# Compared with Evobrutinib and Tolebrutinib, Fenebrutinib Displays Highest In Vitro Potency on both B Cells and Myeloid Progenitor Lineage Cells

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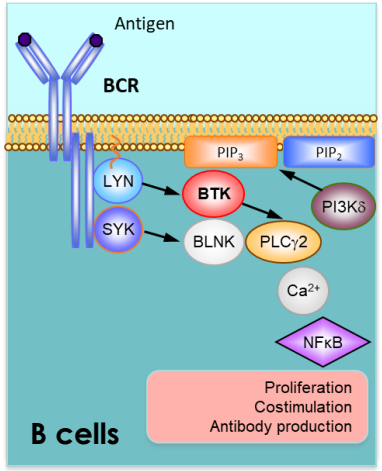
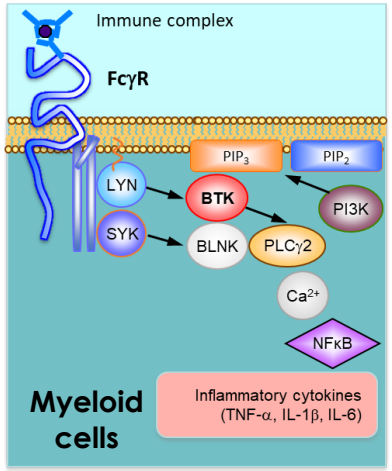
**Safety Poster and B-Cell Subset Depletion Poster - Live Q&A Session:** April 21, 2021 11:00-11:30AM Eastern Time (US and Canada)

**Please join us on Zoom**
**Meeting ID:** 957 4653 7551
**Passcode:** 171494

## Background

- Bruton's tyrosine kinase (BTK) is a non-receptor kinase active in B cells, myeloid cells and myeloid progenitor lineage cells[1,2]
  - It has a key role in B-cell receptor (BCR)and $F_CR$ signaling
  - BTK is an attractive therapeutic target for multiple sclerosis (MS) because of its involvement in acute and chronic peripheral and neuro-inflammation[3]
- Fenebrutinib is a highly selective and reversible (noncovalent) BTK inhibitor[4]
- Fenebrutinib is currently in late-stage clinical development as an investigational oral therapy for MS




**Objective:** To compare the potency of fenebrutinib, tolebrutinib and evobrutinib head-to-head in healthy participants using *in vitro* whole blood activation assays for B cells and myeloid progenitor lineage cells

BTK, Bruton's tyrosine kinase; BCR, B-cell receptor; MS, multiple sclerosis.

1. Schmidt UN, *et al. Int Arch Allergy Immunol* 2004;34:65-78.
2. Brunner C, *et al. Histol Histopathol* 2005;20:945-955.
3. Torke S, Weber MS. *Expert Opin Investig Drugs 2020;*29:1143-1150.
4. Crawford JJ, *et al. J Med Chem* 2018;6:2227-2245.

# Methods: B cell and myeloid progenitor lineage cell activation assays

Fresh whole blood from 11 healthy participants

± BTKi

1 h

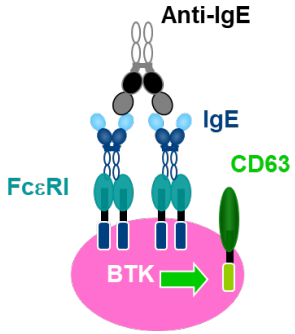
**Anti-IgE**

20 min

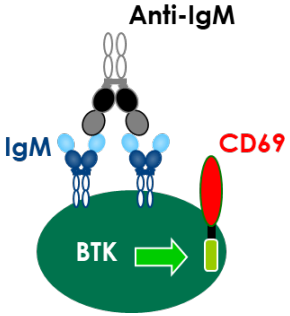
**Anti-IgM**

18 h

**Flow Cytometry**




**FcεR-induced CD63 expression on myeloid progenitor lineage cells (basophils)**

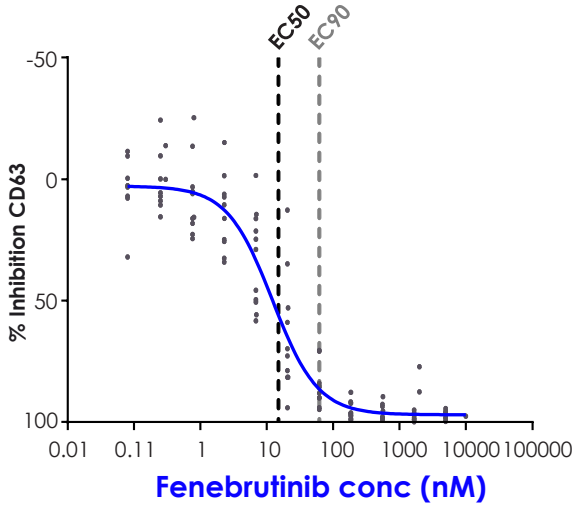


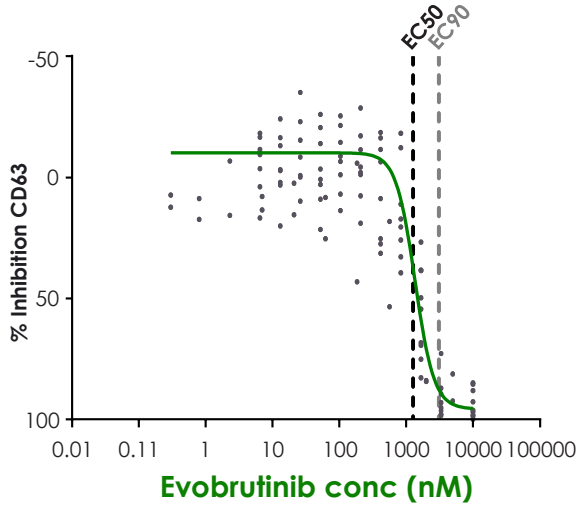

**BCR-induced CD69 expression on B cells**

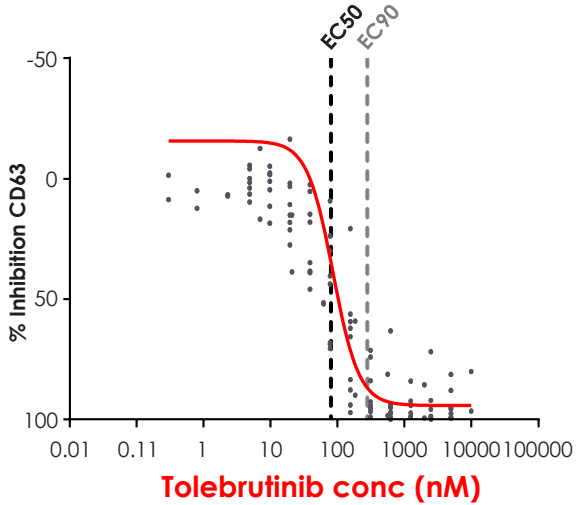
BTKi, Bruton's tyrosine kinase inhibitor; BCR, B-cell receptor; Ig, immunoglobulin.

# Results: Inhibition of myeloid progenitor lineage cell activation

- Head-to-head, **fenebrutinib** is the most potent BTKi when compared with evobrutinib and tolebrutinib in inhibition of $F_cR$ signaling in **myeloid progenitor lineage cells** (basophils)



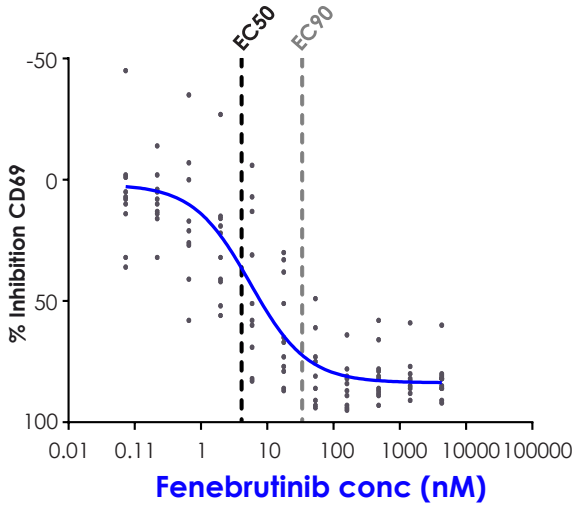



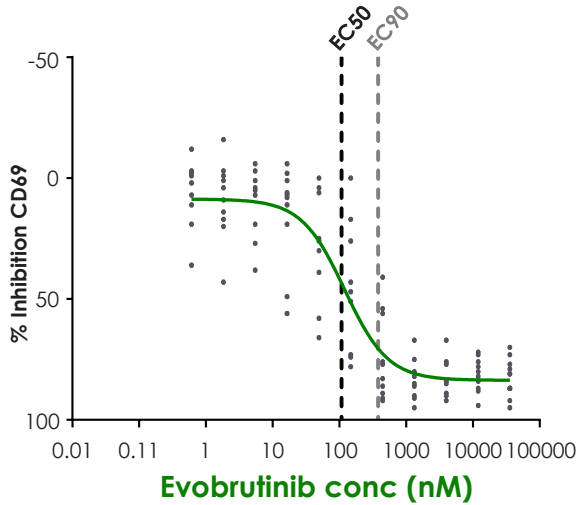

| | Fenebrutinib | Evobrutinib | Tolebrutinib |
|---|---|---|---|
| **$EC_{50}$, nM** (±SEM) | 15 (4) | 1271 (133) | 80 (11) |
| **$EC_{90}$, nM** (±SEM) | 62 (12) | 3102 (560) | 281 (49) |

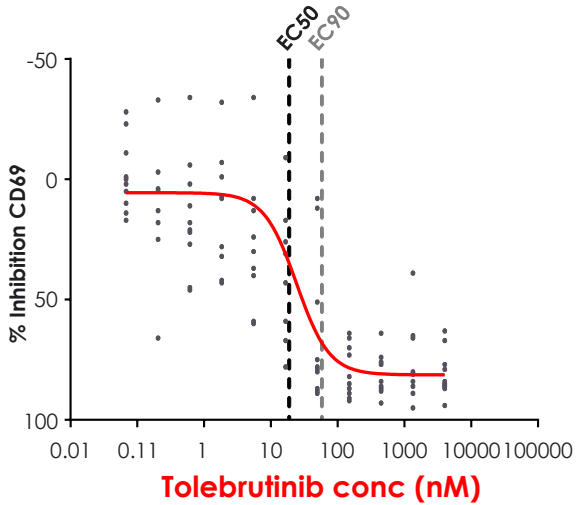
BTKi, Bruton's tyrosine kinase inhibitor; $EC_{50}$, 50% effective concentration; $EC_{90}$, 90% effective concentration.

# Results: Inhibition of B cell activation

- Head-to-head, **fenebrutinib** is the most potent BTKi when compared with evobrutinib and tolebrutinib in inhibition of BCR signaling in **B cells**



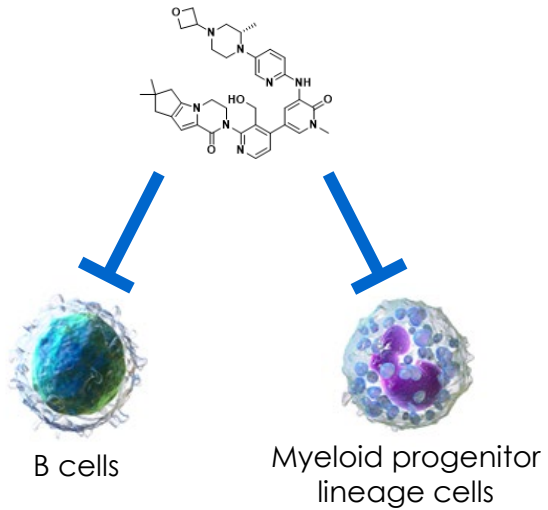

| | Fenebrutinib | Evobrutinib | Tolebrutinib |
|---|---|---|---|
| **$EC_{50}$, nM** (±SEM) | 8 (4) | 161 (42) | 26 (5) |
| **$EC_{90}$, nM** (±SEM) | 65 (28) | 524 (101) | 84 (25) |

BCR, B-cell receptor signaling; BTKi, Bruton's tyrosine kinase inhibitor; $EC_{50}$, 50% effective concentration; $EC_{90}$, 90% effective concentration.

# Conclusions

- Compared with evobrutinib and tolebrutinib, **fenebrutinib** displays the most potent inhibitory capacity *in vitro* on both B cells and myeloid progenitor lineage cells (basophils)
- The noncovalent binding, reversible mechanism and greater selectivity of fenebrutinib may result in a more favorable safety profile (See Presentation S25.005 at this conference)

**Fenebrutinib**




On the basis of its potency, selectivity and noncovalent mode of inhibition, fenebrutinib has the potential to be a **best-in-class BTKi** for multiple sclerosis

BTKi, Bruton's tyrosine kinase inhibitor.