Reduction of Exhaled Nitric Oxide by the DP2 antagonist GB001 in Patients with Mild Atopic Asthma

Poster No. 311

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Background

- Asthma is a heterogeneous condition characterized by different phenotypes/endotypes related to specific biomarkers that may predict therapeutic response in selected patient populations (1). Previous research suggests that Fractional exhaled Nitric Oxide (FeNO) measurement facilitates identification of patients exhibiting Type 2 mediated airway inflammation. FeNO has been investigated as a surrogate marker of airway inflammation which is closely associated with eosinophilic inflammation (2). FeNO could serve as prognostic marker of disease progression and severity, as well as a biomarker of treatment effect (3,4)
- DP2 is a G-protein-coupled receptor selectively expressed by Type 2 T lymphocytes (Th2 and Tc2), eosinophils (Eos), basophils and Type 2 innate lymphoid cells (ILC2s). DP2 signaling promotes the recruitment and activation of eosinophils and basophils and stimulates Th2 cells and ILC2 cells to release Type 2 cytokines including IL-4, IL-5 and IL-13, leading to the development, amplification and persistence of Type 2 inflammation (5).
- Asthmatic patients with high FeNO (≥ 33 ppb) and high blood Eos (≥ 300/μL) have been reported to have increased PGD2 levels (6). Asthmatic patients with both high FeNO levels and high blood Eos compared with those with low levels of both had significantly increased PGD2 and CRTH2 mRNA levels. These results support the association of PGD2 pathway activation with Type 2 inflammatory markers, despite the use of corticosteroids.
- GB001 (formerly ADC3680) is a potent and highly selective oral DP2 antagonist being developed as a once daily oral add-on maintenance treatment for moderate to severe eosinophilic asthma.

Objective

- The objective of this post-hoc analysis was to evaluate FeNO as a baseline marker and an outcome following administration of GB001 or placebo over 28 days in patients with mildly symptomatic, partially controlled atopic asthma.

Methods

- Thirty six subjects with mild to moderate, partly controlled atopic asthma receiving a total daily dose of fluticasone propionate ≤500 mcg or equivalent were randomized in a 2:1 ratio to GB001 30 mg (N=24) or placebo (N=12) once daily for 28 days in this double-blind study. Safety, pharmacokinetic/pharmacodynamic parameters, and markers of asthma control were assessed.
- FeNO was collected at baseline and Day 28, using an ozone/NO_2 chemiluminescence–based analyzer, in accordance with ATS/ERS recommendations (2), at a target constant flow rate of 0.05 L/s. Subjects refrained from eating/drinking for 1 hour before measurement.
- Baseline characteristics and outcomes of subgroups based on low (<35 ppb) and high (≥35 ppb) baseline FeNO were analyzed. A cutoff of 35 ppb was selected based on published data (7). In addition, similar analyses were performed for subgroups based on low (<200 cells/μL) and high (≥200 cells/μL) baseline Eos.

Results

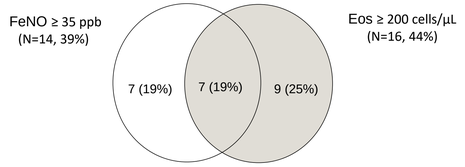
Table 1. Baseline demographic and clinical characteristics for low and high baseline FeNO subgroups and overall study population

Characteristics	Low FeNO (<35 ppb) (N=22)	High FeNO (≥35 ppb) (N=14)	Overall Population (N=36)
Age (years)	33.5 (8.43)	36.4 (9.65)	34.6 (8.90)
Male	20 (91)	13 (93)	33 (92)
BMI (kg/m^2)	28.02 (4.62)	26.42 (3.94)	27.40 (4.38)
Former Smoker	6 (27)	3 (21)	9 (25)
ACQ-7 score	0.82 (0.51)	0.86 (0.41)	0.84 (0.46)
Blood eosinophils (cells/μL)	175 (84)	330 (276)	235 (196)
FeNO (ppb)	18.60 (7.34)	54.44 (13.48)	32.53 (20.34)
Total IgE (kIU/L)	355 (341)	772 (1,295)	517 (857)
FEV_1 % predicted	100 (19)	91 (18)	97 (19)
FEV_1 (mL)	3,951 (943)	3,534 (852)	3,789 (920)

BMI = body mass index; ACQ-7 = Asthma Control Questionnaire, 7-item; FEV_1 = forced expiratory volume in one second. Values are mean (SD) for continuous parameters and n (%) for categorical parameters. There were 6 placebo and 16 GB001 subjects in the low baseline FeNO subgroup, and 6 placebo and 8 GB001 subjects in the high baseline FeNO subgroup.

- Baseline characteristics were generally similar in the low and high baseline FeNO subgroups, with the exceptions of total IgE and blood eosinophils, which were greater in the high baseline FeNO subgroup (**Table 1).** While lung function was normal in the majority of the subjects, FEV_1 was slightly lower in the high baseline FeNO subgroup.
- A total of fourteen subjects (39%) had high baseline FeNO, while a total of 16 (44%) subjects had high baseline Eos (**Figure 1**). Seven (19%) subjects had both high baseline FeNO and Eos. There was a weak correlation between baseline FeNO and Eos (r=0.29).

Figure 1. Number (%) of subjects in high baseline FeNO and Eos subgroups



Percentages are based on the overall population (N=36). Thirteen (36%) subjects (not shown) had both low baseline FeNO and Eos.

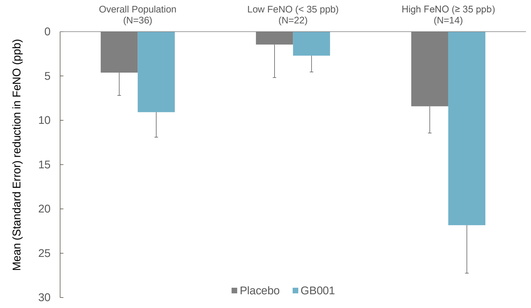
Table 2. Difference (95% confidence interval) in mean change from baseline to Day 28* for GB001 vs Placebo in ACQ-7, FEV_1, FeNO, and Eos outcomes by baseline FeNO and Eos subgroups and for overall population

Outcome	Low FeNO (<35 ppb) (N=22)	High FeNO (≥35 ppb) (N=14)	Low Eos (<200 cells/μL) (N=20)	High Eos (≥200 cells/μL) (N=16)	Overall Population (N=36)
ACQ-7 score	0.02 (-0.42, 0.46)	-0.13 (-0.85. 0.59)	-0.03 (-0.55, 0.48)	-0.07 (-0.64, 0.50)	-0.05 (-0.40, 0.31)
FEV_1 (mL)	34 (-184, 253)	207 (-283, 698)	120 (-138, 378)	81 (-314, 476)	102 (-110, 314)
FEV_1 % predicted	0.8 (-4.8, 6.4)	6.5 (-5.3, 18.2)	3.1 (-3.3, 9.5)	3.0 (-6.7, 12.7)	3.0 (-2.2, 8.3)
FeNO (ppb)	-1.26 (-9.08, 6.56)	-13.42 (-29.55, 2.72)	-7.59 (-20.14, 4.96)	-0.71 (-16.19, 14.77)	-4.47 (-13.70, 4.77)
Eos (cells/μL)	24 (-44, 92)	82 (-116, 280)	11 (-41, 63)	90 (-67, 247)	55 (-26, 136)

ACQ-7 = Asthma Control Questionnaire, 7-item; FEV_1 = forced expiratory volume in one second.
Differences in mean change from baseline and 95% confidence intervals calculated using two-sample t-tests and assuming equal variances in both treatment groups.
*All outcomes were assessed at end of treatment on Day 28, except for Eos, which was assessed on Day 30.

- GB001 demonstrated greater numeric improvements in ACQ-7 and FEV_1 and greater numeric reductions in FeNO relative to placebo in the high baseline FeNO subgroup compared to the low baseline FeNO subgroup and both baseline Eos subgroups (**Table 2**).
- GB001 had minimal effect relative to placebo on FeNO reduction in the high baseline Eos and low baseline FeNO subgroups .
- GB001 demonstrated greater numeric increases relative to placebo in Eos in the high baseline FeNO and Eos subgroups compared to the low baseline FeNO and Eos subgroups.

Figure 2. Mean reduction in FeNO at Day 28 in the overall population and by baseline FeNO subgroups



- There was a greater proportion of GB001-treated subjects with a decrease from baseline in FeNO >10 ppb at Day 28 (or >20% decrease if baseline FeNO was >50 ppb) relative to placebo (10 [42%] versus 2 [18%]).
- In the overall population, GB001 demonstrated slightly greater mean reductions in FeNO at Day 28 relative to placebo (mean [SE]: 9.08 [2.82] vs 4.62 [8.55]). However, FeNO reduction was greater in magnitude and treatment effect in the high versus low baseline FeNO subgroup (**Figure 2**).
- There were no serious treatment-emergent adverse events (TEAEs), severe TEAEs, or TEAEs leading to study drug discontinuation. The overall incidence of TEAEs was 18 (75%) and 10 (83%) for GB001 and placebo, respectively.
- The most common TEAE in GB001-treated subjects was headache (11 [46%] vs 6 [50%] for GB001 vs placebo, respectively), which occurred at a similar incidence and severity as placebo and showed no temporal relationship to study drug administration.

Conclusions

- GB001 resulted in greater numeric improvements in lung function at Day 28 relative to placebo in subjects with high FeNO or high Eos in this partly controlled asthma population with normal lung function in the majority of the subjects.
- There was a marked difference in the magnitude of FeNO reduction and the treatment effect of GB001 relative to placebo on FeNO reduction at Day 28 for subjects with high (≥35 ppm) versus low (<35 ppb) baseline FeNO.
- FeNO, in addition to being a marker of airway inflammation, may be a useful marker for treatment response to GB001. Further studies are required to confirm these findings.

References

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