# GB001 Potently Inhibits $PGD_2$ Metabolite-Induced $DP_2$-Mediated Cell Signaling and Eosinophil Activation

Susan Murphy, Taylor Ismaili, Kristen Taylor Meadows, Sunil Sahdeo, Hector Ortega, Laura Carter, Luisa Salter-Cid
Gossamer Bio, Inc.; San Diego, CA

## BACKGROUND

- GB001 is an oral antagonist of the prostaglandin $D_2$ receptor 2 ($DP_2$) in development for the treatment of moderate-severe asthma (NCT03683576) and chronic rhinosinusitis (NCT03956862)
- $DP_2$ 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]
- $PGD_2$ has multiple metabolites which can also activate and stimulate pathways downstream of $DP_2$

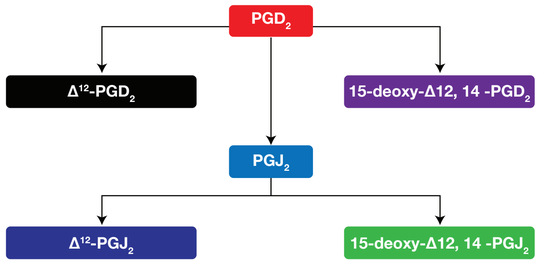
## OBJECTIVE

- Assess GB001 potency against $PGD_2$ and $PGD_2$ metabolite induced cell signaling and eosinophil activation

## METHODS

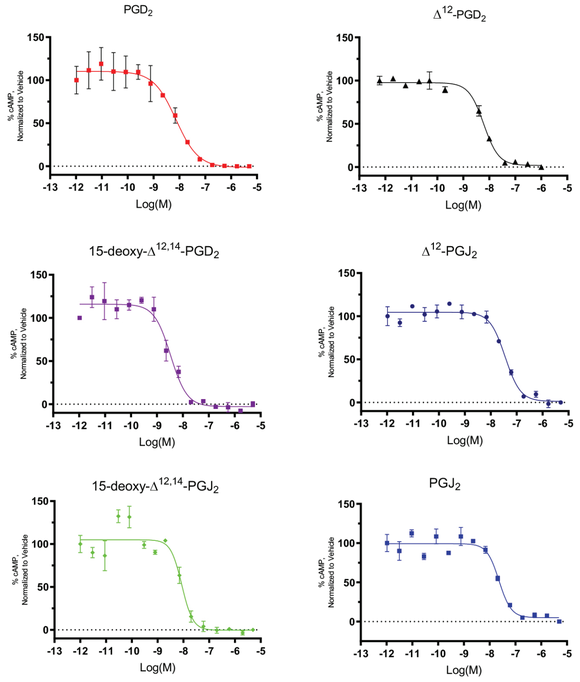
- G-protein activation assays (cAMP) were performed in CHO cells overexpressing human $DP_2$ (CHO-K1, CRTH2 Gi cell line from Discover X)
- $DP_2$ internalization on eosinophils in human whole blood was determined by antibody staining and flow cytometry
- In both assays, cell lines and human whole blood were pretreated with GB001 and then incubated with $PGD_2$ or one of the following metabolites at pre-determined $EC_{80}$ concentrations: $\Delta$12-$PGD_2$, 15-deoxy-$\Delta$12, 14-$PGD_2$, $PGJ_2$, $\Delta$12-$PGJ_2$ and 15-deoxy-$\Delta$12, 14-$PGJ_2$

### Figure 1. $PGD_2$ and its major metabolites




## RESULTS

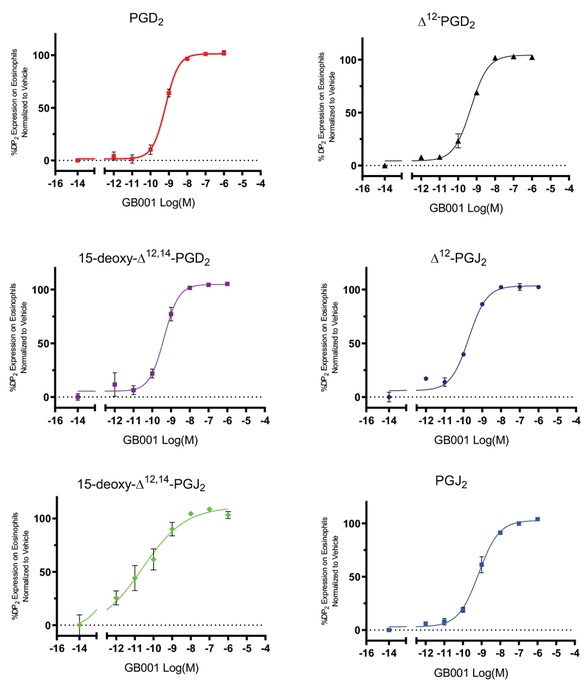
### Figure 2. GB001 inhibits $PGD_2$ metabolite activity in a cAMP assay




Concentration-dependent inhibition by GB001 on Gi-mediated cAMP, induced by metabolites of prostaglandin $D_2$ ($PGD_2$) in CHO-K1 $DP_2$ cells. Shown here is a representative data set from n = 2 experiments. Data are presented as mean ± SD.

- GB001 inhibits the activity of $PGD_2$ in the cAMP assay with an average $IC_{50}$ of 4.3 nM
- GB001 inhibits the activity of all $PGD_2$ metabolites with $IC_{50}$ values between 2.5 and 5.0 nM

### Figure 3. GB001 inhibits $PGD_2$ metabolite activity in a human whole blood $DP_2$ internalization assay




Concentration-dependent inhibition of $DP_2$ receptor internalization by GB001 that is otherwise induced by metabolites of prostaglandin $D_2$ ($PGD_2$). Shown here is a representative data set from n = 5 experiments. Data are presented as mean ± SD.

- GB001 inhibits $PGD_2$-induced receptor internalization with an $IC_{50}$ of 1.63 nM
- GB001 inhibits the activity of all $PGD_2$ metabolites with $IC_{50}$ values ranging from 0.3 to 0.67 nM

### Table 1. $IC_{50}$ for GB001 in cAMP and $DP_2$ internalization assays for all metabolites

| | cAMP | | | Internalization | | |
|---|---|---|---|---|---|---|
| Agonist/Agonist Metabolite | Concentration of Agonist Tested $EC_{80}$ ($\mu$M) | GB001 $IC_{50}$ (nM) Range | n | Concentration of Agonist Tested $EC_{80}$ ($\mu$M) | GB001 $IC_{50}$ (nM) | n |
| $PGD_2$ | 0.1 | 1.2 – 7.4 | 2 | 1 | 1.63 ± 1.1 | 5 |
| $\Delta$12-$PGD_2$ | 0.1 | 0.8 – 3.8 | 2 | 0.5 | .67 ± .32 | 5 |
| 15-deoxy-$\Delta$12, 14-$PGD_2$ | 0.1 | 2.6 – 3.4 | 2 | 1 | .6 ± .3 | 5 |
| $\Delta$12-$PGJ_2$ | 1.0 | 11.2 – 36.1 | 2 | 2.5 | .3 ± .08 | 5 |
| 15-deoxy-$\Delta$12, 14-$PGJ_2$ | 0.3 | 1.3 – 8.7 | 2 | 1.5 | .14 ± .1 | 5 |
| $PGJ_2$ | 0.3 | 2.0 – 23.0 | 2 | 6 | .6 ± .3 | 5 |

Data for cAMP is presented as a range for n = 2; data for internalization (n = 5) is presented as mean ± SD

## CONCLUSION

- GB001 is a potent antagonist of $PGD_2$ and $PGD_2$ metabolites and demonstrates similar potencies against all activators of the $DP_2$ receptor
- Potency data was generated in two independent assays, a cAMP signaling assay in human overexpressing $DP_2$ CHO cells and in human eosinophils in a whole blood assay
- GB001 inhibition of $PGD_2$ metabolite-induced migration and signaling may be beneficial in controlling $PGD_2$-mediated inflammation in allergic disease and asthma

## 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

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

Prepared for the European Respiratory Society virtual meeting, September 5–9, 2020. Abstract 2885.