European Crohn's and Colitis Organisation

# AZD4205, a potent, GI-tract enriched, JAK1-selective inhibitor for treatment of Inflammatory Bowel Disease (IBD)

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# Disclosure of Potential Conflicts of Interest

I am an employee of Dizal (Jiangsu) pharmaceutical and own some shares

# Executive summary of AZD4205

**A unique JAK1 selective inhibitor AZD4205:**

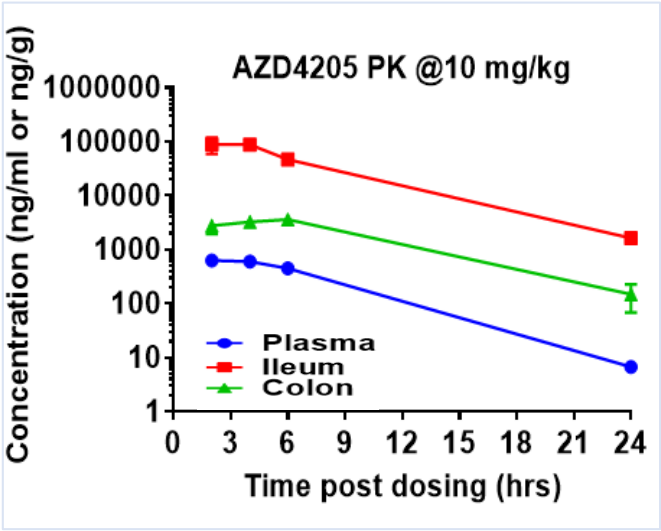
1. AZD4205 is a potent, truly selective JAK1 kinase inhibitor with low DDI risk, and long half life time of ~45 hr in human allowing to hit target harder and continuously cover target
2. It has unique GI-enriched property with over 50-fold higher drug exposure in GI than in blood, which translates into the differential biological effect in ileum vs systemic organ, suggesting much enhanced therapeutic margin for IBD treatment
3. Clinically AZD4205 show encouraging PoM and PoP biomarker signal, inhibits pSTATs and CRP at well tolerated dose

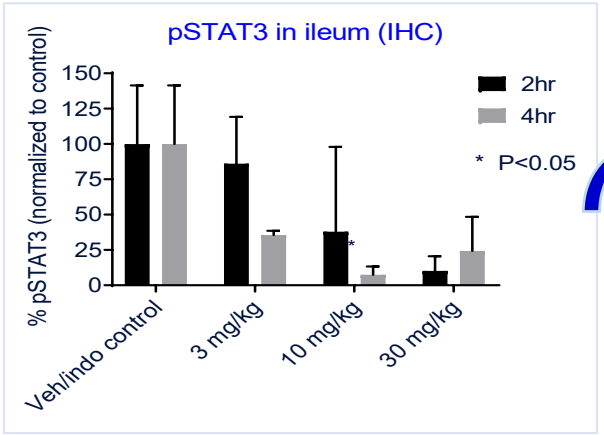
# AZD4205 is a selective JAK1 inhibitor with favorable DMPK property

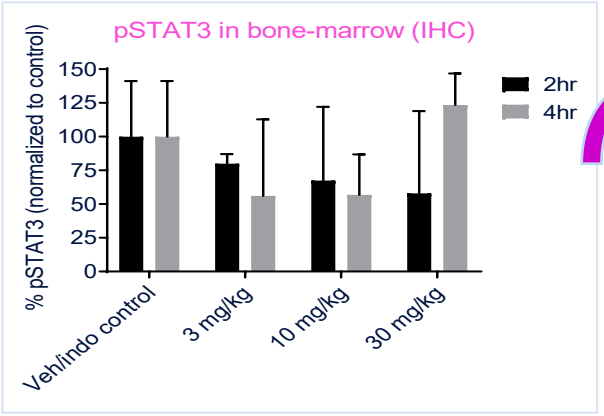
| | Tofacitinib* JAK1/3i | Filgotinib# JAK1/2i | Upadacitinib## JAK1i | AZD4205 |
|---|---|---|---|---|
| Company | Pfizer | Galapagos/Gilead | Abbvie | Dizal |
| JAK1, $IC_{50}$ (nM) | 3.2 | 10 | 45 | 72 |
| JAK2, fold selectivity relative to JAK1 | 1.3× | 2.8× | 2.4× | > 200× |
| JAK3, fold selectivity relative to JAK1 | 0.5× | 81× | 46.7× | > 400× |
| TYK2, fold selectivity relative to JAK1 | 10.6× | 11.6× | 104× | > 400× |

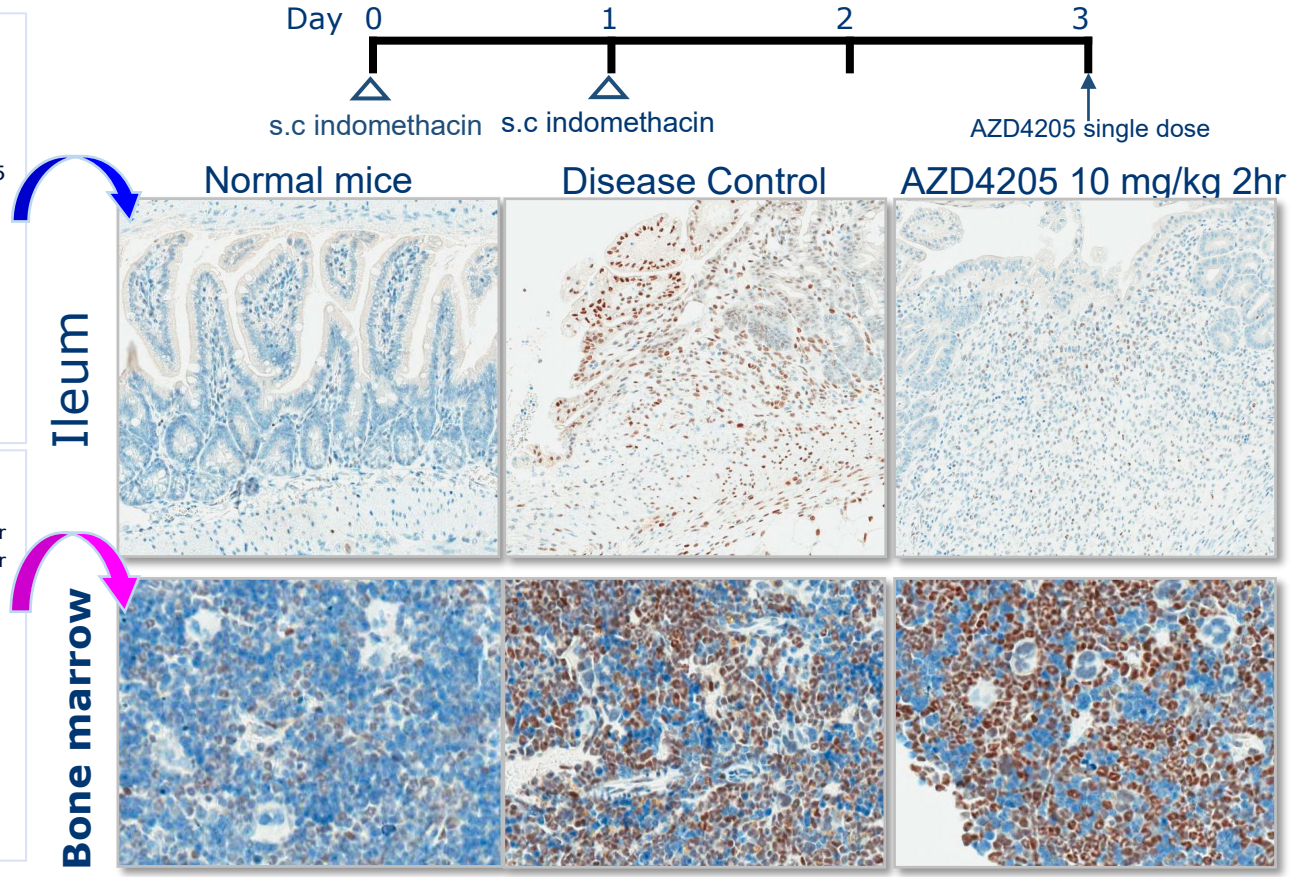
Data extracted from reference
*J Inflammation 2010, 7:41-53
#J Immunol 2013, 191:3568-3577
##Arthritis&Rheumatology 2016, 68:2867-2877

# Higher GI exposure of AZD4205 vs blood translates into more profound pSTAT3 reduction in ileum than in bone marrow in mouse IBD model



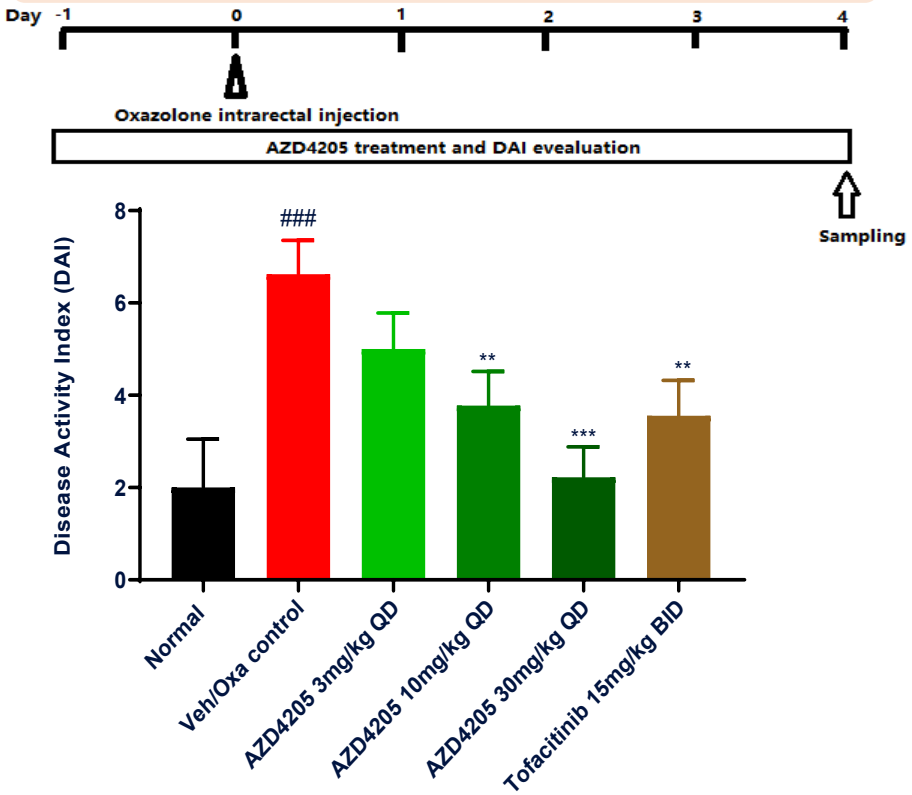



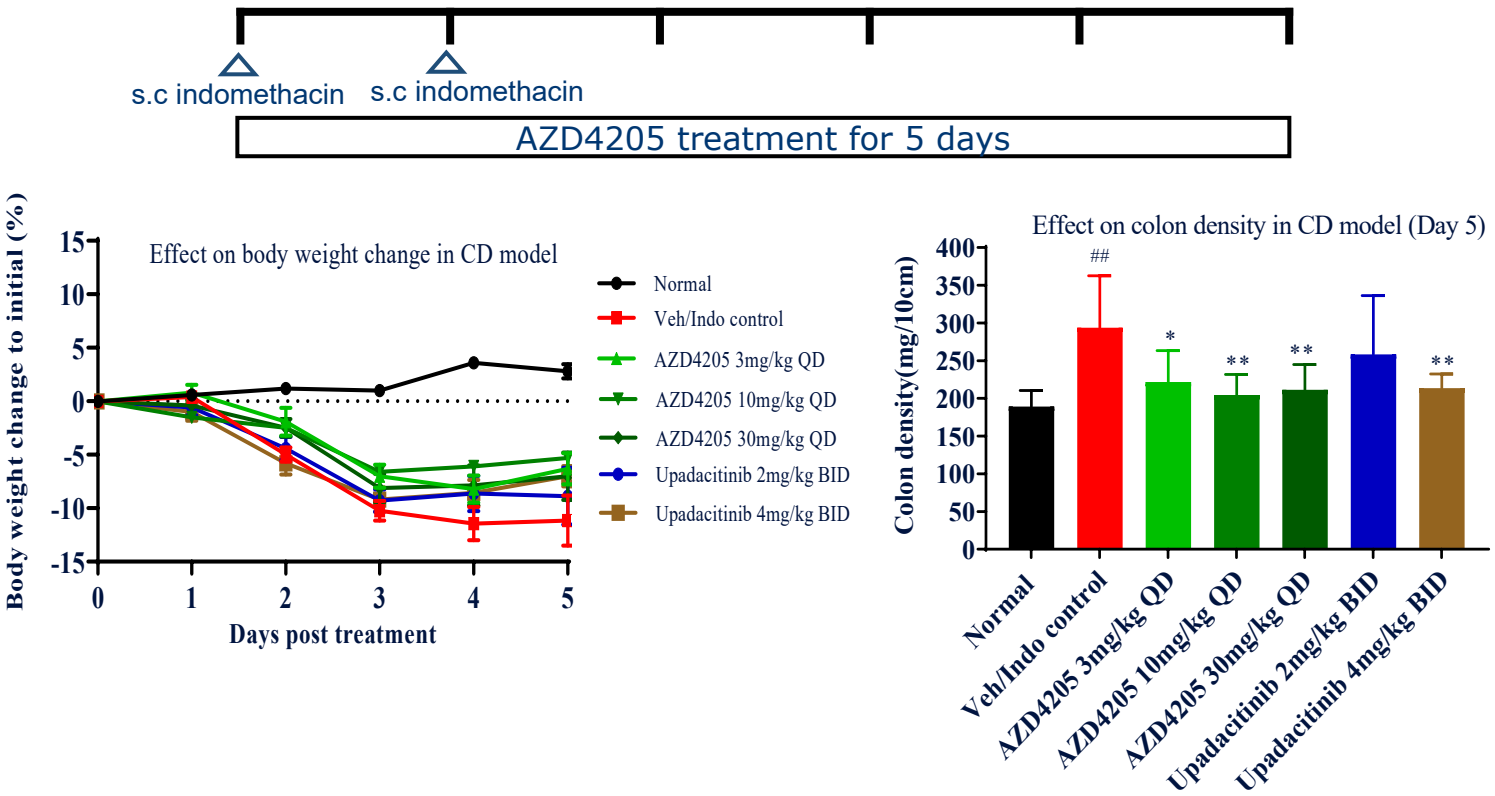



# AZD4205 shows better efficacy than tofacitinib or upadacitinib in mouse IBD models

## Oxazolone-induced colitis model




## Indomethacin-induced Crohn's Disease model

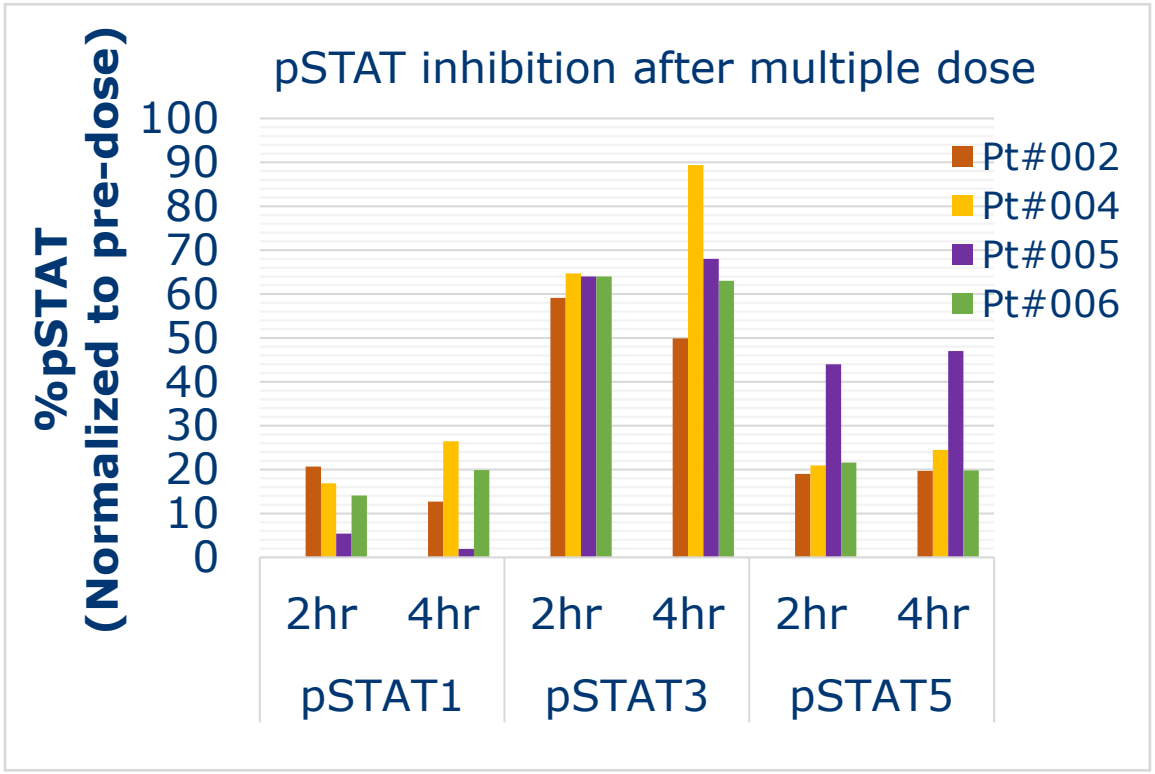


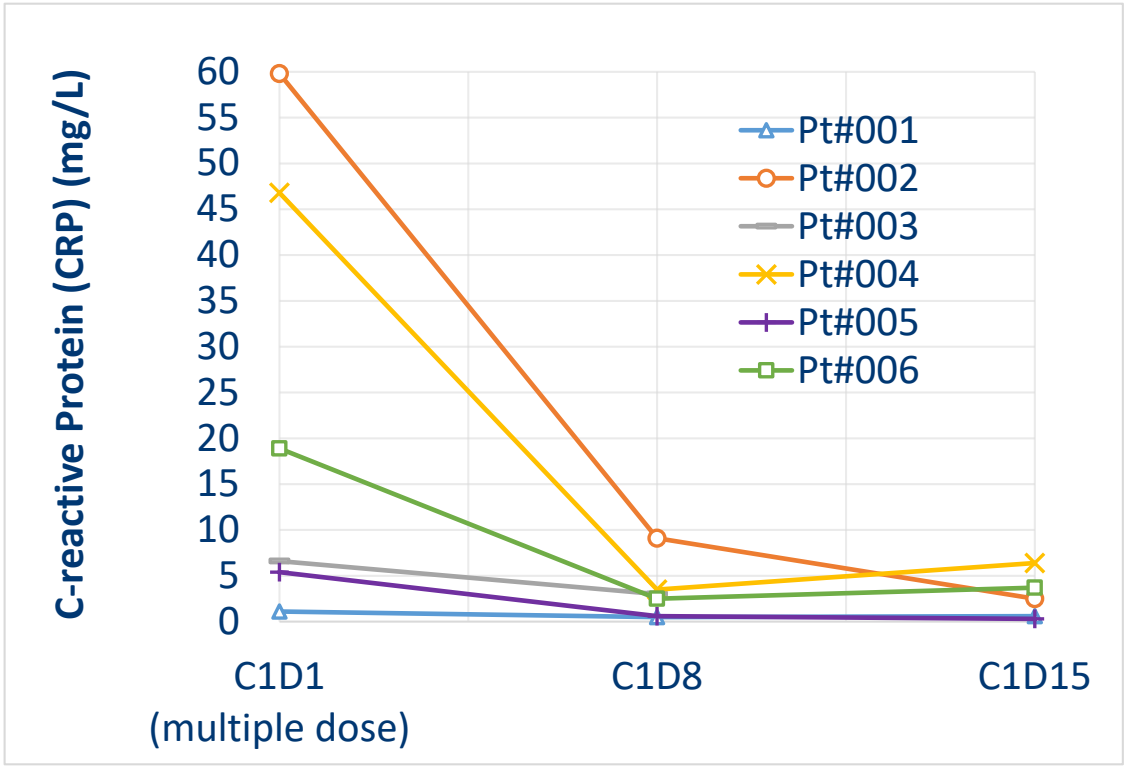

Data are expressed as mean±SEM (n=5-10). * p<0.05, ** p<0.01, *** p<0.001 (vs. Veh control). ## p<0.01, ### p<0.001 (vs. normal). One-way ANOVA, Fisher's LSD post-hoc test

# Human PK/PoM biomarker data of AZD4205

- 6 lung cancer patients dosed with 75 mg AZD4205 (by cutoff of 2018 Nov 20th)
- Significant pSTAT1,5 inhibition at C1D15 or C2D1
- ~45 hr human $T_{1/2}$ of AZD4205

- Majority of pts had abnormal CRP baseline
- AZD4205 can quickly lower CRP to normal range
- Ph II clinical studies in Crohn's Disease and Ulcerative Colitis are under planning



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