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## The effects of calcitriol treatment in glucocorticoid-resistant asthma

*To the Editor:*

Asthma is a chronic inflammatory disease characterized clinically by variable small airways obstruction and hyperresponsiveness and pathologically by airways inflammation and remodeling. The current cornerstone of asthma therapy is anti-inflammatory glucocorticoids. Although glucocorticoids improve clinical features of disease and airways inflammation in most patients, there is a cohort of well-defined asthma patients in whom high-dose glucocorticoid treatment is not only clinically ineffective but also potentially detrimental.[1] Improved understanding and management of glucocorticoid-resistant asthma is vitally important because these patients are very difficult to manage clinically and are at high risk of hospitalization, morbidity, and mortality. A number of mechanisms have been proposed to contribute to glucocorticoid-resistant asthma, including increased expression of nuclear factor kappa B and activating protein 1 (AP-1), increased expression of histone deacetylase, polymorphisms in IL-10, increased expression of the dominant negative isoform of the glucocorticoid receptor beta (GRβ), and vitamin D insufficiency.[2-4]

Our earlier data showed that peripheral blood $CD4^+$ T cells from glucocorticoid-resistant as compared with glucocorticoid-sensitive asthmatic patients failed to synthesize the anti-inflammatory cytokine IL-10 in response to glucocorticoid *in vitro*.[5] The active form of vitamin D (calcitriol; 1,25-dihydroxyvitamin D3 [$1,25(OH)_2D_3$]) when used in combination with glucocorticoid restored this IL-10 response both *in vitro* and *ex vivo* following patient ingestion of calcitriol.[6] These data, together with epidemiologic evidence linking vitamin D insufficiency/deficiency with a poor clinical response to treatment in asthma,[3,4] provided the rationale for this proof-of-concept clinical trial. We characterized a group of patients with severe asthma as glucocorticoid resistant following a standardized, 2-week course of oral prednisolone (Screening) using our previously established and generally accepted criteria.[6] Following a washout period, patients were randomly assigned placebo or 0.25 μg calcitriol twice daily, according to British National Formulary guidelines, for 4 weeks with a repeat course of oral prednisolone during the final 2 weeks. We hypothesized that concomitant calcitriol therapy improves clinical glucocorticoid responsiveness in these patients. It should be noted that calcitriol, a downstream metabolite of 25-hydroxyvitaminD (25[OH]D), would not be expected to restore vitamin D sufficiency, as defined by circulating 25(OH)D: our intention was to address the short-term effects of calcitriol itself. Details of the patient recruitment and study protocol may be seen in the Methods section of this article's Online Repository at www.jacionline.org. There were no differences in patients' demographic characteristics including age, body mass index, atopic status, baseline $FEV_1$, and inhaled glucocorticoid usage between the 2 randomized groups (see Table E1 in this article's Online Repository at www.jacionline.org). There were no serious adverse events, and all such events were self-limiting (see Table E2 in this article's Online Repository at www.jacionline.org). Differential blood leukocyte counts showed a similar increase in circulating neutrophils and reduction of eosinophils in response to both courses of prednisolone therapy in all patients, confirming compliance with this treatment (data not shown).

On the basis of the primary outcome of change in lung function from the initial screening visit to the end of treatment, we saw no significant difference in % predicted $FEV_1$ between the 2 groups ($P = .82$; Table I). Nevertheless, a within-group comparison showing the change in lung function during the initial screening in response to 2-week oral prednisolone (Screening) versus the response to an identical course of prednisolone plus either placebo or calcitriol (Treatment) revealed a modest but significant improvement in absolute and predicted $FEV_1$ within the calcitriol ($P = .03$) but not the placebo arm (Fig 1, *A*). These differences were not apparent in patients randomized to receive calcitriol before the second course of prednisolone, suggesting that calcitriol alone had had no effect on lung function.

**TABLE I.** Primary and secondary outcomes

| Clinical measurement | Screening | | Treatment | |
|---|---|---|---|---|
| | Pre-steroids | Post-steroids | Pre-steroids post-treatment | Post-steroids post-treatment |
| $FEV_1$ (L/s) | | | | |
| Placebo | 1.82 (1.44-2.21) | 1.82 (1.79-2.44) | 1.83 (1.42-2.23) | 2.01 (1.61-2.41) |
| Calcitriol | 1.98 (1.67-2.29) | 1.88 (1.52-2.23) | 1.96 (1.58-2.34) | 2.20 (1.64-2.75) |
| $FEV_1$ (%) | | | | |
| Placebo | 59.9 (48.8-71.0) | 59.9 (48.3-71.3) | 60.6 (46.7-74.7) | 65.9 (55.0-76.8) |
| Calcitriol | 62.5 (55.2-69.8) | 59.5 (49.8-69.2) | 61.6 (53.3-69.9) | 68.1 (55.4-80.7) |
| Serum 25(OH)D (nmol/L) | | | | |
| Placebo | 42.6 (26.5-58.6) | 44.6 (30.7-58.6) | 53.2 (35.4-71.0) | 50.8 (31.2-70.5) |
| Calcitriol | 32.5 (21.5-43.5) | 34.3 (21.5-43.5) | 37.1 (15.9-58.4) | 34.4 (19.6-49.2) |

Note: Data shown as mean ± 95% CIs.

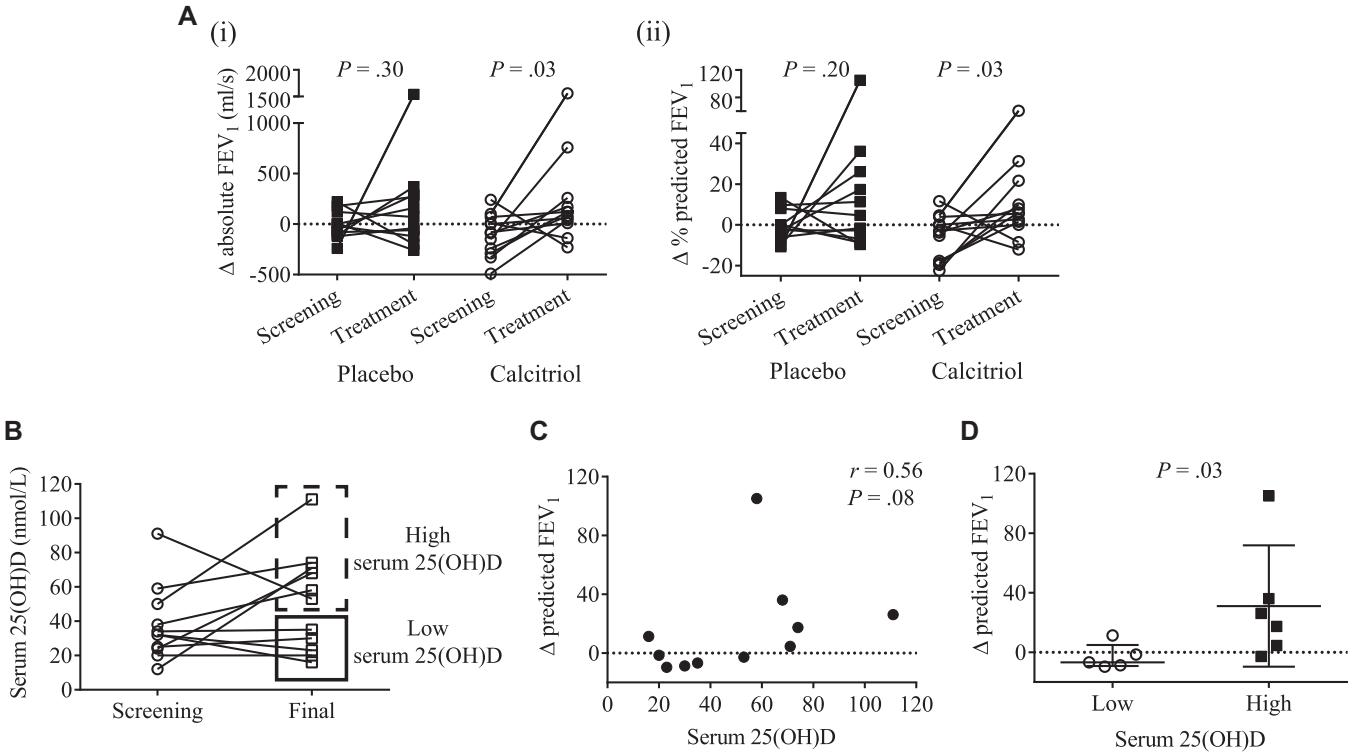


**FIG 1.** Treatment with calcitriol or vitamin D sufficiency improves clinical response to steroids. **A,** Comparison of change in (i) absolute lung function ($FEV_1$ [L]) and (ii) predicted lung function after a 2-week course of prednisolone at screening (pretreatment) and treatment (together with placebo OR calcitriol). **B,** Serum 25(OH)D levels of the placebo group at the beginning as compared with the last visit of the clinical trial. **C,** Correlation between serum 25(OH)D and change in lung function (predicted %) after a 2-week course of prednisolone during the treatment phase of the trial (after placebo treatment). **D,** Comparison of change in predicted lung function after a 2-week course of prednisolone at screening (pretreatment) and treatment (together with placebo treatment) in those defined as high serum 25(OH)D (*closed squares*; >50 nmol/L) or low serum 25(OH)D (*open circles*; <50 nmol/L); data shown as median ± interquartile range.

In the placebo cohort, 4 of the 11 patients showed a more than 10% improvement in their lung function post-prednisolone in the treatment phase than in the screening phase. Retrospective analysis of serum concentrations of 25(OH)D in these patients showed that 6 patients exhibited elevation of their baseline serum 25(OH)D concentrations from start to final visit of study (Fig 1, *B*). A trend for a positive correlation between baseline serum 25(OH)D concentrations and change in predicted lung function following prednisolone ($r = 0.56$, $P = .08$; Fig 1, *C*) was observed. Despite the very low numbers, a greater improvement in $FEV_1$ following prednisolone in those with relatively high (>50 nmol/L; n = 6) as compared with low (<50 nmol/L; n = 5) serum concentrations of 25(OH)D was seen ($P = .03$; Fig 1, *D*).

This study represents the first demonstration to our knowledge that the clinical responsiveness of asthmatic patients to glucocorticoid therapy is subject to manipulation in the short term. Our data show that treatment with a short course of $1,25(OH)_2D_3$

(calcitriol) may modestly improve the clinical glucocorticoid responsiveness in asthma, even in patients classified as clinically glucocorticoid resistant.

This study was not designed to correct or take account of the patients' vitamin D status. Nevertheless, all but 1 of the patients were vitamin D insufficient (<75 nmol/L) and 16 of our patients were deficient (<50 nmol/L)[7] at the commencement of the study and, as shown, unexpectedly 6 of the 11 patients randomized to placebo showed considerable improvement in vitamin D status (insufficient/deficient to sufficient) by the final visit, for reasons one can only speculate on, but that are likely to include exposure to sunlight, dietary intake, and supplementation. Even so, we observed a trend for 25(OH)D concentrations to correlate positively with clinical glucocorticoid responsiveness. A similar observation was made in an independent recent study using asthma exacerbations as a clinical outcome.[8]

Our data indicate that $1,25(OH)_2D_3$ (calcitriol) may improve the clinical response to glucocorticoids in resistant asthma patients. They raise important questions about the design of future studies. On the one hand, the decision to study a well-characterized cohort of glucocorticoid-resistant asthmatic patients produced significant challenges with recruitment and retention, but on the other hand may have facilitated our ability to observe a clinical effect that may be manifest most clearly in this small but important subset of patients. Future studies must address wider cohorts of asthmatic patients and consider other end points. Although our study suggests an impact on glucocorticoid responsiveness, 2 independent studies implicate vitamin D in reducing asthma exacerbation rates.[8,9] Despite the low power of this study, these preliminary clinical data are encouraging and warrant further investigations in larger, ideally clinically well-defined cohorts, including in pediatric asthma patients for whom epidemiologic data are arguably the strongest.

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*Discuss this article on the JACI Journal Club blog: www.jaci-online.blogspot.com.*

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## Immunologic response and safety in birch pollen sublingual versus oral vestibule immunotherapy: A pilot study

*To the Editor:*

To date the efficacy of sublingual immunotherapy (SLIT) in the form of allergy immunotherapy tablets is well documented with a large number of clinical trials and it is accepted as an effective alternative to subcutaneous immunotherapy in the treatment of type I–mediated respiratory allergies in Europe, but is currently not likewise accepted in the United States.[1] The attention of many scientists and clinicians is directed toward how immunologic mechanisms mediate the effect of SLIT and improvement of its efficacy, while reducing adverse effects. Although the immunologic mechanisms of SLIT as well as subcutaneous immunotherapy remain to be elucidated in detail, the induction of regulatory T cells as well as a shift from an allergy-mediating $T_H2$ toward an allergy-preventing $T_H1$ immune response is propagated along with the induction of allergen-specific IgG.[2] Moreover, antibodies with IgE-blocking activities—quantified as the IgE-blocking factor—have been described recently within the allergen-specific IgG fraction, which are hypothesized to correlate with the clinical response to immunotherapy.[3] The common link between these immune reactions are professional

# METHODS

## Study participants

Study participants were recruited at Guy's and St Thomas' National Health Service Foundation Trust and Barts Health National Health Service Trust, tertiary health care centers in London, United Kingdom. The study was approved by the London Bridge Research Ethics Committee (REC ref 06/Q0605/83), and written informed consent was obtained from all participants before enrolment. The study is registered with the UK Clinical Research Network (International Standard Randomized Controlled Trial Number 2937824).

Patients aged 18 to 75 years with a documented history and typical symptoms of asthma for more than 6 months before screening were assessed for eligibility to participate. All study subjects had a prebronchodilator $FEV_1$ of less than 80% predicted and variability in airways obstruction (≥12% in response to bronchodilator or >20% diurnal peak expiratory flow rate variability) documented within the previous 5 years. Individuals were excluded if they suffered from past or present disease, which, as judged by the investigator, might affect the study outcome (other than asthma, rhinitis, or eczema); if serum-corrected calcium was more than 2.65 mol/L; if they were a current cigarette smoker or ex-smoker of less than 5 years with a more than 5 pack-year history; if they were pregnant or lactating females or at risk of pregnancy; if they had a history of a respiratory tract infection and/or exacerbation of asthma within 4 weeks of the screening visit requiring oral glucocorticoid therapy; if they had participated in a study involving an investigational medicinal product in the previous 3 months or had made a blood donation within the last year; if they were currently receiving, or had received, allergen immunotherapy or treatment with lithium carbonate or calcium supplements; or if they were unable to understand or comply with the research protocol. Patients were asked, and agreed not to take any vitamin supplements for the duration of the study. Patients remained on their regular maintenance medication for the duration of the study, including the 4-week washout period. On the day of screening, 8 (34.7%) patients showed more than 20% peak flow variability and 15 (65.3%) showed reversibility to a bronchodilator response. However, all 8 patients who were enrolled on the basis of peak flow variability had shown significant bronchodilator response within 5 years prior to enrolling into the study. All patients who went through the screening period (ie, 2 weeks of oral corticosteroids) had confirmed bronchodilator reversibility.

Glucocorticoid-resistant asthma was defined as less than 10% improvement in baseline $FEV_1$ following a 14-day course of oral prednisolone (Wockhardt UK Ltd, Wrexham, United Kingdom; 40 mg/1.73 $m^2$/d) in eligible patients. Routine spirometry was measured before and after the course of prednisolone using a PC-based spirometer and software (MIR Medical International Research, Rome, Italy/WinspiroPRO). In addition, differential full blood cell counts were performed before and after the course of prednisolone using a LH750 hematology analyzer (Beckman Coulter, Brea, Calif).

Fifty patients were screened for eligibility between April 2009 and September 2012. Twenty-five patients were excluded before or during the screening period: 7 patients did not meet inclusion criteria, 3 declined to participate, 3 were noncompliant with the protocol, and 12 were steroid sensitive (>10% improvement in $FEV_1$ compared with baseline). One patient was lost to follow-up after completion of the screening visits. Twenty-four patients were randomized: 11 were allocated to placebo, 13 to intervention. One patient in the treatment group withdrew because of an adverse event, thought to possibly be related to the study drug (Fig E1; clinical flow diagram), making it 12 patients to complete the treatment group in that arm. There were no serious adverse events, and all events were self-limiting (Table E1).

## Study protocol

The study outline is summarized in Fig E1. Participants who met the eligibility criteria for glucocorticoid-resistant asthma returned following a 4-week washout period and were randomly allocated to commence treatment with either calcitriol 0.25 μg soft capsules (Rocaltrol; Roche Pharmaceuticals, Welwyn Garden City, United Kingdom) or organoleptically identical lactose placebo generated in-house (Pharmacy Production Unit, St Thomas' Hospital NHS Trust, London, United Kingdom) twice daily. Patients were randomized in a 1:1 ratio using a computerized random plan generated by a physician not involved in the trial. Patients and trial investigators were blinded to treatment allocation. Following 2 weeks of calcitriol or placebo treatment, patients were given a second course of oral prednisolone identical to the first while calcitriol or placebo was continued. Spirometry was performed at the beginning and end of this second course of oral prednisolone as before. Serum concentrations of calcium, corrected calcium, albumin, total protein, phosphate, sodium, potassium, urea, creatinine, and 25(OH)D were analyzed. Concentrations of 25(OH)D2 and 25(OH)D3 were determined by isotope-dilution liquid chromatography–tandem mass spectrometry and summed to give values for total 25(OH)D. Sensitivity for this assay was 10 nmol/L. Full blood cell counts were performed as described above. Albumin, phosphate, and total serum calcium concentrations were determined using an Architect ci8200 analyzer (Abbott Diagnostics, Chicago, Ill). Calcium concentration was corrected for serum albumin concentration using the formula: corrected calcium (mmol/L) = total calcium (mmol/L) + 0.02 × (40 – albumin [g/L]).

Power calculations predicted that the study of 40 glucocorticoid-resistant participants would enable detection of an improvement in change in $FEV_1$ from 0.4% to 10% with 80% power, tested at the 2-sided 5% significance level. Because of difficulties with patient recruitment, however, the decision was made to terminate the study after 24 patients completed.

The primary outcome measure was change in $FEV_1$ from screening to the final visit. Secondary outcomes measured included asthma control questionnaire and serum 25(OH)D measurements. There was no difference observed in the asthma control questionnaire scores between the calcitriol and placebo treatment groups. Additional analysis of glucocorticoid response was performed within (screening vs treatment phases) and between groups (calcitriol vs placebo), expressed as absolute values and percentage change. Study subjects were asked to report any adverse events from the day of commencement of the first course of oral prednisolone until 4 weeks after the second course by telephone or e-mail or at study visits.

## Statistical methods

The differences in % predicted $FEV_1$ at 28 days postrandomization between treatment groups was assessed using a linear regression model adjusted for screening values of % predicted $FEV_1$ value and vitamin D status. The analysis was performed on the complete case population, and statistical significance was assessed at the 5% level.

For subsequent subanalyses, data were assessed for Gaussian distribution and equality of variance. Then, for normally distributed data, assessment was done by either an unpaired or a paired (where appropriate) Student *t* test and for non-normally distributed data, Wilcoxon matched-pairs signed test (paired data) and Mann-Whitney *U* test (unpaired). Correlations were nonnormally distributed and were assessed by Spearman rank correlation test. Normally distributed data were presented as the mean ± 95% CIs, and nonnormally distributed data were shown as median ± interquartile range.

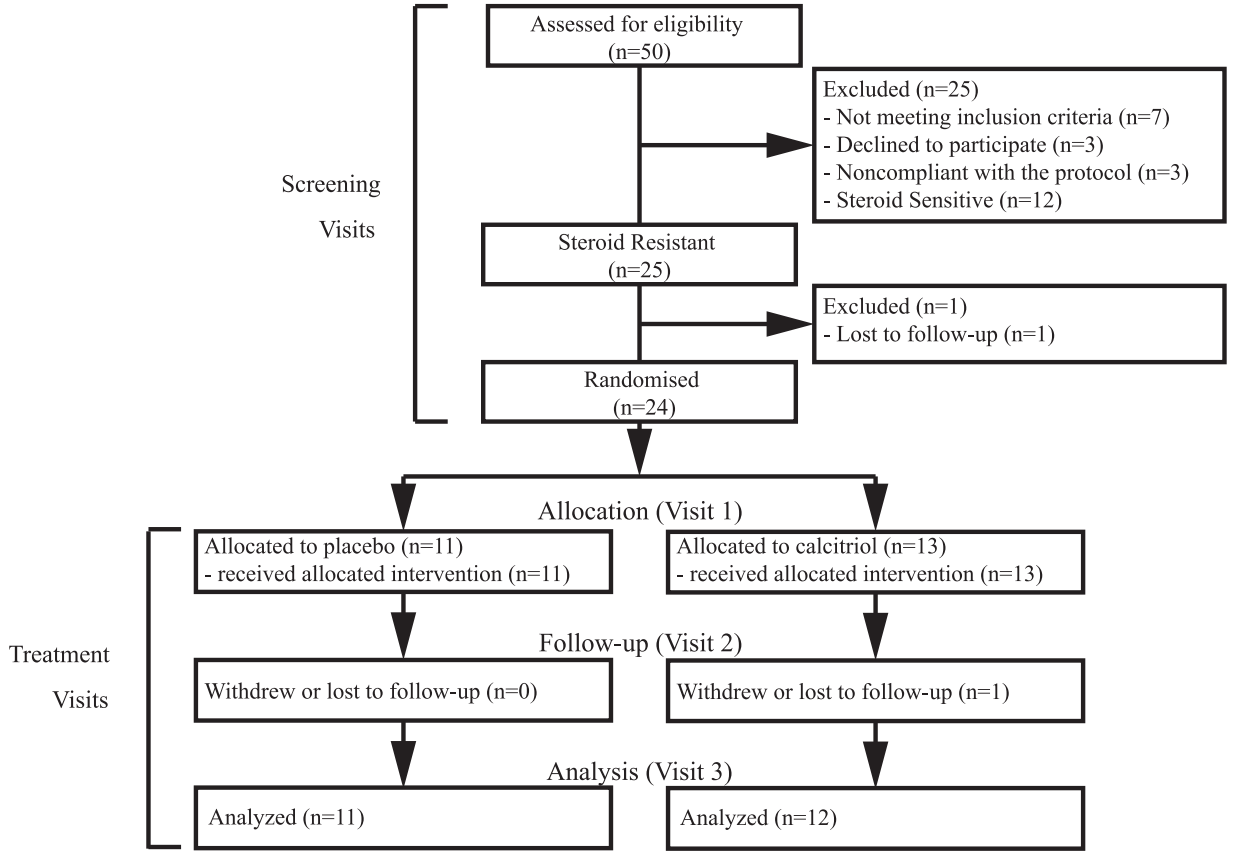


**FIG E1.** Schematic of clinical trial design.

**TABLE E1.** Patients' characteristics

| Characteristic | Placebo | Calcitriol |
|---|---|---|
| Age (y) | 53.5 (47.8-59.1) | 50.3 (39.1-61.6) |
| Ethnic origin | | |
| Caucasian | 9 | 8 |
| African | 2 | 3 |
| Asian | 0 | 1 |
| Sex | | |
| Male | 7 | 7 |
| Female | 4 | 6 |
| Atopic | 10 | 9 |
| BMI | 29.1 (25.0-33.2) | 27.4 (25.5-29.2) |
| Inhaled corticosteroid dose | 1236 (830-1643) | 1267 (849-1684) |
| FENO | 19.9 (15.7-24.1) | 38.4 (20.7-56.0) |
| | n = 11 | n = 12 |

Note: Data are presented as the mean and 95% CI. Atopy was defined by skin prick testing. The dose of inhaled corticosteroids was calculated according to the British Thoracic Society - Scottish Intercollegiate Guidelines Network (BTS-SIGN) Guideline on the management of asthma (Table 8b: Equivalent doses of inhaled steroids relative to BDP and current licensed age indications). Patients were on beclomethasone 1600 μg/d, budenoside 1600 μg/d, or fluticasone 800 μg/d.
*BDP*, Beclomethasone dipropionate; *BMI*, body mass index; *FENO*, fractional exhaled nitric oxide; *25(OH)D*, 25-hydroxyvitamin D.

**TABLE E2.** Side effects documented throughout the trial

| Adverse event | Study phase | Study drug | Related to study drug |
|---|---|---|---|
| Mild indigestion | Screening | Prednisolone | Yes |
| Nausea | Screening | Prednisolone | Possible |
| Increased hunger | Screening | Prednisolone | Yes |
| Coryzal symptoms | Treatment | Placebo | No |
| Diarrhea | Treatment | Placebo | No |
| Coryzal symptoms | Treatment | Calcitriol | No |
| Coryzal symptoms | Treatment | Calcitriol | No |
| Coryzal symptoms | Treatment | Calcitriol | No |
| Constipation, back pain | Treatment | Calcitriol | Possible |
| Bang to head | Treatment | Calcitriol | No |

Note: All effects were nonsevere and resolved spontaneously.