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PA/2247/2019/UK
September 2019

Athena SWAN
Silver Award

Barts and The London
School of Medicine and Dentistry

Queen Mary
University of London

National IBD Doctors Annual Meeting: IBD Treatment: 2020 & beyond

Emerging therapies: drugs that target cytokines or their signalling pathways

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Disclosures

- **Served as consultant and an advisory board participant:**
  - AbbVie, Alergan (Warner Chilcott), Atlantic Healthcare, Celgene, Celtrion, Gilead, GSK, Janssen, MSD, Napp, Pfizer, Shire, Takeda and Vifor Pharma

- **Received speaker fees and sponsorship for academic meetings:**
  - from AbbVie, Alergan (Warner Chilcott), Ferring, Janssen, MSD, Napp, Pfizer, Shire, Tillott's, Takeda

- **Received investigator led research grants**
  - from Pfizer, Shire and Takeda

Drugs that target cytokines or their signalling pathways

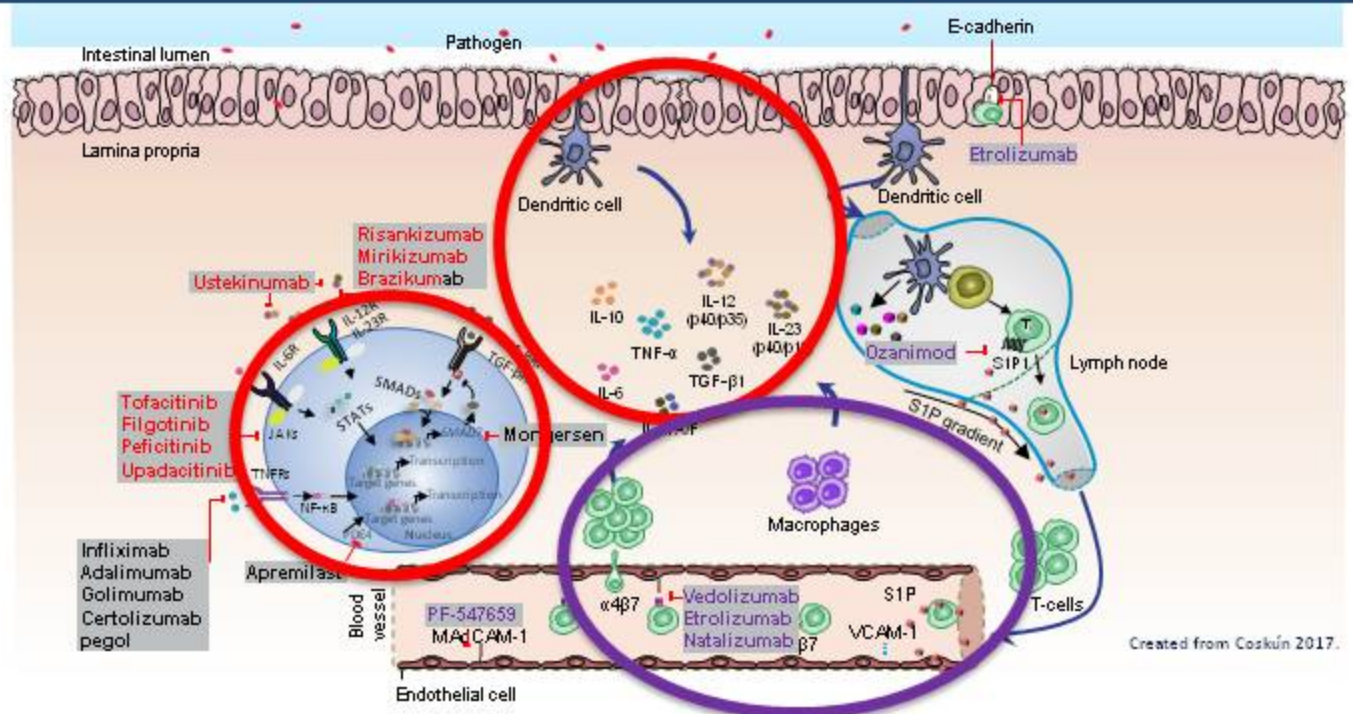
What I am aiming to cover

- Introduction to the mucosal immune system in IBD
  - Highlight drugs that target cytokines and their signalling pathways
- Review of pivotal clinical / safety data
  - JAK inhibitors, now and in the future
  - Ustekinumab in UC
  - Anti p19 agents that target IL-23
- Conclusions

Drugs that target cytokines or their signalling pathways

Understanding the immune pathogenesis drives drug development

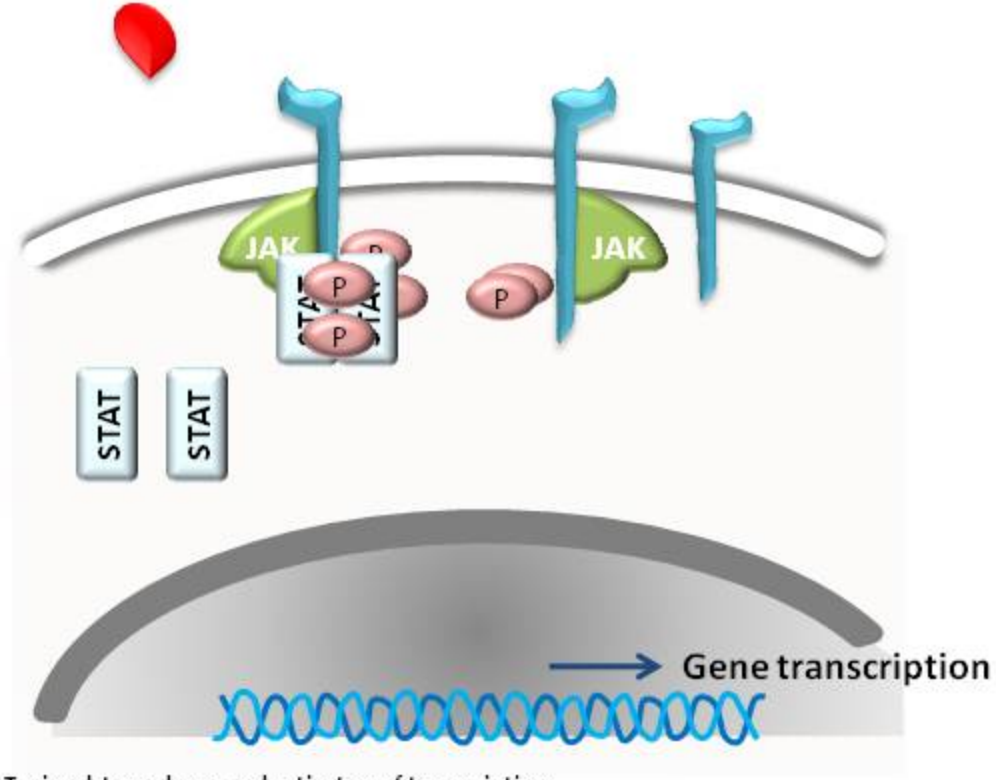
Targeting distinct mechanisms that drive inflammation may provide long-term control and preserve intestinal function in IBD[1,2]



1. Coskún M, et al. *Trends Pharm Sci* 2017;38:127–42; 2. Nielsen OH, et al. *Expert Opin Investig Drugs* 2016;25:709–18.

The Janus Kinase pathway – a gateway to intra cellular signalling

Cytokine receptor binding activates JAK pathway signaling

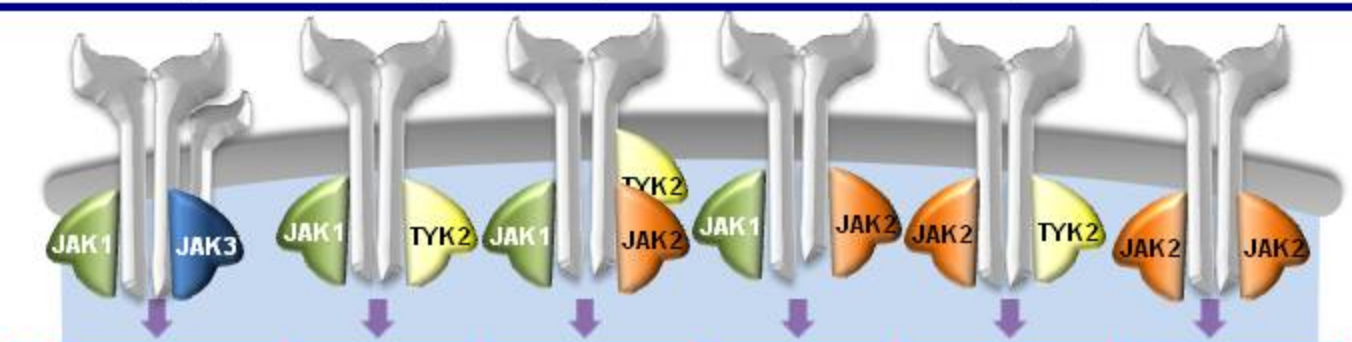


JAK, Janus kinase; P, phosphate; STAT, signal transducer and activator of transcription.

Shuai K and Liu B. *Nat Rev Immunol.* 2003;3:900–11; Rawlings JS, et al. *J Cell Sci.* 2004; 117:1281–3.

The Janus Kinase pathway

Drugs that target the JAK pathway have been developed for IBD



Upadacitinib	More potently inhibits JAK1 over JAK2 and JAK3	**Peficitinib**	More potently inhibits JAK3 over JAK1 and JAK2
Baricitinib	More potently inhibits JAK1 and JAK 2 over JAK3	**Decernotinib**	More potently inhibits JAK3 over JAK1 and JAK2
Filgotinib	More potently inhibits JAK1 over JAK2 and JAK3	**Tofacitinib**	Non-selective (inhibits JAK1, JAK2 and JAK3)

O'Shea JJ, et al. *Annu Rev Med*. 2015;66:311–328; Kiu H, Nicholson SE. *Growth Factors*. 2012;30:88–106.

NK, natural killer; TKY2, tyrosine kinase 2

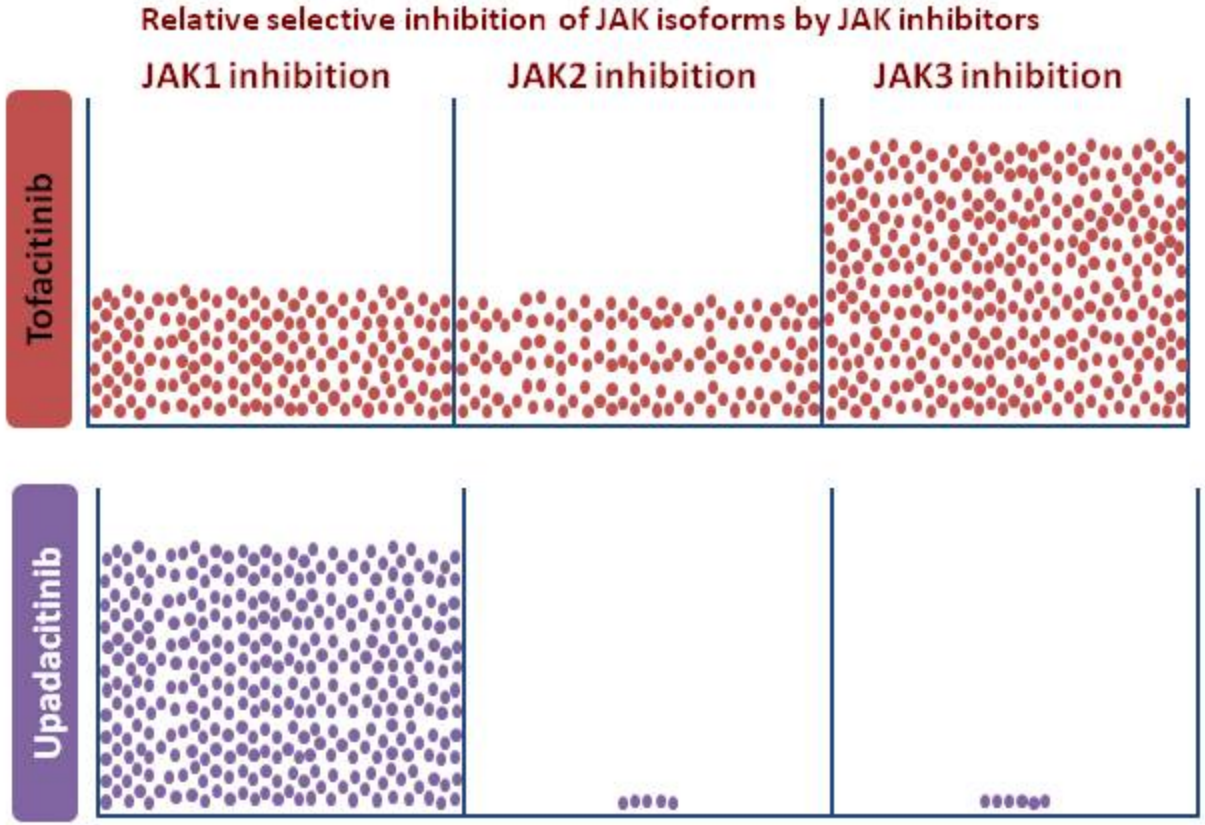
The Janus Kinase pathway

JAKi have distinct specificity dictating efficacy and side effects

Tofacitinib[1,3]
Higher selectivity for JAK3
vs JAK1 (4x) and JAK2 (5x)

Filgotinib[4]
Higher selectivity for JAK1
vs JAK2 (28x)

Upadacitinib[2]
Higher selectivity for JAK1
vs JAK2 (74x) and JAK3 (58x)

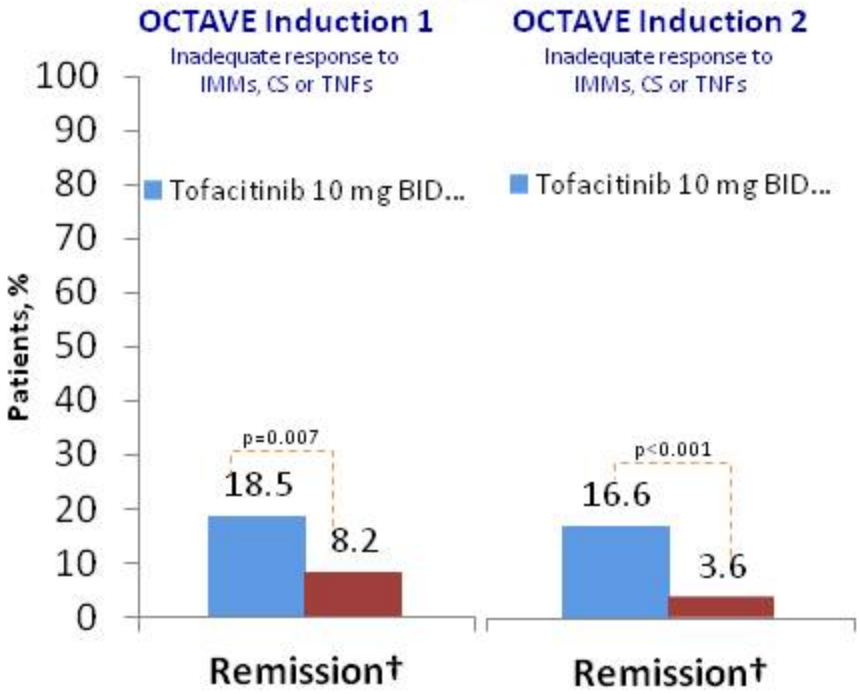


JAK1-3 antagonist: Tofacitinib

Phase III induction and maintenance studies in UC

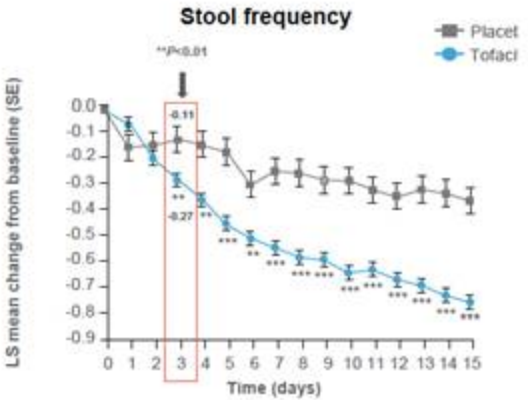
Tofacitinib[1,3]
Higher selectivity for JAK3 vs JAK1 (4x) and JAK2 (5x)

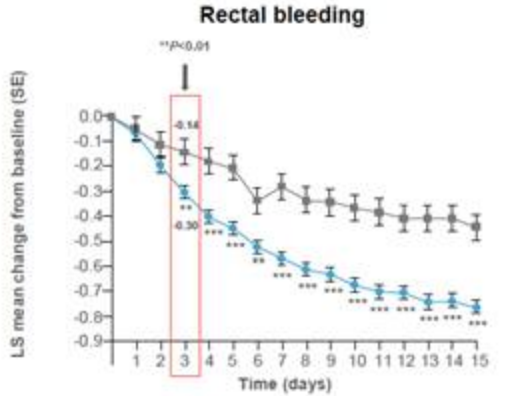
Week 8 results



†Mayo score ≤2 with no subscore >1 and a rectal bleeding score of 0; ‡Mayo endoscopic subscore ≤1.

Sandborn WJ, et al. *N Engl J Med.* 2017;376:1723–36.





JAK1-3 antagonist: Tofacitinib

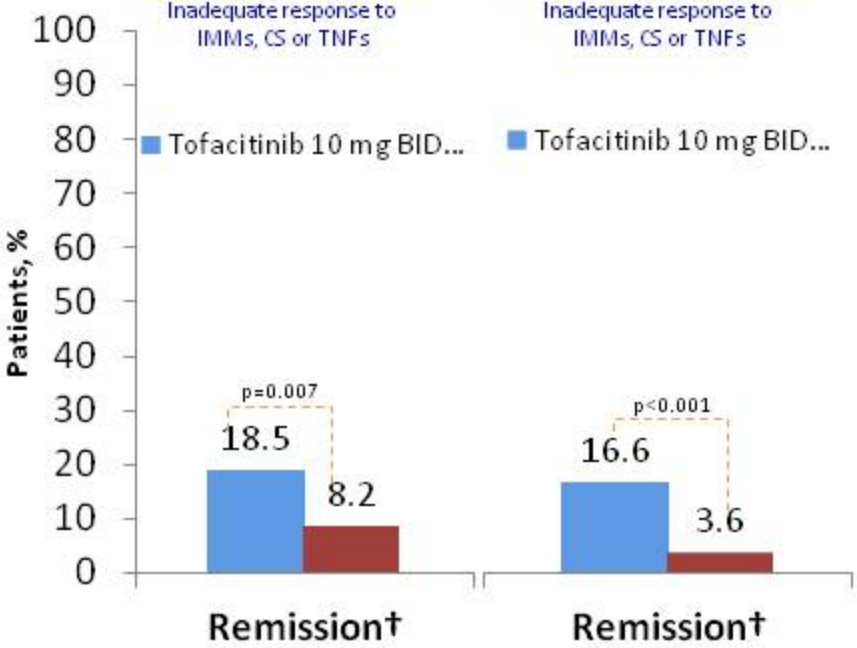
Phase III induction and maintenance studies in UC

Tofacitinib[1,3]
Higher selectivity for JAK3 vs JAK1 (4x) and JAK2 (5x)

Week 8 results

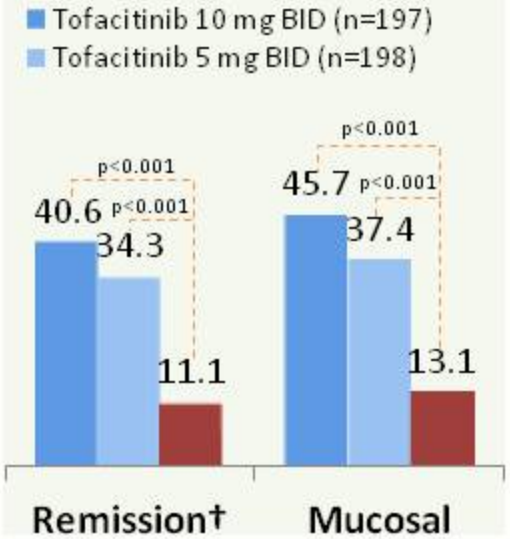
OCTAVE Induction 1
Inadequate response to IMMs, CS or TNFs

OCTAVE Induction 2
Inadequate response to IMMs, CS or TNFs



Week 52 results

OCTAVE Sustain
OCTAVE 1 and 2 completers

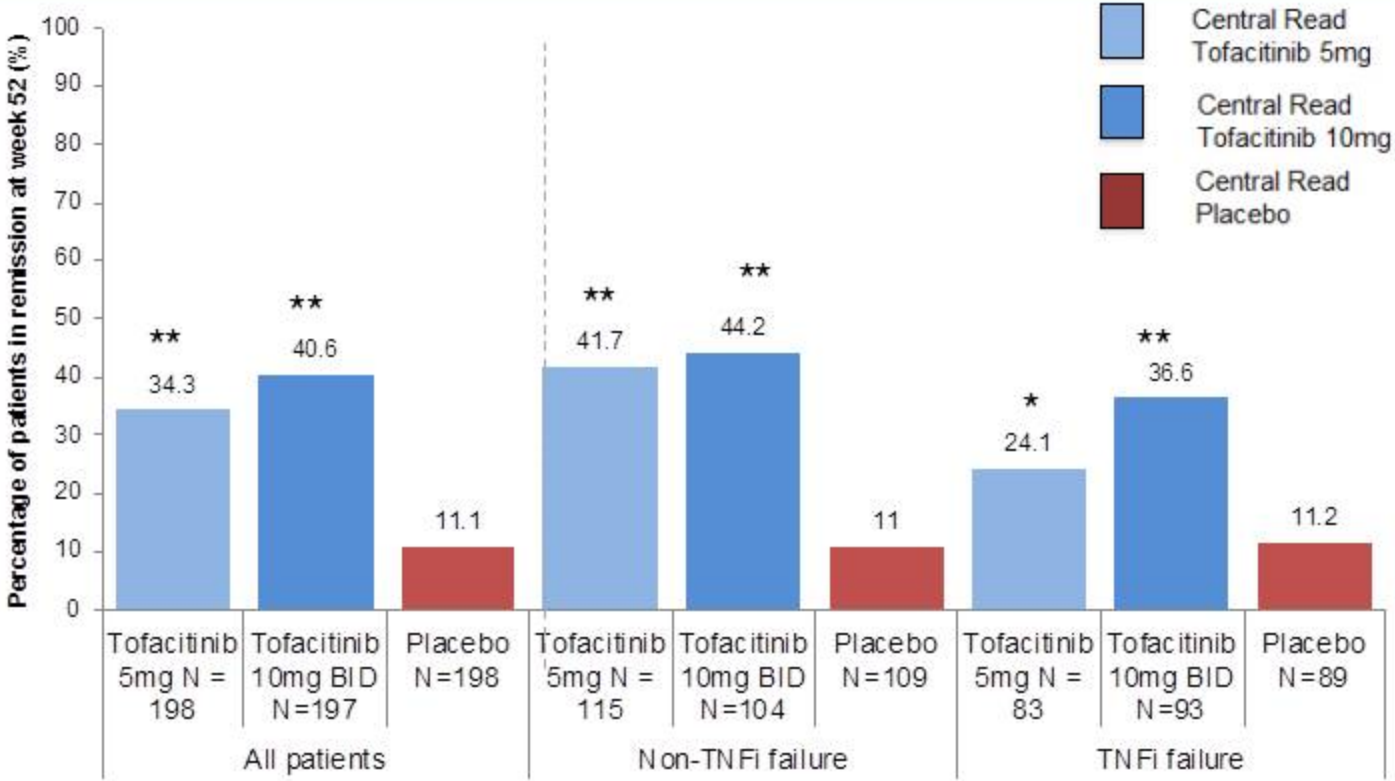


†Mayo score ≤2 with no subscore >1 and a rectal bleeding score of 0; ‡Mayo endoscopic subscore ≤1.

Sandborn WJ, et al. *N Engl J Med.* 2017;376:1723–36.

JAK1-3 antagonist: Tofacitinib

Phase III: remission at week 52 is greater in anti TNF naïve patients



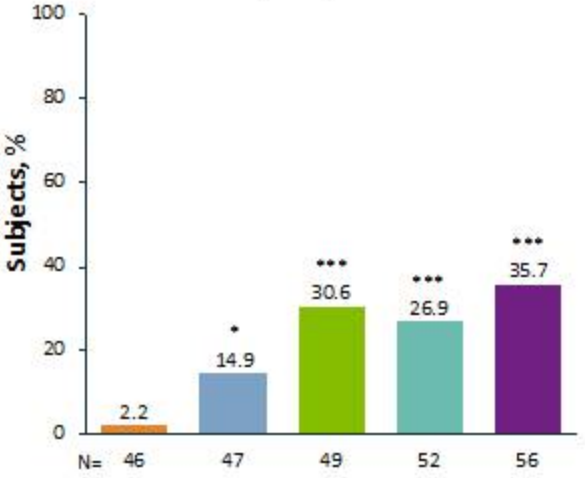
*p<0.05, **p<0.0001 vs placebo, FAS, full analysis set; NRI, non-responder imputation,

Dubinsky MC *et al.* Poster presented at: World Congress of Gastroenterology, October 13–18, 2017, Orlando, FL, USA.

JAK1 antagonist: Upadacitinib

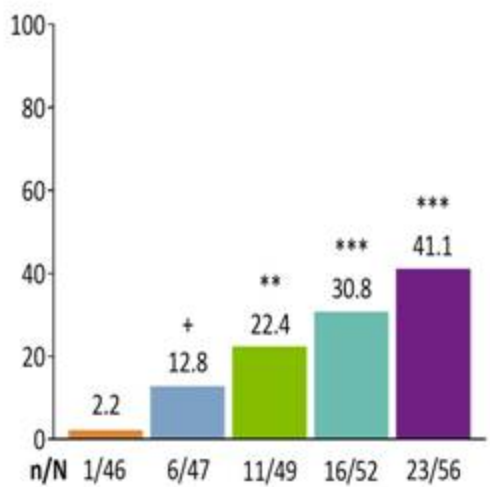
Phase 2b induction study in UC

Upadacitinib[2]
Higher selectivity for JAK1
vs JAK2 (74x) and JAK3 (58x)



Clinical remission: stool frequency subscore ≤ 1
rectal bleeding score = 0, endoscopic score ≤ 1

Endoscopic improvement: endoscopic subscore ≤ 1



Histologic remission: Geboes score < 2.

18

12

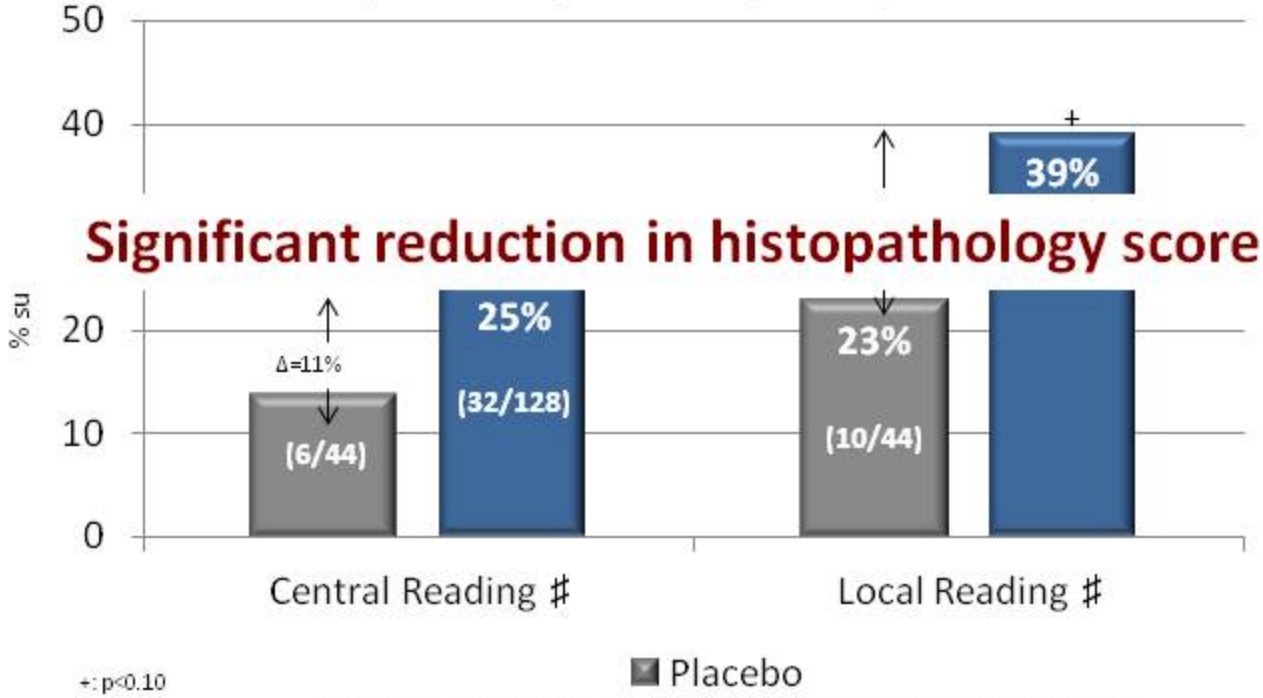
Sandborn et al UEGW, 2018

JAK1 antagonist: Filgotinib

Phase II induction study in CD

FITZROY: SES-CD, Endoscopic response

Improvement by at least 50%, ITT-NRI, Week 10



+: p<0.10

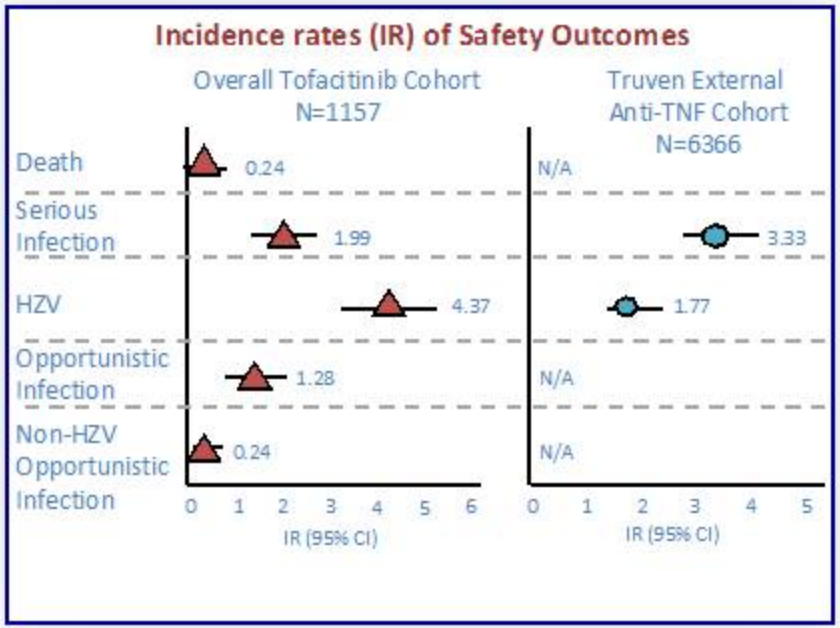
♯: Only using segments explored at both baseline and week 10 (matching segments)

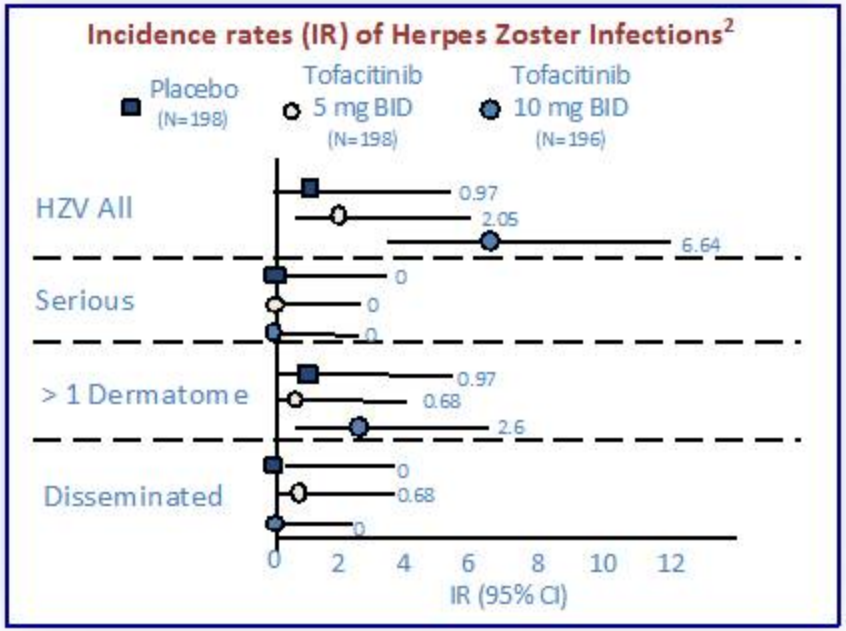
Vermeire et al Lancet. 2017 Jan 21;389(10066):266-275.

JAK1-3 antagonist: Tofacitinib

Safety data from phase III studies in UC

Tofacitinib[1,3]
Higher selectivity for JAK3 vs JAK1 (4x) and JAK2 (5x)





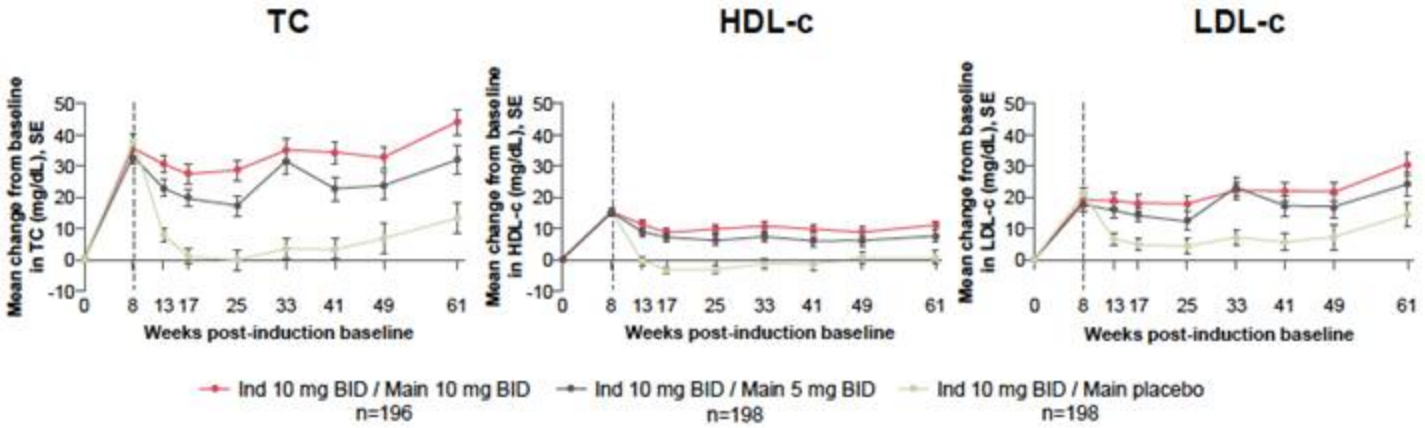
1. Sandborn WJ, et al. Presented at DDW 2018. Abstract 904. 2. Withrop KL, et al. Presented at DDW 2018. Abstract Sa1748.
3. Withrop KL, et al. Presented at DDW 2018. Abstract Sa1770.

JAK1-3 antagonist: Tofacitinib

Safety data from phase III studies in UC

Tofacitinib[1,3]
Higher selectivity for JAK3 vs JAK1 (4x) and JAK2 (5x)

Pooled data from the OCTAVE programme (N=1157)[1†]



- Significant correlation observed between increased lipid levels and reduced CRP[2]
- Lipid increases occurred primarily during the first 8 weeks[2]

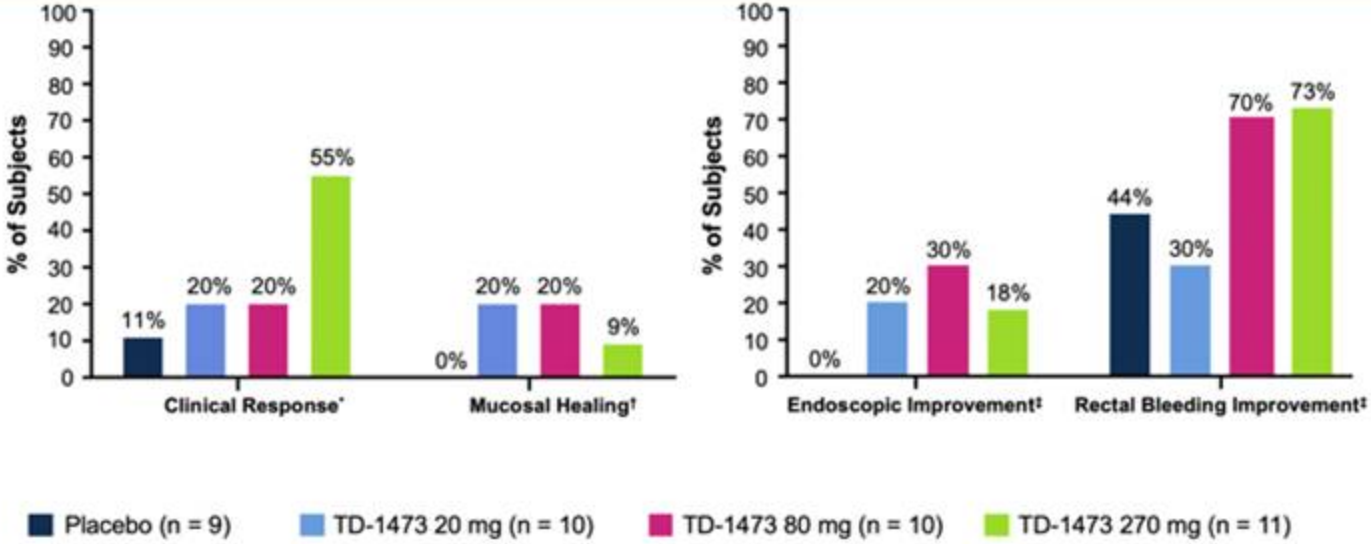
No increased risk of malignancy

Sandborn et al DDW, 2018

JAK1 antagonist: TD1473 – colonic release pan JAK inhibitor

Phase Ib study in moderate to severe UC

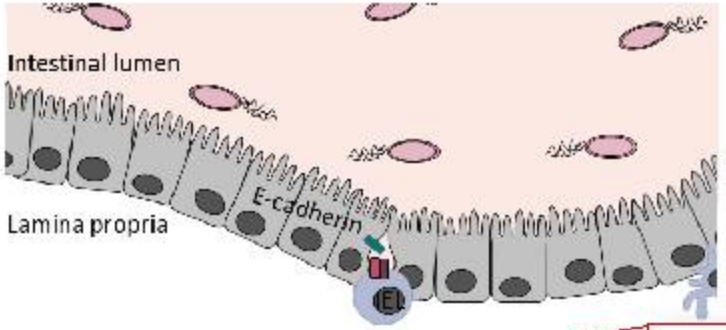
- TD-1473 is an orally administered and gut-selective pan-Janus kinase (JAK) inhibitor
- Double-blind, placebo-controlled, multicenter Phase 1b (n=40)
- Assess the safety, clinical and molecular effects of TD-1473 in UC after 4 weeks

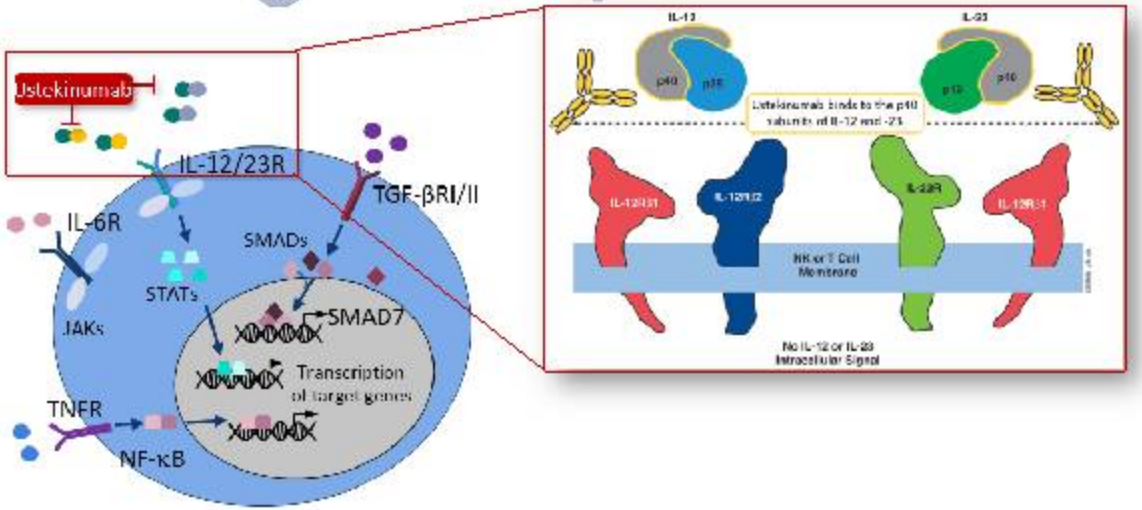


Sandborn W, et al. Presented at DDW, May 2019. Abstract 801.

Drugs that target cytokines or their signalling pathways

What I am aiming to cover

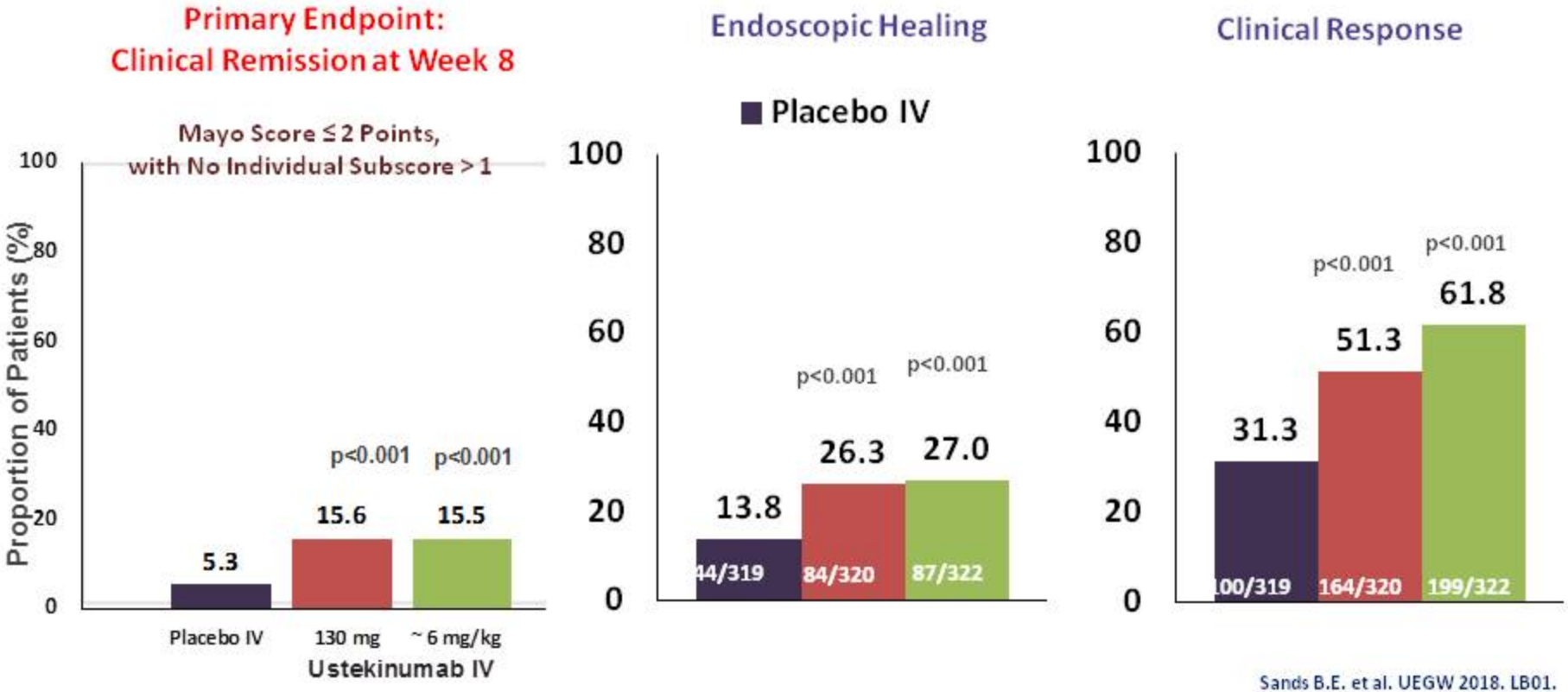




- **Review of pivotal clinical / safety data**
  - JAK inhibitors, now and in the future
  - Ustekinumab in UC – Anti P40

Ustekinumab: IgG1 anti P40 antibody

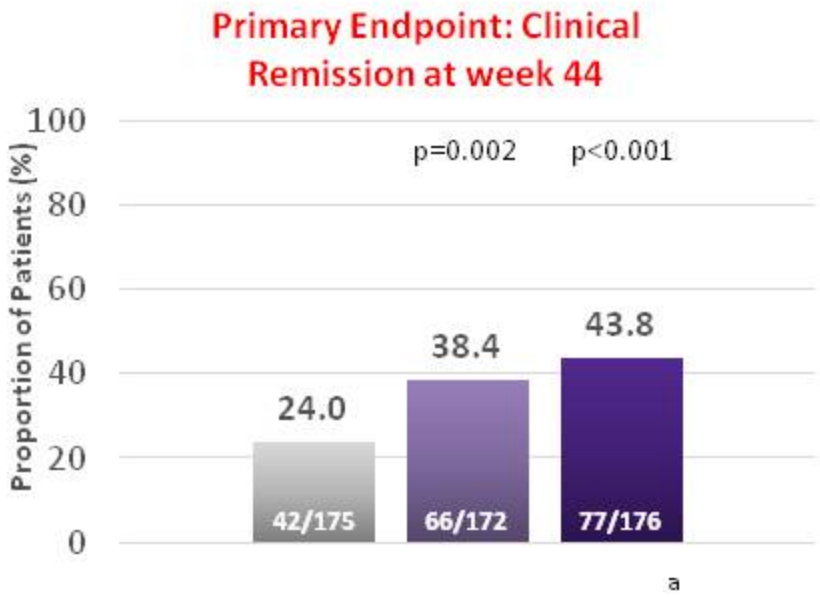
Phase III study in moderate to severe UC – UNIFI induction

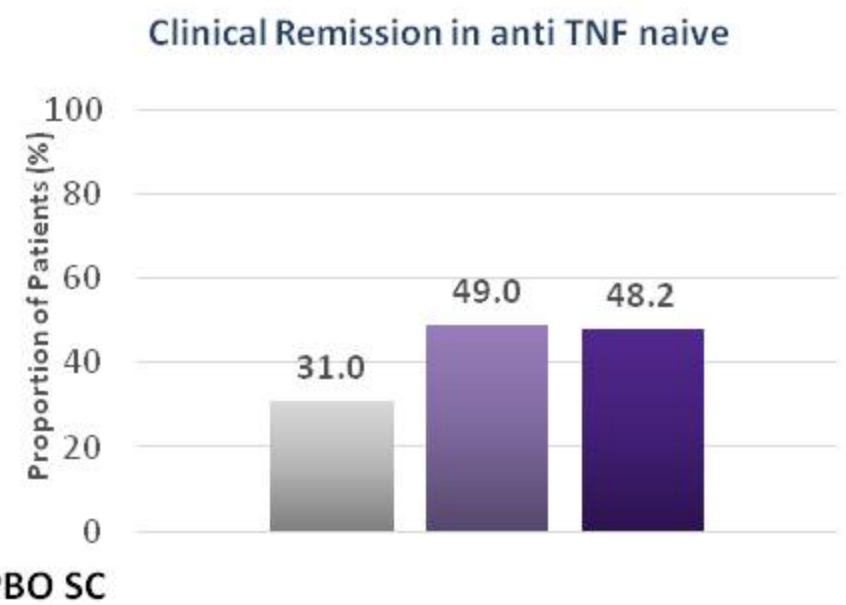


Sands B.E. et al. UEGW 2018. LB01.

Ustekinumab: IgG1 anti P40 antibody

Phase III study in moderate to severe UC – UNIFI Maintenance





Clinical Remission: Mayo score ≤ 2 points with no individual subscore > 1

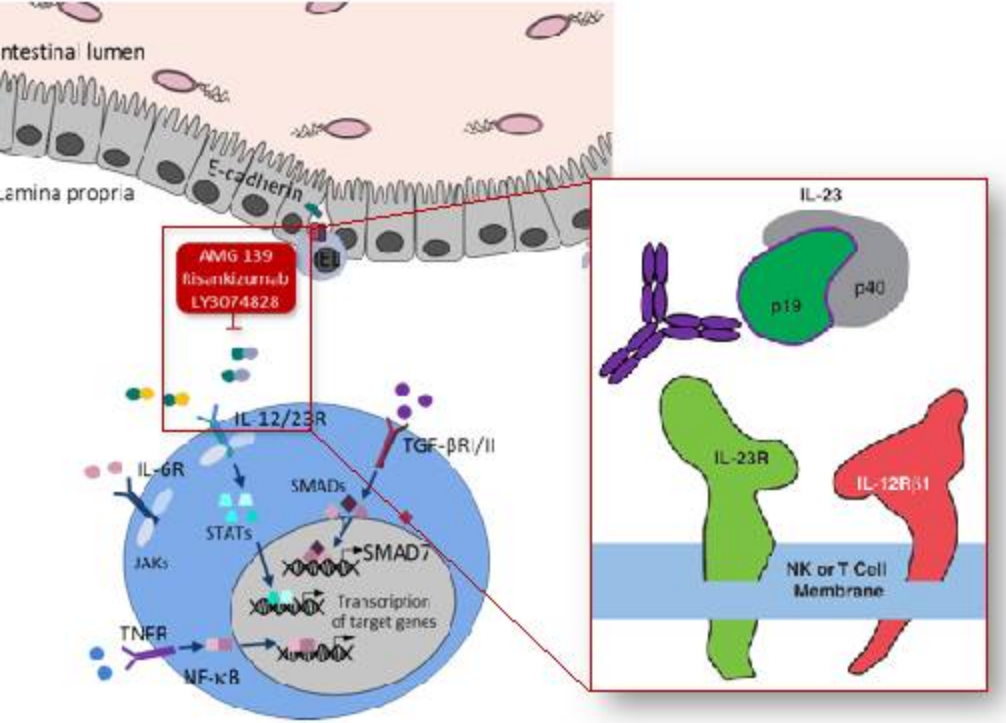
[a]Patients who were in clinical response to UST IV induction dosing and were randomized to PBO SC on entry into this maintenance study.

Sandborn WJ, et al. 14th Congress of ECCO; March 6-9, 2019; Copenhagen, Denmark.

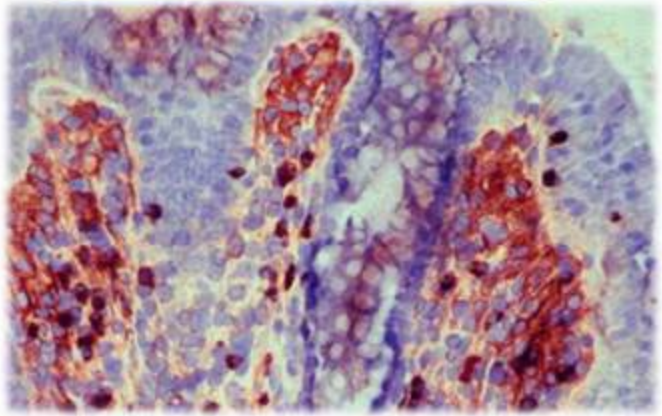
Risankizumab: IgG1 anti P19 antibody

New agent entering phase III trials in both Crohn's and UC

Levels of IL-23 and T_H17-induced cytokines are elevated in the intestinal mucosa and serum of patients with CD and UC



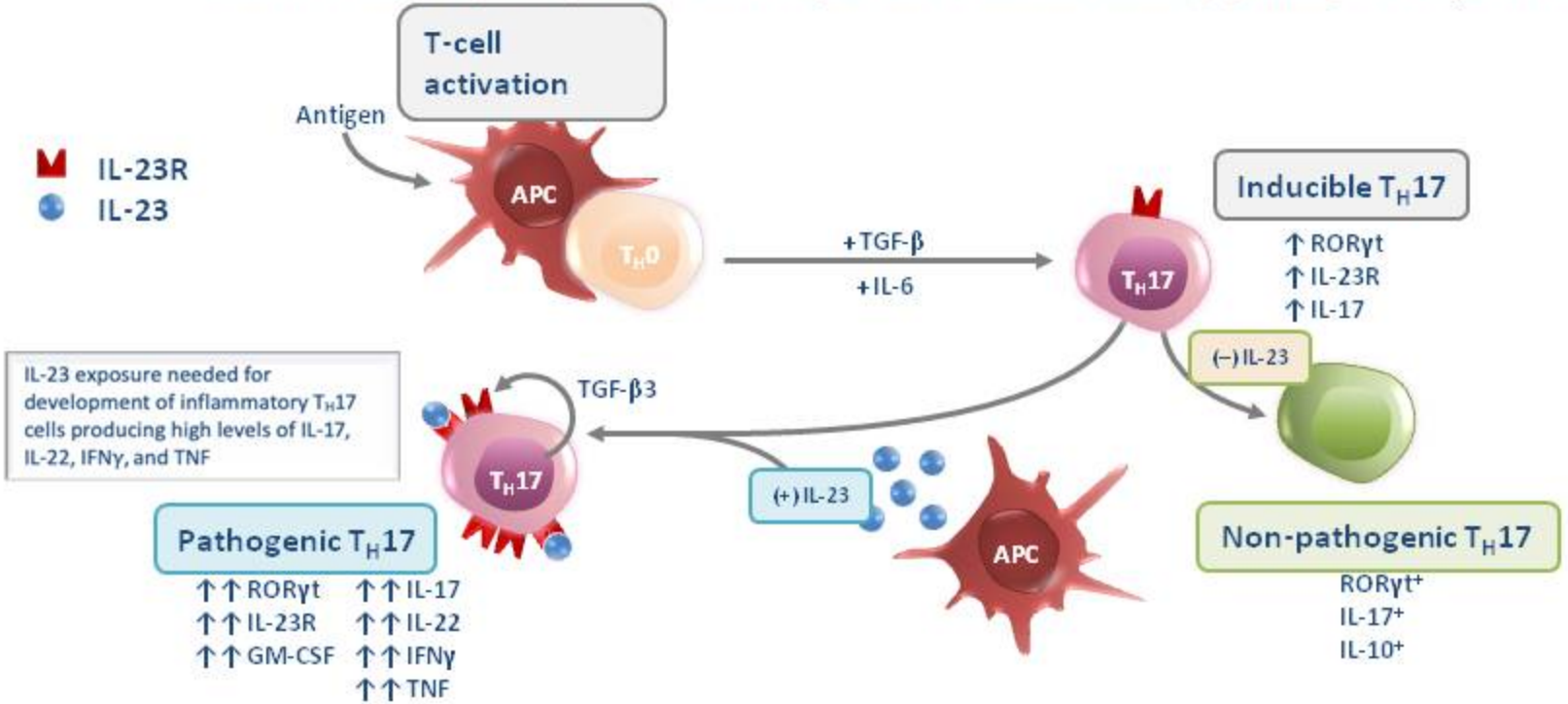
Inflamed colonic mucosa (patient with CD)



Risankizumab: IgG1 anti P19 antibody

New agent entering phase III trials in both Crohn's and UC

Interleukin 23 (IL-23) drives development of inflammatory pathogenic T_H17 cells[1,2]



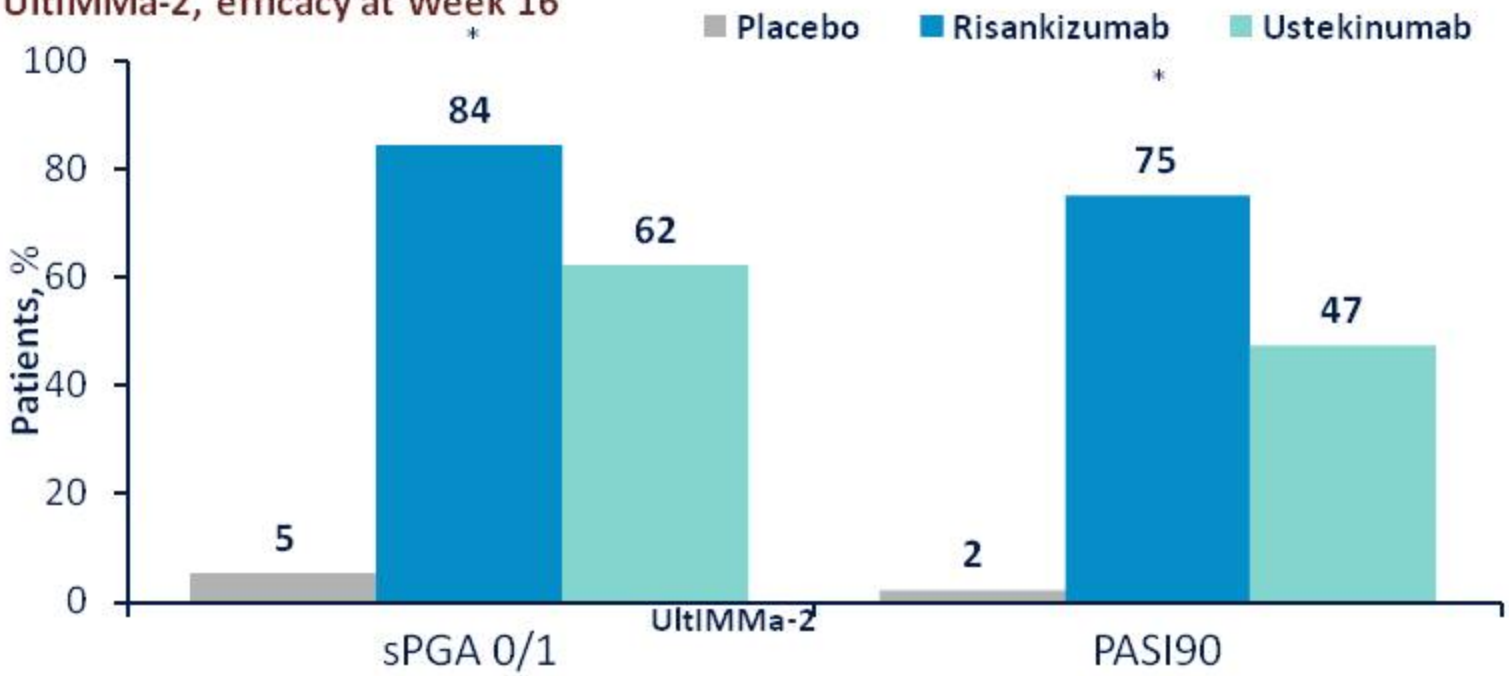
APC, antigen-presenting cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; IL-23R, interleukin-23 receptor; RORγt, retinoic acid receptor-related orphan receptor-γt; TGF-β, transforming growth factor- β; T_H, T helper; TNF, tumour necrosis factor; T_{reg}, T regulatory.

1. Zúñiga LA, et al. *Immunol Rev.* 2013;252:78–88; 2. Gaffen SL, et al. *Nat Rev Immunol.* 2014;14:585–600; 3. Geremia A and Arancibia-Cárcamo CV. *Front Immunol.* 2017;8:1296.

Risankizumab: IgG1 anti P19 antibody

New agent entering phase III trials in both Crohn's and UC

Risankizumab phase 3 psoriasis programme: UltIMMa-2, efficacy at Week 16



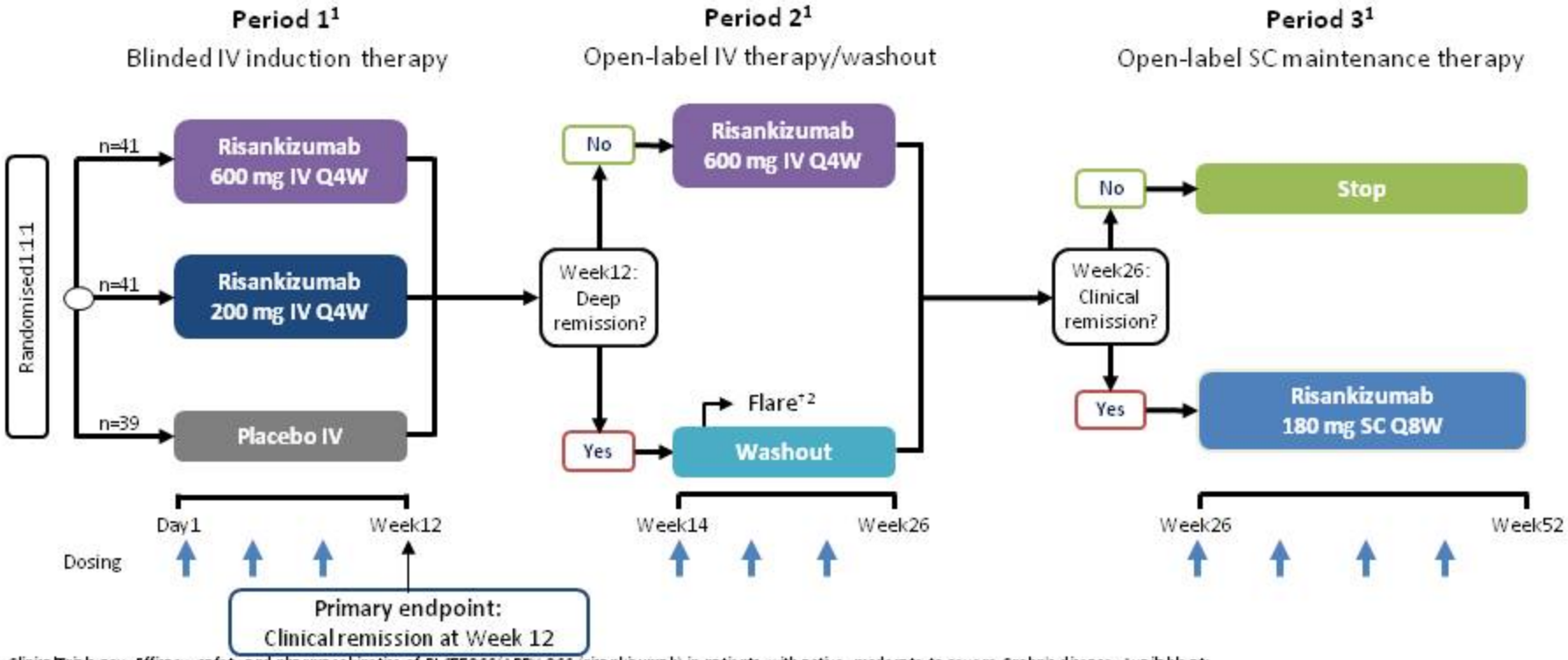
*p<0.0001 compared with placebo and ustekinumab.

PASI90, Psoriasis Area and Severity Index 90% improvement criteria; sPGA0/1, Static Physicians Global Assessment of 0 or 1.

Gordon KB, et al. *Lancet*. 2018;392:650–61.

Risankizumab: IgG1 anti P19 antibody

Phase II study design in Crohn's disease

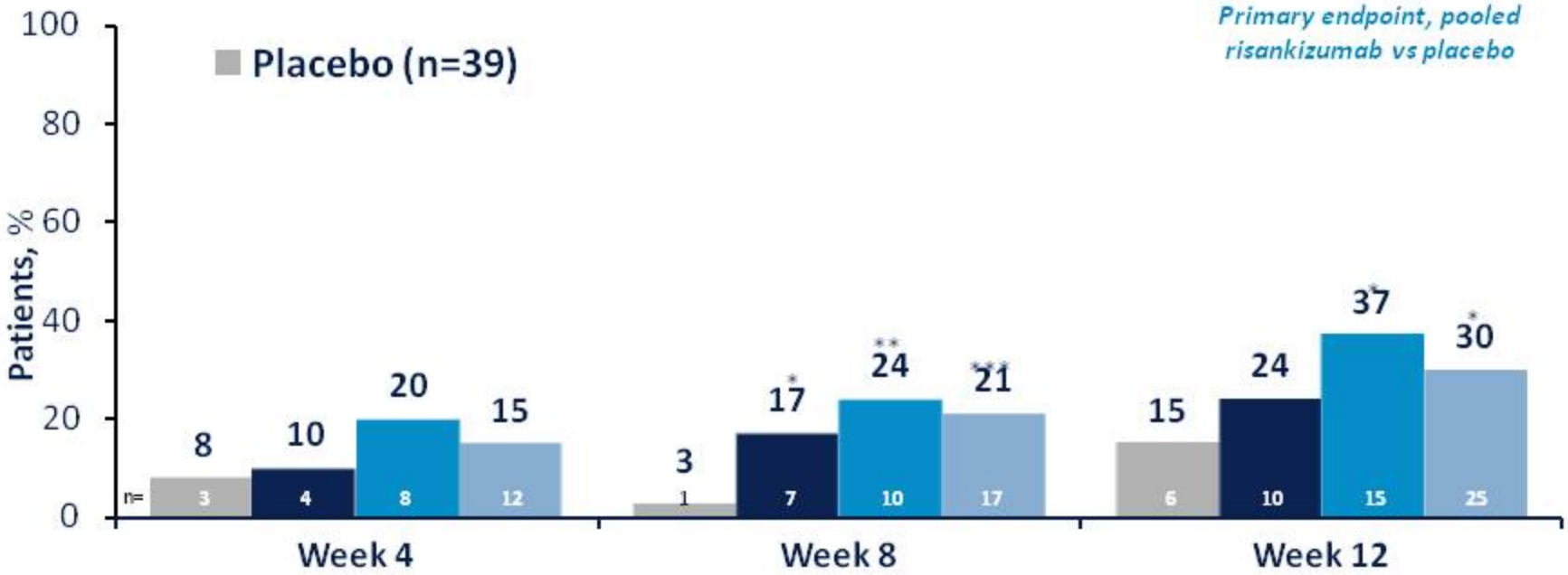


1. ClinicalTrials.gov. Efficacy, safety and pharmacokinetics of BI 655066/ABBV-066 (risankizumab) in patients with active, moderate-to-severe Crohn's disease. Available at: https://clinicaltrials.gov/ct2/show/NCT02031276. Accessed: March 2019; 2. Feagan BG, et al. *Lancet Gastroenterol Hepatol.* 2018;3:671–80.

Risankizumab: IgG1 anti P19 antibody

Phase II trial results in Crohn's disease

Period 1: clinical remission over time



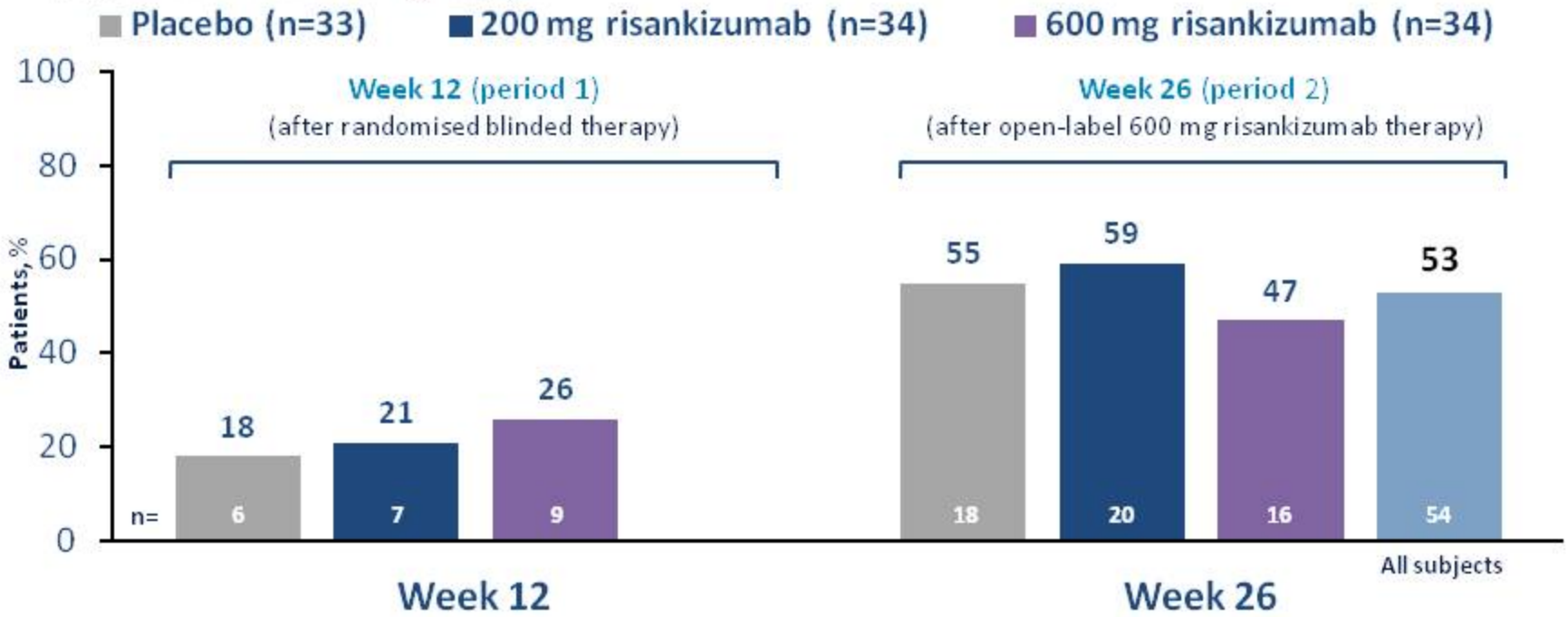
*p<0.05, **p<0.005, ***p<0.001, all comparisons vs placebo. Patients with use of prohibited concomitant medication to treat CD prior to Week 12 were considered treatment failures.
Full analysis set, using non-response imputation for missing values and stratified Cochran-Mantel-Haenszel tests. Clinical remission: CDAI score <150.
CDAI, Crohn's Disease Activity Index.
Feagan BG, et al. *Lancet*. 2017;389:1699–709.

Risankizumab: IgG1 anti P19 antibody

Phase II trial results in Crohn's disease

Period 2: clinical remission† at Weeks 12 and 26

(by period 1 treatment group)

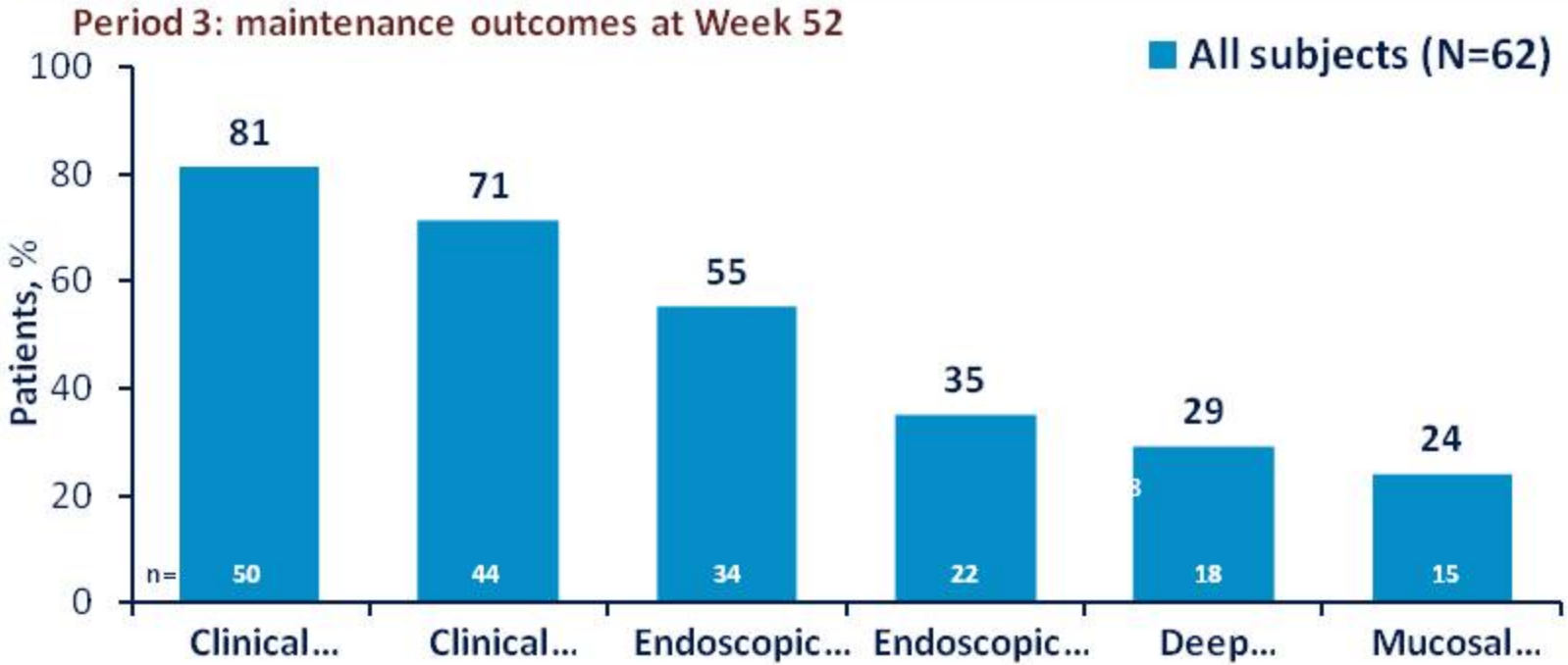


†In patients who received ≥1 dose of IV risankizumab in period 2 (efficacy analysis population). Non-response imputation for missing values. Clinical remission, CDAI <150.

Feagan BG, et al. *Lancet Gastroenterol Hepatol*. 2018;3:671–80.

Risankizumab: IgG1 anti P19 antibody

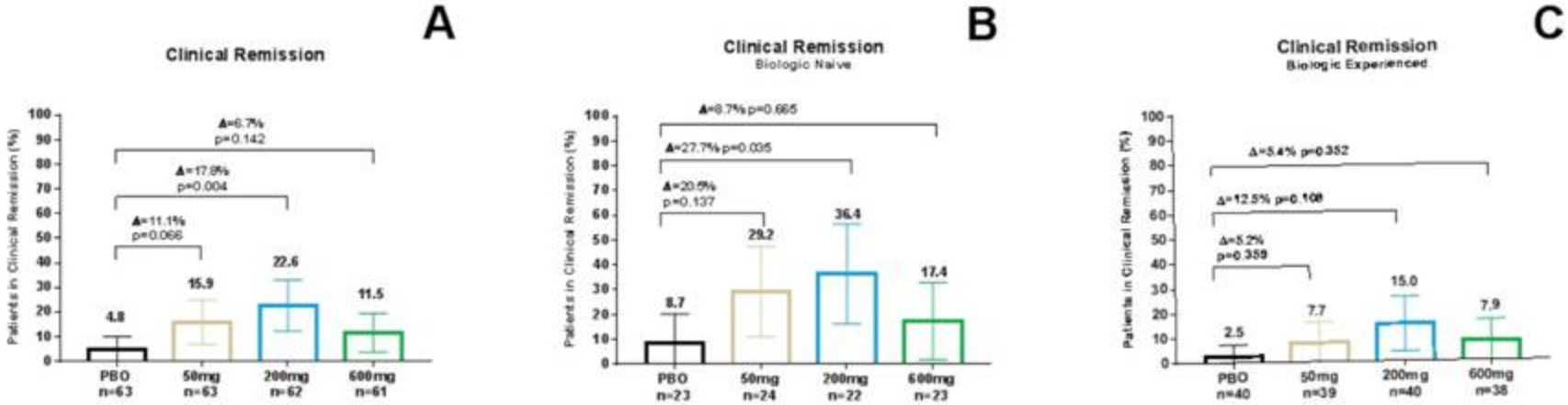
Phase II trial results in Crohn's disease



Full analysis set, using non-response imputation for missing values and stratified Cochran-Mantel-Haenszel tests. Clinical response: CDAI of <150 or a CDAI reduction from baseline of ≥100.
Clinical remission: CDAI of <150. Endoscopic response: >50% reduction in CDEIS from baseline to Week 52. Endoscopic remission: CDEIS of ≤4 at Week 52 (for patients with initial isolated ileitis, CDEIS score of ≤2).
Deep remission, clinical remission and endoscopic remission at Week 52. Mucosal healing, CDEIS surface ulcerated sub-score of 0.
CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity.
Feagan BG, et al. *Lancet Gastroenterol Hepatol*. 2018;3:671–80.

Mirikizumab: IgG1 anti P19 antibody

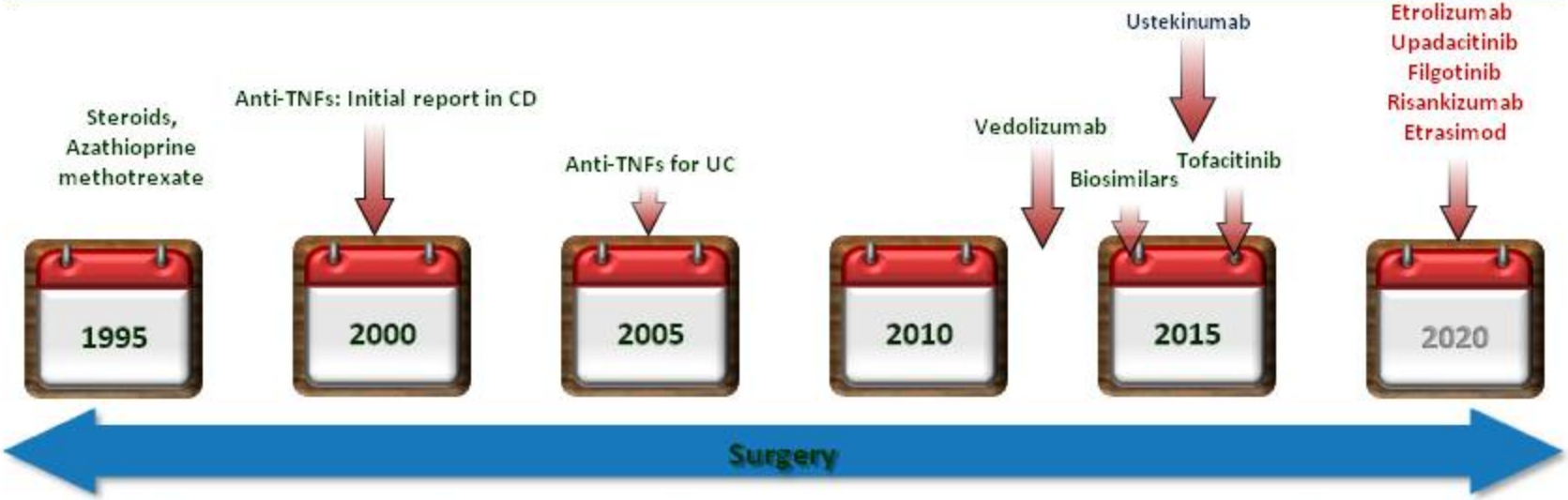
Phase II trial results in Ulcerative Colitis



SANDBORN WJ, et al. Gastroenterology. 2019 Sep 4. pii: S0016-5085(19)41300

Drugs that target cytokines or their signalling pathways

What does this mean for our patients



But will this increased drug choice increased long term remission and improve outcome?

No biologic / small molecule delivers mucosal healing in >50%

Best biologic is the first biologic

All biologics induce antidrug antibodies

Small molecules offer efficacy without immunogenicity but have 'off target' side effects

Currently we are unable to predict which patient will response to each line of therapy

Unclear whether combinations of therapies are more effective whilst remaining safe...?

Use of emerging therapies in IBD needs teamwork…

The IBD MDT at The Royal London Hospital