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3 **TITLE PAGE**

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5 Letter to the Editor

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7 **Vitamin D<sub>3</sub> Therapy on Subjects with Asthma Complicated by Sinonasal Disease:**

8 **Secondary Analysis of a Randomized Trial**

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## 48 **METHODS**

### 49 **Study design and subjects**

50 The present study is a pre-planned secondary analysis of a multi-center, randomized, double-  
51 blinded, placebo-controlled clinical trial (VIDA). The subjects, study design, and primary  
52 endpoints have been previously described<sup>14</sup>. In brief, 408 adult patients with serum 25-  
53 hydroxyvitamin D levels < 30 ng/mL and persistent asthma symptoms despite the use of low  
54 dose ICS were randomized to receive add-on therapy with placebo or high-dose vitamin D3  
55 (100,000 IU loading dose followed by 4,000 IU/day) for 28 weeks. During the ICS stable phase  
56 (phase I, weeks 5-17), study subjects were maintained on inhaled ciclesonide (80 µg/puff) two  
57 puffs twice daily (320 µg/day) for 12 weeks post-randomization. Thereafter, those who met the  
58 asthma stability criteria underwent ciclesonide dose reduction by 50% for 8 weeks (phase IIa,  
59 weeks 18-25) and then by 75% for 8 weeks (phase IIb, weeks 26-33). Asthma treatment failures,  
60 lung function, allergic sensitization, asthma symptoms, control and exacerbations requiring  
61 systemic corticosteroids, and serum 25-hydroxyvitamin D levels were assessed<sup>14</sup>. Asthma  
62 treatment failure was defined as the occurrence of one or more of the following: 1. Pre-  
63 bronchodilator PEF  $\leq$  65% of baseline on any 2 of 3 consecutive scheduled measurements; 2. An  
64 increase in “as needed” levalbuterol use of  $\geq$  8 puffs per 24 h over baseline use for 48 h; 3. Pre-  
65 bronchodilator FEV1  $\leq$  80% of the baseline on two consecutive measurements; 4. Additional  
66 inhaled or oral/parenteral corticosteroid due to asthma; 5. Need for emergency treatment at a  
67 medical facility that was related to, or complicated by, the participant's asthma and which  
68 resulted in systemic corticosteroid treatment or hospitalization for an acute asthma exacerbation;  
69 6. Participant’s refusal to continue study drugs because of lack of satisfaction with treatment; or  
70 7. Physician’s clinical judgment for safety reasons. Asthma exacerbation was defined by meeting

71 criteria for treatment failure AND one or more of the six following: 1. Failure to respond within  
72 48 hours to treatment failure rescue algorithm; 2. FEV1 <50% of baseline on 2 consecutive  
73 measurements; 3. FEV1 <40% of predicted on 2 consecutive measurements; 4. Use of  $\geq 16$  puffs  
74 of "as needed"  $\beta$ -agonist (levalbuterol) per 24 hours for a period of 48 hours; 5. Experiencing an  
75 exacerbation of asthma in the opinion of study investigator or personal physician; or 6. Use of  
76 oral/parenteral corticosteroids due to asthma.

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### 78 **Sinonasal Questionnaire**

79 The presence of sinonasal disease in subjects was determined by using a validated sinonasal  
80 questionnaire (SNQ). SNQ is a five-item, symptom-based instrument developed to screen for  
81 chronic rhinitis and sinusitis<sup>12</sup>. The questionnaire inquires about the presence of sinonasal  
82 symptoms (runny nose, postnasal drip, need to blow the nose, facial pain or pressure, and nasal  
83 obstruction) over the preceding 3 months. Scoring for each item is based on the frequency of  
84 symptoms: never (0), 1-4 times per month (1), 2- 6 times per week (2), and daily (3). The final  
85 score is reported as the average of 5 items with a range between 0 and 3. In asthmatic patients, a  
86  $SNQ \geq 1$  is highly sensitive (0.94, 95% CI 0.81-1.00) and specific (1.00, 95% CI 0.47-1.00) in  
87 determining the presence of sinonasal disease<sup>12</sup>. A decrease in sensitivity and increase in  
88 specificity have been noted with higher cutpoints. Subjects were instructed to complete the SNQ  
89 at week 4 (pre-randomization) and week 17 (end of ICS stable phase I) during their study visits.  
90 The outcome analyses were performed by using  $\geq 1$  and  $\geq 1.5$  as SNQ cutpoints.

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### 92 **Statistical analysis**

93 Baseline characteristics were compared between those with and without sinonasal disease via  
94 chi-square tests for categorical factors, and t-tests or Wilcoxon rank sum tests for those factors  
95 measured on a continuous scale. All analyses were pre-specified except the confirmatory  
96 analysis using a higher SNQ cutpoint of 1.5 for defining the sinonasal disease. Within-group  
97 changes in 25-hydroxyvitamin D levels from baseline to follow-up visit was evaluated by paired  
98 t-tests, and average follow-up visit levels were compared between groups by independent t-tests.  
99 The change in the proportion of participants with sinonasal disease from baseline to follow-up  
100 was analyzed using McNemar's test for paired proportions, whereas the proportion of  
101 participants with sinonasal disease at a given time point was compared between groups with chi-  
102 square tests.

103 The overall rates of treatment failure and exacerbation were compared between those with and  
104 without sinonasal disease in each treatment group by fitting Poisson regression models  
105 containing an effect for sinonasal disease with additional adjustment for partnership, BMI, race,  
106 baseline % predicted FEV1, baseline 25-hydroxyvitamin D level, and baseline asthma  
107 symptoms. Results from these models are reported in terms of adjusted rate ratios and  
108 corresponding 95% confidence intervals.

109 Multivariable logistic regression was applied to investigate potential predictors of persistent  
110 sinonasal disease, defined as sinonasal disease ( $SNQ \geq 1$ ), present at baseline and 12 weeks.  
111 Baseline characteristics were evaluated in the model, and a manual backwards selection  
112 procedure applied to determine the most parsimonious model. Variables considered in the full  
113 model included regimen, partnership, age, BMI, race, gender, baseline % predicted FEV1,  
114 baseline sun exposure, skin pigmentation, baseline skin pigmentation level, baseline 25-  
115 hydroxyvitamin D level, oral corticosteroid responsiveness, bronchodilator reversibility, number

116 of positive allergen skin tests, and season. Variables remaining in the model after backward  
117 selection included partnership, race, gender, age, baseline % predicted FEV1 and season. Results  
118 are reported in terms of adjusted odds ratios, 95% CIs, and p-values.

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139 **Table E1. Baseline characteristics of study subjects**

Variable	No Sinonasal disease	Sinonasal disease	<i>p</i> value
	SNQ < 1 (n = 166) n (%)	SNQ ≥ 1 (n = 242) n (%)	
<b>Demographics</b>			
Male	61 (36.8)	69 (28.5)	0.08
Race/ethnicity			0.02
Black	66 (39.8)	65 (26.9)	
White	74 (44.6)	142 (58.7)	
Hispanic	20 (12.1)	19 (7.9)	
Other <sup>a</sup>	6 (3.6)	16 (6.6)	
BMI (kg/m <sup>2</sup> )	32.4 (9.8)	31.3 (8.2)	0.21
Age at asthma diagnosis	13.7 (13.6)	15.5 (14.6)	0.20
<b>Pulmonary function tests</b>			
Pre-bronch FEV <sub>1</sub> (L)	2.6 (0.8)	2.7 (0.8)	0.20
Pre-bronch FEV <sub>1</sub> % predicted	78.8 (13.6)	81.9 (14.2)	0.03
Pre-bronch FVC (L)	3.6 (1.0)	3.7 (1.2)	0.19
Pre-bronch FEV <sub>1</sub> /FVC	0.7 (0.1)	0.7 (0.1)	0.86
Maximum albuterol reversibility (% change), (n = 406)	16.6 (11.0)	18.2 (12.2)	0.19
Methacholine PC <sub>20</sub> , (n = 391)	0.6 (1.6)	0.7 (1.7)	0.56
<b>Asthma characteristics</b>			
ACT score	19.2 (3.2)	19.0 (3.3)	0.48
AM symptom score (2-week average) <sup>b</sup>	0.4 (0.3)	0.5 (0.4)	0.007
PM symptom score (2-week average) <sup>b</sup>	0.4 (0.4)	0.5 (0.4)	0.006
AM PEF (2-week average, L/min)	382.1 (105.2)	402.0 (104.3)	0.06
PM PEF (2-week average, L/min)	388.3 (106.8)	407.0 (105.8)	0.08
Sputum eosinophils median (IQR), %, (n= 338)	0.3 (0.0-1.4)	0.4 (0.0-1.3)	0.33
Positive skin tests median (IQR), (n = 390)	3 (2-5)	3 (2-6)	0.39
Oral steroid used during the past 12 months	49 (29.5)	77 (31.8)	0.62
ICS used during the past 12 months	69 (41.6)	108 (44.6)	0.54
Level of 25-hydroxyvitamin D (ng/mL)	17.9 (6.9)	19.5 (6.6)	0.02

140 Abbreviations used: SNQ = sinonasal questionnaire score, BMI=body mass index, FEV<sub>1</sub> = forced  
141 expiratory volume in one second; FVC = forced vital capacity, PC<sub>20</sub> = provocative concentration  
142 at which FEV<sub>1</sub> decreased by 20%, ACT = asthma control test, PEF = peak expiratory flow; IQR  
143 = interquartile range, ICS = inhaled corticosteroids.

144 <sup>a</sup> Included Asian/Pacific Islanders, American Indian, Alaskan Native or participant-selected  
145 “other” category.