormalities (Fig 1). Over the following 12 months, she had 2 further hospitalizations with fever, irritability, and drowsiness, on one occasion requiring intensive care owing to worsening

# METHODS

## Study design

This was a 2-center study with a randomized, double-blind, placebo-controlled, 3-way multiple dose, cross-over design. Treatments were randomly assigned (3 treatments, 6 sequences). After screening, eligible subjects entered the study, which comprised three 7-day treatment periods each separated by a 10- to 28-day washout period, which is consistent with the pharmacokinetic properties of GW870086X, showing an elimination half-life of about 15 to 18 hours.[E1] No spacer was used for drug administration during the study.

Subjects had a screening visit 8 to 31 days before treatment and attended a run-in visit 4 to 10 days after the screening AMP challenge and within 21 days before treatment. There was a minimum of 4 days between the run-in visit and the first treatment day. Subjects had 3 treatment periods of 7 days repeat dosing during which they were randomized to receive 1 mg of GW870086X, 3 mg of GW870086X, or matched placebo inhaled once daily in the morning using the Diskhaler dry powder inhaler. Subjects were required to attend the unit on day −1 and from predose to 12 hours postdose on day 1. On day 2, subjects returned on an outpatient basis for dosing and assessments. On day 7, the subjects were required to stay in the unit until at least 28 hours postdose. There was a follow-up visit at least 10 to 14 days after the final treatment period. Inclusion criteria were male, corticosteroid-naive subjects with asthma aged between 18 and 55 years having a prebronchodilator $FEV_1$ of more than 60% of predicted normal at screening, documented sensitivity to inhaled AMP, and a baseline FENO level of more than 25 ppb. All subjects gave their written informed consent before any study-related procedure. This study was approved by the Brent Medical Ethics Committee (05/Q0408/89).

## Measurement of FENO

Standardized FENO measurements were taken using the NIOX analyzer (Aerocrine, Solna, Sweden). The FENO level was measured at an expiratory flow of 50 mL/s, according to standard procedures.[E2] The average of 2 acceptable values was considered for the statistical analysis. FENO measurements were taken at screening and during each treatment period on day 1 predose and 2, 14, 26, 48, and 72 hours postadministration on day 7. In case of concomitant assessments, these measurements were taken immediately before the AMP challenge test (FENO measurements were not available in every subject owing to machine failure, so a reduced data set was available for analysis, especially affecting evaluation of the 3-mg dose data).

## AMP challenge

At screening, subjects underwent an AMP challenge test that was required to show a provocative concentration of AMP that resulted in a $PC_{20}$ of less than 80 mg/mL, according to a standardized challenge protocol previously described.[E3,E4] The reproducibility of the challenge was confirmed by a second challenge performed 4 to 10 days after screening and within 21 days before treatment. To ensure stability, the run-in $PC_{20}$ was required to be within 1.25 doubling doses of the screening $PC_{20}$. The criteria for stable bronchoconstriction in response to inhaled AMP at the run-in visit had to be met. The highest of 3 $FEV_1$ recordings taken before the administration of the diluent was used as the presaline baseline. The challenge was not carried out if $FEV_1$ was less than 60% predicted or the subject had significant asthma symptoms of wheeze, chest tightness, or cough. Subjects inhaled 0.9% saline, nebulised from a breath-activated dosimeter of known output (Markos Mefar, Brescia, Italy). The higher of 2 measurements taken after the inhalation of saline was used as the postdiluent $FEV_1$ to calculate the $PC_{20}$ value. Subjects then inhaled doubling increments of AMP until a 20% or more fall in $FEV_1$ from the postsaline value was achieved or the maximum concentration had been given. If the highest $FEV_1$ between the 2 duplicates was less than 20% below the postsaline $FEV_1$ reference, subjects progressed to the next highest concentration of AMP. Doubling concentrations of AMP ranging from 0.04 to 320 mg/mL were used.

## Lung function

$FEV_1$ and forced vital capacity were measured by spirometry (Vitalograph, Ennis, Ireland). At screening, $FEV_1$ was measured before and 30 minutes after the administration of salbutamol to determine reversibility. During each treatment period, $FEV_1$ was measured predose and 12 and 24 hours postadministration according to American Thoracic Society/European Respiratory Society standards.[E5] For whites of non-European descent, Asians, and blacks, predicted values for $FEV_1$ and forced vital capacity were to be adjusted for race as per the European Coal and Steel Community guidelines.[E6] Values were corrected for body temperature and pressure saturated conditions (saturated with water vapor at body temperature, 37°C, and ambient barometric pressure). Rescue medication (salbutamol) was withheld for at least 8 hours before the administration of each dose of study medication.

## Pharmacokinetics

Predose samples were taken from all subjects. A sparse sampling strategy was used for the pharmacokinetic sample collection. Four samples were collected from each subject postdose on days 1 and 7 in each treatment period as follows: odd numbered subjects—0.08 to 0.5, 1 to 2, 4 to 8, and 22 to 24 hours postdose; even numbered subjects—0.5 to 1, 2 to 4, 8 to 12, and 22 to 24 hours postdose. Plasma samples were analyzed for GW870086X by GlaxoSmithKline (Ware, United Kingdom) using a validated analytical method based on protein precipitation, followed by HPLC/MS/MS analysis. The lower limit of quantification for GW870086X was 20 pg/mL. Modeling techniques using nonlinear mixed effects methods were used to estimate individual and population pharmacokinetic parameters from the sparse sampling of plasma GW870086X concentrations.

## Measurements of systemic effects

Osteocalcin was measured in serum on days 1 and 7 predose and at 1, 4, 8, 12, and 24 hours postdose. Serum samples were analyzed for osteocalcin at Simbec Research Ltd (Merthyr Tydfil, United Kingdom) using a validated commercial ELISA (Quidel Corporation, San Diego, Calif) with a limit of quantification of 4.0 ng/mL. The serum osteocalcin weighted mean (0-24 hours) was derived and a statistical analysis was performed, and ratios comparing each active dose with placebo from the analysis were calculated. Urine samples were analyzed for cortisol at Simbec Research Ltd using a validated LC-MS assay with a limit of quantification of 0.5 ng/mL. The total 24-hour urinary free cortisol and total corrected 24-hour urinary free cortisol (corrected for creatinine) values were derived, and analyzed using a mixed effects model. Ratios comparing each active dose to placebo from the analysis were calculated.

## Safety assessments

Evaluation of the safety profile included collection and monitoring of any AEs throughout the study. Heart rate and blood pressure were measured at screening and in each treatment period before and after drug administration, and routine clinical laboratory assessments were done at screening and at the end of the study.

## Data analysis

We planned to randomize 20 subjects to provide at least 17 subjects completing all 3 periods. This sample size provided more than 90% power to detect a difference of 1.5 doubling doses between GW870086X and placebo using a 2-sided 95% CI. The "all subjects" population was defined as all subjects randomized to treatment who received at least 1 dose of study treatment. This population (n = 21) was used for all analyses except $PC_{20}$ AMP and pharmacokinetics. The modified per protocol population excluded from the all subjects population those subjects with major protocol deviations relating to inclusion/exclusion criteria that could potentially affect the $PC_{20}$ AMP analysis. This population (n = 17) was used to perform a sensitivity of $PC_{20}$ AMP. The "pharmacokinetic concentration" population was defined

as all subjects for whom a pharmacokinetic sample was obtained and analyzed, and was used for all summaries of pharmacokinetic concentration data. The "pharmacokinetic parameter" population was defined as all subjects in the pharmacokinetic concentration population who provided pharmacokinetic parameters, and was used for all summaries and analysis of pharmacokinetic parameters.

AMP $PC_{20}$ was natural log transformed and analyzed using ANOVA for a cross-over design with subject (sequence and subject within sequence), period, and treatment as factors of the model. For each treatment, the least square mean, pairwise treatment effect, the 95% CI, and probabilities (*P* values) were calculated. Estimates for the doubling dose difference (ie, treatment difference on the log scale) between each active dose and placebo were obtained. The following rules were applied for $PC_{20}$ calculation when subjects did not reach a 20% fall in $FEV_1$: if the last AMP concentration inhaled was the highest AMP concentration (320 mg/mL), then the $PC_{20}$ was set to 320 mg/mL; if the last inhaled concentration was less than 320 mg/mL and the corresponding fall from baseline was less than 15%, then the $PC_{20}$ was set to missing; and if the fall was more than 15%, then the $PC_{20}$ was set to the last AMP concentration inhaled. $FEV_1$ area under the curve comparisons were carried out using an analysis of covariance for a cross-over design with subject (sequence and subject within sequence), period, and treatments as factors of the model and predose values on each treatment as covariate.

$F_{ENO}$ concentrations were summarized by treatment and planned relative time. $F_{ENO}$ concentrations were natural log transformed and analyzed using a mixed effects model. Ratios comparing each active treatment to placebo at each time point were calculated.

The total 24-hour urinary free cortisol and total corrected 24-hour urinary free cortisol (corrected for creatinine) values were derived and analyzed. Ratios comparing each active dose with placebo from the analysis were calculated. The serum osteocalcin weighted mean (0-24 hours) was derived and summarized. A statistical analysis of the serum osteocalcin weighted mean (0-24 hours) was performed using a mixed effects model and ratios comparing each active dose with placebo. Safety data AEs, clinical laboratory evaluations (electrocardiogram, heart rate and blood pressure, and lung function tests) were summarized by treatment group. No statistical analysis was performed on the safety data.

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**TABLE E1.** Subjects' demographic characteristics

| Characteristic | N = 21 |
|---|---|
| Age (y), mean (range) | 28 (19-43) |
| Sex: male, n (%) | 21 (100) |
| Body mass index (kg/m$^2$), mean (range) | 24 (19-32) |
| Race, n (%) | |
| Black | 3 (14) |
| Asian | 4 (19) |
| White | 14 (67) |
| $FEV_1$ (L/min), mean ± SD | 550 ± 119 |
| $PC_{20}$ AMP (mg/mL), median (+ geometric SEM) | 16 (19) |
| $FEV_1$ (% predicted), mean ± SD | 87 ± 14 |

**TABLE E2.** *Post hoc* estimates of GW870086X pharmacokinetic parameters in subjects with asthma after repeat inhaled doses

| GW870086X | n | $C_{max}$ (pg/mL) | $T_{max}$ (h) | AUC |
|---|---|---|---|---|
| 1 mg | 19 | 198 (175, 225) | 0.08 (0.08-0.50) | 1361 (1111-1667) |
| 3 mg | 18 | 207 (172, 249) | 4.50 (0.17-8.03) | 3859 (3164-4718) |

Geometric mean (95% CIs) presented for $C_{max}$ and AUC (0-24). Median (range) presented for $T_{max}$. *AUC*, Area under the curve.

**TABLE E3.** Population pharmacokinetic parameters for GW870086X in subjects with asthma after repeat inhaled doses

| Parameter | Estimate | 95% CI | Intersubject variability (%) |
|---|---|---|---|
| $K_a$ ($h^{-1}$) "slow" | 0.202 | 0.13-0.31 | 62 |
| $K_a$ ($h^{-1}$) "fast" | 1.293 | 0.65-2.57 | ND |
| CL/F (L/h) | 652 | 499-851 | 58 |
| V2/F (L) | 183 | Fixed | 89 |
| V3/F (L) | 8955 | 7290-11002 | 55 |
| Q/F (L/h) | 431 | 1898-9811 | 67 |

*CL/F*, Clearance; $K_a$, absorption and elimination; *ND*, not determined; *Q/F*, intercompartmental clearance; *V2/F*, central volume of distribution; *V3/F*, peripheral volume of distribution.

**TABLE E4.** Safety summary (all AEs reported)

| AE | Placebo (n = 20) | 1 mg (n = 19) | 3 mg (n = 18) |
|---|---|---|---|
| Any event | 6 (30) | 13 (68) | 6 (33) |
| Rhinitis | 1 (5) | 4 (21) | 2 (11) |
| Pharyngolaryngeal pain | 2 (10) | 2 (11) | 0 |
| Dyspepsia | 1 (5) | 2 (11) | 0 |
| Headache | 0 | 2 (11) | 0 |
| Back pain | 0 | 1 (5) | 1 (6) |
| Cough | 1 (5) | 1 (5) | 1 (6) |
| Seasonal allergy | 0 | 1 (5) | 1 (6) |
| Ear infection | 0 | 0 | 1 (6) |
| Pyrexia | 0 | 1 (5) | 0 |
| Diarrhea | 0 | 1 (5) | 0 |
| Heart rate increased | 0 | 2 (5) | 0 |
| Dysgeusia | 0 | 1 (5) | 0 |
| Hepatitis* | 0 | 1 (5) | 0 |
| Other | 1 (5) | 1 (5) | 2 (11) |

All values are n (%).
*One subject developed EBV-positive hepatitis.