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GB001 is a Differentiated Potent DP_2 Antagonist With Long Receptor Residence Time and Extended Pharmacodynamic Efficacy

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BACKGROUND

- GB001 is an oral antagonist of the prostaglandin D_2 receptor 2 (DP_2) in development for the treatment of moderate-severe asthma and chronic rhinosinusitis
- DP_2 antagonists block receptor activation and intracellular signaling induced by prostaglandin D_2 (PGD_2), which may inhibit recruitment of airway eosinophils and reduce airway inflammation[1]

OBJECTIVES

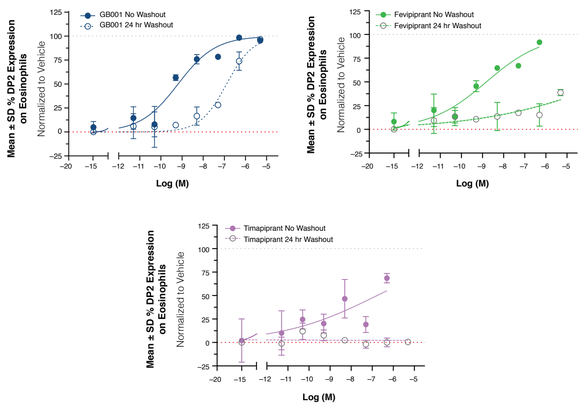
- Evaluate *in vitro* affinity, potency and receptor residence time of GB001
- Assess GB001 activity *in vivo* using asthma mouse models using antigen sensitization and airway challenge

METHODS

- Competitive antagonism and kinetics of GB001 were assessed in a ^{3}H-PGD_2 radioligand displacement assay in isolated DP_2 to characterize insurmountability (which refers to blockage of the receptor by the antagonist despite increasing agonist concentrations)
- *In vivo*, male Balb/c mice were sensitized with antigen (OVA or HDM), challenged with aerosolized antigen, and given poly:IC intratracheally to induce exacerbation
- Mice were dosed 1 hour prior to poly:IC challenge with GB001 via oral gavage. At termination, airway hyper-responsiveness was determined and BALF cells were isolated.
- Human whole blood was stimulated with PGD_2 antagonists for 30 minutes; cells were washed and immediately stimulated with PGD_2 for 1 hour. DP_2 internalization or eosinophil shape change (ESC) was determined by flow cytometry.

RESULTS

Figure 1. GB001 mediates extended inhibition of PGD_2-induced effects in human whole blood



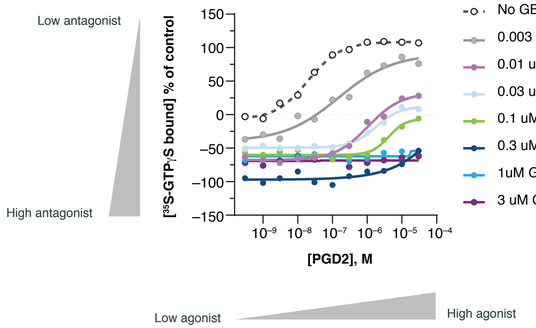
- Both GB001 (IC_{50} 1.2 nM) and fevipiprant (IC_{50} 32 nM) were potent DP_2 antagonists under washout conditions in the PGD_2-induced receptor internalization assay (**Figure 1**, solid lines). Timapiprant demonstrated an $IC_{50} > 1000$ nM in this assay.
- Following compound washout (**Figure 1**, dotted lines), GB001 still inhibited PGD_2-induced internalization (IC_{50} 110 nM) while fevipiprant and timapiprant were no longer able to inhibit receptor internalization ($IC_{50} > 1000$ nM).
- Data is representative of n = 3 for all assays

Table 1. GB001 demonstrates extended functional receptor residence time

	Functional (Ca^{2+} assay)
GB001	4.5 hr
Fevipiprant	1.2 hr
Timapiprant	11 min

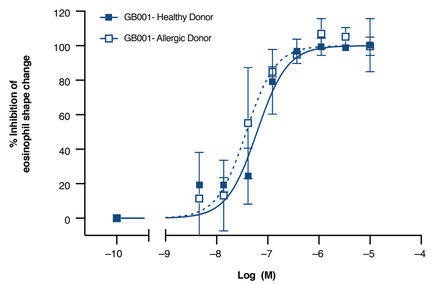
- GB001 showed an extended receptor residence time of 4.5 hours in a functional receptor residence assay (**Table 1**)

Figure 2. GB001 is an insurmountable antagonist



- Insurmountability was assessed using a GTPγS binding assay. Isolated DP_2 membrane preparations were treated with a dose-response of PGD_2 alone or in combination with a range of GB001 concentrations (**Figure 2**)
- GB001 is an insurmountable antagonist as defined by continued blockade of the receptor even with increasing concentrations of PGD_2

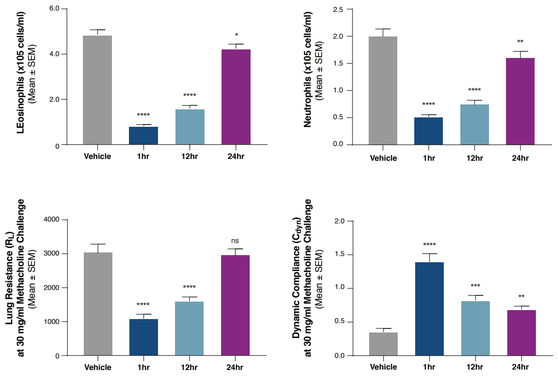
Figure 3. GB001 is a potent antagonist of PGD2-induced eosinophil shape change in a human whole blood assay for both healthy and allergic subjects



(n = 3 for all assays)

- GB001 inhibits PGD_2-induced eosinophil shape change equipotently in both healthy (IC_{50} 54 nM) and allergic (IC_{50} 59 nM) donor blood.

Figure 4. GB001 demonstrates extended reduction in lung infiltrating cells and improved lung function in vivo



n = 10 mice per group
****p < 0.0001, ***p < 0.001, **p < 0.01, *p < 0.05 (*vs vehicle)

CONCLUSIONS

- GB001 is a potent antagonist of DP_2 that demonstrates an extended functional receptor residence time and prolonged pharmacodynamic effects compared to other DP_2 antagonists
- GB001 is an insurmountable antagonist that maintains blocking activity even with increasing concentrations of PGD_2 which occurs in patients experiencing asthma exacerbation
- In the poly:IC induced asthma model, GB001 inhibits immune cell infiltration and improves airway function parameters

REFERENCES

1. Asano K, Sagara H, Ichinose M, et al. *J Allergy Clin Immunol Pract.* 2019 Nov 26. pii: S2213-2198(19)30955-9. doi: 10.1016/j.jaip.2019.11.016.

DISCLOSURES

KTM, SM, TSC, SS, GJO, LC, HO, and LSC are employed by Gossamer Bio, Inc.

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