GB001, a Selective Prostaglandin D_2 Receptor 2 Antagonist, Blocks Signaling in the Peripheral Blood of Healthy Subjects

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INTRODUCTION

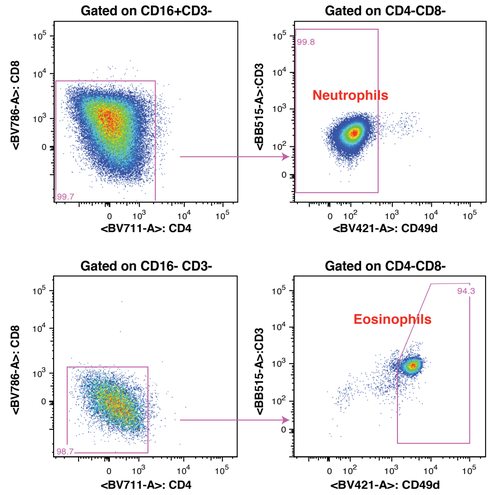
- GB001 is a potent and highly selective oral prostaglandin D_2 receptor 2 (DP_2) antagonist in development for moderate-severe asthma (NCT03683576) and chronic rhinosinusitis (NCT03956862)
- In preclinical studies, GB001 was shown to be an insurmountable antagonist with a prolonged effect[1]
- Preclinical modeling and early clinical studies evaluated 20 mg doses. To further explore the PK/PD of GB001, higher doses were tested.
- We aimed to assess GB001 effects on the prostaglandin D_2 (PGD_2)-responsiveness of multiple cell subsets with a focus on eosinophils

METHODS

- Phase 1, randomized, parallel, double-blind, study in 50 healthy subjects
- GB001 doses of 20, 40, 60, and 80 mg were administered orally once daily for 7 days
- Subjects were followed for an additional 7 days after GB001 dosing
- Whole blood was collected at a series of time points across 14 days of study, stimulated in vitro with a standardized concentration of PGD_2 and analyzed by flow cytometric analysis for quantification of cell subsets (eosinophils, PMN, T, B, NK cells, etc) and activation markers
- Basal and PGD_2-stimulated levels of DP_2, CD11b and eosinophil shape change (ESC) were used to monitor the response to PGD_2 and its inhibition by GB001

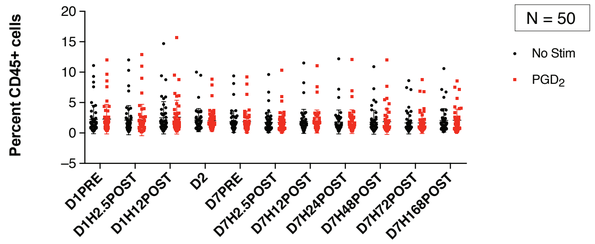
RESULTS

Figure 1. Gating strategy for analysis of eosinophils



- Eosinophils were gated as CD45+/CD3-/CD4-/CD8-/CD49d-hi granulocytes as shown in **Figure 1**

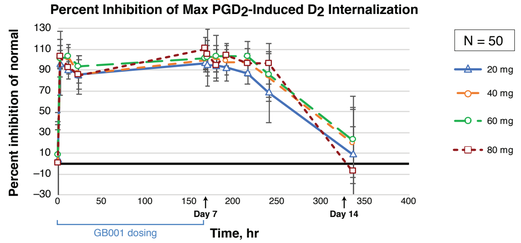
Figure 2. Circulating eosinophil numbers were not altered by GB001 treatment



D1PRE, Day 1 prior to GB001 dosing; D, day; H, hour, POST, post-GB001 dosing.

- Whole blood from healthy subjects (N = 50) was treated *ex-vivo* with PGD_2 or left untreated for 3 hours in vitro prior to flow cytometric analysis for eosinophils
- Treatment with GB001 did not alter the number of circulating eosinophils in these patients (**Figure 2**)

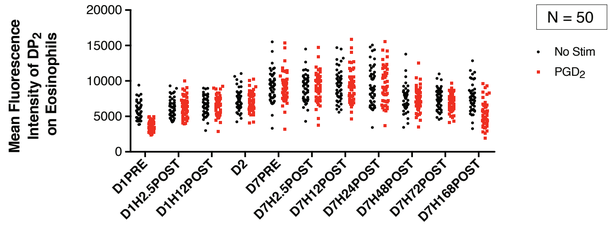
Figure 3. GB001 profoundly inhibits PGD_2-induced internalization of DP_2



Data presented as mean ± SD. Black horizontal line represents 0% inhibition.

- *Ex vivo* PGD_2 stimulation of eosinophils from subjects (pre-dose) led to a reduction in DP_2 signal (**Figure 4**, D1PRE, red vs black)
- Treatment with GB001 resulted in a rapid and profound increase in DP_2, ostensibly by blocking ligand-driven receptor internalization (**Figure 3**)
- This inhibition of the *ex vivo* PGD_2 receptor internalization was maintained through the 7-day course of GB001 treatment (**Figure 3**) equally across all four dose arms
- Receptor internalization from *ex vivo* PGD_2 stimulation returned to baseline levels within 7 days following the last oral dose of GB001 on day 7 (**Figure 3**)

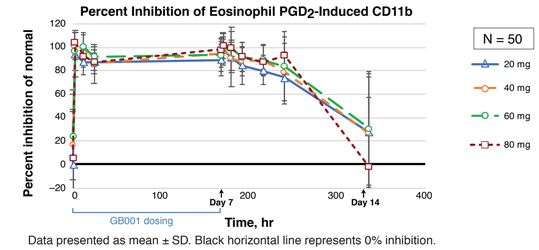
Figure 4. Steady-state levels of DP_2 rise in subjects treated with GB001



D1PRE, Day 1 prior to GB001 dosing; D, day; H, hour, POST, post-GB001 dosing.

- DP_2 levels on eosinophils (pre-dose) dropped by 40% with *ex-vivo* PGD_2 stimulation (D1 PRE, red vs black) (**Figure 4**)
- GB001 treatment completely inhibited PGD_2-induced DP_2 internalization by eosinophils
- Over the 7 days of GB001 treatment, background levels of DP_2 on eosinophils increased (black - **Figure 4**), suggesting that GB001 may be inhibiting a tonic signal that drives lower cell surface receptor levels

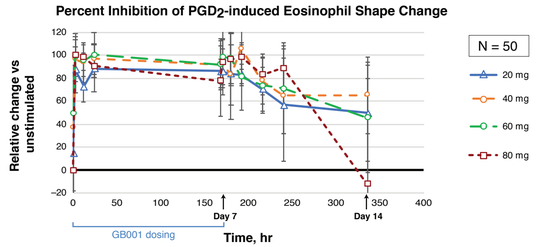
Figure 5. GB001 prevents PGD_2-induced CD11b upregulation



Data presented as mean ± SD. Black horizontal line represents 0% inhibition.

- In cells from untreated subjects, CD11b is rapidly upregulated by 50% following PGD_2 stimulation (data not shown)
- At all doses tested, CD11b induction by PGD_2 is entirely inhibited by GB001 for the 7 days of treatment and recovers to normal levels thereafter (**Figure 5**)

Figure 6. GB001 inhibits eosinophil shape change



Data presented as mean ± SD. Black horizontal line represents 0% inhibition.

- At all doses tested, PGD_2-induced ESC was also inhibited by GB001 with kinetics and duration that paralleled the effects on DP_2 and CD11b (**Figure 6**)

CONCLUSIONS

- In a phase 1 study in healthy subjects, the DP_2 inhibitor GB001 caused rapid, robust, and sustained inhibition of eosinophil responses to PGD_2. For all 4 GB001 dose groups, results were concordant across all endpoints, including target engagement (DP_2 receptor internalization) and PD endpoints (CD11b and ESC).
- Inhibition of these endpoints was similar for GB001 20 mg and higher doses
- The PGD_2 responsiveness of other DP_2^+ cells was similarly impacted (data not presented)
- These data suggest that DP_2 receptor blockade with GB001 may attenuate eosinophilic inflammation in diseases like asthma and chronic rhinosinusitis

REFERENCES

1. Taylor Meadows KR, et al. *J Allergy Clin Immunol* 2020;145(2, Suppl):AB20.

ACKNOWLEDGEMENTS

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